Mechanisms of Diastolic Dysfunction in Heart Failure

Barry A. Borlaug, David A. Kass*

Abnormalities of diastole are common to most forms of congestive heart failure (HF). Diastolic function is broadly defined as the ability of the heart to fill adequately and at normal pressure to charge the ventricular pump for each subsequent contraction. It is determined by both active and passive processes occurring at the level of the myocyte, extracellular matrix, and left ventricular chamber. Forces extrinsic to the myocardium—such as the influence of right heart filling, pericardial and extracardiac constraints, and cardiac preload and afterload also contribute. Nearly half of patients with HF have apparently preserved systolic function, and this has focused attention on diastolic dysfunction as a dominant contributor to symptoms, sparking interest for understanding and treating diastolic abnormalities. This review focuses on the mechanisms determining normal and pathologic cardiac relaxation and distensibility and highlights how these abnormalities may be therapeutically targeted to improve diastolic function in human HF. (Trends Cardiovasc Med 2006;16:273–279) © 2006, Elsevier Inc.

• Introduction
In the normal heart, ventricular pressure decays rapidly after systolic ejection, and the left ventricle thereafter requires low distending pressures to fill. Both features are typically rendered abnormal in the failing heart, resulting in limited cardiac reserve and elevated diastolic and, thus, central venous pressures. Basic research has helped clarify many cellular, molecular, and chamber mechanisms involved and suggested potential novel targets that might improve diastolic function. However, clinical data remain far more limited. This relates in part to technical difficulties in precisely measuring diastolic function, which ideally requires invasive measurement. Noninvasive imaging methods are very useful for revealing diastolic abnormalities—principally by analyzing myocardial tissue motion and filling dynamics (Oh et al. 2006). However, precise therapeutic targeting of these integrated behaviors has been elusive. The situation is further complicated by variability in the definition of diastolic dysfunction and by the fact that a given disease process may produce directionally opposite changes in the different components of diastole (i.e., relaxation and compliance). Quantitative of diastolic function itself is often based on mathematical model assumptions, the validity of which may not broadly apply to all types of heart disease (Senzaki et al. 1999). Finally, most therapies that alter diastole also influence systole and loading conditions, making interpretation of specific effects challenging.

Despite these limitations, recent research is shedding new light on the mechanisms underlying diastolic dysfunction (Kass et al. 2004, Van Heerebeek et al. 2006, Ahmed et al. 2006), and large-scale clinical trials targeting heart failure (HF) with a preserved ejection fraction are now being undertaken. Here, we review current understanding and clinical directions for diastolic dysfunction and its role in HF.

• The Components of Diastole
Diastole is considered to start with the onset of relaxation of ventricular muscle contraction—usually just preceding closure of the aortic valve. Ventricular pressure declines rapidly during the period of isovolumic relaxation and follows a time course most often modeled by a monoeponential waveform, yielding a decay time constant (τ) (Kass 2000) (Figure 1A). Pressure decline is often considered an active process because adenosine triphosphate (ATP) hydrolysis is needed to release tightly bound actin–myosin bonds and for calcium reuptake into the sarcoplasmic reticulum (SR). However, it is also influenced by passive mechanical forces, such as elastic energy stored during contraction that is released during relaxation as elastic recoil. Because this depends upon the extent of systolic sarcomere shortening (i.e., ventricular end-systolic volume), it is influenced by cardiac contractility, extracellular matrix composition, sarcomeric proteins such as titin, and viscoelastic properties. If relaxation is excessively slow, it can elevate not only early but also late diastolic pressures, particularly at faster heart rates, such as during exercise. However, this requires considerable delay, and slowed relaxation generally has less impact on late diastolic filling pressures.

The second phase of diastole occurs upon opening of the mitral valve and, thus, onset of early rapid filling. An advantage of the preceding rapid left ventricular (LV) pressure decline is its facilitation of an atrial–ventricular pressure gradient, which serves as the driving force for ~80% of normal ventricular filling (Figure 1B). Relaxation delay, loss of normal elastic recoil, and increased chamber stiffness all impair formation

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of this gradient and, thus, the rate and net magnitude of early filling.

After early rapid filling, ventricular and atrial pressures equilibrate, and there is essentially no ventricular inflow. During this third phase, termed diastasis, one can best assess the passive diastolic stiffness of the heart by measuring pressures at varying chamber volumes. This curvilinear relation is often modeled by a monoexponential function and quantified by the exponential stiffness coefficient ($\beta$) (diastolic pressure–volume relation [DPVR], Figure 1D). A decrease in diastolic ventricular compliance is reflected by an increase in the curvature (increased $\beta$, fit from the equation $P = az^\beta + P_0$, where $a$ is a scaling coefficient, $V$ is volume, and $P_0$ is the pressure intercept or $P$ at $V = 0$) (Kass 2000). Patients with dilated cardiomyopathy will display a rightward shift of the DPVR, owing to chamber dilation. Although some refer to this as increased chamber distensibility, because the heart can fill at higher volumes while maintaining a lower pressure, it more accurately reflects myocardial remodeling. Despite the remodeling, patients often operate at near-maximal filling, so their effective operant stiffness, which is determined by the local slope of the DPVR, remains elevated above normal (Figure 3D). As previously noted, patients with markedly delayed relaxation may not display a period of diastasis, particularly if the diastolic filling period is shortened, as with tachycardia.

The last component of diastole is atrial contraction. This normally contributes ~20% of total diastolic filling, but in many forms of HF—particularly hypertensive heart disease, and notably in the elderly—limitations of early rapid filling enhance the importance of atrial systole on net filling. Atrial dilation is often observed in these disorders and appears to be a marker for both diastolic dysfunction and poor prognosis (Melenovsky et al. 2005, Takemoto et al. 2005).

**Cellular Mechanisms**

During contraction, intracellular calcium released principally from the ryanodine receptor binds to troponin C, allowing the interaction of actin and myosin in the generation of force. Tension is released when calcium dissociates from the complex and is sequestered into the SR and removed from the myocyte by the sodium/calcium exchanger (NCX). Adenosine triphosphate hydrolysis is required for the dissociation of the thick and thin filaments from the strongly bound rigor state. Elastic recoil of compressed elements (primarily titin, see below) within the myocyte also

**Table 1. Myocardial structure and function in systolic HF and HFnEF**

<table>
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<tr>
<th>Index</th>
<th>Systolic HF</th>
<th>HFnEF</th>
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<tbody>
<tr>
<td>Contractility ($dP/dt_{max}$)</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Peak pressure decay ($dP/dt_{min}$)</td>
<td>↓↓</td>
<td>↓</td>
</tr>
<tr>
<td>Relaxation time constant ($\tau$)</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>LV mass index</td>
<td>↑</td>
<td>↑</td>
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<tr>
<td>LV mass/end diastolic volume</td>
<td>–</td>
<td>↑</td>
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<tr>
<td>Myocyte diameter</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Collagen content/fibrosis</td>
<td>↑</td>
<td>↑</td>
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<tr>
<td>Passive myocyte tension ($F_{passive}$)</td>
<td>↑</td>
<td>↑</td>
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<tr>
<td>$F_{passive}$ drop after PKA</td>
<td>–</td>
<td>↓</td>
</tr>
<tr>
<td>Titin N2BA/N2B ratio</td>
<td>–</td>
<td>↑</td>
</tr>
<tr>
<td>Myocyte calcium sensitivity</td>
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Adapted with permission from Circulation 2006;113:1966-1973.
exerts a restoring force, which affects the velocity of relaxation.

In the human heart, intracellular calcium decline is due in equal parts to reuptake into the SR by the SR calcium adenosinetriphosphatase (SERCA) 2a and cytosolic extrusion by the NCX. Mice, on the other hand, are dominated by SR reuptake (>90%), something worth remembering when evaluating data obtained from this species. SERCA2a is negatively regulated by phospholamban (PLB, Figure 2) (Frank et al. 2002, Del Monte et al. 2002), but when phosphorylated by protein kinase (PK) A or Ca2+-calmodulin-dependent kinase (CaMK), PLB inhibition is attenuated, accelerating relaxation (Figure 2). SERCA2a expression and activity decline in HF (Frank et al. 2002), and PLB hypophosphorylation related to diminished PKA, CaMK activity, and/or increased protein phosphatase (PP1) activity also occurs and slows relaxation (Neumann et al. 2000). Gene transfer with SERCA2a and therapies designed to reduce PLB inhibition of SERCA2a improve the rate of relaxation (Miyamoto et al. 2000, Hoshijima et al. 2002). The former therapy has been studied in a variety of animal models, and ongoing efforts aim at ultimately testing its efficacy in human HF. Additional calcium abnormalities have been proposed to occur by diastolic calcium leak from the ryanodine receptor in association with diminished FK 506-binding protein 12.6 stabilizing protein (Marx et al. 2000). This could increase thick–thin filament interaction during diastole and, therefore, overall chamber stiffness, although the relevance of this mechanism in vivo remains unproven. Finally, NCX is upregulated in HF and may, in part, compensate for loss of SERCA2a function (Hasenfuss et al. 1999). However, increased NCX activity can potentially contribute to calcium loading in the reverse mode (sarcoplasm entry), lengthening the action potential duration and shortening diastole.

Abnormalities of myocardial high energy phosphate metabolism may also impact diastolic stiffness. Detachment of the strongly bound state of actin–myosin requires dissociation of adenosine diphosphate (ADP) and can be impeded by increases in the free concentration of this molecule. Several studies in isolated heart models demonstrated diastolic stiffening coupled to metabolic inhibition or ischemia that was linked to increased free ADP. More recently, abnormal high-energy phosphate metabolism with marked adenosine monophosphate (AMP) degradation and increased free ADP was revealed in an in vivo canine model of diastolic dysfunction induced by AII infusion combined with 2-day tachypacing (Paolocci et al. 2006). These changes were reversed by treatment with an inhibitor of metalloproteinases, and intriguingly, the decline in free ADP and reversal of AMP catabolism, rather than changes in structural proteins, best correlated with improved diastolic compliance.

Another factor regulating diastolic relaxation and stiffness is the sensitivity of the myofilament to calcium, as recently reviewed (Kass and Solaro 2006). This is regulated by the sarcomeric proteins as well as regulatory thin filaments, notably troponin-I. Cyclic AMP and cyclic guanosine monophosphate-dependent PK phosphorylation of troponin-I, modulated by β-adrenergic activation and nitric oxide/natriuretic peptides, decreases Ca2+ binding avidity, assisting a decline in force as calcium falls. Genetic replacement of the skeletal isoform of troponin-I that cannot be PKA phosphorylated or overexpression of a troponin-I that behaves as if constitutively phosphorylated at PKA sites lengthens and hastens relaxation, respectively (Wolska et al. 2001, Takimoto et al. 2004). Additional kinases such as PKC and Rho-kinase appear to influence myofilament calcium sensitivity (Vahebi et al. 2005), the latter acting on troponin T, and may contribute both to contractile depression and prolonged relaxation in the failing heart. More research is needed to clarify the importance of these pathways.

The sarcomeric macromolecule titin is increasingly recognized as a central determinant of both myocyte stiffness and elastic recoil (Granzier and Labeit 2002). Titin spans the entire sarcomere and is expressed as two primary isoforms: a smaller, stiffer N2B and larger, more compliant N2BA. These isoforms are expressed to variable degrees in

![Figure 2. Cellular mechanisms regulating diastole.](image)

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different species, at different time points during cardiac development, and in human HF (Wu et al. 2002, Lahmers et al. 2004, Van Heerebeek et al. 2006). Titin can undergo posttranslational modification by calcium and phosphorylation, dynamically affecting compliance and restoring force and potentially providing a novel target for drug therapies (Yamasaki et al. 2002, Labeit et al. 2003). When the myocyte shortens below its equilibrium or slack length, restorative forces stored within the titin molecule provides a “spring,” which speeds the return to unstressed length. Quantitative or qualitative (e.g., phosphorylation) changes in titin therefore exert effects on early relaxation. As the myocyte is stretched during diastolic filling, titin also confers a passive viscous and elastic resistance to deformation (Wu et al. 2000) likely influencing the DPVR. However, mechanisms leading to titin isoform switching and posttranslational modification, along with its relative role in human HF, remain poorly understood.

- **Extracellular Matrix**

The composition and structure of the extracellular matrix surrounding cardiac myocytes exerts effects on diastolic ventricular compliance (Wu et al. 2000, MacKenna et al. 1994). This is determined not only by the amount and isotype of collagen present but, perhaps more importantly, by the qualitative characteristics of that collagen (glycation, cross-linking) and the ultrastructural location (perimysial rather than endomysial fibers) (Yamamoto et al. 2002). Collagen deposition is enhanced in the setting of pressure-overload hypertrophy, aging, HF, and myocardial infarction. Collagen degradation in myocardial tissue preparations results in reduced diastolic stiffness but requires somewhat extreme levels of tissue digestion (Stroud et al. 2002). Soluble, profibrotic mediators such as transforming growth factor-β (TGF-β), angiotensin-II, and mast cell chymase have each been targeted with the use of pharmacologic inhibitors in animal studies, and the result has been a decline in cardiac fibrosis but somewhat variable improvements in diastolic function (Kuwahara et al. 2002, Diez et al. 2002, Matsumoto et al. 2003).

Qualitative changes in collagen cross-linking, perhaps more than amount, appears to be a potent contributor to increased myocardial stiffness (Badenhorst et al. 2003). Inhibition of glucose-collagen glycation crosslinks, one form of modified collagen that is enhanced with normal aging and diabetes, reduces ventricular stiffness in dogs (Asif et al. 2000) and may have effects in humans as well (Little et al. 2005). Alteration and activation of matrix metalloproteinases (MMPs) and tissue inhibitor of metalloproteinases (TIMPs), as occur in the setting of neurohormonal stress, also appear to play an important role in modulating LV distensibility. Tachypacing with angiotensin-II infusion activates MMPs and increases diastolic stiffness in dogs—effects that can be blocked by coadministration of β-receptor antagonists (Senzaki et al. 2000). This could be a contributing mechanism for improved diastolic function associated with β-blocker therapy. Specific MMP profiles, such as decreased MMP-2 and MMP-13, are associated with LV hypertrophy (LVH), and these changes, together with an increase in TIMP-1, are found in patients with LVH and clinical HF (Ahmed et al. 2006).

- **Effects External to the Left Ventricle**

Of LV diastolic pressure, ~40% is due to extraventricular forces that stem from right ventricular loading and from pericardial interaction (Dauterman et al. 1995). These forces are not often considered in studies assessing intact heart diastolic chamber distensibility or resting pressures, and failure to do so can lead to erroneous data interpretation. For example, acute interventions such as regional ischemia or calcium channel blockade thought to directly alter LV diastolic compliance appear to act, in large part, by altering external forces (Kass et al. 1990, 1993). To best determine diastolic ventricular stiffness (i.e., the DPVR), LV transmural (rather than intracavitary) pressure should be measured, data examined during the period of diastasis (i.e., after early filling but before atrial contraction), and the contribution of external forces minimized by first unloading the right ventricle. While seemingly a tall order, these requirements have been achieved in humans by measuring beat-to-beat pressure–volume data and with the use of rapid inferior vena caval balloon occlusion to generate multiple cycles at varying preload volumes (Kass 2000). Analysis can then be restricted to the diastolic period from each beat that most likely reflects passive stiffness, with external forces largely removed. Such analysis has revealed that steady-state resting DPVRs and those derived from the multiple beat approach can vary considerably. For example, in patients with hypertrophic cardiomyopathy, the steady-state relation appears very flat, whereas the same heart assessed with the use of the multibeat approach during inferior vena cava occlusion reveals a substantially steeper slope and higher β (Pak et al. 1996).

Neurohormonal hyperactivation is common to HF with both preserved and reduced systolic function (Kitzman et al. 2002), and in addition to promoting adverse remodeling and cellular toxicity, this is important for volume retention. A primary increase in central blood volume in tandem with such maladaptive activation can serve to increase LV filling pressures, even in the absence of measurable systolic or diastolic dysfunction (He et al. 2004). Therefore, the finding of elevated cardiac filling pressures in a normal-sized heart does not guarantee diastolic (or systolic) dysfunction, further emphasizing the integrated and multifactorial nature of HF.

Cardiac afterload affects the rate of cardiac relaxation in both animal models and humans (Leite-Moreira and Correa-Pinto 2001, Kawaguchi et al. 2003), with increases in load occurring during late ejection being particularly deleterious. This is important because vascular aging typically imposes increased late systolic loading due to the rapid return of reflected pressure waves and can thus further impair relaxation. Recent mouse transgenic studies suggest that PKA phosphorylation of troponin-I is an important mediator of the load–relaxation independence (Takimoto et al. 2004) and are concordant with reduced PKA activity in HF and heightened load–relaxation dependence.

Despite known afterload effects on the kinetics of relaxation, it remains...
controversial whether prolongation of the early phase of pressure decay results in meaningful pressure elevation. At normal human isovolumic decay rates ($\tau$ of 30-40 milliseconds) (Kawaguchi et al. 2003), LV pressure is expected to drop to <2 mm Hg after ~125 milliseconds. Since diastole typically lasts ~400 milliseconds, even marked prolongation in $\tau$ is unlikely to lead to meaningful elevations in ventricular end-diastolic pressure. Indeed, pharmacologic interventions that prolong relaxation rarely cause a shift in the DPVR in humans (Kass et al. 1993). Although relevant effects may be more manifest at fast heart rates, in vivo human evidence shows that patients with HF and hypertrophy actually augment relaxation to a greater extent with tachycardia, compared with healthy controls (Liu et al. 1993). In animal studies, afterload had to be raised to near 80% of maximum (maximum studies, afterload had to be raised to $\tau$) to raise end-diastolic pressure (Leite-Moreira and Correia-Pinto 2001). Thus, the net impact of prolonged relaxation remains unresolved.

- **Diastolic Dysfunction and Heart Failure with a Normal Ejection Fraction**

Nearly half of all patients with HF have apparently preserved systolic function (ejection fraction [EF] >50%), HF with normal EF (HFnEF), (Kitzman et al. 2002). This is often referred to as diastolic HF, although there is little doubt that there is more than diastolic dysfunction playing a role in the genesis of clinical symptoms, including exercise intolerance, hypertension, blood pressure lability, and rapid-onset pulmonary edema. While some studies have found that systolic function is normal in HFnEF (Baiqu et al. 2005), others have reported subtle systolic dysfunction, although not to the extent as seen in systolic HF (Yu et al. 2002). In a recent study, myocardial properties were determined from human biopsy specimens, contrasting those with HF and low EF to those with HFnEF (Table 1) (Van Heerebeek et al. 2006). Although collagen content was similar in the groups, myocyte diameter, calcium sensitivity, passive tension, and relative expression of titin N2B (stiff isoform) were all higher in HFnEF. The latter also displayed a greater drop in passive tension in response to PKA activation, leading the authors to speculate that PKA-dependent titin phosphorylation may be a viable therapeutic target in this disorder.

In a recent report that used single-beat pressure-volume analysis (i.e., extracardiac factors were not accounted for) and noninvasive volume assessments, patients with known diastolic abnormalities had increased diastolic stiffness, compared with healthy controls (Zile et al. 2004) (Figure 3, curve b versus curve a). However, in another study that used invasive, multibeat DPVR analysis, HFnEF subjects did not appear to have significant diastolic stiffening, and the higher LV end-diastolic pressure observed was more related to external forces, perhaps related to increased total epicardial heart volumes (Figure 3, curve c) (Kawaguchi et al. 2003). Differences in study methods, sample size, and patient population may explain the discrepancy. It is essential to bear in mind that just as systolic dysfunction does not necessitate that patients display clinical congestive HF (Wang et al. 2003), diastolic dysfunction does not guarantee HF symptoms, and other factors also pertain. These factors include increased ventricular systolic and vascular stiffness (Kawaguchi et al. 2003, Hundley et al. 2001), atrial dysfunction (Melenovsky et al. 2005), chronotropic incompetence, and impaired cardiovascular reserve with exercise stress (Borlaug et al. 2005a, 2005b), and all likely contribute to the disease pathogenesis to variable extents in individual patients.

### Table 2. Therapeutic strategies targeting diastolic dysfunction

<table>
<thead>
<tr>
<th>Pathophysiologic target</th>
<th>Cellular target</th>
<th>Examples</th>
</tr>
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<tbody>
<tr>
<td>Isovolumic relaxation</td>
<td>Increase SR Ca$^{2+}$ extrusion</td>
<td>Gene transfer of SERCA or pseudophosphorylated PLN</td>
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<tr>
<td></td>
<td>Increase PLN phosphorylation</td>
<td>$\beta$-adrenergic receptor agonists or $\beta$-ARK inhibitory peptides</td>
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<td></td>
<td>Decrease thin filament Ca$^{2+}$ binding affinity</td>
<td>$\beta$-adrenergic receptor, nitric oxide, and natriuretic peptide agonists; soluble GC activators; PDE3 and PDE5 antagonists; Rho-kinase inhibitors</td>
</tr>
<tr>
<td></td>
<td>Improve myocyte ATP availability/energetics</td>
<td>Revascularization; small molecule agents?</td>
</tr>
<tr>
<td>Increase myocyte distensibility</td>
<td>Modify titin isoform expression or posttranslational modification</td>
<td>Activation of PKA; PKG and PKC activators?</td>
</tr>
<tr>
<td></td>
<td>Decrease diastolic Ca$^{2+}$ leak</td>
<td>Ryanodine receptor-stabilizing agents: FKBP 12.6 (gene transfer or small molecules)</td>
</tr>
<tr>
<td>Increase LV chamber distensibility</td>
<td>Prevention and regression of concentric hypertrophy</td>
<td>Neurohormonal antagonists (RAAS); PDE5 and Rho-kinase inhibitors; many other potential targets</td>
</tr>
<tr>
<td></td>
<td>Prevention and regression of fibrosis</td>
<td>RAAS antagonists; chymase and TGF-$\beta$ inhibitors, MMP modulators, AGE breakers</td>
</tr>
<tr>
<td>Augment atrial emptying function</td>
<td>Prevention of atrial remodeling and dysfunction</td>
<td>Neurohormonal antagonists, maintenance of sinus rhythm</td>
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PLN, phospholamban; GC, guanylate cyclase; RAAS, renin-angiotensin-aldosterone system; AGE, advance glycation endproducts.
followed up for a median of 3 years. Although there was no effect on mortality, candesartan therapy was associated with a modest reduction in hospitalizations for HF. A caveat to these data is that the demographic makeup of the study population was not typical of HFnEF, with most subjects being male and of younger age, and the prevalence of hypertension and ventricular hypertrophy was modest. Another large-scale study of an angiotensin receptor blocker (irbesartan) called “I-Preserve” was initiated in 2002 (Carson et al. 2005). Patients must be >60 years old, with HF and an EF >45%. The trial recently closed enrollment at 4000 patients, and results have yet to be reported. Other therapies targeting fibrosis and related changes in ventricular and arterial stiffness include aldosterone, TGF-β, and chymase antagonists (Kuwahara et al. 2002, Matsumoto et al. 2003). A major trial sponsored by the National Institutes of Health will be initiated in 2006 and test the efficacy of an aldosterone antagonist (spironolactone) for treatment of this disorder. Table 2 summarizes current and future therapeutic targets in diastolic dysfunction.

Because evidence-based guidelines remain lacking, treatment recommendations remain based mostly on expert opinion. Current therapies focus on blood pressure control, judicious diuretic use and, in some cases, on heart rate slowing. However, a number of other novel approaches are being entertained. Given that increased ventricular systolic stiffness and excessive concentric LVH is common in HFnEF (Kawaguchi et al. 2003), therapies targeting hypertrophy may prove very useful. One emerging mediator is Rho-kinase, an important downstream effector of Gq-protein-coupled angiotensin-II signaling. In animal models, the Rho-kinase inhibitor fasudil attenuates angiotensin-II-induced cardiac hypertrophy (Higashi et al. 2003). HMG CoA-reductase inhibitors (statins) also inhibit Rho-kinase activation, and their use has been suggested to improve survival in an retrospective analysis of patients with HFnEF (Fukuta et al. 2005). We recently demonstrated that the phosphodiesterase (PDE) 5 inhibitor sildenafil markedly attenuates the hypertrophic response to pressure overload in mice (Takimoto et al. 2005). In humans, sildenafil suppresses acute β-adrenergic stimulated contractility (Borlaug et al. 2005a, 2005b), and ongoing studies are evaluating whether it can also blunt hypertrophic responses in patients with HFnEF. Because both Rho-kinase and PDE5 inhibitors can reduce LV mass, arterial stiffness, and cause modest vasodilation, they present attractive approaches to the treatment of multiple, potentially synergistic abnormalities in patients with HFnEF.

References


