What Mechanisms Underlie Diastolic Dysfunction in Heart Failure?

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Abstract—Abnormalities of diastolic function are common to virtually all forms of heart failure. However, their underlying mechanisms, precise role in the generation and phenotypic expression of heart failure, and value as specific therapeutic targets remain poorly understood. A growing proportion of heart failure patients, particularly among the elderly, have apparently preserved systolic function, and this is fueling interest for better understanding and treating diastolic abnormalities. Much of the attention in clinical and experimental studies has focused on relaxation and filling abnormalities of the heart, whereas chamber stiffness has been less well studied, particularly in humans. Nonetheless, new insights from basic and clinical research are helping define the regulators of diastolic dysfunction and illuminate novel targets for treatment. This review puts these developments into perspective with the major aim of highlighting current knowledge gaps and controversies. (Circ Res. 2004;94:1533-1542.)

Key Words: myocardium □ dilated cardiomyopathy □ heart failure □ hypertrophy □ compliance □ diastole □ relaxation

The heart spends more than half its time in diastole (relaxing and then filling to prepare for the next ejection). Although abnormalities of diastolic function are well recognized and common to virtually all forms of heart failure, just how they affect basal and reserve function and their relative role in clinical heart failure remain unclear. There are a number of reasons for this. First, diastole assessment ideally requires invasive measurements that are nontrivial to obtain, whereas noninvasive surrogates often reported in clinical studies reflect integrative properties that lack specificity. Second, relatively few animal models recapitulate human diastolic disease, particularly chamber stiffening, which is often normal in murine models despite extensive matrix, myofibrillar, or signaling abnormalities. Third, there are few if any targeted treatments that can specifically test the impact of altering diastolic function on heart failure pathophysiology and outcome. Last, diastolic function has been less amenable to reductionist approaches given the potent roles that chamber geometry, loading (both intrinsic and extrinsic to myocytes), extracellular matrix, and myocardial perfusion all bring to bear.

Another problem is that there is no single definition for diastolic dysfunction; many features can be altered, and any one change or their combination is typically called diastolic dysfunction, although the pathophysiology and functional significance varies greatly. Thus, the term is used to describe slowed force (or pressure) decay and cellular relengthening...
rates, increased (or decreased) early filling rates and deceleration, elevated or steeper diastolic pressure-volume (PV) relations, and filling-rate dependent pressure elevation (viscoelasticity). Clinically, the most common manifestation is an elevated end-diastolic pressure (EDP) and altered filling patterns, but neither of these identifies specific features of diastolic dysfunction.

Despite these difficulties, it remains widely presumed that diastolic abnormalities are important to heart failure pathophysiology, and this is driving new research to elucidate the biochemical and structural mechanisms that underlie it, clarify its role to clinical heart failure, and develop targeted treatments for it. Important insights are being gleaned from genetically engineered models that facilitate molecular hypothesis testing in the intact chamber. Clinical epidemiology is fueling interest because many patients with cardiac failure present with preserved ejection fraction, which has rightly or wrongly focused attention on diastolic dysfunction.1,2

This article reviews recent insights into diastolic dysfunction with heart failure, focusing on unresolved or controversial areas in need of further research. We divide our discussion into 2 primary components: relaxation and diastolic stiffness defined by the length-tension or PV relationship. We avoided discussion of diastolic filling patterns and tissue velocities because these are more integrative in nature and have been dealt with in recent reviews.2-5

How Do Myocytes Control Relaxation?

Myocardial relaxation requires that strongly bound actin-myosin filaments return to a low-force-generating state. Anything that interferes with cross-bridge detachment or with preceding calcium removal from the cytosol has the potential to delay relaxation. This includes prolongation of the Ca\(^{2+}\)-transient because of reduced resequestration into the sarcoplasmic reticulum (SR), abnormal extrusion by the sodium/calcium exchanger (NCX), interference with cross-bridge uncoupling by abnormal high-energy phosphate metabolism, and abnormalities of the contractile proteins themselves affecting their interaction or Ca\(^{2+}\) sensitivity. Furthermore, in intact muscle, force decay is also mediated by the recovery of stored elastic energy generated during systolic contraction, and this can be blunted by heart failure as well. Although much has been learned about each of these processes, many questions about their interplay, regulation, and relative role to relaxation remain unanswered.

Alterations in myocyte-calcium-handling proteins, including the sarcoplasmic reticular Ca\(^{2+}\)-ATPase (SERCA2a) and its modulator phospholamban (PLB),6-9 the SR–Ca\(^{2+}\) release channel and its modulator FK-506 binding protein 12.6 (FKBP12.6), and NCX have all been implicated in altering the calcium transient in failing hearts and contributing to delayed relaxation. SR–Ca\(^{2+}\) uptake activity declines with heart failure often coupled to reduced gene and protein expression of both enzymes.6,10 Both proteins can be serine-phosphorylated by protein kinase A (PKA), and reduced phosphorylation of PLB11 (associated with increased protein phosphatase [PP1]12,13) appears important for relaxation delay. PLB can also be phosphorylated by protein kinase C (PKC-α),8 although higher levels of PKC-α may reduce phosphorylation in part by activating PP1.14 The role of SERCA2a phosphorylation by PKA remains little understood,15 and recent exploration into the molecular nature of PLB–SERCA2a interaction16 suggests that additional sites may also affect their molecular coupling. Both proteins have been modified by gene transfer or genetic engineering, confirming their role in relaxation. Gene transfer with SERCA2a or a negative PLB–mutant improves relaxation.17-19 Removal of PLB deletes inhibitor and potential facilitator functions,20 and the net result can vary depending on the physiologic conditions. For example, restoration of wild-type PLB to PLB-null mice enhances rate-dependent relaxation yet has little effect on basal rates.21

In addition to SERCA2a and PLB, alterations in the ryanodine-sensitive Ca\(^{2+}\) release channel may play a role. PKA hyperphosphorylation and reduced levels of FKBP12.6-stabilizing protein have been suggested to induce diastolic SR–Ca\(^{2+}\) leakage,22,23 and this can be reduced by β-adrenergic blockade.24,25 However, the role and mechanism for PKA modulation of this process in normal tissue has been recently questioned,26,27 and direct evidence that this abnormality can delay relaxation remains lacking. Finally, NCX upregulation in failing myocardium28-30 offset depressed SR–Ca\(^{2+}\) uptake by working in the forward mode to extrude intracellular Ca\(^{2+}\).31 However, Ca\(^{2+}\) entry via the NCX mediated by reduced-peak Ca\(^{2+}\), higher sodium, and action potential prolongation can delay relaxation.30,31 As yet, we do not know whether NCX–Ca\(^{2+}\) flux balance indeed modifies diastolic relaxation in heart failure or in what direction.

Relaxation can also be potent modified by changing the interaction of Ca\(^{2+}\) with the regulatory thin filaments or by modifying the proteins themselves.32 For example, genetic replacement of troponin I (TnI) to a skeletal isoform that cannot be PKA phosphorylated33 or overexpression of a TnI that behaves as if constitutively phosphorylated at PKA sites34 lengthens and shortens relaxation, respectively. Pharmacological manipulation of force–Ca\(^{2+}\) dependence by small molecule inhibitors can favor formation of tightly bound cross-bridges,35,36 although in isolated preparations, they also increase force at diastolic Ca\(^{2+}\) levels.37 The xanthine oxidase inhibitor allopurinol also shifts the force–Ca\(^{2+}\) curve leftward38 but does so without increasing sensitivity at diastolic Ca\(^{2+}\) levels.39 Much of this mechanism is still unknown.

Relaxation can also be delayed by alterations in the molecular motors themselves. One example is the β- (versus α-) myosin heavy chain (MHC) isoform,40 which prolongs force rise and relaxation, although this has less impact in larger mammals and humans because the β-MHC isoform dominates under normal conditions. Another example is myosin mutations that directly affect its binding to actin. Mice harboring the heterozygous mutation R403Q in the α-MHC display profound prolongation of relaxation even at a young age when there is no hypertrophy, myofibrillar disarray, or altered systolic function.41,42 With aging, these mice evolve hyperdynamic contraction with intracavitary pressure gradients, whereas relaxation remains profoundly delayed.43 Importantly, these animals do not manifest heart failure or have elevated diastolic pressures, reminding us that
the link between prolonged relaxation and diastolic failure is far from automatic. More research is needed to identify structure–function relationships in myofilament and thin-filament regulatory proteins that can determine relaxation.

When hearts contract below their unstressed volume (myocyte slack length), they store elastic energy that is then released in the next diastolic period. This process, called elastic recoil, manifests as negative pressure for a given end-systolic volume if cardiac filling is abruptly prevented. Elastin recoil appears diminished in cardiac failure, which may relate to changes in structural or biochemical changes in the extracellular matrix, the inability of the heart to contract below equilibrium (unstressed) volume, or isoform changes in sarcomeric proteins, including titin.

A final comment should be made about how relaxation delay is measured because conclusions can vary greatly depending on the mathematical approach used. Decay waveforms (whether derived from force, pressure, or cell length) are most often fit to monoeponential decay curves. However, this is an arbitrary choice because there is no a priori mechanism underlying this particular waveform. Although the monoeponential fit is reasonable in many instances, it is less so in dilated failing hearts, and its use in this setting yields artificially prolonged relaxation estimates and amplifies an apparent dependence of relaxation delay on EDP. Alternative approaches, such as provided by a logistic model, provide better fits to the failing heart pressure decline data and deserve wider consideration.

Despite the identification of numerous molecular mechanisms that have the potential to alter muscle relaxation mechanics, their interaction and quantitative impact on relaxation remains poorly understood. More studies are needed that incorporate targeted molecular manipulations with relevant muscle and chamber loading to help narrow this information gap. Development of tools to specifically enhance relaxation would also help in determining its net impact on diastolic dysfunction in the failing heart.

How Does Cardiac Load Influence Relaxation?
The failing heart is exposed to increased chamber loading stemming from high filling volume (preload) and wall stress and arterial impedance (afterload). Both types of load can influence basal left ventricular (LV) relaxation rate, but their effects may be more relevant during neurohormonal stimulation. In heart transplant patients, lusitropic effects of sympathetic stimulation during exercise are blunted as preload increases whereas increasing papillary muscle preload stretch to high levels also blocks enhanced relaxation from β-adrenergic stimulation. This could reflect a balance of enhanced myofilament calcium sensitivity at higher preload offset by enhanced shortening below slack-length—enhancing elastic recoil by a titin-dependent mechanism. In intact human hearts, preload modulation of relaxation has seemed increased by heart failure, but this result has been shown to depend mostly on how relaxation is mathematically assessed. Studies using methods that more accurately index pressure decay in these patients find little impact of preload.

Cardiac afterload (particularly that related to arterial resistance and wave reflections) more consistently affects relaxation, yet underlying mechanisms and the significance of this interaction in vivo remain unclear. Studies in intact hearts using abrupt (within-cycle) occlusion of the aorta have imposed loads during late systole at the identical preload and found a nonlinear relation between end-systolic pressure and relaxation rate. The timing of load increase is important, with loads applied later in systole having a greater effect. Clinical studies have measured relaxation delay during isometric hand–grip-induced hypertension, although marked reduction of LV afterload in patients with aortic stenosis slowed LV pressure decay, so this relationship is complex and multifactorial. More recent data suggest that PKA phosphorylation of TnI may play a role in the afterload–relaxation interaction. Mice overexpressing a mutant TnI that behaved as if constitutively phosphorylated at both PKA sites had less afterload-induced relaxation delay than controls, and this was recapitulated in wild-type mice by infusion of isoproterenol to stimulate PKA. The result is intriguing given evidence of reduced PKA–TnI phosphorylation in heart failure and increased relaxation load sensitivity in this condition. Because high afterload is common in heart failure, approaches to blunt its influence on relaxation may be clinically useful.

Is Delayed Relaxation an Important Determinant of Late-Diastolic Stiffness?
Despite recent progress in understanding determinants of myocardial relaxation, we still do not know whether this is an important contributor to late diastolic filling pressures. On the basis of a monoeponential decay model and normal time constant of 30 to 40 ms, one predicts pressure related to decaying LV contraction would be <2 mm Hg after ~125 ms. Because diastole usually extends for an additional 250 ms, this would seem a minor issue. However, decay may not follow a single monoeponential course and can be influenced by superimposition of chamber filling (muscle re-extension) and the force applied at the time of refilling (eg, pressure at time of mitral valve opening). Tachycardia can shorten the available time for relaxation, and in hypertrophied ventricles, may be associated with elevated diastolic pressure. However, this has been shown to reflect atrial contractile force and timing of atrial systole rather than relaxation delay. Myocardial viscosity (even with full relaxation) can also underlie pressure rise at faster filling rates, and has been ascribed to microtubule levels and titin–actin interaction. Yet in normal hearts, viscosity is similar in both early versus late diastole, suggesting it is less likely to reflect ongoing active relaxation but more likely intrinsic strain–rate-dependent properties.

The clinical settings in which relaxation delay might influence late-diastolic pressures most are tachycardia and afterload increase. In patients with cardiac failure symptoms but nondilated hearts and preserved ejection fraction, elevating arterial load can produce marked hypertension-delaying relaxation, and this has been associated with elevated EDP. However, in the animal studies, afterload had to be raised to 80% of maximum (100% being isovolumic contraction) to raise EDP, well above physiologic or even pathophysio-
logic loads. Clinical studies suggesting coupling of relaxation delay with EDP rise have generally not measured transmural LV pressure, thus failing to account for right ventricular (RV) and pericardial constraints, and have neglected neurohumoral activation. On the basis of available data, we believe it unlikely that relaxation delay has a major effect on late-diastolic pressures in most pathophysiologic settings and that relaxation delay and elevation of late-diastolic pressures are usually concurrent events.

How Does Titin Influence Diastolic Chamber Compliance? Over the normal operating range of sarcomeric length (<2.2 μm), a substantial component of diastolic muscle stiffness arises from proteins within the sarcomere itself. This was first shown in isolated myofibrils devoid of ion channels and extracellular matrix yet still comprised of the full complement of intrasarcromeric proteins. Most of this elastic force is now thought to reside in the macromolecule titin, whereas contributions of microtubules (tubulin) and intermediate filaments (desmin) appear <10% at operating sarcomere lengths. Titin is expressed as varying isoforms that impart different mechanical properties, and this likely plays a role in altering passive stiffness in failing hearts. Titin can also be post-translationally modified by Ca²⁺ (even in the diastolic range) and by phosphorylation, blurring notions of passive versus active tone.

The passive tension of titin is associated with an extensible region located at the I-band of sarcomeres, comprised of serially linked but distinct immunoglobulin and PEVK elements. It is expressed in 2 primary isoforms, a smaller N2B, which contains a shorter extensible segment in the I-band, and the larger more compliant N2BA isoform, which has longer segments and more immunoglobulin elements. Relative expression of these isoforms differs among species, with N2B predominating in rodents and greater N2BA observed in larger mammals. This, along with tandem changes in myocardial collagen across species, may determine species-dependent diastolic stiffening. Titin isoform shifting also appears during cardiac development, with a fetal isoform contributing to increased distensibility and declining in maturing heart. In tachypacing-induced heart failure dogs and in spontaneously hypertensive rats, elevation of diastolic muscle stiffness is accompanied by increased N2B expression (shorter, stiffer), whereas in a rat infarct model and in patients with end-stage ischemic (but maybe nonischemic) cardiomyopathy, N2BA expression appears more prominent. In turn, the latter seems to correspond to reduced myocardial stiffness.

Although the correlation of titin isoform and muscle stiffness seems consistent among studies, the direction of isoform switching is not, and mechanisms that might lead to one type of shift over another in heart failure remain unclear. Differences among studies include technical processing of tissue, complexity of disease conditions including chronic pharmacological treatments, species differences, etc. Furthermore, correlations between isoform and function remain based on very limited data, particularly from human samples.

In addition to structural differences, post-translational modification of titin is likely an important mechanism for dynamic modulation of diastolic tension. Titin can be phosphorylated by PKA, and this acutely shifts the diastolic length tension relation downward (ie, enhanced compliance). Furthermore, diastolic tension is produced not only by titin extension but also by titin–actin interaction, and this can be inhibited in a calcium-dependent manner by S100A1, a calcium-binding protein abundantly present in the myocardium. Diastolic tension resulting from titin determines systolic tension by altering net calcium sensitivity of actomyosin interaction. Finally, titin-exerted diastolic force can impact stretch-activated potassium channels.

As noted, titin isoforms and collagen content tend to vary in parallel among species, preserving relative stiffness contributions at lower sarcomere length (titin) and higher length (collagen). However, this relationship may not be maintained in pathological states or with pharmacological interventions that target fibrosis in particular. For example, in a hypertensive rat model, angiotensin II receptor blockade at a dose that did not affect blood pressure prevented myocardial fibrosis but allowed for hypertrophy development with normal myocardial stiffness constant. This suggested a primary role for fibrosis, yet prevention of titin isoform shifting could also have occurred. Given the generally coordinated expression of stiff titin isoforms with interstitial fibrosis, it seems prudent to rule out titin isoform switches before attributing changes in LV stiffness to changes in interstitial fibrosis.

What Is the Impact of Altered Collagen/Fibrosis? The myocardial collagen network is comprised of endomysial fibers that surround individual myocytes and capillaries and interconnect them via filamentous struts, perimysial fibers that interweave muscle bundles, and epimysial fibers, forming a matrix adjacent to epicardial and endocardial endothelium. Perimysial fibers are especially important for diastolic tension generation at high sarcomere lengths. When isolated rat left ventricles are subjected to high filling pressures (30 to 70 mm Hg), these coiled fibers straighten and effectively fix sarcomere length at 2.2 μm.

Many studies have suggested the importance of myocardial fibrosis to diastolic dysfunction. For example, intra-arteriolar collagenase perfusion that reduces perimysial fibers by 70% results in a right shift of the diastolic LV PV relationship with increased sarcomere length. Digestion of purely endomysial fibers has the opposite effect. Recent studies have begun targeting signaling factors to fibrosis, including transforming growth factor-β, the sodium–hydrogen exchanger, angiotensin II receptor–mediated signaling, and chymase, correlating changes in collagen/fibrosis to chamber stiffening. Other studies have degraded collagen in normal and pressure-load hypertrophied papillary muscles with plasmin or oxidized glutathione and hydroxyproline, and inhibited collagen cross-links with β-aminopropionitrile. All studies report reduced chamber diastolic stiffness but with rather extreme modifications of collagen.
Given these data, a direct linkage between fibrosis and stiffness might seem well established, yet controversy exists. Quantitative assessment of fibrosis in various murine transgenic models, larger animal failure models, and even in humans, has not always found correlations between stiffness and collagen content. For example, clear-cut hemodynamic evidence of restriction to diastolic filling (ie, square-root sign) occurs with endomyocardial fibrosis of late-stage Loeffler disease but is absent in pressure-overload LV hypertrophy because of aortic stenosis or arterial hypertension. This has led some to conclude that the quality of collagen (specifically cross-linking and glycation) plays a key role in translating quantity into mechanical stiffness. In such studies, the relative ratio of insoluble (cross-linked) to soluble (cyanogen bromide digestion) collagen is most important. For example, in rats exposed to aortic banding, hypertrophy was accompanied by increased total collagen, yet fall in insoluble/soluble collagen ratio and no change in myocardial stiffness. In contrast, spontaneously hypertensive rats had elevated total collagen and higher insoluble/soluble collagen ratio, which correlated with chamber stiffening. In a model of accelerated diastolic dysfunction from angiotensin II stimulation and tachypacing, there were poor correlations between collagen deposition and stiffness but evidence that metalloproteinase activation may influence stiffness by alternative mechanisms. Finally, advanced glycation endproducts (AGEs) activation may influence stiffness by quick stretches, which disrupted rigor bounds, and possibly by calcium desensitizer (2,3-butanedionemonoxime). The link between cardiomyocyte diastolic constitutive properties and intracellular calcium could be low-grade diastolic cross-bridge cycling, previously shown to coincide with small diastolic cytosolic calcium sparks. In failing hearts, sarcoplasmic reticular calcium leak and potentially enhanced reverse mode current via the NCX may elevate diastolic calcium so that such tone would be more relevant. Elevation of beat frequency in the presence of depressed sarcoplasmic reticular calcium uptake can raise diastolic calcium, although this appears to be less than initially reported, and effects on human diastolic pressures are also modest.

Modifications of myofilament–calcium sensitivity by heart failure could also alter active tone. This includes changes associated with PKA (or phosphoglycerate kinase [PKG]) phosphorylation of myosin light chain 2 and TnI, the latter also likely underlying NO modulation because NO and cGMP increase resting diastolic cell length as a result of PKG-mediated phosphorylation of myofilaments. In intact hearts, the diastolic PV trajectory during filling is displaced downward in patients with dilated cardiomyopathy administered intracoronary substance P (NO-stimulator), whereas 10 days of NO synthase blockade with N\textsuperscript{\textit{H}}-monomethyl-L-arginine in conscious dogs results in the opposite change, even accounting for external load effects.

Diastolic distensibility may also be influenced by myocardial energetics. Hypoxia increases isovolumic resting tension in isolated guinea pig hearts and raises the diastolic PV curve in humans during balloon coronary angioplasty. Reductions in LV diastolic distensibility have also been observed during demand ischemia. In this setting, the idea of reduced diastolic LV distensibility caused by Ca\textsuperscript{2+} overload was recently rebutted by experiments in blood-perfused isovolumic rabbit hearts that demonstrated correction of the ischemia-induced decline in LV diastolic distensibility by quick stretches, which disrupted rigor bounds, and not by a calcium desensitizer (2,3-butanedionemonoxime). Change in high-energy phosphate metabolism may also contribute. For example, inhibition of creatine kinase activity by low-dose iodoacetamide resulted in an increase in free [MgADP] without alterations in [MgATP], [Pi], or [pHi], and in intact hearts, resulted in a 3× increase in ventricular EDP and delayed relaxation. The LVEDP increase correlated with free ADP. This was further supported by data in isolated hypertrophied rat hearts, in which fairly selective increased free [ADP] correlated with increased LVEDP. In vitro motility assays support slowing of cross-bridge detachment by free MgADP and because of competition with MgATP for the substrate site on myosin, and this binding appears dependent on myosin light chain 2. Unfortunately, there have been no previous reported in vivo studies (clinical or experimental) in which modulation of free [ADP] has been definitively linked to changes in chamber distensibility.

Many pharmacological agents modify myocellular [Ca\textsuperscript{2+}], or Ca\textsuperscript{2+} sensitivity, yet repeatedly, such interventions often leave the diastolic PV relation in intact normal heart unaltered, and similar findings have been reported in hypertrophied and failing hearts when assessed by comprehensive PV relations. The contribution of diastolic tone to basal diastolic LV properties is therefore probably small but this does not exclude a potential role in acute and reversible...
clinical settings such as hypertensive pulmonary edema or demand angina. Modulation of factors influencing active tone may have an impact in these settings and warrant further investigation.

What Is the Role of Extrinsic Forces?
The slope of the passive diastolic PV relation (DPVR) ideally using transmural pressure describes the intrinsic stiffness of the ventricle. The primary indication of altered stiffness is a change in the local slope of this relation at a matched preload. However, many if not most interventions studied in vivo displace the PV trajectory during diastolic filling upward or downward with minimal change in shape. In part, this is attributable to the use of chamber pressure (not transmural pressure) and thus impact of external loading conditions and intrathoracic pressure. There are many examples of this, such as acute elevation during exercise or acute coronary occlusion,122 or downward shifts after administration of calcium channel blockers,123,124 angiotensin-converting enzyme (ACE) inhibitors, or sodium nitroprusside. The key question is whether this reflects changes in myocardial stiffness or is largely the result of changes in external constraining forces from the pericardium or right heart. Although relevant studies span a period of >2 decades, this question remains a subject of debate.

Several methods have been used to index the influence of external forces on the diastolic PV trajectory. One is to acutely remove the pericardium, which has been useful to quantify these forces,125 and rule out its influence on stiffening from rapid-pace−induced ischemia.126,127 Another approach more easily translated to humans is deriving the passive DPVR from multiple cardiac cycles, using only late-diastolic data measured after unloading of the right heart by inferior vena caval obstruction.123,128 Here, right heart pressures fall before a decline in LV filling (the decline itself indexes constraint), and the DPVR is then assessed more independent of these forces.128 On the basis of this approach, between 30% and 40% of the resting late-diastolic pressures in humans appear ascribable to external loads. Vertical shifts in the diastolic PV trajectory from resting beats are often minimized when the DPVR is assessed in this manner,123 raising doubts about the presence of true intrinsic stiffness changes. Demand ischemia may be different in this regard,129 although protocols using RV unloading have not been performed. Finally, pharmacological agents can be infused intracoronary to minimize the impact of external loading, although once drained from the coronary sinus, they pass into the venous and arterial systemic circulations, so this influence is blunted but not eliminated. Still, this method has suggested that pharmacological agents such as ACE inhibitors may acutely improve chamber distensibility in both failing130 and hypertrophied hearts.131

Some cardiac disorders display marked disparities between the intact (loaded) DPVR and that measured from multiple cycles with RV unloading. For example, in patients with hypertrophic cardiomyopathy and septal hypertrophy, baseline DPVRs are very flat, although shifted upward at higher pressures.132 DPVRs derived by the latter method are much steeper and follow a completely different relation. The mechanism for such striking disparities remains conjectural. Altered septal geometry with a concatenoid-shaped septum may accentuate ventricular interaction, and filling purely by shape, change after cavity obliteration may allow volumes to rise without stretching sarcomeres. The downward displacement observed with simple reduction of preload in such hearts raises caution when interpreting similar DPVR shifts from vasoactive agents such as calcium channel blockers. DPVRs from human ventricles in isolation have not been studied, and unfortunately, genetically engineered models of hypertrophic disease in rodents41 have not as yet recapitulated diastolic compliance changes observed in human hypertrophic cardiomyopathy. For that matter, and for all their attractive features, small rodent models have generally not been very useful for studying the pathophysiology of diastolic compliance abnormalities because this seems only achieved in these species when there is profound extensive fibrosis or structural changes.

Is There Such a Thing as Diastolic Heart Failure?
Many patients present with symptoms of cardiac failure, including exertional dyspnea, fluid retention, and pulmonary edema, yet have apparent preservation of systolic function. Epidemiologic studies indicate the prevalence of this form of failure is very high among community-based populations, accounting for nearly half of all patients with congestive heart failure.1,133,134 Patients are more often elderly, female, hypertensive, and have ventricular hypertrophy,135 and their symptoms, neurohumoral activation (risk for poor outcome), and overall morbidity and mortality appear similar to those with depressed systolic function. The syndrome has been presump-
tively termed diastolic heart failure, yet this assumes systolic function is indeed normal, that diastolic abnormalities are present and a primary mechanism for disease, and that comorbidities such as chronic lung disease, ischemia, and metabolic disorders play a minor role. Each of these assumptions has been recently brought into question.136,137 Because there are few experimental models for this syndrome and none that truly recapitulate its primary clinical features, most current understanding stems from patient studies.

Diastolic dysfunction is indeed common because most patients have elevated EDP or delayed relaxation, many with normal or reduced diastolic chamber volumes (ie, lower compliance).138 However, accurate analysis of chamber volume on the basis of 3D imaging methods such as MRI or echocardiography remains scant. The majority of data are based on noninvasive parameters that indirectly index diastolic properties often determined under stable resting conditions. Furthermore, many of these indexes are abnormal in elderly hypertensive individuals without symptoms of cardiac failure.139 Invasive data are also based primarily on rest conditions so changes resulting from loading that might have been altered during decompensation are generally missed. Acute valvular insufficiency and systolic depression do not appear to be a feature of such decompensations,140 yet how diastolic dysfunction at rest often in the absence of symptoms is responsible for such decompensation remains unclear.
Recent evidence from a small but well-studied cohort suggests that additional abnormalities may contribute, including ventricular systolic and arterial stiffening. The latter can be more easily linked to arterial blood pressure and symptom lability and diuretic sensitivity, all common in affected patients. In this regard, this disorder may not be a disease of diastole per se, but rather reflect adverse interactions of vascular and ventricular stiffnesses affecting filling and ejection. This is more than an academic distinction because it refocuses attention on pathophysiology and helps target therapies. Diastolic dysfunction is likely a component of the disorder but not the sole target for ameliorating symptoms if other cardiovascular changes are similarly or even more important. Equally lacking are information as to myocardial substrate (very little biopsy or necropsy material has been studied) and genetic and proteomic profiling that might characterize diastolic dysfunction and eventually predict who is likely to develop the disease.

Conclusion

Although much is known about the mechanisms underlying diastolic dysfunction in heart failure, many basic issues remain to be resolved. As depicted in the Figure, clinically relevant diastolic dysfunction integrates abnormalities emanating from sarcomere, extracellular coupling apparatus, myocardial matrix, and cardiac structure and coupling with the vascular system. Much more work is still needed to clarify which are the most meaningful abnormalities that would best serve as primary clinical targets for therapeutic intervention. Models in which diastole is specifically manipulated would greatly help to test its role and to clarify the influences of genetic and post-translational modifications of key proteins. We need to build a more critical and accurate bridge between the findings obtained in reductionist models and the behavior that manifests in intact chambers. At the clinical end of the spectrum, we should focus less on descriptive behaviors and assigning guilt to diastolic abnormalities simply by their presence and more on proof of pathophysiologic relevance and on integrating diastolic findings with coexisting cardiovascular abnormalities. Given our new and powerful tools, answers to these questions are undoubtedly on the way.

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