New Molecular Mechanism in Diastolic Heart Failure

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In contrast to systolic heart failure (SHF), for which knowledge of pathophysiology and therapy has advanced rapidly over the past decade, little is known about diastolic heart failure (DHF). The article by van Heerebeek et al in this issue of Circulation that describes an abnormal distribution of titin isoforms in DHF may herald a new approach to understanding the pathophysiology of this syndrome.

Article p 1966

Recognition of 2 forms of heart failure is not new; almost 70 years ago, Fishberg2 described “those forms of cardiac insufficiency which are due to inadequate diastolic filling of the heart (hypodiastolic failure) [and] the far more common ones in which the heart fills adequately but does not empty to the normal extent (hyposystolic failure)” (p 23). This distinction has stood the test of time, because there is a growing consensus that these 2 clinical syndromes differ in epidemiology, demographics, and origin. Because DHF and SHF represent subgroups of patients with heart failure, they share many clinical features, notably the hemodynamic findings, but it is now clear that they are caused by different pathophysiological mechanisms. Hearts in SHF are characterized by eccentric hypertrophy, progressive left ventricular (LV) dilation, and abnormal LV systolic properties, whereas in DHF, the hearts generally exhibit concentric hypertrophy, normal or reduced LV volume, concentric remodeling, and abnormal diastolic function.3,4 In addition, cardiomyocyte size, shape, and molecular composition differ in these 2 syndromes.

Diastolic Dysfunction and DHF

Diastolic dysfunction refers to mechanical and functional abnormalities present during relaxation and filling, whereas DHF refers to clinical syndromes in which patients with heart failure have little or no ventricular dilatation and significant, often dominant diastolic dysfunction. Diastolic dysfunction can be quantified with indices of LV pressure decline and filling. Abnormal pressure decline is characterized by decreased peak –dP/dt, prolonged isovolumic time constant (τ), and increased isovolumic relaxation time. Abnormal filling is characterized by slow and incomplete filling, increased atrial contribution to filling, and increased chamber stiffness, which can be caused by abnormalities in both cardiomyocytes and the extracellular matrix.5,6 Changes in calcium homeostasis, energetics, myofilaments, and the cytoskeleton can impair cardiomyocyte relaxation and increase stiffness, as can increases in the content of extramyofilament cytoskeletal proteins, such as microtubules, and abnormalities that involve intramyofilament cytoskeletal proteins like titin. At the extracellular matrix level, changes in the amount, composition, and geometry of such matrix proteins as collagen and elastin can alter LV stiffness. By causing decreased or delayed relaxation, slow or incomplete filling, and increased diastolic stiffness, these abnormalities can lead to the development of DHF.

Heart Failure Versus Asymptomatic LV Dysfunction in SHF and DHF

Intermittent symptomatic exacerbations and remissions are common in patients with both SHF and DHF. This unstable clinical course reflects an interplay between the underlying abnormalities in the heart and exacerbating factors that can convert asymptomatic LV dysfunction to symptomatic heart failure. Systolic dysfunction, which reduces the ability of the LV to develop tension and shorten and which generally leads to eccentric LV hypertrophy, is due most commonly to myocardial infarction and, less frequently, dilated cardiomyopathy. Impaired ejection and LV dilatation in SHF reduces ejection fraction, the ratio of stroke volume and end-diastolic volume (EDV). Depending on exacerbating factors such as increased preload (eg, fluid retention), increased afterload (eg, peripheral vasoconstriction), and arrhythmias (eg, atrial fibrillation), systolic dysfunction may or may not be associated with symptomatic heart failure. Until about a decade ago, treatment of SHF sought to alleviate the hemodynamic consequences of these exacerbating factors; diuretics were given to lower preload and vasodilators to reduce afterload. However, most forms of therapy that improve prognosis in SHF are now recognized to slow, and sometimes reverse, the progressive increase in EDV (“remodeling”) in the dilated LV of these patients. The ability of β-adrenergic receptor blockers to inhibit remodeling is especially marked, but similar benefit has been reported after administration of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, aldosterone antagonists, and cardiac resynchronization therapy.7,8

Although the exacerbating factors that worsen symptoms in DHF are similar to those in SHF, the underlying abnormalities are quite different. In DHF, the most common architectural abnormalities are concentric LV hypertrophy or concentric remodeling, both of which are frequently caused by chronic pressure overload (eg, hypertension). Changes

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associated with aging also play a major role in DHF, but much remains to be learned about such age-related changes as decreased rates of LV relaxation and filling and increases in LV and arterial stiffness. What is clear is that changes in LV structure and function that accompany aging make patients with hypertension, diabetes mellitus, or coronary heart disease more vulnerable to the development of DHF.

The structural and functional abnormalities that cause diastolic dysfunction make it especially difficult for the hearts of patients with DHF to meet the challenges posed by an acute increase in preload or afterload or an arrhythmia. This is because diastolic dysfunction impairs the ability of the LV to fill, which, in addition to increasing diastolic pressure, makes it difficult for Starling’s law to enhance cardiac performance. As a result, diastolic dysfunction sets the stage for rapid, often precipitous increases in pulmonary venous pressure. This can explain why patients with abnormal diastolic function who are asymptomatic under most conditions can develop severe acute pulmonary edema after a salty meal, a rapid increase in arterial blood pressure, or the onset of atrial fibrillation.

Ventricular Architecture in Hypertrophied Hearts

Two patterns of cardiac enlargement, initially recognized at the beginning of the 19th century,9 are now generally referred to as eccentric hypertrophy, in which EDV is increased, and concentric hypertrophy, in which wall thickness is increased and EDV can be reduced or unchanged. These architectural patterns are now known to reflect differences in cardiomyocyte size and shape; in eccentric hypertrophy, enlargement is due largely to increased cell length, whereas cross-sectional area is increased in concentric hypertrophy.10 These morphological differences appear to result from sarcomere addition at the ends of the myocytes in eccentric hypertrophy (sarcomere replication in parallel) and throughout the myocyte in concentric hypertrophy (sarcomere replication in series).11

Perhaps the most striking difference between SHF and DHF is the tendency of EDV to increase in SHF, whereas progressive dilatation, by definition, does not occur in DHF. This distinction, which can be attributed to activation of different proliferative signaling mechanisms, has important implications, because therapy that improves prognosis in SHF may not slow progression in DHF (see below).

Cardiomyocyte Composition in Hypertrophied Hearts

Concentric and eccentric hypertrophy are associated with different patterns of activation of growth factors, proto-oncogenes, and the messenger RNAs that encode sarcomeric, sarcoplasmic reticulum, and other proteins.12-14 Cardiomyocyte elongation and thickening result from activation of different signal transduction pathways.15,16 and mechanical stresses applied during systole and diastole can activate different proliferative signaling pathways.17 Exercise-induced “physiological” hypertrophy is accompanied by increased expression of the adult α-myosin heavy chain isoform and a higher content of sarcoplasmic reticulum, whereas expression of fetal β-myosin heavy chain is increased and the content of sarcoplasmic reticulum reduced in the “pathological” hypertrophy associated with chronic pressure overload.18 These differences have recently been found to be associated with activation of phosphoinositide 3′-OH kinase/phosphatidylinositol triphosphate/Akt pathways in physiological hypertrophy19,20 and calcineurin/nuclear factor of activated T cells pathways in pathological hypertrophy.21

Titin Isoforms in SHF and DHF

Evidence that cardiomyocytes in SHF and DHF express different gene products is provided by van Heerebeek et al,1 who examined the titin isoforms in the hearts of patients with these 2 clinical syndromes. Titin is a huge cytoskeletal protein that extends from the Z-lines to the center of the thick filament (Figure), where it contributes to the high resting stiffness of the myocardium.22 Phosphorylation of titin by protein kinase A decreases its stiffness, which, by increasing LV diastolic compliance, helps the heart to fill during sympathetic stimulation.23,24 In addition to its mechanical function, titin contains “hot spots” that participate in cell signaling25; the latter could allow this protein to mediate proliferative responses that generate specific hypertrophy phenotypes when hearts are subjected to different mechanical stresses (see above).

Mammalian hearts contain either of 2 titin isoforms, called N2BA and N2B, or both isoforms.26 A key difference is that the N2B isoform is stiffer than the N2BA isoform, so that it is not surprising that N2B tends to predominate in stiffer ventricles, whereas N2BA occurs in more compliant hearts. Titin isoform expression changes in response to chronic overloading in experimental animals, and an increased con-
tent of the less stiff N2BA isoform has been reported in human dilated cardiomyopathy.\textsuperscript{27} The reduced ratio between the N2BA and N2B titin isoforms in DHF found by van Heerebeek et al\textsuperscript{1} suggests an additional role for titin isoform shifts, because the greater abundance of the stiffer N2B probably contributes to the high diastolic stiffness in DHF.

The role of the cytoskeleton in mediating the proliferative signals that adapt form to function\textsuperscript{11,25,26} could, by activating specific transcriptional pathways, help explain how different patterns of cellular deformation induce various architectural forms of hypertrophy. Signals mediated by different patterns of titin deformation could, for example, allow pressure overload to cause concentric hypertrophy (as occurs in aortic stenosis, which increases systolic stress) and volume overload to cause eccentric hypertrophy (as occurs in aortic insufficiency, which increases diastolic stress). An additional implication of evidence that different titin isoforms are expressed in SHF and DHF\textsuperscript{18} is that the titin isoform might contribute to the differences in ventricular architecture in SHF and DHF and the absence of progressive LV dilatation in DHF.

**Therapeutic Implications**

There are few clinical trials to help guide the treatment of DHF. Several small studies have shown that an angiotensin receptor blocker improves exercise tolerance, and one large, randomized clinical trial (Candesartan in Heart Failure: Assessment of Reduction in Mortality and morbidity [CHARM]-Preserved) suggests that an angiotensin receptor blocker reduces hospitalization for DHF.\textsuperscript{29–31} Most treatment strategies for DHF, however, attempt to alleviate congestive symptoms by reducing LV preload and afterload, attenuating such exacerbating factors as tachycardia and ischemia, and controlling blood pressure in hypertensive patients. It is clear, however, that strategies for DHF should also target the underlying structural, functional, and molecular mechanisms, but success in these efforts may be difficult to achieve, because many pathological mechanisms lead to DHF.\textsuperscript{32} This situation differs from SHF, for which clinical trials have shown that, with the exception of gene polymorphisms, there are few significant differences in the long-term responses of various clinical subgroups to therapy. This uniformity can be explained if a major benefit of effective long-term therapy in SHF is to inhibit progressive cardiomyocyte elongation. Because this therapeutic target is absent in DHF, in which progressive dilatation is not an important cause of clinical deterioration, optimal therapy may have to address the specific pathophysiology that operates in each patient. The titin abnormality described by van Heerebeek et al\textsuperscript{1} provides an example of one such target, because reversal of the titin isoform shift could both improve function and attenuate maladaptive signal transduction.

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**References**


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