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New Molecular Mechanism in Diastolic Heart Failure

Arnold M. Katz, MD; Michael R. Zile, MD

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 al1 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.

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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The natural text contains information on new molecular mechanisms in diastolic heart failure, with a focus on the article by van Heerebeek et al in Circulation. It discusses the contrast between systolic and diastolic heart failure, the recent findings on titin isoforms in DHF, and the differences in pathophysiology between SHF and DHF. The text highlights the importance of understanding these mechanisms for developing targeted therapies and improved patient care.
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, 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. These morphological differences appear to result from sarcomere addition at the ends of the myocytes in eccentric hypertrophy (sarcomere replication in series) and throughout the myocyte in concentric hypertrophy (sarcomere replication in parallel).

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. Cardiomyocyte elongation and thickening result from activation of different signal transduction pathways, and mechanical stresses applied during systole and diastole can activate different proliferative signaling pathways. 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. These differences have recently been found to be associated with activation of phosphoinositide 3'-OH kinase/phosphatidylinositol triphosphate/Akt pathways in physiological hypertrophy and calcineurin/nuclear factor of activated T cells pathways in pathological hypertrophy.

**Titin Isoforms in SHF and DHF**

Evidence that cardiomyocytes in SHF and DHF express different gene products is provided by van Heerebeek et al, 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. Phosphorylation of titin by protein kinase A decreases its stiffness, which, by increasing LV diastolic compliance, helps the heart to fill during sympathetic stimulation. In addition to its mechanical function, titin contains “hot spots” that participate in cell signaling; 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. 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. The reduced ratio between the N2BA and N2B titin isoforms in DHF found by van Heerebeek et al 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 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 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 reduces hospitalization for DHF. Most treatment strategies for DHF, however, attempt to alleviate concomitant 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. 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 cardiac deterioration, optimal therapy may have to address the specific pathophysiology that operates in each patient. The titin abnormality described by van Heerebeek et al 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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