Diastolic and Systolic Heart Failure: Different Stages or Distinct Phenotypes of the Heart Failure Syndrome?

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It remains uncertain if diastolic heart failure (DHF) is a distinct HF phenotype or a precursor stage of systolic HF (SHF). The unimodal distribution of left ventricular ejection fraction (LVEF) in HF, depressed LV long-axis shortening in DHF, and progression to eccentric LV remodeling in hypertension favor DHF and SHF as successive stages. These arguments are countered by the bimodal distribution of LVEF after correction for gender, by the preserved LV twist in DHF and by the low incidence of eccentric LV remodeling in hypertension. Clinical features, LV anatomy and histology, cardiomyocyte stiffness, myocardial effects of diabetes, and the response to HF therapy support DHF and SHF as distinct phenotypes. Comparison of the myocardial signal transduction cascades that drive LV remodeling in DHF and SHF may solve the controversy. This review analyzes arguments supporting DHF and SHF as successive stages or distinct phenotypes of the HF syndrome.

Introduction

Although diastolic heart failure (DHF) currently accounts for more than 50% of all HF cases in Western countries, and although the prognosis in patients with DHF is now considered as poor as the prognosis in patients with systolic HF (SHF) [1••], it remains unresolved if DHF is indeed a distinct HF phenotype or merely a precursor stage of SHF [2]. Because of possible continuity between DHF and SHF, and because diastolic left ventricular (LV) dysfunction is not unique to DHF but also occurs in patients with SHF, DHF was often referred to in recent years as HF with normal LV ejection fraction (LVEF; HFNEF) [3] or HF with preserved LVEF (HFPEF) [4]. Arguments for DHF and SHF as different stages or distinct phenotypes of HF syndrome are listed in Table 1 [5••].

Unimodal Distribution of LVEF

In large registries that recruited HF patients regardless of LVEF, a unimodal distribution of LVEF was observed with a median value ranging from 35% to 40% [6,7]. If DHF and SHF were distinct HF phenotypes, a bimodal distribution should have emerged from these large registries. Such a bimodal distribution, however, appears when HF patients are subdivided by gender. LVEF of male HF patients peaks at 30% whereas LVEF of female HF patients peaks at 60%. The unimodal distribution of LVEF in the overall HF population is therefore related to pooling of HF patients of both genders. In a multivariate risk analysis of DHF versus SHF, female sex was recently again confirmed as an important predictor (OR, 2.29; 95% CI, 1.35–3.90) of DHF [8]. Population studies should account for these gender-specific features of HF phenotype and abstain from reporting on characteristics of a global HF population. The CHARM registry also revealed a peculiar relation between mortality risk and LVEF. Mortality of HF patients was inversely related to LVEF, up to an LVEF value of 45%, at which point mortality leveled off. This inflection of the mortality–LVEF relationship also supports the presence of two distinct HF phenotypes, one for which LVEF is an important prognosticator (SHF) and one for which it is not (DHF).

LV Systolic Function Deficit

In DHF patients, most indices of global LV systolic performance, such as LVEF, LV dP/dt max, and Emax (slope of the LV end-systolic pressure–volume relation) are within normal limits. However, some subtle Doppler echocardiographic measures of LV systolic performance are lower than normal [9]. These subtle measures include tissue Doppler mitral annular shortening velocity, longitudinal strain, and radial strain. Other refined Doppler echocardiographic measures of LV systolic performance, such as LV twist or circumferential strain, are, however, similar in DHF patients and normal controls. The

Table 1. Arguments favoring DHF and SHF as successive stages or distinct phenotypes of the HF syndrome

Successive stages	Distinct phenotypes
Unimodal distribution of LVEF	Clinical features of incident HF
LV systolic function deficit	LV anatomy and histology
Eccentric LV remodeling in hypertensive heart disease	Cardiomyocyte stiffness
Eccentric LV remodeling in hypertrophic cardiomyopathy	Myocardial effects of diabetes
	Responses to heart failure therapy

DHF—diastolic heart failure; HF—heart failure; LV—left ventricular; LVEF—left ventricular ejection fraction; SHF—systolic heart failure.

discordance in DHF between mitral annular shortening velocity, which is lower than normal, and LV twist, which remains unchanged, is especially puzzling. Mitral annular shortening velocity is produced by endocardial and epicardial longitudinal muscle fibers that depart from the mitral annulus, wrap around the apex, and reinsert on the mitral annulus at a location opposite the one from which they originate. Systolic contraction of these fibers creates mitral annular shortening velocity and LV twisting. The discordant changes in DHF of mitral annular shortening velocity and LV twisting suggest that depressed mitral annular shortening velocity results not from a contractile deficit of these longitudinal muscle fibers but a shorter LV long-axis because of LV shrinkage or a shift in LV shape from spherical to ellipsoid. Furthermore, a reduction in mitral annular shortening velocity has been reported absent by some studies in as many as 50% of DHF patients and present in patients with LV hypertrophy without HF. Finally, mitral annular shortening velocity is only a minor contributor to LV stroke volume, which mainly arises from LV minor-axis shortening and has, therefore, little impact on overall LV performance.

LV Remodeling in Hypertensive Heart Disease and Hypertrophic Cardiomyopathy

A frequently cited argument for DHF evolving to SHF is the evolution toward an eccentrically remodeled and dilated LV in hypertensive heart disease [10] and hypertrophic cardiomyopathy [11]. In many previous studies reporting on eccentric LV remodeling in hypertensive heart disease, interval coronary events were either overlooked or significantly higher in patients with hypertension who developed eccentric LV remodeling with a depressed LVEF. A recent, large epidemiologic survey actually observed the opposite; namely, progressive LV shrinkage when hypertensive heart disease evolved to LV failure [12•]. This study obtained LV echocardiograms in controls, patients with hypertension, and patients with hypertension and HF, finding a progressive reduction of LV end-diastolic volume index from 62 mL/m^2 in controls to 60 mL/m^2 in those with hypertension and 56 mL/m^2 in those with hypertension and HF. This study fits into a recently proposed longitudinal framework for the evolution of LV mass during adult life [13], whereby LV mass incessantly increases if elevated in midlife at 45 years of age. This continuous increase in LV mass, especially in women with elevated body mass index and in patients with diabetes, again suggests that once the LV has engaged in concentric LV remodeling because of obesity, diabetes, and arterial hypertension, it will continue to do so throughout the entire adult life course unless coronary artery disease and myocardial ischemia intervene.

An evolution to eccentric LV remodeling with a depressed LVEF has also been suggested to occur in patients with hypertrophic cardiomyopathy, another cardiac disease characterized by concentric LV remodeling and diastolic LV dysfunction. However, a large survey of 1259 hypertrophic cardiomyopathy patients revealed that such evolution was extremely rare, only occurring in 44 patients (3.5%) [11]. Furthermore, because of a significant association with the presence of atrial fibrillation, such an evolution could have resulted from superimposition of tachycardia-cardiomyopathy, which is known to cause LV dilation.

Clinical Characteristics of Incident HF

Cross-sectional registries of HF populations revealed that DHF patients were older, more often women, and frequently had comorbidities such as arterial hypertension, obesity, and diabetes. Such characteristics were also evident in the prospective multicenter registry of hospitalized DHF patients completed by the New York Heart Failure consortium [14]. Seventy-five percent of DHF patients were women and, on average, 4 years older than the men in the registry (72 vs 68 y, respectively). A precipitating event leading to the hospitalization could be identified in 50% of cases and consisted in decreasing frequency of uncontrolled arterial hypertension, nonadherence to prescribed medications, acute coronary syndromes, atrial arrhythmias, and renal or pulmonary insufficiency. Arterial hypertension preexisting on average 10 years before admission was the most frequent comorbidity (75% of patients) followed by obesity (body mass index > 30 kg/m^2; 50% of patients) and diabetes mellitus (50% of patients).

Of special interest are the differences of clinical characteristics and risk factors between DHF and SHF patients at the time of HF onset [8]. Among Framingham Heart Study participants, new onset DHF was predicted by elevated systolic blood pressure (OR, 1.13 per 10 mm Hg;

95% CI, 1.04–1.22), atrial fibrillation (OR, 4.23; 95% CI, 2.38–7.52), and female sex (OR, 2.29; 95% CI, 1.35–3.90) whereas SHF was predicted by prior myocardial infarction (OR, 0.32; 95% CI, 0.19–0.53) and left bundle branch block QRS morphology (OR, 0.21; 95% CI, 0.10–0.46). These findings suggest that DHF and SHF are distinct clinical entities necessitating different strategies for early detection and prevention. Furthermore, in the multiethnic population of the MESA study, 65% of patients who developed HF, had normal LV systolic function, and only 33% had a prior myocardial infarction [15]. This study extended risk factor analysis beyond those established by the Framingham Heart Study, identifying obesity, interleukin-6 (OR, 1.5; 95% CI, 1.10–2.03), C-reactive protein (OR, 1.38; 95% CI, 1.01–1.86), and macroalbuminuria (OR, 4.31; 95% CI, 1.58–11.76) as predictors of incident DHF. These results suggest that obesity contributes importantly to DHF pathogenesis through pathways associated with inflammation.

LV Anatomy and Histology

Myocardial hypertrophy and myocardial fibrosis are prominent pathologic features of failing myocardium. In DHF, myocardial hypertrophy leads to concentric LV remodeling evident from a high LV wall mass–volume ratio and a high relative wall thickness (septal plus posterior wall thickness divided by LV internal diameter) [16,17••]. This pattern of LV remodeling contrasts with LV remodeling observed in SHF patients, who frequently present with a lower than normal LV wall mass–volume ratio and a low relative wall thickness [17••]. Myocardial ultrastructure also differs between DHF and SHF: 1) cardiomyocyte diameter is on average 50% larger in DHF patients than in SHF patients [17••]; 2) DHF patients have lower collagen volume fraction (11%) than SHF patients (16%) [18]; 3) DHF patients mainly have interstitial fibrosis whereas SHF patients have both interstitial and replacement fibrosis [17••]; 4) on electron microscopic images, cardiomyocytes of DHF patients have lower myofibrillar density than cardiomyocytes of SHF patients [17••], who frequently have dropout of myofilaments; and 5) both on electron microscopic and immunofluorescent images stained for α-actinin, DHF patients have significant widening of the Z-disc [18].

Differences in myocardial collagen deposition between DHF and SHF patients reflect dissimilar expression patterns of matrix metalloproteinases (MMPs) and of tissue inhibitors of matrix metalloproteinases (TIMPs). In hypertensive patients with HFNEF [19], there is decreased matrix degradation because of downregulation of MMPs and upregulation of TIMPs, whereas in patients with dilated cardiomyopathy there is increased matrix degradation because of upregulation of MMPs [20]. In patients with aortic stenosis who develop a depressed LVEF, this balance between proteolysis and autoproteolysis shifts [21]. Moreover, one third of the patients presenting with DHF have a normal collagen volume fraction in their endomyocardial biopsy [22]. However, their LV end-diastolic pressure (LVEDP) and LV stiffness modulus are comparable to DHF patients with a high collagen volume fraction in the endomyocardial biopsy. The latter finding suggests that factors other than collagen deposition also contribute to the high in-vivo LV stiffness observed in DHF patients. Intrinsic cardiomyocyte stiffness is one of these factors.

Cardiomyocyte Stiffness

Intrinsic cardiomyocyte stiffness is higher in DHF compared with SHF patients [17••,18,22] and this mainly relates to transcriptional or posttranslational modifications of the cytoskeletal protein titin [23]. Titin functions as a bidirectional spring responsible for early diastolic LV recoil and late diastolic LV stretch. As a result of alternative splicing, human myocardium expresses both the stiff N2B and the compliant N2BA titin isoform. Higher expression of the compliant N2BA titin isoform is observed in SHF patients with eccentric LV remodeling [24,25] but not in DHF patients with concentric LV remodeling [17••]. In SHF patients, higher myocardial expression of the compliant N2BA titin isoform correlates with exercise tolerance because more N2BA and less N2B titin isoform improves diastolic LV distensibility and enhances LV preload reserve during exercise.

Administration of PKA or PKG reduces stiffness of cardiomyocytes isolated from LV myocardium of DHF and SHF patients [26•,27]. A recent study identifies serine residue S469 situated within titin's N2B fragment that is the site responsible for the fall in cardiomyocyte stiffness following phosphorylation by either PKG or PKA26. In animals, the phosphorylation-induced fall of cardiomyocyte stiffness is dependent on titin isoform, with the largest effect observed in rat ventricular myocardium, which has an N2BA–N2B ratio of about 0.1, and the smallest effect in bovine atrial myocardium, which has an N2BA–N2B ratio of about 9. These observations are also consistent with the reported effects of PKA administration on stiffness of cardiomyocytes isolated from LV biopsies of SHF or DHF patients. In cardiomyocytes of SHF patients, who have a higher N2BA–N2B titin isoform ratio, administration of PKA results in a smaller reduction in cardiomyocyte stiffness than in DHF patients, who have a lower N2BA–N2B titin isoform ratio [17••,27]. Furthermore, in normal myocardium, titin isoform phosphorylation parallels titin isoform expression. This concordance between titin isoform expression and phosphorylation is absent in HF myocardium. Lost concordance between titin isoform expression and phosphorylation is especially deleterious for DHF myocardium, which has high N2B titin isoform expression but low N2B titin isoform phosphorylation. As the phosphorylation-induced fall of cardiomyocyte stiffness is titin isoform dependent, low N2B titin isoform phosphorylation explains why cardiomyocytes isolated from DHF patients have both high stiffness and a large response of stiffness to PKA [27].

Myocardial Effects of Diabetes Mellitus

Decreased diastolic LV distensibility is recognized as the earliest manifestation of LV dysfunction induced by diabetes mellitus and frequently becomes the main functional deficit as many patients with diabetes suffer from HFNEF [14]. Decreased diastolic LV distensibility of the heart in those with diabetes has usually been attributed to myocardial deposition of advanced glycation end-products (AGEs) and myocardial fibrosis. A recent study evaluated the relative importance of AGEs deposition, fibrosis, and cardiomyocyte stiffness for diastolic LV distensibility of HF patients with diabetes and no significant coronary artery disease [18]. AGEs deposition and fibrosis were especially important for SHF patients with diabetes, whereas raised cardiomyocyte stiffness was the main contributor to reduced diastolic LV distensibility in DHF patients with diabetes. This study proposes diabetes to harm myocardial function by two distinct pathways consisting, respectively, of AGEs deposition–inflammation–fibrosis and of myocyte hypertrophy–myocyte stiffening. Each pathway is associated with a distinct HF phenotype: AGEs deposition–inflammation–fibrosis with SHF and myocyte hypertrophy–myocyte stiffness with DHF. In the absence of coronary artery disease, previous myocarditis is the most likely cause for SHF. Inflammatory myocardial damage is known to facilitate AGEs deposition [28] and AGEs deposition itself amplifies myocardial inflammation [29]. Most DHF patients suffer from hypertensive heart disease. DM worsens diastolic LV dysfunction induced by hypertensive heart disease through the pathway of myocyte hypertrophy–myocyte stiffening. Higher cardiomyocyte stiffness in diabetes could relate to oxidative modifications of titin, especially in its Z-disc part where titin–actin interaction presets tension on the elastic segments of titin [23].

Response to HF Therapy

In SHF, administration of angiotensin-converting enzyme inhibitors (ACEI), angiotensin II receptor blockers (ARB), or β-blockers (BB) improves total and cardiovascular mortality. As a consequence of modern HF therapy, prognosis in SHF patients significantly improved in the past decade compared with the previous two decades [1••]. Conversely, despite frequent use of the same pharmacologic agents, prognosis of DHF patients remained unaltered during the past decade [1••]. Contrasting efficacy of comparable pharmacologic agents in SHF and DHF was convincingly demonstrated by the neutral outcome of a series of recent trails or registries. In hypertensive patients of the ALLHAT trial, lisinopril was inferior to chlorthalidone for preventing incident DHF but not SHF [30]. The neutral outcome of the I-PRESERVE trial, which assigned DHF patients to the ARB irbesartan or placebo [31••], contrasts sharply with the overwhelmingly positive outcome of the earlier CHARM-Alternative trial, which assigned SHF patients to the ARB candesartan or placebo [32]. Finally, in the OPTIMIZE-HF registry, discharge use of BB had a significant effect on 1-year mortality or hospitalization rates of SHF patients but not of DHF patients [33]. Despite persisting concerns that mainly methodologic issues involving identification and recruitment of DHF patients account for the neutral outcome of DHF trials, the discordant outcome of similar pharmacologic therapy in SHF and DHF is consistent with different myocardial signal transduction cascades driving LV remodeling in both HF phenotypes.

A neutral outcome in DHF compared with a positive outcome in SHF, as occurred with ACEI, ARB, and BB, can be compatible with flawed DHF trial design but a positive outcome in DHF compared with a neutral outcome in SHF, as occurred with statins, can no longer be attributed to trial conception but supports distinct pathophysiologic mechanisms in both conditions. In a preliminary report, DHF patients receiving statins had significantly lower mortality rates than those not receiving statins with a relative risk reduction of 22% [34]. In the same DHF patient population, treatment with ACEI, ARB, or BB had again no discernible effect on survival. This positive outcome of statin therapy in DHF patients contrasts with the recently reported neutral outcome of statin therapy in SHF patients observed in the CORONA trial [35]. The unequal response to similar pharmacotherapy in DHF and SHF supports searching for a specific DHF pharmacotherapy that addresses the distinct structural and functional myocardial abnormalities observed in DHF. These abnormalities relate to cardiomyocyte hypertrophy, turnover of the extracellular matrix during LV remodeling, elevated cardiomyocyte stiffness with higher myocardial expression and less phosphorylation of the stiff N2B titin isoform, and a shift in myocardial metabolism from glucose to free fatty acid use because of frequent comorbidities such as type 2 diabetes and the metabolic syndrome.

Conclusions

This review analyzes arguments supporting DHF and SHF as successive stages or distinct phenotypes of the HF syndrome. The unimodal distribution of LVEF in HF, the presence of an LV long-axis shortening deficit in DHF and the evolution to eccentric LV remodeling in hypertensive heart disease or in hypertrophic cardiomyopathy favor DHF and SHF as successive stages of the HF syndrome. However, these arguments are rebutted by the appearance of a bimodal distribution of LVEF in HF after correction for gender, the unchanged LV systolic twist in DHF, and the very low incidence of eccentric LV remodeling in hypertensive heart disease or hypertrophic cardiomyopathy. The clinical features of incident HF, LV anatomy and histology, cardiomyocyte stiffness, myocardial effects of diabetes, and the response to HF therapy support DHF and SHF as distinct phenotypes of the HF syndrome. Most of these arguments are consistent with different

myocardial signal transduction cascades driving LV remodeling in both HF phenotypes. Elucidation of these phenotype-specific signal transduction cascades could provide inroads for DHF- or SHF-specific therapies.

Clinical Trials Acronyms

ALLHAT—Antihypertensive and Lipid-lowering Treatment to Prevent Heart Attack Trial; CHARM—Chronic Heart Failure: Assessment of Reduction in Mortality and Morbidity; CORONA—Controlled Rosuvastatin in Multinational Trial in Heart Failure; I-PRESERVE—Irbesartan in Heart Failure With Preserved Ejection Fraction; MESA—Multiethnic Study of Atherosclerosis; OPTIMIZE-HF—Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients With Heart Failure.

Disclosure

No potential conflicts of interest relevant to this article were reported.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1.•• Owan TE, Hodge DO, Herges RM, et al.: **Trends in prevalence and outcome of heart failure with preserved ejection fraction.** *N Eng J Med* 2006, **355:**251–259.

This important epidemiologic study revealed increasing prevalence of DHF up to 55% in community-dwelling HF patients and failure during the past decade to improve prognosis in DHF with current HF therapy.

2. De Keulenaer GW, Brutsaert DL: **The heart failure spectrum. Time for a phenotype-oriented approach.** *Circulation* 2009, **119:**3044–3046.
3. Sanderson JE: **Heart failure with a normal ejection fraction.** *Heart* 2007, **93:**155–158.
4. McMurray J, Pfeffer MA: **New therapeutic options in congestive heart failure. Part II.** *Circulation* 2002, **105:**2223–2228.
5.•• Paulus WJ, Tschöpe C, Sanderson JE, et al.: **How to diagnose diastolic heart failure? A consensus statement on the diagnosis of heart failure with normal left ventricular ejection fraction (HFNEF) by the Heart Failure and Echocardiography Associations of the European Society of Cardiology.** *Eur Heart J* 2007, **28:**2539–2550.

This consensus document provides useful flow charts for diagnosis and exclusion of DHF.

6. Cleland JG, Cohen-Solal A, Aguilar JC, et al.: **Management of heart failure in primary care (the IMPROVEMENT of Heart Failure Programme): an international survey.** *Lancet* 2002, **360:**1631–1639.
7. Solomon SD, Anavekar N, Skali H, et al.: **Influence of ejection fraction on cardiovascular outcomes in a broad spectrum of heart failure patients.** *Circulation* 2005, **112:**3738–3744.
8. Lee DS, Gona P, Vasan RS, et al.: **Relation of disease pathogenesis and risk factors to heart failure with preserved or reduced ejection fraction: insights from the Framingham heart study of the national heart, lung, and blood institute.** *Circulation* 2009, **119:**3070–3077.
9. Wang J, Nagueh SF: **Current perspectives on cardiac function in patients with diastolic heart failure.** *Circulation* 2009, **119:**1146–1157.
10. Drazner MH: **The transition from hypertrophy to failure. How certain are we?** *Circulation* 2005, **112:**936–938.
11. Harris KM, Spirito P, Maron MS, et al.: **Prevalence, clinical profile, and significance of left ventricular remodeling in the end-stage phase of hypertrophic cardiomyopathy.** *Circulation* 2006, **114:**216–225.
12.• Lam CS, Roger VL, Rodeheffer RJ, et al.: **Cardiac structure and ventricular-vascular function in persons with heart failure and preserved ejection fraction from Olmsted County.** *Circulation* 2007, **115:**1982–1990.

This comparative analysis of LV function in normals, hypertensive patients, and hypertensive patients with DHF reveals progressive LV shrinkage as DHF develops and strongly argues against progressive eccentric remodeling in hypertensive heart disease.

13. Lieb W, Xanthakis V, Sullivan LM, et al.: **Longitudinal tracking of left ventricular mass over the adult life course: clinical correlates of short- and long-term change in the Framingham offspring study.** *Circulation* 2009, **119:**3085–3092.
14. Klapholz M, Maurer M, Lowe AM, et al.: **Hospitalization for heart failure in the presence of a normal left ventricular ejection fraction: results of the New York heart failure registry.** *J Am Coll Cardiol* 2004, **43:**1432–1438.
15. Bahrami H, Bluemke DA, Kronmal R, et al.: **Novel metabolic risk factors for incident heart failure and their relationship with obesity: the MESA (Multi-Ethnic Study of Atherosclerosis) study** *J Am Coll Cardiol* 2008, **51:**1775–1783.
16. Zile MR, Gaasch WH, Carroll JD, et al.: **Heart failure with a normal ejection fraction: is measurement of diastolic function necessary to make the diagnosis of diastolic heart failure?** *Circulation* 2001, **104:**779–782.
17.•• Van Heerebeek L, Borbely A, Niessen HW, et al.: **Myocardial structure and function differ in systolic and diastolic heart failure.** *Circulation* 2006, **113:**1966–1973.

The first study to compare myocardial histology and contractile function of isolated cardiomyocytes between DHF and SHF.

18. Van Heerebeek L, Hamdani N, Handoko L, et al.: **Diastolic stiffness of the failing diabetic heart: importance of fibrosis, advanced glycation endproducts and myocyte resting tension.** *Circulation* 2008, **117:**43–51.
19. Ahmed SH, Clark LL, Pennington WR, et al.: **Matrix metalloproteinases/tissue inhibitors of metalloproteinases. Relationship between changes in proteolytic determinants of matrix composition and structural, functional, and clinical manifestations of hypertensive heart disease.** *Circulation* 2006, **113:**2089–2096.
20. Spinale FG, Coker ML, Heung LJ, et al.: **A matrix metalloproteinase induction/activation system exists in the human left ventricular myocardium and is upregulated in heart failure.** *Circulation* 2000, **102:**1944–1949.
21. Polyakova V, Hein S, Kostin S, et al.: **Matrix metalloproteinases and their tissue inhibitors in pressure-overloaded human myocardium during heart failure progression.** *J Am Coll Cardiol* 2004, **44:**1609–1618.
22. Borbély A, van der Velden J, Papp Z, et al.: **Cardiomyocyte stiffness in diastolic heart failure.** *Circulation* 2005, **111:**774–781.
23. Borbély A, van Heerebeek L, Paulus WJ: **Transcriptional and posttranslational modifications of titin: implications for diastole.** *Circ Res* 2009, **104:**12–14.
24. Makarenko I, Opitz CA, Leake MC, et al.: **Passive stiffness changes caused by upregulation of compliant titin isoforms in human dilated cardiomyopathy hearts.** *Circ Res* 2004, **95:**708–716.
25. Nagueh SF, Shah G, Wu Y, et al.: **Altered titin expression, myocardial stiffness, and left ventricular function in patients with dilated cardiomyopathy.** *Circulation* 2004, **110:**155–162.
26.• Krüger M, Kötter S, Grützner A, et al.: **Protein kinase G modulates human myocardial passive stiffness by phosphorylation of the titin springs.** *Circ Res* 2009, **104:**87–94.

This study reveals a novel mechanism in which nitric oxide and natriuretic peptides may improve diastolic LV stiffness and could have important implications for a specific DHF therapy.

27. Borbély A, Falcao-Pires I, van Heerebeek L, et al.: **Hypophosphorylation of the stiff N2B titin isoform raises cardiomyocyte resting tension in failing human myocardium.** *Circ Res* 2009, **104:**780–786.
28. Anderson MM, Requena JR, Crowley JR, et al.: **The myeloperoxidase system of human phagocytes generates N-epsilon-(carboxymethyl)lysine on proteins: a mechanism for producing advanced glycation end products at sites of inflammation.** *J Clin Invest* 1999, **104:**103–113.
29. Yeh CH, Sturgis L, Haidacher J, et al.: **Requirement for p38 and p44/p42 mitogen activated protein kinases in RAGE-mediated nuclear factor-kB transcriptional activation and cytokine secretion.** *Diabetes* 2001, **50:**1495–1504.
30. Davis BR, Kostis JB, Simpson LM, et al.: **Heart failure with preserved and reduced left ventricular ejection fraction in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial.** *Circulation* 2008, **118:**2259–2267.
31.•• Massie BM, Carson PE, McMurray JJ, et al.: **Irbesartan in patients with heart failure and preserved ejection fraction.** *N Engl J Med* 2008, **359:**2456–2467.
This article reported on the largest DHF trial to date showing a neutral outcome of irbesartan.
32. Granger CB, McMurray JJ, Yusuf S, et al.: **Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to angiotensin-converting-enzyme inhibitors: the CHARM-Alternative trial.** *Lancet* 2003, **362:**772–776.
33. Hernandez AF, Hammill BG, O'Connor CM, et al.: **Clinical effectiveness of beta-blockers in heart failure: findings from the OPTIMIZE-HF (Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure) registry.** *J Am Coll Cardiol* 2009, **53:**184–192.
34. Fukata H, Sane DC, Brucks S, Little WC: **Statin therapy may be associated with lower mortality in patients with diastolic heart failure: a preliminary report.** *Circulation* 2005, **112:**357–363.
35. Kjekshus J, Apetrei E, Barrios V, et al.: **Rosuvastatin in older patients with systolic heart failure.** *N Engl J Med* 2007, **357:**2248–2261.