HIGHLIGHTED TOPIC | Exploring New Concepts in the Management of Heart Failure with Preserved Ejection Fraction: Is Exercise the Key for Improving Treatment?

Myocardial hypertrophy and its role in heart failure with preserved ejection fraction

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Heinzel FR, Hohendanner F, Jin G, Sedej S, Edelmann F. Myocardial hypertrophy and its role in heart failure with preserved ejection fraction. J Appl Physiol 119: 1233–1242, 2015. First published July 16, 2015; doi:10.1152/japplphysiol.00374.2015.—Left ventricular hypertrophy (LVH) is the most common myocardial structural abnormality associated with heart failure with preserved ejection fraction (HFP EF). LVH is driven by neurohumoral activation, increased mechanical load, and cytokines associated with arterial hypertension, chronic kidney disease, diabetes, and other comorbidities. Here we discuss the experimental and clinical evidence that links LVH to diastolic dysfunction and qualifies LVH as one diagnostic marker for HFP EF. Mechanisms leading to diastolic dysfunction in LVH are incompletely understood, but may include extracellular matrix changes, vascular dysfunction, as well as altered cardiomyocyte mechano-elastic properties. Beating cardiomyocytes from HFP EF patients have not yet been studied, but we and others have shown increased Ca2+ turnover and impaired relaxation in cardiomyocytes from hypertrophied hearts. Structural myocardial remodeling can lead to heterogeneity in regional myocardial contractile function, which contributes to diastolic dysfunction in HFP EF. In the clinical setting of patients with compound comorbidities, diastolic dysfunction may occur independently of LVH. This may be one explanation why current approaches to reduce LVH have not been effective to improve symptoms and prognosis in HFP EF. Exercise training, on the other hand, in clinical trials improved exercise tolerance and diastolic function, but did not reduce LVH. Thus current clinical evidence does not support regression of LVH as a surrogate marker for (short-term) improvement of HFP EF.

HFP EF; diastolic dysfunction; left ventricular hypertrophy; cardiac myocytes; remodeling

LEFT VENTRICULAR HYPERTROPHY: CLINICAL PRESENTATION

Heart failure with preserved ejection fraction (HFP EF) or diastolic heart failure (DHF; as it has been classically referenced) is common, of increasing prevalence, and causes a substantial reduction in prognosis. In the majority of patients with symptomatic HFP EF, a history of hypertensive heart disease, including changes in left ventricular (LV) geometry, such as myocardial hypertrophy, can be found. Myocardial hypertrophy is defined as an increase in ventricular myocardial mass. In clinical practice and in animal studies, LV hypertrophy (LVH) is often assessed by measurement of end-diastolic thickness of septal and LV posterior wall and may be associated with normal or dilated LV cavity. Based on the assessment of the ratio of LV wall thickness and LV internal diameter (relative wall thickness), altered LV geometry in LVH has been classified into three groups: concentric remodeling (enlarged heart with normal relative wall thickness), concentric hypertrophy (increased relative wall thickness, normal internal diameter), and eccentric hypertrophy (increased relative wall thickness, increased internal diameter) (65). In clinical trials, LV mass (LVM) is the most common parameter of LVH and is estimated by algorithms subtracting the volume of the LV cavity from the volume enclosed by the epicardium. LVM, as assessed by echocardiography, is related to body surface area.
(LVM index, LVMI) and sex (65) and has been shown to correlate well with LV weight at necropsy in mice (51) and men (15).

CAUSES AND CONSEQUENCES OF LVH

LVH has long been regarded as a natural response to stabilize LV function in the presence of triggers that increase mechanical (after-)load, such as arterial hypertension or aortic stenosis (31). Indeed, according to Laplace’s law [LV wall stress = (LV pressure × LV radius)/(2 × LV wall thickness)], an increase in LV wall thickness lowers the tension (pressure) acting on the individual myocardial cell. However, the concept of LVH as a compensatory mechanism has been challenged based on clinical observations, as well as experimental models. Clinically, the degree of LVH has been associated with worse outcome (34, 56, 67). LVH [by electrocardiography (ECG)] has been found to be a predictor of sudden cardiac death, and the risk increases with LVH, independent of other risk factors (including coronary artery disease and heart failure) (34). In the Framingham Heart Study and other clinical trials, LVH based on ECG or echocardiographic criteria has been suggested as an independent cardiovascular risk factor (34, 67). Furthermore, diuretics, nonnitrate vasodilators (e.g., diltiazem or prazosin), and inotropes that improve symptoms and hemodynamics of hypertensive heart disease, but not LVH, are generally not associated with improved prognosis in heart failure (11). Most importantly, in animal models of heart failure, pharmacological and genetic interference with hypertrophic signaling cascades did not promote decompensation, but rather were beneficial for LV function and survival (22, 42).

LVH is also observed in athletes as a consequence of repetitive vigorous exercise (or in case of the python snake also by consumption of an extended meal) and during pregnancy (3). However, in the athlete’s heart, hypertrophy is not associated with increased fibrosis or apoptosis and results in normal or increased cardiac function and normal survival (12). Experimental data indicate that it is the type of trigger, not the duration, that initiates signaling for either physiological or maladaptive LVH (92). For instance, chronic exercise training as a physiological stimulus results in an increased level of growth hormone and subsequently insulin-like growth factor I, which mediates cardiomyocyte growth and survival via the phosphoinositide 3-kinase pathway (59, 97). This type of physiological LVH is not associated with diastolic dysfunction or worse prognosis (8, 69, 119) and is not focus of this review.

Comorbidities, such as arterial hypertension, diabetes, or chronic kidney disease, which promote LVH (107, 112), are common in heart failure patients with preserved as well as with reduced ejection fraction (HFrEF). LVH is also often observed in HFrEF (mostly concentric LVH) and HFrEF (often eccentric). However, there is strong and growing cumulative evidence that HFrEF and HFrEF represent different disease entities, as reviewed recently (55). Paulus and Tschöpe (89) have recently proposed a new paradigm, which suggests fundamental differences in the mechanisms that drive LV remodeling and contractile dysfunction in HFrEF and HFrE. Accordingly, a chronic systemic inflammatory disease state and associated cardiac mesenchymal alterations promote contractile dysfunction in HFrEF, whereas HFrEF is driven by dysfunction intrinsic to the cardiomyocytes. Figure 1 combines these observations and shows the pivotal role of LV hypertrophic remodeling in both disease entities. LVH following loss of cardiomyocytes (e.g., acutely with myocardial infarction or chronically with idiopathic cardiomyopathy) often results in HFrEF (red arrows), which is in line with distinct signaling pathways. Vice versa, concentric LVH as a result of multiple cardiovascular risk factors is a common cause for HFrEF (blue arrows) and in clinical settings (as opposed to many experimental models) only infrequently transitions to HFrEF (14, 70). However, eccentric hypertrophy in HFrEF is also observed and potentially indicates a distinct subgroup of patients who may develop HFrEF (50). Alterations at the cardiomyocyte level during LVH contribute to the heart failure pheno-

![Fig. 1. Role of left ventricular (LV) hypertrophy in heart failure.](https://jap.physiology.org/doi/10.1152/japplphysiol.00374.2015)
type. Loss of contractile function within the remaining cardiomyocytes during LV remodeling promotes the transition from LVH to HFpEF. On the other hand, in HFpEF, cardiomyocyte and extracellular matrix passive stiffness are increased (Fig. 1, and see section, CELLULAR MECHANISMS OF CONTRACTILE DYSFUNCTION IN LVH AND HFpEF). Triggers of LVH often also activate cardioprotective signaling in cardiomyocytes (e.g., as triggered by natriuretic peptides); however, the maladaptive pathways prevail during the natural course of the disease (see Ref. 5 for a more detailed review).

**MYOCARDIAL DYSFUNCTION ASSOCIATED WITH PATHOLOGICAL LVH**

The link between maladaptive LVH and diastolic dysfunction was established more than 30 years ago (see Ref. 72 for review). ECG signs of LVH are a strong predictor of diastolic dysfunction (61). In fact, in HFpEF, LVH is the most frequent structural cardiac abnormality. Arterial hypertension is common as a trigger of LVH and present in the majority of HFpEF patients (Table 1). In HFpEF patients, LVH is correlated with hospitalization for heart failure, cardiovascular death, and aborted cardiac arrest (37, 106), underscoring the role of LVH as a prognostic marker. However, underlying pathomechanisms that may link LVH to diastolic dysfunction and HFpEF are still not completely understood. Functional effects of LVH have been extensively studied in hypertrophic cardiomyopathy. In these conditions, global LV systolic function [ejection fraction (EF), LV emptying] is initially augmented, indicating a hypercontractile state (13). HFpEF patients reportedly have more pronounced concentric hypertrophy than patients with hypertensive heart disease without HFpEF (80). HFpEF is an exercise-related syndrome, and LVH correlates with an attenuated increase or even decrease in LV EF (LVEF) during exercise and reduced exercise capacity (81), depending on LVH etiology (104). Patients with a concentric type of LVH performed worst during exercise, attributed to reduced contractile reserve, but also to chronotropic incompetence (63). Lam et al. found a significant, albeit weak, inverse correlation between LVH and exercise capacity (63). Notably, when further adjusting for known confounders, such as age, sex, clinical variables, comorbidities, and medication, the association of exercise capacity and LVH was markedly attenuated or no longer detectable (19).

**ALTERED REGIONAL CONTRACTILITY IN LVH AND HFpEF**

Previous studies have suggested that patients with LVH and preserved EF may have subtle systolic dysfunction not reflected by the EF (7, 95). In recent years, LV deformation during systole has been quantified in multiple planes using speckle tracking echocardiography or MRI tissue tagging. Planes of deformation have been defined related to myocardial fiber orientation, including longitudinal, radial, and circumferential shortening (strain) (108). As reported earlier in this journal (99) and confirmed in other conditions of hypertrophic cardiac remodeling, an increase in radial strain may conceal loss of contractile function along the longitudinal heart axis (longitudinal strain) thus maintaining a preserved global EF (58, 60). Deterioration of regional strain correlates with regional myocardial hypertrophy (127) and parallels increased LVH in rodents (57), in pigs (115), as well as in patients (120). Regional contractile dysfunction is potentially related to increased regional fibrosis (120). In the PARAMOUNT trial, impaired longitudinal strain in HFpEF patients was not correlated to other markers of diastolic dysfunction, but associated with N-terminal prohormones of brain natriuretic peptide, which was interpreted as a sign of systolic dysfunction, despite preserved EF (60). However, others found a reduction in global longitudinal strain in hypertensive patients to be strongly associated with diastolic dysfunction, but not with LVH (28). Notably, a decrease in longitudinal and increase in radial regional strain in response to myocardial stress is a common pattern and has been observed early (i.e., before the onset of global diastolic dysfunction) as recently confirmed in a large-animal model (41) and in patients (86). Impaired regional strain may even occur before LVH manifestation (25). The increase in radial strain may dissipate during the progression of LVH (58). In HFpEF, LVH is associated with a higher degree of spatial heterogeneity in longitudinal strain at rest (100) and even more pronounced dysynchrony in regional contraction during exercise (113). In hypertrophic cardiomyopathy, such regional functional heterogeneity was associated with the distribution of myocardial fibrosis (9). Increased fibrosis has recently been related to the deterioration of regional strain also in a large-animal model of hypertensive heart disease (115). It has to be kept in mind that LV relaxation is also a function of LV afterload (ventricular-arterial coupling, see Ref. 49 for review). For instance, LV relaxation was more prolonged in hypertensive HFP EF patients than nonhypertensive HFpEF patients related to altered LV-arterial coupling (27). In analogy, changes in regional strain in response to exercise may also respond to exercise-induced alterations in afterload, which differ, depending on LVH etiology (104).

In summary, LVH is associated with global diastolic dysfunction and HFpEF in experimental and clinical studies, which is the basis for the inclusion of LVH as a diagnostic marker in the clinical algorithm to detect HFpEF (90). Structural remodeling induces regions of reduced regional strain.
during systole that are compensated by areas of increased contractile function, and this heterogeneity may contribute to diastolic dysfunction and exercise limitation, with and without LVH.

**CELLULAR MECHANISMS OF CONTRACTILE DYSFUNCTION IN LVH AND HFpEF**

Altered contractility in LVH at the organ level is related to structural and functional abnormalities involving the extracellular matrix and fibrous tissue, the vasculature, as well as the cardiomyocytes themselves. See Fig. 2.

LVH is often associated with increased fibrosis, mostly reactive interstitial fibrosis, even though replacement fibrosis following cardiomyocyte apoptosis has also been described (29). An increase in total collagen expression and cross-linking was associated with diastolic dysfunction and HFpEF (48). In chronic kidney disease and in diabetic cardiomyopathy, LV fibrosis and diastolic dysfunction are not necessarily linked to the presence of LVH (24, 75), but fibrosis may promote the progression of LVH to heart failure (23).

LVH, as well as other risk factors, such as age, diabetes, obesity, and hypertension, which are associated with HFpEF, have been linked to coronary microvascular rarefaction in animal models and patients (43, 116). Vice versa, reversal of myocardial hypertrophy (121) or vascular endothelial growth factor gene therapy (105) in murine models of HFpEF increased microvascular density, along with improvement of diastolic function. In mouse models, microvascular rarefaction preceded LVH, suggesting that microvascular dysfunction may also be a cause of diastolic dysfunction, independent of LVH (93). On the other hand, in a pig model of HFpEF (aortic banding), capillary density was unchanged in hypertrophied hearts (21). A recent study in human autopsies supported a link between microvascular rarefaction and HFpEF in a cohort with high prevalence (65%) of coronary artery disease (82). In summary, while microvascular dysfunction and vascular remodeling during LVH may promote HFpEF, the role of microvascular rarefaction in human HFpEF with different leading comorbidities remains to be determined. It has also been postulated that vascular dysfunction, altered extracellular matrix composition, and cytokines modulate cardiomyocyte function in HFpEF (89).

Cardiomyocyte contractile function is controlled by Ca\(^{2+}\)-dependent myofilament activation and relaxation, as well as by passive viscoelastic properties largely determined by the myofilaments (e.g., titin-related stiffness). As in the whole organ, mechanical energy stored in the sarcomeric protein titin during contraction contributes to recoil during relaxation. Vice versa, resting cardiomyocyte tension in diastole is a determinant of contractile force during systole. Thus the relationship between “systolic” and “diastolic” function at the cellular level is expected to be highly interdependent.

Following seminal studies of Paulus’ group (6, 122), who reported significantly increased resting tension in cardiomyocytes from patients with HFpEF correlating with end-diastolic pressure in vivo, increased cardiomyocyte passive stiffness has been confirmed in several animal models with LVH and diastolic dysfunction (36, 45). The large sarcomeric protein titin acts as a molecular spring and is a main determinant of passive stiffness (68). Interestingly, titin-dependent stiffness is increased in patients with arterial hypertension and HFpEF, but not in patients with hypertension alone (128), supporting its mechanistic role. As titin-associated proteins also may be involved in mechanosensing and hypertrophic signaling, it is currently unclear whether altered titin function is the cause or effect of LV hypertrophic remodeling (62). In addition, hypophosphorylation of myofilaments, leading to increased Ca\(^{2+}\) sensitivity, may also contribute to impaired cardiomyocyte relaxation in HFpEF (35).

Due to the limited availability of myocardial samples that would allow isolation of functional cardiomyocytes, active cardiomyocyte contraction has not been studied in human HFpEF. In LVH in the absence of ischemia, an increase in cardiomyocyte size is achieved by the addition of sarcomeres in parallel in concentric hypertrophy or sequentially (longitudinally) in eccentric hypertrophy (102). Experimental evidence suggests that, also at the cellular level, hypertrophy is associated with altered contractile function. Studies in several animal models with LVH (e.g., aortic stenosis, hypertension, diabetes, or kidney dysfunction) have demonstrated impaired active cardiomyocyte relaxation (26, 73, 78). Cardiomyocytes from animals models with hypertrophied, nonfailing hearts show cytosolic Ca\(^{2+}\) transients with normal or increased amplitude, often with slowed Ca\(^{2+}\) decay during diastole and increased diastolic intracellular Ca\(^{2+}\) concentration ([Ca\(^{2+}\)]\(_{i}\)), indicating increased cytosolic Ca\(^{2+}\) load, which may contribute to slowed cardiomyocyte relaxation and promote remodeling (77, 84). However, most small-animal models of LVH with signs of

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**Fig. 2.** Cellular pathomechanisms linking LV hypertrophy to diastolic dysfunction. See text for details. ECM, extracellular matrix.
diastolic dysfunction and congestion as observed in clinical HFrEF rapidly progress into severe HFrEF. Recently, larger animal models mimicking common clinical conditions (e.g., advanced age, hypertension) with preserved EF have been developed and may allow a better understanding of the heterogeneity of regional myocardial contractility and cellular function (35, 41). Yet, to date, active cellular contractile function in stable HFrEF has not been well studied, and a clear correlation between in vitro cardiomyocyte relaxation and diastolic function in vivo is lacking. The few studies on human myocardial biopsies from HFrEF patients did not report on function in intact cardiomyocytes. We have recently compared LV cardiomyocytes from nonfailing healthy and from remodeled hypertrophied donor hearts [EF > 45%, Fig. 3 (44, 71)] and found a preserved Ca$^{2+}$ transient amplitude, with a prolonged cytosolic Ca$^{2+}$ decay (71), suggesting an early increase in cytosolic Ca$^{2+}$ load in human LV remodeling. Based on current evidence, we propose that, in LVH with preserved EF, availability of cytosolic [Ca$^{2+}$] is not limiting but rather promotes contraction, whereas elevated [Ca$^{2+}$] may contribute to slowed myofilament relaxation during diastole. Further studies are needed to address the role of cardiomyocyte cytosolic Ca$^{2+}$ decay in HFrEF.

It is fair to say that diastolic dysfunction is also observed in the absence of LVH, as only about one-half of the patients in clinical HFrEF trials have LVH (Table 1 and Fig. 1, see also Ref. 91). In some animal models, diastolic dysfunction precedes the development of LVH (17). Risk factors, such as insulin resistance (88) and diabetes mellitus (76), may contribute to diastolic dysfunction in the absence of LVH.

CLINICAL TREATMENT OF LVH AND ITS EFFECTS ON HFrEF

In a variety of heart failure models (e.g., rodents, rabbit, dogs), interference with LV hypertrophic signaling pathways reliably reduces LVH and improves diastolic function, often independent of alterations in blood pressure (22, 38, 110). While these observations support a role for LVH in mediating diastolic dysfunction and as a therapeutic target, many of these models later develop HFrEF, which impedes translation of these results to the multifactorial setting of clinical HFrEF.

It has to be kept in mind that diastolic function is a function of afterload; thus treatment effects may also, at least in part, reflect reduced arterial resistance and not improved LV compliance per se (1). A larger number of prospective randomized trials have confirmed regression of LVH with standard antihypertensive therapies, such as angiotensin receptor blockers, angiotensin-converting enzyme inhibitors, Ca$^{2+}$ antagonists, or spironolactone (4, 16, 54), but also novel approaches, such as renal sympathetic denervation (103). A causal relationship between a reduction in LVH and improved diastolic function, however, is less well established in clinical studies. Early reports suggested that the beta blockers teratol or sotalol improve diastolic function independently from their effects on LVH (46, 118). In the last 2 decades, smaller uncontrolled studies reported improved diastolic function following LVH reduction induced by current antihypertensive therapy, aortic valve replacement in aortic stenosis, or renal sympathetic denervation (47, 101, 103, 117, 124), while others did not (32, 109, 123). Larger randomized controlled trials, such as PRE-SERVE [Prospective Randomized Enalapril Study Evaluating Regression of Ventricular Enlargement; enalapril (16)] or ASCOT [Anglo-Scandinavian Cardiac Outcomes Trial; amlodipine ± perindopril (2)], however, did not show any association between a reduction in LVH and improvement in diastolic filling, whereas the LIFE [Losartan Intervention For Endpoint reduction in hypertension study; losartan or atenolol (126)] study did. Mineralocorticoid-receptor antagonists, such as eplerenone and spironolactone, reliably reduce LVH. Mineralocorticoid-receptor antagonists were more consistently (e.g., Refs. 83, 96), but also not always (33), associated with improved diastolic function. However, as shown in the Aldo-DHF trial, the decrease of LVMI with aldosterone was not accompanied by an improvement of exercise capacity in patients with mild to moderate HFrEF (20), which is further questioning the “obvious” link between exercise capacity and LVMI. Taken together, inhibition of neurohumoral activation promotes regression of some, but not all, maladaptive changes, leading to contractile dysfunction in LVH.

The multifactorial origin of diastolic dysfunction in clinical settings may also explain the weaker association between LVH regression and improvement of diastolic function. In the RELAX trial, the presence of LVH did not affect treatment efficacy with sildenafil (98), indicating that a better understanding of the cellular mechanisms linking LVH to HFrEF is warranted to refine therapeutic approaches. Hypertrophic remodeling is, in part, counterbalanced by anti-hypertrophic pathways, including cyclic guanosine monophosphate (cGMP)-dependent signaling triggered by nitric oxide or natriuretic peptides (5). HFrEF has been linked to reduced cGMP-mediated signaling, and, in experimental conditions, increasing cGMP by inhibition of phosphodiesterase 5 (PDE5, by sildenafil) attenuated LVH and diastolic dysfunction (85). Surprisingly, sildenafil failed to improve diastolic dysfunction or LVH in the RELAX trial (98), questioning PDE5 as a therapeutic target at least in an unselected cohort of heart failure patients.
EXERCISE EFFECTS ON LVH AND HFpEF

Disturbed diastolic function and increased vascular stiffness are major contributors to exercise limitation in patients with HFpEF. Although they demonstrated a significant improvement of exercise capacity and quality of life, they failed to demonstrate an improvement of cardiac systolic or diastolic function or of LVH (40, 52, 114). Similar findings were made under more controlled conditions in a translational large-animal model of HFpEF (74). In a prospective clinical approach, the multicenter Exercise Training in Diastolic Heart Failure Pilot study (Ex-DHF-P) randomized patients with New York Heart Association class II-III, LVEF ≥ 50%, echocardiographic evidence of diastolic dysfunction, sinus rhythm, and ≥1 additional cardiovascular risk factor to 32 sessions of supervised, combined endurance/resistance exercise training (n = 44) or to usual care (n = 20) (18). Peak oxygen consumption after 3 mo (primary endpoint) significantly improved with training, resulting in a between-group difference of 3.3 ml·kg⁻¹·min⁻¹ (P < 0.001). Also, the resting LV filling index (E/e'), the left atrial volume index, and different quality of life dimensions were improved after follow-up (87). Again, as also reported in previous trials, LVH did not change after training.

Several reasons might contribute to the actual lack of evidence regarding the link between improved exercise capacity, improved cardiac diastolic function, and the regression of LVH. In all available studies, the intervention period was limited (12, 16, or 24 wk). Furthermore, patients were not classified using a comparable diagnostic algorithm as now recommended for the diagnosis of HFpEF (79, 90). Last, the induction of physiological adaption of the myocardium induced by exercise training might cover the beneficial effects of exercise training on detrimental cardiac remodeling processes in this HF population with preserved LVEF. Future studies are, therefore, urgently needed to further elaborate the effects of exercise training on cardiac structure and function. The ongoing Exercise Training in Diastolic Heart Failure (Ex-DHF) study will randomize n = 320 patients (1:1 ratio) to exercise training or usual care and will have an individual 12-mo follow-up (IRCTN 86879094; http://www.controlled-trials.com). Since LVH is part of the specific inclusion criteria used in Ex-DHF, this study might help to better understand the effects of exercise training on LVH in this condition.

SUMMARY AND CONCLUSION

Experimental and clinical studies indicate that maladaptive LVH, i.e., in the presence of pathological stimuli, can per se induce diastolic dysfunction and thus contribute to the HFpEF phenotype. Mechanisms are diverse and probably etiology specific and include vascular dysfunction and potentially vascular rarefaction, changes in the extracellular matrix composition, including increased fibrosis, and alterations of the intrinsic active and passive contractile properties of the cardiac myocyte. In the multifactorial clinical setting of HFpEF, diastolic dysfunction and HFpEF are also observed in the absence and independent of LVH in a considerable number of patients. A reduction of LVH is not necessarily associated with an improvement of diastolic function. Thus current clinical evidence does not support regression of LVH as a surrogate marker for short-term improvement of HFpEF.

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1242 Hypertrophy in HFpEF •

Review

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