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Myocardial Hypertrophy and Its Role in Heart Failure with Preserved Ejection Fraction

Frank R. Heinzel[1], **Felix Hohendanner**[1], **Ge Jin**[2,3], **Simon Sedej**[3], and **Frank Edelmann**[1]

[1]Department of Cardiology, Charité - Universitätsmedizin Berlin, Augustenburgerplatz 1, 13353 Berlin, Germany

[2]Cardiology Department, The Second Affiliated Hospital & YuYing Children's Hospital Wenzhou Medical University, China

[3]Division of Cardiology, Medical University of Graz, Auenbruggerplatz 15, 8036 Graz, Austria

Abstract

Left ventricular hypertrophy (LVH) is the most common myocardial structural abnormality associated with heart failure with preserved ejection fraction (HFpEF). LVH is driven by neurohumoral activation, increased mechanical load and cytokines associated with arterial hypertension, chronic kidney disease, diabetes and other co-morbidities. Here we discuss the experimental and clinical evidence that links LVH to diastolic dysfunction and qualifies LVH as one diagnostic marker for HFpEF. Mechanisms leading to diastolic dysfunction in LVH are incompletely understood but may include extracellular matrix changes, vascular dysfunction as well as altered cardiomyocyte mechano-elastical properties. Beating cardiomyocytes from HFpEF patients have not yet been studied, but we and others have shown increased Ca^{2+} 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 HFpEF. In the clinical setting of patients with compound co-morbidities, 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 HFpEF. 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 HFpEF.

Left Ventricular Hypertrophy – Clinical Presentation

Heart failure with preserved ejection fraction (HFpEF) 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 HFpEF, a history of hypertensive heart disease including changes in 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, left ventricular (LV)

Corresponding author: Prof. Dr. med. Frank R. Heinzel, Ph.D., Department of Cardiology, Charité - Medical University Berlin, Augustenburgerplatz 1, 13353 Berlin, Germany. frank.heinzel@charite.de.

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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 substracting 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 gender (65) and has been shown to correlate well with LV weight at necropsy in mice (51) and men (15).

Causes and Consequences of Left Ventricular Hypertrophy

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, non-nitrate 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 consequences 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, results in normal or increased cardiac function and normal survival (12). Experimental data indicates 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 IGF-1 which mediates cardiomyocyte growth and survival via the phosphoinositide 3-kinase (PI3K) pathway (59; 97). This type of physiological LVH is not associated with diastolic dysfunction or worse prognosis (8; 69; 119) and not focus of this review.

Co-morbidities, 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 (HFrEF) ejection fraction. LVH is also often observed in HFpEF (mostly concentric LVH) and HFrEF (often eccentric). However, there is strong and growing cumulative evidence that HFpEF and HFrEF represent different disease entities as reviewed recently (55). Paulus and Tschöpe have recently proposed a new paradigm which suggests fundamental differences in the mechanisms that drive LV remodeling and contractile dysfunction in HFpEF and HFrEF (89). Accordingly, a chronic systemic inflammatory disease state and associated cardiac mesenchymal alterations promote contractile dysfunction in HFpEF, 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 HFpEF (blue arrows) and in clinical settings (as opposed to many experimental models) only infrequently transitions to HFrEF (14; 70). However, eccentric hypertrophy in HFpEF is also observed and potentially indicates a distinct subgroup of patients that may develop HFrEF (50). Alterations at the cardiomyocyte level during LVH contribute to the heart failure phenotype. Loss of contractile function within the remaining cardiomyocytes during LV remodeling promotes the transition from LVH to HFrEF. On the other hand, in HFpEF, cardiomyocyte and extracellular matrix passive stiffness are increased (Fig. 1, and see section “Cellular Mechanisms”). Triggers of LVH often also activate cardio-protective signaling in cardiomyocytes (e.g. as triggered by natriuretic peptides), however, the maladaptive pathways prevail during the natural course of the disease (see (5) for a more detailed review).

Myocardial Dysfunction Associated with Pathological Left Ventricular Hypertrophy

The link between maladaptive LVH and diastolic dysfunction has been established more than 30 years ago (see (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 or 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 (HCM). In these conditions, global LV systolic function (ejection fraction, 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 ejection fraction 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, gender, clinical variables, co-morbidities and medication, the association of exercise capacity and LVH was markedly attenuated or no longer detectable (19).

Altered Regional Contractility in Left Ventricular Hypertrophy and HFpEF

Previous studies have suggested that patients with LV hypertrophy and preserved ejection fraction may have subtle systolic dysfunction not reflected by the ejection fraction (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 fibre 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 a loss of contractile function along the longitudinal heart axis (longitudinal strain) and maintaining a preserved global ejection fraction (58; 60). Deterioration of regional strain correlates with regional LVH (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 NTproBNP, 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 dyssynchrony in regional contraction during exercise (113). In HCM 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 (49) for review). For instance, LV relaxation was more prolonged in hypertensive HFpEF patients than non-hypertensive 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 Left Ventricular Hypertrophy 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.

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 co-morbidities 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 visco-elastical 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 who reported significantly increased resting tension in cardiomyocytes from patients with HFpEF correlating with end-diastolic pressure in vivo (6; 122), 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 cause or effect of LV hypertrophic remodeling (62). In addition, hypo-phosphorylation 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, non-failing hearts show cytosolic Ca^{2+} transients with normal or increased amplitude, often with slowed Ca^{2+} decay during diastole and increased diastolic $[Ca^{2+}]_I$ 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 diastolic dysfunction and congestion as observed in clinical HFpEF 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 HFpEF 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 HFpEF patients did not report on function in intact cardiomyocytes. We have recently compared LV cardiomyocytes from non-failing healthy and from remodeled hypertrophied donor hearts (ejection fraction > 45%, Figure 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 ejection fraction 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 HFpEF.

It is fair to say that diastolic dysfunction is also observed in the absence of LVH, as only about half of the patients in clinical HFpEF trials have LVH (Table 1 and Figure 1, see also (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 Left Ventricular Hypertrophy and its Effects on HFpEF

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 HFpEF.

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 (ARB), angiotensin converting enzyme inhibitors (ACEI), 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 betablockers teratorol or sotalol improve diastolic function independently from their effects on LVH (46; 118). In the last two 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 PRESERVE (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 study did (Losartan Intervention For Endpoint reduction in Hypertension study; losartan or atenolol, (126)). Mineralocorticoid-receptor antagonists (MRA) such as epleronone and spironolactone, reliably reduce LVH. MRAs were more consistently (e.g. (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 HFpEF (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 LV hypertrophy to HFpEF 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). HFpEF 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 HFpEF patients. PDE9 inhibition may be superior to PDE5 by more selectively increasing cGMP related to natriuretic peptide signaling (66). The angiotensin-receptor-neprilysin-inhibitor LCZ696 also reduced LVH and improved diastolic function in experimental conditions (125), a benefit in outcome in HFpEF patients is being evaluated in the ongoing larger PARAGON-HF trial.

Exercise Effects on Left Ventricular Hypertrophy and HFpEF

Disturbed diastolic function and increased vascular stiffness are major contributors to exercise limitation in patients with HFpEF (10; 39; 53). The subsequent rise in LV filling pressure at rest and/or during exercise has been suggested to be directly related to the severity of HF symptoms in HFpEF patients.

Several single center trials addressed the role of exercise training on exercise capacity and cardiac function 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 (NYHA) class II-III, left ventricular ejection fraction (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 (VO2) after 3 months (primary endpoint) significantly improved with training, resulting in a between group difference of 3.3mL/kg/min ($P<0.001$). Also the resting left ventricular filling index (E/e'), the left atrial volume index and different QoL 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 weeks). 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 months follow-up (ISRCTN 86879094, 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.

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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 independently 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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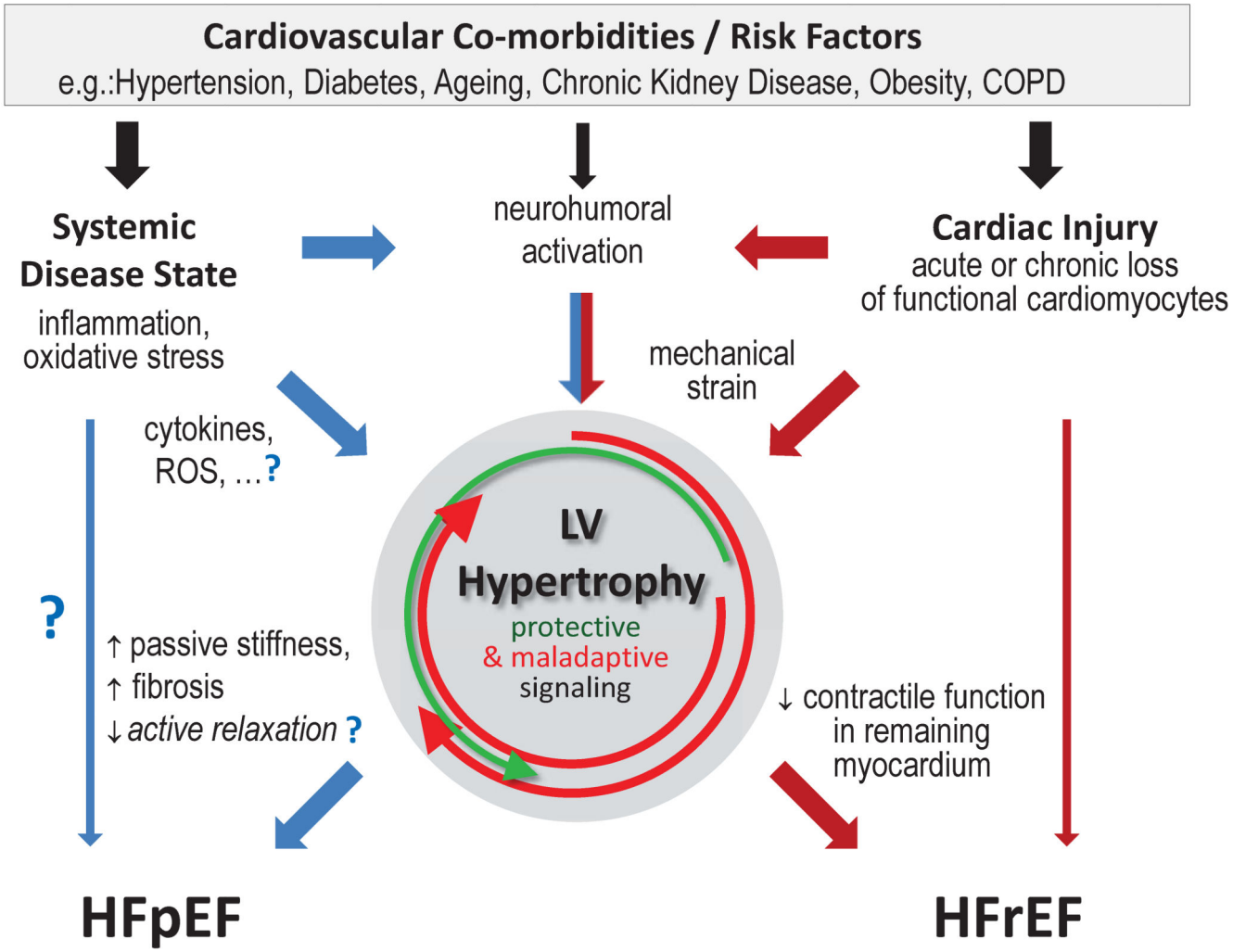

Figure 1.

Role of left ventricular hypertrophy in heart failure. Based on (89), heart failure with preserved (HFpEF) and reduced (HFrEF) ejection fraction are driven by different pathomechanisms (blue and red arrows). While both share some degree of neurohumoral activation (middle), the proposed paradigm suggests systemic low-grade inflammation and oxidative stress are more prominent mediators of HFpEF whereas cardiomyocyte injury is pivotal in HFrEF. Downstream signaling activates some protective (green circular arrow) but overwhelmingly maladaptive (red circular arrows) pathways (5). Left ventricular hypertrophic remodeling is common but not inevitable (thin arrows), however, the cellular phenotype differs in HFpEF vs HFrEF. See text for more details.

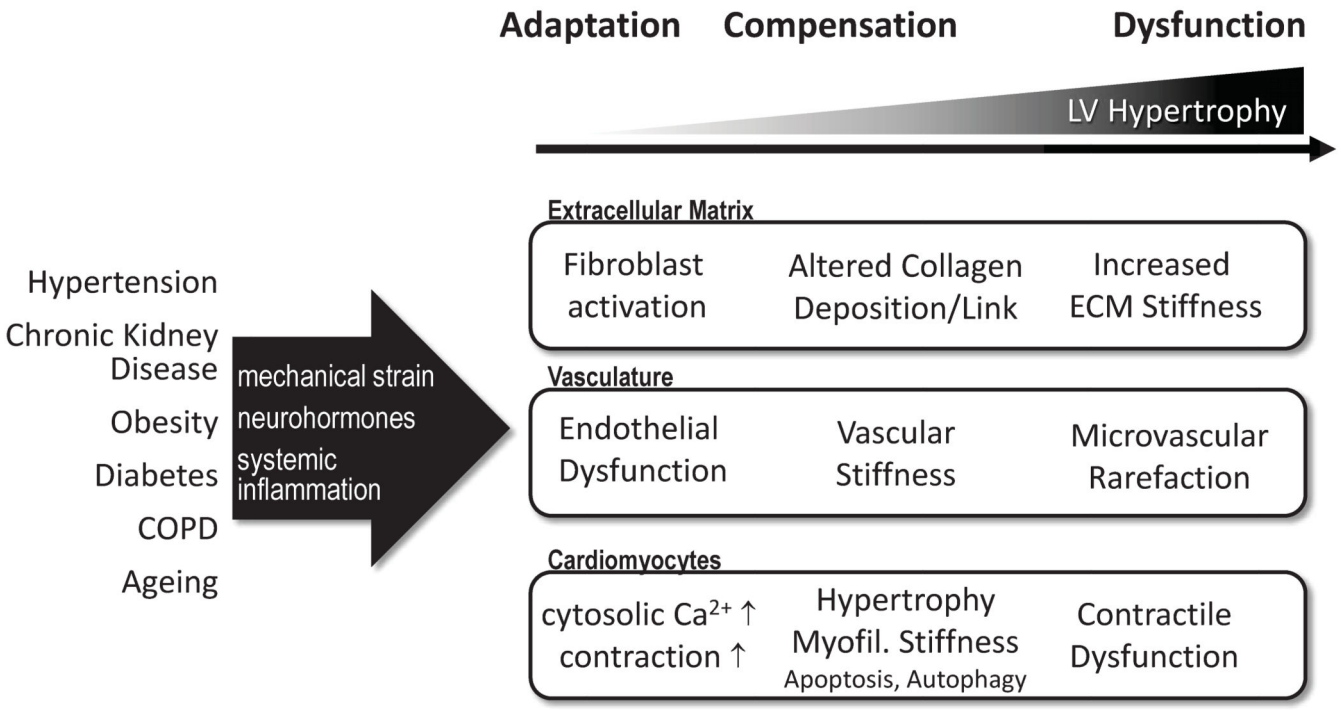

Figure 2.
Cellular pathomechanisms linking left ventricular hypertrophy to diastolic dysfunction. See text for details.

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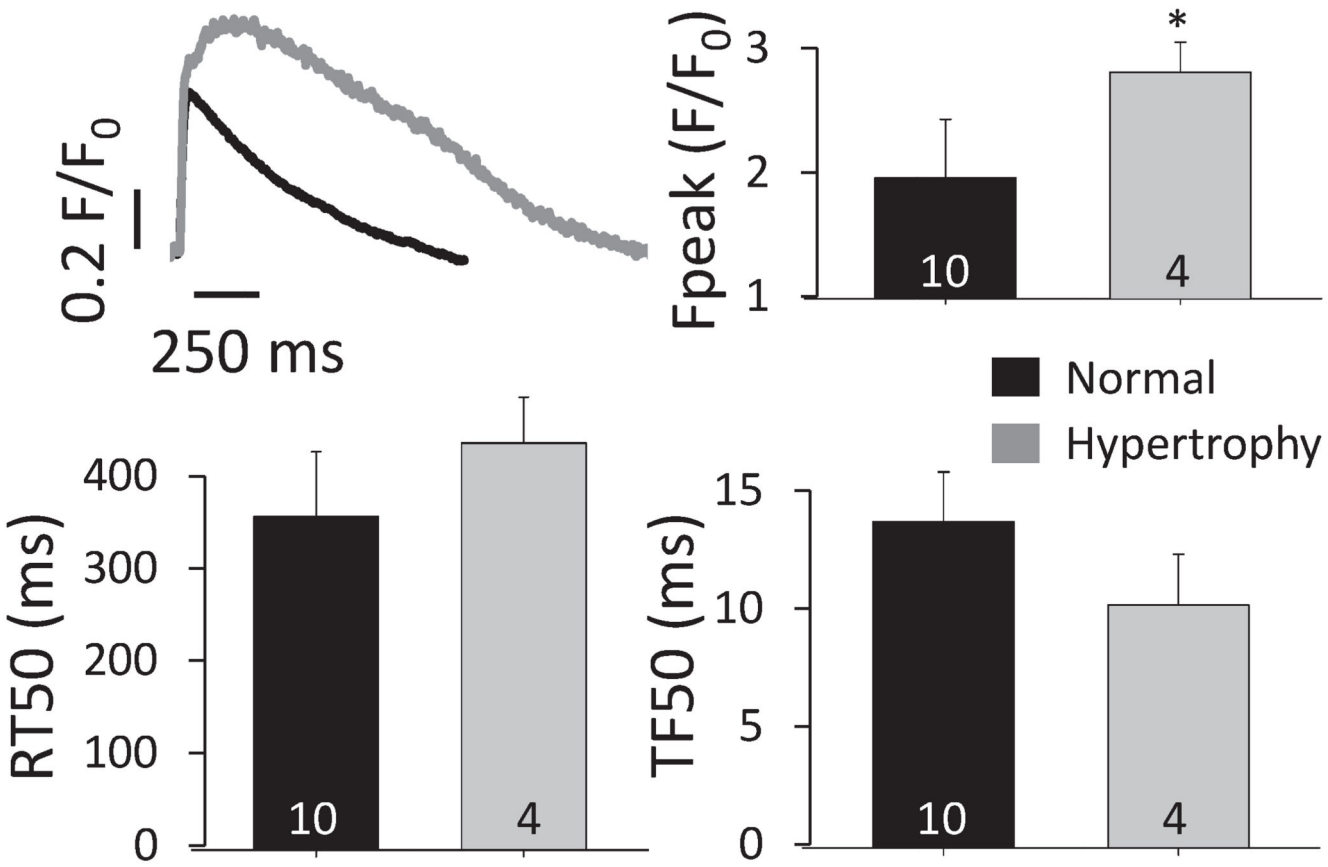

Figure 3.

Upper left: Example [Ca2+]i transients from healthy (N=3) and remodeled hearts (N=2, ejection fraction ? 45%; 1 with concentric remodeling and 1 with eccentric hypertrophy). Ca2+ transient amplitude (upper right) was significantly increased, changes in time to half maximal release (TF50, lower left) and relaxation (RT50, lower right) did not reach significance (number in bars indicate number of cells, error bars=S.E.M.).

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Table 1

Prevalence of arterial hypertension and left ventricular hypertophy (LVH) in randomized controlled trials on heart failure with preserved ejection fraction.

Study Acronym	N	Art. Hypertens.	LVH	Reference
RELAX	216	85%	48%	(98)
TOPCAT substudy	935	91%	47%	(106)
CHARM-ES	312	64%	52%	(94)
PARAMOUNT	279	94%	n.a.*	(111)
I-PRESERVE substudy	745	92%	29%	(129)
Aldo-DHF	422	92%	n.a.*	(20)

N.a. = not available.

RELAX: PhosphodiesteRasE-5 Inhibition to Improve CLinical Status And. EXercise Capacity in Diastolic Heart Failure; TOPCAT: Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist; CHARM-ES: Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity-Preserved Echocardiographic Substudy; PARAMOUNT: Prospective comparison of ARNI with ARB on Management Of heart failUre with preserved ejectioN fraction; I-PRESERVE: Irbesartan in Heart Failure with Preserved Ejection Fraction Study; Aldo-DHF: Aldosterone Receptor Blockade in Diastolic Heart Failure

*mean left ventricular mass index was 83±25 g/m^2 (males; normal reference range 49-115 g/m^2 (64)) and 77±20 g/m^2 (females; normal reference range 43-95 g/m^2) in I-preserve (30) and 109±28 g/m^2 in Aldo-DHF (20).