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ORIGINAL ARTICLE

Hypertension in African Americans with Heart Failure: Progression from Hypertrophy to Dilatation; Perhaps Not

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Abstract
Aim Concentric hypertrophy is thought to transition to left ventricular (LV) dilatation and systolic failure in the presence of long standing hypertension (HTN). Whether or not this transition routinely occurs in humans is unknown.
Methods We consecutively enrolled African American patients hospitalized for acute decompensated volume overload heart failure (HF) in this retrospective study. All patients had a history of HTN and absence of obstructive coronary disease. Patients were divided into those with normal left ventricular ejection fraction (LVEF) and reduced LVEF. LV dimensions were measured according to standard ASE recommendations. LV mass was calculated using the ASE formula with Devereux correction.
Results Patients with normal LVEF HF were significantly older, female and had a longer duration of HTN with higher systolic blood pressure on admission. LV wall thickness was similarly elevated in both groups. LV mass was elevated in both groups however was significantly greater in the reduced LVEF HF group compared to the normal LVEF HF group. Furthermore, gender was an independent predictor for LV wall thickness in normal LVEF HF group.
Conclusion In African American patients with HF our study questions the paradigm that concentric hypertrophy transitions to LV dilatation and systolic failure in the presence of HTN. Genetics and gender likely play a role in an individual's response to long standing hypertension.

Keywords Normal LVEF heart failure · Reduced LVEF heart failure · Left ventricular mass · Hypertension

1 Introduction

Heart failure (HF) in African Americans occurs at an earlier age, is associated with more advanced left ventricular dysfunction, and presents with a worse clinical class at the time of diagnosis as compared to whites [1]. It is also associated with higher morbidity and mortality [1]. Unlike whites in whom coronary artery disease is the most common etiology of HF, African Americans often have a non-ischemic etiology with hypertension being the most prevalent antecedent clinical risk factor [2–7]. African Americans have more severe hypertension (HTN), and associated left ventricular hypertrophy (LVH) is 2–3-fold more common in African Americans as compared with whites [8]. The severity of HTN and more frequent presence of LVH may lead to a higher incidence of HF compared with other races.

It has been thought that the initial response to HTN, concentric hypertrophy with preserved left ventricular ejection fraction (LVEF), progresses to reduced LVEF with a dilated LV when left untreated. The transition from preserved LVEF HF with concentric LV hypertrophy to LV dilatation has been demonstrated in animal models including the spontaneously hypertensive rat [9], or after aortic banding [10], or through transgenic manipulation [11]. However to our knowledge no longitudinal studies have been performed in hypertensive humans demonstrating the transition from concentric LVH and preserved

Study performed at Rutgers University-New Jersey Medical School, Newark, New Jersey.

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LVEF HF to LV dilatation with reduced LVEF in the absence of an ischemic insult.

In an attempt to better understand the role of HTN in HF, we identified non-ischemic African American patients who were admitted with volume overload decompensated HF and compared within the group those with a normal LVEF with concentric hypertrophy vs. those with a reduced LVEF and dilated LV.

2 Methods

2.1 Study Group

African American patients with history of hypertension (defined as BP $\geq$140/90), 18 years of age and older hospitalized for decompensated (volume overloaded) HF with a non-ischemic etiology were consecutively enrolled from June 1, 2003 to December 31, 2005 in this retrospective study. These patients were admitted through our ED, after presenting with dyspnea at rest, evidence of pulmonary congestion on CXR ($\geq$2/3 of lung fields) and treated with IV diuretics. Patients who presented with a predominant low output syndrome were excluded. Transthoracic 2D echocardiography was obtained within 1 week of admission. Excluded were: patients with renal insufficiency (serum creatinine >3.0 mg/dl or requiring dialysis), significant coronary disease (defined as prior myocardial infarction, percutaneous coronary intervention, coronary artery bypass grafting, or coronary stenosis >50 % by coronary angiography and patients with a positive stress test in the absence of a normal cardiac catheterization), valvular dysfunction (aortic or mitral valve area $\leq$1.5 cm^2, aortic or mitral valve regurgitation >2+), prior valve replacement, severe COPD, viral myocarditis, congenital hypertrophic cardiomyopathy, and infiltrative cardiomyopathies. Also excluded were patients with a history of alcohol abuse or cocaine use. Patients were divided into 2 groups—those with a normal left ventricular ejection fraction (LVEF) of >50 % (as generally accepted by others [12] and those with a reduced LVEF of <50 %. This protocol was approved by the Institutional Review Board for Human Studies at the University of Medicine and Dentistry of New Jersey and the human subjects gave informed consent for the study.

2.2 Echocardiography

Transthoracic echocardiographic images were obtained with the patient in the left lateral decubitus position using commercially available ultrasound equipment (Siemens's Sequoia with a 2.0–3.5-MHz transducer). Four standard echocardiographic views were obtained with each acquisition: parasternal long and short axis views and apical 2 and 4 chamber views.

LV septal (S) and posterior wall (PW) thickness and LV end systolic and diastolic dimension (LVESD and LVEDD) was measured by using 2D-guided M-mode echocardiography according to the recommendations of the American Society of Echocardiography [13]. LV mass was calculated: $0.832[(PW + S + LVEDD)^3 \ LVEDD] + 0.6$ (ASE formula/Devereux correction) and indexed to $height^{2.7}$ (meters) [14]. Normal LV mass is 49.2 and 46.7 $g/m^{2.7}$ in males and females respectively. Relative wall thickness (RWT) was calculated as 2 $\times$ PWTd/LVIDd.

The presence and severity of mitral and aortic regurgitation were assessed with color Doppler imaging and image-guided pulsed Doppler studies with semi-quantitative grading [15]. Aortic valve area was calculated from the continuity equation and mitral valve area from pressure half-time analysis.

2.3 Statistical Methods

Summary statistics are presented as mean $\pm$ standard deviation for continuous data or median and interquartile range when indicated and percentages for categorical data. For all comparison's, a student *t* test was used. Logistic regression and Pearson Correlation analysis were used. Only p values <0.05 were considered statistically significant. Analyses were conducted with the Statistical Analysis System (SAS Institute, Carry, North Carolina).

3 Results

One hundred and twenty five consecutive patients were enrolled, 60 who had normal LVEF ($\geq$50 %) and 65 with a reduced LVEF (<50 %).

Demographic, clinical and echocardiographic data on the two groups are presented in Table 1 and Fig. 1. Medications at baseline in both the groups are presented in Fig. 2.

Patients with normal LVEF (65.2 $\pm$ 10 %) vs. those with reduced LVEF (23.1 $\pm$ 7 %) HF were significantly older (66 $\pm$ 14 vs. 62.0 $\pm$ 12 years; $p < 0.04$) female (68 vs. 38 %; $p < 0.001$) with longer duration of HTN (20 $\pm$ 6 vs. 12 $\pm$ 8 years; $p < 0.001$) and a higher systolic blood pressure on admission (157 $\pm$ 33 vs. 144 $\pm$ 26 mmHg; $p < 0.04$).

LV wall thickness was similar in both groups. LV mass was elevated in both groups but significantly greater in the reduced LVEF HF group (88.0 $\pm$ 29.0 vs. 68.1 $\pm$ 31 $g/m^{2.7}$ $p < 0.003$). Left ventricular end diastolic dimension (LVEDD) was significantly greater in the reduced LVEF vs. the normal LVEF HF group (6.09 $\pm$ 0.9 vs. 4.90 $\pm$ 0.9 cm;

Table 1 Clinical and echocardiographic data

	Normal LVEF HF (n = 60)	Reduced LVEF HF (n = 65)	p-value
Age (years)	66 ± 14	62.0 ± 12	0.04
Sex (female)	68 % (41/60)	38 % (25/65)	0.001
Serum creatinine (mg/dl)	1.3 ± 0.9	1.2 ± 0.1	NS
Duration of hypertension (years)	20 ± 6	12 ± 8	<0.001
Mean SBP at admission (mmHg)	157 ± 33	144 ± 26	0.04
Mean DBP at admission (mmHg)	86 ± 23	86 ± 20	NS
LVEF (%)	65.2 ± 10	23.1 ± 7	<0.001
LV septal thickness (cm)	1.30 ± 0.3	1.31 ± 0.3	NS
LV posterior wall thickness (cm)	1.27 ± 0.2	1.28 ± 0.3	NS
LVEDD (cm)	4.90 ± 0.9	6.09 ± 0.9	<0.001
Relative wall thickness	0.55 ± 0.14	0.43 ± 0.12	<0.001
LV mass ($g/m^{2.7}$)[a]	68.11 ± 31	88.0 ± 29.0	<0.003

[a] Normal LV mass = 49.2 and 46.7 $g/m^{2.7}$ in males and females, respectively

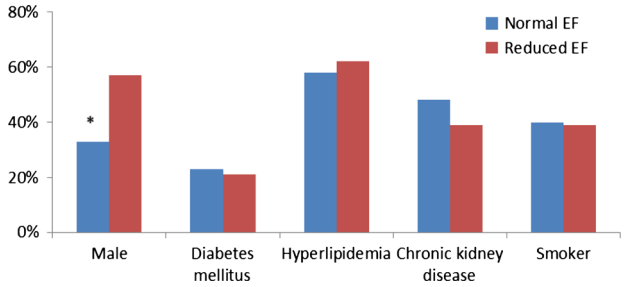
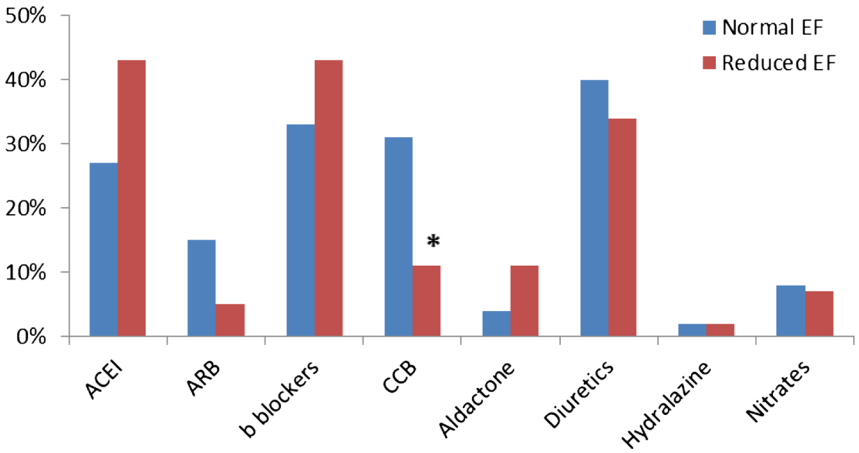


Fig. 1 Baseline characteristics in normal LVEF and reduced LVEF HF groups. *Asterisk* indicates significant difference (p 0.02) in gender between normal EF and reduced EF groups

Fig. 2 Baseline medications in normal LVEF and reduced LVEF HF groups. *Asterisk* indicates significant difference (p 0.02) in calcium channel blocker intake between normal EF and reduced EF groups. *ACEI* angiotensin converting enzyme inhibitor, *ARB* angiotensin receptor blocker, *CCB* calcium channel blocker



$p < 0.001$), which resulted in significant differences in relative wall thickness (0.55 ± 0.14 vs. 0.43 ± 0.12; reduced LVEF vs. normal LVEF respectively, $p < 0.001$).

By logistic regression analysis using variables including age, hyperlipidemia, diabetes mellitus, smoking, chronic kidney disease and sex, we found that only gender (p 0.02) was an independent predictor for high left ventricular mass/BSA when both groups were combined (Table 2). Further testing these variables in two groups separately, i.e., normal LVEF HF and reduced LVEF HF, gender was independent predictor for high left ventricular mass/BSA in normal LVEF HF group alone (p 0.006) and not in reduced LVEF HF group (Table 2). Using Pearson Correlation (Table 3) analysis, diastolic BP and LVEF were two variables that showed correlation with LV Mass/BSA.

4 Discussion

Hypertension, common in African Americans, is an identified risk factor for the development of HF with normal and reduced LVEF [7, 16–18]. The paradigm of hypertensive heart disease suggests that the initial response to HTN is concentric hypertrophy [19] that transitions with time to LV dilatation and reduced LVEF through poorly understood mechanisms resulting in the syndrome of heart failure [20]. At the cellular level, concentric hypertrophy is associated with an increase in myocyte width, whereas LV dilation is associated with an increase in myocyte length [21]. Our study suggests that concentric hypertrophy and LV dilatation may be two independent and distinct responses to HTN.

Classic definitions of concentric hypertrophy vs. eccentric hypertrophy focus on the presence of increased LV mass in both, but with increased wall thickness in the concentric group and increased chamber dimension in the

Table 2 Logistic regression analysis for prediction of high LV mass/BSA

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	Age	-.015	.024	.383	1	.536	.985	.940	1.033
	HLD(1)	.118	.676	.030	1	.862	1.125	.299	4.228
	DM(1)	-.242	.784	.095	1	.757	.785	.169	3.646
	Smoke(1)	-.134	.672	.040	1	.842	.874	.234	3.264
	CKD(1)	.139	.699	.040	1	.842	1.149	.292	4.525
	Sex(1)	1.778	.769	5.340	1	.021	5.916	1.310	26.723
	Constant	1.993	1.552	1.650	1	.199	7.339		

a. Variable(s) entered on step 1: Age, HLD, DM, Smoke, CKD, Sex.

Variables in the Equation

LVEF			B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
									Lower	Upper
Normal EF	Step 1[a]	Age	.000	.030	.000	1	.991	1.000	.943	1.060
		HLD(1)	.515	.883	.340	1	.560	1.674	.296	9.458
		DM(1)	-.239	1.041	.052	1	.819	.788	.102	6.063
		Smoke(1)	-.767	.893	.737	1	.391	.465	.081	2.674
		CKD(1)	1.039	1.057	.966	1	.326	2.827	.356	22.444
		Sex(1)	2.887	1.049	7.575	1	.006	17.939	2.296	140.176
		Constant	-.748	1.937	.149	1	.699	.473		
Low EF	Step 1[a]	Age	-.029	.076	.146	1	.702	.971	.837	1.127
		HLD(1)	-16.653	8069.021	.000	1	.998	.000	.000	.
		DM(1)	-.978	1.722	.323	1	.570	.376	.013	10.996
		Smoke(1)	16.582	7922.170	.000	1	.998	15897623.18	.000	.
		CKD(1)	.167	1.714	.009	1	.922	1.182	.041	33.981
		Sex(1)	17.954	7953.754	.000	1	.998	62700786.12	.000	.
		Constant	20.498	8069.022	.000	1	.998	798426120.1		

a. Variable(s) entered on step 1: Age, HLD, DM, Smoke, CKD, Sex.

eccentric group. Our eccentric hypertrophy group had the added characteristic of increased wall thickness in addition to increase LV mass and chamber dimensions, perhaps identifying a new group not normally noted in the classic paradigmatic representations [21].

In our study, patients with normal EF HF as compared to those with reduced EF HF were older and had a longer duration of hypertension, which was more severe on presentation. There were no identifiable demographic, clinical or phenotypic differences between the groups to explain why some patients developed concentric hypertrophy and others LV dilation with reduced LVEF suggesting that initial adaptive responses to HTN may be either concentric or LV dilation and is likely genetically determined.

In animal models, the mechanisms involved in LVH development and its transition to HF are multifactorial and controversial [21]. Several mechanisms responsible for this transition have been proposed, including deregulated responses to various stress factors resulting in excessive activation of matrix metalloproteinases (MMPs) [22], decreased nitric oxide production and release of reactive oxygen species (ROS) as well as neurohumoral activation leading to altered intracellular calcium handling [23], apoptosis, and cardiac fibrosis [24].

Nitric oxide (NO), produced by endothelial NO synthase (eNOS), plays a central role not only in the physiology of vascular endothelial function but also in protecting against hypertension and hypertension induced cardiac injury [25]. NO exerts antihypertrophic effect [26] and both NO administration and endogenous NO production prevent cardiac hypertrophy [27, 28]. This is supported by animal models where selective decreases in eNOS cardiac protein result in cardiac hypertrophy [29, 30] and heart failure [31] and by transgenic mice models where overexpression of eNOS protein protects against cardiac hypertrophy [32, 33]. Similarly, in the hypertrophic model of rats, chronic administration of exogenous NO donor restored cardiac eNOS protein level and prevented the progression to maladaptive cardiac remodeling [34]. Human studies have demonstrated variable levels of eNOS in failing hearts [35, 36] and that eNOS expression and activity increases in response to various therapies in patients with heart failure

Table 3 Pearson correlation analysis in the entire population

	DBP	LVEDD	RWT	EF	LVMASS	MASSBSA	LVIDBSA
SBP							
Pearson correlation	0.703	−0.005	0.185	0.216	0.201	0.179	−0.054
Sig. (2-tailed)	0.000	0.965	0.096	0.051	0.070	0.108	0.631
N	82	32	82	82	82	82	82
DBP							
Pearson correlation		0.193	0.096	−0.078	0.397	0.316	0.000
Sig. (2-tailed)		0.032	0.390	0.488	0.000	0.004	0.999
N		32	82	32	82	82	82
LVEDD							
Pearson correlation			−0.692	−0.515	0.693	0.656	0.767
Sig. (2-tailed)			0.000	0.000	0.000	0.000	0.000
N			92	92	92	92	92
RWT							
Pearson correlation				0.372	−0.007	−0.008	−0.574
Sig. (2-tailed)				0.000	0.95D	0.938	0.000
N				92	92	92	92
EF							
Pearson correlation					−0.329	−0.287	−0.389
Sig. (2-tailed)					0.001	0.006	0.000
N					92	92	92
LVMASS							
Pearson correlation						0.927	0.465
Sig. (2-tailed)						0.000	0.000
N						92	92
MASSBSA							
Pearson correlation							0.673
Sig. (2-tailed)							0.000

[37]. NOS, however has multiple isoforms that localize to separate compartments within the myocytes causing differing and often opposing effects. For example nitric oxide synthase 1 (NOS1) located on the sarcoplasmic reticulum (SR) [38] upregulates cardiomyocyte sarcoplasmic reticulum Ca^{2+} (SR Ca^{2+}) influx and excitation–contraction coupling [39, 40]. NOS1 expression and activity are significantly increased in the failing animal [41] and human hearts [42]. NOS1 overexpression in transgenic mice is associated with cardiac hypertrophy, increased LV dilation and decreased LV ejection fraction in some models and preserved LV function in other [43, 44]. Similarly, conflicting observations have been made in transgenic models of inducible NOS (iNOS) [35, 45, 46]. The relative contributions of these various isoforms of NOS have not been definitively ascertained in humans with HF. It is possible that dysregulation of NOS1, iNOS, or eNOS might play a role in differential manifestation of HF in patients with hypertension and may be a useful target to prevent adverse LV remodeling in the presence of hypertension.

Increased numbers of African Americans with HF have diminished release of nitric oxide (NO), increased inactivation of NO caused by increased oxidant stress [47], and impaired antioxidant defenses [48]. There is diminished response to sodium nitroprusside infusion in African Americans compared to Whites ($p < 0.001$) [49]. Nitrates, as NO donors when combined with hydralazine (vasodilator), appear to enhance NO bioavailability and in a retrospective analysis of HF mortality in the vasodilator-heart failure trials (V-HeFT) I and II, Carson et al. [50] demonstrated potential differences in response to NO therapy in African Americans vs. Whites. The V-HeFT I study demonstrated improved survival in African Americans with heart failure treated with isosorbide dinitrate-hydralazine vs. placebo ($p < 0.004$). Thus NO deficiency may be an important contributor for HF in African Americans and NO enhancement a beneficial therapy.

Interstitial changes in the extracellular matrix (ECM) contribute to cardiac remodeling and the development of

heart failure, however the mechanisms are only partially understood [51]. Increased collagen synthesis by different signaling molecules cause fibrosis [52] and may play a key role in the remodeling process in response to hypertension. Metalloproteinase (MMPs), which are inhibited by tissue inhibitors of matrix metalloproteinases (TIMPs) break down collagen. Of the many isoforms, MMP 9 [53] and TIMPs 1 and 2 [22] are found to play important role in humans. Disequilibrium between MMPs and TIMPs resulting in increased metalloproteinase activity, leads to increased degeneration of collagen crosslinks causing ventricular dilatation [54, 55]. Acute pressure overload in animals is associated with increased myocardial MMP expression [56] and activity [57]. MMP 9-gene inactivation or TIMP 1-gene overexpression in mice significantly reduces hypertrophic growth of cardiomyocytes and prevents dilatation during acute LV pressure overload [58]. Results from human studies support this hypothesis with increased plasma levels of MMP 9 in patients with dilated cardiomyopathy [62]. In a subset of patients from the Framingham Heart Study, plasma levels of TIMP 1 are positively associated with left ventricular mass and increased plasma levels of MMP 9 is associated with left ventricular dilation [53]. TIMPs also have cell growth-promoting, antiapoptotic, and steroidogenic activities [59, 60] that seem to be independent of MMP inhibition. Thus structural changes that occur within the myocardial ECM affect overall structure and function of the myocardium. Further work is required to elucidate the role of the MMP and TIMP in response to hypertension in humans, particularly African Americans. It might be reasonable to speculate that African Americans with concentric hypertrophy may have higher expression of TIMP and those with eccentric hypertrophy may have higher expression of MMP.

Our normal LVEF HF patients were predominately women. Prior studies have also shown that patients with normal LVEF HF are more likely to be female with a history of HTN and elevated LV mass [61]. Gender differences have been demonstrated to affect cardiac remodeling. When confronted with pressure overload, the LV hypertrophies more and dilates less in women than in men [62]. A reduced rate of myocyte loss in women and transcriptional regulation by estrogens of genes implicated in cardiac hypertrophy may contribute to persistent gender related differences in cardiac remodeling [63–65].

These observations from animal and human studies suggest that dysregulated responses to stress factors may trigger variable activation of different signaling pathways, which might determine whether the resultant hypertrophy is concentric, or LV dilatation with adverse remodeling. It seems plausible that genetic factors and gender determine the preponderance of activation of one or several pathways over others. Studies to dissect signaling pathways of hypertrophy might lead to the development of novel therapeutic strategies to prevent or reverse cardiac remodeling and heart failure in African Americans.

5 Study Limitations

This study examined patients who were hospitalized for volume overload decompensated left HF and may not reflect the full pathophysiology in an ambulatory population. This is not a controlled longitudinal study. However, we believe that it is significantly hypothesis generating since it identifies a relatively homogenous population: African American, hypertensive with similar co-morbidities treated predominantly in our institution in Newark, NJ. While the influence of differing medical regiments, duration of treatment and compliance cannot be excluded as contributory to the observed differences in remodeling that we note, we believe that this is not significantly likely since these patients are predominantly treated at our institution and are from the surrounding community. Nonetheless we have begun a longitudinal assessment of our patient population. Duration of HTN was determined by first documentation in the medical record or the patient's recollection of first diagnosis. Our observations were made in African–American patients admitted with volume overload acute decompensated heart failure in the absence of ischemic heart disease and are not generalizable to other racial or clinical populations.

6 Conclusions

In a consecutive cohort of hypertensive African American patients hospitalized for volume overload decompensated left heart failure, those with eccentric hypertrophy and reduced LVEF were younger, male and had a shorter duration of hypertension as compared with those with concentric hypertrophy and normal LVEF.

These findings appear to be in contrast to the classic paradigm of hypertensive heart disease where sequential evolution from concentric to eccentric hypertrophy is described and suggests that genetics and gender may play an important role in determining the individual's response of concentric vs. eccentric hypertrophy.

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Conflict of interest Authors have no conflict of interest.

References

1. Yancy CW. Heart failure in African Americans: a cardiovascular enigma. J Card Fail. 2000;6(3):183–6.
2. A trial of the beta-blocker bucindolol in patients with advanced chronic heart failure. N Engl J Med. 2001;344(22):1659–1667.
3. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF). Lancet. 1999;353(9169):2001–2007.
4. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. The SOLVD Investigators. N Engl J Med. 1991;325(5):293–302.
5. Packer M, Bristow MR, Cohn JN, Colucci WS, Fowler MB, Gilbert EM, Shusterman NH. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. U.S. Carvedilol Heart Failure Study Group. N Engl J Med. 1996;334(21):1349–55.
6. Cohn JN, Archibald DG, Ziesche S, Franciosa JA, Harston WE, Tristani FE, et al. Effect of vasodilator therapy on mortality in chronic congestive heart failure. Results of a Veterans Administration Cooperative Study. N Engl J Med. 1986;314(24):1547–52.
7. Cohn JN, Johnson G, Ziesche S, Cobb F, Francis G, Tristani F, et al. A comparison of enalapril with hydralazine-isosorbide dinitrate in the treatment of chronic congestive heart failure. N Engl J Med. 1991;325(5):303–10.
8. Drazner MH, Dries DL, Peshock RM, Cooper RS, Klassen C, Kazi F, et al. Left ventricular hypertrophy is more prevalent in blacks than whites in the general population: the Dallas Heart Study. Hypertension. 2005;46(1):124–9.
9. Pfeffer JM, Pfeffer MA, Mirsky I, Braunwald E. Regression of left ventricular hypertrophy and prevention of left ventricular dysfunction by captopril in the spontaneously hypertensive rat. Proc Natl Acad Sci USA. 1982;79(10):3310–4.
10. Litwin SE, Katz SE, Weinberg EO, Lorell BH, Aurigemma GP, Douglas PS. Serial echocardiographic-Doppler assessment of left ventricular geometry and function in rats with pressure-overload hypertrophy. Chronic angiotensin-converting enzyme inhibition attenuates the transition to heart failure. Circulation. 1995;91(10):2642–54.
11. Molkentin JD, Lu JR, Antos CL, Markham B, Richardson J, Robbins J, et al. A calcineurin-dependent transcriptional pathway for cardiac hypertrophy. Cell. 1998;93(2):215–28.
12. Libby P, Bonow RO, Mann DL, Zipes DP, Braunwald E. Heart disease a textbook of cardiovascular medicine. In: Fedfield MM, editor. Heart failure with normal ejection fraction. Philadelphia: Saunders Elsevier; 2008. p. 641–56.
13. Schiller NB, Shah PM, Crawford M, DeMaria A, Devereux R, Feigenbaum H, et al. Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. American Society of Echocardiography Committee on Standards, Subcommittee on Quantitation of Two-Dimensional Echocardiograms. J Am Soc Echocardiogr. 1989;2(5):358–67.
14. Devereux RB, Pini R, Aurigemma GP, Roman MJ. Measurement of left ventricular mass: methodology and expertise. J Hypertens. 1997;15(8):801–9.
15. Cooper JW, Nanda NC, Philpot EF, Fan P. Evaluation of valvular regurgitation by color Doppler. J Am Soc Echocardiogr. 1989;2(1):56–66.
16. Casale PN, Devereux RB, Milner M, Zullo G, Harshfield GA, Pickering TG, Laragh JH. Value of echocardiographic measurement of left ventricular mass in predicting cardiovascular morbid events in hypertensive men. Ann Intern Med. 1986;105(2):173–8.
17. Ghali JK, Liao Y, Simmons B, Castaner A, Cao G, Cooper RS. The rognostic role of left ventricular hypertrophy in patients with or without coronary artery disease. Ann Intern Med. 1992;117(10):831–6.
18. Levy D, Garrison RJ, Savage DD, Kannel WB, Castelli WP. Prognostic implications of echocardiographically determined left ventricular mass in the Framingham Heart Study. N Engl J Med. 1990;322(22):1561–6.
19. Grossman W, Jones D, McLaurin LP. Wall stress and patterns of hypertrophy in the human left ventricle. J Clin Invest. 1975;56(1):56–64.
20. Katz AM. Cardiomyopathy of overload. A major determinant of prognosis in congestive heart failure. N Engl J Med. 1990;322(2):100–10.
21. Opie LH, Commerford PJ, Gersh BJ, Pfeffer MA. Controversies in ventricular remodelling. Lancet. 2006;367(9507):356–67.
22. Heymans S, Schroen B, Vermeersch P, Milting H, Gao F, Kassner A, et al. Increased cardiac expression of tissue inhibitor of metalloproteinase-1 and tissue inhibitor of metalloproteinase-2 is related to cardiac fibrosis and dysfunction in the chronic pressure-overloaded human heart. Circulation. 2005;112(8):1136–44.
23. Yano M, Ikeda Y, Matsuzaki M. Altered intracellular Ca^{2+} handling in heart failure. J Clin Invest. 2005;115(3):556–64.
24. Johar S, Cave AC, Narayanapanicker A, Grieve DJ, Shah AM. Aldosterone mediates angiotensin II-induced interstitial cardiac fibrosis via a Nox2-containing NADPH oxidase. FASEB J. 2006;20(9):1546–8.
25. Bredt DS, Snyder SH. Nitric oxide: a physiologic messenger molecule. Annu Rev Biochem. 1994;63:175–95.
26. Kempf T, Wollert KC. Nitric oxide and the enigma of cardiac hypertrophy. Bioessays. 2004;26(6):608–15.
27. Calderone A, Thaik CM, Takahashi N, Chang DL, Colucci WS. Nitric oxide, atrial natriuretic peptide, and cyclic GMP inhibit the growth-promoting effects of norepinephrine in cardiac myocytes and fibroblasts. J Clin Invest. 1998;101(4):812–8.
28. Cheng TH, Shih NL, Chen SY, Lin JW, Chen YL, Chen CH, et al. Nitric oxide inhibits endothelin-1-induced cardiomyocyte hypertrophy through cGMP-mediated suppression of extracellular-signal regulated kinase phosphorylation. Mol Pharmacol. 2005;68(4):1183–92.
29. Grieve DJ, MacCarthy PA, Gall NP, Cave AC, Shah AM. Divergent biological actions of coronary endothelial nitric oxide during progression of cardiac hypertrophy. Hypertension. 2001;38(2):267–73.
30. Piech A, Dessy C, Havaux X, Feron O, Balligand JL. Differential regulation of nitric oxide synthases and their allosteric regulators in heart and vessels of hypertensive rats. Cardiovasc Res. 2003;57(2):456–67.
31. Paulus WJ. The role of nitric oxide in the failing heart. Heart Fail Rev. 2001;6(2):105–18.
32. Janssens S, Pokreisz P, Schoonjans L, Pellens M, Vermeersch P, Tjwa M, et al. Cardiomyocyte-specific overexpression of nitric oxide synthase 3 improves left ventricular performance and reduces compensatory hypertrophy after myocardial infarction. Circ Res. 2004;94(9):1256–62.
33. Ruetten H, Dimmeler S, Gehring D, Ihling C, Zeiher AM. Concentric left ventricular remodeling in endothelial nitric oxide synthase knockout mice by chronic pressure overload. Cardiovasc Res. 2005;66(3):444–53.
34. Ruiz-Hurtado G, Fernandez-Velasco M, Mourelle M, Delgado C. LA419, a novel nitric oxide donor, prevents pathological cardiac remodeling in pressure-overloaded rats via endothelial nitric oxide synthase pathway regulation. Hypertension. 2007;50(6):1049–56.
35. Drexler H, Kastner S, Strobel A, Studer R, Brodde OE, Hasenfuss G. Expression, activity and functional significance of inducible

nitric oxide synthase in the failing human heart. J Am Coll Cardiol. 1998;32(4):955–63.
36. Ennezat PV, Van Belle E, Asseman P, Cohen-Solal A, Evans T, Lejemtel TH. Steady endothelial nitric oxide synthase expression in heart failure. Acta Cardiol. 2007;62(3):265–8.
37. Morawietz H, Rohrbach S, Rueckschloss U, Schellenberger E, Hakim K, Zerkowski HR, et al. Increased cardiac endothelial nitric oxide synthase expression in patients taking angiotensin-converting enzyme inhibitor therapy. Eur J Clin Invest. 2006;36(10):705–12.
38. Xu KY, Huso DL, Dawson TM, Bredt DS, Becker LC. Nitric oxide synthase in cardiac sarcoplasmic reticulum. Proc Natl Acad Sci USA. 1999;96(2):657–62.
39. Barouch LA, Harrison RW, Skaf MW, Rosas GO, Cappola TP, Kobeissi ZA, et al. Nitric oxide regulates the heart by spatial confinement of nitric oxide synthase isoforms. Nature. 2002;416(6878):337–9.
40. Khan SA, Skaf MW, Harrison RW, Lee K, Minhas KM, Kumar A, et al. Nitric oxide regulation of myocardial contractility and calcium cycling: independent impact of neuronal and endothelial nitric oxide synthases. Circ Res. 2003;92(12):1322–9.
41. Bendall JK, Damy T, Ratajczak P, Loyer X, Monceau V, Marty I, et al. Role of myocardial neuronal nitric oxide synthase-derived nitric oxide in beta-adrenergic hyporesponsiveness after myocardial infarction-induced heart failure in rat. Circulation. 2004;110(16):2368–75.
42. Damy T, Ratajczak P, Shah AM, Camors E, Marty I, Hasenfuss G, et al. Increased neuronal nitric oxide synthase-derived NO production in the failing human heart. Lancet. 2004;363(9418):1365–7.
43. Burkard N, Rokita AG, Kaufmann SG, Hallhuber M, Wu R, Hu K, et al. Conditional neuronal nitric oxide synthase overexpression impairs myocardial contractility. Circ Res. 2007;100(3):e32–44.
44. Loyer X, Gomez AM, Milliez P, Fernandez-Valasco M, Vangheluwe P, Vinet L, et al. Cardiomyocyte overexpression of neuronal nitric oxide synthase delays transition toward heart failure in response to pressure overload by preserving calcium cycling. Circulation. 2008;117(25):3187–98.
45. Fukuchi M, Hussain SN, Giaid A. Heterogeneous expression and activity of endothelial and inducible nitric oxide synthases in end-stage human heart failure: their relation to lesion site and beta-adrenergic receptor therapy. Circulation. 1998;98(2):132–9.
46. Patten RD, Denofrio D, El-Zaru M, Kakkar R, Saunders J, Celestin F, et al. Ventricular assist device therapy normalizes inducible nitric oxide synthase expression and reduces cardiomyocyte apoptosis in the failing human heart. J Am Coll Cardiol. 2005;45(9):1419–24.
47. Kalinowski L, Dobrucki IT, Malinski T. Race-specific differences in endothelial function: predisposition of African Americans to vascular diseases. Circulation. 2004;109(21):2511–7.
48. Ferdinand KC. African American heart failure trial: role of endothelial dysfunction and heart failure in African Americans. Am J Cardiol. 2007;99(6B):3D–6D.
49. Cardillo C, Kilcoyne CM, Cannon RO 3rd, Panza JA. Racial differences in nitric oxide-mediated vasodilator response to mental stress in the forearm circulation. Hypertension. 1998;31(6):1235–9.
50. Carson P, Ziesche S, Johnson G, Cohn JN. Racial differences in response to therapy for heart failure: analysis of the vasodilator-heart failure trials. Vasodilator-Heart Failure Trial Study Group. J Card Fail. 1999;5(3):178–87.
51. Mann DL, Bristow MR. Mechanisms and models in heart failure: the biomechanical model and beyond. Circulation. 2005;111(21):2837–49.
52. Mann DL. Stress-activated cytokines and the heart: from adaptation to maladaptation. Annu Rev Physiol. 2003;65:81–101.
53. Sundstrom J, Evans JC, Benjamin EJ, Levy D, Larson MG, Sawyer DB, et al. Relations of plasma matrix metalloproteinase-9 to clinical cardiovascular risk factors and echocardiographic left ventricular measures: the Framingham Heart Study. Circulation. 2004;109(23):2850–6.
54. Bradham WS, Bozkurt B, Gunasinghe H, Mann D, Spinale FG. Tumor necrosis factor-alpha and myocardial remodeling in progression of heart failure: a current perspective. Cardiovasc Res. 2002;53(4):822–30.
55. Polyakova V, Hein S, Kostin S, Ziegelhoeffer T, Schaper J. Matrix metalloproteinases and their tissue inhibitors in pressure-overloaded human myocardium during heart failure progression. J Am Coll Cardiol. 2004;44(8):1609–18.
56. Schubert A, Walther T, Falk V, Binner C, Loscher N, Kanev A, et al. Extracellular matrix gene expression correlates to left ventricular mass index after surgical induction of left ventricular hypertrophy. Basic Res Cardiol. 2001;96(4):381–7.
57. Nagatomo Y, Carabello BA, Coker ML, McDermott PJ, Nemoto S, Hamawaki M, Spinale FG. Differential effects of pressure or volume overload on myocardial MMP levels and inhibitory control. Am J Physiol Heart Circ Physiol. 2000;278(1):H151–61.
58. Heymans S, Lupu F, Terclavers S, Vanwetswinkel B, Herbert JM, Baker A, et al. Loss or inhibition of uPA or MMP-9 attenuates LV remodeling and dysfunction after acute pressure overload in mice. Am J Pathol. 2005;166(1):15–25.
59. Visse R, Nagase H. Matrix metalloproteinases and tissue inhibitors of metalloproteinases: structure, function, and biochemistry. Circ Res. 2003;92(8):827–39.
60. Lambert E, Dasse E, Haye B, Petitfrere E. TIMPs as multifacial proteins. Crit Rev Oncol Hematol. 2004;49(3):187–98.
61. Klapholz M, Maurer M, Lowe AM, Messineo F, Meisner JS, Mitchell J, 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(8):1432–8.
62. Douglas PS, Katz SE, Weinberg EO, Chen MH, Bishop SP, Lorell BH. Hypertrophic remodeling: gender differences in the early response to left ventricular pressure overload. J Am Coll Cardiol. 1998;32(4):1118–25.
63. Pernenkil R, Vinson JM, Shah AS, Beckham V, Wittenberg C, Rich MW. Course and prognosis in patients > or =70 years of age with congestive heart failure and normal versus abnormal left ventricular ejection fraction. Am J Cardiol. 1997;79(2):216–9.
64. Sugden PH, Clerk A. Akt like a woman: gender differences in susceptibility to cardiovascular disease. Circ Res. 2001;88(10):975–7.
65. Olivetti G, Giordano G, Corradi D, Melissari M, Lagrasta C, Gambert SR, Anversa P. Gender differences and aging: effects on the human heart. J Am Coll Cardiol. 1995;26(4):1068–79.