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

Pallavi Solanki · Ramzan M. Zakir · Rajiv J. Patel · Sri-Ram Pentakota · James Maher · Christine Gerula · Muhamed Saric · Edo Kaluski · Marc Klapholz

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 ≥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 (≥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 ≤1.5 cm², 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 + LVESD)² - LVEDD] + 0.6 (ASE formula/Devereux correction) and indexed to height²/7 (meters) [14]. Normal LV mass is 49.2 and 46.7 g/m² in males and females respectively. Relative wall thickness (RWT) was calculated as 2 × 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 ± 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, Cary, North Carolina).

3 Results

One hundred and twenty five consecutive patients were enrolled, 60 who had normal LVEF (≥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 ± 10 %) vs. those with reduced LVEF (23.1 ± 7 %) HF were significantly older (66 ± 14 vs. 62.0 ± 12 years; p < 0.04) female (68 vs. 38 %; p < 0.001) with longer duration of HTN (20 ± 6 vs. 12 ± 8 years; p < 0.001) and a higher systolic blood pressure on admission (157 ± 33 vs. 144 ± 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 ± 29.0 vs. 68.1 ± 31 g/m² p < 0.003). Left ventricular end diastolic dimension (LVEDD) was significantly greater in the reduced LVEF vs. the normal LVEF HF group (6.09 ± 0.9 vs. 4.90 ± 0.9 cm;
Table 1  Clinical and echocardiographic data

<table>
<thead>
<tr>
<th></th>
<th>Normal LVEF HF (n = 60)</th>
<th>Reduced LVEF HF (n = 65)</th>
<th>p-value</th>
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<tr>
<td>Age (years)</td>
<td>66 ± 14</td>
<td>62.0 ± 12</td>
<td>0.04</td>
</tr>
<tr>
<td>Sex (female)</td>
<td>68% (41/60)</td>
<td>38% (25/65)</td>
<td>0.001</td>
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<td>Serum creatinine (mg/dl)</td>
<td>1.3 ± 0.9</td>
<td>1.2 ± 0.1</td>
<td>NS</td>
</tr>
<tr>
<td>Duration of hypertension (years)</td>
<td>20 ± 6</td>
<td>12 ± 8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean SBP at admission (mmHg)</td>
<td>157 ± 33</td>
<td>144 ± 26</td>
<td>0.04</td>
</tr>
<tr>
<td>Mean DBP at admission (mmHg)</td>
<td>86 ± 23</td>
<td>86 ± 20</td>
<td>NS</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>65.2 ± 10</td>
<td>23.1 ± 7</td>
<td>&lt;0.001</td>
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<tr>
<td>LV septal thickness (cm)</td>
<td>1.30 ± 0.3</td>
<td>1.31 ± 0.3</td>
<td>NS</td>
</tr>
<tr>
<td>LV posterior wall thickness (cm)</td>
<td>1.27 ± 0.2</td>
<td>1.28 ± 0.3</td>
<td>NS</td>
</tr>
<tr>
<td>LVEDD (cm)</td>
<td>4.90 ± 0.9</td>
<td>6.09 ± 0.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Relative wall thickness</td>
<td>0.55 ± 0.14</td>
<td>0.43 ± 0.12</td>
<td>&lt;0.001</td>
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<tr>
<td>LV mass (g/m²²)</td>
<td>68.11 ± 31</td>
<td>88.0 ± 29.0</td>
<td>&lt;0.003</td>
</tr>
</tbody>
</table>

* Normal LV mass = 49.2 and 46.7 g/m²² 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

Hypertension in African Americans with Heart Failure

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 dilatation 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.

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 dilatation 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...
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 mal-adaptive 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 2 Logistic regression analysis for prediction of high LV mass/BSA

<table>
<thead>
<tr>
<th>Variables in the Equation</th>
<th>B</th>
<th>S.E</th>
<th>Wald</th>
<th>df</th>
<th>Sig.</th>
<th>Exp(B)</th>
<th>95% C.I.for EXP(B)</th>
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<td>.536</td>
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<td>.862</td>
<td>1.126</td>
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<tr>
<td>DM(1)</td>
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<td>.095</td>
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<td>.757</td>
<td>.785</td>
<td>.169 3.646</td>
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<td>.672</td>
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<td>.974</td>
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<td>1.149</td>
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<td>1</td>
<td>.021</td>
<td>5.916</td>
<td>.130 26.723</td>
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</table>

**Constant**               | 1.993| 1.552| 1.650| 1  | .199 | 7.339  |                     |

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

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

<table>
<thead>
<tr>
<th>Variables in the Equation</th>
<th>B</th>
<th>S.E</th>
<th>Wald</th>
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<td>1</td>
<td>.006</td>
<td>17.939</td>
<td>2.296 140.176</td>
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**Constant**               | -.749| 1.937| 1.149| 1  | .699 | 473    |                     |

**Low EF Step 1**          |      |      |      |    |      |        |                     |

| Age                      | -.029| .076 | .146 | 1  | .702 | .971   | .837 1.127          |
| HLD(1)                   | -.1683| 8069.021| .000 | 1  | .998 | .000   | .000 0.00          |
| DM(1)                    | -.978| 1.722| .323 | 1  | .570 | .376   | .013 10.996         |
| Smoke(1)                 | 16.502| 7922.170| .000 | 1  | .998 | 15.997623.18 | .000 0.00          |
| CKD(1)                   | .157 | 1.714| .009 | 1  | .922 | 1.182  | .041 33.981         |
| Sex(1)                   | 17.954| 7953.754| .000 | 1  | .998 | 62700766.12| .000 0.00          |

**Constant**               | 20.498| 8069.022| .000 | 1  | .998 | 798426120.1  |                     |

* a. Variable(s) entered on step 1: Age, HLD, DM, Smoke, CKD, Sex.
[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\textsuperscript{2+} (SR Ca\textsuperscript{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
Remodeling. It seems plausible that genetic factors and hypertrophy is concentric, or LV dilatation with adverse ways, which might determine whether the resultant trigger variable activation of different signaling pathways 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 MMPs and TIMPs 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 regimens, 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.

Acknowledgments None.

Conflict of interest Authors have no conflict of interest.
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