Review: Heart Failure with Preserved Ejection Fraction in African Americans

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Heart failure (HF) affects 5,700 000 people in the United States, with heart failure with preserved ejection fraction (HFPEF) being responsible for between 30%–50% of acute admissions. Epidemiological studies and HF registries have found HFPEF patients to be older, hypertensive and to have a history of atrial fibrillation. These findings, however, may not be fully applicable to African Americans, as they have been poorly studied making up only a minority of the test subjects. This review article is intended to discuss the pathophysiology and epidemiology of HFPEF within African Americans, highlight the differences compared to Caucasian populations and review current treatment guidelines. Studies looking at African Americans in particular have shown them to be younger, female and have worse diastolic dysfunction compared to Caucasian populations. African Americans also have been shown to have a worse mortality outcome especially in patients without coronary artery disease. The treatment of HFPEF is primarily symptomatic with no survival benefit seen in randomized controlled trials. Mechanisms postulated for the worse prognosis in African Americans with HFPEF include: greater incidence of hypertension and diastolic dysfunction, undefined race-driven genetic predispositions or relative resistance to medications that treat HF in general. The biological predispositions may also be compounded by inequality of healthcare access; something still felt to exist today. Prospective studies and randomized controlled trials need to be conducted with particular emphasis on African American populations to fully elucidate this disease and to formulate race specific treatment outcomes for the future. (*Ethn Dis*. 2012;22[4]:432–438)

Key Words: African Americans, Heart Failure, Diastolic Heart Failure, Heart Failure with Preserved Ejection Fraction, Diastolic Dysfunction

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Introduction

Heart failure (HF) affects 5,700,000 people in the United States, with an annual incidence of about 6 per 1000 person-years for Caucasians and 9.1 per 1000 person-years for African Americans.[1] Heart failure with preserved ejection fraction (HFPEF), also known as diastolic heart failure, is a clinical syndrome in which patients have symptoms and signs of heart failure (HF) but with near normal left ventricular ejection fraction and evidence of diastolic dysfunction. Of patients admitted to hospital with clinical heart failure, 30%–50% have evidence of HFPEF.[2] Epidemiological studies and HF registries comparing HFPEF with heart failure with reduced ejection fraction (HFREF) have provided key insights into the etiology of the disease; however these studies comprise mainly Caucasians, thus casting doubt on the applicability of the results to African Americans.[2,3] Evidence exists indicating that African Americans have a greater incidence of hypertension and diastolic dysfunction compared to matched Caucasians, both of which may correlate to differences in etiology and clinical outcomes in HFPEF.[4,5] This review discusses the pathophysiology and epidemiology of HFPEF within African Americans, highlights the differences compared to Caucasian populations, and reviews current treatment guidelines.

Pathophysiology and Clinical Presentation

The pathophysiology behind HFPEF involves progressive hypertrophy and fibrosis of the left ventricle due to increases in afterload. This results in impaired left ventricular relaxation and reduced left ventricular compliance, termed diastolic dysfunction. Overtime this process can result in reduced ventricular volumes with increased left ventricular and atrial pressures.[6] Reduced cardiac output, activation of neuro-humoral systems, and increased backwards pressure present clinically as fatigue, exercise intolerance and dyspnea.[7] The signs and symptoms of HFPEF are often difficult to distinguish from those of HFREF (Table 1), thus imaging is needed to aid diagnosis. The Echocardiography and Heart Failure Associations of the European Society of Cardiology established guidelines for diagnosis of HFPEF in 2007.[8] Diagnosis can be made with the presence of three important clinical features: 1) signs or symptoms of HF; 2) evidence of normal or mildly abnormal LV systolic function with echo evidence of EF>50% and reduced LV end-diastolic volume index (<97 mL/m^2); and 3) evidence of abnormal LV diastolic dysfunction seen by Doppler ($E/e' > 15$).[8]

African Americans and Ventricular Dysfunction

Hypertension has been shown to be more common among African Americans

This review discusses the pathophysiology and epidemiology of HFPEF within African Americans, highlights the differences compared to Caucasian populations, and reviews current treatment guidelines.

Table 1. Prevalence of specific symptoms and signs in systolic vs diastolic HF. Data shown are percentage of patients in each group with the corresponding signs and symptoms. Adapted from Zile et al[34]

	Diastolic Heart Failure (EF>50%)	Systolic Heart Failure (EF<50%)
Symptoms		
Dyspnea on exertion	85	96
Paroxysmal nocturnal dyspnea	55	50
Orthopnea	60	73
Physical examination		
Jugular venous distension	35	46
Rales	72	70
Displaced apical impulse	50	60
S_3	45	65
S_4	45	66
Hepatomegaly	15	16
Edema	30	40
Chest radiograph		
Cardiomegaly	90	96
Pulmonary venous hypertension	75	80

with a greater mortality and morbidity when compared with Caucasians.[5] This propensity for hypertension is thought to be the main mechanism behind the greater diastolic dysfunction[9]; however studies indicate that other factors may also play a role. Sharp et al looked at 449 White and 60 Afro-Caribbean participants from a single center participating in the ASCOT (Anglo-Scandinavian Cardiac Outcomes Trial). Patients had hypertension but no evidence of heart failure. Left ventricular structure and function was measured using tissue Doppler echocardiography. Results showed that after controlling for confounding variables (age, sex, systolic blood pressure, pulse pressure, cholesterol, smoking, ejection fraction, left ventricular mass index, and diabetes mellitus), Black populations in the study had a greater degree of diastolic impairment than Caucasian Europeans (measured by tissue Doppler; E/e′: 8.89 vs. 7.93, $P<.003$).[4] Kizer et al looked at 1060 African American and 580 Caucasian hypertensive patients in a population-based cohort study. Using echocardiogram, it was found that after controlling for confounding variables (age, sex, body mass index, diabetes mellitus, mean arterial pressure, duration of hypertension, and antihypertensive treatment) African American participants had a higher left ventricular mass (173.9 vs 168.3 grams, $P<.006$), relative wall thickness (.355 vs .340 grams, $P<.001$) and incidence of left ventricular hypertrophy when compared to Caucasians.[10] It is clear that hypertension is more common in African Americans and contributes to greater diastolic dysfunction; however, other variables beyond just hypertension may also play a role. Potential mechanisms postulated include poor access to health care with longer duration of undetected hypertension,[11] greater vascular reactivity,[12] or race-driven genetic predispositions.[4]

SEARCH STRATEGY FOR CLINICAL REVIEW

The studies included in this clinical review were obtained through a MEDLINE and PUBMED search using key words: heart failure, left ventricle, preserved, diastolic dysfunction, ejection fraction, African American, Black, race and ethnicity. The time period for the search was from the inception of the searched databases to 31 December 2011. Several online databases were electronically searched and hand searching of reference lists of obtained articles and previously identified reviews was carried out. Abstracts, unpublished studies and articles published in languages other than English were excluded. For inclusion, studies were required to measure EF in patients and distinguish patients according to type of HF (ie, HFPEF and HF reduced EF).

EPIDEMIOLOGY OF HFPEF IN CAUCASIANS AND AFRICAN AMERICAN POPULATIONS

Large HF registries and epidemiological studies, such as OPTIMIZE[3] and ADHERE[2] have provided much information about the demographics, co-morbidities and outcomes in patients with HFPEF. In general, patients admitted to hospital with HF and found to have HFPEF, in comparison to those with HFREF, are older, female, have a history of hypertension and atrial fibrillation, and less likely to have coronary artery disease (Table 2).[13] Less consistent associations, which may reflect an older population with HFPEF include worse renal function, chronic renal diseases and anemia.[13,14] From the literature search we conducted, many of the studies did not include African Americans in their cohort, or if they did, failed to undertake sub-group analysis. This makes many of the conclusions detailed above less applicable to African Americans (Table 3). Of the studies that did include race subgroup analysis, African Americans hospitalized with HF were more likely to have HFREF than HFPEF, however further comments were not made. In a specific study looking at an African American population, Ilksoy et al conducted a retrospective chart review of 89 patients admitted to an urban teaching hospital with diagnoses of HF. In their study 30% of patients admitted were diagnosed with HFPEF, and they tended to be older and female compared

Table 2. Comparison between preserved and reduced systolic function groups. Adapted from the ADHERE database[2]

Characteristic	Systolic Function		
	Preserved ($n = 26,322$)	Reduced ($n = 25,865$)	*P*
Age, yrs, mean ± SD	73.9 ± 13.2	69.8 ± 14.4	<.0001
Women, %	62	40	<.0001
African American, %	17	22	<.0001
Hypertension, %	77	69	<.0001
CAD, %	50	59	<.0001
Diabetes mellitus, %	45	40	<.0001
Chronic renal insufficiency, %	26	26	.98
History of heart failure, %	63	72	<.0001
Prior myocardial infarction, %	24	36	<.0001
Cardiac valvular disease, %	21	22	.13
Peripheral vascular disease, %	17	17	.33
Ventricular tachycardia, %	3	11	<.0001

to those with HFREF (Table 4).[15] The lower incidence of HFPEF in African Americans is thought to be because by the time of hospitalization, a significant proportion of patients who have HF have already developed significant systolic dysfunction mainly due to a combination of poorly controlled hypertension and renal disease.[16]

COMPARISON OF AFRICAN AMERICANS AND CAUCASIANS WITH HFPEF

Some studies have emerged that compare the demographics and comorbidities of African Americans with HFPEF to Caucasian populations directly. Agoston et al conducted a retrospective comparative analysis of 192 African American and 256 Caucasian patients admitted with HF as part of the Veterans Health Administration health care system. Twenty-seven percent of both the Caucasian and African American groups admitted with HF had HFPEF. The baseline characteristics were similar between the two groups with exception of significantly higher diastolic blood pressures and creatinine, with a lower incidence of coronary artery disease within the African American cohort.[16] East at al conducted a study looking at 2740 White and 563 African American patients with class II to IV symptoms and preserved ejection fraction. Compared with Caucasian patients, African American patients with HFPEF were younger, female, more likely had a history of hypertension and diabetes mellitus but were less likely to have CAD (Table 5).[17] Klaphoz et al[18] looked at 619 patients admitted to hospitals in New York with a diagnosis of HFPEF; African Americans made up 30% of the study population. Results from the study also observed that African Americans were more likely to be younger, had a history of hypertension and worse renal function.

MORBIDITY AND MORTALITY IN CAUCASIANS AND AFRICANS WITH HFPEF

Population studies comprising mainly Caucasian patients with HFPEF have shown mortality rates comparable to HFREF during hospitalization.[19,20] However some studies have, in fact, reported lower mortality in HFPEF compared to HFREF.[2,3,21] Somaratne et al[22] published the largest systematic meta-analysis of mortality in 7,688 HFPEF patients with 16,831 HFREF patients from 17 studies, and noted a 50% lower hazard for mortality in HFPEF compared with HFREF. Possible reasons for this improved mortality include better renal function and lack of persistent hypotension during the hospital course.[2] Despite possible improved mortality, HFPEF continues to have significant morbidity with studies showing similar length of hospitalization, decline in functional status, and rehospitalization compared to HFREF.[23] Again, the majority of these larger studies did not specifically discern if this mortality benefit was seen in African American populations (Table 2). Of the smaller studies, Agoston et al demonstrated that African Americans with HFPEF did have improved mortality compared to HFREF.[16]

COMPARISON OF CAUCASIANS AND AFRICAN AMERICANS WITH HFPEF

Of the studies that included African American populations: OPTIMIZE,[3] ADHERE[2] and Klapholz et al[18] did not specifically mention any mortality differences between the races that were diagnosed with HFREF. Agoston et al demonstrated improved survival in populations with HFPEF, which was not significantly different between races.[16] In contrary to this finding, East et al demonstrated a 34% higher adjusted mortality risk (hazard ratio [HR], 1.34; 95% CI, 1.13–1.60), when comparing survival of African Americans without coronary artery disease with their Caucasian counterparts.[17] This increased mortality was not seen in patients with coronary artery disease. The authors propose that a predisposition to hypertension, greater diastolic dysfunction and resistance to angiotensin converting enzyme inhibitor (ACE) treatment may account for the mortality disparity seen.

TREATMENT

Randomized controlled trials (RCT) involving the use of beta-blockers,[24]

Table 3. Percentage of African Americans within study populations and author comments within recent heart failure studies looking at HFPEF

Study Name and Author	Type HF Studied	HFPEF (*n*)	HFREF (*n*)	% AA with HFPEF	% AA with HFREF	Race Specific Conclusions
ADHERE Yancy et al [2]	acute	26,322	25,865	17	22	Significantly less AA in HFPEF vs HFREF
OPTIMIZE Fonarow et al [3]	acute	20,118	21,149	21	15	Significantly less AA in HFPEF vs HFREF
I-Preserve Trial Massie et al [27]	chronic	4128	n/a	2	n/a	No race specific comparisons made
East et al [17]	acute	3303	n/a	17	n/a	Direct comparison study: AA significantly higher mortality risk especially in non-ischemic disease
Eurofailure Survey Lenzen et al [35]	acute	3148	3658	NI	NI	No comments or comparisons made
Felker et al [14]	chronic	3039	1858	26%	38%	Significantly less AA in HFPEF vs HFREF
CHARM trial Yusuf et al [21]	chronic	3023	n/a	4	n/a	No race specific comparisons made
DIAMOND-CHF Study Gustafsson et al [36]	acute	2218	3022	NI	NI	Nil
SENIORS trial Flather et al [24]	acute	2128	n/a	NI	NI	Nil
Varadarajan et al [37]	acute	970	1287	11	10	No comments or comparisons made
EFFECT Study Bhatia et al [19]	acute	880	1570	NI	n/a	Nil
PEP-CHF trial Cleland et al [25]	acute	850	n/a	NI	n/a	
NYHF registry Klapholz et al [18]	acute	619	Nil	30	Nil	AA with HFPEF: younger, more hypertension, No diff in mortality or length of stay
Philbin et al [38]	acute	550	741	7	3 (non Caucasian)	No comments or comparisons made
Grigorian Shamagian et al [39]	acute	416	n/a	NI	n/a	Nil
Dauterman et al [40]	acute	352	430	14	15	No significant race differences
Rochester Epidemiology Project Bursi et al [41]	acute and chronic	308	248	NI	NI	Nil
Ahmed et al [42]	acute	238	200	14	19	No significant race differences
Framingham Heart Study Lee et al [20]	chronic	220	314	NI	NI	Nil
Parkash et al [43]	acute	220	258	NI	NI	Nil
Cardiovascular Health Study Gottdiener et al [44]	chronic	170	99	19.00%	24%	No significant race differences
UK-HEART Study MacCarthy et al [45]	chronic	163	359	NI	NI	Nil
Kerzner et al [46]	acute	162	211	42 (non White)	50 (non White)	Significantly less AA in HFPEF vs HFREF
Yip et al [47]	chronic	132	43	NI	NI	Nil
Berry et al [48]	acute	130	398	NI	NI	Nil
Agoston et al [16]	acute	120	327	40	44	AA: higher BP, creatine vs white. No mortality difference
Varela-Roman et al [49]	acute	66	163	NI	NI	Nil
Ilksoy et al [15]	acute	26	63	100	100	AA with HFPEF: older and women

NI, not included

ACE inhibitors,[25] and angiotensin receptor blockers (ARB)[21] have failed to show any survival benefit compared to placebo in patients with HFPEF. The ACC/AHA reviewed the evidence and produced guidelines stating that the treatment of HFPEF should revolve around the control of hypertension, control of ventricular rate in patients with atrial fibrillation, the use of diuretics to control pulmonary congestion and peripheral edema and coronary revascularization in patients with coronary heart disease in whom ischemia is judged to have an adverse effect on diastolic function.[26] Some of these trials did, however, demonstrate a significant difference in secondary outcomes compared to placebo. The PEP-CHF (Perindopril for Elderly People with Chronic Heart Failure) showed that treatment with perindopril significantly decreased heart failure hospitalization, improved NYHA classification, and the 6-minute corridor walk distance at 1-year follow-up.[25] The CHARM-Preserved study also demonstrated significant reduction in HF admissions at one year.[21] African American populations were largely under-represented in all of the major RCTs looking at pharmacotherapy in HFPEF, making up only 4% and 2% of study groups in the CHARM-study and I-PRESERVE trials respectively.[21,27] While the SENIORS trial and the PEP-CHF trial did not include race in the demographic analysis at all (Table 3).[24,25]

Even though there is no evidence specifically in HFPEF, inferences may be drawn from RCTs involving HFREF and African American populations. It is well-documented that African American populations differ in their response to various medical therapies in HFREF. Exner et al demonstrated that enalapril therapy is associated with a significant reduction in the risk of hospitalization

Table 4. Baseline clinical characteristics of African American patients with heart failure. Adapted from Ilksoy et al[15]

Characteristic	All HF ($n = 89$)	Systolic Dysfunction ($n = 63$)	Diastolic Dysfunction ($n = 26$)	*P*
Sex				.02
Men	44 (49.4%)	36 (57.1%)	8 (30.8%)	
Women	45 (50.6%)	27 (42.9%)	18 (69.2%)	
Age, yrs				.01
Mean ± SD	60.0 ± 16.1	57.2 ± 14.5	66.9 ± 17.9	
Median	60.5	57.4	70.6	
IQR	49.2–71.9	48.2–66.0	61.9–76.1	
Length of stay, days				.55
Mean ± SD	4.9 ± 3.7	4.8 ± 3.3	4.9 ± 4.6	
Median	4.0	4.0	3.0	
No. of readmissions in past 30 days				.32
0	70	47	23	
1	17	14	3	
No. of readmissions in past year				.11
0	46	28	18	
1	17	15	2	
≥2	24	18	6	

for heart failure among Caucasian patients with left ventricular dysfunction, but not among similar African American patients.[28] Another study, the Beta-Blocker Evaluation of Survival Trial (BEST), found that patients with heart failure who were Caucasian derived greater benefit from beta-blocker therapy compared to matched African American populations.[29] African Americans have also shown race-specific treatment benefits in heart failure. The African American Heart Failure Trial (A-HeFT) showed the risk of death was reduced by 43% in African Americans treated with isosorbide mononitrate and hydralazine (ISMN-H) with a significant reduction in hospitalizations.[30] Proposed mechanisms underlying this disparity include genetic differences resulting in a less active renin–angiotensin system[31] a lower bioavailability of nitric oxide,[32] and polymorphisms in alpha and beta-adrenergic receptors.[33]

Despite the lack of direct evidence, patients are still discharged on an ACE/ARB, calcium channel blocker or BB following acute admission with HFPEF, and this does not significantly differ between Caucasians and African Americans.[15,16] Thus, it could be hypothesized that the drug resistance mechanisms may also contribute to the greater diastolic dysfunction and worse clinical outcomes experienced by African Americans in HFPEF. To date, there have been no studies looking specifically at the treatment of HFPEF in African Americans. However, as with the A-HeFT trial in HF with reduced EF, studies looking specifically at treatment within African Americans need to be conducted to allow better understanding and create more appropriate race specific treatment guidelines.

Table 5. Baseline characteristics of the study populations: Adapted from East et al[17]

Variables[a]	African American (n=563)	White (n=2740)	*P*
Female	71	52	<.01
Age, y	58	65	<.01
Hypertension	73	55	<.01
Diabetes	32	24	<.01
Hyperlipidemia	17	22	.02
Peripheral vascular disease	12	15	.03
Cerebral vascular disease	9	9	.98
NYHA class IV	19	18	.52
Valvular heart disease	13	11	.12
Moderate mitral regurgitation	12	14	.37
Previous AMI	19	27	<.01

[a] All variables reported in percentage, except age, as noted.

Direct comparison studies have shown African Americans with HFPEF are younger females, more likely to have hypertension with worse diastolic dysfunction and less likely to have CAD compared to Caucasian populations.

CONCLUSIONS

Results from studies looking at HFPEF may not be fully applicable to African American populations due to small representation in the studies. Direct comparison studies have shown African Americans with HFPEF are younger females, more likely to have hypertension with worse diastolic dysfunction and less likely to have CAD compared to Caucasian populations. This reduced incidence of CAD probably reflects the younger African American population, coupled with a greater likelihood of systolic failure in those with prior ischemic disease. Mortality

rates have varied between studies, with some indicating no mortality difference and others showing up to 34% worse mortality in African Americans without coronary artery disease compared to Caucasians. The propensity for African American populations to have greater left ventricular hypertrophy, diastolic dysfunction, worse renal function are the most likely contributing factors to younger age of onset and greater mortality. Indeed, left ventricular hypertrophy in itself has been shown to be an independent risk factor for death.[17] Mechanisms including a genetic predisposition and increased medication resistance may play a role in the different outcomes in HFPEF. However, many still believe that prognosis in HFPEF is primarily due to disparity in health care access. As such, dedicated prospective studies and RCTs like the A-HeFT trial, which look primarily at African Americans, need to be conducted to provide further insight and allow race specific treatment guidelines to be created.

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