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Normal Coronary Arteries in Afro-Caribbean Patients with Heart Failure and Reduced Ejection Fraction: An Unresolved Equation

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Abstract

Background: Previous research has shown that Afro-Caribbean patients with Left Ventricular Dysfunction are manly hypertensives and half of them developed Heart Failure (HF) due to non-ischemic causes. The proportion and characterization of patients with reduced Ejection Fraction (HFrEF, EF < 40%) and angiographycally documented Non-Ischemic (NICM) vs Ischemic Dilated Cardiomyopathy (IDCM) in this population remains incompletely understood.

Objective: To evaluate the prevalence of IDCM vs NIDCM by angiographic criteria in patients with HFrEF and the impact of the lifetime cardiac risk factors leading to the same outcome in Afro-Caribbean population.

Methods: We compared the demographic data, risk factors and clinical features in Afro-Caribean patients with HFrEF who underwent coronary angiography in a single institution from January 01, 2015 to September 02, 2017. The patients were categorized into two groups according to absence (Group 1-NIDCM) or presence (Group 2-IDCM) of angiographic evidence of obstructive coronary artery disease-CAD- Patients diagnosed with congenital or valve heart diseases were excluded from the analysis.

Results: From a total of 380 patients evaluated during the study period, 67 patients were included in the analysis. The prevalence of patients with NIDCM was 55%. With the exception of age (59 vs 65, $p < 0.03$) and confirmed myocardial infarction (2 vs 25%, $p < 0.04$) there were no significant differences ($p < 0.05$) in the prevalence of CAD risk factors.

Conclusion: Among Afro-Caribbean patients with HFrEF, angiographycally proven NIDCM was more frequent that IDCM, suggesting that despite both groups of patient's exposure to the similar CAD risk factors, other factors play an important role in etiology of the left ventricle failure. Further research is needed to refine the pathophysiologic, clinical and therapeutic implications of these results.

Keywords: *Afro-Caribbean; Heart Failure; Coronary angiography; Demographics; Risk Factors*

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Introduction

Ischemic heart disease accounts for approximately two thirds of cases of patients with heart failure with reduced ejection fraction in the U.S. [1] and identifying ischemic disease as the primary etiology not only has treatment and long-term prognostic implications but is also associated with worse long-term outcomes [2]. On the other hand, Multi-ethnic studies [3] have found that African Americans have the highest proportion of incident Heart Failure not preceded by clinical myocardial infarction (75%), moreover, systematic literature review among the Afro-Caribbean populations and Caribbean immigrants living in UK , compared to other ethnic groups studies [4] have shown that the prevalence of coronary heart disease (CHD) and peripheral artery disease is lower in Afro-Caribbean populations : the prevalence of CHD ranged from 0-7% in Afro-Caribbean compared to 2-22% in Caucasians. In a study between 211 Afro-Caribbean living in UK patients [5] the researchers noted that the most common cause of heart failure was nonischemic cardiomyopathy –NIDCM- (27.5% Afro-Caribbeans vs 19.9% whites; $P < 0.001$). with other etiologies such a cardiac amyloidosis accounting for up to 11 % of the cases. Afro-Caribbeans also had lower rates of ischemic dilated cardiomyopathy –IDCM_ (13% versus 41%; $P < 0.001$. It has been observed that In African Americans, the higher percentage of cases of heart failure is attributable to modifiable risk factors such as hypertension, hyperglycemia, left ventricular hypertrophy, and smoking, and fewer cases are due to ischemic heart disease [3,6], namely : Nonischemic cardiomyopathy (NIDCM) predominates in African Americans, whereas ischemic cardiomyopathy (IDCM) predominates in whites. Currently, the information about Heart Failure in Afro-Caribbean patients is still limited. In a previous publication [7] we found that the presence or the absence of the most important traditional cardiovascular factors (Hypertension and Diabetes), which have been described as strongly correlated with coronary artery disease, are not necessarily predictive of angiographycally-proven NIDCM vs. IDCM in a Jamaican population with HFrEF. Moreover, we have documented [8] that Jamaican patients with heart failure and Left Ventricular Systolic Dysfunction (EF < 50%) are mainly hypertensive with or without diabetes and half of them develop left ventricular systolic dysfunction due to non-ischemic causes. In addition they have shown a distinct etiological but similar clinical profile when they were classified according with the EF in Heart Failure with mid-range (HFmrEF) vs. HF with reduced Ejection Fraction (HFrEF). Finally, additional studies [9] indicate that the overall proportion of patients with normal or minimal stenosis of coronary artery (< 50% narrowing in the luminal diameter) is greater in African Americans than in whites for both men and women, nevertheless, the clinical and angiographic correlation of Afro-Caribbean patients with Heart Failure and reduced Ejection Fraction (HFrEF, EF < 40 %) remains incompletely understood.

Objectives

We therefore evaluated: (I) The proportion of patients with Heart Failure with reduced ejection fraction (HFrEF; EF < 40%) and angiographycally normal vs angiographycally abnormal coronary arteries, and (II) The impact of the lifetime cardiac risk factors and clinical features in the development of angiographycally proven Ischemic (IDCM) vs Non Ischemic Dilated cardiomyopathy (NIDCM) in Afro-Caribbean population.

Methods

Design

Cross-sectional study

Sample

We analyzed data from patients with the diagnostic of Heart Failure in the Heart Institute of the Caribbean, Jamaica, between January 1, 2015 and September 2, 2017. We reviewed the records of all elective coronary angiographies and abstracted the following: demographic data, medical history including arterial hypertension, Diabetes Mellitus, Dyslipidemia, Obesity and Smoking, the presence of Left Bundle branch Block , Atrial Fibrillation and defined history of Coronary artery Disease (history of myocardial infarction or coronary artery bypass grafting or percutaneous intervention), echocardiographic data between one year before or after the procedure including calculated left ventricular ejection fraction (LVEF), the Left ventricle end diastolic dimension (LVEDD) and the relative wall thickness (RWT) based cardiac geometry. We selected only patients with heart failure and reduced ejection fraction (HFrEF) that persisted with

an unknown etiology after initial non-invasive clinical assessment. Inclusion criteria were: left ventricular ejection fraction < 40%, the presence of Left ventricular dilatation according with the American Society of Echocardiography guidelines (10) (LVEDD > 58.4 mm for Males and > 52.2 mm for females) and age > 18 years. Patients with congenital heart disease, or significant valvular heart disease were excluded from the analysis. The sample was divided into two groups: Patients with Angiographycally normal coronaries (NIDCM) and Patients with angiographic evidence of obstructive coronary artery disease (IDCM). The angiographic criteria used were based on previously published definitions by Felker., *et al*. [11] , which considered as ischemic etiology patients with obstructive lesions (> 75%) in two or more epicardial vessels or left main coronary artery or the proximal anterior descending branch. The starting date of follow-up was the time of coronary angiography and the last date of follow-up was considered as the last outpatient visit recorded in our electronic medical records.

Statistical analysis

Continuous variables were expressed as means ± standard deviation and were compared using the Student's t test. Categorical variables were compared using Fisher exact test.

Results

A total of 380 patients were evaluated during the study period. After the initial outpatient evaluation and use of eligibility criteria, only 67 (17%) patients with heart failure and reduced ejection fraction who had coronary angiography were included in the analysis. The Demographic data, associated cardiac risk factors, information about myocardial remodeling and severity of heart dysfunction such as LVEF, LV dilatation, LV hypertrophy, wide QRS complex (LBBB) and the presence of cardiac comorbidities (Atrial fibrillation) are shown in the Table . Thirty-seven patients (55%) belonged to Group 1 and Thirty (44.8%) to Group 2. Patients had a mean of 1.5 (± 1.1) risk factors for coronary artery disease in Group 1 and 1.76 (± 1.2) in Group 2 (p = 0.41). A trend was observed: among patients of Group 2, there were more male and the history of hypertension, diabetes, dyslipidemia, and smoking was more frequent. In contrast, among patients of Group 1, there were more obese, more women, and they showed greater ventricular dilatation, more reduced systolic function, higher proportion of eccentric LV hypertrophy and Atrial Fibrillation. However, only the Age (p < 0.03) and a defined history of Myocardial Infarction (p < 0.04) proved to be the only significant differences between Group 1 and Group 2.

Demographics And other Characteristics	Group 1 Non Ischemic DCM N = 37	Group 2 Ischemic DCM N = 30
Male Sex, %	58	60
Age, mean ± SD	59 ± 11	65 ± 9.8 (*)
Hypertension, %	62	66.6
Diabetes, %	40.5	46.6
Hypertension and Diabetes, %	32.4	36.6
Dyslipidemia, %	29.7	40
Smoking, %	8	13.3
Obesity, %	18.9	16.6
Risk Factors, n ± SD	1.5 ± 1.1	1.76 ± 1.2
LVEF (%), mean ± SD	30 ± 6.9	32 ± 8
LVEDD (mm), mean ± SD	65.8 ± 7.6	63.9 ± 8.9
Relative wall thickness (RWT), mean ± SD	0.29 ± 0.10	0.30 ± 0.10

Left Bundle Branch Block, %	18.9	20
Atrial Fibrillation, %	8	6
History of Myocardial Infarction, %	2	26 (*)

(*) Group 1 vs Group 2, $p < 0.05$: Age ($p < 0.03$) and History of MI ($p < 0.04$).

Table 1: *Afro-Caribbean Heart Failure.*

Discussion

This study confirms what has been suggested in our previous observations [7,8] that the proportion of Afro-Caribbean patients from Jamaica that develop Heart Failure with reduced ejection Fraction (HFrEF), as the final outcome (Dilated Cardiomyopathy) are associated mostly (55%) with angiographycally defined nonischemic dilated cardiomyopathy (NIDCM) and less with angiographycally documented obstructive coronary artery disease (IDCM). These data not only coincide with observations which indicate that in African Americans, the higher percentage of cases of heart failure is attributable to modifiable risk factors such as hypertension, hyperglycemia, left ventricular hypertrophy, and smoking, and fewer cases are due to ischemic heart disease [3,6] but also with others reporting that in Afro-Caribbean patients [5] the most common cause of heart failure is nonischemic cardiomyopathy (NIDCM).

In addition, a higher frequency of normal coronaries and less frequent coronary stenosis has been found in older African-American men [37]. African Americans have less obstructive coronary artery disease on angiography, but may have a similar or greater total burden of coronary atherosclerosis [38]. Accordingly, and based on our findings it is reasonable to think that Jamaican Afro-Caribbean patients have similarities with African Americans in the etiological sense of heart failure, namely, nonischemic cardiomyopathy predominates or is at least about the half of the cases of heart failure with reduced ejection fraction (HFrEF) and similarly to African Americans, Hypertension, Diabetes, Obesity, and chronic kidney disease all portend subsequent heart failure are common but hypertension is the main culprit. [12,13]. We found that the frequency of Hypertension goes between 62% (Group 1) to 66.6% (Group 2). We have previously reported that [8] HFrEF was associated with dilated hypertensive heart Disease-(DHHD) in 30.3%. In the present study the prevalence of eccentric hypertrophy (Relative wall Thickness < 0.42) was almost universal and it is well known that Left ventricular mass increases disproportionately in hypertension, relative to the ability of the microvasculature to perfuse the hypertrophied myocardium both at rest and during exercise, thereby proving to be a 'set up' for chronic sub endocardial hypo perfusion [40].

On the other hand this study reveals that 40.5% of patients in Group 1 and 46.6% of patients in group 2 are diabetic. Diabetes is associated with Coronary Microvascular Dysfunction (CMD) not only in the heart but also in other organs such as the eye, kidney, and brain, so deserves specific mention. Chronic hyperglycemia is associated with significantly reduced endothelial-dependent and endothelial-independent coronary vasodilator function [39], therefore, it is obvious that the burden of cardiovascular disease risk factors in Jamaica remains very high but the association between exposure and outcome is complex, since although these patients have been exposed during their lifetime to the same risk factors (such as hypertension and diabetes) and both develop the same outcome, i.e. Dilated Cardiomyopathy, only about half of them will end showing obstructive coronary artery disease by angiographic criteria. Impaired endothelial function, as evidenced by impaired digital and brachial artery vasomotion, is very common in African Americans [14-16]. The small arteries of African Americans are less elastic than those of whites and Chinese [17] The underlying mechanism may be related to increased oxidative stress, decreased nitric oxide availability, exaggerated vasoconstrictor response, and attenuated responsiveness to vasodilators and nitric oxide [18-21], consequently it is valid to assume that these same pathophysiological alterations could be related to the clinical and angiographic profile of Afro-Caribbean patients with HFrEF. If Heart Failure is a Coronary Artery Disease Problem or Hypertension Problem is beyond of debate in the present paper, however we believe Hypertension and CAD frequently coexist. The two conditions also interact synergistically with each other as risk factors for heart failure. Also, the relative impact of the two conditions may differ according to age, gender, race and other factors.

Our data suggest that at least in a portion of our patients coronary artery disease (epicardial or microvascular; clinically overt or silent) could lead to decreased perfusion of the myocardium (both acutely and chronically), thereby predisposing to myocardial damage with its sequel of decreased myocardial function [23]. It is well established that blacks face a higher burden of blood-pressure related conditions including heart failure, compared to whites in whom CAD is more often a culprit [22,23] however other non-ischemic etiologies deserve to be examined: In a previously published clinical study [8] we have documented that 52% of Afro-Caribbean Heart Failure in our population was associated with non-ischemic conditions. In this group are included a 24% with dilated HDD and 14% with dilated cardiomyopathy (DCM) of unknown etiology. In relation with this topic Campbell., *et al*. [24] described twenty one cases of DCM documented with necropsy occurred in the Jamaica community and Tulloch Reid., *et al*. [25] have reported the association of HTLV-1 seropositivity and unexplained dilated cardiomyopathy in Jamaican patients. Tulloch Reid has also reported the experience of 26 cases (45 ± 11 years-old) with unexplained dilated cardiomyopathy at Kingston Public Hospital [26], however more data about HF in Afro-Caribbean community is needed. Since we do not routinely perform testing for cardiac amyloidosis (ATTR V122I), it is possible that some of these subjects may be confused with other etiologies. According with Dungu., *et al*. [27] about 4% of African-Americans possess the V122I variant of transthyretin, associated with cardiac amyloidosis (ATTR) and 10% of Afro-Caribbean heart failure population have ATTR V122I, often misdiagnosed as hypertensive heart disease (HHD).

The therapeutic applications of these theories have been demonstrated in the A-HEFT -African-American Heart Failure Trial. It is clear that differences exist in the prevalence and causation of congestive heart failure and in the associated morbidity and mortality, consistent with population-based variations in the mechanisms of heart failure. Studies have suggested that persons who identify themselves as black may have, on average, a less active renin–angiotensin system and a lower bioavailability of nitric oxide than those self-identified as white [28] It has been hypothesized that combined hydralazine and nitrate therapy enhances nitric oxide bioavailability since nitrates serve as nitric oxide donors and hydralazine is an antioxidant that reduces consumption of nitric oxide [29]. In addition the ACC/AHA/HFSA guideline update [30] has given a Class I recommendation for the clinical strategy of angiotensin receptor–neprilysin inhibitors (ARNI) and the association between race and baseline characteristics, outcomes, and efficacy of sacubitril/valsartan in PARADIGM-HF has been examined [31]: it has been reported that the benefit of sacubitril/valsartan over enalapril was consistent in blacks (N = 428) and whites. By increasing the levels of natriuretic peptides, bradykinine and adrenomedullin, the drug Sacubitril decrease vasoconstriction, sodium retention and maladaptive remodeling [32]. Accordingly, it is necessary to develop more experience and research with this drugs in Afro-Caribbean patients. Finally, it is important to recognize that, the same socioeconomic factors that have been implicated in African American patients with Heart Failure which can also influence Afro-Caribbean populations such delay in seeking treatment for worsening symptoms, failure to recognize symptoms, limited disease awareness, inadequate access to health care, noncompliance with follow-up appointments, and poor adherence to recommended treatment [33-36].

Study Limitations

This study has the limitations that are common to all observational studies in order to investigate the relationship between exposures, such as cardiac risk factors and outcomes (Heart Failure, Dilated cardiomyopathy, and coronary angiography findings). Our findings are reported for a single referral Centre and included only patients with undetermined etiology who underwent coronary angiography in order to exclude CAD. The authors recognize that a larger sample and more appropriately designed studies must be done in order to provide more valid results. In addition the angiographic findings must be correlated with a coronary microcirculation dysfunction assessment (i.e. myocardial perfusion nuclear scan) and/or cardiovascular magnetic resonance (CMR). Additional investigation to investigate other potential causes may not have been completed in all patients. By doing this we could get more accurate clinical scenarios, prognosis and therapeutic recommendations.

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