


Parasympathetic Dysfunction in Black African Patients with Heart Failure: A Cross-Sectional Study in Sub-Saharan Africa

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Abstract

Background: Heart Failure (HF) is a major public health problem worldwide. Neurohormonal changes associated with HF are current therapeutic targets. The parasympathetic system in HF has not been well studied especially in black Africans. **Aim:** This study aimed to report on the prevalence and determinants of parasympathetic dysfunction in patients with heart failure in sub-Saharan Africa. **Methods:** We conducted a cross-sectional study between December 2017 and April 2018 in the outpatient and inpatient departments in two teaching hospitals in Yaounde-Cameroon. Cases were patients with HF matched with controls without HF according to age, sex, and risk factors (hypertension, diabetes, and obesity). We assessed the parasympathetic function via the Deep Breathing Test using an electrocardiograph. **Results:** We recruited 35 patients in each group. The mean age was 57 ± 11.68 years. Vagal dysfunction was seen in 51.4% of cases and 11.4% of controls (aOR: 10.1 [95% CI: 2.7 - 38.3], $p = 0.001$). This risk increased with the severity of HF-aOR: 11.8, [95% CI: 1.8 - 77.9], $p = 0.01$ for dyspnea stage III-IV, and aOR: 9.27, [95% CI: 1.3 - 65.3], $p = 0.025$ for HF with reduced Ejection fraction. This risk was not associated with the classic cardiovascular risk factors. **Conclusion:** Parasympathetic dysfunction as assessed with the Deep Breathing Test was seen in over half of the patients with HF and this was associated with the severity and type of HF.

Keywords

Heart Failure, Parasympathetic Dysfunction, Heart Rate Variability, Deep Breathing Test

1. Introduction

Heart failure (HF) is the inability of the heart to provide blood flow necessary for the needs of the body, both at rest and during exercise, without the expense of raised filling pressures. It is a public health problem worldwide with increasing prevalence due to the aging of the population [1]. It is associated with high morbidity and high health expenditure [2] [3] [4]. About fifty percent of patients with HF die suddenly, while the other half die due to the progression of the disease to the terminal stage [5]. The cause of sudden death is often due to arrhythmia as a result of autonomic dysfunction [6]. The autonomic nervous system (ANS) is made up of sympathetic and parasympathetic branches. They play an important role in the progression of heart failure. The ANS is the first neuro-hormonal response mechanism in HF. This response in HF is characterized by sympathetic hyperactivity, and parasympathetic dysfunction [6]. This neuro-hormonal response is initial compensatory mechanisms with long term adverse effects on the heart. La Rovere *et al.* [7] demonstrated that parasympathetic dysfunction and the loss of heart rate variability predicted poor outcome in patients with HF complicating myocardial infarction. Boombhi *et al.* [8] demonstrated a reduction of heart rate variability in a group of patients with HF. Most studies on autonomic dysfunction in HF have focused on the sympathetic system. Recently, vagal stimulation as a therapeutic option has highlighted the importance of the parasympathetic system in the pathogenesis of HF [9] [10].

Data on the prevalence and determinants of parasympathetic dysfunction in HF are lacking in black Africans residing in sub-Saharan Africa. This study aimed to report on the prevalence and determinants of parasympathetic dysfunction in patients with heart failure in sub-Saharan Africa.

2. Methods

Study design and Setting. We carried out a cross-sectional study in two University teaching hospitals in Yaounde-General Hospital (YGH) and Central hospital (YCH). This study was carried out between December 2017 and April 2018. Yaounde is the political capital of Cameroon, sub-Saharan Africa. The population is over 2 million inhabitants. The YGH and YCH are first and second category hospitals that serve as teaching hospitals for both undergraduate and graduate students.

Study participants. These were prospectively recruited from the out-patient department and the hospitalization units of the hospitals. We recruited consenting patients (cases) aged ≥ 18 years of both sexes with an established diagno-

sis of heart failure (clinical and echocardiographic criteria) and who were receiving regular care in the teaching hospitals. Sex and age (± 5 years) matched controls with similar risk factors were also recruited from the out-patient consultation. We excluded patients with significant arrhythmia-Atrial fibrillation, atrial flutter, frequent premature supraventricular and ventricular ectopic beats, and ventricular tachycardia. We also excluded current smokers.

Variables and measurements: After signing the informed consent form, we performed a face-to-face interview for both cases and controls. We collected data sociodemographic data (age, sex, profession, marital status), cardiovascular risk factors (hypertension and diabetes). Symptoms of left and right heart failure were collected [11]. We classified dyspnea according to the New York Heart Association grade. Data on cardiac ultrasound was collected from the patients' records (cases). We classified heart failure as reduced ejection fraction (HFrEF) when the left ventricular ejection fraction (LVEF) was $<40\%$, mid-range (HFmEF) when the LVEF was $40\% - 49\%$, and preserved ejection fraction (HFpEF) when the LVEF was $\geq 50\%$. Data on the treatment of heart failure was also collected from the patient records. We measured the resting heart rate by auscultating the heart. The blood pressure was measured after 10 minutes of rest with an electronic blood pressure device OMRON HEM-7200 – E2. A standard cuff size was used. Average of two blood pressure readings $> 140/90$ mmHg taken 5 minutes apart were considered elevated. We measured the height (m) with a stadiometer, and the weight (kg) in light clothing and no shoes with a Seca® scale balance-SECA 877, Classe III. We calculated the Body Mass Index (BMI) as the weight (kg)/height². Normal weight was defined as BMI $18 - 24.9$ kg/m², overweight as BMI $25 - 29.9$ kg/m², and obesity as BMI ≥ 30 kg/m². We performed a complete physical examination in search of signs of heart failure [11].

We then performed a resting 12 lead ECG (cases and controls) with an HP PageWriter 100® electrocardiograph using standard technique. This was to rule out significant arrhythmia.

Finally, we performed a deep breath test (DBT) for both cases and controls to assess for parasympathetic dysfunction. The DBT consists in recording the ECG while the patients slowly take in a deep breath for over 5 seconds, and then breaths out calmly for over 5 seconds. The total recording time of the DBT was one minute. The D1, D2, and D3 leads were considered for the DBT. The RR interval between the QRS complexes was measured with a graduated ECG rule. Six longest and six shortest RR intervals were identified (Figure 1). The average of the six longest RR and the six shortest RR intervals were noted. We then calculated the E/I ratio as the longest mean RR interval divided by the shortest RR interval. Parasympathetic dysfunction was defined as an E/I ratio less than normal for age [12].

Study size and statistical analysis: A convenient sample of all eligible participants was considered for this study. Data were analyzed using the software IBM-Statistical Package for Social Sciences (IBM-SPSS) 21.0. The Shapiro Wilk

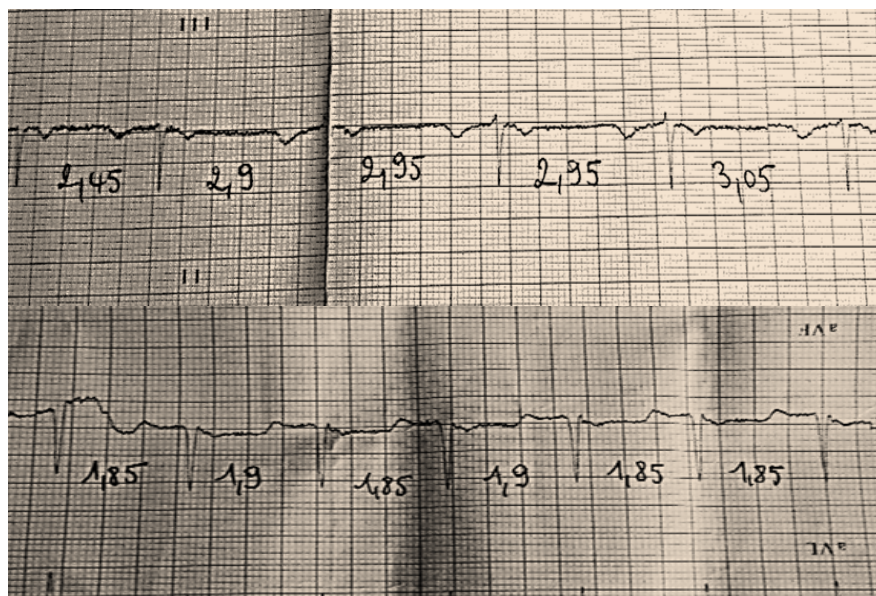


Figure 1. Assessing parasympathetic dysfunction with a deep breathing test in patients with heart failure. The upper panel shows a patient with heart failure without vagal dysfunction, while the lower panel shows a patient with heart failure and vagal dysfunction.

test was used to evaluate for normality of the data. Qualitative data are presented as counts and percentages. A comparison between qualitative data was assessed with the Chi-squared test or Fisher exact test where appropriate. Quantitative variables are presented as means (SD) or median (IQR). Quantitative data were compared using the Student t-test or the Wilcoxon signed-rank test where appropriate. A p-value < 0.05 was considered statistically significant for the observed differences or associations.

Ethical statement: Ethical clearance was obtained from the Institutional Review Board of the Faculty of Medicine and Biomedical Sciences, University of Yaounde1. Administrative authorization was obtained from the local hospital administration. We carried out this work following the declarations of Helsinki. We report this work following the STandard for Reporting OBservational studies in Epidemiology (STROBE) checklist.

3. Results

Participants: A total of 162 patients were approached, of whom 4 refused to participate. Fifty-one patients were excluded for non-fulfilling the inclusion criteria. Of the 107 eligible patients, 44 had HF (9 excluded for lack of echocardiogram data). The 35 patients with HF included in the analysis were matched with 35 controls according to sex, age, and cardiovascular risk factors (**Figure 2**).

Descriptive data: The mean age was 57.3 ± 11.7 years, and ranged from 30 to 80 years. The male to female sex ratio was 0.94. In both groups, 42 (60%) were obese, 12 (17.1%) had diabetes, and 54 (77.1%) had hypertension. The signs and symptoms of heart failure are shown in **Table 1**. Ten patients (28.6%) had severe dyspnea (Stage 3 and 4). All cases (100%) had left heart failure, of whom 14

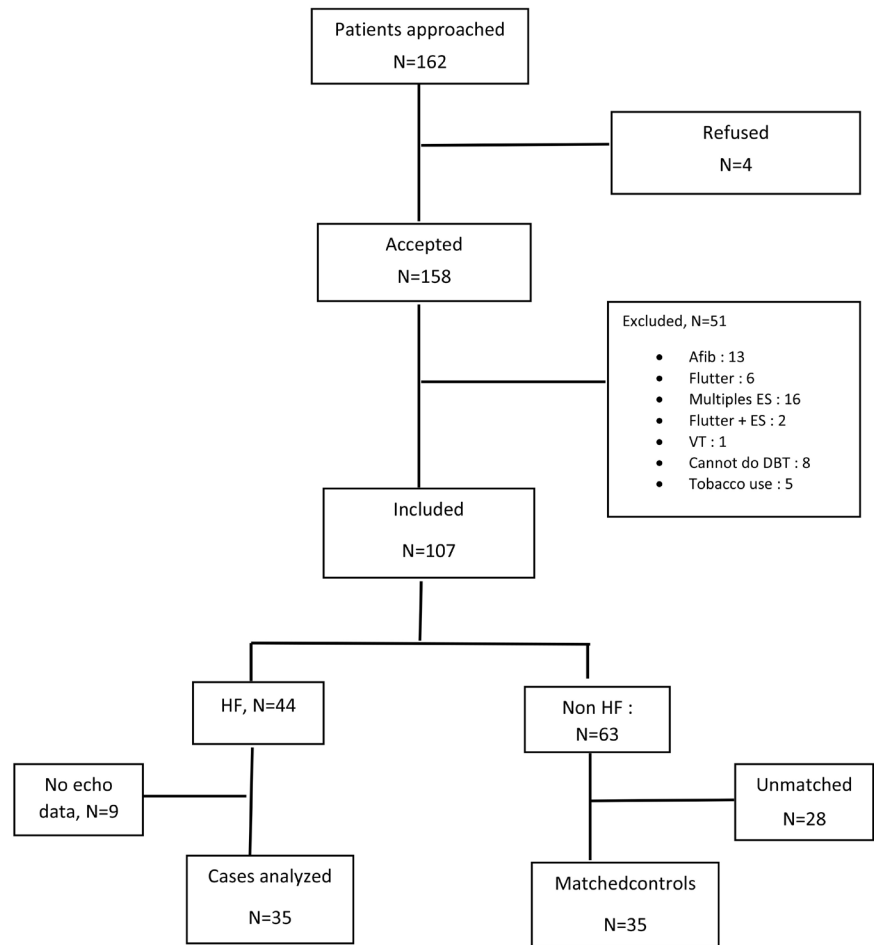


Figure 2. Flow chart of the participants (Afib: Atrial fibrillation; ES: Extra-systoles; VT: Ventricular tachycardia; DBT: Deep Breath Test).

Table 1. Symptoms, signs, and treatment in the heart failure group.

Variables	Frequency (n)	Percentage (%)
Dyspnea grade		
I	0	0
II	25	71.4
III	8	22.9
IV	2	5.7
Signs of heartfailure		
Lung crepitations	2	5.7
Pleural effusion	2	5.7
Galop rythme	0	0
Hepatomegaly	3	8.5
Harzer's sign	3	8.5
Hepato-jugular reflux	4	11.4
Pedaledema	7	23.3
Jugular veinous distension	1	2.9

Continued

Treatment of heartfailure		
Angiotensin Receptor Blocker	2	5.7
Angiotensin-Converting Enzyme Inhibitor	18	51.4
Beta-blocker	3	8.6
Diuretics	31	88.6
Anti-coagulants	8	22.9
Anti-arrhythmics	3	8.6

(40%) also had signs of right heart failure. Of those with HF, 12 (34.3%) had LV ejection fraction < 40%. Four patients (11.4%) were not on treatment for heart failure. Diuretics were the most frequently prescribed medicines (**Table 1**).

Outcome data and main results: Patients with HF had a significantly higher heart rate and blood pressure. Also, patients with HF had significantly lower maximum RR and E/I ratio (**Table 2**). The determinants of vagal dysfunction are shown in **Table 3**. Vagal dysfunction was seen in 18 (51.4%) cases with HF and 4 (11.4%) controls without HF (OR: 8.2, [95% CI: 2.4 - 28.2], $p = 0.001$). The risk was significantly higher in those with HFrEF (OR: 9.4, [95% CI: 1.6 - 53.6], $p = 0.012$). There was a non-significant higher risk in those with diabetes or obesity. This risk was not associated with sex and hypertension.

After adjusting for Diabetes and Obesity, independent predictors of vagal dysfunction were Heart failure (aOR: 10.1 [95% CI: 2.7 - 38.3], $p = 0.001$), the severity of HF (aOR: 11.8, [95% CI: 1.8 - 77.9], $p = 0.01$ for dyspnea stage III - IV), and HFrEF (aOR: 9.27, [95% CI: 1.3 - 65.3], $p = 0.025$).

4. Discussion

We carried out a cross-sectional study to assess for the prevalence and determinants of parasympathetic dysfunction (PSD) in patients with heart failure using the Deep Breath Test (DBT) in a group of black African patients with Heart Failure (HF) in sub-Saharan Africa. Compared to those without HF, parasympathetic dysfunction was significantly higher in those with HF. Half of the patients with HF had parasympathetic dysfunction, and this was associated with the severity of the disease.

Data on parasympathetic dysfunction in black Africans with heart failure are lacking to the best of our knowledge. Also, many studies on autonomic dysfunction in HF have focused on the sympathetic system. There are several technics in assessing autonomic function. The DBT is specially designed to assess the parasympathetic system [12]. In a group of 25 patients with stage 3 and 4 HF (compared with 21 normal subjects) who underwent 15-minutes of spectral analysis, Saul *et al.* [13] found out that all the components of spectral power were decreased especially for domain frequencies > 0.04 Hz. They showed that the vagal tone was reduced, associated with relative preservation of sympathetic modulation in patients with congestive HF. Casolo *et al.* [14] showed a reduction in

Table 2. Mean values of hemodynamic and parasympathetic function parameters.

Variables	Heart failure	Non-Heart failure	p-value
Heart rate (beats/minute)	90.3 ± 14.5	77.8 ± 11.7	<0.001
Systolic Blood Pressure (mmHg)	133.3 ± 11.3	124.3 ± 8.8	<0.001
Diastolic Blood Pressure (mmHg)	76.1 ± 10.5	70.1 ± 7.3	0.007
Body Mass Index (kg/m ²)	31.4 ± 5.2	30.5 ± 4.9	0.5
Maximum RR (mm)	21.3 ± 4.1	25.2 ± 4.8	0.001
Minimum RR (mm)	19.2 ± 3.5	20.4 ± 3.1	0.134
E/I ratio	1.11 ± 0.1	1.23 ± 0.1	<0.001

Table 3. Determinants of Parasympathetic dysfunction (PSD).

Variable	PSD, n (%)	No PSD, n (%)	OR (95% CI)	p-value
Sex				
Male	13 (34.2)	25 (65.8)	1.3 (0.5 - 3.7)	0.585
Female	9 (28.1)	23 (71.9)	1	
Hypertension				
Yes	16 (29.6)	38 (70.4)	0.7 (0.2 - 2.3)	0.553
No	6 (37.5)	10 (62.5)	1	
Diabetes				
Yes	6 (50)	6 (50)	2.6 (0.7 - 9.3)	0.136
No	16 (27.5)	42 (72.5)	1	
Obesity				
Yes	16 (38.1)	26 (61.9)	2.3 (0.8 - 6.8)	0.146
No	6 (21.4)	22 (78.6)	1	
Heart failure				
Yes	18 (51.4)	17 (48.6)	8.2 (2.4 - 28.2)	0.001
No	4 (11.4)	31 (88.6)	1	
Severe HF (NYHA III/IV)				
Yes	7 (70)	3 (30)	3 (0.6 - 14)	0.173
No	11 (44)	14 (56)	1	
Type of HF				
HFrEF	10 (83.3)	2 (16.7)	9.4 (1.6 - 53.6)	0.012
HFpEF	8 (34.8)	15 (65.2)	1	

PSD: Parasympathetic dysfunction. OR: Odds Ratio. CI: Confidence Interval. NYHA: New York Heart Association. HFrEF: Heart Failure with reduced Ejection Fraction. HFpEF: Heart Failure with preserved Ejection Fraction.

vagal tone in a group of 20 patients with congestive HF (stages 2, 3, and 4) compared with normal subjects after analysis of the time domain of the heart rate variability on 24-hour Holter ECG recordings. Several studies using spec-

tral analysis, parameters of heart rate variability decreased with the severity of heart failure [15] [16] [17]. Our findings using DBT corroborates with these studies.

Overall, we observed a non-significant association of male sex with PSD. Huikuri *et al.* [18] observed that females are prone to PSD dysfunction. The mechanism of sex with the occurrence of PSD is not well known. Diabetes is a well-established risk for PSD [19]. We observed a non-significant higher risk of PSD in diabetics. Our study lacked power due to the small number of diabetics. After adjusting for diabetes, the odds of PSD increased suggesting a significant confounder in the occurrence of PSD in HF. Hypertension was not shown to be associated with PSD. However, this has been reported by several high powered studies with focus on hypertension [20]. We observed a non-significant higher risk of PSD in obese patients. Obesity is associated with PSD as reported by Karason *et al.* [21]. In our study, obesity is a significant confounder in the occurrence of PSD in HF.

Limitations: The main limitation of this study is the small sample size, resulting in loss of precision as shown by the large confident interval. Also, we did not take into account ischemic heart disease, which is also associated with autonomic dysfunction. Despite this limitation, this is the first study assessing parasympathetic dysfunction in a group of black Africans with heart failure. We have used a simple method (DBT) to assess for parasympathetic dysfunction in a low-income setting.

5. Conclusion

Parasympathetic dysfunction assessed with Deep Breath Test is frequent in black Africans with HF. This is associated with the clinical severity (NYHA class) of the disease and low ejection fraction (LVEF < 40%). Further studies are needed in a larger sample of patients with HF using different methods to assess parasympathetic dysfunction in HF patients. This will help choose the optimal screening strategy.

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Authors' Contribution

Conception and design: BH, SNA, ID, SK. Data collection: BH, SNA, ID, LMF, BJ, CNN, AM, JB. Data analysis and interpretation: BH, ID, SNA, AMJ, AM, SK. Drafting of the manuscript: BH, ID, SNN, AMJ. All the authors have read and approved the final version for publication.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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