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The Prevalence of Sleep Disordered Breathing and Associated Risk Factors in Acute Congestive Heart Failure Patients in Mozambique

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Shelton Lo

Committee in Charge:

Professor Harvey Checkoway,
Chair Professor Eric Hekler
Professor Suzi Hong
Professor Atul Malhotra

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ABSTRACT OF THE THESIS

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Shelton Lo

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Professor Harvey Checkoway, Chair

Sleep disordered breathing (SDB) is common in patients with congestive heart failure (CHF), yet these conditions have not been well characterized in developing countries; this includes Mozambique, a sub-Saharan African country. Diagnosing SDB in individuals with CHF is important because, in theory, treating SDB in these patients may improve symptoms associated with and caused by CHF.

Between September of 2014 and April of 2017, 159 hospitalized patients with acute congestive heart failure were referred to the Maputo specialized cardiology unit and consecutively enrolled, utilizing a convenience sampling method, in a cross-sectional observation study in Mozambique, East Africa. Based on inclusion criteria, we analyzed the occurrence of SDB and associated risk factors in 153 patients with CHF (64 male, 95 female) in the Mozambique hospitalized patient population.

The overall occurrence of SDB in patients with CHF was 66.0%. Of patients with SDB, those with central sleep apnea were 67.3%. Males were 27% more likely to have SDB than females; no differences in age. Furthermore, those with a low left ventricular ejection fraction (below 55%) were 4.7 times more likely to have SDB, compared to those who did not. More specifically, those with a low left ventricular ejection fraction were more likely to have central sleep apnea, compared to those that do not.

We conclude that demographic and background information, supplemented by a few simple laboratory tests, may allow physicians to screen for SDB conditions in patients with CHF, and the need for the development of diagnostic tools for this patient population in Mozambique.

Introduction:

Congestive heart failure (CHF) is a common condition which is rising in prevalence all over the world[1] due to the aging population. This indicates that, as they age, patients with CHF are surviving longer over time but experiencing associated health complications as well. In the US alone, over 6 million adults suffer from CHF. Acute CHF has been well studied in affluent countries, but there is still a paucity of data in developing countries[2], such as in Mozambique, which is a sub-Saharan African country, and requires more research to be evaluated. In current literature, the epidemiology of CHF rates in sub-Saharan Africa remains unclear. But research shows that in sub-Saharan Africa, 42.5% of the hospital admissions are due to heart failure complications, with a 3-year mortality rate of up to 70%[9]. These numbers represent a large portion of the hospitalized patients, reflecting a major disease burden. This contributes to increased co-morbidity, health complications, healthcare costs, and mortality rates in Mozambique. While these rates are high, there is a paucity of evidence related to preventable risk factors to CHF in Mozambique. Considering the high morbidity of CHF in the Mozambique hospitalized patient population, this observation indicates that further research is necessary to study and evaluate the preventable risk factors that may contribute to the development of CHF and to explore potential interventions. Currently, known risk factors for CHF commonly include high blood pressure, obesity, old age, and pre-existing cardiovascular conditions.

Of particular importance, studies have suggested that up to 80% of patients with acute CHF may have evidence of SDB (i.e., obstructive or central sleep apnea) [10]. Studies suggest that SDB may worsen prognosis in these patients and that intervention

targeting SDB as a risk factor may improve outcomes, although data are not definitive[2,11-13]. Primarily, in developing countries, data are sparse and therapeutic options are quite limited. In theory, SDB may be an important therapeutic target in certain patients with CHF, especially in developing areas. This indicates that addressing and treating SDB in these patients may potentially improve symptoms produced by heart failure. Based on this, there is a need for research to better understand SDB as a potential risk factor for CHF within Mozambique.

The number of patients with sleep apnea has been estimated to be up to 1 billion people worldwide[14]. In a study from Switzerland, the prevalence estimates of moderate to severe SDB is 49.7% in men, and 23.4% in women[15]. These rates represent an enormous increase over the last twenty years, in part due to the increasing prevalence of obesity and the aging of the population[16]. However, SDB prevalence rates in patients with CHF are less clear worldwide. Furthermore, data are even more sparse for inpatients with acute CHF in the sub-Saharan Africa population. Based on current literature reviewing SDB risk factors, patients with SDB have a higher BMI and prevalence of snoring compared to those who do not[17]. Furthermore, old age, atrial fibrillation and hypocapnia are likely risk factors as well, in patients with SDB, though more research is required. However, within patients with SDB, risk factors between two types of sleep apnea- central, and obstructive, may differ and remain unknown in the Mozambique population.

As mentioned, SDB is commonly seen in patients with acute and chronic CHF, and is hypothesized to worsen prognosis, although interventional data have been somewhat mixed and unclear[18,19]. Given common risk factors for SDB and CHF (e.g.,

obesity), research addressing the temporal relation between risk factors and these conditions is warranted. More importantly, sleep testing has not been frequently performed in a systematic manner in developing countries; thus, the study's goal was to highlight the importance of recognizing and screening for SDB conditions in the Mozambique patient population. The study aimed to evaluate whether SDB would be common in a patient population with CHF.

Our primary objective was to define the prevalence of SDB in acute CHF in our Mozambique patient population and identify potential risk factors for its occurrence. Our secondary objective was to stratify SDB by type, and identify potential predictors of SDB in such patients. Our overarching goal was to highlight the importance and need to diagnose and address SDB in patients with CHF, and further, to prompt the development of potential strategies for targeted intervention in this vulnerable population.

Methods:

This cross-sectional observation study was conducted at the Maputo Central Hospital in Maputa, Mozambique between September of 2014 and April of 2017. This hospital utilizes a referral population of the Mozambique patients, thus providing a valuable clinic to conduct our work. Utilizing a convenience sampling method, all patients (in Maputo Central Hospital, Maputo, Mozambique), who were all referred to the Maputo specialized cardiology unit (tertiary referral center) by the emergency department or by a transfer from another hospital center and subsequently diagnosed with CHF, were contacted and invited to participate in the study. Patients were eligible if they were ages 18 years or older and diagnosed with acute CHF within 48 hours of hospitalization. Acute CHF was defined by clinical criteria via physical examination based on The Sub-Saharan Africa Survey on Heart Failure (THESUS-HF) [20]. Patients with CHF had acute dyspnea with two or more signs, measured through a cardiac exam, including: crackles, limbs edema, elevated venous jugular pressure, hepatomegaly, and ascites, as assessed by the study physician. Participants were excluded if they were currently pregnant, submitted to a cardiac surgery prior to study initiation, or diagnosed with any mental disorders. Based on this, N=159 patients with CHF who met our eligibility criteria were enrolled in the study. Of the 159 selected patients, 6 were later excluded because of incomplete data; thus, 153 patients were included in the final analysis.

To ensure participant safety, a trained research coordinator was designated as the overseer of the following procedures in Mozambique, though limited resources precluded a comprehensive documentation of all procedures. All participants provided

written informed consent, which was approved by the Maputo Central Hospital Ethics Committee, Faculty of Medicine of Eduardo Mondlane University Ethics Committee, and by the Mozambican National Bioethics Committee.

The following candidate variables and their classifications were included as measures: sleep apnea status, age, gender, LVEF status, obesity status, and HIV status[17]. For LVEF status, any percentage below 55% was evaluated as having a low ventricular ejection fraction status, indicating potential heart issues[21]. A BMI over 30 kg/m2 was classified as being obese. HIV status was classified as either HIV positive or HIV negative. Participants provided demographic information in a self-report questionnaire conducted by their physician during a normal medical routine visit. Data from review of the patients' medical history, physical examination, and echocardiographic results were tabulated. In addition, all enrolled patients performed a 12-Lead EKG and an echocardiogram, according to European Society of Cardiology Guidelines of Echocardiography (Echo machine Philips HD7 XE)[22].These data were acquired and interpreted by a licensed cardiologist, who was blinded to the sleep apnea results. Sleep testing was recorded by a trained blinded nurse, and was measured using the Apnea Link device (Resmed, Inc)[23]. Nurses at the cardiology ward started the device at 7:00pm and stopped it at 6:00am of the following day. All data were de-identified and sent via HIPAA compliant transmission to a blinded registered polysomnographic technologist under the supervision of an American Academy of Sleep Medicine professional board certified sleep medicine physician. We used a modification of the Chicago criteria (9/1999) where apneas were defined based on 10 seconds cessation of airflow[24]. Hypopnea was defined based on a discernible

decrement in airflow with evidence of a 3% or more desaturation. Cheyne Stokes breathing was defined based on a waxing and waning breathing pattern characteristic of this condition. The presence or absence of Cheyne Stokes was then recorded. We used an Apnea Hypopnea Index (AHI) cutoff value of above 5/h, based on these criteria, to evaluate its presence among patients with CHF. To enhance comparability of our study results to those reported in current literature, we decided *a priori* to use an AHI cutoff of 5/h for SDB analyses[25]. For echocardiography, the median value of LVEF was used for analysis. Echocardiogram and demographic data were entered on an excel document by a blinded biologist and sent securely to research staff at University of California, San Diego and stored on the RedCap database afterwards. Data analysis was conducted by blinded research assistant.

Logistic regression analyses were performed to model the association between various variables and their relationship with SDB and their relationship with central sleep apnea. All data were analyzed with R software modules (RStudio, Version 1.1.456 – 2009-2018 RStudio, Inc.) for descriptive statistics and multiple logistic and regression analyses. Standard formulae were used to calculate rates and 95% confidence intervals. P-values <.05 were considered statistically significant.

Results:

Sleep Apnea Status: Demographic and clinical characteristics are shown in Table 1. Overall, of the 153 patients, 64 (41%) were male and 95 (60%) were female. The average age was 40 years old. The average ejection fraction was 33.2%; 127 participants were classified as having a low (< 55%) ventricular ejection fraction. The average weight was 63.7 kg, and the mean BMI was 23.7 kg/m2. 20 participants were considered obese, and 37 participants were HIV positive. Using an AHI cutoff of 5/h, the overall occurrence of SDB in patients with CHF was 66.0%; of central sleep apnea was 67.3%. Of the 101 patients with SDB, 48% of them were male, and the average age was 41 years old. The mean weight was 66.9kg, and the mean BMI was 24.4 kg/m2. 15 of them were obese. In patients with SDB, the average ejection fraction was 30.9%. 88 of these 101 patients with SDB were classified as having a low ventricular ejection fraction, and 23 participants with SDB were HIV-infected. Out of the 52 patients who did not have SDB, the mean age was 36 years old, and 44% of them were male. Their average weight and BMI was 54.0 kg and 21.5 kg/m2, respectively. Two were considered obese. In these 52 participants, the average ejection fraction was 42.7%, and 26 of them were considered to have a low ventricular ejection fraction. 12 out of the 52 patients were HIV-infected.

Type of Sleep Apnea: Clinical characteristics, stratified by type of sleep apnea, are shown in Table 2. Of the 101 patients with SDB, 68 of them had central sleep apnea. Of these 68, the average age was 43 years old, and 57.4% were male. The mean weight was 67.9kg and mean BMI was 24.5 kg/m2. In patients who had central sleep apnea, the average ejection fraction was 26.7%, and 62 out of the 68 had a low

ventricular ejection fraction. Eight patients were considered obese, and 18 were HIV-infected. Of the 33 patients who did not have central sleep apnea (i.e., other), their average age was 36 years old and 18% of them were male. These patients had a mean weight of 63.3kg with an average BMI of 23.7 kg/m2. Their mean ejection fraction was 39.5%, which was significantly higher than those who had central sleep apnea. Even so, 28 out of the 33 patients still had a low left ventricular ejection fraction. Seven of them were considered obese, and 6 of them were HIV positive.

Risk factors, stratified by SDB status and type, are displayed in Table 3 and 4. In patients with SDB compared to those without SDB, age, obesity status, and HIV status showed no significant difference. However, females were 73% (p-value = 0.007, CI 0.097-0.678) less likely to have sleep apnea than males, after controlling for all other variables. Furthermore, those with a low ventricular ejection fraction (indicated as 55% or below) are 4.7 times (p-value = 0.008, CI 1.5-15.4) more likely to have SDB, compared to those that do not. Within patients who had SDB, there were no significant differences in age, obesity status and HIV status, when comparing those with central sleep apnea and those without. Males were more likely to have central sleep apnea versus females. After controlling for all other variables, those with a low left ventricular ejection fraction (indicated as 55% or below) were more likely to have central sleep apnea, compared to those that do not.

Discussion:

To our knowledge, this is the first study conducted to evaluate the prevalence of SDB in patients with CHF in the sub-Saharan Africa community. The study's findings add to the current body of literature regarding SDB breathing in patients with acute CHF, primarily addressing the gap of research present in the Mozambique population. In the study participants, the proportion of SDB in patients with CHF was over 60%. This percentage is comparable to values observed in North America, but it was higher than anticipated, given the lack of obesity and other major risk factors in this population. In addition, there was an alarming prevalence of Cheyne Stokes breathing in patients with acute CHF, even though this breathing pattern is generally uncommon in females and young adults[26], hence should be further explored. Therefore, these results suggest that there may be other risk factors that may increase one's likelihood of developing central sleep apnea in this population, which should be further explored in other patients with CHF.

To date, this is the first report of its kind to include these risk factors and conditions in the Mozambique population of patients with CHF. Studying differences across cultures is important because the etiology of CHF conditions appears to vary by country, e.g. coronary artery disease, which is one possible condition of CHF, is relatively uncommon in sub-Saharan Africa[3,4] . In contrast, other diseases that may be related to CHF, such as HIV, rheumatic heart disease, hypertensive heart disease, peri-partum cardiomyopathy, and idiopathic dilated cardiomyopathy, are quite common in Mozambique[6,78]. Many of these African patients are fairly lean and young; thus their respiratory function (e.g. sleep-disordered breathing), a possible indicator of CHF, is

predicted to be quite different from patients with CHF in the USA or other well-resourced countries. Based on current literature, this finding suggests that SDB may be very common in the population of CHF patients, but is probably being underdiagnosed. Our present findings are consistent with this concept and highlight the importance of diagnosing SDB in patients with CHF. In doing so, physicians will be able to treat the SDB conditions in these patients, which ultimately, may improve other symptoms produced by CHF.

In the United States, prior studies have reported a high prevalence of SDB in both patients with acute as well as patients with chronic congestive heart failure[27]. To address this issue, reports indicated that nasal CPAP (continuous positive airway pressure), which is a popular intervention in the United States, can improve left ventricular ejection fraction in patients with acute CHF. However, CPAP therapy is not currently available in Mozambique; hence the study team was unable to assess the impact of such an intervention to help these patients with CHF. Nonetheless, the data from this study should help raise awareness regarding this important issue in this vulnerable population. In addition, we have ongoing efforts to prompt and motivate stakeholders, both in San Diego and Mozambique, to utilize the results from this study to assess for optimal strategies of screening and diagnosing SDB conditions in patients with CHF in this population.

Due to logistical constraints, our sample was small; the SDB and risk factor result estimates represent the patients with CHF in the Maputo Central Hospital but may not accurately reflect all patients with CHF in Mozambique. This situation may be because Maputo Central Hospital utilizes a patient referral method. Although we attempted to

enroll a consecutive series of patients with CHF, we used a convenience sampling method since equipment and personnel were limited, despite our best efforts. Thus, similar studies utilizing larger sample sizes are recommended. Instead, these results seek to highlight the need to screen and address SDB conditions in patients with CHF in the Mozambique population and provide a case for increased investment on understanding this health issue in Mozambique.

Despite the potential strength and novelty of our study, we acknowledge a number of limitations as well. First, many patients with prolonged apneas had profound desaturations which were difficult to quantify accurately. However, such technological limitations e.g. pulse oximetry, are common to many studies in this field. Second, interventions may not function similarly across different populations due to various social, economic, and cultural forces that could heavily influence sleep behaviors. This concern is important in the Mozambique population with its vast and diverse behavioral patterns; hence, further research should explore how these effects may differ across varying populations. Third, despite the research team's best efforts, there remained missing data including incomplete Doppler information on some of the echocardiograms performed. Nonetheless, we believe that our study was quite rigorous given the local conditions and the data we obtained were robust particularly given the constraints of performing research in under-resourced countries.

In this study, validated questionnaires, which were previously translated into Portuguese, were used to conduct the assessments. Hence, the data provide reassurance that these questionnaires may be effective for the purposes and objectives described in this study. Of particular note though, many of the Epworth

questions do not pertain to the Mozambique population since a large number of them do not have a television or drive a vehicle, minimizing the relevance of the questionnaire in this local population[28,29]. Nevertheless, due to high cost and lack of technology readily available in developing countries such as Mozambique, utilizing questionnaires may be helpful since it could provide a low cost and low burden screening assessment tool for breathing issues among patients with CHF, as shown in several studies . Such instruments may be used to stratify patients' needs and to prioritize further objective testing procedures. The knowledge about likelihood of developing SDB could also help to guide both patient and physician disease management (e.g. aggressiveness of diuretic therapy)[30].

In summary, the present study demonstrates that in patients with CHF, there is a high likelihood of SDB comorbidity. Furthermore, there are various risk factors correlated with CHF that may differ for central sleep apnea versus non-central sleep apnea. These observations are in line with the concept that these two conditions have different underlying pathogenesis. There is a high prevalence of SDB and unique risk factors in the patients with CHF in this population, which allows for multiple avenues of potential interventions for the sub-Saharan Africa community. Further work is imperative to address these issues.

Increased awareness of these conditions as possible risk factors in patients with CHF may alter the approach to medical therapy and may be used as a screening tool/assessment for CHF. Our findings indicate that demographic information, including BMI and age, may allow physicians to risk stratify patients with CHF for evaluation of SDB. Once diagnosed, specific therapy aimed at treating SDB may be

incorporated. Although ours was not a prevalence study of CHF, the fact that we were able to detect so many cases of SDB in patients with CHF in our study adds to the literature that these SDB is common in patients with CHF, and needs to be assessed by physicians.

Future research should evaluate the dose-response relationship between the severity of SDB and CHF, while remaining cognizant of various culture factors. Due to the alarming prevalence rate of SDB in patients with CHF, we encourage the development of a systematic screening guideline for SDB in these patients. Therefore, patients with CHF should be screened for SDB, along with the reported related factors and predictors.

Appendix:

Table 1: Study Population Clinical Characteristics by SDB Status			
	Total	SDB	No SDB
Number of patients	153	101	52
Age yrs (n)	40	41	36
Male (%)	41	48	44
Weight (kg)	63.68	66.9	54.02
Ejection Fraction (%)	33.2	30.92	42.7
Low Ventricular Ejection Fraction (n)	127	88	26
BMI (kg/m2)	23.7	24.4	21.51
Obese (>30 kg/m2) (n)	20	15	2
HIV + (n)	37	23	12

Table 2: Study Population Clinical Characteristics by Sleep Apnea Type			
	Total SDB	CSA	No CSA
Number of patients	101	68	33
Age (n)	41	43	36
Male (%)	48	57.4	18
Weight (kg)	66.9	67.9	63.3
Ejection Fraction (%)	30.92	26.7	39.5
Low Ventricular Ejection Fraction (n)	88	62	28
BMI (kg/m2)	24.4	24.5	23.7
Obese (n)	15	8	7
HIV + (n)	23	18	6

Table 3: Risk Factors Stratified by SDB Status	
	SDB
Age (n)	40 ± 16
Male (n)	64 (41%)
HIV + (n)	37(24%)
Obese (n)	20 (13%)
Ejection Fraction (%)	33.2 ± 0.34

*P-Values > .05 are considered statistically significant.

Table 4: Risk Factors Stratified by Sleep Apnea Type

	Central Sleep Apnea	P-Value
Age (n)	41 ±- 14	0.13
Male (n)	48 (48%)	0.03*
HIV + (n)	23 (23%)	0.32
Obese (n)	15 (15%)	0.17
Ejection Fraction (%)	30.92 ± 0.24	0.05*
*P-Values > .05 are considered statistically significant.		

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