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Diagnostic Performance of N Terminal-Pro Brain Natriuretic Peptide (NT-ProBNP) in the Assessment of Dyspnea in Heart Failure and Chronic Obstructive Pulmonary Disease in a Group of Patients in Sub–Saharan Africa (SSA): An Analytical Cross-Sectional Study

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Background: Heart failure (HF) and Chronic Obstructive Pulmonary Disease (COPD) are two conditions frequently responsible of dyspnea. The clinical distinction between these two etiologies is challenging in clinical practice, particularly in developing countries where access to imagery is

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limited. Thus, natriopeptides, secreted during the stretching of cardiomyocytes, could be a more accessible method for the etiological diagnosis of dyspnea.
Objective: The aim of this cross-sectional study was to evaluate the diagnostic performance of NT-pro BNP in the assessment of dyspnea during heart failure and COPD.
Methods: The population consisted of patients with dyspnea caused by heart failure according to Framingham criteria or COPD diagnosed according to GOLD criteria. The NT-pro BNP levels and left ventricular ejection fraction was assessed. The ROC curve and the Youden index was used to determine the diagnostic performance of the test and the threshold of significance was set at 0.05.
Results: Of the 45 subjects recruited, 32 had heart failure and 13 had COPD. The NT-pro BNP levels were higher in HF patients (3725.5 [651 – 9945] pg/ml) compared to the COPD patients (316 [32- 1307] pg/ml); p=0.02. The NT-pro BNP levels was correlated to dyspnea in both groups (r=0.75; p<0.001 in HF patients and r=0.91; p<0,001 in COPD patients). The diagnostic threshold obtained was 497 pg/ml with a sensitivity of 81%, a specificity of 69% and a Youden's index of 0.5.
Conclusion: The diagnostic performance of NT-proBNP is acceptable in distinguishing between heart failure and COPD.

Keywords: Diagnosis; NT-proBNP; dyspnea; heart failure; chronic obstructive pulmonary disease.

1. INTRODUCTION

Dyspnea is a common symptom in adults. Its prevalence in the general population is variable according to studies and estimated between 9 and 59% [1]. It is a frequent clinical presentation, found in about 7.4% of patients in the emergency room, 15 to 50% of patients in cardiology consultations and around 60% of patients in pneumology [1,2]. Dyspnea can have several causes, the main ones being respiratory and cardiac, in particular heart failure (HF) and chronic obstructive pulmonary disease (COPD) [3]. These pathologies are characterised by a particularly worse prognosis, especially in the case of late diagnosis [4,5]. An European study estimated the one-year mortality of chronic and acute heart failure at 6.4% and 23.6% respectively [6]. COPD in the other hand is responsible for approximately 3.17 million deaths worldwide each year, 90% in low- and middle-income countries [7].

Although being a frequent symptom, the presence of dyspnea poses a major diagnostic problem as clinical examination is often insufficient in determining its cause[8]. Therefore, paraclinical assessment is necessary, with heart ultrasound and spirometry which is often required to differentiate between the two major causes. Technical difficulties such as the cost of the equipments and the lack of skilled operators are possible factors preventing the access to these assessment tools in sub-Saharan Africa.

As a result of this and other challenges, there is increasing interest of exploring other reliable and easily accessible diagnostic methods. Brain Natriuretic Peptide (BNP) is a natriopeptide secreted by cardiac myocytes in response to chamber stress and have shown to have a diagnostic, prognostic and therapeutic utility in heart failure [9]. The high sensitivity of this test allows reasonable exclusion of heart failure as a probable cause, if normal [9]. However, the rise in NT-proBNP levels is not specific to heart failure and can be observed in some conditions such as COPD [10].

1.1 Aim

The aim of this study was therefore to determine the diagnostic performance of NT-proBNP in the assessment of dyspnea in heart failure and COPD.

2. METHODOLOGY

2.1 Study Framework

We conducted a cross-sectional study, from January to July 2020 in three hospitals in Yaoundé: Yaoundé Central Hospital, Jamot Hospital and Yaoundé Emergency Center.

2.2 Participants

These are all patients over the ages of 21, with dyspnea and whose etiological diagnosis of dyspnea was either heart failure diagnosed according to Framingham criteria [11] or COPD diagnosed according to GOLD criteria [12]. Other inclusion criteria were a negative COVID-19 PCR test, no history of cirrhosis or pulmonary arterial hypertension, and a glomerular filtration rate ≥ 60 ml/min/1,73m².

The HF group consisted of HF patients without COPD, whereas the COPD group consisted of COPD patients without HF.

2.3 Data Collection

Data collection was done anonymously. Each participant was assigned a 3-digit number to identify the collected samples and the data collection form. The data was recorded in a database accessible only to the research team.

The study was conducted in strict accordance with the principles of the Declaration of Helsinki.

For each participant, we reported socio-demographic data, cardiovascular risk factors and the severity of dyspnea according to the New York Heart Association (NYHA) classification. Serum NT-proBNP levels was determined in a 5 mL peripheral venous sample. The test was performed using the commercial VIDAS NT-proBNP2 kit (Biomerieux, France) on a VIDAS automated immunoanalyzer using the sandwich enzyme-linked immunosorbent assay with a final fluorescent detection called ELFA (Enzyme Linked Fluorescent Assay).

The systolic ejection fraction of the left ventricle was assessed by the SIMPSON method by a cardiologist with the SONOSCAPE S50 cardiac ultrasound machine. The modified Simpson Biplane method is the recommended method of quantifying left ventricular systolic function. This method estimated the left ventricular systolic function by assessing the variation of left ventricular volumes between systole and diastole. These volumes are measured by manually tracking of the endocardial borders of the left ventricle in bi-plane mode, apical 4-chamber, and apical 2-chamber views [13].

2.4 Statistical Analysis

We built a database using Excel 2013 software, realized analyzes using SPSS software version 22. Values were expressed as median (interquartile range) and frequency (percentage) where necessary. The Pearson correlation coefficient was used to assess the correlation between quantitative variables. The Receiver Operational Curve and the Youden's index was used to determine the threshold value.

3. RESULTS

3.1 General Characteristics of the Study Population

Of the 80 subjects who met our criteria, 33 refused to participate and 2 had impaired renal function. We analysed data from 45 patients, 32 with heart failure and 13 with COPD, of which 44.4% were women (sex ratio male/female 1.25). The mean age was 56 ± 17 years in heart failure patients and 60 ± 16 years in COPD patients. The general characteristics of the study population are presented in Table 1.

3.2 Evaluation of NT-proBNP Levels

NT-proBNP levels were higher than normal in both groups. However, this elevation was greater in patients with HF 3725.5 [651 – 9945] pg/ml than in COPD patients 316 [32 – 1307] pg/ml (p=0.029).

There was a positive correlation between the severity of dyspnea (NYHA) and NT-proBNP levels in HF patients (r=0.75, p<0.001) and in COPD patients (r=0.91; p<0.001).

There was a negative correlation between NT-proBNP levels and left ventricular ejection fraction (LVEF) in HF patients r= -0.53; p=0. 005.

3.2.1 Diagnostic threshold for differential diagnosis

We found three threshold values 349 pg/ml (sensitivity: 90%; specificity: 53%); 3333 pg/ml (sensitivity 53%; specificity 84%) and 497 pg/ml (sensitivity: 81%; specificity: 69%). The table 2 shows the thresholds values and their characteristics.

The Received-Operating-Characteristic curve showing the ability of NT-proBNP to differentiate heart failure from COPD is shown in Fig. 1. At a threshold of 497 pg/ml, the area under the curve was 0.8 [0.6 – 0.9]; p=0.002 and the Youden's index was 0.5.

4. DISCUSSION

We conducted an analytical cross-sectional study to determine the diagnostic value of NT-proBNP in the context of dyspnea due to heart failure or COPD. It appears that NT-pro BNP levels were

increased in HF patients more than in COPD and correlates with dyspnea in both groups. The threshold value of NT-proBNP of 497 pg/ml differentiate HF from COPD with a sensitivity of 81% and a specificity of 69% and a Youden index of 0.5.

Table 1. Characteristics of the study population

	HF (n=32)	COPD (n=13)
Sex n (%)		
Female	17 (53.1)	3 (23.1)
Age n (%)		
<45 years	9 (28.1)	3 (23.1)
45-60 years	3 (9.4)	2 (15.4)
>60 years	20 (62.5)	8 (61.5)
Cardiovascular risk n (%)		
Diabetes	4 (12.5)	2 (15.4)
Hypertension	15 (46.9)	3 (23.1)
Tobacco	6 (18.8)	8 (61.5)
Alcohol	0 (0.00)	9 (69.20)
Dyspnea, NHYA n (%)		
NYHA 1	5 (15.62)	3 (23.09)
NYHA 2	11 (34.37)	2 (15.38)
NYHA 3	5 (15.62)	4 (30.77)
NYHA 4	11 (34.37)	4 (30.77)

Table 2. Threshold values of NT-proBNP and their characteristics

NT-proBNP (pg/ml)	Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)	Negative Predictive Value (%)	Youden's index
349	90	53	64.1	35.4	0.43
497	81	69	55.1	44.3	0.50
3333	53	84	39.7	59.8	0.37

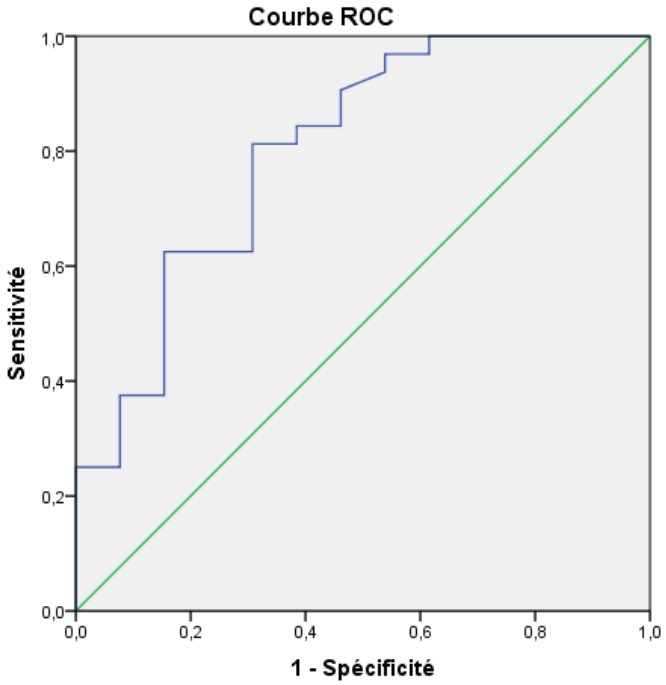

Fig. 1. Received-Operating-Characteristic curve of NT-proBNP

Pro-BNP is a 108 amino acid precursor peptide of the BNP which is stores in the myocytes. It is divided into the biologically active form BNP and the inactive form N-terminal-proBNP [14]. Both are secreted from ventricles in case of increase ventricular wall tension. In heart failure fluid overload causes an increase in pressure on the left ventricular wall and the release of BNP [15]. In COPD, the wall tension caused by the right ventricular dysfunction is lower than those of heart failure, and so is the secretion of BNP [16]. The effects of BNP include diuresis, natriuresis, vasodilation, and inhibition of aldosterone synthesis and renin secretion, with the aim of reducing the ventricular pressure or volume overload [14,17].

NT-pro BNP has no biological function but is secreted with BNP and is not affected by exogenous BNP. Compared to the biologically active BNP, half-life estimated to be about 22 minutes, NT-proBNP has an estimated half-life of 2 hours, and is therefore a more reliable biomarker [14]. In this study, serum levels of NT-proBNP were significantly higher in heart failure patients, compared to COPD patients; a finding supported by the conclusions of Januzzi et al [18]. These results can be explained by the physiopathology of heart failure. Indeed, the myocardial dysfunction in heart failure is associated with volume expansion and/or pressure overload [19]. The resulting myocytes stretch will induce the synthesis of BNP [20]. Apart from being a diagnostic and prognostic factor in HF, NT-proBNP is a prognostic factor in multiple cardiac and non-cardiac pathologies and even in asymptomatic individuals [10]. These levels are particularly high in COPD, but remain lower than in HF [10]. Mechanisms underlying high plasma levels in COPD is not well understood. Several mechanisms have been suggested, including hyperinflation, which could lead to a decrease of cardiac function with an increase in NT-proBNP levels [21]. Another mechanism is related to hypoxia and hypercapnia leading to a contraction of the pulmonary arterioles and an increase in pulmonary arterial pressures and therefore NT-proBNP levels [22].

In both groups, NT-proBNP levels were correlated with dyspnea NYHA stages. Similar results were found by Janussi et al in heart failure patients and Yung et al in COPD patients [18,22]. In HF and COPD, myocardial dysfunction and increased pulmonary pressures are observed, the latter being responsible for dyspnea. Thus, the increase in NT-proBNP levels depends on myocardial dysfunction as does dyspnea.

Our results suggest that a level of NT-proBNP higher than 497 pg/ml would be in favour of HF while concentrations lower than 497 pg/ml would be in favour of COPD, with a sensitivity of 81%, a specificity of 69% and an AUC of 0.8. According to Delacour et al a diagnostic test with an AUC between 0.7 and 0.9 is moderately informative [23]. Therefore NT-proBNP can be used to distinguish between HF and COPD. However, the positive predictive value is 55.1%, far below the recommended 80-85% [24]. The findings reported in this study should be interpreted in light of certain study weaknesses. The small sample size of this study is particularly limiting. Nevertheless, the results obtained are clinically important and provide data to guide future research.

5. CONCLUSION

Our results suggest that NT-proBNP levels are higher in HF patients than COPD patients. The diagnostic performance of NT-proBNP is acceptable, at the threshold of 497 pg/mL, to distinguish between heart failure and COPD. It would therefore be very useful for the etiological diagnosis of dyspnea especially in resources limited countries, where imaging is not always available.

6. LIMITATIONS

The data collection was done during the covid-19 pandemic. This made it difficult to recruit patients without the appropriate facilities, even the willingness of patients in this context was not easy to obtain.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT

Each participant provided written informed consent before undertaking any study procedures.

ETHICAL APPROVAL

The study was approved by the Institutional Ethical Review Board of the Centre region of Cameroon with the ethical clearance N° CE-07541/CRERSHC/2020.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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