Pulse amplitude ratio under noninvasive ventilation as a new method in the diagnosis of heart failure in patients with acute exacerbation of chronic obstructive pulmonary disease

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Research Article

Keywords: non-invasive ventilation, chronic obstructive pulmonary disease, heart failure, pulse amplitude ratio

Posted Date: February 24th, 2022

DOI: <https://doi.org/10.21203/rs.3.rs-1374416/v1>

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Abstract

Background: Heart failure (HF) is commonly associated with acute exacerbation of chronic obstructive pulmonary disease (AECOPD) but its role is often underestimated.

Aim of study: To evaluate the performance of a new diagnostic technique based on the measurement of the pulse amplitude ratio (PAR) using non-invasive ventilation (NIV) for the early identification HF in patients admitted to the emergency department (ED) for AECOPD.

Methods: This is a prospective observational study including patients presenting to the ED with AECOPD. Each included patient received NIV with inspiratory pressure support (PS) set at 5 and 30 cmH₂O for 15 min in random order. We measured plethysmographic pulse pressure (PP) at PS of 5cmH₂O (PP5) and 30 cmH₂O (PP30). We calculated the PAR under NIV (PAR_{NIV}) as the PP30 /PP5 ratio. Patients were divided into two groups: a group identified as having HF (HF group) and a group without HF (non HF group). The diagnostic performance of PAR_{NIV} was assessed by standard methods.

Results: 73 patients were included in this study: 32 in HF group and 41 in non HF- group. The two groups had comparable demographic and clinical characteristics at admission. The mean values of PAR_{NIV} was significantly higher among HF patients (0.86 versus 0.71; $p < 0.01$). The area under the receiver operating characteristic curve of PAR_{NIV} was 0.75. Using the best cut-off (0.6), the sensitivity of PAR_{NIV} was 93% with a specificity 21%, a positive predictive value of 48%, and a negative predictive value of 81%. Correlation between PAR_{NIV} and BNP was significant ($r = 0.52$; $p = 0.002$)

Conclusion: Measurement of PAR_{NIV} in patients presenting to the ED with AECOPD had a good diagnostic performance for the detection of HF and could represent an interesting alternative for the currently available methods.

The study was registered in the Clinical Trial Registration System (clinicaltrials.gov) under the study number NCT05189119.

Introduction

Chronic obstructive pulmonary disease (COPD) is a universally prevalent chronic disease. It is a major public health problem due to its increasing prevalence, high morbidity and mortality rates (1). On average, a COPD patient suffers one to four exacerbations per year. The origin of these exacerbations is not easy to determine, but most often a viral or bacterial infection is incriminated. HF is commonly associated with acute exacerbations of COPD (AECOPD), but this association is frequently underestimated (2–5). Symptoms and signs of HF are particularly difficult to identify and interpret, especially in obese and elderly subjects (4, 6–9). Therefore, the use of additional investigation methods, such as echocardiography and invasive hemodynamic exploration, is decisive for the diagnosis, but they cannot be considered in the emergency room on a routine basis (10). The tendency to generalize cardiac

ultrasound is still limited by its dependency on the operator skills and experience (11, 12). Brain Natriuretic Peptide (BNP) is now widely used for the diagnosis of HF (13). However, a BNP value in the grey zone does not allow the determination of the etiology of dyspnea; this is the case for approximately 30% of patients consulting the emergency room for dyspnea (14). In addition, elevated BNP levels are observed in the elderly, in patients with renal failure, chronic pulmonary disease and hypoxemia (15). Alternative diagnostic method has been proposed, based on the effect of Valsalva maneuver (VM) on blood pressure (16). VM consists of forced exhalation with a closed glottis, which leads to an increase in intra thoracic pressures, the effect of which on the blood pressure curve depends on whether there is or not HF. Several studies have shown that this maneuver could identify patients with HF through the measurement of the PAR (17–19). Recently, Boubaker et al. found that VM could be used to identify HF in patients with AECOPD (20). However, VM is sometimes not easy to be correctly performed for patients who have difficulties to breath. Thus, we propose, in this study, an alternative method to VM. It consists in applying a positive pressure through NIV with inspiratory support. We aimed to evaluate the value of a new method of measuring PAR based on the application of pressure support ventilation (PSV) to assist in the early diagnosis of HF in patients presenting to the ED with AECOPD.

Patients And Methods

This is a prospective observational study of patients who presented to the ED of Fattouma Bourguiba University Hospital (Tunisia) with acute dyspnea in the context of AECOPD. The study protocol has been prepared in accordance with the revised Helsinki Declaration for Biomedical Research Involving Human Subjects and Guidelines for Good Clinical Practice. The study was approved by the ethics committee of our institution; the patient's informed consent was obtained before the start of the protocol. The study was registered in the Clinical Trial Registration System (clinicaltrials.gov) under the study number NCT05189119. This study is reported according to the “Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)” statement guidelines for observational cohort studies.

Study population

Inclusion criteria

Adult patients with a history of COPD who consulted the emergency department for moderate to severe AECOPD defined as acute worsening of respiratory symptoms that result in additional therapy were included (2). COPD is defined according to the criteria of the American Thoracic Society as a progressive airflow limitation that is not fully reversible associated with a chronic inflammatory response of the lungs to noxious particles or gases (21).

Exclusion criteria

Patients with hemodynamic instability (cardiogenic shock, myocardial infarction), coma and severe hypoxemia or acidosis ($\text{pH} < 7.1$) were excluded. Patients with contraindications to NIV (Glasgow score < 12 , swallowing disorder, severe bronchial obstruction, massive retention of secretions despite

bronchoscopy, vomiting, those with anatomical or functional upper airway obstruction or ongoing upper gastrointestinal bleeding or ileus), non-cooperative patients as well as those who refused to give consent were also excluded.

Methodology

Patients' demographic characteristics, medical histories, number of COPD exacerbations during the last 12 months, smoking and current drug treatment, as well as clinical examination data including blood pressure, heart rate, respiratory rate, pulse oxygen saturation, and temperature were collected. Complementary examination findings were also recorded (electrocardiogram, chest X-ray, cardiac ultrasound, BNP, blood gas, and standard biological tests). Patients were prepared for monitoring with three-lead electrode ECG and a plethysmographic sensor on the finger to obtain two simultaneous records. The plethysmographic PAR was calculated using a data acquisition and analysis device (BIOPAC Systems, CA, USA). Each enrolled patient received NIV applied through an oro-nasal mask with a positive end expiratory pressure of 4 cmH₂O, inspiratory oxygen fraction ensuring pulse oxygen saturation $\geq 94\%$, and inspiratory pressure support (PS) set at 5 and 30 cmH₂O. The 2 PS levels were investigated for 15 min in random order, with 10 min spontaneous breathing in between the ventilation periods to return to baseline level. Three successive measurements of PAR during inspiration time were taken 5 minutes after each level of pressure support onset. The following calculations were performed: PP5 which is the average of the plethysmographic pulse pressure measured during three inspiratory cycles recorded under PS = 5 cmH₂O. PP30 which is the average of the plethysmographic pulse pressure measured during three inspiratory cycles recorded under PS = 30 cmH₂O (Fig. 1). We defined PAR_{NIV} as the PP30/PP5 ratio. All the measurements were performed by the same investigators who were not aware of the clinical and biological details of the patient. The treating physicians were blinded to the results. The patients were divided into two groups: a group of patients having HF (HF group) and a group of patients without HF (non HF group). The diagnosis of HF was made by two experts on the basis of clinical data, cardiac ultrasound findings and BNP values (22). In case of a disagreement, a third senior physician was consulted and adjudicated the case.

Statistical analysis

Qualitative data were expressed with frequencies and percentage. Chi-square test or Fisher exact test were used to compare qualitative variables as appropriate. Normality was assessed with the Shapiro-Wilk test for continuous variables. Data are presented as mean (standard deviation) or median (interquartile range) for continuous variables according to their distribution. Comparison of data between the groups was performed using a two-sample Student's t-test or non-parametric tests, as appropriate. We calculated the sensitivity, specificity, negative predictive value and positive predictive value of PAR_{NIV} using the best cut-off. The choice of the PAR threshold was based on the level having the best sensitivity and specificity on the ROC curve (Youden index). A p-value less than 0.05 was statistically significant. The correlation between PAR_{NIV} and BNP and between PAR_{NIV} and left ventricular ejection fraction (LVEF) was assessed. All data were analyzed using the SPSS version 20.0 statistical software.

Results

Over the 2-month study period extending from November 2021 to December 2021, 73 patients were included, among whom 32 had a confirmed diagnosis of HF. Table 1 summarizes the characteristics of the overall population. The mean age was 67 ± 9 years for the HF group and 68 ± 10 years for the non HF group. A male predominance was observed in both groups, with 26 male patients (81%) in the HF group and 36 patients (87%) in the non HF group. Previous history of hypertension was found in 46% of patients and coronary artery disease in 25% in the HF group. This proportion represented 34% and 10%, in the non HF group with no statistically significant difference. Mean BNP values were 195 ± 190 pg/ml in the non HF group patients and 3421 ± 1200 pg/ml in the HF group ($p < 0.001$). LVEF was $43.9 \pm 11\%$ and 60 ± 13.5 in the HF and non HF groups respectively ($p < 0.001$). Mean PAR values were 0.86 ± 0.12 in the HF group and 0.71 ± 0.14 in the non HF group ($p < 0.01$) (Fig. 2). The area under the ROC curve for PAR_{NIV} was 0.75 with the best threshold at $PAR_{NIV}=0.6$ (Fig. 3). Using this cut-off, the sensitivity was 93%, specificity 21%, positive predictive value 48%, and negative predictive value 81%. The correlation between PAR_{NIV} and BNP was significant ($r = 0.52$; $p = 0.002$) (Fig. 4). PAR_{NIV} was inversely correlated with LVEF ($r = -0.337$; $p = 0.005$) (Fig. 5).

Table 1
Patients' baseline characteristics

	HF group n = 32	Non HF group n = 41	<i>P</i>
Age years, mean $\pm$ SD	67 $\pm$ 9	68 $\pm$ 10	NS
Sex-ratio M/F	26/6	36/5	NS
Smoking (pack-years), mean (SD)	42.8 (15.9)	44.6 (15.7)	NS
Body mass index (kg / m ²), mean (SD)	26.5 (4.3)	26.5 (5.8)	NS
Exacerbations within the past year, mean (SD)	2.4 (1.5)	2.1 (0.9)	NS
Past medical history, n (%)			
Chronic heart failure	12 (37)	2 (4)	< 0.001
Coronary artery disease	8 (25)	4 (10)	0.08
Hypertension	15 (46)	14 (34)	0.27
Diabetes	8 (25)	9 (21)	0.75
Atrial fibrillation	7 (22)	3 (7)	0.14
Clinical parameters, mean $\pm$ SD			
SBP (mmHg)	137 $\pm$ 23	142 $\pm$ 32	NS
DBP (mmHg)	72 $\pm$ 17	79 $\pm$ 22	NS
Respiratory rate (c/min)	29 $\pm$ 8	27 $\pm$ 7	NS
Heart rate (b/min)	103 $\pm$ 16	106 $\pm$ 24	NS
Temperature (°C), mean (SD)	37.1 (0.5)	37.1 (0.6)	NS
Biology			
pH, median (IQR)	7.33 (0.04)	7.32 (0.05)	NS
PaCO ₂ (KPa), median (IQR)	6,03 (2.2)	7,01 (1)	NS
PaO ₂ (KPa), median (IQR)	9,1 (3.2)	8,8(3)	NS
HCO ₃ ⁻ (mmol/l), mean $\pm$ SD	24 $\pm$ 5	25 $\pm$ 4	NS
SaO ₂ (%), mean $\pm$ SD	88 $\pm$ 6	82 $\pm$ 9	NS

Abbreviations: LVEF: Left Ventricular Ejection Fraction, M/F: male/female, SD: standard deviation, IQR: interquartile range, SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure, PaCO₂: partial pressure of carbon dioxide, PaO₂: partial pressure of oxygen, HCO₃⁻, Serum bicarbonate level, SaO₂: arterial oxygen saturation, BNP: Brain natriuretic peptide.

	HF group n = 32	Non HF group n = 41	P
BNP(pg/ml), mean $\pm$ SD	3421 $\pm$ 1200	195 $\pm$ 190	< 0.001
LVEF (%) : mean $\pm$ SD	43.9 $\pm$ 11	60 $\pm$ 13.5	< 0.001
Abbreviations: LVEF: Left Ventricular Ejection Fraction, M/F: male/female, SD: standard deviation, IQR: interquartile range, SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure, PaCO ₂ : partial pressure of carbon dioxide, PaO ₂ : partial pressure of oxygen, HCO ₃ ⁻ , Serum bicarbonate level, SaO ₂ : arterial oxygen saturation, BNP: Brain natriuretic peptide.			

Discussion

In our study, we proposed a new method using NIV as a mean of HF diagnosis during AECOPD. We found the following main results: 1. The PAR_{NIV} was higher in the HF group compared to the non HF group. 2. There was a correlation between the PAR_{NIV} value and BNP as well as between the PAR_{NIV} and LVEF. 3. Using the best cut-off (0.6) the PAR_{NIV} had a good sensitivity (93%). HF and COPD are two common conditions in clinical practice. Both conditions share common risk factors, such as advanced age, smoking, and systemic inflammation which explain their frequent coexistence. Among the co-morbidities most commonly associated with COPD, congestive HF is the most difficult to diagnose leading to a potential detrimental delay in the management of patient's condition, or on the contrary, to unnecessary treatment (6). HF diagnostic uncertainty can be as high as 40% (23). Chest X-ray and ECG are easily accessible diagnostic tests, but their value in identifying HF is limited in COPD patients (4, 9, 24). BNP values, as isolated markers of HF, are sometimes insufficient given that a number of non-cardiac conditions may be associated with BNP elevation (13). Diagnosing HF without echocardiography is often challenging and the best diagnostic approach remains unclear. Besides, echocardiography is not always accessible in the ED, and measurements depend on the operator experience. Moreover, the poor acoustic window caused by pulmonary air trapping may hinder accurate echocardiographic assessment of HF in 10–35% of COPD patients, particularly in those with more severe degrees of airflow obstruction (24). The study of the effect of intra-thoracic pressure variation on the cardiovascular system is likely to provide insight into cardiac function and help in the early and rapid diagnosis of HF. This principle has been applied in numerous studies for the identification of left ventricular dysfunction. One of the most recent studies was conducted by Remmen et al. in which VM and hemodynamic exploration by a Swan-Ganz catheter were performed (25). The results showed a very good correlation between pulmonary capillary wedge (pressure PCWP) and PAR ($r = 0.63$; $p < 0.001$). The area under the ROC curve of PAR for the diagnosis of HF (PCWP > 15 mmHg) was 0.85. This correlation still remains valid even in patients with arrhythmias. Similar results were found in the study of Wilemann et al. who performed invasive hemodynamic exploration by right catheterization and analyzed the blood pressure response to VM in 42 patients in a stable state (26). They found a very strong correlation between PCWP and PAR ($r = 0.75$; $p < 0.001$). In addition, treatment-induced changes in PCWP correlated well with changes in PAR ($r = 0.93$; $p < 0.001$). McIntyre et al. found similar results when they replaced VM with the application of intrathoracic

positive pressure using airway occlusion under continuous positive airway pressure (27). In mechanically ventilated patients, Zema et al. showed that an abnormal response to VM was associated with a simultaneous increase in central venous pressure and PCWP (28). The rectangular shape of blood pressure record under VM was consistently associated with an increase in PCWP within a range of 20 to 37 mmHg. In a recent study, Boubaker et al. showed that plethysmographic PAR during VM was higher in patients with AECOPD with left ventricular dysfunction compared to those without left ventricular dysfunction (0.78 vs. 0.38, $p = 0.01$). Similarly, they reported that PAR value was not significantly different between COPD group with left ventricular dysfunction and a third group with heart failure and no COPD diagnosis ($p = 0.78$). The area under the ROC curve for plethysmographic PAR to detect left ventricular dysfunction was significantly higher compared to that of the Boston score (0.92 vs 0.76; $p = 0.02$) (20). In practice, VM is difficult to apply in COPD patients in respiratory distress. Therefore, in our study, we proposed the application of NIV using two levels of PS (5 and 30 cmH₂O) to simulate the effects of VM. To our knowledge, this is the first study to use this method as a diagnostic tool of HF in AECOPD patients.

Our study has some limitations. First, we used the plethysmographic signal instead of the invasive blood pressure records. It is true that this signal can be modified by artifacts, but it was shown that the respiratory variations of the invasive and non-invasive blood pressure values were correlated (29). Second limitation of the present research that deserves to be highlighted is the choice of the level of PS. This level must be sufficient to create the intrathoracic pressure necessary to induce an effect on the cardiovascular system. We have used a level of 30 cmH₂O because beyond this level there is a risk of increasing leakage through the respiratory circuit and abdominal distension. Finally, our technique does not allow to affirm the role of HF in the actual exacerbation episode of COPD.

In conclusion, the PAR_{NIV} measurement could become in the future a useful index to facilitate the diagnosis of HF in AECOPD patients. Our results should be confirmed on a larger sample of patients.

Abbreviations

HF: Heart failure

COPD: Chronic obstructive pulmonary disease

AECOPD: acute exacerbation of chronic obstructive pulmonary disease

PAR: pulse amplitude ratio

NIV: non-invasive ventilation

ED: emergency department

PS: pressure support

PP: plethysmographic pulse pressure

AUC: area under roc curve

BNP: Brain Natriuretic Peptide

VM: Valsalva maneuver

PSV: pressure support ventilation

LVEF: left ventricular ejection fraction

PCPW: pulmonary capillary wedge pressure

Declarations

Ethics approval and consent to participate

The study protocol has been prepared in accordance with the revised Helsinki Declaration for Biomedical Research Involving Human Subjects and Guidelines for Good Clinical Practice. The study was approved by the ethics committee of our institution (Fattouma Bourguiba University hospital ethic committee). For all included patients, written informed consent was obtained before enrollment.

Consent for publication

Not applicable

Availability of data and materials

The datasets generated and/or analysed during the current study are not publicly available but are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Authors' contributions

SN and RB conceived the study and 0write the manuscript. SN and RB participated in the design of the study. SN and KBHA revised the manuscript. AS, IC, MAM, ZM and KB collected the data. KB, MHG and HB participated in the design of the study and performed the statistical analysis. All authors discussed the results and commented on the manuscript.

Acknowledgements

The authors acknowledge all of our Research Laboratory members who contributed greatly to this study.

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Figures

Figure 1

Measurement of Pulse amplitude ratio using plethysmographic blood pressure signal under non-invasive ventilation with two levels of pressure support (5 and 30 cmH2O). PP5= average of 3 consecutive pulse pressure values under pressure support of 5 cmH2O. PP30= average of 3 consecutive pulse pressure values under pressure support of 30 cmH2O.

Abbreviations: HF: heart failure.

Figure 2

Pulse amplitude ratio under non-invasive ventilation in patients with heart failure (HF group) and patients without heart failure (non HF group)

Abbreviations: PAR_{NIV}: Pulse amplitude ratio under non-invasive ventilation, HF: heart failure.

Figure 3

Area under the ROC curve of Pulse amplitude ratio under non-invasive ventilation.

Abbreviations: PAR_{NIV}: Pulse amplitude ratio under non-invasive ventilation, AUC: Area under the ROC curve.

Figure 4

Correlation between Pulse amplitude ratio under non-invasive ventilation and BNP values.

Abbreviations: PAR_{NIV}: Pulse amplitude ratio under non-invasive ventilation, BNP: brain natriuretic peptide.

Figure 5

Correlation between Pulse amplitude ratio under non-invasive ventilation and left ventricular ejection fraction values.

Abbreviations: PAR_{NIV}: Pulse amplitude ratio under non-invasive ventilation, LVEF: left ventricular ejection fraction.