# Value of inferior vena cava diameter respiratory change as a marker of heart failure in COPD exacerbation

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# Abstract

**Introduction:** Chronic obstructive pulmonary disease (COPD) is a frequent disease affecting mainly the elderly and males. Dyspnea is the most common reason for consultation for patients with COPD in ER. Distinguishing between pulmonary and/or cardiac origin can be challenging, hence the interest in ultrasound and in particular the study of the collapsibility index of the inferior vena cava ( $\Delta$ IVC).

**Objective:** To determine the value of the  $\Delta$ IVC in the diagnosis of heart failure (HF) patients with acute exacerbation of COPD (AECOPD).

**Methods:** This is a prospective study conducted in the ED of three Tunisian university hospitals from January 2022 to Mars 2022 including patients with AECOPD. During this period, 401 patients met the inclusion criteria. The final diagnosis of HF is based on the opinion of two emergency experts after consulting the data from the clinical examination, cardiac echocardiography, and BNP level. The  $\Delta$ IVC was calculated by Two experienced emergency physicians who were blinded from the patient's clinical and laboratory data, using the formula: (IVC max-IVC min) / IVC min x 100. A cut-off of 15% was used to define the presence (<15%) or absence of HF ( $\geq$ 15%). The left ventricular ejection fraction (LVEF) is also measured (cut-off preserved/reduced).

**Results:** The study population is relatively elderly with an average age of 67.2 years, predominantly male (68.9%), and characterized by heavy comorbidity and cardiopulmonary risk factors. The patients were divided into two groups according to the final diagnosis of HF; 165 patients (41.1%) had a final diagnosis of HF (HF group) and 236 patients (58.9%) without HF (non-group). Patients in the HF group had more comorbidities with higher rates of hypertension (p=0.001), chronic HF (CHF), coronary artery disease, and diabetes. The assessment of the performance of the  $\Delta$ IVC in the diagnosis of HF showed a sensitivity of 37.4% and a specificity of 89.7% using the threshold of 15%, which appears to be associated with the best diagnostic performance; the positive predictive value is 70.9% and the negative predictive value is 66.7%. The area under the ROC curve is 0.71(95%, CI 0.65 – 0.76).  $\Delta$ IVC values were not different between HF patients with reduced LVEF (LVrEF) and those with preserved LVEF (LVpEF)

**Conclusion:** Our main results show that the  $\Delta$ IVC has a good value for ruling out HF in COPD patients consulting emergency rooms for acute dyspnea.

Keywords: COPD; Heart Failure; Ultrasound; Inferior Vena Cava Diameter; Outcomes

## INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a respiratory condition characterized by bronchial obstruction due to airway and/or alveolar damage. It is an increasingly common disease and a major public health problem. According to the latest Global Initiative for Obstructive Lung Disease report, COPD is the fourth leading cause of death in the world(1,2). It resulted in more than 3 million deaths in 2019(1). The incidence of COPD is 3.7% in Tunisians aged 40 years and over(3). The evolution of COPD is marked by recurrent lifethreatening exacerbations that increase the deterioration of respiratory function and progression to chronic respiratory failure(4,5).

Consequently, any exacerbation must be treated promptly and adequately. This requires a good identification of the triggering factor for immediate and targeted etiological treatment(6,7). Among the commonest etiologic factors of acute exacerbation of COPD (AECOPD) is heart failure (HF) and the association of COPD with cardiovascular comorbidities is frequent. More than 20% of AECOPD are associated with HF(5), but this association is thought to be underestimated as the available diagnostic tools to identify HF in COPD patients consulting for dyspnea lack specificity(8–10). The gold standard in the diagnosis of HF is cardiac ultrasound and brain natriuretic peptide (BNP) testing, but these methods are problematic in terms of their availability in the emergency department (ED) and the need for an experienced sonographer.

Ultrasound of the inferior vena cava (IVC) is an easy, convenient, and validated examination for the diagnosis of HF by measuring the collapsibility index ( $\Delta$ IVC)(13–16). Indeed, the IVC is a compliant vessel whose diameter changes during the respiration cycle. Changes in IVC diameter are generally accentuated when the IVC intravascular pressure is low, and they decrease when IVC is congested. This feature is the basis for the diagnosis of HF, which is characterized by a decrease in the respiratory IVC diameter variation(17). COPD is associated with structural changes in the pulmonary vessels and right heart dysfunction classically. These conditions increase IVC congestion and reduce IVC inspiratory collapse even though there is no left HF. Therefore, it is expected that the specificity of  $\Delta$ IVC in the diagnosis of HF will decrease in AECOPD. Thus, our study aimed to assess the value of  $\Delta VCI$  in the diagnosis of HF in AECOPD in the emergency department for acute exacerbation.

#### **METHODS**

#### **Study design**

This is a prospective study conducted in the ED of three Tunisian university hospitals: Fattouma Bourguiba Monastir, Sahloul Sousse, and Farhat Hached Sousse from January 2022 to March 2022.

#### **Study population**

Inclusion criteria: patients aged more than 18 years, and consulting the ED for AECOPD were included. AECOPD is defined as an acute event characterized by worsening respiratory symptoms beyond day-to-day variations, requiring modification of treatment(1). Exclusion criteria: Patients with hemodynamic instability (presence of peripheral signs of shock, use of vasoactive drugs) or respiratory distress, use of mechanical ventilation, and/or altered consciousness (Glasgow Coma Score  $\leq$ 13) were excluded. Similarly, patients not consenting to the protocol were excluded

#### **Data collection**

After the consent of included patients, data from the clinical examination and complementary examinations were collected. A systematic collection of the following clinical data was performed including age, sex, body mass index (BMI), cardiovascular risk factors such as hypertension, diabetes, dyslipidemia, smoking, HF, and baseline New York Heart Association (NYHA) dyspnea stage. For all included data on physical examination, patients, electrocardiogram, standard biological tests, BNP level, and cardiac ultrasound data were collected. Cardiac ultrasound is performed using a 5-MHz convex probe device (Sonsonite Inc, Bothell, WA). Two experienced emergency performed physicians IVC diameter measurements during the study. Evaluations took 2 to 3 minutes for each technique, with the patient lying supine if tolerated or in a semirecumbent position with the head-of-bed elevated to 30°. The anteroposterior diameter of the IVC was measured at its maximum diameter during expiration and its minimal diameter during inspiration by TM mode at the subxiphoid region proximal to the confluence of the hepatic veins. Measurements were averaged

over 3 respiratory cycles to account for variations in respiratory efforts. The IVC collapsibility index is calculated by the following formula:  $\Delta IVC = (max IVC diameter)$ - min IVC diameter)/max IVC diameter. Measurements of the IVC were obtained during passive respiration. A  $\Delta$ IVC <15% is retained to define the presence of HF. The left ventricular ejection fraction (LVEF) is also measured (cutoff preserved/reduced). The operator was unaware of the patient's clinical and laboratory data. The final diagnosis of HF is based on the opinion of two emergency experts after consulting the data from the clinical examination, cardiac echocardiography, and BNP level.

## Statistical analysis

Quantitative variables are expressed by mean or median and compared with Student's t-test or non-parametric tests according to their distribution. The comparison of qualitative data is performed by the Chi-2 test. Sensitivity, specificity, positive and negative predictive values, likelihood ratios, and the receiver operating characteristic (ROC) of  $\Delta$ IVC for determining the diagnosis of HF were calculated with the corresponding 95% CIs with a test of significance set at P <0.05. Statistical calculations were performed with SPSS 21.0 (SPSS Inc, Chicago, Ill).

## RESULTS

During the study period, 431 patients with AECOPD were included. Thirty patients (6.9%) were excluded because of the inability to visualize the IVC. The patients were divided

into two groups according to the final diagnosis of HF; 165 patients (41.1%) had a final diagnosis of HF (HF group) and 236 patients (58.9%) without HF (non-HF group). The characteristics of the patients are summarized in Table 1. The mean age of the population was 67.2±12.2 years; hypertension was the most common cardiovascular risk factor (41.3%), 34.1% of patients had diabetes, and 15% had a history of chronic HF (CHF). Patients in the HF group had more comorbidities with higher rates of hypertension (p= 0.001), CHF, coronary artery disease, and diabetes. The mean LVEF was 40.2% in HF patients and 63.2% in non-HF patients (p<0.001). Sixty-five patients (39.4%) in the HF group had a preserved LVEF. The mean  $\Delta$ IVC was 20.5% $\pm$ 5.1% in the HF group, and  $35.2\% \pm 6.5\%$  in the non-HF group (p<0.001). The mean  $\Delta$ IVC in the HF subgroup with reduced LVEF (LVrEF) was 20.2%±6.1%, and  $20.8\% \pm 7.3\%$  in the HF subgroup with preserved LVEF (LVpEF). The distribution of patients according to  $\Delta$ IVC value intervals is shown in Figure 1.



Figure1: Distribution of patients according to  $\Delta IVC$ value intervals

Almost half of the patients (47.4%) had  $\Delta$ IVC >30%. Table 2 shows the diagnostic performance of  $\Delta$ IVC using different thresholds. For a threshold of 15% which appears to be associated with the best diagnostic performance, the sensitivity and specificity of  $\Delta$ IVC were 37.4% and 89.7% respectively; the positive predictive value is 70.9% and the negative predictive value is 66.7% (Table 2). The area under the ROC curve is 0.71(95%, CI 0.65 -0.76) (Figure 2).

## DISCUSSION

This study showed that the discriminatory power of  $\Delta$ IVC in the diagnosis of HF in AECOPD is acceptable. With a cutoff of 15%, the  $\Delta$ IVC has good specificity but low sensitivity. More precisely, a  $\Delta$ IVC value over 15% cannot exclude HF while patients with  $\Delta$ IVC below 15% are more likely to have HF.  $\Delta$ IVC values were not different between HF patients with LVrEF and those with LVpEF.

Patients with COPD are at high risk for cardiovascular disease, including HF(14). The prevalence of congestive HF in COPD patients in different series ranges from 7% to 30%(18). The diagnosis of one of these conditions may mask the other (16,17) and this combination presents many diagnostic and therapeutic dilemmas(19). Importantly, HF often is undetected in patients with AECOPD(20,21). Identifying HF in AECOPD in a rapid and noninvasive manner is very important in the ED. BNP is increasingly

Table1: Baseline patients' characteristics							
	Heart Failure n= 165 (41.1%)	Non- Heart Failure n= 236 (58.9%)	Р	Overall population			
Age (years), mean (SD)	70 (10)	64(12)	< 0.001	67.2(12.2)			
Sex-ratio	1.75	2. 63	0.07	2.2			
Comorbidities, n (%)	1.75	2.03	0.07	2.2			
Chronic heart failure	51(30.9)	11(4.6)	< 0.001	62(15.5)			
	× ,	11(4.6)		62(15.5)			
Coronary artery disease,	32(19.3)	21(8.8)	0.003	53(13.2)			
Hypertension Diabetes	92(55.7)	74(31.3)	0.001	166(41.4)			
	70(42.4)	67(28.3)		137(34.2)			
Chronic kidney disease, n (%)	20(14.7)	10(5.6)	0.1	30(7.5)			
NYHA, n(%)							
Ι	1(0.6)	11(4.6)	0.02	12(3.7)			
II	26(15.7)	62(26.2)	0.015	88(27.1)			
III	62(37.5)	81(34.2)	0.018	143(44)			
IV	37(22.4)	45(19.1)	0.03	82(25.2)			
Fever, n (%)	26 (15.7)	45 (19.1)	0.2	71(17.7)			
Systolic blood pressure (mmHg), mean (SD)	136(21.5)	139(31.7)	0.59	137.8(57.1)			
Diastolic blood pressure (mmHg), mean (SD)	73.15 (15.7)	76.17 (23.2)	0.1	74.9(18.5)			
Orthopnea, n(%)	42(25.4)	57(24.1)	0.46	99(24.9)			
Respiratory rate (cycle/min), mean (SD)	28.5 (9.7)	27.12 (7.9)	0.07	27(9.7)			
cardiac frequency (bpm), mean (SD)	102.1 (24.5)	106.2 (22.4)	0.24	104.4(38.7)			
Atrial fibrillation, n(%)	46(27.9)	35(14.8)	0.01	81(20.2)			
pH, mean (SD)	7.35 (1.03)	7.35 (0.08)	0.06	7.36(0.07)			
PaCO <sub>2</sub> (KPa), mean (SD)	6.8 (6.5)	7.6 (5.6)	0.25	7.3(6.4)			
PaO <sub>2</sub> (KPa), mean (SD)	11.5 (8.8)	12 (7.2)	0.52	11.8(8.7)			
HCO <sub>3</sub> <sup>-</sup> (mmol/l), mean (SD)	25.8 (8.3)	27 (9.2)	0.09	26.9(10.8)			
SaO <sub>2</sub> (%), mean (SD)	89.8 (7.1)	89.7 (10.2)	0.85	89.8(12.8)			
BNP (pg/ml), median [ IQR]	306 [172-672]	69 [29-154]	< 0.001	165[58-432]			

Abbreviation: NYHA (New York Heart Association), bpm (beat per minute), BNP (Brain Natriuretic Peptide) PaCo2(pulmonary partial pressure of Carbone dioxide, PaO2 (pulmonary partial pressure of oxygen), SD( Standard Deviation ), IQR( Interquartile Range)

used in clinical practice as a marker of HF but lacks specificity in many clinical situations. In particular, BNP levels of up to 500 pg/mL may be observed in cases of right ventricular dilatation (22–24). Tung et al showed that in COPD patients with a history of HF, the specificity of BNP is only 47%(25). To better identify HF, a more efficient test is needed. Based on its usefulness for the detection of hemodynamic congestion, IVC ultrasonography has been recently proposed in HF diagnosis. The IVC is a compliant blood vessel subject to extramural pressure and its caliber varies with respiration(26), blood volume(27), and right heart function(28). In cases of congestive HF, volume overload dilates the IVC to the limits of its elasticity such that the increase in pressure during expiration leads to a minimal increase in diameter. Previous studies have shown that changes in IVC diameter correlate with ventricular filling pressures(29–31). In patients with chronic HF referred for a right heart catheterization, IVC diameter performed

Table 2: Performance of the ΔIVC in the diagnosis of HF with different thresholds.									
ΔIV C (%)	Se (%)	Sp (%)	PPV (%)	NPV (%)	LR +	LR -			
5	4.9	96.5	50.1	59.2	1.4	0.9			
10	17.4	94.4	68.5	62	3.1	0.8			
15	37.5	89.7	70.9	66.7	3.5	0.7			
20	50.3	81.9	66.1	70.2	2.7	0.6			

Abbreviations: Se (Sensibility), Sp (Specificity), PPV( Positive Predictive value), NPV(Negative Predictive value) LR (Likelihood-Ratio).



Figure 2: Receiver Operating Characteristic curve

the best among several indexes (area under the receiver operating characteristic curve, 0.89) at identifying those with pulmonary capillary wedge pressures  $\geq$  15 mm Hg (32) . $\Delta$ VCI measurement in patients with acute undifferentiated dyspnea was shown to provide a good diagnostic approach in the ED. Blehar et al. reported a sensitivity of 0.93 and a specificity of 0.84 for detecting HF in 14 out of 46 patients for a  $\Delta VCI < 15\%(33)$ . Anderson et al. reported a sensitivity of 0.52 and a specificity of 0.86 for detecting HF in 44 out of 101 patients for a  $\Delta$ IVC <20%(34). Yamanoğlu et al. reported а sensitivity of 0.84 and a specificity of 0.92 for detecting HF using a  $\triangle$ VCI cut-off <52%(35). Miller et al. reported a sensitivity of 0.80, and a specificity of 0.81 for detecting HF in 35 out of 89 patients for a  $\triangle$ IVC <33%(36). So, except the

study of Anderson et al., all the cited studies reported a good sensitivity and specificity with variable thresholds. In this study, we confirmed the good specificity of  $\Delta$ IVC contrary to what one might expect in patients with a prevalence of pulmonary hypertension and cor pulmonale that can exceed 50%(37). Reduced right ventricular compliance and/or increased filling pressures in COPD patients, especially during acute exacerbation, expose the right atrium to pressure load and dilatation and this should decrease respiratory IVC diameter changes. The fact that mean  $\triangle$ IVC is 24% in our HF patients means that IVC collapsibility was not altered in our AECOPD patients. To our opinion, these results emerge from 3 main causes. The first cause is probably related to the possibility that our patients were not severe enough to have a significant elevation of pulmonary artery pressure and systemic venous congestion. The second cause is related to the respiratory system mechanics of AECOPD patients which are characterized by the development of dynamic hyperinflation and intrinsic positive endexpiratory pressure or PEEPi(38). Initiation of inspiratory flow requires inspiratory force to overcome PEEPi, which translates into an increased inspiratory effort during the triggering phase and generates high variations of intrathoracic pressure. These variations could be amplified by a simultaneous rise in intraabdominal pressure (39) making the IVC more easily compressible. The third reason is related to the location of IVC diameter measurement and probe orientation as variations of IVC diameters

are significantly lower when recorded close to the right atria(40).

This study was limited first by its smaller size and the possible selection bias from the convenience sampling methodology. Second, our results could not be extrapolated to all AECOPD because severe patients were excluded. Third, we did not assess the reproducibility of the  $\Delta$ IVC because we assumed that its reproducibility is generally good. Fourth, the blinded nature of the study may not be fully respected, but all provisions were made to reduce this bias. Fifth, we did not measure the direct impact of valvular diseases on IVC diameters, such as in the case of tricuspid or mitral regurgitation. This fact may affect sensitivity, but not specificity. Finally, the  $\Delta VCI$  was measured after a lag time, approximately 4 hours following ED admission (methods), a period during which the patient condition could be improved by treatment. This would be responsible for a decrease in the sensitivity of the  $\Delta$ IVC in the diagnosis of HF.

## CONCLUSION

In summary, there are no studies that have specifically sought for assessment of IVC collapsibility index performance in the diagnosis of HF in AECOPD. Our results suggest that IVC collapsibility may still be considered in the diagnostic approach of HF in AECOPD patients, at least as a ruling-out test. In patients with  $\Delta$ IVC value >15%, HF cannot be excluded, while patients with  $\Delta$ IVC under 15% are more likely to have HF. Further studies are needed to better objectify its diagnostic performance alone or in combination with other markers of HF.

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