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Original Article

Evaluation of oxygen content-based index, FShuntE, for identifying the etiology in acute dyspnea: a cross-sectional clinical study in 1,035 subjects

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Abstract: The difference between pulmonary and cardiac causality in the diagnosis of acute dyspnea is critical to the outcomes of patients since dyspnea is correlated to severe conditions, such as pneumothorax or pulmonary embolism and progressive chronic conditions. The B-type natriuretic peptide (BNP) has been widely used to diagnose heart failure but with low diagnostic specificity. The arterial blood gas analysis has been suggested as a viable and cost-effective diagnostic marker, although the optimal implementation parameters and values remain unclear. The present study evaluated the diagnostic accuracy of oxygen content-based index and the estimated shunt fraction (FShuntE) for the differential diagnosis between the pulmonary and acute cardiac dyspnea. A total of 1,077 patients with acute dyspnea were enrolled from April 2012 to August 2014 consecutively in this cross-sectional study. The FShuntE values and the levels of N-terminal pro-B type NP (NT-proBNP) were measured. A total of 42, or 42 of 1,077 patients were excluded due to incomplete data. The final clinical diagnoses included 464 pulmonary cases (M/F=239/225, median age 68 years) and 571 cardiac cases (M/F=256/315, median age 67 years) of acute dyspnea. A significant FShuntE elevation was observed in the pulmonary cases. An FShuntE threshold of 8.35% exhibited a sensitivity and specificity of 63.57% and 90.09%, respectively (positive likelihood ratio of 3.116). The alternative thresholds ranged from 6.35-10.35% with the sensitivity increasing progressively from 57.09 to 68.30% and the specificity decreasing progressively from 92.67 to 84.48%. The area under the curve (AUC) of the combination of the FShuntE and the NT-proBNP parameters was 0.942 with a 95% confidence interval (CI) of 0.928-0.955, whereas the sensitivity and specificity were 88.97% and 88.36%, respectively. The FShuntE was demonstrated as useful in the differential diagnosis of the pulmonary and cardiac involvement in acute dyspnea.

Keywords: Acute dyspnea, differentiation diagnosis, FshuntE, oxygen content-based index

Introduction

Dyspnea is defined as the subjective experience of breathing discomfort that consists of qualitatively distinct sensations varying in intensity, according to the American Thoracic Society [1]. The incidence of dyspnea cases contributes up to 3.5% of the total emergency department visits in the USA [2]. The symptoms have been associated with illness, severity, and mortality. Notably, in the case of cardiac mortality, dyspnea is a significant risk contributor as compared to angina [3].

The pathophysiology of acute dyspnea is not well defined. The symptoms have been suggested to originate from the interaction of pathways that affect the stimulation of the receptors of the upper and lower airway, the lung parenchyma, and the excessive stimulation of the respiratory center by central and peripheral chemoreceptors [4]. According to the specific causes, dyspnea may be categorized as cardiac and/or pulmonary that originate from distinct pathophysiological conditions, such as pneumothorax or pulmonary embolism [5]. The underlying causes of acute dyspnea cannot be distin-

guished directly at the initial clinical settings. The results of the diagnostic imaging and blood examination tests may be unavailable initially; during this period, the exacerbation of dyspnea may be critical for the development of life-threatening diseases [6]. The use of cardiac plasma biomarker, such as a B-type natriuretic peptide (BNP), has been demonstrated as a diagnostic tool for acute dyspnea, whereas the medical history and the scores of vital parameters are used for assessing the prognosis of disease [7-11]. BNP or N-terminal pro-BNP (NTproBNP) has been used diagnostically in dyspnea patients, in order to determine the etiology of the disease [8, 9]. Recent studies have indicated that although the use of BNP may not provide a definite diagnosis, it can lead to further unnecessary examinations and additional healthcare costs [11] at typical diagnostic thresholds (93-450 pg/mL for NT-proBNP and 40-100 pg/mL for BNP) [10, 12, 13]. Consequently, the clinical BNP guidelines are increasing in complexity, including scaled thresholds based on the condition, age, and the likelihood of the disease in the patient [11, 14, 15]. Thus, developing novel biomarkers and their clinical application to the pathological dyspnea is essential in order to improve diagnostic performance and cost-efficiency.

The index "fraction of the measured transpulmonary shunt" (FShunt) is used to characterize the concentrations of blood gases in acute dyspnea. It is *calculated* by the shunt equation quantifying the extent that venous blood bypasses oxygenation in the capillaries of the lungs [16]. The FShunt can be used in the diagnosis of hyperoxia, normoxia, and hypoxia and excludes the diagnosis of hyperoxemia, normoxemia, and hypoxemia [16]. The evidence for the use of FShunt in the case of dyspnea is scarce in the literature and has been examined as an indicator of pulmonary venous admixture at various oxygen fractions in anesthetized sheep and horses administered dobutamine [17]. Hitherto, the use of FShunt for the determination of intrapulmonary shunt in acute dyspnea patients from cardiac and/or pulmonary causes has not been investigated, although the intrapulmonary shunt and gas exchange parameters utilizing the Qs/Qt fraction have been explored in healthy individuals following administration of dobutamine and dopamine [18]. The determination of FShunt is relatively difficult in emergency departments, as the central venous blood is required for the analysis. The use of specific analytical equipment, such as the ABL800 FLEX, has been adopted to estimate the FShunt value (FShuntE) in the absence of venous blood.

The present study aimed to access the diagnostic accuracy of the oxygen content-based index and FShuntE for the differential diagnosis between pulmonary and acute cardiac dyspnea. Herein, we analyzed 1,035 patients with acute dyspnea with respect to FShuntE and NTproBNP levels.

Materials and methods

General design of study

This cross-sectional clinical study was conducted at the Pulmonology Unit of the Department of Cardiology and Emergency Services at Beijing Geriatric Hospital from April 2012 to August 2014. A total of 1,077 patients with clinical signs and symptoms of acute dyspnea, unrelated to previously known underlying cardiac or pulmonary pathology, were enrolled consecutively, and conventional clinical diagnostic outcome (including chest X-ray, electrocardiography, and echocardiography) and FShuntE data collected.

The present study was conducted in accordance with the ethical principles for human experimentation stated in the Declaration of Helsinki and all applicable amendments as defined by the International Conference on Harmonization Good Clinical Practice Guidelines (ICH GCP E6 R2) to safeguard the rights, safety, and well-being of the subjects. Moreover, the integrity of the data acquired during the study is preserved. The study protocol was approved by the Ethics Committee of the Beijing Geriatric Hospital and written informed consent was obtained from all subjects prior to participation in the study.

Patient selection for analysis

All consecutive acute dyspnea patients presenting for emergency evaluation and care at the hospital were requested to participate in the study unless they were unable to speak or understand the local language sufficiently, for instance, patients with dementia or other mental disorders, in order to comprehend the study procedures or provide consent.

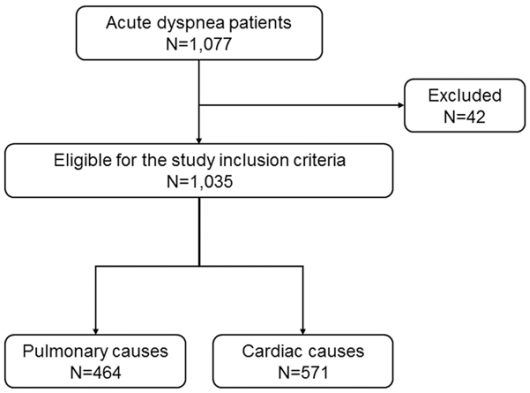

Figure 1. Schematic representation of the study.

The patients included in the analysis fulfilled the following criteria: (1) clinical signs or symptoms of acute dyspnea; (2) respiratory rate ≥ 22 times/min during clinical evaluation; (3) low-flow oxygen (≤ 5 L/min) inhalation upon clinical evaluation. Those patients were excluded from the analysis who (1) required invasive or no-ninvasive mechanical ventilation; (2) required emergency resuscitation (i.e., CPR); (3) had a medical history of hemopathy, malignant tumors, shunt congenital heart disease, pulmonary resection, and massive pleural effusion; (4) had incomplete clinical data.

Demographic and clinical data

The demographic and clinical data were obtained from the medical records of all subjects, including age, gender, medical history, current medications, and ethnicity.

In the Emergency Care Unit, all acute dyspnea patients were evaluated according to the standard of care of the hospital, which included electrocardiography, echocardiography, chest X-ray or CT scanning, and blood examination. The vital signs were recorded, including blood pressure, heart rate, respiratory rate, lung signs, displaced apex beat, third heart sound, peripheral edema, and extent of heart failure using the New York Heart Association (NYHA) score (I, II, III, or IV) [19]. These data were collected by echocardiogram (Philips iu22; Philips Healthcare, DA Best, Netherlands), chest X-ray or CT scan, and electrocardiogram (ECG; GE MAC 1600 with Cardiosoft v. 6. 5; GE Healthcare, London, UK). In the case of subjects that consented to participate in the study, echocardiograms, ECGs, and clinical assessments were conducted independently by physicians blinded to the other care data.

The acute cardiac dyspnea (heart failure) was differentially diagnosed according to the Framingham criteria [20]. Briefly, the criteria are summarized as follows: A. Major criteria: Paroxysmal nocturnal dyspnea or orthopnea, neck vein distension, rales, cardiomegaly, acute pulmonary edema, S3 gallop, increased venous pressure ≥ 16 cm water, circulation time ≥ 25 s, and hepatojugular reflux. B. Minor criteria: ankle edema, night cough, dyspnea on exertion, hepatomegaly, pleural effusion, vital capacity decreased 1/3rd from maximum, and tachycardia rate > 120/min [20].

Calculation of FShuntE data

The arterial blood samples were immediately sent to the laboratory for analysis of the FShuntE values by the blood gas analysis on the ABL800 FLEX analyzer v. 6.10 (Radiometer, Denmark) using an arterial blood gas needle. The formula for FShunt calculation is as follows:

$$FShunt = \left[1 + \frac{ctO_2(a)-ctO_2(\bar{v})}{ctO_2(A)-ctO_2(a)}\right]^{-1}$$

where $ctO_2(a)$ indicates total oxygen in arterial blood, $ctO_2(A)$ indicates total oxygen in the alveolar air, and $ctO_2(\bar{v})$ indicates total oxygen in the mixed venous blood.

For no venous sample measured, $ctO_2(a)$-$ctO_2(\bar{v})$ was replaced with constant 2.3 mmol/L to calculate the FshuntE according to the reference manual of ABL800 FLEX (http://biomed.au.dk/fileadmin/www.biomed.au.dk/faenotypering/Pdf/Radiometer-ABL-700-serie.pdf).

Data quality control

All data were double-entered and cross-validated by the study staff for quality control and then analyzed using EpiData v. 3.1 (EpiData Association, Odense, Denmark).

Statistical analysis

The statistical analyses were carried out using SPSS v. 19.0 (SPSS, Inc., Chicago, IL, USA). The continuous variables were summarized by mean ± standard deviation or median (upper and lower quartiles), and the categorical variables were summarized as number and per-

Table 1. Baseline demographic and clinical characteristics of patients with acute dyspnea treated in emergency care based on final diagnosis (cardiac or pulmonary diagnosis)

Parameters	Pulmonary diagnosis (N=464) M: Q1-Q3	Cardiac diagnosis (N=571) M: Q1-Q3	*P*-value
Sex (M/F)	239/225	256/315	0.241
Age	68: 59-77	67: 57-75	0.001
LVEF (%)	68: 64-73	57: 43-66	<0.001
LAD	31: 27-34	39: 32-46	<0.001
LVEDD	46: 41-49	52: 45-58	<0.001
BUN	7.0: 5.3-9.1	8.4: 6.1-12.0	<0.001
Cr	68: 56-81	96: 71-132	<0.001
ALT	19: 13-27	17: 12-27	0.337
AST	22: 16-30	20: 15-29	0.027
TBIL	11.0: 8.3-14.3	12.5: 8.7-18.0	<0.001
Fshunt (%)	20.7: 13.0-31.6	2.4: -2.4-8.7	<0.001
Concomitant disease (n/%)			
Hypertension	240 (51.7%)	432 (75.7%)	<0.001
Diabetes mellitus	88 (19.0%)	185 (32.4%)	<0.001
DCM	0 (0)	35 (6.1%)	<0.001
Valvulopathy	5 (1.1%)	15 (2.6%)	0.072
CAD	164 (35.3%)	460 (80.6%)	<0.001
COPD	409 (88.1%)	138 (24.2%)	<0.001
PIF	36 (7.8%)	0 (0)	<0.001
Asthma	57 (12.3%)	21 (3.7%)	<0.001
Pulmonary infection	148 (31.9%)	77 (13.5%)	<0.001
Pleural effusion	10 (2.2%)	71 (12.4%)	<0.001

Abbreviations: M: Q1-Q3 median: 25th-75th percentile; LVEF, left ventricular ejection fraction; LAD, left atrial diameter; TBIL, total bilirubin; Lac, Lactate; LVEDD, left ventricular end diastolic diameter; PATD, pulmonary artery trunk diameter; Cr, creatinine; PO_2, arterial oxygen pressure; PCO_2, partial pressure of carbon dioxide; SO_2, oxygen saturation; Fshunt, shunt fraction; ALT, alanine transaminase; AST, glutamic oxaloacetic transaminase; PIF, pulmonary interstitial fibrosis; CAD, coronary artery disease.

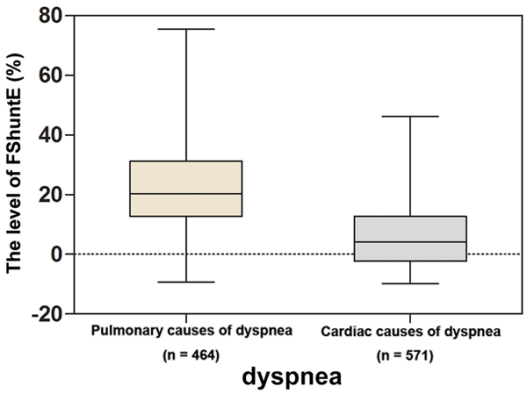

Figure 2. The level of FShuntE in patients with acute dyspnea. The median level of FShuntE in the patients diagnosed with pulmonary disease was 20.35% (25th percentile, 12.83%; 75th percentile, 31.2%), and the median level of FShuntE in the patients diagnosed with primary cardiac disorder was 4.2% (25th percentile, -2.3%; 75th percentile, 12.7%).

centages. Pearson's χ^2-tests were used to explore the associations between the categorical data. Student's t-test was used to compare the numerical data in two groups. The two-tailed tests were performed with a significance level of 0.05 (P<0.05). The receiver operating curves (ROC) were generated based on FShuntE and/or NT-proBNP measurements, while the area under the curve (AUC) was estimated. Sensitivity, specificity, and Youden's index of FShuntE and/or NT-proBNP in pulmonary diagnosis were calculated, and a cut-off value was obtained. The correlation between the sensitivity and specificity was determined by the FShuntE value, and the optimal FShuntE thresholds elucidated.

Results

General condition of subjects and final diagnosis

A total of 1,077 acute dyspnea patients were screened and recruited. All participants were of Han Chinese ethnicity. 1,035 patients fulfilled all the criteria for inclusion in the analysis and completed the study. A large number of subjects was included, since a majority was excluded based on missing single points of data that were not essential for the primary analysis. Among the enrolled patients, 464 (44.8%) cases presented pulmonary disease, while 571 (55.2%) patients were with cardiac causes (**Figure 1**).

The patients were grouped based on the final diagnosis. The demographics and the baseline clinical characteristics are shown in **Table 1**. The patients diagnosed with pulmonary dyspnea comprised of 239 males and 225 females, with a mean age of 68.34 ± 10.61 years, whereas the patients diagnosed with cardiac

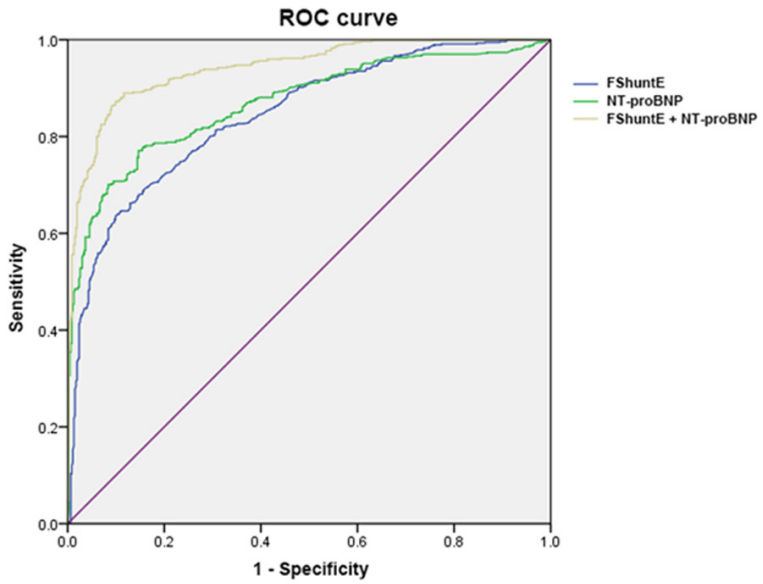

Figure 3. ROC of FshuntE and/or NT-proBNP in the diagnosis of pulmonary dyspnea. The AUC of FShuntE in the diagnosis of pulmonary dyspnea was 0.844 with 63.57% sensitivity and 90.09% specificity; whereas, the AUC of NT pro-BNP was 0.869 with a 77.06% sensitivity and 85.34% specificity. The AUC of the combination of FShuntE and NT pro-BNP in the diagnosis of pulmonary dyspnea was 0.942 with a sensitivity of 88.97% and specificity of 88.36%. ROC, receiver operating characteristic; AUC, area under the curve.

dyspnea comprised of 256 males and 315 females, with a mean age of 66.05 ± 11.06 years. The mean value of the corresponding biochemical and pulmonary parameters (LVEF, LAD, LVEDD, BUN, Cr, AST, and TBIL) was significantly different between the two groups (**Table 1**, P<0.05). In addition, the incidence of concomitant diseases altered significantly between the cardiac and the pulmonary dyspnea group (P<0.001), except valvulopathy (**Table 1**).

FShuntE level

1035 were found to be fully eligible patients. The level of FShuntE (%) parameters was significantly higher in the patients with pulmonary dyspnea as compared to those with underlying cardiac disease (**Figure 2**). The median level of FShuntE in the final pulmonary diagnosed patients was 20.35% (25th percentile, 12.83%; 75th percentile, 31.2%), whereas that in primary cardiac diagnosed patients was 4.2% (25th percentile, -2.3%; 75th percentile, 12.7%) (**Figure 2**).

FShuntE diagnostic performance

The ROC curve analysis assessed the diagnostic performance of FShuntE in patients with cardiac and pulmonary dyspnea. The AUC of the ROC curve for the FShuntE parameter in the patients with a final pulmonary diagnosis was 0.844. Based on the cut-off value of 8.35%, the sensitivity and specificity of FShuntE were 63.57% and 90.09%, respectively to differentiate the pulmonary dyspnea from cardiac dyspnea. On the other hand, the AUC of the parameter NT pro-BNP in the patients with final pulmonary diagnosis was 0.869, and the cut-off value was 2059 pg/mL with 77.06% sensitivity and 85.34% specificity (**Figure 3**). A high AUC was derived from the combination of the two latter parameters in the case of pulmonary dyspnea: 0.942 [95% confidence interval (CI): 0.928-0.955] with a sensitivity of 88.97% and specificity 88.36% (**Figure 3**).

Optimization of diagnostic performance of FShuntE

The sensitivity and specificity of the test performance of FShuntE necessitate an adequate balance in order to provide reasonable diagnostic inferences from the data measured. The diagnostic performance of FShuntE at the threshold of 8.35% (cut-off value from ROC of FshuntE for differential diagnosis) was analyzed initially (**Table 2**). At this threshold, the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (PLR), and negative likelihood ratio (NLR) were 63.57%, 90.09%, 88.75%, 66.77%, 6.41, and 0.40, respectively, with respect to the subjects diagnosed with pulmonary dyspnea (**Table 2**). Other tolerable thresholds ranged from 6.35-10.35% with the sensitivity increasing progressively from 57.09 to 68.30% and the specificity decreasing progressively from 92.67 to 84.48% (**Table 2**). The PPV, NPV, PLR, and NLR parameters remained at similar levels without apparent increasing or decreasing trends within this range (**Table 2**).

Discussion

The present study, for the first time, investigated the diagnostic performance of oxygen con-

Table 2. Diagnostic performance of Fshunt (%)

Fshunt (%) Threshold	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	PLR	NLR
6.35	57.09	92.67	90.56	63.70	7.79	0.46
7.35	60.95	91.59	89.92	65.59	7.25	0.43
8.35	63.57	90.09	88.75	66.77	6.41	0.40
9.35	64.97	87.28	86.28	66.94	5.11	0.40
10.35	68.30	84.48	84.42	68.41	4.40	0.38

Abbreviations: PPV, positive predictive value; NPV: negative predictive value; PLR: positive likelihood ratio; NLR: negative likelihood ratio.

tent-based index, FShuntE, as a diagnostic indicator of the underlying pulmonary or cardiac cause of acute dyspnea. The results revealed that FShuntE was an accurate diagnostic marker with a range of 6.35-10.35% detection threshold, for the diagnosis of the pulmonary and cardiac dyspnea. The optimal value required to achieve the optimal balance of sensitivity and specificity was set at an FShuntE threshold of 8.35%. Its diagnostic value was similar to that of NT-proBNP (AUC: 0.844 *vs*. 0.869). The AUC value of the combination of FShuntE and NT-proBNP was higher than that noted in FShuntE or NT-proBNP alone. Since the latter parameters could be estimated using standard laboratory equipment in emergency departments, the use of FShuntE may be a viable alternative indicator of the differential diagnosis in patients with acute dyspnea presented at the Emergency Care Units.

Since obtaining mixed central venous blood in a majority of clinical settings is difficult, only a few previous studies that have examined the use of FShunt for differentiating the etiology of acute dyspnea are available in human. The result by Andreassen et al. measuring the shunt level in cardiac patients requiring supplementary oxygen was similar to that in our study [21]. Another study estimated the pulmonary gas exchange parameters in patients with heart failure and the shunt level was also consistent with our study [22]. In 2012, Araos et al. [17] reported that FShunt was a robust indicator of venous admixture (Qs/Qt) at various fractions of inspired oxygen (FIO(2)s) in sheep models undergoing lung ventilation, with a potential clinical utility as a surrogate measure of Qs/Qt. Notably, FShunt indicated the out-of-balance effect of ventilation/perfusion ratios, which is crucial in pulmonary-related dyspnea (such as COPD and asthma), wherein the increases in the shunt fraction are large and readily apparent. Similarly, Balchum et al. [23] previously reported a significant pulmonary arteriovenous shunting imperceptible by pulmonary angiography in COPD, subsequently linked to pulmonary arteriovenous shunting in COPD. In cases reports by Harrow et al. [24], a 51-year-old female patient undergoing pulmonary artery angiography for arteriovenous fistula after Swan-Ganz catheter balloon block revealed an FShunt that was reduced from 37% to 9% during dyspnea. These studies confirmed the occurrence of the intrapulmonary anatomic shunt and/or functional shunt in patients with lung diseases, and elevated Fshunt was related to pulmonary diseases. This phenomenon was in agreement with the results of the current study. A study on the FshuntE change in cardiac failure patients is yet lacking. In the case of acute cardiac failure, according to the pathological mechanisms, the left atrial pressure would increase and reverse the transmission through the pulmonary vein, as a result of inhibiting and reducing the shunt. The present study corroborated with this phenomenon.

Herein, the diagnostic value of FshuntE in the differential diagnosis of pulmonary and/or cardiac involvement in acute dyspnea was high. Moreover, the FshuntE showed a relatively higher diagnostic specificity than NT-proBNP. In addition, the commonly used biomarkers in dyspnea, such as BNP and NTproBNP, exhibited poor diagnostic specificity. Thus, the results of the present study indicated that FshuntE could be used as a potentially valuable marker to diagnose pulmonary and/or cardiac involvement in acute dyspnea due to its high specificity. These results also provide evidence that the combination of FshuntE and NTproBNP can improve the sensitivity than FshuntE alone.

Nevertheless, the present study has some limitations. Considering the mechanical ventilation, massive pleural effusion and high-flow oxygen inhalation (> 5 L/min) could obviously affect the FShuntE value; hence, these patients were excluded from the study population. As a result, additional studies are essential in order to verify the effects of FShuntE in the differential diagnosis of dyspnea in this population.

Furthermore, the present study demonstrated that FShuntE values were significantly higher in acute dyspnea patients with pulmonary conditions as compared to those with underlying cardiac disease, thereby offering a differential diagnosis of acute dyspnea patients, based on the elevation of the FShuntE values (%). FShuntE was proved to be a clinically useful biochemical indicator for the differential diagnosis of pulmonary and/or cardiac involvement in acute dyspnea. In addition, the FShuntE can be utilized practically by conventional laboratory assessment tools and methods readily available at most facilities, with minimal additional cost and time.

Disclosure of conflict of interest

None.

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References

[1] Parshall MB, Schwartzstein RM, Adams L, Banzett RB, Manning HL, Bourbeau J, Calverley PM, Gift AG, Harver A, Lareau SC, Mahler DA, Meek PM, O'Donnell DE; American Thoracic Society Committee on Dyspnea. An official American thoracic society statement: update on the mechanisms, assessment, and management of dyspnea. Am J Respir Crit Care Med 2012; 185: 435-452.

[2] Niska R, Bhuiya F, Xu J. National hospital ambulatory medical care survey: 2007 emergency department summary. Natl Health Stat Report 2010; 6: 1-31

[3] Abidov A, Rozanski A, Hachamovitch R, Hayes SW, Aboul-Enein F, Cohen I, Friedman JD, Germano G and Berman DS. Prognostic significance of dyspnea in patients referred for cardiac stress testing. N Engl J Med 2005; 353: 1889-1898.

[4] Coccia CB, Palkowski GH, Schweitzer B, Motsohi T and Ntusi NA. Dyspnoea: pathophysiology and a clinical approach. S Afr Med J 2016; 106: 32-36.

[5] Burki N. Acute dyspnea. Is the cause cardiac or pulmonary or both. Consultant 2005; 45: 209-212.

[6] Mantuani D, Frazee BW, Fahimi J and Nagdev A. Point-of-care multi-organ ultrasound improves diagnostic accuracy in adults presenting to the emergency department with acute dyspnea. West J Emerg Med 2016; 17: 46-53.

[7] Lund N, Rohlen A, Simonsson P, Enhorning S, Wessman T, Gransbo K and Melander O. High total carbon dioxide predicts 1-year readmission and death in patients with acute dyspnea. Am J Emerg Med 2015; 33: 1335-1339.

[8] Maisel A, Mueller C, Adams K Jr, Anker SD, Aspromonte N, Cleland JG, Cohen-Solal A, Dahlstrom U, DeMaria A, Di Somma S, Filippatos GS, Fonarow GC, Jourdain P, Komajda M, Liu PP, McDonagh T, McDonald K, Mebazaa A, Nieminen MS, Peacock WF, Tubaro M, Valle R, Vanderhyden M, Yancy CW, Zannad F, Braunwald E. State of the art: using natriuretic peptide levels in clinical practice. Eur J Heart Fail 2008; 10: 824-839.

[9] Mueller C, Laule-Kilian K, Scholer A, Frana B, Rodriguez D, Schindler C, Marsch S and Perruchoud AP. Use of B-type natriuretic peptide for the management of women with dyspnea. Am J Cardiol 2004; 94: 1510-1514.

[10] Barents M, van der Horst IC, Voors AA, Hillege JL, Muskiet FA and de Jongste MJ. Prevalence and misdiagnosis of chronic heart failure in nursing home residents: the role of B-type natriuretic peptides. Neth Heart J 2008; 16: 123-128.

[11] Dickstein K, Cohen-Solal A, Filippatos G, McMurray JJ, Ponikowski P, Poole-Wilson PA, Strömberg A, van Veldhuisen DJ, Atar D, Hoes AW, Keren A, Mebazaa A, Nieminen M, Priori SG, Swedberg K; ESC Committee for Practice Guidelines (CPG). ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the task force for the diagnosis and treatment of acute and chronic heart failure 2008 of the European society of cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). Eur J Heart Fail 2008; 10: 933-989.

[12] Fuat A, Murphy J, Brennan G, Mehrzad A, Johnston J and Smellie W. Suspected heart failure in primary care-the utility of N-terminal pro b-type natriuretic peptide (NT proBNP) as a prescreening test for secondary care referral-a real life study. European Heart Journal 2005; 26: 181.

[13] Hildebrandt P and Collinson PO. Amino-terminal pro-B-type natriuretic peptide testing to assist the diagnostic evaluation of heart failure in symptomatic primary care patients. Am J Cardiol 2008; 101: 25-28.

[14] Chronic heart failure: national clinical guideline for diagnosis and management in primary and secondary care: partial update [Internet]. London: Royal College of Physicians (UK); 2010.

[15] Krishnaswamy P, Lubien E, Clopton P, Koon J, Kazanegra R, Wanner E, Gardetto N, Garcia A, DeMaria A and Maisel AS. Utility of B-natriuretic peptide levels in identifying patients with left ventricular systolic or diastolic dysfunction. Am J Med 2001; 111: 274-279.

[16] Iluchev D. A new index for assessing arterial oxygen profile in patients with respiratory failure. Folia Med (Plovdiv) 1996; 38: 39-43.

[17] Araos JD, Larenza MP, Boston RC, De Monte V, De Marzo C, Grasso S, Haskins SC, Crovace A and Staffieri F. Use of the oxygen content-based index, Fshunt, as an indicator of pulmonary venous admixture at various inspired oxygen fractions in anesthetized sheep. Am J Vet Res 2012; 73: 2013-2020.

[18] Bryan TL, van Diepen S, Bhutani M, Shanks M, Welsh RC and Stickland MK. The effects of dobutamine and dopamine on intrapulmonary shunt and gas exchange in healthy humans. J Appl Physiol (1985) 2012; 113: 541-548.

[19] The Criteria Committee of the New York Heart Association. Nomenclature and criteria for diagnosis of diseases of the heart and great vessels. 1994.

[20] Roger VL. Epidemiology of heart failure. Circ Res 2013; 113: 646-659.

[21] Andreassen S, Rees SE, Kjaergaard S, Thorgaard P, Winter SM, Morgan CJ, Alstrup P and Toft E. Hypoxemia after coronary bypass surgery modeled by resistance to oxygen diffusion. Crit Care Med 1999; 27: 2445-2453.

[22] Rees SE, Kjaergaard S, Perthorgaard P, Malczynski J, Toft E and Andreassen S. The automatic lung parameter estimator (ALPE) system: non-invasive estimation of pulmonary gas exchange parameters in 10-15 minutes. J Clin Monit Comput 2002; 17: 43-52.

[23] Balchum OJ, Jung RC, Turner AF and Jacobson G. Pulmonary artery to vein shunts in obstructive pulmonary disease. Am J Med 1967; 43: 178-185.

[24] Harrow EM, Beach PM, Wise JR Jr, Lynch C, Graham WG, Wight G. Pulmonary arteriovenous fistula. Preoperative evaluation with a Swan-Ganz catheter. Chest 1978; 73: 92-94.