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Combination of Quantitative Capnometry, N-Terminal Pro-brain Natriuretic Peptide, and Clinical Assessment in Differentiating Acute Heart Failure from Pulmonary Disease as Cause of Acute Dyspnea in Pre-hospital Emergency Setting: Study of Diagnostic Accuracy

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Aim To determine the diagnostic accuracy of the combination of quantitative capnometry (QC), N-terminal pro-brain natriuretic peptide (NT-proBNP), and clinical assessment in differentiating heart failure (HF)-related acute dyspnea from pulmonary-related acute dyspnea in a pre-hospital setting.

Methods This prospective study was performed in the Center for Emergency Medicine Maribor, Slovenia, January 2005 – June 2007. Two groups of patients with acute dyspnea apnea were compared: HF-related acute dyspnea group (n = 238) vs pulmonary-related acute dyspnea (asthma/COPD) group (n = 203). The primary outcome was the comparison of combination of QC, NT-proBNP, and clinical assessment vs NT-proBNP alone or NT-proBNP in combination with clinical assessment, in differentiating HF-related acute dyspnea from pulmonary-related acute dyspnea (asthma/COPD) in pre-hospital emergency setting, using the area under the receiver operating characteristic curve (AUROC). The secondary outcomes end points were identification of independent predictors for final diagnosis of acute dyspnea (caused by acute HF or pulmonary diseases), and determination of NT-proBNP levels, as well as capnometry, in the subgroup of patients with a previous history of HF and in the subgroup of patients with a previous history of pulmonary disease.

Results In differentiating between cardiac and respiratory causes of acute dyspnea in pre-hospital emergency setting, NT-proBNP in combination with PetCO2 and clinical assessment (AUROC, 0.97; 95% confidence interval [CI], 0.90-0.99) was superior to combination of NT-proBNP and clinical assessment (AUROC, 0.94; 95% CI, 0.88-0.96; P = 0.006) or NT-proBNP alone (AUROC, 0.90; 95% CI, 0.85-0.94; *P* = 0.005). The values of NT-proBNP≥2000 pg/mL and PetCO2 ≤ 4 kPa were strong independent predictors for acute HF. In the group of acute HF dyspneic patients, subgroup of patients with previous COPD/asthma had significantly higher PetCO2 (3.8 ± 1.2 vs 5.8 ± 1.3 kPa, P = 0.009). In the group of COPD/asthma dyspneic patients, NT-proBNP was significantly higher in the subgroup of patients with previous HF (1453.3 ± 552.3 vs 741.5 ± 435.5 pg/mL, P = 0.010).

Conclusion In differentiating between cardiac and respiratory causes of acute dyspnea in pre-hospital emergency setting, NT-proBNP in combination with capnometry and clinical assessment was superior to NT-proBNP alone or NT-proBNP in combination with clinical assessment.

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In patients presenting with acute dyspnea in pre-hospital setting, the early and correct diagnosis may present a significant clinical challenge (1,2). Physical examination, chest radiography, electrocardiography, and standard biological tests often fail to accurately differentiate heart failure (HF) from pulmonary causes of dyspnea (3). Timely differentiation of HF from other causes of dyspnea may permit the early institution of appropriate medical therapy (4-6). Brain natriuretic peptide (BNP) and amino-terminal pro-brain natriuretic peptide (NT-proBNP) have been proposed as early markers of HF and demonstrated to be useful for diagnosing and excluding HF in emergency department (7-9). A combination of BNP or NT-proBNP testing and standard clinical assessment has been suggested to be superior to either tool used in isolation (7,8,10). Some previous studies have also suggested that quantitative capnometry (QC) may be useful in differentiating between cardiac and obstructive causes of respiratory distress (11,12). Therefore, we hypothesized that a new combination of NT-proBNP testing, standard clinical assessment, and partial pressure of end-tidal CO2 (PetCO2) would optimize evaluation and differentiation of acute dyspnea in a pre-hospital setting.

The aim of this study was to determine the accuracy of combination of QC, NT-proBNP, and clinical assessment in differentiating acute HF from obstructive pulmonary disease (COPD/asthma) as a cause of acute dyspnea in pre-hospital emergency setting.

SUBJECTS AND METHODS

Study design and setting

This prospective cohort study was performed in the pre-hospital emergency setting (Center for Emergency Medicine Maribor, Slovenia, Europe) between January 2005 and June 2007. The study was approved by the Ethical Review Board of the Ministry of Health of Slovenia.

Patients

During the period of the study, 546 consecutive patients with acute dyspnea were treated by emergency teams (emergency physician, register nurse, and medical technician/driver in an ambulance-car or at pre-hospital emergency medical center). After pre-hospital care, all patients were admitted to the University Clinical Center Maribor and followed until discharge.

To be eligible for the study, a patient had to present with shortness of breath as the primary complaint (defined as either the sudden onset of dyspnea without history of chronic dyspnea or an increase in the severity of chronic dyspnea). Exclusion criteria were age <18 years, history of renal insufficiency, trauma, severe coronary ischemia (unless patient's predominant presentation was dyspnea), and other causes of dyspnea: pneumonia, pulmonary embolism, carcinoma, pneumothorax, pleural effusion, intoxications (drugs), anaphylactic reactions, upper airway obstruction, bronchial stenosis, and gastroesophageal reflux disorder, according to the history, clinical status, and additional laboratory tests available in pre-hospital setting (D-dimer, troponin, C-reactive protein).

There were 441 patients who met the criteria for inclusion in the survey. Hundred and five patients were excluded from the study. Recruitment, exclusion, and subsequent grouping of all patients are shown in the flowchart (Figure 1).

Data collection

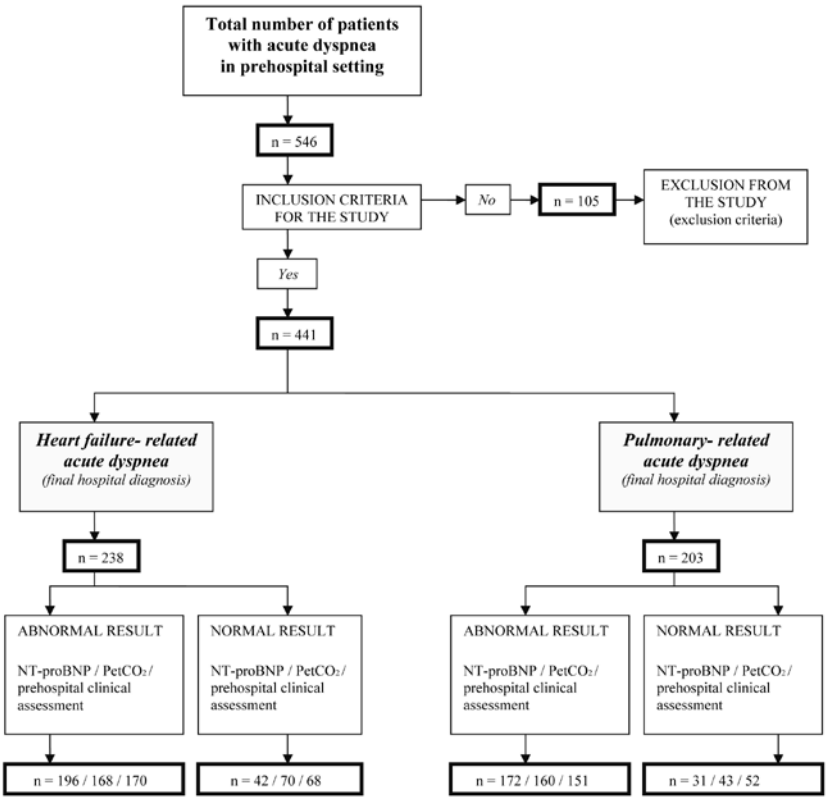
After enrollment, patient's demographic characteristics, symptoms and signs, medical history, medication use, chest X-ray, and standard blood test results (after admission to the hospital) were recorded.

Our protocol for clinical assessment of HF-related acute dyspnea (the pre-hospital clinical assessment for HF) was designed based on Boston (13) and Framingham criteria for HF (14) (Table 1). We did not use certain criteria from the original protocols, which were not available in the prehospital setting (eg, chest radiography).

For additional evaluation of patients with suspect obstructive causes of dyspnea, we included criteria for clinical assessment of severe asthma (diffuse polyphonic bilateral and particular expiratory wheezes, chest tightness, shortness of breath, using accessory muscles of breathing, signs of hyperinflation, atopic condition, personal or family history of asthma, tachypnea, previous asthma and asthma medications, and the value of modified Boston criteria for HF≤5) (15,16) and criteria for chronic obstructive pulmonary disease (COPD) exacerbation (history of COPD, COPD medications, cough, worsening dyspnea, increased sputum production and volume, increased sputum purulence, rhonchi and rales, modified Boston criteria for HF≤5) (17).

The final hospital diagnosis of HF-related acute dyspnea and pulmonary-related acute dyspnea (the hospital reference standard for HF and pulmonary diseases: asthma/

Figure 1.



The flow diagram of recruitment, exclusion, and subsequent grouping of all patients in the study.

COPD) was confirmed by cardiologist and/or intensive care physician in the University Clinical Center Maribor, using the reference standard definition for HF and pulmonary diseases in accordance with previously cited instruments (13-19), including chest X-ray, echocardiographic examination, cardiac functional assessment (exercise test), pulmonary function test, full blood count, biochemistry, and invasive investigation or angiography (17).

According to these criteria, identification of independent predictors for final diagnosis of acute dyspnea (caused by acute HF or pulmonary diseases) was performed by examination of 26 variables (Table 2): age, sex, nocturnal dyspnea, orthopnea, cough, sputum production, fever, murmur, lung rales, wheezes, pulse rate, jugular venous distension, lower extremity edema, ECG, history of COPD/asthma medications or HF medications, troponin T, $PetCO_2$, Sao_2, NT-proBNP, the need for endotracheal intubation, previous arrhythmia, history of previous, acute myocardial infarction (AMI), congestive heart failure (CHF), or COPD, and the value of modified Boston criteria for HF. Central venous pressure (CVP) in the field was assessed by the visualization of external jugular vein. This correlates well with catheter-measured CVP (18) and may give a reliable estimate of CVP, categorized as low (<5 cm H2O) or high (≥10 cm H2O) when the top of the external jugular veins is >3 cm of vertical distance above the sternal angle.

Two groups of patients (HF-related acute dyspnea group and pulmonary-related acute dyspnea [asthma/COPD] group) were further divided according to previous history of HF or COPD/asthma (acute HF dyspneic patients with previous history of HF, acute HF dyspneic patients with previous history of COPD/asthma, acute COPD/asthma dyspneic patients with previous history of HF, acute COPD/asthma dyspneic patients with previous history of COPD/asthma) for determination of NT-proBNP levels, as well as for capnometry.

TABLE 1. Study protocol for prehospital clinical assessment of HF (modified Boston criteria)*

Criterion	Point value†
Medical history:	
rest dyspnea	4
orthopnea	4
paroxysmal nocturnal dyspnea	3
dyspnea while walking on level area	2
dyspnea while climbing	1
Physical examination:	
heart rate abnormality (1 point if 91-110 beats per minute; 2 points if more than 110 beats per minute)	1 or 2
jugular venous elevation (2 points if greater than 5 cm H_2O; 3 points if greater than 5cm H_2O plus hepatomegaly or edema)	2 or 3
lung rales (1 point if basilar; 2 points if more than basilar)	1 or 2
wheezing	3
third heart sound	3
hepatojugular reflux	1
Additional minor criteria:	
ECG changes (HLV, old AMI or non specific ST-T changes, arrhythmia)	1
night cough	1
murmur	1
without sputum and/or fever	1
previous AMI, arrhythmia, or HF	1
HF medications	1

*Boston criteria: see reference 13.
†Point value: No more than 4 points are allowed from each of 3 categories; hence the composite score (the sum of the subtotal from each category) has a possible maximum of 12 points. The diagnosis of heart failure is classified as "definite" at a score 8 to 12 points, "possible" at a score 5 to 7 points, and "unlikely" at a score of 4 points or less.
‡Abbreviations. AMI – acute myocardial infarction, HLV – hypertrophy of the left ventricle, HF – heart failure.

Measurements

NT-proBNP. During initial evaluation (before application of medicines), a 5-mL sample of blood was collected into a tube containing calcium disodium edetate for blinded measurement of NT-proBNP. The level of NT-proBNP was measured using a Cardiac Reader (Roche Diagnostics, Mannheim, Germany) and recorded in the special protocol. The test was finished within 15 minutes.

PetCO2. PetCO2 was obtained by Lifepak 12 (Medtronic Physiocontrol, Corporate Headquarters, Redmond, WA, USA); an average $PetCO_2$ value of the first three measurements in the first minute after endotracheal intubation or nasal measurement was registered.

Blinding (masking) of physicians

The raters who made the diagnosis (in pre-hospital setting – pre-hospital emergency physicians, at admission to hospital – internists at emergency department, and at discharge from the hospital with the final diagnosis – cardiologists or/and intensive care physicians) were blinded to the results of NT-pro-BNP. In addition, the investigators of NT-proBNP did not collaborate in making the final diagnosis.

On the other hand, pre-hospital emergency physicians were not blinded to the value of PetCO2 because QC represents the routine method in Slovenian pre-hospital emergency medicine. To avoid bias, the value of PetCO2 was recorded by the emergency physician in the field but did not affect the diagnosis. The raters who made the diagnosis in the hospital were blinded to the values of pre-hospital PetCO2.

Statistical analysis

Univariate comparison was made with χ^2 test for categorical variables and unpaired ***t*** test for continuous variables with normal distribution (age, pulse rate, PetCO2, NT-proBNP, Sao_2, modified Boston criteria for HF). The normality of distribution was tested with Kolmogorov-Smirnov test. Odds ratio (OR) and 95% confidence interval (CI) were calculated to examine risk of acute HF (for adjusted using multiple logistic regression).

TABLE 2. Univariate analysis for all demographic and clinical variables pertinent to diagnosis of acute HF or pulmonary disease (n = 441)*

Variable†	Pulmonary-related dyspnea (n = 203)	Acute HF-related dyspnea (n = 238)	P‡
Age	50.3 ± 14.8	67.9 ± 10.5	0.001
Sex (male/female) (%)	65.3/34.7	58.1/41.9	0.760
Nocturnal dyspnea (Y/N)	13/190	79/159	<0.001
Orthopnea (Y/N)	16/187	91/147	<0.001
Cough (Y/N)	110/93	62/176	<0.001
Sputum production (Y/N)	55/148	15/223	<0.001
Fever (Y/N)	48/155	14/224	<0.001
Murmur (Y/N)	10/193	69/169	<0.001
Rales (Y/N)	24/179	141/97	<0.001
Wheezes (Y/N)	150/53	90/148	<0.001
Pulse rate/min	112.1 ± 18.5	103.5 ± 14.8	0.640
Jugular venous distension (Y/N)	6/197	55/183	<0.001
Lower extremity edema (Y/N)	26/177	114/124	<0.001
ECG-normal sinus rhythm (Y/N)	164/39	101/137	<0.001
Asthma/COPD medications (Y/N)	179/24	43/195	<0.001
HF medications (Y/N)	56/147	162/76	<0.001
Troponin ***t*** > 0.03 ng/mL (Y/N)	26/177	86/152	<0.001
$PetCO_2$ (kPa)	6.4 ± 1.1	3.8 ± 1.2	0.006
NT-proBNP (pg/mL)	687.2 ± 479.5	2756.8 ± 885.3	0.004
Sao_2 (%)	74.6 ± 9.6	69.8 ± 12.3	0.730
ETI (Y/N)	8/195	21/217	0.026
Previous arrhythmia (Y/N)	14/189	95/143	<0.001
Previous AMI (Y/N)	15/188	80/158	<0.001
Previous CHF (Y/N)	38/165	164/74	<0.001
Previous COPD (Y/N)	159/44	51/187	<0.001
Modified Boston Criteria for diagnosing HF§	5.7 ± 1.9	10.2 ± 1.61	<0.001

*Abbreviations: Y – yes, N – no, $PetCO_2$ – partial pressure of end-tidal CO_2, NT-proBNP – amino-terminal pro-brain natriuretic peptide, HF – heart failure, CHF – congestive heart failure, AMI – acute myocardial infarction, Sao_2 – arterial oxygen saturation, ETI – endotracheal intubation; COPD – chronic obstructive pulmonary disease.

†Results are presented as mean ± standard deviation for normally distributed data or ratio or percentage for other variables.

‡Univariate comparison was made with χ^2 test for categorical variables and *t* test for continuous variables. For the evaluation of diagnostic accuracy, patients were divided into two groups: HF-related acute dyspnea and pulmonary related acute dyspnea (COPD/asthma).

§Boston Criteria according to ref. 13.

The area under the receiver operating characteristic curve (AUROC) was used to determine the diagnostic accuracy of combination of QC, NT-proBNP, and clinical assessment vs NT-proBNP alone or NT-proBNP in combination with clinical assessment in differentiating acute HF from COPD/asthma in pre-hospital emergency setting. We compared the areas under different curves using the technique proposed by Hanley and McNeil (20) and Jannuzi (8). Single areas were calculated and compared with univariate Z score testing.

Univariate analysis was performed for all variables pertinent to diagnose HF or pulmonary disease, and multivariate analysis was performed to simultaneously identify potential independent predictor variables of a final diagnosis of acute HF. Significant variables identified by univariate analysis with a ***P*** value <0.05 were entered into a logistic regression analysis. This enabled adjusted OR (for confounding) to be calculated and identified any factor that affected the primary outcome variable (HF). Variables considered in the analysis were age, nocturnal dyspnea, orthopnea, cough, sputum production, fever, murmur, rales, wheezes, jugular venous distension, lower extremity edema, ECG-normal sinus rhythm, asthma/COPD medications, HF medications, troponin *t* > 0.03 ng/mL, PetCO2, NT-proBNP, endotracheal intubation, previous AMI, HF, or COPD, and modified Boston criteria for HF.

Sensitivity, specificity, and negative and positive predictive values were estimated for NT-proBNP and

PetCO2 for different cut-off points. As established in PRIDE study (10), the suggested NT-proBNP concentrations for identifying acute HF were greater than 450 pg/mL for patients younger than 50 years and greater than 900 pg/mL for patients aged 50 years or more, whereas 300 pg/mL was suggested as an optimal cut-off point for excluding HF. The suggested $PetCO_2$ values for identifying acute HF were 4 kPa or less, and the cut-off point for excluding HF was $PetCO_2 \geq 8$ kPa.

NT-proBNP levels, as well as capnometry, were determined in the subgroup of patients with a previous history of pulmonary disease but finally diagnosed as acute HF, and in the subgroup of patients with a history of HF but finally diagnosed as acute pulmonary disease (COPD/asthma).

AUROC analysis was performed using Analyze-It software (Leeds, UK) whereas other analyses were performed using SPSS software (SPSS, Inc., Chicago, IL, USA).

RESULTS

The baseline clinical and demographic characteristics of the study population are presented in Table 2. Mean age in the group of patients with acute HF was 68.9±10.5 years; 188 (58%) were men. HF group was significantly older.

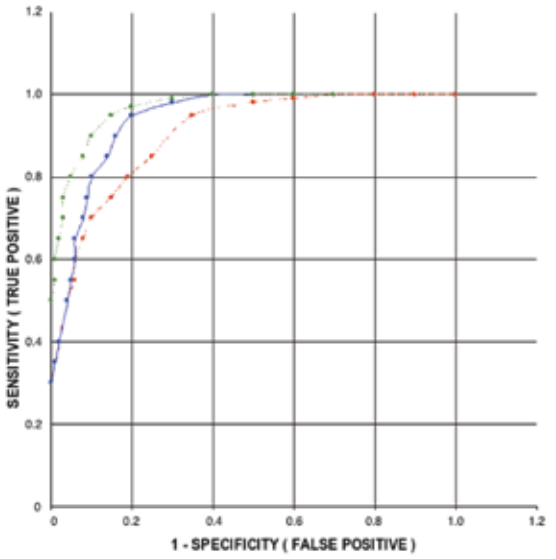
Diagnostic accuracy of combination of QC, NT-proBNP, and clinical assessment in differentiating HF-related acute dyspnea from pulmonary-related acute dyspnea

By using of AUROC, the sensitivity and 1- specificity were compared for different cut-off points for NT-proBNP alone vs combination of NT-proBNP + clinical assessment vs combination of NT-proBNP + clinical assessment + PetCO2 (Figure 2). The AUROC from NT-proBNP + PetCO2 + clinical assessment (AUROC, 0.97; 95% CI, 0.90-0.99) was superior to NT-proBNP + clinical assessment (AUROC, 0.94; 95% CI, 0.88-0.96; $P=0.006$) and NT-proBNP testing alone (AUROC, 0.90; 95% CI, 0.85-0.94; $P=0.005$). Diagnostic modality with the combination of the NT-proBNP + clinical assessment was superior to NT-proBNP testing alone ($P=0.010$).

Identification of independent predictors for final diagnosis of acute dyspnea

For the identification of a final diagnosis of acute HF, we examined 23 variables (Table 2) in multivariable logistic regression analysis; 11 variables remained significant after analysis (Table 3). These included an elevated NT-proBNP (as a strongest predictor of acute HF), rales, orthopnea, HF medications, troponin T, PetCO2, and previous HF. Asthma medications, cough, fever, and ECG with normal sinus rhythm independently predicted respiratory causes of dyspnea.

Figure 2.



Area under receiver-operating curve (AUROC): comparison of NT-proBNP versus combination NT-proBNP + clinical assessment versus combination NT-proBNP + clinical assessment + PetCO2. The AUROC was used for discrimination for NT-proBNP, PetCO2, clinical assessment and combination of all three methods. The areas under the different curves were compared with each other using the technique proposed by Hanley and McNeil (19) and Jannuzi (8). Single areas were calculated and compared with univariate Z score testing. The AUROC from NT-proBNP + clinical assessment + PetCO2 was superior to others diagnostic modality ($P < 0.001$). Red – NT-proBNP 0.90 (95% CI 0.85-0.94), blue – NT-pro-BNP + clinical judgement (95% CI 0.88-0.96), green – NT-pro-BNP + clinical judgement + $petCO_2$ 0.97 (95% CI 0.90-0.99).

Negative and positive predictive values for NT-proBNP and PetCO2 for different cut-off points

In Table 4 and Table 5, sensitivity, specificity, positive and negative predictive value are presented for different cut-off points for NT-proBNP and PetCO2 for the diagnosis of acute HF. The value ≥2000 pg/mL for NT-proBNP and value ≤4 kPa for PetCO2 are strongly independent predictors for acute HF.

TABLE 3. Multiple logistic regression analysis of factors used for differentiating between patients with HF-related acute dyspnea and pulmonary-related acute dyspnea in prehospital emergency setting

Factor*	OR (95% CI)†	*P*‡
NT-proBNP	13.6 (7.2-25.7)	<0.001
Rales	5.8 (1.9-12.4)	0.010
Orthopnea	7.5 (2.2-19.8)	<0.001
HF medications	2.8 (1.5-4.8)	0.008
Troponin T	1.9 (1.1-3.9)	0.020
$PetCO_2$	6.9 (2.4-17.5)	<0.001
Previous HF	6.8 (2.2 -19.7)	<0.001
Asthma/COPD medications	0.14 (0.04-0.53)	0.030
Cough	0.32 (0.18-0.79)	0.039
ECG – normal sinus rhythm	0.44 (0.24-0.85)	0.038
Fever	0.19 (0.06-0.58)	0.018

*Abbreviations: NT-proBNP – amino-terminal pro-brain natriuretic peptide, PetCO2 – partial pressure of end-tidal CO2, HF – heart failure; COPD – chronic obstructive pulmonary disease; OR – odds ratio; CI – confidence interval.
†Univariable screening was performed on clinical, historical, ECG and biochemical variables to identify potential predictors of acute HF. Odds ratios for the presence of acute HF were generated and expressed with 95% CI.
‡Multivariable analysis with logistic regression was used to identify potential predictor variables of a final diagnosis of acute HF (variables from univariate analysis with $P < 0.05$ for entry into model).

TABLE 4. Test characteristics of NT-proBNP for the diagnosis of acute HF for different cut-off points*

	Test characteristics of NT-proBNP (%; 95% CI)			
Value of NT-proBNP (pg/mL)	sensitivity	specificity	negative predictive value	positive predictive value
300	99 (92-100)	54 (45-65)	98 (91-100)	51 (42-62)
700	98 (90-100)	65 (55-72)	97 (89-100)	59 (50-68)
1000	90 (82-97)	76 (68-83)	92 (80-99)	68 (62-77)
2000	84 (77-94)	83 (72-90)	88 (78-94)	76 (69-85)
3000	67 (55-80)	95 (88-99)	71 (64-80)	93 (84-99)

*Abbreviations: NT-proBNP – amino-terminal pro-brain natriuretic peptide; CI – confidence interval.

TABLE 5. Test characteristics of $PetCO_2$ for the diagnosis of acute heart failure for different cut-off point*

	Test characteristics of $PetCO_2$ (%; 95% CI)			
Value of $PetCO_2$ (kPa)	sensitivity	specificity	negative predictive value	positive predictive value
9.3	97 (92-100)	33 (27-40)	98 (92-100)	30 (25-37)
8.0	94 (88-98)	41 (35-47)	92 (87-99)	35 (31-39)
6.7	90 (80-97)	62 (55-70)	91 (86-94)	42 (36-48)
5.3	82 (76-89)	76 (70-79)	86 (80-91)	63 (58-69)
4.7	76 (71-83)	85 (79-91)	78 (72-83)	68 (63-75)
4.0	68 (60-76)	91 (86-96)	69 (63-72)	76 (70-82)
3.3	61 (55-69)	96 (90-99)	60 (52-66)	83 (76-90)

*Abbreviations: $PetCO_2$ – partial pressure of end-tidal CO_2.

NT-proBNP levels, and capnometry, in subgroup of patients with a previous history of HF or of pulmonary disease

In the group of acute HF dyspneic patients, we did not find any significant difference in the value of NT-proBNP between subgroup with previous acute HF and previous COPD/asthma, but we found significantly higher $PetCO_2$ in the subgroup with previous COPD/asthma. In the group of COPD/asthma dyspneic patients, we found significantly higher value of NT-proBNP in the subgroup with previous HF (Table 6).

We did not observe any adverse events from performing the index tests or the reference standard.

DISCUSSION

To our knowledge, this is the first prospective study specifically designed to assess the utility of NT-proBNP testing in combination with PetCO2 and routine clinical assessment for the diagnosis of acute HF in pre-hospital setting. Our study showed that the combination of NT-proBNP, clinical assessment, and capnometry proved to be useful in differentiating HF from pulmonary causes of acute dyspnea and had a significantly better AUROC for the diagnostic accuracy than each method alone or a combination of two of them.

Timely differentiation of HF from other causes of respiratory distress may permit the early institution of appropriate medical therapy. The symptoms and signs of COPD/asthma exacerbation may frequently be difficult to differentiate from those of acute HF and when the two diagnoses coexist, treatment decisions become incrementally more complex (21-23).

Routine BNP testing of dyspneic patients in emergency department has been demonstrated to be a useful method for diagnosing and excluding acute HF (7-10). The introduction of BNP measurement in patients with uncertain diagnosis may reduce the error rate by over 50% (19).

Measurement of the PetCO2 in the field has already become a standard procedure to ensure proper

TABLE 6. Subgroup analysis of amino-terminal pro-brain natriuretic peptide (NT-proBNP) and partial pressure of end-tidal CO2 ($PetCO_2$) values in a group of acute heart failure (HF)-related dyspnea (n = 238) and pulmonary related dyspnea (n = 203)

	Patients with					
	acute HF*-related dyspnea			pulmonary related dyspnea		
	previous history of HF (n = 164)	previous history of COPD*/asthma (n = 51)	*P*	previous history of HF (n = 38)	previous history of COPD/asthma (n = 159)	*P*
NT-proBNP (pg/mL)	2885.6 ± 944.4	2395.4 ± 864.4	0.368	1453.3 ± 552.3	741.5 ± 435.5	0.010
$PetCO_2$ (kPa)	3.8 ± 1.2	5.8 ± 1.3	0.009	5.1 ± 1.2	6.2 ± 1.5	0.297

*Abbreviations: HF – heart failure; COPD – chronic obstructive pulmonary disease.

placement and function of the endotracheal tube and to monitor the adequacy of ventilation (24,25). Some previous studies have also suggested that QC may be useful in differentiating between cardiac and obstructive causes of respiratory distress (11,12).

PetCO2 is reported to have a prognostic value in patients with HF at rest and during exercise testing (26,27). Matsumato et al (28) found that PetCO2 could become a new ventilatory abnormality marker for impaired cardiac output response. Brown et al (11) found that PetCO2 levels for pulmonary edema/CHF patients differed significantly from those of asthma/COPD patients. We also found a significant difference in $PetCO_2$ values between HF and COPD/asthma, and concluded that capnometry could represent an objective additional method for differentiating acute dyspnea in pre-hospital setting. With adding the PetCO2 in our study, we improved the sensitivity and specificity in differentiating the cause of acute dyspnea (especially in COPD patients with severe exacerbation and coexisting HF).

Combination of NT-proBNP and PetCO2 presents two different ways and mechanisms of verification of HF. It introduces an opportunity for integration of biochemical and pathophysiologic measurement in a new complementary method. Both devices are accessible in the field and present an effective way in differentiating respiratory distress in prehospital setting. Our study confirmed that the combination of these two parameters had a strong diagnostic value.

We also found an association between the history of previous COPD/asthma or HF and the current values of NT-proBNP and PetCO2. Our results showed that higher values of NT-proBNP in acute dyspneic patients due to COPD/asthma correlated with a history of HF, and higher values of PetCO2 in acute dyspneic patients due to HF correlated with a history of COPD/asthma. Similarly, Morrison et al (23) reported significantly higher BNP levels in patients with HF than in patients with pulmonary disease. Patients with history of HF but with current COPD diagnosis had higher BNP levels than patients without history of HF.

Tung et al (29) found that in patients without previous HF, median NT-proBNP levels were higher than in patients with new-onset HF than in those with COPD/asthma exacerbation. High clinical suspicion for acute HF detected only 23% of patients with new-onset HF, whereas 82% of these patients had elevated NT-proBNP levels. In patients who had both previous acute HF and COPD/asthma, median NT-proBNP levels were significantly higher in those with acute HF than in those with COPD/asthma exacerbation. McCullough et al (30) investigated whether BNP could distinguish new-onset HF in patients with a history of COPD/asthma presenting with dyspnea to the emergency department and concluded that the yield of adding routine BNP testing in these cases was approximately 20%.

The prehospital emergency physicians offer the earliest treatment of acute dyspnea, performed as close as clinically possible to the event. Based on clinical judgment alone, it is sometimes very difficult to distinguish cardiac from respiratory causes of dyspnea. In fact, even in experienced centers, diagnostic accuracy is lower than 80% (19). If the prehospital physicians have the values of NT-proBNP and PetCO2 at their disposal, the diagnostic dilemmas in differentiating causes of respiratory distress are reduced and the treatment possibilities in clinical obscure cases are mainly improved. This is particularly important for more complex treatment (eg, diuretics, morphine, vasodilatators, or inotropes).

This study has some limitations: 1) prehospital emergency physicians were not blinded to the values of PetCO2 because capnometry represents the routine prehospital test. In our opinion, this fact did not induce bias because the physicians were unaware of the differential diagnostic importance of PetCO2 for the purpose of the study (in the differentiation of cardiac and pulmonary causes of shortness of breath – blindness for the purpose of the study); 2) in the

majority of patients, spirometry or simple forced expiratory volume in one second (FEV1) were not measured and evaluated, thus the severity of COPD/asthma is not differentiated in the study; and 3) severe additional factors may have an impact of the reliability of PetCO2 (some patients in the study hyperventilated, had periodic breathing, were intubated, or had ventilation/perfusion mismatch) (31).

In conclusion, NT-proBNP in combination with capnometry and clinical assessment was superior to NT-proBNP alone or NT-proBNP in combination with clinical assessment in differentiating between cardiac and respiratory causes of acute dyspnea in prehospital emergency setting. QC and NT-proBNP measurement can improve the differentiation and treatment of acute dyspnea in the first hours of its appearance. Wider use of these routine procedures can be helpful for emergency physicians in everyday work, but further investigation (eg, a larger multicentric study) is needed to confirm the utility of these methods in the prehospital setting.

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Preliminary results of this study were presented (as oral presentation) on 4th Mediterranean Emergency Medicine Congress, Sorento, Italy, 2007, and were printed in the form of abstract Utility of the Quantitative Capnometry (QC) and Rapid Bedside Test for N-Terminal Pro-brain Natriuretic Peptide (Pro-BNP) in the Evaluation of Respiratory Distress in Prehospital Setting – Preliminary Results. J Emerg Med 2007; 33 (3):322.

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