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Relationship Between Blood Gas and NT-ProBNP in Patients Presenting with Dyspnea

Dispne ile Başvuran Hastalarda Kan Gazı ve NT-ProBNP İlişkisi

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Abstract

Aim: Dyspnea can be caused by different systems, and the negative predictive value of N_terminal pro-brain natriuretic peptide (NT-proBNP) is indicative of heart failure. We aimed to evaluate the relationship between blood gases and NT-proBNP in patients presenting with dyspnea and to determine the guiding factors in the differential diagnosis.

Material and Method: Patients admitted to our hospital with dyspnea and who underwent NT-proBNP and venous blood gas tests at the same time were included in the study. Demographic data, comorbidities, and laboratory data were recorded. The relationship between NT-proBNP and venous blood gas parameters was evaluated. p<0.05 was considered significant.

Results: The mean age of the 523 patients was 74±12.83 years, with 50.3% of the patient population identified as male. In the total group, NT-proBNP demonstrated a positive correlation with age (p<0.001) and a negative correlation with current bicarbonate ($cHCO_3$) (p<0.001), standard bicarbonate (HCO_3) (p<0.001), pCO_2 (p=0.022), and BE (p<0.001). In patients with chronic kidney disease (CKD), NT-proBNP demonstrated a moderately negative correlation with $cHCO_3$ (p=0.008), HCO_3 (p=0.019), and BE (p=0.010). In patients with heart failure (HF), there was a moderate negative association between NT-proBNP and $cHCO_3$ (p=0.002), HCO_3 (p=0.001), and BE (p=0.001).

Conclusion: In the absence of definitive evidence of heart failure in a dyspneic patient, it is reasonable to consider the potential contribution of impaired renal function to the overall evaluation.

Keywords: NT-proBNP, venous blood gas, heart failure, chronic kidney disease

Öz

Amaç: Dispne farklı sistemlerden kaynaklanabilen bir bulgu olup N_terminal pro brain natriüretik peptid (NT-proBNP)'in negatif prediktif değeri kalp yetmezliği için yol göstericidir. Nefes darlığı şikayeti ile başvuran hastalarda kan gazı ve NT-proBNP arasındaki ilişkiyi değerlendirerek ayırıcı tanıda yol gösterici faktörleri belirlemeyi amaçladık.

Gereç ve Yöntem: Çalışmaya dispne ile hastanemize başvuran ve NT-proBNP ve venöz kan gazı tetkikleri aynı zamanda yapılan hastalar alındı. Demografik verileri, eşlik eden hastalıkları ve laboratuvar verileri kaydedildi. NT-proBNP ve venöz kan gazı parametreleri arasındaki ilişki değerlendirildi. p<.05 anlamlı kabul edildi.

Bulgular: Çalışmaya katılan 523 hastanın yaş ortalaması 74±12.83 yıl olup %50,3'ü erkekti. Total grupta NT-proBNP ile yaş (p<.001) arasında pozitif yönde, aktüel bikarbonat ($cHCO_3$) (p<,001), standart bikarbonat (HCO_3) (p<,001), pCO_2 (p=,022) ve BE (p<,001) ile negatif yönde anlamlı korelasyon bulundu. Kronik böbrek hastalığı (CKD) olanlarda NT-proBNP ile $cHCO_3$ (p=,008), HCO_3 (p=,019), BE (p=,010) orta düzeyde negatif yönde ilişki vardı. Kalb yetmezliği (HF) olanlarda NT-proBNP ile $cHCO_3$ (p=,002), HCO_3 (p=,001), BE (p=,001) arasında orta düzeyde negatif yönde ilişki vardı.

Sonuç: Dispneik hastanın NT-proBNP ve kan gazları değerleri kesin kalp yetmezliğine işaret etmiyorsa, böbrek fonksiyonlarındaki bozulmanın değerlendirme denklemine katılması uygun görünmektedir.

Anahtar Kelimeler: NT-proBNP, venous blood gas, heart failure, chronic kidney disease

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INTRODUCTION

Shortness of breath, defined as the sensation of difficulty in breathing in and out, constitutes an emergency. The condition has a cardiac and pulmonary origin. Given the similarity in the clinical picture, the use of guiding markers is of great importance in the process of differential diagnosis. A delay in diagnosis and treatment results in an increased risk of morbidity and mortality. N-terminal brain natriuretic peptide (NT-proBNP) is released from cardiac myocytes in response to myocardial strain, volume load, and increased end-diastolic pressure. It serves as a diagnostic and prognostic marker for heart failure.[1-3] An elevated NT-proBNP level may be observed in patients with end-stage renal disease, even in the absence of heart failure. An increase in volume load, left ventricular hypertrophy, and hypertension, as well as delayed renal elimination, are all involved.[4]

Venous blood gas analysis represents a rapid and straightforward method for estimating systemic carbon dioxide and pH levels, which can also be performed in emergency settings Venous blood pH may assist in differentiating between metabolic and respiratory causes of dyspnea symptoms. Venous blood pH is approximately 0.02 to 0.04 lower than arterial blood. The assessment of pH is conducted in conjunction with the partial pressure of carbondioxide (pCO_2) and bicarbonate (HCO_3). An elevated pCO_2 (impaired excretion of carbondioxide) indicates respiratory acidosis, whereas a reduced pCO_2 (hyperventilation) suggests respiratory alkalosis. An elevated bicarbonate level, indicative of augmented bicarbonate reabsorption, denotes metabolic alkalosis. Conversely, a diminished venous bicarbonate concentration, suggestive of bicarbonate loss and acid accumulation, signifies metabolic acidosis.[5,6] The normal pH range in arterial blood gas is 7.35-7.45; the bicarbonate level is 21-27 mEq/L, the carbondioxide level is 35-45 mmHg, the base excess (BE ±3), and the lactate level is less than 1.9 mmol/L. The BE value indicates the quantity of acid and base that should be added to attain a pH of 7.40 at 37 degrees Celsius and a partial oxygen pressure of 40 mmHg.[7,8] The BE is evaluated in conjunction with lactate in order to detect metabolic balance disorders. Lactate is a metabolite that is formed as a result of anaerobic metabolism in tissues and serves as an indicator of hypoxia or hypoperfusion.[9]

METHODS

Ethics statement

This retrospective study was conducted with the decision number 24.06.07.07.02/09 dated 07.06.2024 of the Ufuk University Non-Interventional Clinical Research Evaluation Ethics Committee. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The study included patients admitted to the hospital with dyspnea between January 1, 2018, and January 1, 2024, who underwent NT-proBNP and venous blood gas examinations at the same time. The demographic data of the patients, including age, gender, and known diseases, as well as the NT-proBNP, venous blood gas pH, pCO_2, pO_2, standard HCO_3 (bicarbonate that should be present in the blood under 40 mmHg pCO_2 at 37 degrees), current $cHCO_3$ (patient's current bicarbonate value), BE, lactate, and glucose levels, were recorded. Laboratory values, including albumin, blood urea nitrogen, glomerular filtration rate (calculated with Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) 2021), sodium, potassium, calcium, and C-reactive protein (CRP), were obtained retrospectively from the hospital record system. The relationship between NT-proBNP and venous blood gas parameters was evaluated, and a p-value of less than 0.05 was considered statistically significant.

Statistical analysis

Analyses were conducted using Statistical Package for Windows 22.0 version (IBM SPSS Statistic, Armonk, NY, IBM Corp. 2013). Categorical variables were presented as frequency (n) and percentage (%). The conformity of continuous variables to normal distribution (-3, +3) was tested with Skewness and Kurtosis and expressed as arithmetic mean standard deviation values. Quantitative data that were not normally distributed were presented as the median and interquartile range (IQR). A chi-square test was applied for categorical variables. Venous blood gas was applied considering the difficulty of obtaining arterial blood gas in emergency admission and the known differences determined by studies between venous and arterial blood gas. If venous blood gas is taken from the central vein, 0.03-0.05 is added to pH, if taken from the periphery, then 0.02-0.04 is added, and pCO_2 is subtracted by 4-5mmHg, 3-8mmHg, respectively, and base excess (BE) is evaluated as 0.15 higher, and lactate is evaluated as 0.12 higher. Patients with history, clinical and laboratory results pointing out pulmonary embolism, anemia, pneumothorax, bronchial asthma and carbon monoxide poisoning were not included in the study. The relationship between NT-proBNP and blood gas was evaluated using the Spearman correlation. $p<0.05$ was considered significant.

RESULTS

The mean age of the 523 patients was 74±12.83 years, with 50.3% of the participants being male. The distribution of demographic and laboratory data is presented in **Table 1**, and the prevalence of comorbid conditions is presented in **Table 2**. A statistically significant difference was observed between males and females with regard to the prevalence of chronic obstructive pulmonary disease (COPD) ($p=0.05$). The prevalence of hypertension was significantly higher in women than in men ($p<0.001$). There were no statistically significant differences between the sexes with regard to the prevalence of diabetes mellitus, chronic kidney disease, coronary artery disease, and cerebrovascular disease.

Table 1. Demographic and laboratory data of the study group

Variables	mean±sd, median(IQR)
Gender	
Male	50.3% (263)
Female	49.7% (260)
Age (year)	74±12.83
NT-proBNP (pg/mL)	2575 (6994)
$cHCO_3$ (mEq/L)	24.4±5.51
HCO_3 (mEq/L)	25.62±4.55
pH	7.4 (.08)
pCO_2 (mmHg)	43.73±9.62
pO_2 (mmHg)	47.44±19.61
BE (mmol/L)	1.7 (6.2)
EF (%)	41.25±25.06
Hemoglobin (g/L)	11.89±2.23
Glucose (mg/dL)	102 (43)
Albumin (g/L)	32.65±6.37
Creatinine (mg/dL)	1.27 (1.04)
GFR (ml/min/1.73 m^2)	51.21±28.09
Sodium (mmol/L)	138 (5)
Potasium (mmol/L)	4.17±.67
Calcium(mg/dL)	8.59±0.67
CRP (mg/L)	20.3 (62.5)

NT-proBNP: N-terminal brain natriuretic peptide HCO_3: standard bicarbonate, $cHCO_3$: Current bicarbonate, pCO_2: Partial pressure of carbondioxide, pO_2: Partial pressure of oxygen, BE: Base excess, EF: Ejection fraction

Table 2. Co-morbid Diseases

Diseases	Gender	(+) % (n)	(-) % (n)	X^2	p
Diabetes mellitus	Male	48.4 (123)	52 (140)	.685	.432
	Female	51.6 (131)	48(129)		
Hypertension	Male	46.1 (187	65 (76)	12.97	<.001
	Female	53.9 (219)	35 (41)		
Chronic kidney disease	Male	49.2 (65)	50.6 (198)	.077	.841
	Female	50.8 (67)	49.4 (193)		
Coroner artery disease	Male	54.3 (146)	46.1 (117)	3.52	.066
	Female	45.7 (123)	53.9 (137)		
Cerebrovascular disease	Male	41.8 (23)	51.3 (240)	1.76	.184
	Female	58.2 (32)	48.7 (228)		
Chronic obstructive pulmonary disease	Male	57.1 (84)	47.6 (179)	3.84	.050
	Female	42.9 (63)	52.4 (197)		

HF NT-proBNP≤300 negative, <50 age≥400 pg/mL,50-74 age≥900 pg/mL,>75age≥1800 pg/mL positive, T2DM NT-proBNP≤50 negative <50 age≥75 pg/mL,50-74 age≥150 pg/mL,>75 age ≥300 pg/mL positive, In CKD, NT-proBNP is added according to GFR. In obesity, it is subtracted according to BMI

NT-proBNP demonstrated a positive correlation with age (p<.001) and a negative correlation with $cHCO_3$ (p<0.001), HCO_3 (p<0.001), pCO_2 (p=0.022), and BE (p<0.001). a significant negative correlation with laboratory parameters, including albumin (p<0.001), GFR (p<0.001), calcium (p <0 .001), and hemoglobin (p<0.001), and a significant positive correlation with glucose (p=0.047), blood urea nitrogen (p<0.001), creatinine (p<0.001), and CRP (p<0.001) (**Table 3**).

Table 3. Spearman's correlation between NT-proBNP and blood gas and laboratory variables

Variables		NTproBNP
age	r	.233**
	p	<.001
$cHCO_3$	r	-.172**
	p	<.001
HCO_3	r	-.166**
	p	<.001
pH	r	-.085
	p	.052
pCO_2	r	-.100*
	p	.022
pO_2	r	.085
	p	.052
BE	r	-.178**
	p	<.001
Lactate	r	.050
	p	.250
Glucose	r	.087*
	p	.047
Albumin	r	-.261**
	p	<.001
BUN	r	.407**
	p	<.001
Creatinine	r	.434**
	p	<.001
Sodium	r	-.071
	p	.103
GFR	r	-.458**
	p	<.001
Potassium	r	.002
	p	.968
Calcium	r	-.312**
	p	<.001
CRP	r	.252**
	p	<.001
Hb	r	-.300**
	p	<.001

*Correlation is significant at the 0.05 level, ** Correlation is significant at the 0.01 level, NT-proBNP:N-terminal brain natriuretic peptide HCO_3: standard bicarbonate, $cHCO_3$:current bicarbonate, pCO_2: Partial pressure of carbondioxide, pO_2: Partial pressure of oxygen, BE:Base excess

The relationship between NT-proBNP and venous blood gases in co-morbid conditions was evaluated, and a weakly significant negative correlation was observed between NT-proBNP and $cHCO_3$ (p=0.002), HCO_3 (p=0.002), pCO_2 (p=0.028), and BE (p=0.004) in patients with diabetes mellitus (DM). In patients with hypertension (HT), a weak negative correlation with age (p=0.001), $cHCO_3$ (p=0.001), HCO_3 (p=0.002), pCO_2 (p=0.017), and BE (p=0.001). In patients with heart failure (HF), a moderate negative correlation was observed $cHCO_3$ (p=0.002), HCO_3 (p=0.001), and BE (p=0.001). In patients with chronic kidney disease (CKD) (GFR<59 Stage III,IV,V), a moderate negative association was observed $cHCO_3$ (p=0.008), HCO_3 (p=0.019), and BE (p=0.010).

In patients with coronary artery disease (CAD), a moderately negative correlation with $cHCO_3$ (p=0.001), HCO_3 (p=0.001), pH (p=0.023), and BE (p=0.001). In patients with COPD, a significant and moderate negative correlation with $cHCO_3$ (p=0.012), HCO_3 (p=0.014), pH (p=0.014), and BE (p=0.035) (**Table 4**). When the chest radiographs of the cases were examined, the cardiothoracic ratio was at the upper limit of normal in 31%, increased in 65%, and pleural effusion was present in 4%.

DISCUSSION

Dyspnea is a prevalent condition among patients admitted to the emergency department. Cardiac and pulmonary causes are the most common causes, and it is also important to evaluate the contribution of chronic kidney disease. NT-proBNP is a valuable diagnostic marker for heart failure, with a high negative predictive value (1.4). A venous blood gas test is a valuable diagnostic tool that can be used to assess acid-base status and certain metabolic alterations. There is an indirect correlation between pH and NT-proBNP. This relationship manifests as a reduction in pH and elevated lactate levels, which result from inadequate delivery of oxygen and nutrients to tissues, particularly in patients with heart failure. In the event of acidosis, there is a reduction in the contractility of the cardiac muscle, which in turn results in an increase in NT-proBNP. A low pH and high NT-proBNP level is typically indicative of an unfavorable prognosis.[5,8,9] In this study, we conducted a comparative analysis of NT-proBNP and blood gas analysis values in patients admitted to our hospital with dyspnea. By comparing the laboratory values, we sought to identify the parameters that should be considered when developing a diagnosis and treatment plan. Our findings indicated that renal function should be taken into account when interpreting NT-proBNP values.

The weak negative correlation between NT-proBNP and $cHCO_3^-$, HCO_3^-, pCO_2^-, and BE in patients with DM and HT suggests that there is a partial shift in the acidotic direction in blood gas, which indirectly affects the heart. Venous blood gas analysis is a diagnostic and monitoring tool used in the evaluation of cardiac and pulmonary diseases. It is also employed in the follow-up of diabetic ketoacidosis and euglycemic ketoacidosis.[10,11] It is postulated that increased acidity causes a weak increase in NT-proBNP, which in turn exerts a negative effect on the heart muscle. A literature search yielded no studies that simultaneously compared NT-proBNP and venous blood gas analysis in patients presenting to the emergency room with dyspnea. Consequently, the available data on the identified patients were evaluated. A weak negative correlation between NT-proBNP and venous blood gas parameters was observed in patients with DM and HT who also had coronary artery disease or chronic obstructive pulmonary disease. In the meta-analysis conducted by Su et al.[12] it was demonstrated that NT-proBNP exhibited significant differences across distinct COPD stages and disease progression, as evaluated based on data from 29 studies comprising 8,534 participants. The negative correlation between NT-proBNP and bicarbonate and BE observed in our study is consistent with the results of the meta-analysis.[13] reported in a prospective study including 8062 patients with different glucose levels that NT-proBNP levels measured at baseline and in the development of cardiovascular death and myocardial infarction showed a relationship in patients with prediabetes and diabetes that was not seen in normoglycemic patients. It was observed that NT-proBNP may serve as a predictor of unfavorable outcomes in dysglycemic patients with coronary syndrome and normal left ventricular systolic function. The negative correlation between venous blood gas parameters and NT-proBNP observed in patients with coronary artery disease, as in COPD patients, was consistent with the results of this study.

Table 4. Relationship Between NT-proBNP and Venous Blood Gas Parameters in Co-morbid Conditions

NTproBNP		DM+ n=254	DM- n=269	HT+ n=406	HT- n=117	HF+ n=254	HF- n=269	CKD+ n=132	CKD- n=391	CAD+ n=269	CAD- n=254	CVA+ n=55	CVA- n=468	COPD+ n=147	COPD- n=376
age		,055	,370**	,161**	,374**	,108	,312**	,109	,258**	,053	,413**	,115	,242**	,109	,167**
	p	.385	.000	.001	.000	.087	.000	.211	.000	.383	.000	.401	.000	.187	.001
$cHCO_3$		-,192**	-,154*	-,170**	-,260**	-,192**	-,237**	-,232**	-,107*	-,204**	-,135*	-,062	-,180**	-,207*	-,107*
	p	.002	.011	.001	.005	.002	.000	.008	.034	.001	.031	.654	.000	.012	.039
HCO_3		-,193**	-,138*	-,152**	-,232*	-,202**	-,212**	-,204*	-,088	-,204**	-,114	-,170	-,161**	-,202*	-,100
	p	.002	.023	.002	.012	.001	.000	.019	.083	.001	.069	.216	.000	.014	.052
pH		-,072	-,085	-,060	-,071	-,105	-,099	-,107	-,025	-,138*	-,015	-,112	-,076	-,138	-,047
	p	.251	.165	.225	.445	.096	.106	.222	.627	.023	.814	.416	.101	.096	.363
pCO_2		-,138*	-,086	-,119*	-,163	-,095	-,172**	-,165	-,071	-,106	-,095	,029	-,113*	-,082	-,090
	p	.028	.158	.017	.080	.132	.005	.059	.162	.084	.129	.832	.014	.323	.081
BE		-,182**	-,174**	-,157**	-,291**	-,211**	-,231**	-,222*	-,108*	-,199**	-,147*	-,135	-,180**	-,174*	-,120*
	p	.004	.004	.001	.001	.001	.000	.010	.034	.001	.019	.326	.000	.035	.020
Lactate		,043	,055	,033	,109	,044	,068	,007	,085	,095	,026	-,079	,062	,029	,048
	p	.498	.370	.510	.243	.490	.267	.933	.093	.120	.681	.565	.181	.725	.350

NT-proBNP: N-terminal brain natriuretic peptide HCO_3: Standard bicarbonate, $cHCO_3$: Current bicarbonate, pCO_2: Partial pressure of carbondioxide, pO_2: Partial pressure of oxygen, BE: Base excess.

In patients under the age of 50 with acute symptoms, an NT-proBNP value below 300 pg/mL is indicative of a negative diagnosis of heart failure. The range of 300 to 450 pg/mL is considered to be within the range of values that may warrant further investigation. In non-acute cases, values below 125 pg/mL are indicative of the absence of heart failure, while a range of 125-500 pg/mL is considered to be within the suspicious range.[14] It was suggested that if GFR is <30 ml/min/1.73 m², 35% should be added to NT-proBNP levels, if it is between 30-45, 25%, if it is between 45-60, 15% should be added to NT-proBNP levels in the grey zone, and if BMI is 30-35 kg/m², 25% should be subtracted, if it is between 35-40, 30% should be subtracted, and if it is over 40, then 40% should be subtracted from NT-proBNP levels.[15] It has been reported that estimated GFR and atrial fibrillation correlate better with NT-proBNP.[16] The low volume overload of 4% in the study group requires attention in the grey zone.

The moderate negative correlation observed between NT-proBNP and HCO_3, $cHCO_3$, and BE in patients with heart failure was also observed in patients with chronic kidney disease. It is established that circulatory failure in heart failure may have a deleterious impact on renal function and that impaired renal function may similarly affect cardiac function. In both instances, an acidotic picture is observed in the venous blood gas. In light of the moderately negative relationship between NT-proBNP and blood gas parameters observed in both heart failure and chronic kidney disease, it seems appropriate to include renal function in the evaluation of NT-proBNP in heart failure within the suspicious zone values, both diagnostically and therapeutically. NT-proBNP testing increases diagnostic accuracy and therefore should be a standard procedure of the evaluation of patients presenting to the emergency department with dyspnea.[17] Renal dysfunction in the gray zones should not be ignored, and the strong relationship between heart and kidney disease should be taken into account. Because the kidney plays a role in both excretion and metabolism of NT-proBNP.

Limitation

The findings obtained in this study reveal the comparison of blood gas and NT-proBNP results of patients admitted to our hospital with dyspnea at hospital admission. However, the limitations of the study should be considered. Monocentric, the limited sample size, the short-term coverage of the data results, and the fact that long-term results were not evaluated prevent the generalizability of these results. Since it is indirectly possible that diseases affecting blood gas parameters also affect NT-proBNP values, the study requires a more detailed evaluation of the effects of renal function on these laboratory data with larger patient groups.

CONCLUSION

It is of the utmost importance that patients presenting to the emergency department with dyspnea be evaluated rapidly and that the diagnosis and treatment be initiated without delay. NT-proBNP is a valuable marker for excluding the diagnosis of heart failure, and venous blood gas analysis is an easily performed method in emergency departments. In the absence of definitive evidence of heart failure in a dyspneic patient, it is reasonable to consider the possibility of impaired renal function as a contributing factor in the evaluation process.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Ufuk University Non-interventional Clinical Research Ethics Committee (Date: 07.06.2024, Decision No: 24.06.07.07.02/09).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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