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RESEARCH ON BLOOD LEVEL OF BRAIN NETRIURETIC PEPTIDE (BNP) ON PATIENTS WITH CARDIOGENIC PULMONARY EDEMA TREATED WITH NONINVASIVE POSITIVE PRESSURE VENTILATION

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Introduction

Acute cardiogenic pulmonary edema (ACPE) is a common, with a potential of fatal cardiac due to acute respiratory distress. This disease is usually seen in emergency rooms, accounted for approximately 20% hospitalized heart failure. It also has a very poor prognosis with mortality rate up to 20% for inpatients and 25-35% for all patients in the first year because of the progression of disease, complications or when the disease comes to the end stage. However, the unsatisfactory prognosis may be caused by the inaccurate diagnosis and the inconsistent in treatment regimens. In 2002, the Food and Drug Administration of the United States of America or FDA has allowed the use of BNP testing for diagnosis, prognosis and treatment patients with heart failure. In the other side, noninvasive positive pressure ventilation (NPPV) should be considered for ACPE patients.

The data of ACPE listed above were came from foreign researchers, urged us desire to perform this research:

"Research on blood level of Brain Netriuretic Peptide (BNP) on patients with cardiogenic pulmonary edema treated with noninvasive positive pressure ventilation " for the following purposes:

- Survey the clinical presentation, arterial blood gas measurements and changes in serum level of BNP in ACPE patients treated with NPPV.
- Study the correlation between the clinical presentation, arterial blood gas measurements, serum level of BNP and successful outcome of NPPV in ACPE patients.

This 117-page thesis is divided into 6 parts which are the Introduction (3 pages), Overview (40 pages), Methods (19 pages), Results (22 pages) and Discussion (30 pages) and the final part is Conclusions and Suggestions (3 pages). In addition, this study also presented information with 47 tables, 12 charts, 5 diagrams and 4 pictures. 112 references are quoted including 9 Vietnamese and 103 English.

Practical significance:

This study evaluated the responses of ACPE patients with NPPV based on the difference between two values of BNP serum concentration, which measured at the initial admission and six hours of NPPV treatment. The finding then would help the attending physicians decide to whether continue using NPPV or to start invasive ventilation in ACPE patients.

Chapter 1: OVERVIEW

1.1. BACKGROUND OF ACPE:

1.1.1. Definition:

ACPE is defined as a pulmonary edema condition due to dramatically increased capillary hydrostatic pressure, results in forcing fluid from pulmonary capillary into the interstitial and alveoli.

1.1.2. Clinical presentation and laboratory tests:

1.1.2.1. Clinical presentation:

Symptoms may include dyspnea, tachypnea, anxiety, restlessness and coughing. In severe cases, patients may develop cough producing

frothy sputum that may be tinged with blood. During the attack episodes, respiratory rate increases, SpO_2 reduces and usually below 90%, lung auscultation reveals crackles (moist rales) with or without wheezing and abnormal heart sounds (gallop T3). The individual may report feeling as if they are "drowning" or that they cannot get enough air. Excessive sweating, pale, shaking chill and cyanosis may reflect a low cardiac output and an increased sympathetic stimulation.

1.1.2.2. Laboratory tests:

Enlargement of the cardiac silhouette, pulmonary congestion and redistribution of pulmonary blood flow toward the apex of the lung are often showed on chest x-ray. Echocardiogram may detect dilated heart chambers, reduced ejection fraction or regional dyskinesia. BNP level $\geq$ 500pg/ml is useful of making an ACPE diagnosis.

1.1.2.3. Diagnosis:

There is still no definitive diagnosis of ACPE. Therefore, patients are usually diagnosed based on the associated clinical features of both acute heart failure and acute pulmonary edema.

1.2. ROLE OF SERUM CONCENTRATION OF BNP:

1.2.1. Follow-up treatment:

In hospitalized patients, if BNP serum level is not much different from the background level which is likely not to indicate a decompensation heart failure. According to Maisel et al., congestion heart failure condition with an increasing of BNP level of 50% more than basal level often accompanied with a worsening development of the disease. Increasing serum concentration of BNP correlated with overload phenomenon and suggests an increase in diuretic dose.

1.2.2. Prognosis:

Discharged BNP serum level may predict the readmission ability. In an Italian study performed in NYHA class III-IV heart failure patients, a lower BNP level of 46% than admission level or an absolute BNP value < 300 pg/ml were indicated a low risk of re-hospitalization. In other study, BNP level after one week ≥ 500 pg/ml or a reduction of BNP level less than 50% compared to the admission value showed a longer hospitalization and a higher readmission ability and mortality.

1.3. NONINVASIVE POSITIVE PRESSURE VENTILATION:

Two ventilation patterns are usually applied in ACPE patients: continuous positive airway pressure and bi-level positive airway pressure. The key point is to set and adjust the appropriate pressure and volume according to every stage of the disease in order to maintain the correct level of oxygen administered.

1.4. MANAGEMENT OF ACPE:

1.4.1. Noninvasive positive pressure ventilation:

Recently, NPPV is considered as the priority administration prior to intubation and invasive ventilation. According to the clinical practice guidelines of the Canadian Medical Association for emergency care, bi-level positive airway pressure or continuous positive airway pressure is the first choice for treatment ACPE patients (Class IA).

1.4.2. Medications:

- ***Furosemide:*** the initial dose is 20 to 40mg given IV as a single dose, maybe increased to 100mg to a maximum of 200mg if an inadequate response is seen.
- ***Morphine*****:** indicated in anxious or panic patients, initial dose is 3-5mg IV, the 2th and the 3rd dose similar to the initial dose may be given every 15 minutes if needed.
- ***Nitroglycerin:*** the initial dose is 0.2 µg/kg/min given as a continuous IV infusion, raised by 5-10 µg every 5-10 minutes to desired effect.
- ***Angiotensin converting enzyme inhibitor and Angiotensin receptor blocker:*** administered in ACPE patients with a high blood pressure.
- ***Digitalis:*** administered in ACPE patients with rapid atrial fibrillation and a narrow QRS complex. The initial dose is 0.25mg, repeated after 2 hours if there is not effective.
- ***Dopamine:*** initial dose ≥ 5 µg/kg/min effects of increased myocardial contractility and vasoconstriction then increased blood pressure. High dose of dopamine may cause arrhythmia.
- ***Dobutamine:*** indicated in ACPE patients with systemic hypoperfusion, low cardiac output or pulmonary congestion. Initial dose starts at 2-3 µg/kg/min, and maybe increased to 15 µg/kg/min.
- ***Nesiritide:*** not available in Viet Nam.

1.5. RELATED STUDIES:

In 2004, Nguyen Thi Du et al. had measured the mean serum level of BNP in hypertension patients with heart failure (NYHA class III-

IV) was 68.02 ± 473.86 pg/ml and without heart failure was 13.61 ± 13.60 pg/ml (sensitivity of 92% and specificity of 100%).

In the study of Hoang Anh Tien et al. performed in 132 patients with heart failure, suggested that the optimal cut-off of BNP serum concentration for cardiovascular mortality prognosis was 2175 pg/ml (81.52% sensivity; 69.87% specificity; and area under the curve (AUC) = 0.82; $p < 0.01$). The optimal increasing NT-proBNP cut-off after one week of treatment was 28.08 pg/ml for predicting cardiac mortatlity (65.24% sensitivity; 54.78% specificity and AUC = 0.61; $p < 0.01$).

Ta Manh Cuong et al. had quantified serum concentration of NT-proBNP in 106 patients in different classes and etiologies of chronic heart failure (NYHA/ACC criteria). There were significant differences among serum concentration of NT-proBNP and NYHA classes; in contrast, there were no statistical significances between NT-proBNP level and etiologies of heart failure.

Chapter 2: METHODS

2.1. SETTING:

2.1.1. Subjects:

In every ACPE patient indicated treatment with NPPV for the minimum of six hours, two blood samples are taken in order to measure BNP serum level and arterial blood gas, the first sample at starting NPPV and the second sample at six hours after.

2.1.2. Location and Time:

We collected ACPE patients who were admitted to the intensive care units at Gia Dinh People's Hospital and 115 People's Hospital, between September 2011 and May 2014.

2.2. PROCEDURES:

2.2.1. Study design: Prospective, interventional study.

2.2.2. Selective criteria: Patients diagnosed acute heart failure (according to the criteria of Canadian Cardiovascular Society, 2012) with clinical pulmonary edema presentation; who also had serum admission BNP levels ≥ 500 pg/ml and required NPPV for at least six hours.

2.2.3. Exclusion criteria: Patients suffered from renal failure (serum creatinine > 1.6 mg/dl) and obese patients with BMI ≥ 25 kg/m^2 were excluded.

2.2.4. Sample size: 70 patients.

2.2.5. Devices: Vela Comprehensive ventilator, Ciba Corning 238 pH/Blood Gas analyzer, MAP Lab Plus analyzer to measure serum concentration of BNP and reagents of Peninsula Laboratories.

2.2.6. Evaluation criteria and NPPV-stop criteria: Patients became conscious and contactable. Patients had respiratory rate < 25 breaths per min, heart rate < 100 beats per min, stable blood pressure, PaO_2 ≥ 90% and had no acid-base disorders in arterial blood gas.

2.2.7. Patient subgroups:

- ***Failure group*:** Patients required intubation due to remain adverse clinical presentation despite six hours of NPPV or died.

- ***Success group*:** Patients became more conscious and contactable, had stable vital signs, no wheezing, breathed easily and showed no acid-base disorders in arterial blood gas until discharged from the hospital.

2.2.8. Statistical analysis: IBM SPSS Statistics software, version 20.0.

Chapter 3: RESULTS

3.1. CLINICAL PRESENTATION, ARTERIAL BLOOD GAS MEASUREMENTS AND CHANGES IN SERUM LEVEL OF BNP IN ACPE PATIENTS TREATED WITH NPPV:

3.1.1. Clinical presentation and arterial blood gas measurements:

3.1.1.1. Age distribution: The mean age of total patients was 74.69 years. There was no statistical significance between success and failure groups ($p > 0.05$).

3.1.1.2. Gender distribution: There was no statistical significance ($p > 0.05$).

***3.1.1.3. Chief complaint*:** 91.4% of patients complained of dyspnea, and 8.6% of chest pain.

3.1.1.4. Clinical presentation and laboratory tests: The majority of patients had pulmonary distress symptoms, lung congestion signs and more than 60% of patients got acidosis at admission.

3.1.1.5. Length of hospital stay: The mean length of hospital stay ± SD was 10.26 ± 5.7 days, and there was no statistical significance between two groups ($p > 0.05$).

3.1.1.6. Length of ventilation: Length of ventilation was shorter in success group and there was a statistical significance between two groups (12.58 ± 16.95 hours vs. 14.07 ± 6.97 hours; $p < 0.05$).

3.1.1.7. Motivating factors: 30% of patients got physical exertion; 20% quitted treatment; 18.6% got infection; 17.1% got inadequate treatment; 10% got arrhythmias and 4.3% used traditional medicine.

3.1.1.8. Medical history: There was no statistical significance ($p < 0.05$).

3.1.1.9. Ejection fraction: The mean ejection fraction ± SD was 45.75 ± 10.58%.

3.1.1.10. Electrocardiogram: 21.4% of patients suffered from arrhythmias.

3.1.1.11. Etiologies: 71.4% of ACPE patients got hypertension, 61.47% got ischemic myocardial disease and 34.3% got heart valve disease. Moreover, 37% of patients had hypertension and ischemic myocardial disease, 20% had both hypertension and heart valve disease, and 10% had both ischemic heart disease and heart valve disease.

3.1.1.12. Changes in vital signs before and after ventilation:

- Before ventilation: Vital signs were not statistically different between success and failure groups ($p > 0.05$).
- After ventilation in success group:

Table 3.18. Changes in vital signs before and after ventilation in success group

Vital sign	Before ventilation	After ventilation	P-value
Pulse (beat/min)	122.69 ± 17.32	90.52 ±12.53	< 0.01
Systolic BP (mmHg)	158.56 ± 26.24	113.27 ± 18.44	< 0.01
Diastolic BP (mmHg)	91.73 ± 15.05	71.06 ± 11.56	< 0.01
Respiratory rate (breath/min)	29.44 ± 5.03	18.62 ± 2.19	< 0.01
SpO_2 (%)	82.71 ± 10.13	97.04 ± 2.39	< 0.01

Comment: *After six hours of ventilation, vital signs had significantly improved ($p < 0.01$).*

- After ventilation in failure group:

Table 3.19. Changes in vital signs before and after ventilation in failure group

Vital sign	Before ventilation	After ventilation	P-value
Pulse (beat/min)	116.17 ± 21.36	112.50 ± 16.56	> 0.05
Respiratory rate (breath/min)	27.21 ± 4.27	25.56 ± 6.52	> 0.05
SpO_2 (%)	83.56 ± 7.73	89.89 ± 12.06	> 0.05
Systolic BP (mmHg)	145.83 ± 29.21	125.56 ± 21.69	< 0.05
Diastolic BP(mmHg)	83.89 ± 15.01	73.06 ± 12.96	< 0.05

Comment: Changing in pulse, respiratory rate and SpO_2 had no significance ($p > 0.05$). In the other hand, there were significantly different in blood pressures ($p < 0.05$).

- ***Changes in pulse before and after ventilation:*** there was a statistical significance among the positive and negative difference of pulse in success and failure groups ($p < 0.01$).
- ***Changes in systolic blood pressure before and after ventilation:*** there was a statistical significance between the positive and negative difference of systolic blood pressure in success and failure groups ($p < 0.01$).
- ***Changes in diastolic blood pressure before and after ventilation:*** there was a statistical significance between the positive and negative difference of diastolic blood pressure in success and failure groups ($p < 0.05$).
- ***Changes in respiratory rate before and after ventilation:*** there was a statistical significance between the positive and negative difference of respiratory rate in success and failure groups ($p < 0.001$).
- ***Changes in SpO_2 before and after ventilation:*** there was a statistical significance between the positive and negative difference of SpO_2 in success and failure groups ($p < 0.05$).

3.1.1.13. Changes in blood gas measurements before and after ventilation:

- Before ventilation: There were no differences in blood gas parameters between two groups ($p > 0.05$).
- After ventilation in success group:

Table 3.27. Changes in blood gas measurements before and after ventilation in success group

Blood gas parameter	Before ventilation	After ventilation	P-value
pH	7.30 ± 0.10	7.41 ± 0.05	< 0.001
$PaCO_2$ (mmHg)	42.87 ± 10.80	35.82 ± 5.78	< 0.001
PaO_2 (mmHg)	59.03 ± 14.39	113.91 ± 48.21	< 0.001
HCO_3^- (mEq/l)	20.63 ± 5.12	23.30 ± 5.18	< 0.001

Comment: *After six hours of ventilation, acidosis condition had improved (pH increased from 7.3 to 7.41; HCO_3^- increased from 20.63 to 23.3; p <0.001); PaO_2 raised from 59.03 to 113.91 mmHg (p < 0.001) and $PaCO_2$ also decreased from 42.87 to 35.82 mmHg (p < 0.001).*

- After ventilation in failure group:

Table 3.28. Changes in arterial blood gas measurements before and after ventilation in failure group

Blood gas parameter	Before ventilation	After ventilation	P-value
pH	7.30 ± 0.12	7.36 ± 0.19	> 0.05
$PaCO_2$ (mmHg)	37.16 ± 14.34	35.86 ± 18.61	> 0.05
PaO_2 (mmHg)	58.37 ± 9.59	60.59 ± 13.56	> 0.05
HCO_3^- (mEq/l)	18.69 ± 5.80	19.62 ± 5.55	> 0.05

Comment: Arterial blood gas parameters had no significant improvement (p > 0.05).

3.1.2. Changes in BNP serum level before and after ventilation:

- Before ventilation: There was no statistical significance BNP serum concentration between success and failure groups (p > 0.05).

- After ventilation:

Table 3.32. BNP serum level before and after ventilation in success and failure groups

BNP (pg/ml)	Before ventilation	After ventilation	P-value
Success group	1533.75 ± 1125.51	908.53 ± 606.59	< 0.001
Failure group	2089.93 ± 1452.28	2397.15 ± 1514.79	> 0.05

Comment: *In success group, BNP level at the time of 6 hours of ventilation was statistically lower than BNP level at admission (p < 0.001). There was no significance in BNP level in failure group (p > 0.05).*

3.2. DETERMINING THE PREDICTIVE VALUES FOR SUCCESSFUL NPPV IN ACPE PATIENTS:

3.2.1. ROC curve predicts statistical difference:

3.2.1.1. AUC of vital signs:

Table 3.33. AUC of vital signs

Vital sign difference	AUC	P-value	95%CI
Pulse difference (beat/min)	0.81	< 0.001	0.68 – 0.94
Respiratory rate difference (breath/min)	0.79	< 0.001	0.67 – 0.92
Systolic BP difference	0.73	0.06	0.61 - 0.85
Diastolic BP difference	0.48	0.83	0.32 – 0.64
SpO_2 difference (%)	0.64	0.08	0.46 – 0.82

Comment: There were only two (pulse and respiratory difference) of five vital signs had statistical significance (p < 0.05).

3.2.1.2. Cut-off of positive and negative predictive values:

- ***Pulse difference:*** AUC of pulse difference was 0.81 (p = 0.001). Cut-off of pulse difference was 15.5 beats/min with 84.61% sensitivity and 66.67% specificity.
- ***Respiratory rate difference:*** AUC of respiratory rate difference was 0.795 (p = 0.0001). Cut-off of respiratory rate difference was 4.5 breaths/min with 96.2% sensitivity and 50% specificity.
- ***BNP difference:*** AUC of BNP difference was 0.801 (p = 0.0001). Cut-off of BNP difference was 219.94 pg/ml with 73.08% sensitivity and 72.22% specificity.
- ***BNP difference percentage:*** AUC of BNP difference percentage was 0.764 (p < 0.001). Cut-off of BNP difference percentage was 26.05% with 65.4% sensitivity and 72.22% specificity.

3.2.1.3. AUC of arterial blood gas parameters: Changes in arterial blood gas parameters had no significance (p > 0.05).

3.2.1.4. AUC of BNP difference and BNP difference percentage: Changes in BNP difference and BNP difference percentage were statistically significant (p < 0.05).

Table 3.40. The AUC of differences

Difference	AUC	P-value	95%CI
Pulse difference (beat/min)	0.81	< 0.0001	0.68- 0.94
Respiratory rate difference	0.79	< 0.0001	0.67 - 0.92
BNP difference (pg/ml)	0.80	< 0.0001	0.67 - 0.93
BNP difference percentage (%)	0.76	0.001	0.64 - 0.89

3.2.2. Relationships between differences and success probability:

3.2.2.1. Univariate analysis between differences and success probability:

Table 3.41. Univariate relationships between differences and success probability

Difference	Success (n = 52)	Failure (n = 18)	OR (95%CI)	P-value
Respiratory rate difference	10.9 ± 4.54	2.89 ± 7.77	0.771 (0.667–0.893)	< 0.001
Pulse difference (beat/min)	31.75 ± 18.47	2.56 ± 28.53	0.934 (0.901–0.969)	< 0.001
BNP difference (pg/ml)	625.24 ± 821.43	- 307.11 ± 813.52	0.998 (0.997–0.999)	0.001

Comment: There were statistically significant in differences of respiratory rate, pulse, BNP between success or failure rate (p<0.001).

3.2.2.2. Multivariate analysis between differences and success probability:

Table 3.42. Multivariate relationships between differences and success probability

Difference	Success (n = 52)	Failure (n = 18)	OR (95%CI)	P-value
Respiratory rate difference	10.9 ± 4.54	2.89 ± 7.77	1.23 (0.99 – 1.52)	0.054
Pulse difference (beat/min)	31.75 ± 18.47	2.56 ± 28.53	1.06 (1.01– 1.11)	0.010

BNP difference (pg/ml)	625.24 ± 821.43	307.11 ± 813.52	1.002 (1.001 – 1.004)	0.014

Comment: There were only two differences (pulse and BNP) had statistical significance with success prognosis (p = 0.001).

3.2.2.3. Logistic regression analysis between BNP difference and success probability:

Table 3.43. Relationship between BNP difference and success probability

	Slope coefficient (β)	**P-value**	**OR**	**95%CI**
BNP difference	-0.002	0.001	0.998	0.997 - 0.999
Constant	-0.784	0.015	0.457	

From data listed in table 3.43, we suggested our logistic regression formula:

$$\text{Log}\left(\frac{p}{1-p}\right) = \alpha + \beta X \Longleftrightarrow -0{,}784 - 0{,}002 \text{ x BNPdifference}$$

ntly associated with the probability of success. When the BNP difference elevated 1 pg/ml, the failure NPPV risk decreased by one time (OR = 0.998; 95%CI = 0.997-0.999; p = 0.001).

3.3. SUCCESS AND FAILURE RATE:

After six hours, the success rate of NPPV was 74.3% and the failure rate was 25.7%.

Chapter 4: DISCUSSION

4.1. CLINICAL PRESENTATION, ARTERIAL BLOOD GAS MEASUREMENTS AND CHANGES IN SERUM LEVEL OF BNP IN ACPE PATIENTS TREATED WITH NPPV:

From the data collected, we offer the following discussions:

4.1.1. Age:

Mean age of both success and failure groups were 75 years. This groups were at high risk for heart diseases and cardiovascular problems which were leading causes of hospitalization. Mihai Gheorghiade et al. reported the mean age of total ACPE patients in their research approximately 75 years which was similar with ours. The other study conducted in the United States also cited that ACPE patients usually admitted to hospital in their 70's (about 71 to 76 years).

4.1.2. Gender:

There were no significant differences in sex distribution. In 2008, a review of the correlation between gender and Europe hospitalized patients due to ACPE, there was a significant lower rate of hospitalized female compared with male patients. The reasons for this smaller percentage remained unclear, but maybe related to the difference of cardiovascular risk between two genders, especially smoking habit in males was the major risk. Otherwise, according to the retrospective study of Fonarow et al. in 2005, included 263 hospitals, ACPE patient rate in female was higher than in male, maybe explained by the higher of female life expectancy. It showed the

disunion in sex distribution of ACPE patients in many studies because of the differences in specific cardiovascular risks, geography feature and life expectancy in every single area.

4.1.3. Length of hospital stay:

The mean length was approximately ten days, and there was no statistical significance between success and failure groups. In 2008, Owais et al. reported that length of hospital stay in some Europe nations lasted about six to 14 days, mean length was 9 days and this data was two times higher than previous data published from the United States (mean length of 4.3 days). Owais raised the main reason more likely from the dissimilarity in geography, organization and health care systems among different nations and continents.

4.1.4. Length of ventilation:

The mean length of ventilation was approximately 12 hours and 58 minutes. In comparison with the research of author Akihiro in Japan, our ventilation time was slightly shorter, but doubled that of author Hassan's data. The difference may be raised from our willing to gradually reduce the ventilator settings to the lowest level in order to avoid recurrent pulmonary edema, despite the prior recovery of vital signs and blood gas parameters. However, ventilation length of success group was shorter than failure group about one hour. There was an individual in failure group spent 120 hours of ventilation, so that the total ventilation length of this group was a little longer than it had to be. The best advantage of NPPV compared with invasive ventilation was patients not be intubated. Patients would interface with ventilator through a face mask, so they could temporarily stop

breathing machine in a limited time for eating or personal hygiene. Thus, patients could be ventilated for a long term if well tolerated and in a close monitoring. According to Baptista et al., ACPE patients had well responses with NPPV should be considered to maintain this mode of ventilation until all medical problems recovered.

4.1.5. Motivating factors:

Lacking of knowledge about the disease led to physical exertion or quitting treatment or denying routine health checkup etc. were some of many subjective reasons worsening the disease, which ultimately lead to hospitalization. 50% of admission cases had motivated by exertion and quitting treatment regimen. This showed that the outpatient treatment guidelines in our hospitals still had many limitations.

4.1.6. Medical history:

Most patients in our study had medical history of cardiovascular diseases or other medical problems. The individual might have one or more conditions, for example hypertension and diabetes or ischemic heart disease. In our study, 93% of patients got a history of high blood pressure. A report of decompensation heart failure in the United States in 2006, prevalence of decompensation heart failure patients with a history of hypertension was > 90% and with ischemic heart disease was 50-59%. That previous data was similar with our results (61.4%). The combination of many ailments on an individual usually happened in female elderly. In the ADHERE research, patients with history of hypertension and ischemic heart disease or diabetes mellitus occupied a very high percentage (91%). Our data also showed that ACPE

inpatients likely got at least one major cardiovascular risk.

4.1.7. Etiologies:

Hospitalized ACPE patients in our study with hypertension, ischemic heart disease and heart valve disease were 71.4%, 61.47% and 34.3% respectively. Nesbitt et al. supposed that 90% of chronic heart failure patients arisen from high blood pressure. Some previous research had marked that ACPE patients usually had one or more comorbidities. Practically, in heart failure individuals with major comorbidities such as ischemic heart disease, hypertension or diabetes, echocardiogram should be indicated in order to detect mitral regurgitation due to degenerative valve. The primary cause of heart failure, in fact, hardly identified. A meta-analysis published in England in 2011 reported that 26% of ischemia-induced heart failure patients had hypertension, and 34% of them previously got silent myocardial infarction.

4.1.8. Vital signs:

Our results were similar with Bersten et al.'s data published. Singh et al. reported that the individuals responded well with NPPV, the pulse and respiratory rate were reduced in the first hour and continuously decreased in the following hours; then the author deduced that pulse and respiratory rate could be used to predict a successful NPPV. Naughton et al. also showed the decreasing in systolic and diastolic blood pressures resulted from improvement of cardiac output and a transient reduction in left ventricular pressure. The researchers concluded that in ACPE patients treated with NPPV, a reduced heart rate was sensitive to the preload changes and maybe

related to the resume of endothelial perfusion and better left ventricular diastolic filling. The reducing heart rate below 100 beats per minute was a predictive factor for successful NPPV. So our data showed no difference with data from foreign researchers listed above.

Furthermore, we collected the patient's vital signs for two times, at admission and after six hours of ventilation, and made the difference of every sign (pulse difference, respiratory rate difference, etc.). If the differences were higher than 0 indicated a decrease of vital signs and the opposite indicated an increase. We recognized both the decrease and increase in differences correlated to a successful and fail NPPV respectively. In our study, there were rare cases that failure NPPV patients had a decreased pulse differences and successful NPPV patients had increased pulse differences. To solve this problem, we created ROC curve with sensitivities and specificities of these cases. There was a corresponding in changes of pulse, respiratory rate and blood pressure before and after ventilation. The reduced SpO_2 after six hours of ventilation showed a statistical remark with the success outcomes. Therefore, every single sign's difference had the predictive meaning of NPPV results. The last important thing we would like to emphasize in this part that, in data analysis duration, we should carefully identify the exact predictive factors and excluded the biases in order to bring out the accurate outcomes.

4.1.9. Arterial blood gas parameters:

After six hours of ventilation, arterial blood gas parameters and acid-base balance were resumed. Othman et al. had previously reported the homological results. He suggested that the improvement

of blood gas coefficients resulted from the reduction in intrapulmonary shunts and increase in alveolar ventilation, helped oxygen exchange more easily. In a meta-analysis review, Kallet et al. had showed a statistical significance between blood gas recovery and the outcomes. According to Ferrer et al., the $PaCO_2$ reduction due to increasing intrathoracic pressure and elevated functional residual capacity would resume the inhalation threshold by positive end-expiratory pressure and recover the alveolar ventilation.

4.1.10. Changes in BNP level in ACPE patients before and after six-hour-NPPV:

We performed study in 70 ACPE patients who were in NYHA class III-IV heart failure and had the mean admission BNP level approximately 1676.77 ± 1231.22 pg/ml (presented the severe heart failure and an overload volume condition). According to Fonarow et al, there was a correlation between the first day hospitalized BNP level with mechanical ventilation rate and hospital mortality. However, it was just only one BNP sample which could not be reflected the clinical progression or treatment responses or death prognosis in heart failure patients, particularly ACPE patients. A reduction in BNP serum level during treatment period affirmed patients were in advantageous recovery. Otherwise, patients were likely processing to the bad prognosis. However the variability of BNP level had a statistical significance was still unclear. We thus measured BNP serum level for two times in every single patient, the first sample at admission and the second sample after six hours of ventilation, in order to evaluate the patient's response with NPPV. In

success group, the mean of total second BNP levels were significant lower than the first's mean. Similar results were not recorded in failure group. Doust et al. did a review on 19 studies in 10 years (from 1994 to 2004) about the correlation between BNP serum level and heart failure. They concluded that "a BNP increase of 100 pg/ml caused a 35% increase in risk of death". The changes in BNP level thus reflected the clinical progression and treatment responses. Most of patients in success group had positive differences of BNP level (between pre-ventilation and post-ventilation levels) and just a few of them had negative values. On the opposite, most of patients in failure group had negative BNP differences and a few of positive. ROC curve of BNP difference was created and the AUC of BNP difference was calculated 80.1% ($p = 0.001$). We chose BNP cut-off of 220 pg/ml with sensitivity of 73.8% and specificity of 72.22%. Furthermore, we also performed ROC curve of sensitivity and false positive of BNP difference percentage and then deduced the AUC was 76.4% ($p = 0.001$) with cut-off of 26% with sensitivity of 65.7% and specificity of 72.22%.

In RED study, authors had collected 287 individuals with acute heart failure with the mean admission BNP level about 822 pg/ml. They found that in patients without cardiovascular events, after 24 hours of admission, mean BNP decreased to level of 593 pg/ml (25.9%; AUC = 0.64%; $p < 0.001$). Patients who discharged with a reduction BNP level of more than 46% (AUC = 0.7; $p < 0.001$) compared with admission level and the discharge BNP level below 300 pg/ml indicated a likely lower rate of re-hospitalization and

mortality. Our results were interestingly similar with RED's data. In the other side, we recognized in success group, there also the reduction of vital signs (such as pulse, respiratory rate, blood pressure, SpO_2) and blood gas parameters (pH, PaO_2, HCO_3^-) in most of patients. The opposite results were reported in the failure group. So that, we suggested beside the BNP level, there were not only vital signs but also arterial blood gas measurements played roles in predicting the prognosis of ACPE patients. In our process, we continued creating the ROC curves of every single element of vital signs and blood gas parameters, and calculated the sensitivities and specificities.

From data in table 3.25, there were only two statistical differences (pulse and respiratory rate). We then created the ROC curve by sensitivity and false positive of pulse difference, and calculated AUC of pulse difference of 80.9% ($p = 0.001$) with cut-off of 16 beats per minute (sensitivity of 66.67% and specificity of 84.61%). We also made ROC curve by sensitivity and false positive of respiratory rate, and AUC of respiratory rate difference of 0.795 ($p = 0.001$) with cut-off of 5 breaths per minute (sensitivity of 96.2%, specificity of 55.56%).

4.2. PREDICTIVE VALUES FOR THE SUCCESSFUL NPPV IN ACPE PATIENTS:

In patients with acute respiratory distress, particularly in ACPE patients, critical care physicians often used arterial blood gas parameters in order to decide which patients indicated NPPV or invasive ventilation and to evaluate patient's unexpected responses

with ventilation mode. An elevated $PaCO_2$ and/or a reduced PaO_2 were signalized poor responses with the ventilation mode. However, a decreased $PaCO_2$ and/or an increased PaO_2 could not be used in ACPE patient prognosis. Practically, arterial blood gas sampling by direct vascular puncture was not a simple procedure, and often practiced in the emergency setting by physicians in order to avoid major complications. Arterial blood gas sampling might be difficult to perform in patients who are uncooperative (panic, dyspnea, etc.) or in who are unable to position properly for the procedure or who previously had anticoagulation agents. The differences of arterial blood gas parameters in our study did not predict the NPPV outcomes. After a logistic regression analysis, there were only pulse difference, respiratory rate difference and BNP difference statistically related to the success rate; other differences were not significant ($p > 0.05$).

Furthermore, when we made a multivariate regression analysis, there was no statistical significance between respiratory rate difference and outcome prediction any more. That meant respiratory rate was the bias which affected the correlations between BNP or pulse difference and outcome prognosis. Singh et al. reported that patients who responded well likely had a reduction in pulse and respiratory rate. Alasdair et al. also agreed NPPV had a remarkable improvement in pulse after one hour of ventilation (4 beats per min, 95%CI: 1-6, $p = 0.004$). Many recent reviews also showed advantages of NPPV in resuming heart rate in patients with increased cardiac output, ejection fraction, end-diastolic volume and hypoperfusion. Gray et al. concluded that heart rate reduction was the predictive

factor for well-responsive NPPV in ACPE patients. Our results were similar with many prior major data published, and we once again proved the advantages of NPPV for decreasing heart rate in ACPE patients. Besides, BNP difference also took part in predicting the NPPV outcomes.

Success or failure predictive values:

- ***Pulse difference***: Logistic regression analysis showed us that with every single beat increased per minute, the failure risk decreased by 0.93 time; deduced every ten beats increased per minute, the failure risk decreased by 9.3 times (95%CI, $p < 0.01$).
- ***BNP difference:*** With every 1 pg/ml increased of BNP difference, the failure risk decreased by one time (95%CI, $p < 0.01$).

Following the utilizing BNP in heart failure treatment guidelines, the admission BNP level and the changes in BNP level during hospitalization were used to make an accurate prognosis because of the linear correlation between BNP level and mortality. In fact, BNP serum level previously had a remarkable significance in diagnosis, prognosis and treatment follow-up. This blood marker once again had proved itself in our study in ACPE patients treated with NPPV.

In conclusion, when a ACPE patient treated with NPPV, BNP serum level should be tested twice, one at admission and one after six hours of NPPV. If BNP serum level fell of more than 220 pg/ml (or $\geq$ 26%) compared with admission level, there likely had a successful NPPV prognosis. Otherwise, a reduction of BNP level less than 200 pg/ml (or $<$ 26%) indicated a failure probability with sensitivity of 73.8% and specificity of 72.22%.

There were strongly correlations between BNP difference, pulse difference and success or failure probability. In patients with the same pulse difference, an elevation of 1 pg/ml of BNP difference after six-hour-NPPV indicated one-time reduction of failure NPPV risk (OR = 1.0024; 95%CI: 1.0005-1.0044; p = 0.014). In those with the same BNP difference, an increase of 10 beats of pulse difference after six-hour-NPPV indicated a reduction of 10.6 times of failure NPPV risk (OR =1.06; 95%CI: 1.01-1.11; p = 0.01).

Interestingly, in patients with vital signs (such as blood pressure, respiratory rate, SpO_2) and blood gas parameters resumed after six hours of NPPV but had an elevated BNP level or pulse, also indicated a failure ability of NPPV. In other hand, patients with a decreased BNP level or pulse likely had a successful NPPV. It presented that BNP or pulse difference in ACPE patients significantly correlated with predicting probability of successful or fail NPPV.

4.3. SUCCESS AND FAILURE RATES:

Our success percentage was similar with Winck's results, while comparing with Shirakabe's data, ours was a little lower. This difference may be related to our higher admission BNP level and heart failure NYHA classes. In addition, we recognized that success rate majorly depended on the admission-to-ventilation-duration and the starting supplemental oxygen concentration. In practice, our patients usually admitted to the hospital lately because of many objectively reasons and ventilators with inhaled-oxygen adjusting system (FiO_2) did not widely available in our emergency departments. That led us not only many limitations in this study but also the high failure rate.

Nouira et al. collected 200 ACPE patients with admission BNP levels above 400 pg/ml. After a six-hour-NPPV, patients were repeated a BNP level test. The outcomes were not surprising, patients with BNP level > 500 pg/ml and hypercapnia indicated a high rate of intubation and mortality compared with whose < 500 pg/ml and normal $PaCO_2$ ($p < 0.009$). In addition, bi-level positive airway pressure mode resumed clinical features quicker than continuous positive airway pressure mode ($p < 0.01$). That indicated the key role of NPPV in treating ACPE patients.

CONCLUSIONS AND SUGGESTIONS

CONCLUSIONS:

After analyzed BNP serum level in 70 ACPE patients treated with NPPV at Gia Dinh People's and 115 People's hospitals between September 2011 and May 2014, we concluded some following main points:

Clinical presentation, arterial blood gas measurements and changes in BNP serum level:

- Most patients in our study were elderly and there was not significant in gender distribution. 50% of motivating factors were physical exertion and quitting treatment. 91.4% of chief complains were dyspnea. Priority of patients admitted to hospital with pulmonary distress symptoms, such as tachycardia, tachypnea, and a reduced SpO_2. 71.4% of patients got hypertension, 21.4% got arrhythmia and

more than 50% got atrial fibrillation. 92% of patient had a history of hypertension and 61.4% had coronary artery heart disease.

- ACPE patients with at least six hours of NPPV had resumed vital signs, arterial blood gas parameters and BNP serum level ($p < 0.05$).
- Mean NPPV length was 12 hours and 58 minutes, and length of hospital stay was approximately 10.26 days.

Predictive values for the successful NPPV in ACPE patients:

- BNP difference before and after six-hour-NPPV ≥ 220 pg/ml indicated a success probability with sensitivity of 73.8%. Specificity of 72.22% and AUC = 0.801 ($p = 0.0001$). BNP difference < 220 pg/ml seemed to relate with a fail NPPV or need of intubation.
- If BNP level at the start of NPPV was 1 pg/ml higher than six-hour-NPPV level, the risk of intubation decreased by one time (OR = 0.998; 95%CI: 0.997-0.999; $p = 0.001$).
- There was a statistical correlation between pulse difference, BNP difference and failure probability. In patients with same pulse difference, an elevation of 1 pg/ml of BNP difference after six-hour-NPPV than before ventilation one indicated a one-time reduction of failure NPPV risk (OR = 1.0024; 95%CI: 1.0005-1.0044; $p = 0.014$). In those with same BNP difference, an increase of 10 beats of pulse difference after six-hour-NPPV indicated a reduction of 10.6 times of failure NPPV risk (OR =1.06; 95%CI: 1.01-1.11; $p = 0.01$).
- Success rate of NPPV in ACPE patients was 74.3%.

SUGGESTIONS:

1/ ACPE patients treated with NPPV should be carefully monitored pulse rate and serum concentration of BNP before and after ventilation for an accurate prognosis and a timely appropriate intervention.

2/ NPPV should be considered early in severe ACPE patients in order to significantly decrease the need of intubation.

LIST OF PUBLICATIONS

1. **Nguyen Tien Duc**, Le Duc Thang, Tran Van Thi (2010), "The role of positive airway pressure ventilation in the treatment of acute cardiogenic pulmonary edema", *Journal of Practical Medicine*, Vol.8, pp.38-40.
2. **Nguyen Tien Duc**, Le Thi Bich Thuan, Ho Kha Canh (2013), "Preliminary study of B-type natriuretic peptide concentration variations in acute pulmonary edema patients' serum treated with noninvasive positive pressure ventilation", *The Medical Journal*, Vol.15, pp.171-177.
3. **Nguyen Tien Duc**, Le Thi Bich Thuan, Ho Kha Canh (2015), "Evaluation on the effectiveness of cardiogenic pulmonary edema treatment with positive airway pressure ventilation at the intensive care department at Gia Dinh People's Hospital, Ho Chi Minh city", *Journal of Practical Medicine*, Vol.1 (949), pp.8-12.