Scholars Journal of Applied Medical Sciences
Abbreviated Key Title: Sch J App Med Sci
ISSN 2347-954X (Print) | ISSN 2320-6691 (Online)
Journal homepage: https://saspublishers.com

OPEN ACCESS

Critical Care Medicine

Compare the Serum Level of BNP between Weaning Successful and Weaning Failed Patients

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DOI: 10.36347/sjams.2021.v09i09.028 | **Received:** 11.08.2021 | **Accepted:** 17.09.2021 | **Published:** 25.09.2021

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Abstract **Original Research Article**

Background: Weaning is the term frequently used to describe the gradual reduction of ventilatory support from patient who's pulmonary and other conditions are improving. Delayed weaning from ventilatory support expose patients to unnecessary complications. Patients should therefore be weaned from mechanical ventilation as quickly as possible. ***Objective:*** The purpose of the study was to compare the serum level of BNP between weaning successful and weaning failed patients. ***Methodology:*** This study was a prospective cohort study. This study was conducted in the Department of Anesthesia, Analgesia and Intensive Care Medicine at Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh over a period of 2 years. Study population was selected for weaning from mechanical ventilation support for the first time in the age group of more than 18 years with both sexes. Patients with pre-existing diseases that elevate the plasma BNP level were excluded from the study. Weaning criteria was selected by ICU consultant following the standard ICU protocol for every patients enrolled in this study. Patients were subdivided into weaning success and weaning failure groups according to the outcome of weaning process. Plasma BNP level of all patients was measured before and after 2 hours of spontaneous breathing trial. Each blood sample (3ml) was collected by ICU lab technician into a vacutainer with EDTA for anticoagulation. Blood samples were sent to the biochemistry lab and analysis was done by chemiluminescent microparticle immunoassay (CMIA). Serial arterial blood gases done within ICU lab before and after 2hours of SBT and 12hourly up to 48 hours. Patients who were extubated would be followed up for 48 hours after SBT. ***Result:*** A total number of 30 patients were recruited for this study. One-third (33.3%) of the patients failed on SBT. The mean age of weaning success and failure groups were 54.90±9.787 years and 57.60±10.091 years respectively. The mean percent changes of BNP (pg/ml) during 2-h of SBT in weaning success and failure groups were 38.41±9.379 and 59.51±2.940 respectively, the difference was statistically significant (p=0.01). The receiver-operating characteristic curve (R0C) analysis for BNP as a predictor of weaning outcome, showed that the area under the curve (AUC) was 0.89. It was found that change of BNP level < 42.5% from baseline had the best combination of sensitivity (90%) and specificity (80%) in predicting weaning outcome. ***Conclusion:*** Plasma BNP level can be used as a predictor of weaning outcome among the patients under mechanical ventilation. During weaning of mechanically ventilated patients, role of plasma BNP level as a predictor of successful weaning outcomes is to be evaluated.

Key words: Respiratory Care, ventricular cardiomyocytes, weaning failure.

INTRODUCTION

Weaning a patient from mechanical ventilation is an art and very unpredictable as well. The current parameter used to predict successful weaning which is American College of Chest Physician (ACCP) and Association of Respiratory Care (AARC) Respir care (2002) have shown variable predictive value. About 75% of patients who meet specific criteria can tolerate spontaneous breathing trial (SBT) and the rest of the patients fail to tolerate SBT. On the other hand, 30% of patients who never satisfy weaning criteria can be weaned from ventilator [1]. That is why; weaning

criterias and tools should be more precised to predict the outcome of weaning accurately.

There are many causes and pathophysiological mechanism that impair weaning from mechanical ventilation, among them weaning induced cardiac dysfunction is an important one [2]. Patients with cardiac dysfunctions require more time to wean from mechanical ventilation than the patients without cardiac abnormalities [3]. Cardiac dysfunction like heart failure can be easily diagnosed by traditional methods such as echocardiography, cardiac CT scan and pulmonary artery catheterization. But weaning induced cardiac dysfunctions which become overt at the time of SBT is very difficult to predict with these tools, as each of them has some limitation like- operator-dependency, low sensitivity, lack of availability at the bed side and invasive procedure. Plasma B-type natriuretic peptide (BNP) is another noninvasive biomarker to demonstrate these cardiac dysfunctions.

BNP is secreted by ventricular cardiomyocytes in response to myocardial stretch by volume or pressure overload [5]. During two hours of SBT which is currently the most accurate index for predicting the weaning success, there is an increase of in cardiac preload and afterload of the both side of heart caused by intrathoracic pressure shift, increase catecholamine secretion and work of breathing [5].

B-type natriuretic peptide is a plasma neurohormone composed of 32 peptides and has been first identified in pig brain and therefore named brain natriuretic peptide [4]. However, BNP is subsequently discovered to be present in high concentration in cardiac tissue. Before its activation, BNP is stored as a 108–amino acid polypeptide precursor, pro-BNP, in secretary granules of both ventricles and to a lesser extent, in the atria [6]. After pro BNP is secreted, it is cleaved by convertage enzyme named corin, to the 76-peptide, biologically inert N- terminal fragment NT-pro BNP and the 32-peptide, biologically active hormone BNP [7].

BNP has diuretic, natriuretic and antihypertensive effect. It has also anti proliferative effect on fibroblast in progressive heart failure. The recommended threshold of less than 100pg/ml to rule out heart failure, more than 500pg/ml to rule in heart failure and intermediate range of 100 to 500pg/ml cannot be used alone to rule out or rule in heart failure [8]. BNP is a sensitive (>98%) and specific (>95%) serum marker for cardiovascular dysfunction. Plasma BNP levels are elevated in patients with- left ventricular dysfunction, acute congestive heart failure, right ventricular dysfunction, acute coronary syndrome, valvular heart diseases and after cardiac resynchronization therapy (CRT) [10, 11]. Falsely high level of BNP may be seen in females, with advancing age and in the presence of renal failure [12, 13].

BNP has been proposed as a novel biomarker to help guide decision making in the readiness for the liberation of mechanical ventilation following a spontaneous breathing trial [14]. Current evidence on the predictive ability of BNP on weaning failure has been uncertain, and has not been integrated into clinical practice guideline. This present study was undertaken to evaluate the plasma level of B-type natriuretic peptide (BNP) as a predictor of weaning outcome among the patients under mechanical ventilation.

OBJECTIVES

General objectives

To compare the serum level of BNP between weaning successful and weaning failed patients

Specific objectives

1. To measure the serum level of BNP before and after 2hours of spontaneous breathing trial (SBT) among patients under mechanical ventilation.
2. To compare the serum level of BNP between weaning successful and weaning failed patients.

METHODOLOGY

Type of study	**This study was a prospective cohort study**
Place of study	This study was conducted in the Department of Anaesthesia, Analgesia and Intensive Care Medicine at Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh.
Study period	This study was carried out from July 2018 to June 2020 for a period of two (02) years.
Study population	The total sample size was 30 patients. According to the weaning outcome these patients would be designed a Group A (Weaning success group) and Group B (Weaning failure group).
Sampling technique	This study population was selected by purposive sampling technique.

SELECTION CRITERIA

Inclusion Criteria

- All patients who were intubated and had shown improvement or resolution of the underlying cause of respiratory failure.
- Sedation stopped during the previous 48 hours and analgesia might continue.
- Patients age more 18 years.
- Patients of both sexes.
- Patients whose relatives give written inform consent.

Exclusion Criteria

- Patients with heart failure (right or left), pulmonary hypertension, valvular heart diseases and atrial fibrillation.
- Patients having Acute (creatinine>350mmol/l) or Chronic renal diseases under Renal Replacement Therapy (RRT).
- Patients with cirrhosis of liver.
- Patients with tracheostomy.
- Patients with hyperthyroidism as this condition may be associated with increased BNP level.
- Prolonged cardiac arrest with poor neurological prognosis.
- Patients having no written inform consent.

DATA COLLECTION

The study was done in ICU of BSMMU. Patients during the study period were selected if they fulfilled the inclusion criteria. The relevant information was recorded in the data collection sheet. The data collection was done by the researcher himself.

STATISTICAL ANALYSIS

Statistical analysis was performed by Windows based software named as Statistical Package for Social Science (SPSS), versions 22.0 (IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp). Continuous data that were normally distributed were summarized in terms of the mean, standard deviation, median, minimum, maximum and number of observations. Categorical data were summarized in terms of frequency counts and percentages. For end points analysis, Chi-squre test was used for categorical data and Student Test for continuous data. Receiver operator characteristic (ROC) analysis was used to detect the predictive value of BNP. Every effort was made to obtain missing data. A two-sided P value of less than 0.05 was considered to indicate statistical significance.

RESULT

Table-1: Age Distribution of Study Population. Group-A (Weaning success) and Group-B (Weaning failure) (N-30)

Age Group	Weaning Group		Total	P value
	Group-A	Group-B		
32 to 40 Years	2(10.0%)	1(10.0%)	3(10.0%)	0.49*
40 to 60 Years	14(70.0%)	5(50.0%)	19(63.3%)	
60 to 72 Years	4(20.0%)	4(40.0%)	8(26.7%)	
Mean±SD	54.90±9.787	57.60±10.091	55.80±9.79	0.48**

Range: 32 to 72 years; *Chi-square test was performed to see the level of significance; ** P value was calculated by unpaired t test to see the level of significance.

Table 1 showed the age distribution of study population. In weaning success group, the most common age group was 40 to 60 years which was 14(70.0%) cases followed by 60 to 72 years and 32 to 40 years age group which was 4(20.0%) cases and 2(10.0%) cases respectively. In weaning failure group, the most common age group was 40 to 60 years which was 5(50.0%) cases followed by 60 to 72 years and 32 to 40 years age group which was 4(40.0%) cases and 1(10.0%) case respectively. The mean age with SD of weaning success and failure group were 54.90±9.78 years and 57.60±10.09 years respectively. The age range of study population was 32 to 72 years. The difference of age group of weaning success and failure groups were not statistically significant (p value=0.48).

Table-2: Gender Distribution of Study Population. Group-A (Weaning success) and Group-B (Weaning failure) (N=30)

Gender	Weaning Group		Total	P value
	Group-A	Group-B		
Male	18(90.0%)	4(40.0%)	22(73.3%)	0.004
Female	2(10.0%)	6(60.0%)	8(26.7%)	
Total	**20(100.0%)**	**10(100.0%)**	**30(100.0%)**	

Male: Female=2.75:1; Chi-square test was performed to see the level of significance.

Table 2 showed the distribution of study population according to gender. In this study male was

predominant in number than female which was 22(73.3%) cases and 8(26.7%) cases respectively. Among 20 cases of weaning success group male was more than female which were 18(90.0%) cases and 2(10.0%) cases respectively. In 10 cases of weaning failure group female was more than male which was 6(60.0%) cases and 4(40.0%) cases respectively. The male and female difference between weaning success and failure groups was statistically significant (p value=0.004). The ratio between male and female was 2.75:1.

Table-3: BNP level (pg/ml) in Gender Distribution of Study Population. Group-A (Weaning success) and Group-B (Weaning failure) (N=30)

BNP Value	Gender	Mean±SD	P value
Before SBT	Male	44.97±20.40	0.001
	Female	67.70±22.25	
After 2-h of SBT	Male	146.51±130.28	0.007
	Female	302.60±130.67	

SBT- Spontaneous breathing trail. P value was calculated by unpaired t test to see the level of significance.

Table 3 shows the distribution of study population according to gender. Before SBT, the mean with standard deviation of BNP in male and female was 44.97±20.402 and 67.70±22.254 respectively. The difference of BNP value of male and female before SBT was statistically significant (p=0.001). After SBT, the mean with standard deviation of BNP in male and female was 146.51±130.28 and 302.60±130.679 respectively. The difference of BNP value of male and female after SBT was statistically significant (p=0.007).

Table-4: Chronic Co-Morbidities of Study Population. Group-A (Weaning success) and Group-B (Weaning failure) (N=30)

Chronic Co-Morbidities	Weaning Group		Total	P value
	Group-A	Group-B		
COPD+HTN+DM	1(5.0%)	0(0.0%)	1(3.3%)	0.20
DM	5(25.0%)	1(10.0%)	6(20.0%)	
DM+HTN	7(35.0%)	8(80.0%)	15(50.0%)	
DM+IHD	2(10.0%)	0(0.0%)	2(6.7%)	
HTN	1(5.0%)	1(10.0%)	2(6.7%)	
HTN+IHD	4(20.0%)	0(0.0%)	4(13.3%)	
Total	**20(100.0%)**	**10(100.0%)**	**30(100.0%)**	

COPD= Chronic Obstructive Pulmonary disease; HTN=Hypertension; DM=Diabetes mellitus; IHD=Ischemic heart disease; Chi-square test was performed to see the level of significance.

Table 4 showed the chronic co-morbidities of study population. In weaning success group most, common co-morbidity was diabetes mellitus with hypertension which was 7(35.0%) cases followed by diabetes mellitus, hypertension with ischemic heart disease and diabetes mellitus with ischemic heart disease which were 5(25.0%) cases, 4(20.0%) cases and 2(10.0%) cases respectively. In weaning failure group diabetes mellitus with hypertension was the most common which was 8(80.0%) cases. The difference of chronic co-morbidities between weaning success and failure groups was not statistically significant (p value=0.20).

Table-5: Weaning Score between Weaning Success and Weaning Failure Group before SBT. (N=30)

Weaning Group	Mean±SD	P value
Group-A	5.2±0.52	0.67
Group-B	5.1±0.74	

P value was calculated by unpaired t test to see the level of significance.

Table 5 showed the distribution of weaning score between weaning success and failure groups before SBT. The mean weaning score with standard deviation in success and failure groups was 5.2±0.52 and 5.1±0.74 respectively. The difference between the success and failure group was not statistically significant (p=0.671).

Table-6: ABG and Clinical Variables of Group-A (Weaning Success) and Group-B (Weaning Failure) after SBT. (N=30)

Variables	Weaning Group	Mean±SD	P Value
P^H	Group-A	7.39±0.03	0.02
	Group-B	7.34±0.05	
PO_2	Group-A	96.3±9.60	0.01
	Group-B	56.9±5.95	
PCO_2	Group-A	38.5±3.58	0.05
	Group-B	47.8±7.93	
Sat%	Group-A	95.3±1.46	0.05
	Group-B	79.0±14.07	
Systolic BP	Group-A	130.6±9.31	0.83
	Group-B	129.5±14.83	
Pulse	Group-A	77.7±8.06	0.86
	Group-B	78.2±6.83	
RR	Group-A	20.5±2.35	0.01
	Group-B	24.6±3.72	

SBT=spontaneous breathing trial; PO_2 = partial pressure of oxygen; PCO_2=partial pressure of carbon dioxide; P value was calculated by unpaired t test to see the level of significance.

Table 6 showed the ABG of weaning success and failure groups. The mean values of P^H after SBT of weaning success and failure groups were 7.39±0.03 and 7.34±0.05. The difference of mean value of P^H of these weaning groups was statistically significant (p value=0.02). The mean values of partial pressure of oxygen (PO_2) after SBT of weaning success and failure groups were 96.3±9.598 and 56.9±5.953. The difference of mean value of partial pressure of oxygen (PO_2) between these weaning groups was statistically significant (p value=0.01). The mean values of partial pressure of carbon dioxide (PCO_2) after SBT of weaning success and failure groups were 38.45±3.576 and 47.80±7.927. The difference of mean value of partial pressure of carbon dioxide (PCO_2) these weaning groups was statistically significant (p value=0.05). The mean values of arterial oxygen saturation after SBT of weaning success and failure groups were 95.35±1.461 and 79.00±14.07. The difference of mean value of arterial oxygen saturation between these weaning groups was statistically significant (p value=0.05). The mean values of Systolic BP after SBT of weaning success and failure groups were 130.6±9.31 and 129.5±14.83. The difference of mean value of systolic BP between these weaning groups was not statistically significant (p value=0.81). The mean value of pulse after SBT of weaning success and failure groups were 77.7±8.06 and 78.2±6.83. The difference of mean value of pulse between these groups was not statistically significant (p value=0.86). The mean value of respiratory rate after SBT of weaning success and failure groups were 20.5±2.35 and 24.6±3.72. The difference of mean value of respiratory rate between these weaning groups was statistically significant (p value=0.01).

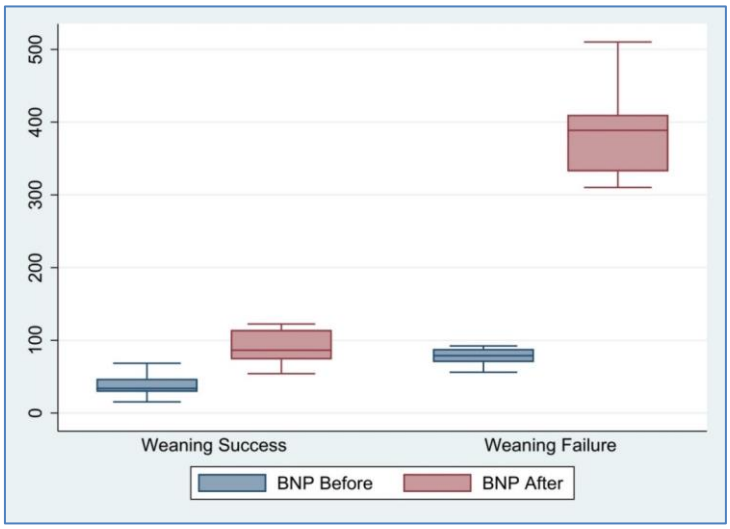

Fig-I: Showing the BNP Level (pg/ml) before and After SBT between Weaning Success and Failure Groups

The boxplot shows the different values of BNP in weaning success and failure groups before and after SBT. There were no outliers in success group. However, in failure group after SBT there was no outlier. The median value of BNP was not equal in success and failure group which had reflected the

disparity of values of BNP before and after SBT. In contrast the median BNP value of failure group before SBT was below the normal value of BNP and there was a very high median value of BNP after SBT.

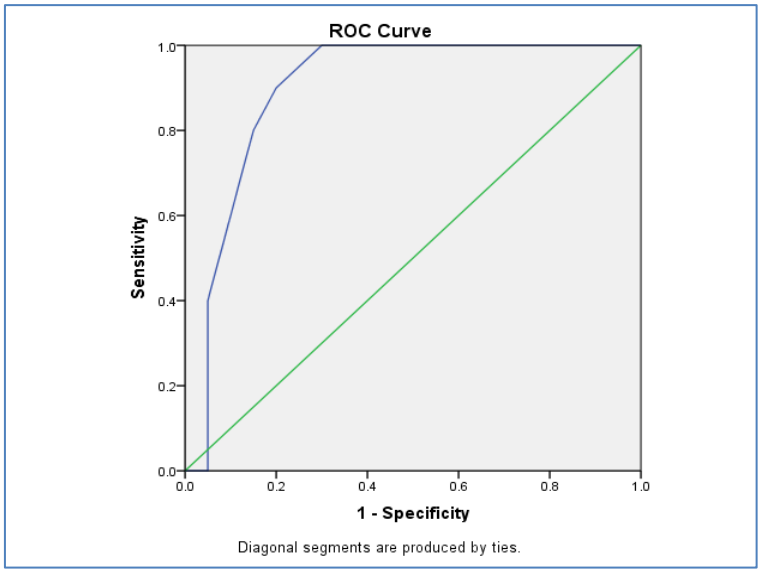

Fig-II: Predictive value of percent change of BNP in weaning failure.

The area under the ROC curve for percent change of BNP in SBT failure was 0.89 (95%CI 0.782-1.00). The best percentage change was 42.5, with a sensitivity of 90%, a specificity of 80%.

DISCUSSION

Weaning patients from mechanical ventilation is always challenging for the clinician. A successful weaning from mechanical ventilation depends not only on adequate respiratory strength and endurance but also an optimal performance of other organs including heart. Patient´s cardiovascular function may be compromised by alteration in lung volumes and intrathoracic pressure during withdrawal of mechanical ventilation and may be an important cause of weaning failure [15]. Plasma B-type natriuretic peptide (BNP) is secreted by ventricular cardiomyocyte in response to myocardial stretch and it is correlated to left ventricular filling pressure [16]. Since cardiac dysfunction can cause weaning failure in mechanically ventilated patients, the aim of this study is to evaluate the role plasma B-type natriuretic peptide (BNP) as a predictor of weaning outcome.

A total number of 30 patients were recruited for this study after fulfilling the inclusion and exclusion criteria. According to the outcome of SBT they were subdivided into two groups, weaning success (n=20) and weaning failure group (n=10). Regarding age distribution in weaning success group and weaning failure group the most common age group was 40 to 60 years. The difference of age group of weaning success and failure groups were not statistically significant (p=0.49). From this finding it is very clear that the mean age of the patients in weaning success and failure groups were more or less equivalent (p=0.48).

According to the gender distribution, this study showed male was predominant in number than female but weaning failure was more common in female patients. The male and female difference between weaning success and failure groups were statistically significant (p=0.004). The ratio between male and female was 2.75:1. Similar to this present study, Chien *et al*. have reported that male patients are more commonly under mechanical ventilation [17]. In this present study male was double than female. In another study Zapata *et al*. have reported a predominance of male over female which is consistent with the present study [18]. In this study female were more prone to weaning failure than male, which is supported by the study [19]. The study demonstrates that female gender (0.401 [0.216-0.745]; p=0.004) LTC-MP (3.017 [1.027–8.862]; p = 0.046) is independent risk factor for an unsuccessful SBT.

The mean BNP values among male and female were recorded in this study and found that the mean BNP values were higher in female than male both before and after SBT, which was statistically significant (p=0.001). The study finding is similar to the study finding of Redfield *et al*. in which BNP level is 32 % higher in female than male (CI=15% to 51%, p < 0.001) by Shionogi assay and 80% higher by Bisite assay (CI=50% to 116%, p < 0.001).

The chronic co-morbidities of study population were observed in this study. Diabetes mellitus with hypertension was the most common co-morbidity which was 15 (50.0%) cases among weaning failure and success groups. The difference of chronic co-morbidities between weaning success and failure groups was not statistically significant (p value=0.206). The most common co-morbidities among the all age groups

(<65year to ≥65years) are hypertension (18.5%, 89.7%), ischemic heart disease (7.5%, 75.1%) and diabetes mellitus (4.3%, 33%), which is similar with this present study [20]. Level of BNP can be elevated by hypertension in the presence of left ventricular hypertrophy [21]. In this study both groups had hypertension as their common co-morbidity so there is no chance of bias in result regarding hypertension. Controlled diabetes mellitus has no impact over BNP level but it can be altered in the presence of chronic heart diseases.

A standard weaning protocol was set for weaning but still 10 (33.3%) out of 20 (66.7%) patients fail to wean from mechanical ventilation after 2-h of SBT. This finding is consistent with the American College of Chest Physician (ACCP) and Association of Respiratory Care (AARC) Respir care, states that about 75% of patients who meet specific criteria can tolerate SBT and the rest of the patients fail to tolerate SBT. This study finding is also supported by Heunks, where the prevalence of weaning failure is 20% to 30%.

After 2-h of SBT, there was a significant change in ABG variable like P^H, mean partial pressure of oxygen (Pao_2), mean partial pressure of carbon dioxide (Pco_2), mean arterial oxygen saturation (Sat%) between weaning success and failure groups. In clinical variable the mean respiratory rate differed significantly between the two weaning groups (p=0.01). This significant change occurred due to SBT failure. According to EI Maraghi *et al*. 2014, patients with weaning failure sharing the similar features which is consistent with this study [22]. These parameters act as major tools deciding weaning failure [23].

The boxplot shows the change of BNP level (pg/ml) between weaning success and failure groups. Through this boxplot we can see the disparity of BNP level between the two weaning groups before and after 2-h of SBT. BNP is a known cardiobiomarker which is potentially elevated due to some cardiac diseases; it can also increase after unsuccessful weaning. In this study there was an initial increase of BNP level before SBT which was due to intrathoracic pressure shifting and stress at the onset of SBT. BNP elevation before SBT is an independent factor for weaning failure, which is consistent with this study finding [23].

The percent change in the BNP level has been evaluated by using ROC curve. The area under the curve was 0.89. It was found that an increase of BNP level < 42.5% from base line had the best combination of sensitivity (90%) and specificity (80%) in predicting extubation failure. The disparity in predictive value between this study and other could be due to small sample size and large-scale change of BNP level during SBT. In this study 21 out of 30 patients had hypertension which was significantly higher than other studies, could be a cause of high BNP level among the study population. Similarly, significant changes were found in this study in ABG and clinical variables during breathing trail, regarding the study of Chien and EI Maraghi. These changes had an impact on plasma BNP elevation. Acute hypoxia (PAO_2 <60mm of Hg and Sat%<90) results rapid increase of cardiac BNP gene transcription which significantly rise plasma BNP. Amdani *et al*. states that there is significant positive correlation between natriuretic peptide and partial pressure of carbon dioxide ($Paco_2$), which is consistent with these study findings [24]. After all the discussion it is found that BNP have some predictive role regarding weaning outcome.

CONCLUSIONS

It was significantly increased in weaning failure group which was evaluated by ROC curve. So, plasma BNP level can be used to predict the weaning outcome of mechanically ventilated patients. During weaning of mechanically ventilated patients, role of plasma BNP level as a predictor of successful weaning outcomes is to be evaluated.

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