ISSN: 2377-4630

Sindhvananda et al. Int J Anesthetic Anesthesiol 2019, 6:085
DOI: 10.23937/2377-4630/1410085
Volume 6 | Issue 1
Open Access

International Journal of
Anesthetics and Anesthesiology

ORIGINAL ARTICLE

N-Terminal Pro-Brain Natriuretic Peptide in Post Cardiac Surgery as a Predictor of Ventilator-Weaning Outcomes

Wacharin Sindhvananda, MD, MPH, PhD[1,2*], Chonlada Bunpeth, MD[2] and Nuthathai Chareonkulnawanun[3]

[1]*Department of Anesthesiology, Chulalongkorn University, Bangkok, Thailand*

[2]*Cardiovascular Thoracic and Intensive Care Centre, Chulalongkorn Hospital, Thailand*

[3]*Division of Anesthesiology, Bhumibol Adulyadej Hospital, Thailand*

***Corresponding author:** *Wacharin Sindhvananda, MD, MPH, PhD, Department of Anesthesiology, Chulalongkorn University, Bangkok, Thailand, Tel: 662-649-4000*

Abstract

Purpose: An increase of NT-proBNP has been proved to be a predictor for ventilator weaning failure in several medical conditions. However, relation between NT-proBNP and ventilator-weaning outcomes after cardiac surgery has not yet been elucidated. This study was to investigate relationship between blood NT-proBNP and ventilator-weaning outcomes.

Methods: A prospective analytical study was at Cardiovascular-thoracic intensive care unit. Cardiac-surgery patients (age 18-80 Y, consented and without exclusion criteria) were included. Blood NT-proBNP was sampling at pre-operation time and at weaning. Early-weaning outcomes were categorized into simple, difficult, and prolong weaning. Late-weaning outcomes were reintubation and suspicious cardiopulmonary compensations. Blood NT-proBNPs were compared among/between early and late-weaning outcomes. Area under the curve and sensitivity/specificity at various cut-off values for poor weaning outcomes were analyzed.

Results: A final of 134 patients were analyzed. The mean NT-proBNPs (pre-operation and weaning) were 1,417.8 and 4,532.5 pg/ml, respectively. wide variations of NT-proBNPs were observed. NT-proBNPs were not significantly related to difficult, prolong, and reintubation; but significantly related to suspicious cardiopulmonary compensations. AUC range were 0.43-0.65.

Conclusions: NT-proBNP increased 4-5-fold after cardiac surgery. A significant increase was related to sympathetic activation, not weaning-induced LV load. Due to low sensitivity, NT-proBNPs were not good predictors for difficult or prolong weaning and reintubation in post cardiac surgery.

Keywords

NT-proBNP, Reintubation, Weaning failure, Cardiac surgery

Introduction

Weaning mechanical ventilation in post cardiac surgery has remained problematic, especially in insufficient cardiopulmonary reserve patients. Too early weaning ventilation might stimulate the exaggerate inflammation process [1]. The over cardiopulmonary compensations that occur during ventilator weaning might lead to lethal acute respiratory and heart failure [2-4].

Recently, an increase of blood N-terminal pro B-type natriuretic peptides (NT-proBNP) has been used to monitor left ventricular (LV) distension [5-7]. During ventilator-weaning, spontaneous breathing trial (SBT) leads to a decrease of intrathoracic pressure that brings about an increase of venous return and then LV loading [6]. NT-proBNP are increasingly secreted during LV wall stress [7]; therefore, an increase of blood NT-proBNP has been assumed to be impending heart failure (HF) and indicates poor weaning outcomes. Some past investigations showed the fruitful results of both preoperative and postoperative NT-proBNP predicting weaning failure [8-11]. However, the past studies focused the scope of outcomes only WF, which were failed SBT and reintubation. We considered that some cases presented ambiguous signs of intolerance which leaded to difficulty in decision making of

Citation: Sindhvananda W, Bunpeth C, Chareonkulnawanun N (2019) N-Terminal Pro-Brain Natriuretic Peptide in Post Cardiac Surgery as a Predictor of Ventilator-Weaning Outcomes. Int J Anesthetic Anesthesiol 6:085. doi.org/10.23937/2377-4630/1410085

Accepted: March 07, 2019: **Published:** March 09, 2019

weaning management [12]. NT-proBNP might be helpful such of this condition. This study was primarily aimed to investigate blood NT-proBNP was related to 1) Early ventilator-weaning outcomes (simple, difficult, and prolong) and 2) Late ventilator-weaning outcomes (reintubation). The secondary objective was qualification of NT-proBNPs as tools to indicate poor ventilator-weaning outcomes.

Methods

The study was a prospective observational study (Clinical Trial Registry Number = TCTR20181011003) that was approved by the Medicine Faculty of Chulalongkorn university Ethics Committee (IRB no. 213-60, Date of Approval: June, 15, 2017-2018), and written informed consent was obtained from all patients. We included all of the patients aged 18-80 years who underwent elective cardiac surgery with CPB at Chulalongkorn Hospital. The study period was June, 2017 to June, 2018. The exclusion criteria were chronic renal failure needed dialysis, IABP or ECMO or positive ventilatory support or oxygen therapy needed before surgery and consent refusal. The patients were anesthetized according to our standard institutional protocol for open heart surgery. Anesthesia was induced by fentanyl (2-3 mcg/kg), midazolam (0.05-0.1 mg/kg) or with etomidate (0.2-0.3 mg/kg), and pancuronium bromide (0.1 mg/kg). Anesthesia was maintained with sevoflurane and fentanyl as needed. After the tracheal intubation, all of the patients received invasive mechanical ventilation with a tidal volume (TV) of 8 ml/kg, positive end-expiratory pressure (PEEP) of 5 to 8 cmH_2O, and fraction of inspired oxygen (FiO_2) of 0.6 to 1 to maintain the arterial oxygen saturation above 95%. During surgery, the patients were established a central venous line and indwelling radial artery catheter. Pre-operative information, including demographic data, pre-operative left ventricular ejection fraction (LVEF), Cardiac Risk Index (CRI) and basic laboratory data were obtained for all of the patients. The intraoperative data, including the cardiac procedure and CPB duration, fluid or blood (product) replacement and the use of inotropes or vasopressors, were also recorded. Postoperative laboratory data was obtained approximately an hour (h) after ICU arrival.

Blood samples were collected from indwelling radial catheter before surgery (NT-proBNP *pre*) and at 10-20 min after beginning the first episode of ventilator-weaning (NT-proBNP *wean*). Blood samples (3 ml) were collected into tubes containing 2 mg/ml ethylenediaminetetra-acetic acid (EDTA), blood samples were centrifuged at 2390 g for 5 min to obtain plasma, which was stored at 20 °C prior to analysis. NT-proBNP was measured using a commercially available immunoassay kit (Elecsys pro BNP; Roche Diagnostics, Basel, Switzerland) by laboratory staffs. The results of NT-pro BNP analysis were disclosed later and not used for any decision makings.

Weaning protocol

After ICU admission, initial setting of CMV with pressure-controlled ventilation (FiO_2 = 0.6-1.0, Pi to achieve TV of 8 ml/kg, respiratory rate (RR) = 12 bpm, PEEP = 5-7 cmH_2O) were provided as appropriated. The initial weaning was started if the patients were hemodynamically stable, as defined by the absence of bleeding (chest tube drainage < 300 ml/h for 2 h), low-dose of epinephrine/norepinephrine (< 0.1 mcg/kg/min), low-dose of dopamine, dobutamine (< 3 mcg/kg/min), heart rate (HR) < 120 bpm, and adequate pulmonary reserve, as defined P/F ratio > 300, vital capacity > 10 ml/kg. Also, other parameters were within normal values. Then, the degree of ventilatory support was reduced as stated in the institution protocol of weaning process (started at SIMV; RR 6-8 bpm, at the previous setting of Pi, and pressure support (PS) 5-10 cmH_2O, adjusted to SIMV; RR 4 bpm, PS 5 cmH_2O). SBT (CPAP 5-8 cmH_2O or t-piece) was started then if the patients were still awake and hemodynamically stable after the SIMV weaning process. Time duration of SBT test was planned maximum at 60 min.

At the process of weaning (SIMV or SBT), discontinuation of weaning was decided if the patient presented with one or more of the following: RR 30 bpm; HR > 120 bpm; SpO_2 < 90% or PaO_2 < 60 mmHg; respiratory acidosis (pH < 7.3 or $PaCO_2$ > 50 mmHg); signs of respiratory distress [13,14].

Increase of ventilatory support (SIMV; RR 4-8 bpm with PS 5-10 cmH_2O or else as appropriate). Treatment for causes of weaning discontinuation were also provided. Weaning process was re-established when patient conditions met the weaning criteria.

Extubation was done in patients who had not one of the above-mentioned signs at 60 min of SBT. Post-extubation respiratory care including reintubation was provided as indicated in the institution protocol.

Early and late-weaning outcomes

Early-weaning outcomes were assessed and categorized into 3 characteristics [15]. Simple weaning (SIMPLE) was defined as extubation in the first attempt of SBT or extubation was done within 12 h after the begin of weaning. Difficult weaning (DIFFICULT) was defined as failure of the first attempt of SBT or extubation was done within 48 h and prolong weaning (PROLONG) was defined as extubation was not successful within 48 h after the begin of weaning.

Late-weaning outcomes were assessed after extubation for 3 days into 2 aspects. First, cardiac and pulmonary compensations that were probably beyond normal compensations (or suspicious compensations) were observed. Suspicious cardiac compensations were defined as new arrhythmias, urine output < 0.5 ml/kg/h, Blood pressure (BP) and HR changed >

15-20% of the values before extubation. Suspicious pulmonary compensations were defined as RR > 24 bpm, oxygen therapy/non-invasive positive ventilation added, and thoracoabdominal dyssynchrony. Second, cardiopulmonary decompensations that needed intubation and ventilatory support (REINTUBATION) was counted.

Poor ventilator-weaning outcomes

In the present study, poor ventilator-weaning outcomes included difficult weaning, prolong weaning, reintubation and suspicious cardiopulmonary compensations.

Statistical analysis

The baseline characteristics, basic laboratory data, the intra-operative data, the measured values of NT-proBNP *pre* and NT- proBNP *post*, and the transformed values of NT-proBNP (difference: NT-proBNP *wean* minus NT-proBNP *pre*, ratio: NT-proBNP *wean* divided by NT-proBNP *pre*) were compared regard to the early weaning outcomes. Continuous data analyzed by ANOVA and post-hoc test (Tukey-Kramer procedure). Non-continuous data analyzed by chi-square test and post-hoc test (Fisher exact test).

Reintubation were described with frequency and percentage in total events. Additionally, Suspicious cardiac and pulmonary compensations were independently described with frequency and percentage in total events. The measured and transformed values of NT-proBNP were compared between reintubation and no reintubation (None), also between existed (EXIST) and no (NONE) suspicious cardiopulmonary compensations by independent t-test or Mann Whitney U test.

The receiver operating characteristic curve (ROC) were analyzed for poor weaning outcomes by all the NT-proBNP indices (the measured and transformed values of NT-pro BNP) to identify AUC. Sensitivity and specificity were analyzed on various cut off values of NT-proBNP at wean. The statistical analyzes were performed using SPSS version 11.0 (SPSS Inc., Chicago, IL). A two-sided *P*-value of 0.05 was considered statistically significant.

The sample size was calculated from an incidence of reintubation of in post cardiac surgery of 6.6% [16] and the reported rate of prolonged ventilation > 48 h up to 9% [17,18]. The calculate sample size at the confidence level 95% was 126 samples [19]. Additional 20% of the calculated sample size was planned to enroll.

Results

There were totally 156 patients enrolled in this study. Incomplete blood sample taken were in 11 patients; 4 patients were extubated in OR; 4 patients had serious cardiovascular instability so that SBT could not be provided within 24 h; and management errors lead to missing in 3 patients. Finally, 134 patients remained in the study: 40 of female (29.9%), 94 (70.1%) of male. The mean age was 58.1 + 12.47 Y. The operations were 55 of CABG (44%), 44 of valvular surgery (32.8%), 16 of combined surgery (11.9%), 13 of aortic surgery (9.7%), and 6 of congenital surgery (4.5%). CRI > 2 was in 91 (67.9%) patients.

Regarding early-weaning outcomes, there were 101 of SIMPLE (74.5%), 25 of DIFFICULT (18.7%) and 8 of PROLONG (5.9%). Two patients in PROLONG needed ventilatory support more than a week; thus, these patients did not include in statistical analysis for late-weaning outcomes. Regard to late-weaning outcome, reintubation was found in 6 patients (4.6%); 5 of them were reintubated within 24 h and the other was reintubated within 48 h after extubation. Suspicious cardiac and pulmonary compensations were found in 62 (46.3%) and 50 (37.3%) patients respectively. The most common sign of suspicious cardiac compensation was paroxysmal supraventricular dysrhythmias. The most common signs of suspicious pulmonary compensation were tachypnea (RR > 24 bpm).

Demographic, intraoperative, and laboratory data were classified (Table 1). Elderly, low pre-operative and postoperative GFR were significantly related to PROLONG and REINTUBATION. The mean of pre-operative WBC in REINTUBATION was a very much increase with significant difference. There was a significant lower postoperative hematocrit in REINTUBATION. LVEF was totally averaged 58.1% [95% CI: 55.8-60.4].

The mean NT-proBNP *pre* and NT-proBNP *wean* were 1,417.8 pg/ml (95% CI [1,100-1,700], Range [39-8,937]) and 4,532.5 pg/ml (95% CI [3,460-5,600], Range [46-35,000]) respectively. NT-proBNP *wean* was much higher than NT-proBNP *pre* with statistical significant (*P*-value = 0.001). The NT-proBNP *pre* was not significantly different among type of operation (*P*-value = 0.676).

The mean NT-proBNP *wean* of PROLONG was 8243.2 with 95% CI [-476-17,000], which was higher than the mean NT-proBNP *wean* of DIFFICULT that was 5114.5 with 95% CI [2,240-7,980] and the mean NT-proBNP *wean* of SIMPLE that was 4,094.4 with 95% CI [3,030-5,150]. The mean NT-proBNP *wean* was the highest value and the widest variation without statistical significance. The mean ratio of increased NT-proBNP after cardiac surgery in total was 4.82 with 95% CI [3.8-4.82]. None of significant difference of NT-pro BNP indices among early-weaning outcomes and REINTUBATION was detected (Table 2).

Significant higher values of both NT-proBNP *pre* and NT-proBNP *wean* in who presented suspicious cardiopulmonary compensations (Table 3). Demographic, intraoperative, and laboratory data were not significant difference when compared between NONE and existed pulmonary compensation. But for cardiac compensa-

DOI: 10.23937/2377-4630/1410085 ISSN: 2377-4630

Table 1: Demographic, intraoperative, and laboratory data.

Variables	Early-weaning outcomes			*P*-value	Late-weaning outcomes		*P*-value
	SIMPLE (*n* = 101)	DIFFICUL (*n* = 25)	PROLON (*n* = 8)		None (*n* = 126)	REINTUBATIO (*n* = 6)	
Age (Y)	58 (56-60)	54 (47-60)	72 (68-76)	0.001*,†	57.3 (55-59.5)	66.3 (60.4-72.3)	0.029*
Male (*n*)	72 (71%)	18 (72%)	4 (50%)	0.437	90 (72%)	3 (50%)	0.234
BMI	24.2 (23-24.8)	24.3 (22.1-26.7)	24.6 (17.9-31.3)	0.946	23.9 (23-24.6)	27.6 (22.8-32.4)	0.030*
COPD (*n*)	6 (5.9%)	1 (4.0%)	(0%)	0.584	7 (5.6%)	0 (0%)	0.551
Pre-O_2 Sat (%)	97.37 (95.6-99.1)	97.94 (96.9-98.9)	97.3 (96.4-98.2)	0.984	97.5 (96-98.9)	96.6 (95.1-97.9)	0.769
Pre-hct (%)	39.5 (38-40.1)	40.4 (37.0-43.1)	34.3 (31.5-37.1)	0.038*,†	39.6 (38-40.7)	36.5 (32.2-40.8)	0.214
Pre-WBC	7.5 (6.7-8.3)	7.5 (6.5-8.5)	7.5 (3.4-11.7)	0.999	7.1 (6.7-7.5)	14.1 (2.9-25.3)	0.001*
Pre-GFR	87.6 (84-91.3)	88.3 (75.4-101.1)	57.9 (42.3-73.6)	0.001*,†	87.6 (84-91.5)	66.1 (51.5-80.9)	0.034*
LVEF (%)	58.5 (56-61.1)	58.6 (52.9-64.4)	52.7 (55.8-60.4)	0.505	58.2 (56-60.6)	57.8 (43.2-72.4)	0.943
Operation Type (*n*)				0.090			0.644
CABG	46	7	2		52	2	
Valve	34	7	3		40	3	
Aneurysm	9	3	1		13	0	
Congenital	2	4	0		6	0	
Combined	10	4	2		15	1	
CPB time (min)	139 (130-147)	139 (123-155)	147 (106-188)	0.872	140 (132-147)	136 (101-172)	0.864
inotrope > 1 (*n*)	36 (35.6%)	14 (56%)	4 (50%)	0.151	51 (40.8%)	2 (33.3%)	0.535
PRC Volume (ml)	354.8 (308-401)	414.8 (280-550)	502.5 (331-419)	0.208	374.6 (328421)	378.0 (236-520)	0.966
Post-hct (%)	30.8 (29-31.7)	30.4 (28.4-32.4)	27.5 (24.9-30.1)	0.130	30.9 (30-31.7)	24.8 (22.1-27.5)	0.001*
Post-WBC	14.6 (13.-15.9)	15.6 (12.5-18.7)	12.9 (3.9-22.1)	0.644	14.5 (13-15.6)	18.2 (7.9-28.5)	0.187
Post-GFR	95.4 (91-99.4)	96.8 (80.7-112.8)	60.5 (43.5-77.4)	0.001*,†	95.5 (91-99.9)	70.8 (55.6-86.0)	0.020*

Notes: Values are mean (95% CI) and number (frequency), BMI: Body Mass Index; Pre (Post)-X: Pre-operative (Postoperative)-X; Pre-operative (Postoperative)-X; O_2sat = Oxygen saturation at FiO_2 = 0.2; hct = Hematocrit, WBC = White blood cell count; CPB time = Duration under cardiopulmonary bypass machine; GFR(ml/min/1.73m^2); WBC (cell/mm^3/10^3); BMI (kg/m^2); PRC volume = Volume of intraoperative PRC transfusion For ANOVA: * = Significance among 3 groups, † = Post hoc significance between SIMPLE-PROLONG and DIFFICULT-PROLONG but without significance between SIMPLE-DIFFICULT.

DOI: 10.23937/2377-4630/1410085 ISSN: 2377-4630

Table 2: NT-proBNP indices and early-weaning outcomes, REINTUBATION.

NT-pro BNP Indices	Early-weaning outcomes			*P*-value	Late-weaning outcomes		*P*-value
	SIMPLE (*n* = 101)	DIFFICULT (*n* = 25)	PROLONG (*n* = 8)		None (*n* = 126)	REINTUBATION (*n* = 6)	
Pre	1291.9 ± 1776.1	1661.6 ± 1863.5	2245.9 ± 2915.1	0.29	1397.4 ± 1878.5	1652.1 ± 2253.3	0.85
Wean	4094.4 ± 5449.9	5114.5 ± 7311.9	8243.2 ± 11578.9	0.18	4505.7 ± 6456.3	4591.2 ± 4402.6	0.75
Difference	2802.6 ± 4236.1	3452.9 ± 6172.7	5997.4 ± 8924.9	0.21	3108.3 ± 5144.2	2939.0 ± 2260.8	0.94
Ratio	4.7 ± 5.7	4.8 ± 3.1	6.1 ± 10.3	0.83	4.9 ± 6.2	3.7 ± 1.9	0.63

Note: Values are in mean ± S.D, picogram/ml.

Table 3: NT-proBNP indices and suspicious cardiopulmonary compensations.

NT-pro BNP Indices	Suspicious Cardiac compensations		*P*-value	Suspicious Pulmonary compensations		*P*-value
	EXIST (*n* = 62)	NONE (*n* = 70)		EXIST (*n* = 50)	NONE (*n* = 82)	
Pre	1785.8 ± 2141.5	1068.3 ± 1555.3	0.03*	2006.3 ± 2401.9	1038.8 ± 1369.1	0.004*
Wean	6013.9 ± 7376.9	3123.3 ± 4942.4	0.01*	6767.7 ± 8015.8	3086.7 ± 4595.3	0.001*
Difference	4222.1 ± 5947.5	2055.1 ± 3816.4	0.01*	4761.5 ± 6465.3	2047.8 ± 3585.1	0.002*
Ratio	4.7 ± 5.6	4.9 ± 6.5	0.83	4.9 ± 5.9	4.8 ± 6.2	0.84

Note: Values are in mean ± S.D, picogram/ml, *$p < 0.05$ significant.

Table 4: NT-proBNP indices and ROC analysis on poor weaning outcomes.

NT-pro BNP Indices	DIFFICULTY	PROLONG	REINTUBATION	Suspicious Cardiac compensation	Suspicious Pulmonary compensation
Pre	0.597	0.626	0.586	0.635	0.621
Wean	0.576	0.588	0.605	0.632	0.636
Difference	0.455	0.545	0.650	0.609	0.619
Ratio	0.537	0.432	0.537	0.494	0.512

Note: values are area under the curve.

tions, significant differences were found in CPB time (*P*-value = 0.044), PRC transfusion (*P*-value = 0.020), and postoperative hematocrit (*P*-value = 0.001). The CPB time of EXIST and NONE were 154.8 (95% CI = 144-166) and 125.6 (95% CI = 118-133) min, respectively. Intraoperative PRC transfusion of EXIST and NONE were 429.1 (95% CI = 350-528) and 324.6 (95% CI = 281-368) ml, consecutively. Postoperative hematocrit of EXIST and NONE were 29.7% (95% CI = 28.6-30.9) and 31.3% (95% CI = 30.2-32.4), respectively.

ROC analysis demonstrated that AUC of the NT-proBNP indices on poor ventilator-weaning outcomes were approximately 0.43-0.65 (Table 4). NT-proBNP *wean* was used to calculate sensitivity, specificity, and accuracy on various cut-off values. Fair sensitivity and specificity were demonstrated (Table 5).

Discussion

As BNPs and its derivatives are increasingly secreted by left ventricular cells in case of LV distention. Besides, a short period of LV distention after weaning might lead to acute HF. However, in the moment of impending HF, a high value of BNP/NT-proBNP might help to predict a near future HF. As a result, hypotheses of using BNP/NT-proBNP as an indicator for ceasing ventilator weaning in order to avoid disaster HF were tested as follows. Chien JY, et al. [20] investigated in total 52 patients with acute respiratory failure (ARF). SBT trial was done after causes of ARF were treated. He observed 'failed SBT' (at 120 min) in aspect of 'extubation failure' and found patients who failed SBT had significant higher mean value of BNP than another group of 'extubation success' [20]. Zapata L, et al. [9] studied in total 100 SBT-trial patients measuring clinical AHF and ARF as the end points. They found significant higher values of BNP and NT-proBNP in patients who had AHF and ARF. He also demonstrated the cut-off point of NT-proBNP was 1,343 pg/ml [9]. Gerbaud E, et al. [8] studied in 44 patients after AHF that diagnosed by echocardiography. During SBT, they found the mean NT-proBNP of 'failed SBT' group was over 8,000 pg/ml and the cut-off level was 3,900 pg/ml [8]. Lara TM, et al. [21] investigated in total 101 post CABG with the end point of WF (defined as failed the first SBT within 60 min together with reintubation within 48 h). The author concluded that increases of BNP during SBT was associated with postoperative complication and WF [21]. Ma G, et al. [22] studied in total 51 postoperative cancer patients with pulmonary complications. The measured outcome was WF (defined as reintubation within 48 h). They demonstrated an increase of NT-proBNP in the WF group also analyzed the NT-proBNP cut-off value that was < 448 pg/ml indicated weaning success with 68% of sensitivity and 85% of specificity [22]. Despite the fact that all the mentioned studies demonstrated favourable results, some inconsistency were notice, such as differences in the outcome measurement of WF, the contexts, and

Table 5: The cut off values of NT-proBNP *wean* and its qualification as tools.

NT-proBNP (pg/ml)	Test (%)	DIFFICULT	PROLONG	REINTUBATION	Suspicious Cardiac compensation	Suspicious Pulmonary compensation
7000	Sensitivity	24.2 (11.1-42.3)	37.5 (8.5-75.5)	16.7 (0.4-64.1)	29.0 (18.2-41.9)	36.0 (22.9-50.8)
	Specificity	83.2 (74.4-89.9)	82.5 (74.7-88.7)	81.6 (73.7-87.9)	91.4 (82.3-96.8)	92.7 (84.8-97.3)
	Accuracy	68.7 (60.1-76.4)	79.9 (72.1-86.3)	78.6 (70.6-85.3)	62.1 (53.3-70.4)	71.2 (62.7-78.8)
5000	Sensitivity	27.3 (13.3-45.2)	62.5 (24.5-91.5)	16.7 (0.4-64.1)	35.5 (23.7-48.7)	38.0 (24.7-52.8)
	Specificity	75.3 (65.7-83.3)	75.4 (66.9-82.6)	74.4 (65.8-81.8)	84.3 (73.6-91.9)	82.9 (73.0-90.3)
	Accuracy	63.4 (54.7-71.6)	73.1 (64.8-80.4)	71.8 (63.2-79.3)	61.4 (52.5-69.7)	65.9 (57.2-72.9)
3000	Sensitivity	51.5 (33.5-69.2)	62.5 (24.5-91.5)	66.7 (22.8-95.7)	54.8 (41.5-67.5)	56.0 (41.2-70.0)
	Specificity	60.4 (50.1-69.9)	58.7 (49.6-67.4)	59.2 (50.1-67.9)	70.0 (57.9-80.4)	67.1 (55.8-77.1)
	Accuracy	58.2 (49.4-66.7)	58.9 (50.1-67.4)	59.54 (50.6-68.1)	62.9 (54.1-71.1)	62.9 (54.1-71.1)

Note: Values are in mean (95% CI), %.

the cut-off values. Therefore, it was still questionable to apply NT-proBNP as a weaning index in post cardiac surgery.

In the present study, we designed to study NT-proBNP due to its stability in blood circulation. Unlike the previous studies, we observed and separately evaluated into early and late-weaning outcomes. For the early-weaning outcome, we did not categorized the weaning outcome into dichotomous outcomes (success or failure). As we considered that it was impossible to need NT-proBNP assisted decision making of extubation in the SIMPLE. Also, we considered that the DIFFICULT was the patients needed a delay of weaning for a short period for some easy and correctable causes that might not be the same causes of the PROLONG. As a result, the analysis that took 3 situations into account were more reasonable and applicable than taking only the success and the failure into accounts. In other words, lesser selection bias than the previous studies. Unlike previous studies, we evaluated late WF (reintubation) separately from early WF (failed SBT and Prolong) since we considered that reintubation which was counted as long as 48 h might be caused by factors that were different from early WF. In addition, we designed to collect blood sampling once at SIMV since proceeding to SBT would be harmful for those who had suboptimal cardiopulmonary reserve but presented ambiguous signs of intolerance. As a result, the present study was more applicable and lesser measurement bias than the previous studies.

Jogia PM, et al. [23] demonstrated postoperative NT proBNP is a 4-fold higher than pre-operative values after cardiac surgery [23]. Corresponding to the mentioned study, we found the average NT proBNP *wean* was 4,500 pg/ml and the average ratio of increases was 4.8. Causes to an increase of NT-proBNP after cardiac surgery has not been obviously elucidated. But, inflammation (IL-6) was demonstrated to be associated with the increase of NT-proBNP [24]. That means increases of NT-proBNP are caused by inflammation itself without LV distension [25-27]. As known, post cardiac surgery are related to much degree of inflammations.

The present study demonstrated that NT proBNP *wean* was the highest value in the PROLONG, which were more advance age, lower pre-operative and postoperative GFR than the others. Like previous reports, these characteristics were demonstrated associated prolong mechanical ventilation [18]. However, these characteristics were associated with increase of NT-proBNP due to low excretion of NT proBNP induced by renal dysfunction [28]. As a result, increase NT-proBNP after cardiac surgery especially in who needs prolong ventilation is most likely interfered by characteristics of patients. Therefore, postoperative NT-proBNP that increases during ventilator weaning could not confirm it is solely the pure effect of weaning-induced LV load.

Regard to late weaning outcomes, this present paper demonstrated that all the NT-proBNP indices were not related to REINTUBATION. Since all the reintubation events in the present study were occurred in more than 24 h after extubation, we thus proposed that the cardiac-in-origin might not be a major cause of reintubation in that period of time. Based on, the study findings, more advance age, higher pre-operative WBC count, more severity of postoperative anemia, and lower pre and post-operative GFR were found in REINTUBATION with statistical significance. Past studies demonstrated and explained that these factors were related to muscle weakness. For examples, a large scale study (n = 8.809) that reported patients who had low GFR (< 60 L/min/1.73 m^2) was significantly associate with having restrictive lung pathology (low FVC and FEV1/FVC) [29]; postoperative anemia especially in elderly has been investigated that anemia was related to pulmonary complication due to muscle cellular oxygen deprivation [30]. Furthermore, there was a time gap before reintubation that some new serious events (such as sudden stroke, pleural effusion, and pulmonary embolism) could possibly happen after cardiac surgery. That means postoperative reintubation is caused by more component of non-cardiac causes than cardiac causes. As a result, this study found that NT-proBNP *wean* could not predict reintubation in post cardiac surgery.

We consider that suspicious cardio-pulmonary compensations occurred after extubation might be warning signs of serious conditions. Therefore, we postulated that increases of NT-pro-BNP at weaning indicate LV loading that might probably be relevant to poor LV function. As being poor LV function, cardio-pulmonary compensations might occur in a high degree of severity after extubation. Interestingly, this study found NT-proBNP *wean* also NT-proBNP *pre* was significantly higher in patients who presented suspicious cardiac and pulmonary compensations than who had not. Past studies mentioned that NT-proBNP acts as neurohormonal mediators and is secreted in case of sympathetic activation [28,31]. That meant patients who had suspicious cardiopulmonary compensations after extubation had previously exposed to sympathetic activation in both pre-operative and intra-operative periods. Intra-operative conditions that induced sympathetic activation were longer CPB time and more PRC transfusion. In spite of the significance of NT-proBNPs (between EXIST and NONE) and the analysis was done under the sufficient sample sizes (> 30 both), probabilities to predict suspicious cardiopulmonary compensations (approximately 0.63) was not good enough to accept NT-proBNP as a predictive index. Corresponding to a meta-analysis by Litton E, et al. they demonstrated the probability of association between NT-proBNP and atrial fibrillation after cardiac surgery was 0.6 [32]. In sum, an increase NT-proBNP was significantly associated with postoperative cardiopulmonary compensations but was not good to be a predictive index.

We analyzed the indices of NT-proBNP to evaluate their feasibilities as a predicted tool indicating the poor weaning outcomes. The analysis showed all of the probabilities were less than 0.7, which should be interpreted that NT-proBNP was not a good predicted tool for poor weaning outcomes. However, we tried to analyze sensitivity and specificity by using the recommended cut-off values from the past studies. We found overall low sensitivity. Reasons of low sensitivity in the context of cardiac surgery were as follows. The first reason was a wide range biological variability of NT-proBNP. Past investigations demonstrated biological variability of NT-proBNP [33,34]. Despite there have not been clear understanding of the biological variability, but anemia was reported to be an independent factor to cause 54% variability of NT-proBNP [35]. In fact, events of acute or chronic anemia are common in the peri-operative cardiac surgery. The second reason was variability of secretion depending on cardiac pathology. In other words, not all LV distension secretes NT-proBNP. Some past studies reported that a reversible NT-proBNP secretion in particular LV pathologies. Zheng YR, et al. found a low NT-proBNP instead of an increased value in AHF caused by ischemia [36]. Lemaire F, et al. [37] found that NT-proBNP would not be rising in case of an increased PAOP but no an increase of LVEDV [37]. In sum, the mechanism of NT-proBNP secretion is still unclear and more complexity than we have ever postulated. Finally, long-lasting of NT-proBNP (up to 120 min) leads to increase opportunity of detection, however at the time of investigation, high level of NT-proBNP was more likely to occur by accumulation than by the recent secretion of weaning-induced LV loading. Therefore, repeated stimulations of secretion that commonly occur in cardiac surgery can cause a high value of NT-proBNP in the first postoperative day. In sum, appearance of blood NT-proBNP in cardiac surgery are multi-factorial. LV distension or loading is not the only factor to increase NT-proBNP.

Despite the main results of this present study were in negative finding, but the results regarding patients' characteristic promoted our ideas that 1) Appearance of blood NT-proBNP depends much degree on renal function and 2) Weaning failure especially reintubation after cardiac surgery does not cause only by cardiac-in-origin. The limitation in the present study was the sample size of PROLONG and REINTUBATION was small. Therefore, we could not perform subgroup analysis. For future studies, to prove the usefulness of NT-proBNP in cardiac surgery should consider renal insufficiency as a major confounding factor whereas no past study focused.

Conclusions

The present study revealed an 4-5-fold increase of NT-proBNP after cardiac surgery. The increase of NT-proBNP after cardiac surgery are from other causes than weaning-induced LV load. Sympathetic activity was significantly related to increase of NT-proBNP. NT-proBNP *pre* and NT-proBNP *wean* were less likely to be a predictor for poor weaning outcomes after cardiac surgery due to lack of sensitivity.

Acknowledgements

Authors would like to thank for colleagues in assistance of data collections, and processing paper works for funding.

References

1. Routsi C, Papas V, Zakynthinos S (2013) Neurormonal and inflammatory responses during weaning trials from mechanical ventilation. OA Critical Care 1: 13.
2. Teboul JL, Monnet X, Richard C (2010) Weaning failure of cardiac origin: Recent advances. Crit Care 14: 211.
3. Meade MO, Guyatt G, Butler R, Elms B, Hand L, et al. (2001) Trials comparing early vs late extubation following cardiovascular surgery. Chest 120: 445S-453S.
4. Amri P, Zahra Mirshabani S, Hossein Ardehali S (2016) Weaning the patient from the mechanical ventilator: A review article. Arch Crit Care Med 1: e8363.
5. MacIntyre NR (2012) Evidence-based assessments in the ventilator discontinuation process. Respir Care 57: 1611-1618.
6. Porhomayon J, Papadakos P, Nader ND (2012) Failed weaning from mechanical ventilation and cardiac dysfunction. Critical Care Research and Practice.
7. Krittayaphong R, Boonyasirinant T, Saiviroonporn P, Thanapiboonpol P, Nakyen S, et al. (2008) Correlation between NT-pro BNP levels and left ventricular wall stress, sphericity index and extent of myocardial damage: A magnetic resonance imaging study. J Card Fail 14: 687-694.
8. Gerbaud E, Erickson M, Grenouillet-Delacre M, Beauvieux MC, Coste P, et al. (2012) Echocardiographic evaluation and N-terminal pro-brain natriuretic peptide measurement of patients hospitalized for heart failure during weaning from mechanical ventilation. Minerva Anestesiol 78: 415-425.
9. Zapata L, Vera P, Roglan A, Gich I, Ordonez-Llanos J, et al. (2011) B-type natriuretic peptides for prediction and diagnosis of weaning failure from cardiac origin. Intensive Care Med 37: 477-485.
10. Grasso S, Leone A, De Michele M, Anaclerio R, Cafarelli A, et al. (2007) Use of N-terminal pro-brain natriuretic peptide to detect acute cardiac dysfunction during weaning failure in difficult-to-wean patients with chronic obstructive pulmonary disease. Crit Care Med 35: 96-105.
11. Krzych LJ, Szurlej D, Kołodziej T, Machej L, Weglarzy A, et al. (2011) Diagnostic accuracy of pre-operative NT-pro BNP level in predicting short-term outcomes in coronary surgery: A pilot study. Kardiol Pol 69: 1121-1127.
12. Galas F, Hajjar L, Lara T, Nozawa E, Feltrim M, et al. (2010) A prospective evaluation of hemodynamic indexes to predict weaning from mechanical ventilation in patients after cardiac surgery. Crit Care 14: 232.

13. Silva MGB e, Borges DL, Costa M de AG, Baldez TEP, da Silva LN, et al. (2015) Application of mechanical ventilation weaning predictors after elective cardiac surgery. Braz J Cardiovasc Surg.
14. Nemer SN, Barbus CS (2011) Predictive parameters for weaning from mechanical ventilation. J Bras Pneumol 37: 669-679.
15. Zein H, Baratloo A, Negida A, Safari S (2016) Ventilator weaning and spontaneous breathing trials; an Educational Review. Emerg (Tehran) 4: 65-71.
16. Shoji CY, de Figuereido LC, Calixtre EM, Calitxtre EM, Rodriques CDA, et al. (2017) Reintubation of patients submitted to cardiac surgery: A retrospective analysis. Rev Bras Ter Intensiva 29: 180-187.
17. Trouillet JL, Combes A, Vaissier E, Luyt CE, Ouattara A, et al. (2009) Prolonged mechanical ventilation after cardiac surgery: Outcome and predictors. J Thorac and Cardiovasc 138: 948-953.
18. Totonchi Z, Baazm F, Chitsazan M, Seifi S, Chitsazan M (2014) Predictors of prolonged mechanical ventilation after open heart surgery. J Cardiovasc Thorac Res 6: 211-216.
19. Browner WS, Newman TB, Hulley SB (2013) Estimating sample size and power: Applications and Examples. In: Hulley SB, Cummings SR, Browner WS, Grady DG, Newman TB, Designing clinical research: an epidemiologic approach. (4th edn), Lippincott Williams & Wilkins, Philadelphia, PA, 81.
20. Chien JY, Lin MS, Huang YC, Chien YF, Yu CJ, et al. (2008) Changes in B-type natriuretic peptide improve weaning outcome predicted by spontaneous breathing trial. Crit Care Med 36: 1421-1426.
21. Lara TM, Hajjar LA, de Almeida JP, Fukushima JT, Valente Barbas CS, et al. (2013) High levels of B-type natriuretic peptide predict weaning failure from mechanical ventilation in adult patients after cardiac surgery. Clinics (Sao Paulo) 68: 33-38.
22. Ma G, Liao W, Qiu J, Su Q, Fang Y, et al. (2013) N-terminal prohormone B-type natriuretic peptide and weaning outcome in postoperative patients with pulmonary complications. J Int Med Res 41: 1612-1621.
23. Jogia PM, Kalkoff M, Sleigh JW, Bertinelli A, La Pine M, et al. (2007) NT-pro BNP secretion and clinical endpoints in cardiac surgery intensive care patients. Anaesth Intensive Care 35: 363-369.
24. Jernberg T, Lindahl B, Siegbahn A, Andren B, Frostfeldt G, et al. (2003) N-Terminal pro-brain natriuretic peptide in relation to inflammation, myocardial necrosis, and the effect of an invasive strategy in unstable coronary artery disease. J Am Coll Cardiol 42: 1909-1916.
25. Pongratz G, Melzer M, Straub RH (2012) The sympathetic nervous system stimulates anti-inflammatory B cells in collagen-type II-induced arthritis. Ann Rheum Dis 71: 432-439.
26. Ogawa T, de Bold AL (2012) Brain natriuretic peptide production and secretion in inflammation. Journal of Transplantation.
27. van Diepen S, Roe MT, Lopes RD, Stebbins A, James S, et al. (2012) Baseline NT-pro BNP and biomarkers of inflammation and necrosis in patients with ST-segment elevation myocardial infarction: insights from the APEX-AMI trial. J Thromb Thrombolysis 34: 106-113.
28. Weber M, Hamm C (2006) Role of B-type natriuretic peptide (BNP) and NT-pro BNP in clinical routine. Heart 92: 843-849.
29. Kim YS, Kim HY, Ahn HS, Sohn TS, Song JY, et al. (2016) Glomerular filtration rate affects interpretation of pulmonary function test in a Korean general population: Results from the Korea National Health and Nutrition Examination Survey 2010 to 2012. Korean J Intern Med 31: 1101-1109.
30. Partridge J, Harari D, Gossage J, Dhesi J (2013) Anaemia in the older surgical patient: A review of prevalence, causes, implications and management. J R Soc Med 106: 269-277.
31. Karakas M, Haase T, Zeller T (2018) Linking the sympathetic nervous system to the inflammasome: Towards new therapeutics for atherosclerotic cardiovascular disease. Eur Heart J 39: 70-72.
32. Litton E, Ho KM (2012) The use of pre-operative brain natriuretic peptides as a predictor of adverse outcomes after cardiac surgery: A systematic review and meta-analysis. Eur J Cardiothorac Surg 41: 525-534.
33. Richards AM (2007) Variability of NT-proBNP levels in heart failure: Implications for clinical application. Heart 93: 899-900.
34. Roselló-Lletí E, Calabuig JR, Morillas P, Cortes R, Martinez-dolz Luiz, et al. (2012) Variability of NT-proBNP and its relationship with inflammatory status in patients with stable essential hypertension: A 2-Year follow-up study. PLoS One 7: e31189.
35. Tirmenstajn-Jankovic B, Dimkovic N, Perunicic-Pekovic G, Radojicic Z, Bastac D, et al. (2013) Anemia is independently associated with NT-proBNP levels in asymptomatic predialysis patients with chronic kidney disease. Hippokratia 17: 307-312.
36. Zheng YR, Ye LF, Cen XJ, Lin JY, Fu JW, et al. (2017) Low NT-proBNP levels: An early sign for the diagnosis of ischemic heart failure. Int J Cardiol 228: 666-671.
37. Lemaire F, Teboul JL, Cinotti L, Giotto G, Abrouk F, et al. (1988) Acute Left Ventricular Dysfunction during Unsuccessful Weaning from Mechanical Ventilation. Anesthesiology 69: 171-179.