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Pooled analysis of central venous pressure and brain natriuretic peptide levels in patients with extubation failure

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Abstract. Background: extubation failure is related to prolonged hospital stay, high mortality and care cost. In recent years, cardiovascular insufficiency has been considered as a common cause of failed extubation, and some studies have shown that central venous pressure (CVP) and brain natriuretic peptide (BNP) can predict the extubation outcome. Therefore, we conducted a pooled analysis to evaluate that the CVP and BNP levels in critically ill patients subjected to mechanical ventilation are predictors of extubation failure.

Methods: Three online electronic databases such as web of science, EMBASE, and Cochrane Library are systematically searched up to October 2021. All data are analyzed using Review Manager 5.4. The pooled analysis results were performed depending on standardized mean differences (SMD) with 95% confidence intervals (CI) of the CVP and BNP levels for each study.

Results: A total of 13 studies with 47 561 participants were included in our study. Our results showed that elevated CVP levels were significantly associated with the risk of failed extubation (SMD: 0.54, 95% CI: 0.07 to 1.02, $P=0.03$). This association also appeared after extubation (SMD: 1.39, 95% CI: 0.37 to 2.40, $P=0.008$), but it did not appear before extubation (SMD: 0.04, 95% CI: -0.50 to 0.59, $P=0.88$). Similarly, Our results also showed that increased BNP levels is closely related to extubation failure (SMD: 0.72, 95% CI: 0.48 to 0.96, $P < 0.00001$). This relationship also occurs before (SMD: 0.60, 95% CI: 0.29 to 0.90, $P=0.0001$) and after (SMD: 0.92, 95% CI: 0.54 to 1.30, $P < 0.00001$) extubation.

Conclusions: This study showed that elevated CVP and BNP levels are associated with risk of extubation failure in critically ill patients. Compared with CVP level, BNP level is a more sensitive and accurate predictor of extubation failure.

Key words: central venous pressure, brain natriuretic peptide, extubation failure, pooled analysis.

Introduction

Extubation from mechanical ventilation is a very challenging process for clinicians in Intensive Care Unit (ICU). Premature extubation was associated with the probability of reintubation, ICU length of stay, or patient mortality.^{1–2} Any delayed extubation may lead to ventilator-acquired pneumonia, prolonged hospital stay and high mortality.^{3–5} Therefore, it is of great significance to accurately predict the time of extubation.

Traditionally, respiratory failure is considered to be the main cause of exudation failure, so previous studies have focused on breathing-related parameters, including rapid shallow breathing index (f/V_t), respiratory rate, minute ventilation, and cough intensity.^{6–7} Unfortunately, these factors do not predict extubation so accurately.⁸ In recent years, more and more studies have proved that cardiac dysfunction plays an important role in exudation failure, and respiratory diseases have a certain impact on cardiac function.^{9–10} Thus, it is urgent to establish a simple and effective method to detect the extubation time for cardiac dysfunction.

Central venous pressure (CVP) reflects right atrial force, which is affected by cardiac function, blood volume and vascular tension. Brain natriuretic peptide (BNP) is mainly secreted by cardiomyocytes to cope with myocardial stretch and volume overload. Both are important indicators for monitoring cardiac function and volume. Previous studies have shown that the effect of BNP on extubation is controversial, and there are few studies on the effect of CVP on extubation. On basis of the current studies, we systematically reviewed the literature and conducted a pooled analysis to determine the relationship between elevated BNP and CVP and extubation failure.

Materials and methods

Search strategy

In order to identify qualified original articles, two independent researchers systematically searched three online electronic databases, such as web of science, EMBASE, and Cochrane Library, using the following keywords: “extubation,” “weaning,” “disconnect of mechanical ventilation,” “discontinuation of mechanical ventilation” AND “central venous pressure,” “CVP,” “Brain natriuretic peptide,” “BNP,” “brain natriuretic peptide”. Articles are searched up to October 2021, and are limited to published English studies. In addition, we manually searched relevant review literature and references of included studies to identify potentially relevant articles. If there is a disagreement, a third researcher will discuss the decision.

Inclusion and exclusion criteria

The inclusion criteria were as follows: The patient was hospitalized in the ICU and received no less than 24 hours of mechanical ventilation; The CVP and BNP levels were monitored before and after extubation; The patient was ready to stop mechanical ventilation and was followed up for at least 24 hours after weaning from MV. The exclusion criteria were as follows: Duplicate studies, reviews, case reports, abstracts or letters; CVP is affected by many factors such as increased intra-abdominal pressure, cough and drugs; Potential factors that interfere with BNP, such as kidney disease, sepsis, and drugs.

Data extraction and quality assessment

The two researchers independently screened the titles and abstracts in the included studies, then checked the full text according to the inclusion and exclusion criteria. Extract the following information: the first author's name, publication year, age, male (%), country, sample size, timing of BNP and CVP measurement, methods and durations of SBT and definition of extubation failure. When there are differences in data extraction, it can be discussed with the third researcher. The Newcastle-Ottawa scale was used to assess the quality of the included studies.¹¹

Statistical analysis

All data are analyzed by Review Manager 5.4. Standard mean differences (SMD) and corresponding 95% confidence intervals (CIs) of the CVP and BNP levels were collected and calculated for each study. Heterogeneity is evaluated by calculating the I^2 -squared (I^2) index. I^2 values of 75–100%, 50–75% and 25–50% were considered as high, moderate, and low heterogeneous respectively. If there was significant heterogeneity ($I^2 > 50\%$ or $P < 0.05$), a random effect model was used. Otherwise, the fixed effect model is applied.

The mean and standard deviation (SD) was estimated using Luo's approach and Wan's method respectively when the median and interquartile range (IQR) was provided.^{12–13} We performed subgroup analysis based on the levels of CVP and BNP before and after extubation to explore heterogeneity. Funnel plots were used to find potential publication bias. When the P value is less than 0.05, it is considered statistically significant.

Results

Study processing

Using our search strategy, a total of 1234 potentially original studies were identified from online database. After excluding duplications, there are still 874 studies remaining. After careful screening of titles and abstracts,

841 studies that did not meet the inclusion and exclusion criteria were excluded. After carefully reading the main body of the remaining 33 studies, 20 studies were excluded. In the end, 13 qualified studies met the inclusion and exclusion criteria. The studies screening process is shown in Figure 1. Meanwhile, Table 1 lists the basic characteristics of the included studies. Because NOS scores are at least 6, all studies are of high quality.

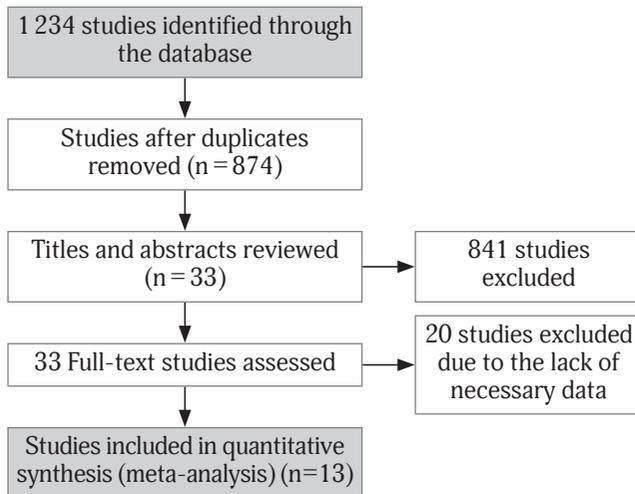


Fig. 1. Selection process for studies included in the pooled analysis

CVP and extubation

We found eight studies are about the relationship between the CVP level and extubation failure. The random effect pooled SMD was 0.54 (95% CI: 0.07 to 1.02, $P=0.03$) (Fig. 2). Subgroup analysis based on the extubation time showed that the results of pooled analysis were consistent with the connection between elevated CVP level and extubation failure after (SMD: 1.39, 95% CI: 0.37 to 2.40, $P=0.008$) extubation. However, this connection has no significant correlation before (SMD: 0.04, 95% CI: -0.50 to 0.59, $P=0.88$) extubation. No significant publication bias was found about the CVP level and extubation failure because we obtained a roughly symmetrical funnel shape (Fig. 3).

BNP and extubation

We also found seven studies are about the association between the BNP level and extubation failure. The random effect pooled SMD was 0.72 (95% CI: 0.48 to 0.96, $P < 0.00001$) (Fig. 4). Based on the subgroup analysis of extubation time, we found that the pooled results were consistent with the relationship between high BNP level and extubation failure before (SMD: 0.60, 95% CI: 0.29 to 0.90, $P = 0.0001$) and after (SMD: 0.92, 95% CI: 0.54 to 1.30, $P < 0.00001$) extubation. No publication bias was also observed about the BNP level and extubation (Fig. 5).

Table 1. Characteristics of studies

Study	Country	Age (ES/EF)	Male (%)	Setting	N (ES/EF)	Indicator	Timing of extubation	Methods and durations of SBT	Definition of EF	NOS
Dodgen 2013	USA	—	8	Cardiovascular ICU	152/12	CVP	Before and after extubation	Volume control and 30 min SBT	Reintubation within 96 h	6
Dubo 2019	Chile	54 ± 21/ 47 ± 24	81	Medical-surgical ICU	154/11	CVP	Before and after extubation	T-piece and 60–120 min SBT	Reintubation within 48 h	7
Gupta 2014	Australia	—	53	Cardiovascular ICU	40/15	CVP	Before and after extubation	Volume and 30 min SBT	Reintubation within 96 h	6
Konomi 2016	Greece	54 ± 21/ 69 ± 16	40	Multidisciplinary ICU	27/15	CVP and BNP	Before and after extubation	T-piece and 2 h SBT	SBT failure or reintubation within 48 h	6
Ma 2013	China	62.3 ± 12.0/ 59.1 ± 3.9	85.7	ICU	22/7	CVP	Before extubation	T-piece and 120 min SBT	Reintubation within 48 h	6
Saugel 2012	Germany	63.5 ± 14.5/ 64.6 ± 8.4	86	Medical ICU	54/7	CVP	Before extubation	—	Reintubation within 48 h	7
Zapata 2011	Spain	61.6 ± 14.7/ 66.7 ± 9.7	68	ICU	58/10	CVP and BNP	Before and after extubation	T-piece and 30–120 min SBT	Reintubation within 48 h	8
Zhao 2021 MIM-IC-IV	—	64 ± 16/ 68 ± 15	—	ICU	13,433/ 2,756	CVP	Before extubation	—	Reintubation	7

Study	Country	Age (ES/EF)	Male (%)	Setting	N (ES/EF)	Indicator	Timing of extubation	Methods and durations of SBT	Definition of EF	NOS
Zhao 2021 ZS	China	60 ± 13 / 63 ± 12	—	ICU	451 / 51	CVP	Before extubation	—	NIV, reintubation or death within 48 h	8
Farghaly 2015	Australia	53.81 ± 18.9 / 57.14 ± 12.9	43	Respiratory ICU	16 / 14	BNP	Before and after extubation	PSV and 2 h SBT	SBT failure or reintubation within 48 h	8
Maraghi 2014	Egypt	46 ± 10.35 / 54 ± 9.25	32	ICU	25 / 7	BNP	Before and after extubation	T-piece and 2 h SBT	SBT failure or reintubation within 48 h	6
Soumer 2012	France	59 ± 14 ± 15	59	Multidisciplinary ICU	57 / 29	BNP	Before and after extubation	T-piece and 60 min SBT	Noninvasive or invasive ventilation) within 48 h after extubation	7
Tanios 2016	United States	—	48	ICU	56 / 29	BNP	Before extubation	PSV and 2 h SBT	SBT failure	6
Haji 2018	Australia	63.5 ± 4.6 / 77 ± 2.7	64	ICU	42 / 11	BNP	After extubation	PSV and 60 min SBT	Nonscheduled NIVM, or death within 48 h	7

Abbreviations: EF — extubation failure; ES — extubation success; ICU — intensive care unit; SBT — spontaneous breathing trail; BNP — brain natriuretic peptide; CVP — central venous pressure; NIV — noninvasive ventilation; NIVM — noninvasive ventilation mask

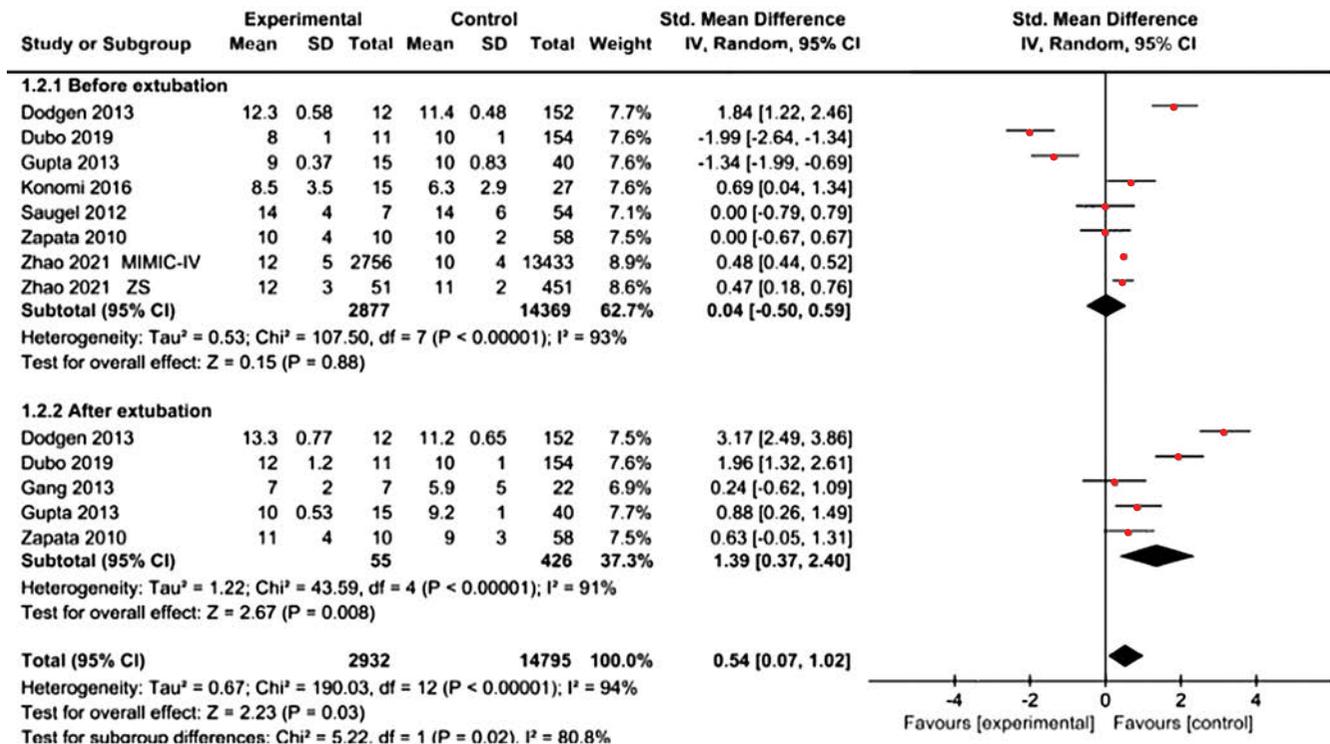


Fig. 2. The CVP levels standard mean difference between extubation failure and extubation success groups

Discussion

In our study, we revealed association of high CVP and BNP level with an increased risk of extubation failure in critically ill patients from mechanical ventilation. This

association was also found in the BNP levels before extubation, and both BNP and CVP levels after extubation. However, this association did not appear in the CVP level before extubation. Thus, these results indicate that the

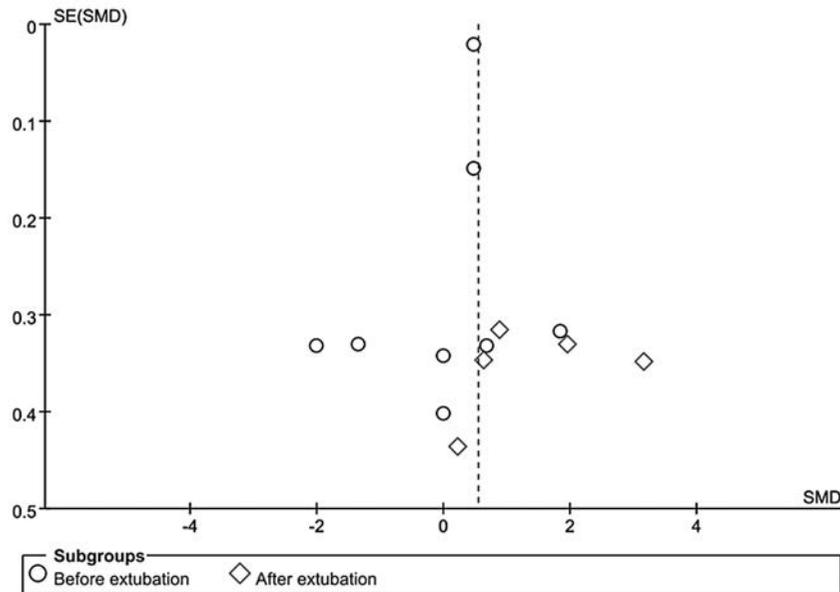


Fig. 3. Funnel plots of studies evaluating association of the CVP levels with extubation failure

Study or Subgroup	Experimental		Control		Total	Weight	Std. Mean Difference IV, Random, 95% CI	Std. Mean Difference IV, Random, 95% CI
	Mean	SD	Mean	SD				
1.1.1 Before extubation								
Farghaly 2015	152.2	55.2	146.14	31.9	16	8.4%	0.13 [-0.58, 0.85]	
Konomi 2016	643	382	361	523	27	9.8%	0.58 [-0.07, 1.22]	
Maraghi 2014	592.5	271.7	543	131.1	25	6.6%	0.29 [-0.56, 1.13]	
Soummer 2012	464.66	356.34	175.05	191.66	57	14.2%	1.11 [0.63, 1.59]	
Tanios 2016	878	784	557	768	56	15.1%	0.41 [-0.04, 0.86]	
Zapata 2011	468.04	507.4	224.53	268.36	58	9.0%	0.77 [0.09, 1.46]	
Subtotal (95% CI)			104		239	63.0%	0.60 [0.29, 0.90]	
Heterogeneity: Tau ² = 0.05; Chi ² = 7.43, df = 5 (P = 0.19); I ² = 33%								
Test for overall effect: Z = 3.86 (P = 0.0001)								
1.1.2 After extubation								
Farghaly 2015	175.7	52.6	148.71	33.18	16	8.1%	0.61 [-0.13, 1.34]	
Haji 2018	750.02	1,245.22	269.88	291.68	42	9.0%	0.78 [0.09, 1.46]	
Maraghi 2014	795.29	256.37	407.32	202.41	25	5.3%	1.76 [0.81, 2.72]	
Soummer 2012	527.49	628.47	174.46	190.14	57	14.6%	0.89 [0.42, 1.35]	
Subtotal (95% CI)			61		140	37.0%	0.92 [0.54, 1.30]	
Heterogeneity: Tau ² = 0.03; Chi ² = 3.88, df = 3 (P = 0.27); I ² = 23%								
Test for overall effect: Z = 4.75 (P < 0.00001)								
Total (95% CI)			165		379	100.0%	0.72 [0.48, 0.96]	
Heterogeneity: Tau ² = 0.05; Chi ² = 13.32, df = 9 (P = 0.15); I ² = 32%								
Test for overall effect: Z = 5.81 (P < 0.00001)								
Test for subgroup differences: Chi ² = 1.71, df = 1 (P = 0.19), I ² = 41.4%								

Fig. 4. The BNP levels standard mean difference between extubation failure and extubation success groups

measurement of CVP and BNP levels may be useful indicators for patients with extubation from mechanical ventilation. Moreover, compared with CVP level, BNP level is a more sensitive predictor of extubation failure.

In the process of extubation from mechanical ventilation, the intrathoracic pressure is formed from positive to negative, which promotes the systemic venous blood reflux increases the right ventricular preload and augmented left ventricular transmural pressure and afterload.²⁷ Moreover, emotional stress and potential hypoxia during extubation

may lead to sympathetic excitation. Many critically ill patients have undiagnosed or subclinical cardiovascular diseases and improper fluid management, and cardiovascular compensation are often hindered by potential critical illnesses. Thus, insufficient cardiac reserve may lead to subsequent respiratory insufficiency and failed extubation.²⁹

Both CVP and BNP can monitor heart function and volume. Critically ill patients in the ICU often require an indwelling central venous catheter to monitor cardiac function and fluid replacement.

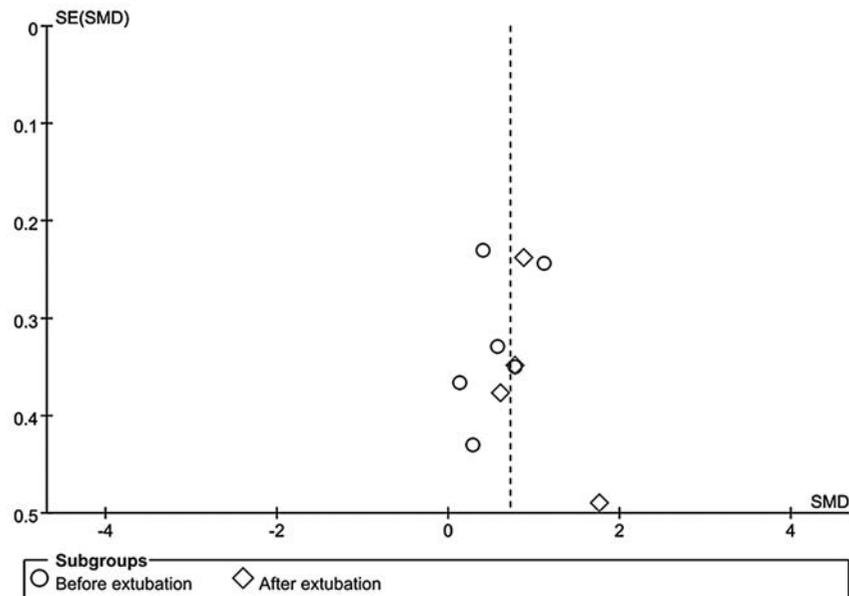


Fig. 5. Funnel plots of studies evaluating association of the BNP levels with extubation failure

There are few studies on the relationship between extubation and CVP level. Our study suggested that pooled CVP levels are associated with extubation failure, and this association is also seen after extubation. This result is consistent with Dubo's finding which an early raised CVP levels after extubation increases the risk of extubation failure.²⁰ However, this association was not observed before extubation. Since cardiovascular dysfunction may be difficult to detect in patients with positive pressure ventilation²⁹, it is difficult to detect cardiac dysfunction before extubation by CVP.

BNP has been proved to be a sensitive serum marker of cardiovascular dysfunction.³⁰ Zapata et al.¹⁵ and Lara et al.³¹ found compared with patients with successful extubation, patients with failed extubation had higher BNP before and after extubation. Our study confirmed also that the high BNP level was significantly associated with an increased risk of extubation failure. Similarly, this association appeared before and after extubation. Some studies have shown that increased BNP after extubation is a predictive factor for extubation failure.^{29,31} Our study revealed that elevated BNP levels before extubation increase the risk of extubation failure, since BNP is a sensitive indicator of cardiac insufficiency, potential cardiac insufficiency can be detected as soon as possible. In addition, the fixed model for studies on the BNP levels and extubation failure, but there is substantial heterogeneity about CVP study, which may be due to the different participants and different study designs, so the random model is used.

Our study has some limitations, which must be discussed. First, the included studies are far from enough and may affect the accuracy of the results. Second, although

CVP can reflect cardiac function more specifically, its monitoring is affected by many factors, such as the patient's position, the accuracy of the measurement method, and the patency of the pipeline, but these factors are all controllable. Third, although BNP can detect cardiac insufficiency earlier, its level may be affected by some factors such as age, obesity and renal function. Finally, since we do not have the original data for drawing the ROC curves, we cannot determine the reliable cut-off point of the CVP and BNP tests.

Conclusion

Our study showed that elevated CVP and BNP levels are related to the risk of extubation failure. More importantly, compared with CVP level, BNP level is a more sensitive and accurate predictor of extubation failure.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent to public

Not applicable.

Availability of data and materials

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Competing interests

The authors declare that they have no competing interests.

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Author Contributions Statement

C.J.H. and W.B.B. wrote the main manuscript text, and Z.L.L. prepared figures 1–5 and Table 1. All authors reviewed the manuscript.

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Об'єднаний аналіз центрального венозного тиску та рівнів натрійуретичного пептиду мозку у пацієнтів із невдачею екстубації

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Резюме. Мета: невдача екстубації пов'язана з тривалим перебуванням у стаціонарі, високою смертністю та вартістю лікування. В останні роки серцево-судинну недостатність розглядали як поширену причину невдалої екстубації, і деякі дослідження показали, що центральний венозний тиск (CVP) і мозковий натрійуретичний пептид (BNP) можуть передбачити результат екстубації. Тому ми провели об'єднаний аналіз, щоб оцінити, що рівні CVP і BNP у важкохворих пацієнтів, які піддалися штучній вентиляції легень, є предикторами невдачі екстубації.

Методи: систематичний пошук у трьох електронних базах даних, як-от Web of Science, EMBASE та Cochrane Library, здійснюється до жовтня 2021 року. Усі дані аналізуються за допомогою Review Manager 5.4. Результати сукупного аналізу були виконані залежно від стандартизованих середніх відмінностей (SMD) з 95% довірчими інтервалами (CI) рівнів CVP і BNP для кожного дослідження.

Результати: всього у наше дослідження було включено 13 досліджень із 47 561 учасником. Наші результати показали, що підвищені рівні CVP були значно пов'язані з ризиком невдалої екстубації (SMD: 0,54, 95% CI: 0,07–1,02, P = 0,03). Ця асоціація також з'явилася після екстубації (SMD: 1,39, 95% CI: 0,37–2,40, P = 0,008), але вона не з'явилася до екстубації (SMD: 0,04, 95% CI: 0,50–0,59, P = 0,88). Аналогічно, наші результати також показали, що підвищення рівня BNP тісно пов'язане з невдачею екстубації (SMD: 0,72, 95% CI: 0,48–0,96, P < 0,00001). Цей зв'язок також виникає до (SMD: 0,60, 95% CI: 0,29–0,90, P = 0,0001) і після (SMD: 0,92, 95% CI: 0,54–1,30, P < 0,00001) екстубації.

Висновки: це дослідження показало, що підвищені рівні CVP і BNP пов'язані з ризиком невдачі екстубації у пацієнтів із критичними станами. Порівняно з рівнем CVP, рівень BNP є більш чутливим і точним предиктором невдачі екстубації.

Ключові слова: центральний венозний тиск, недостатність екстубації, мозковий натрійуретичний пептид, об'єднаний аналіз.

Объединенный анализ центрального венозного давления и уровня натрийуретического пептида в головном мозге у пациентов с неудачей экстубации

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Резюме. Цель: неудача экстубации связана с длительным пребыванием в стационаре, высокой смертностью и стоимостью лечения. В последние годы сердечно-сосудистая недостаточность рассматривалась как частая причина неудачной экстубации, и некоторые исследования показали, что центральное венозное давление (CVP) и уровень натрийуретического пептида головного мозга (BNP) могут предсказывать исход экстубации. Поэтому мы провели объединенный анализ, чтобы оценить, что уровни CVP и BNP у пациентов в критическом состоянии, подвергающихся искусственной вентиляции легких, являются предикторами неудачи экстубации.

Методы: систематический поиск ведется по трем электронным онлайн-базам данных, таким как Web of Science, EMBASE и Cochrane Library, вплоть до октября 2021 года. Все данные анализируются с помощью Review Manager 5.4. Результаты объединенного анализа были выполнены в зависимости от стандартизованных средних различий (SMD) с 95% доверительными интервалами (CI) уровней CVP и BNP для каждого исследования.

Результаты: всего в наше исследование было включено 13 исследований с участием 47 561 человека. Наши результаты показали, что повышенные уровни CVP были в значительной степени связаны с риском неудачной экстубации (SMD: 0,54, 95% CI: 0,07–1,02, P = 0,03). Эта ассоциация также появлялась после экстубации (SMD: 1,39, 95% CI: 0,37–2,40, P = 0,008), но не появлялась до экстубации (SMD: 0,04, 95% CI: 0,50–0,59, P = 0,88). Точно так же наши результаты показали, что повышенные уровни BNP тесно связаны с неудачей экстубации (SMD: 0,72, 95% CI: 0,48–0,96, P < 0,00001). Эта взаимосвязь также наблюдается до (SMD: 0,60, 95% CI: 0,29–0,90, P = 0,0001) и после (SMD: 0,92, 95% CI: 0,54–1,30, P < 0,00001) экстубации.

Выводы: это исследование показало, что повышенные уровни CVP и BNP связаны с риском неудачной экстубации у пациентов в критическом состоянии. По сравнению с уровнем CVP уровень BNP является более чувствительным и точным предиктором неудачи экстубации.

Ключевые слова: центральное венозное давление, недостаточность экстубации, мозговой натрийуретический пептид, объединенный анализ.