Neurally adjusted ventilatory assist versus pressure support ventilation in patient-ventilator interaction and clinical outcomes: a meta-analysis of clinical trials

Chongxiang Chen[1,2#], Tianmeng Wen[3#], Wei Liao[1]

[1]Department of Intensive Care Unit, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Guangzhou 510060, China; [2]Guangzhou Institute of Respiratory Diseases, the First Affiliated Hospital of Guangzhou Medical University, State Key Laboratory of Respiratory Disease, Guangzhou, 510120 China; [3]School of Public Health, Sun Yat-sen University, Guangzhou 510000, China

Contributions: (I) Conception and design: C Chen; (II) Administrative support: W Liao; (III) Provision of study materials or patients: C Chen; (IV) Collection and assembly of data: T Wen; (V) Data analysis and interpretation: C Chen; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Wei Liao. Department of Intensive Care Unit, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Guangzhou 510060, China. Email: liaowei1631@163.com.

Background: The objective of this study was to conduct a meta-analysis comparing neurally adjusted ventilatory assist (NAVA) with pressure support ventilation (PSV) in adult ventilated patients with patient-ventilator interaction and clinical outcomes.

Methods: The PubMed, the Web of Science, Scopus, and Medline were searched for appropriate clinical trials (CTs) comparing NAVA with PSV for the adult ventilated patients. RevMan 5.3 was performed for comparing NAVA with PSV in asynchrony index (AI), ineffective efforts, auto-triggering, double asynchrony, premature asynchrony, breathing pattern (Peak airway pressure (Paw_{peek}), mean airway pressure (Paw_{mean}), tidal volume (V_T, mL/kg), minute volume (MV), respiratory muscle unloading (peak electricity of diaphragm ($EAdi_{peak}$), P 0.1, V_T/EAdi), clinical outcomes (ICU mortality, duration of ventilation days, ICU stay time, hospital stay time).

Results: Our meta-analysis included 12 studies involving a total of 331 adult ventilated patients, AI was significantly lower in NAVA group [mean difference (MD) −12.82, 95% confidence interval (CI): −21.20 to −4.44, I^2=88%], and using subgroup analysis, grouped by mechanical ventilation, the results showed that NAVA also had lower AI than PSV (Mechanical ventilation, MD −9.52, 95% CI: −17.85 to −1.20, I^2=87%), (Non-invasive ventilation (NIV), MD −24.55, 95% CI: −35.40 to −13.70, I^2=0%). NAVA was significantly lower than the PSV in auto-triggering (MD −0.28, 95% CI: −0.51 to −0.05, I^2=10%), and premature triggering (MD −2.49, 95% CI: −3.77 to −1.21, I^2=29%). There were no significant differences in double triggering, ineffective efforts, breathing pattern (Paw_{mean}, Paw_{peak}, V_T, MV), and respiratory muscle unloading ($EAdi_{peak}$, P 0.1, V_T/EAdi). For clinical outcomes, NAVA was significantly lower than the PSV (MD −2.82, 95% CI: −5.55 to −0.08, I^2=0%) in the duration of ventilation, but two groups did not show significant differences in ICU mortality, ICU stay time, and hospital stay time.

Conclusions: NAVA is more beneficial in patient-ventilator interaction than PSV, and could decrease the duration of ventilation.

Keywords: Neurally adjusted ventilatory assist (NAVA); pressure support ventilation (PSV); patient-ventilator interaction

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Introduction

Assisted ventilatory modes target at satisfying the ventilator insufflation to the patient's effort. However, they always do not match patients' effort. Mismatching between patient demand and level of assistance is potentially harmful; under assistance and over assistance may both produce patient-ventilator asynchrony and lead to poor clinical outcomes (1,2). Asynchrony can be improved by optimum adjustment of ventilator settings [e.g., a lower level of support, inspiratory trigger, setting up external positive end expiratory pressure (PEEP)], although asynchronies still exert and influence ventilated patients after optimal adjustments.

Pressure support ventilation (PSV) is one of the main assisted ventilatory modes. The problem of this kind of technology is ventilator asynchrony, a mismatch between the patient's neural output and the ventilator's inspiratory and expiratory times (2). NAVA, a new mode of ventilator, uses the electrical activity of the diaphragm to drive the ventilator deliver positive pressure to trigger and cycle inspiration in proportion to the patients' effort (3). The NAVA can adapt each change in the patient's ventilatory demand, and better keep a harmonious relationship between the ventilator assistance and the patient's effort. The advantage of NAVA is to identify the start of neural exhalation, which cannot be recognized by PSV. Nowadays, a new setting of NAVA occurs, which is named neurally controlled pressure support ventilation, it sets the NAVA level at 15 cmH_2O/uv with an upper airway pressure (Paw) limit to obtain the same overall Paw applied during pneumatically triggered and cycled-off pressure support (4-7).

Furthermore, some studies showed that the NAVA could improve patient-ventilator synchrony and create a more natural breathing pattern, which leaded to better comfort and oxygenation (8,9). All the advantages above make NAVA an attractive alternative for patients experiencing clinically significant asynchrony. Before 2019, only one letter published for this theory (10), which merely talking about asynchrony index (AI). In 2019, two recent meta-analysis studies about NAVA have been published (11,12). In the meta-analysis conducted by Pettenuzzo *et al.* (12), they included the studies contained exact AI value or severe level of AI (AI >10%), but our study only contained the articles talking about exact AI value. The number of studies containing exact AI value in their article is 14, however, we found 5 articles cannot include in our studies, one of them was not published in English (13), 3 of them exactly did not contain AI value in their studies through reading the whole articles (7,14,15), the last one contained many AI value in different levels of support (16), so we cannot choose the best one to include in our meta-analysis. In the end, we try to collect and take the published studies to make another meta-analysis for confirmation.

Methods

Search strategy

Two investigators independently searched the articles in the databases (PubMed, the Web of Science, Scope, Medline). The reference lists of eligible studies and relevant papers were also manually searched and reviewed. Searching terms included "NAVA", "neurally adjusted ventilatory assist" and "asynchrony". In PubMed, we used ("Neurally adjusted ventilated assist" or "NAVA") and ("asynchrony" or "synchrony") for search strategy. Searching terminal date was 2019/6/13. Firstly, we found 406 articles after duplications excluded by reading the title and abstract, and then excluded 101 articles by reading the title and abstract. Finally, 12 articles were left after reading the whole articles (4,5,9,17-25) (*Figure 1*).

Inclusion and exclusion

Inclusions contain: (I) researched study comparing NAVA with PSV in adult patients, (II) primary outcome: asynchrony index, (III) only be published in English.

Exclusions contain: (I) review, retrospective research, case report, (II) insufficient data in the articles (insufficiency of data mainly indicated that the study did not contain the exact asynchrony index value (e.g., Asynchrony index >10% is not the same as the exact asynchrony index value (continuous variable).

Definition

Ventilator asynchrony can be classified as ineffective efforts, double-triggering, auto-triggering, and premature triggering (26,27). AI, one of the important indicators, is defined as the number of asynchrony events divided by the total respiratory cycles computed as the sum of the number of ventilator cycles (triggered or not) and of wasted efforts (12). Ineffective efforts occur when the patient's inspiratory effort fails to trigger a ventilator breath (28,29).

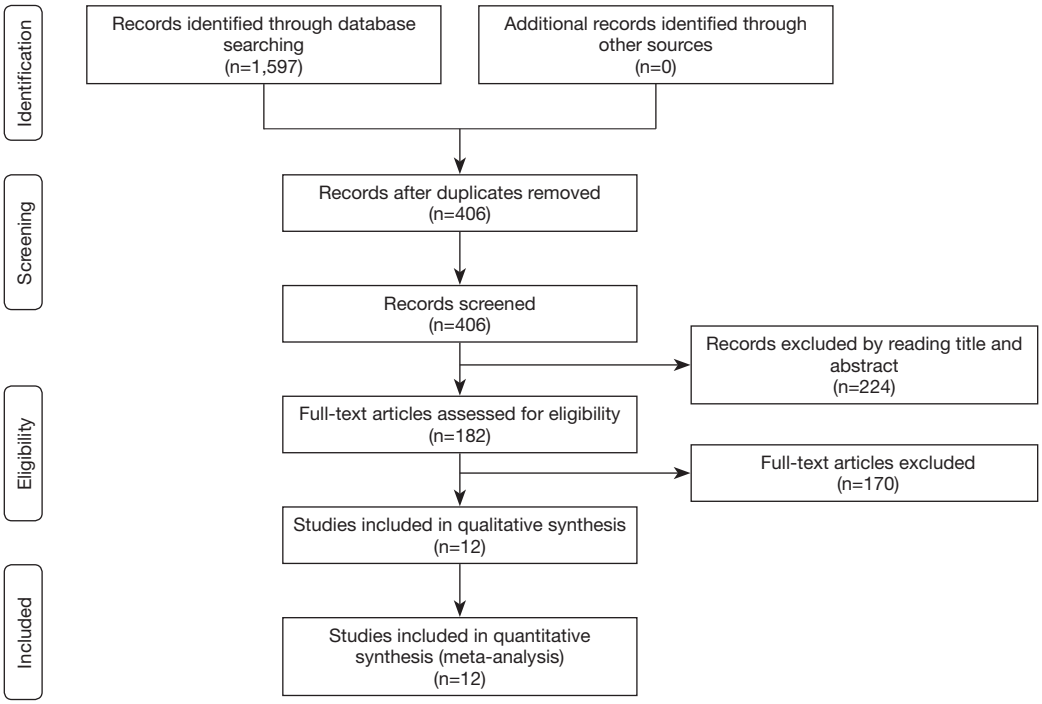

Figure 1 Flow diagram of choosing the appropriated articles.

Double triggering occurs when the patient's ventilatory demand is high and the ventilator inspiratory time is short (30). Auto triggering is a cycle transmitted by the ventilator in the absence of patient effort and can be generated by cardiogenic oscillations or leaks in the ventilator circuit (31).

Data elected

Two authors independently reviewed the identified abstracts and selected articles to full review. The third reviewer addressed the discrepancies. For each selected publication, the following baseline and study characteristics were extracted: first author, publication year, country, participant characteristics, predications for enrolling in the study, and the baseline characteristics of these studies were concluded (*Table 1*). The risk of bias of the included studies was shown in *Figure 2* and *Figure 3*. The results showed that all the studies were comparable and could be integrated (all were prospective studies). Efficacy outcome measures were AI, ineffective efforts, auto-triggering, double triggering, premature triggering, V_T, MV, Paw_{peak}, Paw_{mean}, $EAdi_{peak}$, P0.1, V_T/EAdi, ICU mortality, duration of ventilation, ICU stay time, and hospital stay time.

Risk of bias assessment

Risk of bias of trials included in this meta-analysis was assessed according to the recommendations of the Cochrane Handbook of Systematic Reviews of Interventions, in the following domains: selection bias (random sequence generation and allocation concealment), performance bias (blinding of participants and personnel), detection bias (blinding of outcome assessment), attrition bias (incomplete outcome data), and reporting bias (selective outcome reporting) (http://handbook.cochrane.org). Jadad scale used to calculate the quality of every enrolled study. The quality appraisal mostly based on whether the authors added quality appraisal indicators (e.g., whether said in the article about the concealment of randomization, whether said about the randomization number occurring) in their articles.

Statistic analysis

We pooled data and used mean difference [MD, with 95% confidence interval (CI)] for continuous outcomes: AI, ineffective efforts, auto-triggering, double triggering, premature triggering, Paw_{peak}, Paw_{mean}, V_T, MV, EAdi, P 0.1, EAdi/V_T, , duration of ventilation, hospital stay time, and ICU stay time. Odds ratio (OR) was used for dichotomy

Table 1 Baseline characteristics of these studies

Study	Type	Time (Published)	Country	Jadad scale	Participant	Age (NAVA *vs.* PSV)	Male/total (NAVA *vs.* PSV)	Invasive/non-invasive	Precondition
Kuo *et al.*	RCT	2016	China (Taiwan)	1+1+0+1=3	One RCC	79.3±6.2 *vs.* 76.9±9.3	11/14 *vs.* 13/19	Invasive	SBT was applied with a PEEP =5 cmH_2O; PSV =8 cmH_2O
Schmidt *et al.*	Randomized, cross-over	2012	France	1+1+0+0=2	One ICU	64 [58–77] (cross-over)	7/17 (cross-over) event 17:17	Non-invasive	PEEP =4 cmH_2O; V_T =6–8 mL/kg; SPO_2 =92–96%
Piquilloud *et al.*	Randomized, cross-over	2012	Switzerland	1+1+0+0=2	2 centers	70 [64–78] (cross-over)	6/3 (cross-over)	Non-invasive	NAVA level 0.5 uV; 30 min for placement of nasogastric tube, 20 min for NIV
Ferreira *et al.*	Randomized, cross-over	2017	Brazil	2+2+1+0=5	One ICU	60 [19–82] (cross-over)	13/20 (cross-over)	Invasive	PEEP =5 cmH_2O; PSV =5 cmH_2O
Demoule *et al.*	RCT	2016	France	1+2+0+1=4	11 centers	66 [61–77] *vs.* 64 [53–77] (baseline)	47/62 *vs.* 39/66 (baseline); event 53:50	Invasive	FiO_2, and PEEP according to guidelines; V_T =6–8 mL/kg (ideal body weight)
Schmidt *et al.*	Non-randomized cross-over	2015	France	0+0+0+1=1	One ICU	67 [63–75] (cross-over)	10/16 (cross-over) event 16:16	Invasive	V_T =6–8 mL/kg; FiO_2, and PEEP were maintained throughout the study (FiO_2 ≤50%, PEEP ≤5 cmH_2O); 20 min stabilization followed by 10 min recording
Mussi *et al.*	RCT	2016	Italy	1+1+0+1=3	One ICU	66.8±17.3 *vs.* 69.8±15	5/13 *vs.* 9/12	Invasive	V_T =5–8 mL/Kg (PBW); unsedated or moderate sedation
Patroniti *et al.*	Randomized, cross-over	2011	Italy	1+1+0+0=2	One ICU	38–80 (cross-over)	9/15 (cross-over)	Invasive	Limit peak airway pressure at 35 cmH_2O
Longhini *et al.*	Randomized, cross-over	2019	Italy	2+2+0+0=4	One ICU (China)	68–86 (cross-over)	9/10 (cross-over)	Non-invasive	V_T =6–8 mL/Kg (ideal body weight)
Longhini *et al.*	Randomized, cross-over	2017	Italy	2+2+0+0=4	One ICU (China)	None (adult)	None	Non-invasive	V_T =6–8 mL/Kg (ideal body weight);
Mauri *et al.*	Randomized, cross-over	2012	Italy	1+1+0+0=2	One ICU	46±13 (cross-over)	7/10 (cross-over)	Invasive	V_T =3–5 mL/kg, peak inspiratory pressure below 30 cmH_2O, respiratory rate ≤35/min
Yonis *et al.*	non-randomized cross-over	2015	France	0+0+0+1=1	One ICU	66.3±11 (cross-over)	19/30 (cross-over)	Invasive	V_T =6–8 mL/kg (PBW); sedation was stopped; patents met the general and respiratory criteria for PSV

AI, asynchrony index; NAVA: neurally adjusted ventilatory assist; PSV, pressure support ventilation; RCT, randomized controlled trial; ICU, intensive care unit; RCC, respiratory care center; COPD, chronic obstructive pneumonia dysfunction; PEEP, positive end expiratory pressure; SBT, spontaneous breathing trail; PBW, predicted body weight.

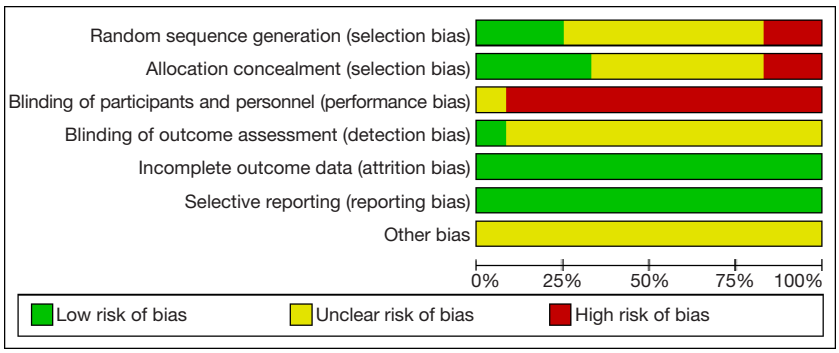

Figure 2 Risk of bias graph.

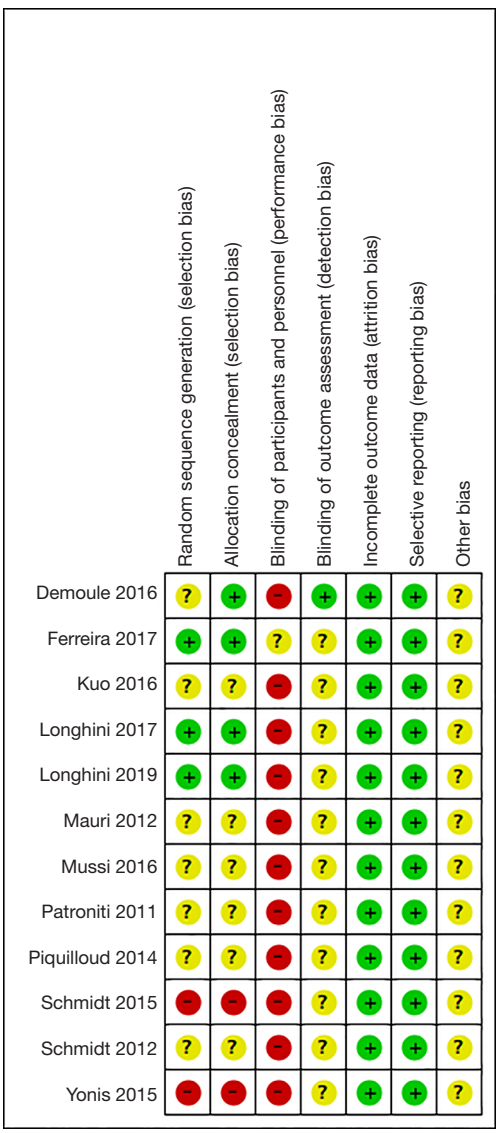

Figure 3 Risk of bias summary.

variable: ICU mortality. We would use a fixed-effect model if there was no considerable heterogeneity among studies. We would use a random-effects model if the I^2 statistic was above 50% and Cochran's Q statistic had a P value ≤0.1. Subgroup analyses were performed to compare AI grouped by mechanical ventilation, and by adult because of the high heterogeneity. Funnel plots were used to screen for potential publication bias. All statistical analyses were carried out with Review Manager 5.3 (The Cochrane Collaboration).

Results

We found 406 articles after duplications excluded, and then excluded 224 articles by reading the title and abstract. Finally, 12 articles were left after reading the whole articles (4,5,9,17-25) (*Figure 1*). The studies included in our meta-analysis were all prospective clinical trials, published from 2012 to 2019. The studies were conducted in China (19), France (17,21,22,25,32), Switzerland (20), Brazil (18), and Italy (4,5,9,23,24). *Table 1* presents the basic characteristics of included trials and demographic data of participants. Two trials were multicenter studies and the Jadad Scales of all included studies ranged from 1 to 5, the relatively low scores of the included studies must result from the particularity of these studies that investigated the kinds of ventilation modes. In these studies, the blind methods cannot be implemented. However, all the studies included in our meta-analysis were prospective studies, so it is higher quality than common retrospective studies. The risk of bias and Jadad score showed that the most the studies contained were randomized studies (only two of them were non-randomized studies), although only four of them the randomized allocation methods. The blindness cannot be

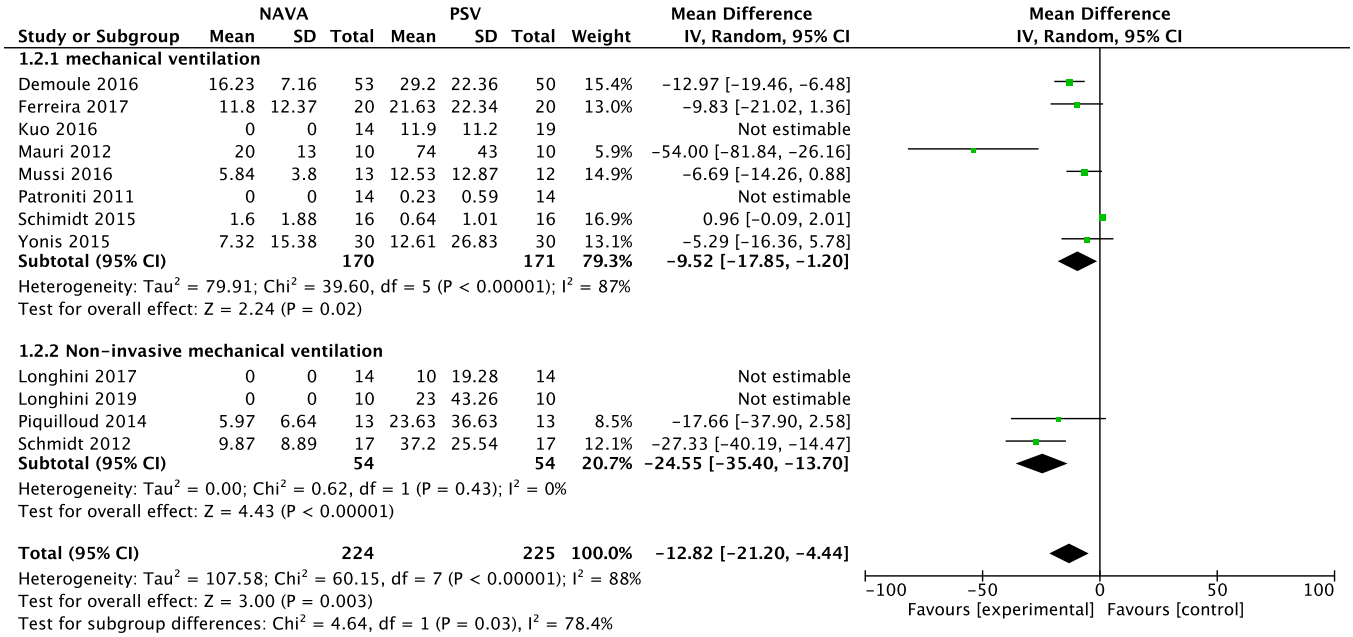

Figure 4 Subgroup analysis of divided by whether mechanical ventilation of asynchrony index.

applied in all the studies. Other bias in *Figure 2* and *Figure 3* mainly talked about publish bias and so on (*Figure 2*, *Figure 3* and *Table 1*).

Patient-ventilator asynchrony

AI

For the AI, our study included 12 studies with a total of 331 adult patients; the results comparing groups were significantly lower in NAVA group (224 patients) than PSV group (225 patients) [mean difference (MD) −12.82, 95% confidence interval (CI): −21.20 to −4.44]. Heterogeneity testing showed that I^2=88%, indicating high heterogeneity. Because of the high heterogeneity, we used the subgroup analysis to solve it. Subgroup analysis grouped by mechanical ventilation showed that the AI of NAVA was lower than PSV in invasive mechanical ventilation (MD −9.52, 95% CI: −17.85 to −1.20, I^2=87%), and non-invasive ventilation (NIV) (MD −24.55, 95% CI: −35.40 to −13.70, I^2=0%). Subgroup analysis grouped by randomized research design (randomized design or non-randomized design) demonstrated that NAVA had lower AI in randomized design (MD −16.79, 95% CI: −25.35 to −8.24, I^2=69%), and did not show benefit in non-randomized design (MD 0.36, 95% CI: −3.24 to 3.96, I^2=18%). Subgroup analysis grouped by Jadad score ≥4 or <4 showed that the AI of NAVA was lower than PSV in Jadad score ≥4 (MD −12.18, 95% CI: −17.79 to −6.57, I^2=0%), and <4 (MD −13.93, 95% CI: −24.79 to −3.08, I^2=88%) (*Figures 4-6*).

Ineffective efforts

For presenting the result of ineffective efforts, our study included 6 studies (9,20-22,24,25) involving a total of 197 events, and showed that NAVA (99 patients) was not significantly different from PSV (98 patients) (MD 0.05, 95% CI: −0.19 to 0.28, I^2=0%), although lacking significantly different evidence. Heterogeneity testing showed that I^2=0%, indicating high heterogeneity (*Figure 7*).

Auto-triggering

For the result of Auto-triggering, our study enrolled 6 studies (9,20-22,24,25), including a total of 197 events, and the result demonstrated that NAVA (99 patients) was significantly lower than the PSV (98 patients) (MD −0.28, 95% CI: −0.51 to −0.05, I^2=10%). Heterogeneity testing showed that I^2=10%, indicating low heterogeneity (*Figure 8*).

Double triggering

For presenting the result of Double triggering, our study enrolled 6 studies (9,20-22,24,25), including a total of 197 events, and demonstrated that NAVA (99 patients) was not significantly higher than PSV (98 patients) (MD

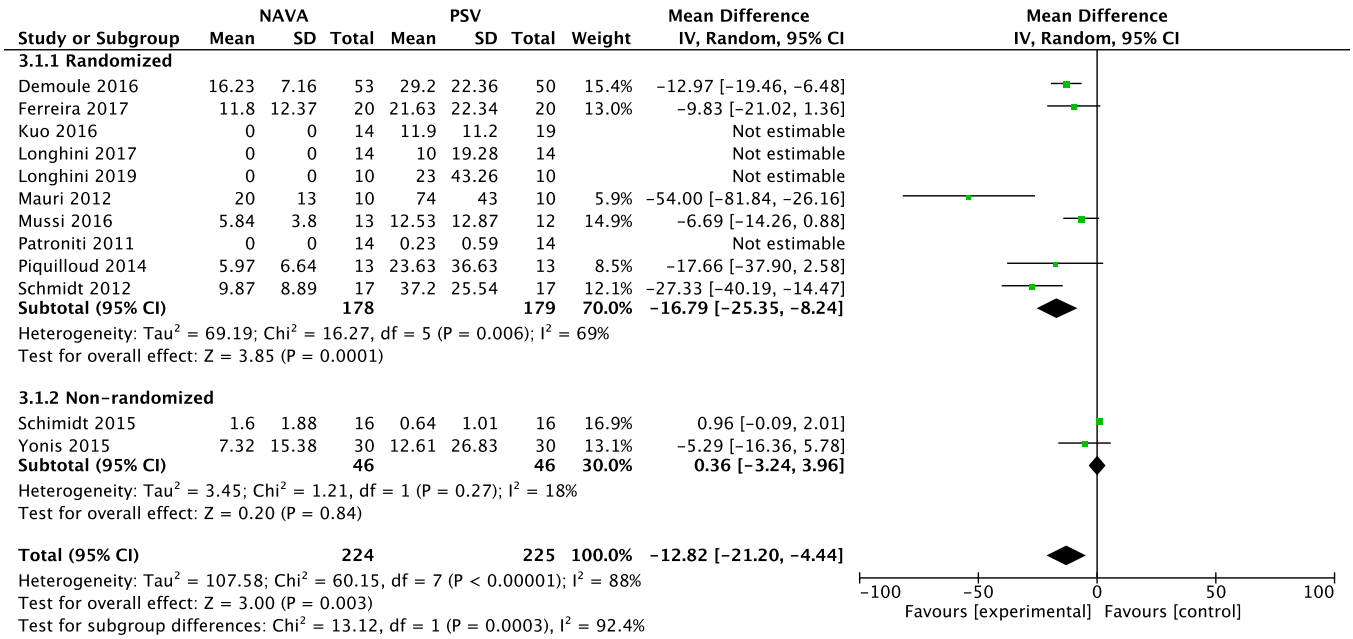

Figure 5 Subgroup analysis of divided by randomization of asynchrony index.

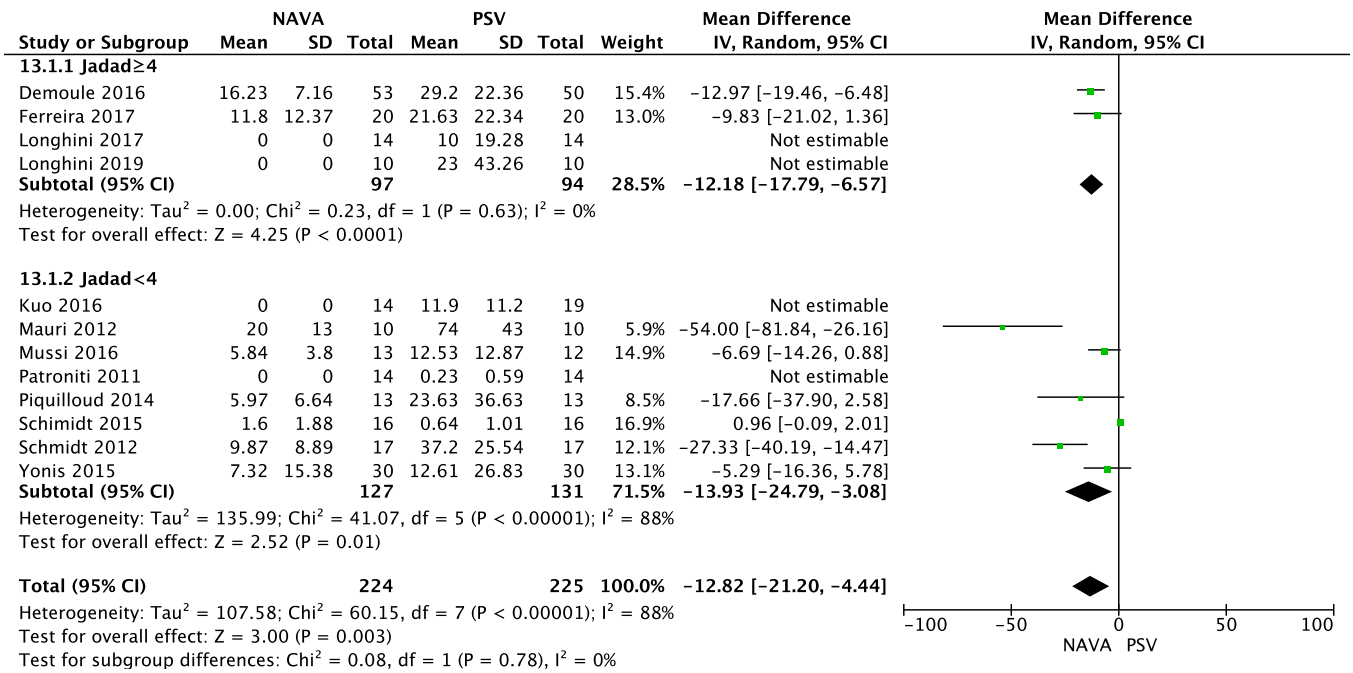

Figure 6 Subgroup analysis of divided by Jadad scores of studies.

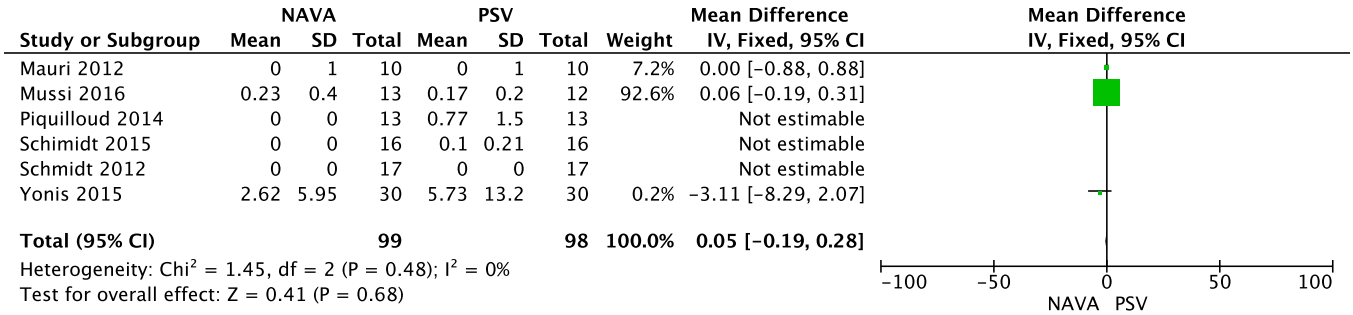

Figure 7 Ineffective efforts of patients.

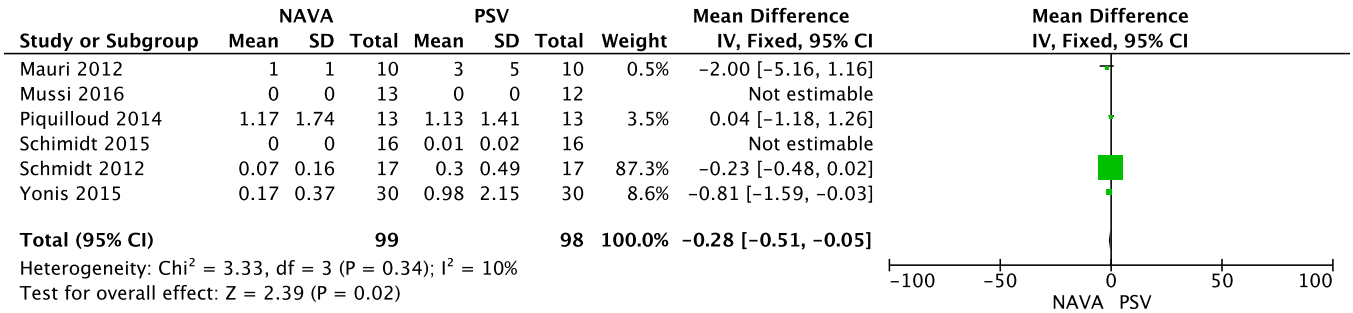

Figure 8 Auto triggering of patients.

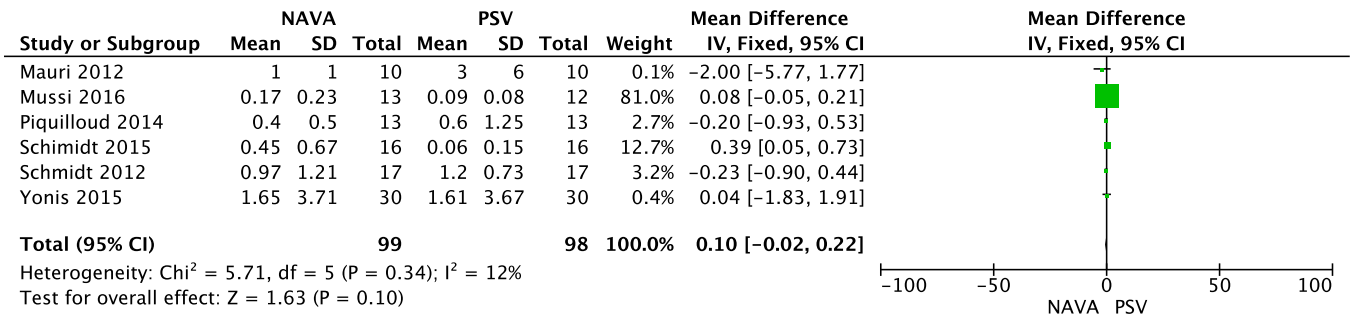

Figure 9 Double triggering of patients.

0.10, 95% CI: -0.02 to 0.22, I^2=12%). Heterogeneity testing showed that I^2=12%, indicating low heterogeneity (*Figure 9*).

Premature triggering

For presenting the result of premature triggering, our study included 3 studies (20,21,24) and a total of 80 events, and showed that NAVA group (40 patients) was significantly lower than PSV group (40 patients) in premature triggering (MD -2.49, 95% CI: -3.77 to -1.21, I^2=29%). Heterogeneity testing showed that I^2=29%, indicating low heterogeneity (*Figure 10*).

Clinical outcomes

ICU mortality

For the result of ICU mortality, our study included 3 studies (9,17,19) and a total of 186 patients, ICU mortality (OR 0.50, 95% CI: 0.23 to 1.08, I^2=0%) did not reflect significant difference in groups. Heterogeneity testing showed that I^2=0%, indicating low heterogeneity (*Figure 11*).

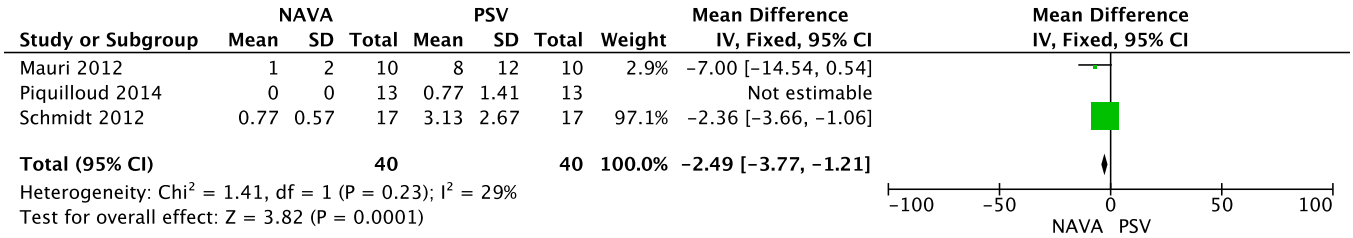

Figure 10 Premature triggering of patients.

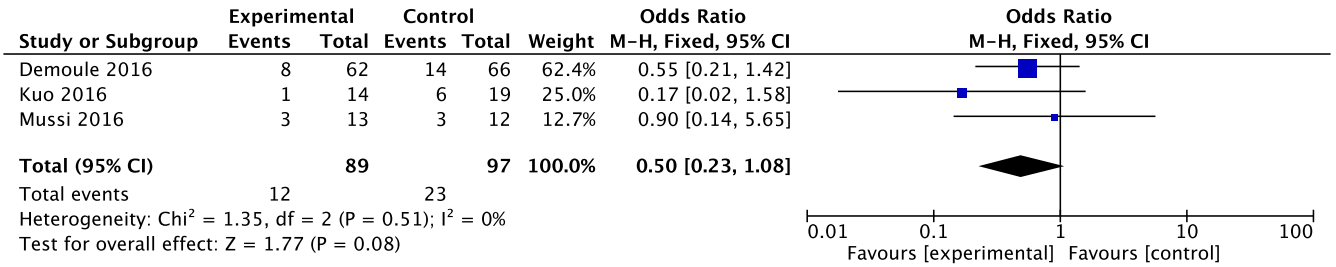

Figure 11 ICU mortality of patients.

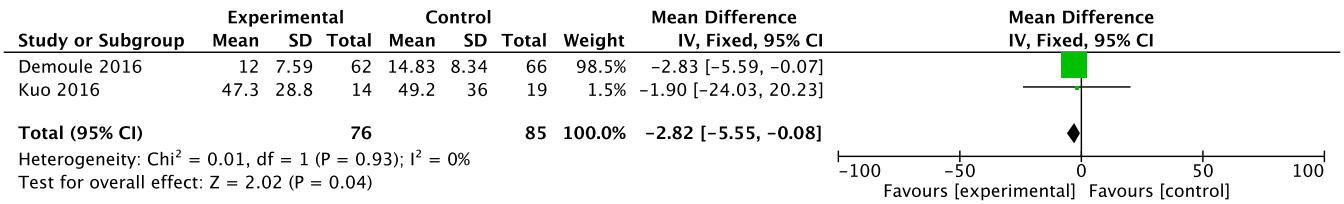

Figure 12 Duration of ventilation of patients.

Duration of ventilation

For the result of ventilation days, our study included 2 studies (17,19) and a total of 161 patients, and showed that NAVA was significantly lower than PSV in ventilation days (MD −2.82, 95% CI: −5.55 to −0.08, I^2=0%). Heterogeneity testing showed that I^2=0%, indicating low heterogeneity (*Figure 12*).

ICU stay time

For the result of ICU days, our study included 2 studies (17,19)and a total of 161 patients, ICU days (MD 1.96, 95% CI: −2.09 to 6.01, I^2=0%) did not reflect significant difference in groups. Heterogeneity testing showed that I^2=0%, indicating low heterogeneity (*Figure 13*).

Hospital stay time

For the result of hospital days, our study included 2 studies (17,19) and a total of 161 patients, hospital days (MD 2.07, 95% CI: −1.99 to 6.13, I^2=0%) did not reflect significant difference in groups. Heterogeneity testing showed that I^2=0%, indicating low heterogeneity (*Figure 14*).

Breathing pattern respiratory muscle unloading

For the Breathing pattern (Paw_{peak}, Paw_{mean}, V_T, MV) and respiratory muscle unloading ($EAdi_{peak}$, P 0.1, VT/EAdi), NAVA and PSV did not show significant differences (*Figures S1-S7*).

Potential publication bias of AI was performed and shown as funnel plot. The result of funnel plot showed that it might exist publication bias for the AI outcome (*Figure 15*).

Discussion

Comparing NAVA with PSV, our study showed that NAVA

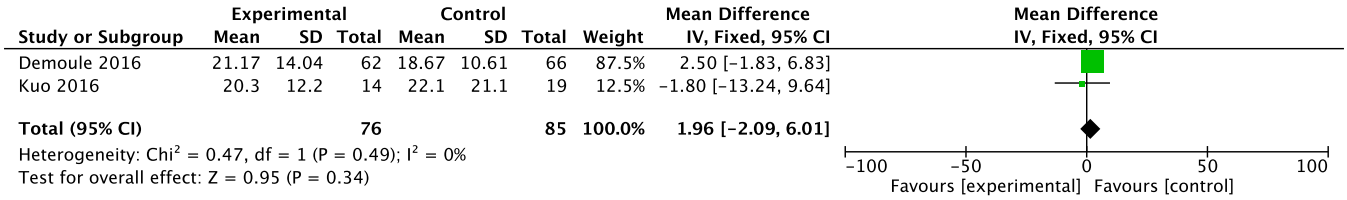

Figure 13 ICU stay time of patients.

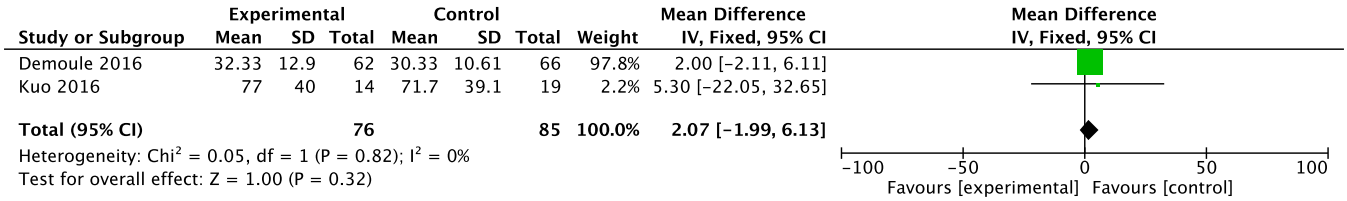

Figure 14 Hospital stay time of patients.

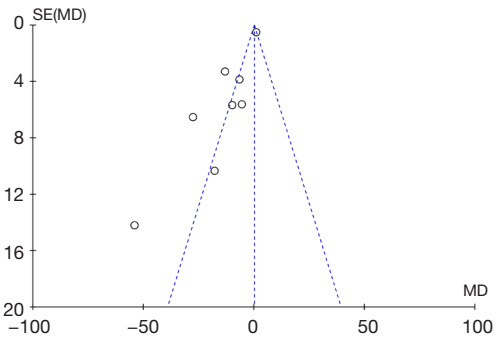

Figure 15 Funnel plot of AI comparing NAVA with PSV. AI, asynchrony index; NAVA, neurally adjusted ventilatory assist; PSA, pressure support ventilation.

could significantly help for patient-ventilation interaction (AI, auto triggering, premature triggering) in adult ventilated patients. The results were similar to the meta-analysis conducted by Pettenuzzo *et al.* (12). However, their studies did not contain the subgroup analysis between invasive and non-invasive mechanical ventilation, the comparisons of respiratory muscle unloading, and clinical outcomes.

As the primary outcome in our study, AI is defined as the number of asynchrony events divided by the total respiratory cycles computed as the sum of the number of ventilator cycles (triggered or not) and of wasted efforts (12). The computation of AI as the percentage of patents with AI greater than 10% (i.e., severe asynchrony) was also considered in clinical practice, as this threshold of asynchrony was found to be associated with worse clinical outcome (12).

Subgroup analyses grouped by mechanical ventilation, randomized design, and Jadad scores all showed NAVA had lower AI than PSV. During NIV, the occurrence of leaks may greatly affect patient-ventilator interactions, thereby be difficult to determine the optimal settings of ventilator (33). In NAVA, assistance is delivered based on neural triggering, which is not affected by leak, and can improve the tolerance.

In theory, according to the mechanism of NAVA, the EAdi triggers the assist when the patient initiates an inspiratory effort, and a decrease in EAdi terminates the assist. NAVA does not depend on measurements of airway pressure or flow and keeps the assist synchronous with the inspiratory efforts (14,34-37). Thus, NAVA has two important features: the transmitted pressure is simultaneous with the diaphragmatic activity, and the V_T is controlled by the output of the patient's respiratory center (3).

In our study, the duration of ventilation significantly decreased in NAVA group than the control group. Ventilator asynchrony is associated with prolonged mechanical ventilation, prolonged ICU and hospital stays, and increased mortality (26). Although in our study, two groups were not significantly different in the ICU mortality, ICU stay time and hospital stay time.

In our study, the ventilator-related complications (e.g., barotrauma, VAP) were lack in the comparisons. Under assistance and over assistance may both produce patient-

ventilator asynchrony that is associated with poorer clinical outcomes. In our study, the duration of ventilation is longer in NAVA than PSV. The longer duration of mechanical ventilation is associated with increased incidence of ventilator-associated pneumonia.

In clinical practice, when patient-ventilator asynchrony cannot be reversed by sedation or up-regulate PEEP, NAVA could be the good choice. In these 12 enrolled articles, only 8 studies showed underlying disease [chronic obstructive pneumonia disease (19), acute respiratory distress syndrome, (24), and acute respiratory failure (4,9,17,20,22,23)] that led to mechanical ventilation. In theory, NAVA application in patients at risk of patient-ventilator asynchrony, ventilator-induced lung injury, and respiratory muscle atrophy should be recommended. Nowadays, some studies using EAdi signal in mechanically ventilated adults for detecting asynchrony, and titrating neural drive and sedation. Furthermore, NAVA could reduce the economic burden of ICU patients. NAVA has its limitations, such as contraindications to EAdi catheter placement (e.g., recent gastric or esophageal surgery and the presence of esophageal varicose veins), presence of a tracheotomy, a progressive infectious process (e.g., nosocomial pneumonia, nosocomial bacteremia, and hemodynamic failure) (25).

In addition, NAVA also has some problems. In the one hand, the accurate positioning of the NAVA catheter is necessary (38). In the other hand, the body position, PEEP and intra-abdominal pressure can all affect the position of the diaphragm (39).

Conclusions

NAVA is more beneficial in ventilator-people interaction and clinical outcomes than PSV.

Acknowledgments

None.

Footnote

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

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Supplementary

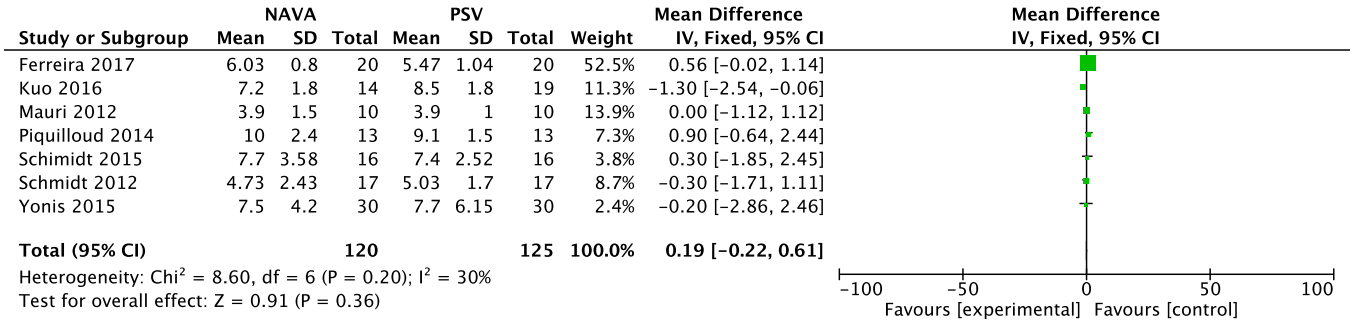

Figure S1 Ventilation volume/kg.

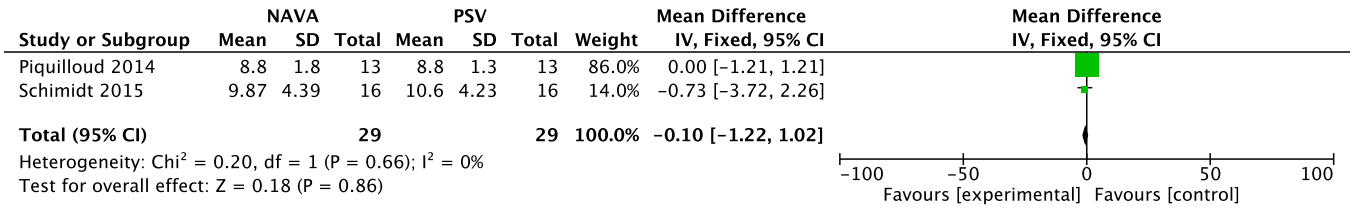

Figure S2 Mean paw.

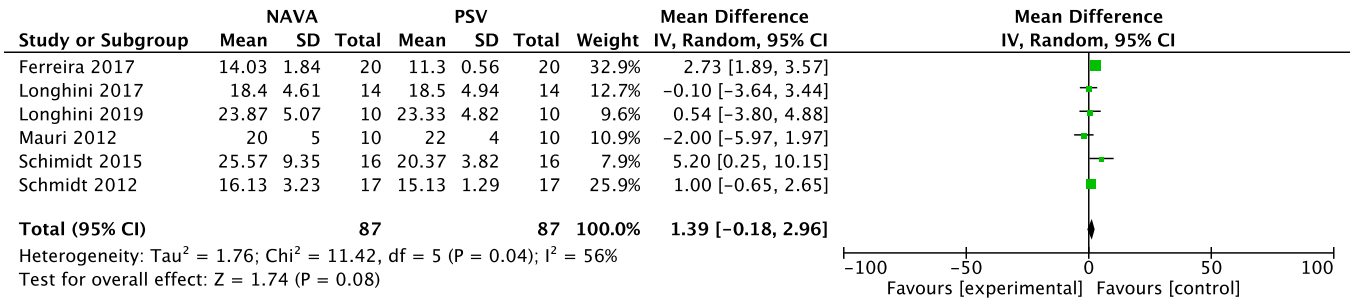

Figure S3 Peak paw.

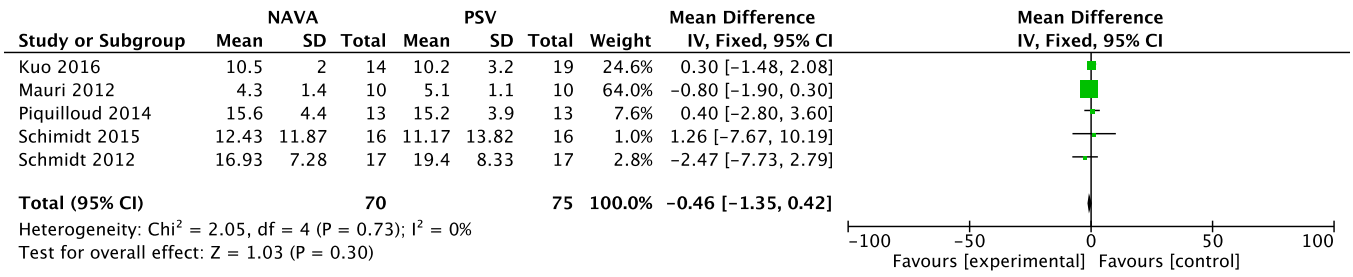

Figure S4 Minute ventilation volume.

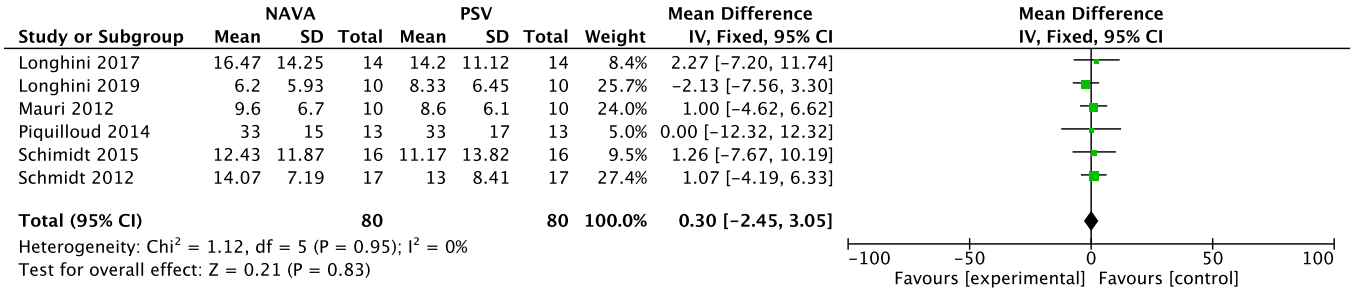

Figure S5 Peak Edi.

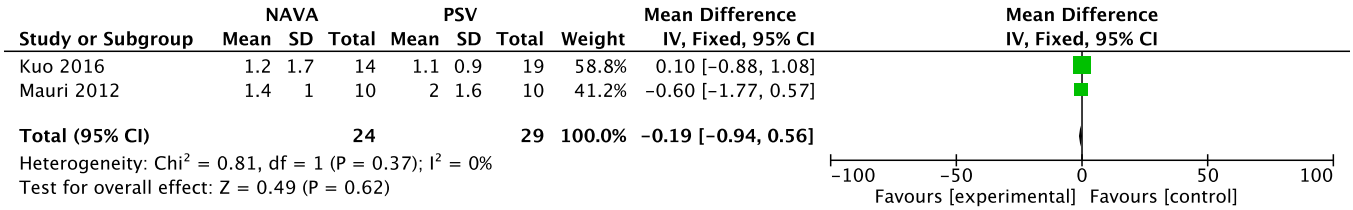

Figure S6 P 0.1.

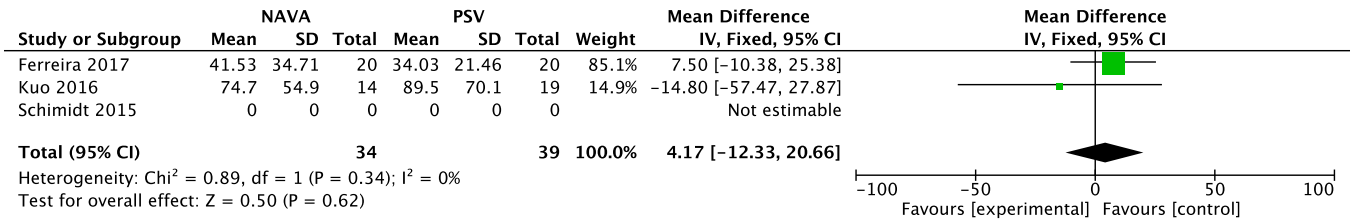

Figure S7 VT/Edi.