The influence of drugs used for sedation during mechanical ventilation on respiratory pattern during unassisted breathing and assisted mechanical ventilation: a physiological systematic review and meta-analysis

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Summary

Background Sedation management has a major impact on outcomes in mechanically ventilated patients, but sedation strategies do not generally consider the differential effects of different sedatives on respiration and respiratory pattern. A systematic review was undertaken to quantitatively summarize the known effects of different classes of drugs used for sedation on respiratory pattern during both spontaneous breathing and assisted mechanical ventilation.

Methods This was a systematic review and meta-analysis conducted using Ovid MEDLINE, Embase, Cochrane Database of Systematic Reviews, and Cochrane Central Register of Controlled Trials up to June 2020 to retrieve studies that measured respiratory parameters before and after the administration of opioids, benzodiazepines, intravenous and inhaled anaesthetic agents, and other hypnotic agents (PROSPERO #CRD42020190017). A random-effects meta-analytic model was employed to estimate the mean percentage change in each of the respiratory indices according to medication exposure with and without mechanical ventilation. Risk of bias was assessed using the Cochrane risk of bias assessment tools.

Findings Fifty-one studies were included in the analysis. Risk of bias was generally deemed to be low for most studies. Respiratory rate decreased with the administration of opioids in both non-ventilated patients (18% decrease, 95% CI 12–24%) and ventilated patients (26% decrease, 95% CI 15–37%) and increased with inhaled anaesthetics in non-ventilated patients (83% increase, 95% CI 49–118%) and ventilated patients (50% increase, 28–72%). In non-ventilated patients, tidal volume decreased following administration of inhaled aesthetics (55% decrease, 95% CI 25–86%), propofol (36% decrease, 95% CI 20–52%), and benzodiazepines (28% decrease, 95% CI 17–40%); in patients receiving assisted mechanical ventilation, tidal volume was not significantly affected by sedation. Administration of other hypnotic agents was not associated with changes in respiratory rate or tidal volume.

Interpretation Different classes of drugs used for sedation exert differential effects on respiratory pattern, and this may influence weaning and outcomes in mechanically ventilated patients.

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Keywords: Mechanical ventilation; Sedation; Control of breathing; Respiratory failure

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Research in context

Evidence before this study

Sedation and analgesia is used in the ICU to ensure patient comfort and safety while on life support. Guidelines on sedation and analgesia management in critically ill patients focus on the management of wakefulness. Although sedation and analgesia are often used to facilitate mechanical ventilation and sedation management is strongly associated with prolonged ventilator-dependence, their specific effects on ventilatory control have not been systematically reported.

Added value of this study

Different sedative and analgesic drug classes exert important characteristic differential effects on respiratory pattern (tidal volume and respiratory rate) during both unassisted and assisted breathing.

Implications of all the available evidence

Strategies for managing sedation and analgesia in critically ill patients need to account for the specific effects of different drug classes on respiratory drive, effort, tidal volume, and respiratory rate, as these may affect the risk of lung and diaphragm injury and the ability to be liberated from mechanical ventilation.

Introduction

In critically ill patients, multiple noxious stimuli contribute to agitation and delirium, elevated respiratory drive, ventilator asynchrony, premature extubation, and removal of feeding tubes or lines, and sedation may be required for comfort and safety.[1] At the same time, many studies have reported a link between sedation management and adverse clinical outcomes in critically ill patients, including increased mortality, prolonged mechanical ventilation, and long-term cognitive dysfunction.[2] Clinical practice guidelines have defined best practices in sedation management to optimize outcomes.[3–6] The ABCDEF ICU Liberation Bundle emphasizes the importance of limiting sedation to promote earlier extubation, reduce delirium, and improve long-term outcomes.[4]

There is increasing recognition that sedation might affect clinical outcomes in mechanically ventilated patients by virtue of its direct effects on the control of breathing. Excessive sedation may suppress respiratory drive and effort, leading to diaphragm atrophy and weakness, with attendant risks of difficult weaning and prolonged mechanical ventilation.[7] Conversely, inadequate sedation may allow excessive respiratory drive and effort to injure the lung and diaphragm.[8,9] To prevent this, sedation could be directly titrated according to respiratory parameters such as tidal volume, expiratory occlusion pressure, and airway occlusion pressure ('lung-protective sedation' or 'lung- and diaphragm-protective sedation).[10,11]

To optimize application of sedation to control respiratory effort, an appreciation for the effects of different classes of drugs used for sedation on respiratory effort and ventilatory pattern is essential. We undertook a systematic review and meta-analysis to quantitatively summarize the effects of different drugs used for sedation on tidal volume, respiratory rate, and respiratory drive and effort during both spontaneous breathing and assisted mechanical ventilation. We hypothesized that different classes of drugs would exert differential effects on ventilatory pattern and respiratory drive and effort.

Methods

This systematic review protocol was prepared in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P) statement. This study was conducted from June 2020 through October 2022. This systematic review has been registered in the international prospective register of systematic reviews (PROSPERO #CRD42020190017).

Eligibility criteria

We aimed to identify original studies of adults ≥18 years of age where at least one of the sedating medications of interest was administered and a parameter of respiratory control (full search list below) was measured. We included retrospective, prospective, and case–control designs published in peer-reviewed journals or as conference abstracts. Eligible studies included healthy volunteers, patients undergoing procedural sedation, peri-operative patients, and critically ill patients. We excluded animal studies, studies including coadministration of a sedative other than those commonly used, studies using non-invasive ventilation, administration routes other than intravenous or inhalational administration, and studies where the dose of medication administered or timing of respiratory parameter measurement were unclear. Studies where commonly administered sedatives were compared to a less commonly used sedative, only the study arm using the medication of interest was included.

Information sources

Searches were executed in the following databases on June 18, 2020: Ovid MEDLINE ALL, Ovid Embase, Cochrane Database of Systematic Reviews (Ovid), and Cochrane Central Register of Controlled Trials (Ovid). Results were limited to human studies and adults. No

other limits were applied. Additional search methods included searching the reference lists of the included studies. See Appendix for database search strategies.

Search strategy

A comprehensive search strategy was initially developed for Ovid Medline using a combination of database-specific subject headings and text words which combined the two concepts of ICU sedation and control of breathing. The search strategy was then customized for each database.

Selection process

Studies that met the following criteria were included: those which documented one or more of study medications: opioids (morphine, hydromorphone, fentanyl, remifentanil, sufentanil), benzodiazepines (diazepam, midazolam, lorazepam), intravenous anesthetic agents (propofol, ketamine, etomidate), symapatholytics (dexmedetomidine), and inhaled anaesthetic agents (isoflurane, sevoflurane, desflurane); and evaluated one or more of the following components of respiratory control: respiratory rate, ratio of inspiratory to expiratory time (I:E ratio), tidal volume (V_T), measures of inspiratory effort using esophageal and gastric pressures (ΔP_{es}), diaphragmatic electrical activity (EA_{di}), diaphragm electromyography (needle and surface), diaphragm ultrasonography, airway occlusion pressure ($P_{0.1}$), end-tidal carbon dioxide ($ETCO_2$), arterial partial pressures (PaO_2 and $PaCO_2$) and pulse oximetry (SPO_2).

Data collection process

Duplicate search results were removed using an automated reference manager. Two reviewers (DQ and JW) independently screened abstracts for inclusion criteria and any discrepancies were resolved by consensus and a third reviewer (MS).

Data items

Fourteen independent reviewers (AS, CK, CO, IK, KH, KM, MM, MW, RG, RZ, SB, SP, TH, UK) extracted data, including: author, year of publication, study design, patient population, number of patients included in each study and intervention arm, gender, age and weight distributions, type and dose of medication administered, mode of ventilation, respiratory parameter being measured and time after medication administered that the parameter was measured. Sample size and means and SD or medians with IQRs were also recorded where means and SD were not available. Where available, appendices were checked for any missing parameters. Discrepancies in the datasets were adjudicated by a third reviewer (DQ).

Study risk of bias assessment

Study quality was assessed by the Cochrane risk of bias assessment tool appropriate to each clinical study design; the risk of bias tool for randomized studies (RoB 2)[12] and Risk of Bias in Non-randomized Studies - of Interventions tool (ROBINS-I)[13] was used for non-randomized studies. For randomized studies, the risk of bias was assessed as "low", "uncertain" or "high" in the following areas: generation of random sequence, allocation concealment, blinding of participants and professionals, blinding of outcome assessors, incomplete outcomes, selective outcome reporting, and other sources of bias. For non-randomized studies, studies were evaluated for preliminary consideration of confounders and co-interventions and the risk of bias was then assessed as "low", "uncertain" or "high" in the following areas: confounders, selection of participants, classification of interventions, deviation from intended intervention, missing data, measurement of outcomes and reported results. Disagreements were resolved by a third reviewer (DQ).

Statistical analysis

For the analysis, studies were grouped according to whether they enrolled non-intubated spontaneously breathing patients or patients on mechanical ventilation. After completing the literature search, we decided that measures of gas exchange ($EtCO_2$, PaO_2 and $PaCO_2$ and SpO_2) were not relevant to the research question, so these measurements were excluded from analysis.

There was substantial heterogeneity between studies in the timing and numbers of assessments, dosing, drug combinations, and study design (with some studies having only a single arm and others having multiple arms). This led to several decisions on how to summarize the data. First, we restricted the primary analyses to arms in which only a single sedative agent was administered to avoid the potential confounding effects of multiple sedatives. Studies with simultaneous exposure to multiple drugs were included as a secondary analysis. Second, we restricted on-treatment measurements to those obtained within the 72 min after administration. Third, we used the percentage change between the mean at baseline and the mean of the follow-up measurements as the within-arm outcome. Finally, we were forced to abandon within-study between-sedative comparisons and instead pool results across all the arms that used only a given sedative, then compare these pooled results between sedative. There were too few studies, and too many combinations, to allow present summaries each for head-to-head comparison of sedative and too little connectedness to allow a network meta-analysis of these data.

The following analysis was repeated separately for each respiratory parameter: (1) the baseline means and standard errors were calculated in each arm; (2) the averages of the follow-up means and the pooled follow-up standard deviations were calculated in each arm; (3) The percent change from baseline to follow-up was

calculated in each arm, along with its standard error (assuming a correlation between baseline and follow-up of 0.3); (4) an inverse-variance weighted meta-analysis was used to estimate the mean change from baseline and its 95% confidence interval for each sedative; (5) random effects meta-regression was used to estimate pairwise differences in mean percent change between the sedatives evaluated (these computations provide the values for physiological effects reported in the manuscript). Unreported standard deviations (SD) were estimated in a single imputation through linear regression of the arm-specific SD on the arm-specific mean, separately within the mechanically ventilated and non-mechanically ventilated arms. All analyses were conducted using R version 4.2.1, using R packages *meta* and *ggplot*.

Role of funding
This study did not receive any funding support.

Results
The initial search returned a total of 12,554 results including 8960 unique citations. After applying automated methods to remove case reports, animal studies and alternative routes of administration, a total of 1485 abstracts were screened yielding a total of 51 studies eligible for inclusion in the analysis (Fig. 1). The characteristics of the studies included are listed alphabetically in Table 1. The studies of patients receiving mechanical ventilation reported use of pressure support ventilation mode in all cases.

Risk of bias in studies
Risk of bias was assessed for each study pertaining to sources of error in measurement of respiratory parameters and time. The corresponding ROB2 or ROBINS-I are contained in Appendix I. Risk of bias was generally deemed to be low for most studies.

Tidal volume
Twenty studies with a total of 24 arms reported the influence of sedation on tidal volume in patients breathing without mechanical ventilation. Tidal volume decreased following administration of inhaled sevoflurane (55% decrease, 95% CI 25–86%, p = 0.0004, 1 arm),[28] propofol (36% decrease, 95% CI 20–52%, p < 0.0001, 4 arms),[16,41,54,60] and benzodiazepines (28% decrease, 95% CI 17–40%, p < 0.0001, 10 arms)[14,19,27,43,47] (Fig. 2). There was no statistically significant association between medication administration and change in tidal volume for opioids (11% decrease, 95% CI 28% decrease-5% increase, 6 arms)[39,55,56] and other hypnotic agents (9% decrease, 95% CI 23% decrease-6% increase, 6 arms)[23,36,41,44,49] (Fig. 2).

Five studies with a total of six arms reported the effect of sedation on tidal volume in patients receiving pressure support ventilation. Mean percentage changes in tidal volume were close to zero though confidence intervals were wide for opioids (2% increase, 13% decrease-16% increase, 3 arms),[22,24,45] other hypnotic agents (5% increase, 19% decrease-29% increase, 1 arm),[25] propofol (4% decrease, 28% decrease-20% increase, 1 arm),[25] and inhaled sevoflurane (0% decrease, 24% decrease-24% increase, 1 arm)[40] (Fig. 2).

The results of each meta-analysis and corresponding forest plots are presented in the Appendix. Secondary analyses including studies using multiple sedatives are reported in eTable 1.

Respiratory rate
A total of 44 studies with 56 arms reported respiratory rate in patients breathing without mechanical ventilation. Opioids were associated with a statistically significant mean reduction in respiratory rate of 18% (95% CI 12–24%, p < 0.0001, 24 arms),[15,20,21,33,35,39,46,51,55,56,61,62,65] whereas inhaled sevoflurane was associated with an increase in respiratory rate of 83% (95% CI 49–118%, p < 0.0001, 1 arm).[28] Mean percent changes in respiratory rate were close to zero and not statistically significant with exposure to benzodiazepines (2% decrease, 95% CI 9% decrease-6% increase, 16 arms),[19,26,27,29,37,42,43,47,50,59,63,64] other hypnotic agents (2% decrease, 95% CI 9% decrease-5% increase, 17 arms),[17,23,26,29–32,34,36,41,44,48,49,59] and propofol (4% increase, 6% decrease-14% increase, 9 arms)[16,17,30,41,52,54,60,61,63] (Fig. 2).

Nine studies with a total of 10 arms were included in the analysis of respiratory rate in patients receiving pressure support ventilation. Opioids were associated with a mean decrease in respiratory rate of 26% (95% CI 15–37%, p < 0.0001, 4 arms).[22,24,45,66] Conversely, inhaled sevoflurane was associated with a mean increase in respiratory rate of 50% (95% CI 28–72%, p < 0.0001, 1 arm)[40] Mean percent changes were close to zero and not statistically significant with exposure to benzodiazepines (8% decrease, 95% 29% decrease-13% increase, 1 arm),[58] other hypnotic agents (2% decrease, 95% CI 14% decrease-10% increase, 3 arms),[25,57,58] and propofol (2% decrease, 23% decrease-19% increase, 1 arm)[25] (Fig. 2).

Other parameters
Two studies in patients undergoing pressure support ventilation reported that administration of opioids reduced airway occlusion pressure ($P_{0.1}$) by 10% (95% CI 5–14%, 2 arms).[22,24] One study with two arms in patients receiving pressure support ventilation reported that there was no significant change in diaphragm electrical activity following administration of dexmedetomidine (–4%, 95% CI –19 to 10%, 1 arm) or propofol (2%, 95% CI –12 to 15%, 1 arm).[25] One study in patients receiving pressure support ventilation reported that remifentanil was associated with a decrease in esophageal pressure swing of 36% (95% CI 10–60%, 1 arm).[45] Another study in non-intubated subjects reported an

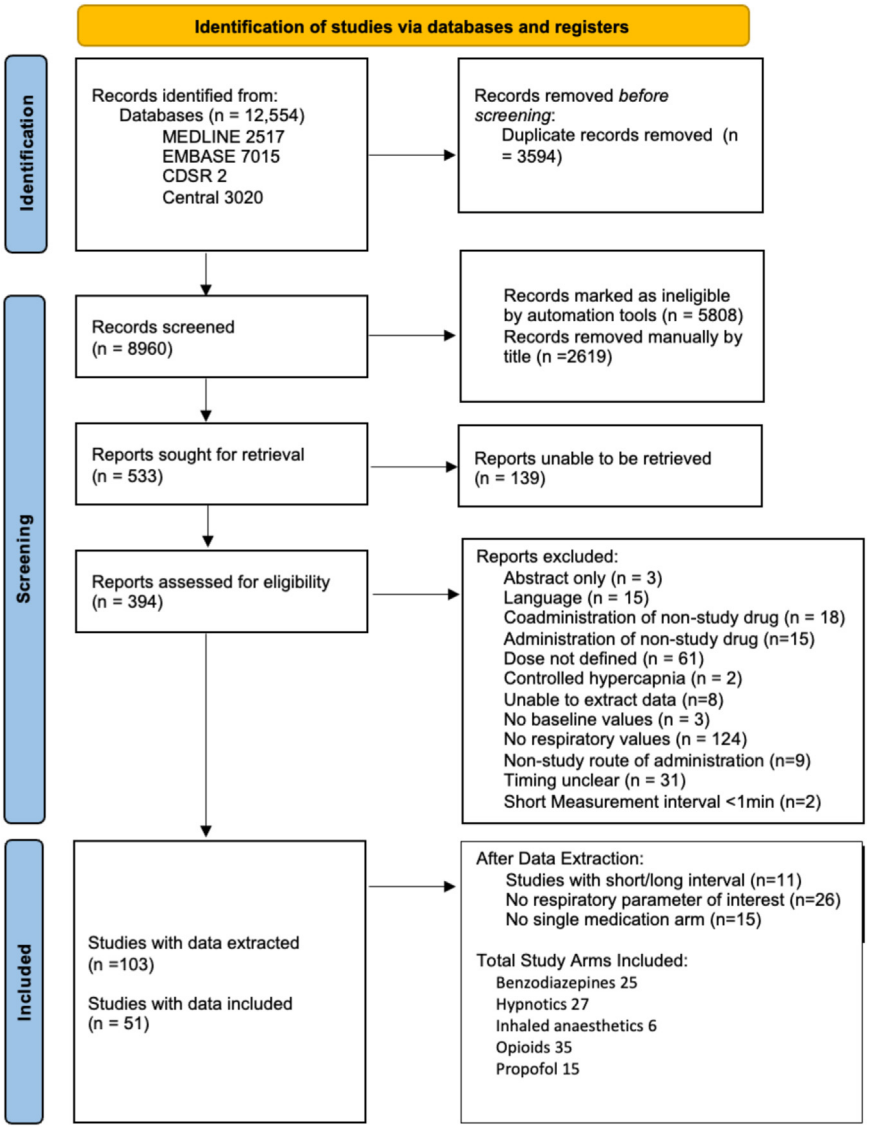

Fig. 1: PRISMA flow diagram outlining study inclusion.

increase in resistive work of breathing following administration of midazolam.[43]

Discussion

In this systematic review and meta-analysis, different classes of drugs used for sedation in the ICU exerted distinct effects on respiratory control, as indicated by changes in respiratory rate and tidal volume. Opioids produced a statistically significant decrease in respiratory rate independent of mechanical ventilation. Conversely, inhaled anaesthetic agents significantly increased the respiratory rate in patients with and without mechanical ventilation. In the absence of mechanical ventilatory support, significant decreases in tidal volume were observed following receipt of volatile anaesthetics, propofol and benzodiazepines, but no detectable changes were observed in tidal volume in the presence of pressure support ventilation. Other hypnotic agents did not produce any statistically significant change in respiratory rate or tidal volume in either ventilated or non-ventilated patients.

There is a growing appreciation for the impact of sedation on the outcomes of mechanical ventilation. This was recently highlighted by the findings of the WEANSAFE study. This large epidemiological study of weaning in the ICU found that moderate or deep levels of sedation were among the only modifiable factors strongly associated with both a delay in attempts at liberation from mechanical ventilation and weaning

Study	Population	N	Medications	Dose	Mechanical ventilation (Y/N)	Respiratory parameter
Alexander (1992)[14] Cross-over RCT	Healthy volunteers	10	Midazolam	0.1 mg/kg	N	Vt
Alimohammadi (2014)[15] Cohort	Peri-procedural	67	Fentanyl	1 mcg/kg	N	RR Vt
Aliverti (2011)[16] Cohort	Peri-procedural	15	Propofol	2 mg/kg + 7.5 mg/kg/h	N	RR Vt
Arain (2002)[17] RCT	Peri-procedural	40	Dexmedetomidine Propofol	1 mcg/kg + 0.4 mcg/kg/h 75 mcg/kg/h	N	RR
Aydin (2004)[18] RCT	Peri-procedural	70	Fentanyl	0.7 mcg/kg	N	RR
Berggren (1987)[19] Cross-over RCT	Healthy volunteers	8	Midazolam Diazepam	0.05–0.15 mg/kg 0.15–0.45 mg/kg	N	RR Vt
Cao (2017)[20] Cohort	Peri-partum	60	Fentanyl	2 mcg/kg	N	RR
Casey (2010)[21] RCT	Post-operative		Remifentanil	0.5–1 mcg/kg	N	RR
Cavaliere (2002)[22] Cohort	ICU	10	Remifentanil	0–0.25 mcg/kg/min	Y	RR Vt $P_{0.1}$
Choi (1985)[23] Cross-over RCT	Healthy volunteer	6	Etomidate	0.3 mg/kg	N	RR Vt
Conti (2004)[24] Cohort	ICU	12	Sufentanil	0.25 mcg/kg/h	Y	RR Vt $P_{0.1}$
Conti (2016)[25] RCT	ICU	20	Dexmedetomidine Propofol	0.46 mcg/kg/h 1.08 mg/kg/h	Y	RR Vt EAD_i
Demiraran (2007)[26] RCT	Peri-procedural	50	Midazolam Dexmedetomidine	1 mcg/kg + 0.2 mcg/kg/h	N	RR
Denaut (1975)[27] Cross-over RCT	Healthy volunteer	20	Lorazepam Diazepam	2.5 mg 10 mg	N	RR Vt
Doi (1987)[28] Cohort	Healthy volunteer	21	Sevoflurane	1.71 MAC	N	RR Vt
Eren (2011)[29] RCT	Peri-procedural	125	Dexmedetomidine Midazolam	1 mcg/kg 0.02–0.06 mg/kg	N	RR
Ghali (2011)[30] RCT	Peri-procedural	60	Dexmedetomidine Propofol	1 mcg/kg + 0.35 mcg/kg/h 0.7 mg/kg + 1.25 mg/kg/h	N	RR
Ghasemi (2018)[31] RCT	Peri-procedural	60	Dexmedetomidine	0.5 mcg/kg/h	N	RR
Hall (2000)[32] Cross-over RCT	Healthy volunteer	7	Dexmedetomidine	0.5 mcg/kg + 0.2–0.6 mcg/kg/h	N	RR
Hwang (1996)[33] RCT	Peri-operative	42	Fentanyl	1 mcg/kg	N	RR
Jense (2008)[34] Cohort	Post-operative	14	Dexmedetomidine	0.52 mcg/kg + 0.29 mcg/kg/h	N	RR
Joshi (2007)[35] RCT	Post-operative	141	Fentanyl Sufentanil	2 mcg/kg 0.2 mcg/kg	N	RR
Kawaai (2010)[36] Cross-over RCT	Healthy volunteers	13	Dexmedetomidine	0.5 mcg/kg + 0.2–0.4 mcg/kg/h	N	RR Vt
Kunusoth (2019)[37] RCT	Peri-procedural	60	Midazolam	0.1 mg/kg	N	RR
Lau (1993)[38] Cohort	Post-operative	20	Midazolam Fentanyl	0.07 mg/kg 0.8 mcg/kg	N	RR
Leino (1999)[39] Cross-over RCT	Healthy volunteer	6	Morphine	0.039 mg/kg + 0.215 mg/kg/h	N	RR Vt
Lesage (2009)[40] RCT	Post-operative	80	Sevoflurane Midazolam Fentanyl	8% 9 mcg/kg 0.6 mcg/kg	Y	RR Vt
Lodenius (2016)[41] Cross-over RCT	Healthy volunteer	11	Dexmedetomidine Propofol	0.59 mcg/kg + 0.53 mcg/kg/h 74.5 mcg/kg + 48.6 mcg/kg/h	N	RR Vt

(Table 1 continues on next page)

Study	Population	N	Medications	Dose	Mechanical ventilation (Y/N)	Respiratory parameter
(Continued from previous page)						
McHardy (2000)[42] RCT	Peri-procedural	81	Midazolam Propofol	1.2–1.3 mg 11 mg	N	RR
Montravers (1992)[43] Cross-over RCT	Healthy volunteer	10	Midazolam	0.1 mg/kg	N	RR Vt
Morel (1986)[44] Crossover RCT	Healthy volunteer	8	Ketamine	1 mg/kg	N	RR Vt
Natalini (2011)[45] Cross-over RCT	ICU	14	Remifentanil	0.05 mcg/kg/min	Y	RR Vt ΔP_{es}
Niesters (2013)[46] Cross-over RCT	Healthy volunteer	20	Remifentanil	50 mcg	N	RR
Ninomiya (2016)[47] Cross-over RCT	Healthy volunteer	21	Midazolam	0.05 mg/kg	N	RR Vt
Nunez-Ponce (2014)[48] RCT	Peri-procedural	60	Dexmedetomidine	0–0.7 mcg/kg/h	N	RR
Ogawa (2008)[49] Cohort	Healthy volunteers	13	Dexmedetomidine	0.5 mcg/kg + 0.2 mcg/kg/h	N	RR Vt
Prabhudev (2017)[50] RCT	Peri-procedural	144	Midazolam Fentanyl	0.035 mg/kg 50 mcg	N	RR
Preston (1987)[51] RCT	Healthy volunteers	15	Morphine	7.5–30 mg	N	RR
Rasmussen (2006)[52] RCT	Peri-procedural	39	Propofol	4 mg/kg/h	N	RR
Rocco (2010)[53] Cohort	ICU	36	Remifentanil	0.07 mcg/kg/min	Y	RR
Rosa (1992)[54] Cohort	Peri-procedural	10	Propofol	0–1.2 mg/kg	N	RR Vt
Samuel (1977)[55] Cohort	ICU	10	Morphine	0.14 mg/kg	Y	RR Vt
Sarton (1999)[56] Cross-over RCT	Healthy volunteer	16	Morphine Fentanyl or Morphine	100 mcg/kg 30 mcg/kg/h 30 mcg/kg/h	N	RR Vt
Senoglu (2009)[57] Cohort	ICU	15	Dexmedetomidine	0.5 mcg/kg/h	Y	RR
Senoglu (2010)[58] RCT	ICU	40	Dexmedetomidine or Midazolam	1 mcg/kg + 0.5 mcg/kg/h 0.05 mg/kg + 0.1 mg/kg/h	Y	RR
Sivasubramani (2019)[59] RCT	Peri-procedural	60	Midazolam or Dexmedetomidine	0.05 mg/kg 0.17 mg/kg + 0.5 mcg/kg/h	N	RR
Spens (1996)[60] RCT	Peri-procedural	69	Propofol	2.5 mg/kg	N	RR Vt
Tanaka (1998)[61] Cohort	Peri-procedural	30	Fentanyl Propofol ± Fentanyl	2 mcg/kg 0.5 mg/kg + 3 mg/kg/h 2 mcg/kg	N	RR
Thakore (2009)[62] RCT	Post-operative	100	Fentanyl	0.2 mcg/kg + 0.4 mcg/kg/h	N	RR
Umuroglu (1997)[63] RCT	Peri-procedural	30	Propofol Midazolam	1.25 mg/kg + 3 mg/kg/h 0.1 mg/kg + 0.1 mg/kg/h	N	RR
Van de Velde (2005)[64] RCT	Peri-partum	50	Remifentanil Diazepam	0.115 mcg/kg/min 14.5 mg	N	RR

Table 1: **Characteristics of included studies.**

failure.[67] This literature review focused on physiological effects on ventilatory control sheds additional insights on the precise interactions between sedation and ventilation.

Pressure support ventilation may mask the effect of sedation on respiratory effort. In the absence of ventilation, specific sedatives reduced tidal volume. This reduction in tidal volume can arise from an increase in airway resistance with a consequent increase in the work of breathing, or from depression of respiratory drive and effort.[43] The effects of sedation on respiratory effort and mechanics are complex; Aliverti et al. found that diaphragm contractility was more depressed than rib cage muscle contractility following administration of

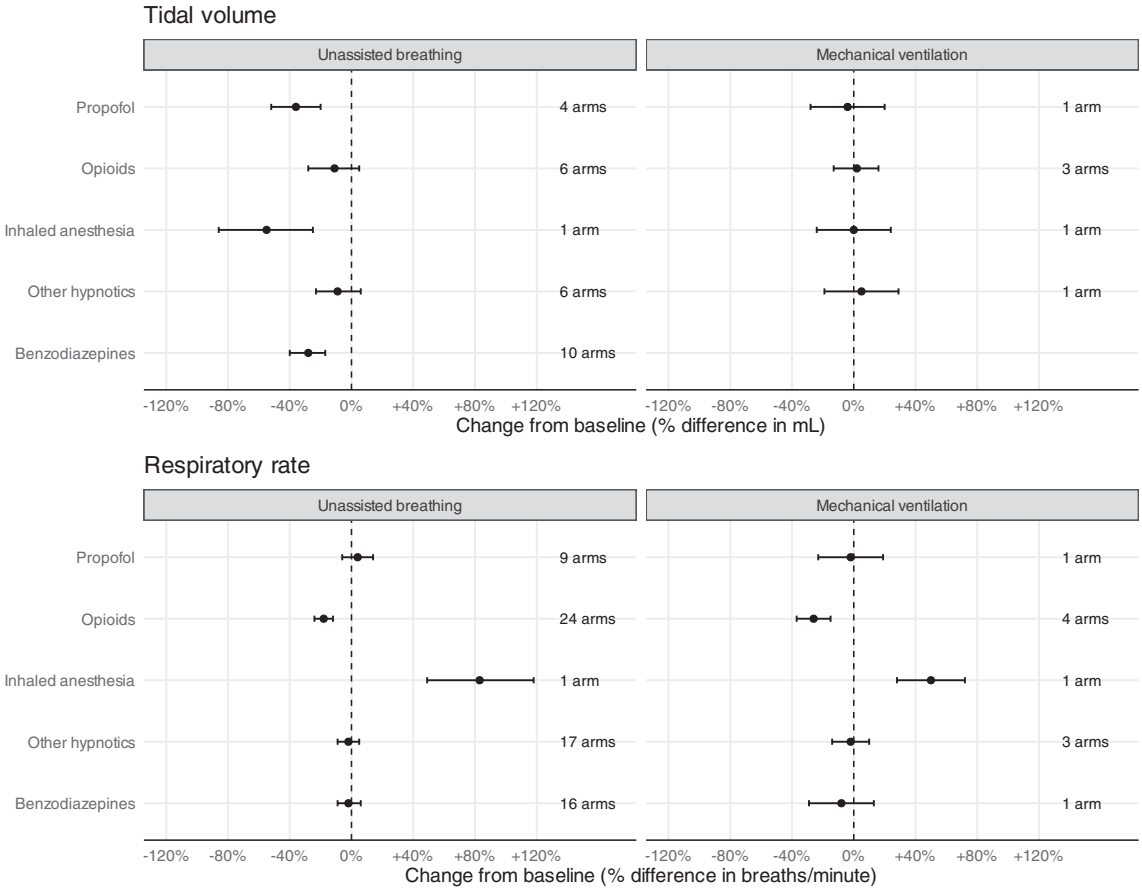

Fig. 2: Influence of different sedative classes on tidal volume and respiratory rate in patients who are on mechanical ventilation and not on mechanical ventilation. Dots are point estimates for the mean and bars span 95% confidence intervals for the mean.

propofol.[16] Because tidal volume during pressure support ventilation is largely determined by respiratory mechanics, ventilation likely masks the effect of sedation on respiratory effort. This observation suggests that the effects of sedation on respiratory effort should be directly monitored. Respiratory effort is an important mediator of clinical outcomes: decreased respiratory effort from sedation can contribute to disuse atrophy and dysfunction of the diaphragm.[68,69] In contrast, these agents may be favourable in patients with high effort levels to reduce respiratory effort and high tidal volumes to mitigate the risk of patient self-inflicted lung injury and diaphragm injury from excessive ventilatory effort.[9,70] During the weaning phase, depression of respiratory effort may contribute to weaning failure and it may be preferable to avoid sedatives that depress respiratory effort or respiratory rate. Clinicians should appreciate the potential for certain sedatives to depress respiratory effort in mechanically ventilated patients without any apparent effect on respiratory rate or tidal volume.

Our study identified propofol, benzodiazepines and inhaled anaesthetics as agents which may decrease respiratory effort, as evidenced by a decrease in tidal volume rather than respiratory rate. The mechanism for reduced respiratory effort is different for each class of sedative. Propofol has been previously shown to reduce minute ventilation beyond an isolated reduction in respiratory rate and this depression in ventilatory response occurs in a non-linear dose dependent manner.[71,72] This is thought to occur through a reduction in the ventilatory response to hypercapnia seen even at subanaesthetic doses of propofol.[73] As noted above, the effects of benzodiazepines are complex, as tidal volume may fall as a consequence of increased upper airway resistance. Administration of diazepam decreased phrenic nerve conduction by up to 80%.[74] Inhaled anaesthetics decrease tidal volume and increase respiratory rate through unclear mechanisms, though some studies have demonstrated an increase in $PaCO_2$, which may in part explain an increase in respiratory rate.[75]

These findings have important implications for managing patients with acute respiratory failure. Limiting lung stress during ventilation is critical to preventing lung injury, and sedatives that reduce respiratory effort and tidal volume may preferred in the acute phase of lung injury. Notably, because they induce a rapid shallow breathing pattern, inhaled anesthetics may be the ideal sedative for lung- and diaphragm protective ventilation; the rapid respiratory rate will maintain diaphragm activity (since the patient will trigger the ventilator) but with a reduction in effort and tidal volume to avoid barotrauma and diaphragmatic myotrauma. This sedation strategy may be most beneficial to facilitate the early weaning of neuromuscular blockade.

Opioids are widely known to depress respiratory rate through direct inhibition of the central nervous system.[76] Depression of neural respiratory rate during weaning of mechanical ventilation can delay the transition to spontaneous ventilation as patients will not trigger the ventilator unless their intrinsic neural respiratory rate exceeds the set rate. This could in theory contribute to prolonged mechanical ventilation and subsequent diaphragm disuse. Analgesia-first sedation strategies are currently recommended to ensure pain control in mechanically ventilated patients.[77] Opioids in low doses have minimal effects on respiratory drive, and avoiding excessive doses of opioids might facilitate weaning from the ventilator.[24]

Drugs classified as "other hypnotic agents" (e.g., ketamine, dexmedetomidine) appear to have little or no effect on tidal volume or respiratory rate as indicated by our study. This may make them useful agents for conscious sedation and management of agitation during the weaning phase of mechanical ventilation. This may be particularly true with ketamine which has both amnestic and analgesic properties where patients are also experiencing a component of pain, such as post-operative, trauma or burn patients.[78] Further clinical investigation is required to clarify the potential value of this strategy. Given the known adverse effects of etomidate on adrenal function, it is not likely to benefit patients even though it can effectively maintain respiratory drive and respiratory rate during sedation.

There are several limitations with our study. Medications were grouped by classes to facilitate analysis and we did not examine differences between agents within a single group. This is most important in the "other hypnotics" group as medications like dexmedetomidine and ketamine act through different mechanisms. Additionally, our analytical approach could not account for differences in dose or duration of administration, although the dosages studied were within the typical range of doses employed in clinical practice. It is well known that medications possess strikingly different context-sensitive half-times and this likely modifies the physiological effects of these agents on respiratory control. Finally, we had insufficient information from this review to draw conclusions about the effects of sedation on other relevant respiratory parameters including airway occlusion pressure, electrical activity of diaphragm and esophageal pressures. There is a marked paucity of studies reporting these parameters with administration of sedatives prohibiting inclusion in a systematic review.

In summary, different sedative classes exert different effects on respiratory control. Opioids reduce respiratory rate with less effect on tidal volume. Inhaled anesthetics decrease tidal volume with a corresponding increase in respiratory rate. Benzodiazepines and propofol are associated with a reduction in tidal volume without any effect on respiratory rate. Hypnotic agents have little or no effect on average on either respiratory rate or tidal volume. This information can help guide the selection of sedatives to optimize management of mechanically ventilated patients in the acute and weaning phases of respiratory failure.

Contributors

Quickfall and Goligher conceived the idea. Quickfall, Sklar, and Goligher designed the study. Quickfall and Sklar led the data collection. Tomlinson conducted the analysis. Quickfall prepared the first draft of the manuscript, and all authors revised the manuscript for intellectually important content. Quickfall, Sklar, Tomlinson, and Goligher had access to the primary data for analysis. All authors reviewed the final version of the manuscript. agreed to submit the manuscript for publication.

Data sharing statement

Data and review protocol used for this analysis will be available following publication upon reasonable request submitted to the corresponding author subject to the investigators' approval of a proposed analysis plan.

Declaration of interests

Dr. Goligher reports receiving grants from the Canadian Institutes of Health Research and National Sanitarium Association; consulting fees from Lungpacer Medical, Stimit LLC, and Bioage; honoraria for lectures from Vyaire, Draeger, and Getinge; advisory board participation for Getinge (current) and Lungpacer (previous); and receipt of equipment for research from Timpel and Lungpacer.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2023.102417.

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