The role of acute hypercapnia on mortality and short-term physiology in patients mechanically ventilated for ARDS: a systematic review and meta-analysis

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Abstract
Purpose: Hypercapnia is frequent during mechanical ventilation for acute respiratory distress syndrome (ARDS), but its effects on morbidity and mortality are still controversial. We conducted a systematic review and meta-analysis to explore clinical consequences of acute hypercapnia in adult patients ventilated for ARDS.

Methods: We searched Medline, Embase, and the Cochrane Library via the OVID platform for studies published from 1946 to 2021. “Permissive hypercapnia” defined hypercapnia in studies where the group with hypercapnia was ventilated with a protective ventilation (PV) strategy (lower $V_T$ targeting 6 ml/kg predicted body weight) while the group without hypercapnia was managed with a non-protective ventilation (NPV); “imposed hypercapnia” defined hypercapnia in studies where hypercapnic and non-hypercapnic patients were managed with a similar ventilation strategy.

Results: Twenty-nine studies (10,101 patients) were included. Permissive hypercapnia, imposed hypercapnia under PV, and imposed hypercapnia under NPV were reported in 8, 21 and 1 study, respectively. Studies testing permissive hypercapnia reported lower mortality in hypercapnic patients receiving PV as compared to non-hypercapnic patients receiving NPV: OR = 0.26, 95% CI [0.07–0.89]. By contrast, studies reporting imposed hypercapnia under PV reported increased mortality in hypercapnic patients receiving PV as compared to non-hypercapnic patients also receiving PV: OR = 1.54, 95% CI [1.15–2.07]. There was a significant interaction between the mechanism of hypercapnia and the effect on mortality.

Conclusions: Clinical effects of hypercapnia are conflicting depending on its mechanism. Permissive hypercapnia was associated with improved mortality contrary to imposed hypercapnia under PV, suggesting a major role of PV strategy on the outcome.

Keywords: Hypercapnia, ARDS, Hemodynamics

Introduction

Mechanical ventilation is a frequently used supportive technique for acute respiratory distress syndrome (ARDS). The main purpose of mechanical ventilation in this setting is to maintain oxygenation, lower oxygen consumption and reduce respiratory work. Despite
the clear benefits of this therapy, the mechanical forces generated by the ventilator can cause worsening injury in previously damaged lungs (ventilator induced lung injury, VILI). To minimize VILI, a strategy of lung protective ventilation (PV) involving lower tidal volume ($V_T$ targeting 6 ml/kg predicted body weight) is recommended [1]. In practice, PV may elevate carbon dioxide ($CO_2$) levels in the blood inducing hypercapnia. “Permissive” hypercapnia, which results from lowering $V_T$ to achieve PV is, therefore, generally accepted to minimize VILI. In addition, some authors have suggested a specific beneficial role for hypercapnia in the experimental setting [2].

Recent evidence suggests that acute hypercapnia could have harmful physiological and clinical effects in patients with ARDS, particularly impacting the hemodynamic system [3–5]. The fact that hypercapnia is specifically driven by $V_T$ reduction from non-protective ventilation (NPV) to PV (“permissive” hypercapnia) or is rather the result of ARDS severity, may have a major role in its net clinical effect, given the associated benefits of PV on VILI and survival [1, 6].

The aim of the current review and meta-analysis was to summarize the clinical consequences of acute hypercapnia in mechanically ventilated patients while considering its mechanism (“permissive” or not). The primary objective was to determine the association between acute hypercapnia and mortality in adult patients mechanically ventilated for ARDS. The secondary objective was to identify association between acute hypercapnia and hemodynamics (systemic and pulmonary circulation) in adult patients mechanically ventilated for ARDS.

Methods

Search strategy and selection criteria

We performed this study in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [7]. The following electronic databases were searched via the OVID platform on November 2018: MEDLINE® In-Process & Other Non-Indexed Citations, MEDLINE (1946 to present), Embase (1980 to present), The Cochrane Library, incorporating the Cochrane Database of Systematic Reviews (Cochrane Reviews), the Database of Abstracts of Reviews of Effects, the Cochrane Central Register of Controlled Trials, the Health Technology Assessment Database, and the NHS Economic Evaluation Database. To identify any recent studies for which there are currently no full publications, the following conference proceedings were examined for relevant abstracts (and posters/slide decks, if available) from 2011 to 2018:

American Thoracic Society, European Respiratory Society, European Society of Intensive Care Medicine, International Symposium on Intensive Care and Emergency Medicine, International Society for Pharmacoeconomics and Outcomes Research (International and European meeting), and Society for Critical Care Medicine. Research was updated on November 2021 with the same research method. The search strategies used are detailed in online resource, Appendix A. Potentially relevant studies were screened by two independent reviewers in separate databases. We included all studies with mechanically ventilated patients reporting acute hypercapnia with no restriction on severity of hypercapnia, intervention, countries, or study design (we included cross-sectional studies, case–control studies, cohort studies, database/registries analyses, hospital records analyses, and randomized controlled trials). We excluded studies in children and animals and focused primarily on studies written in English. After the removal of the duplicates, two reviewers independently screened titles and abstracts to obtain relevant articles for full text analysis (first pass). Full-text publications of all potentially relevant citations identified at first pass were reviewed for eligibility (2nd pass). Eligible papers were then independently selected for inclusion if they involved adult patients fulfilling ARDS criteria as per the Berlin definition (considering “acute lung injury” as per the previous definition as mild ARDS; 3rd pass) [8]. Papers on the use of extracorporeal carbon dioxide removal for ultraprotective ventilation were excluded. Any disagreement was resolved by discussion with a third reviewer. This study was registered in the International Prospective Register of Systematic Reviews (PROSPERO) database (registration number CRD42020159018). Ethical approval was not required.

Data analysis

The following data were independently extracted by the review authors from each selected study: year of publication, study design, $PaCO_2$, and ventilation strategy (defined as PV if targeting 6 ml/kg predicted body weight of $V_T$ [1] and NPV otherwise), hemodynamics (pulmonary and systemic circulation) and mortality.
For quality (risk of bias) assessment, we used the risk-of-bias tool (RoB2) [9] for randomized controlled trials (RCTs) and the Quality Assessment Tool for Quantitative Studies produced as part of the Effective Public Health Practice Project for observational studies (including prospective interventional studies) [10]. For every study, each component was rated as: strong, moderate or weak, and used to assign an overall rating for the study.

Definitions
We used the term “permissive hypercapnia” to define hypercapnia in studies where the group with hypercapnia was ventilated with a PV strategy (lower $V_T$ targeting 6 ml/kg predicted body weight) while the group without hypercapnia was managed with a NPV strategy. We used the term “imposed hypercapnia under PV” to define hypercapnia in studies were hypercapnic and non-hypercapnic patients were both managed with a PV strategy. We used the term “imposed hypercapnia under NPV” to define hypercapnia in studies were hypercapnic and non-hypercapnic patients were both managed with a NPV strategy [11]. Hypercapnia was primarily the result of the chosen ventilation strategy (PV or NPV), and the strategy was mostly guided irrespective of PaCO₂ values.

Statistical analysis
We conducted a meta-analysis of observational prospective and retrospective studies. Data were summarized using medians and interquartile ranges (IQRs) or mean ± standard deviation (SD) where appropriate [12]. The odds ratio (OR) with 95% confidence interval (CI) was calculated for death.

We adopted a random effect model with Mantel–Haenszel method for individual study effects, to assess the population OR and 95% confidence interval for death according to hypercapnia. We used the Knapp–Hartung adjustment for test statistics and confidence intervals [13]. Between study variances and their square roots were adjusted by the Sidik–Jonkman estimator [14]. We quantified heterogeneity using $I^2$ and Q statistics, with values greater than 50% regarded as being indicative of moderate-to-high heterogeneity [15]. To measure the dispersion of the pooled effect across study settings, we generated predictions intervals [16]. Results were visualized through forest plot.

We performed prespecified subgroup analyses according to the mechanism of hypercapnia (permissive or imposed). Test for differences in effect sizes between subgroups was performed using mixed-effect model, with a random-effect model for the overall effect size for each subgroup, and a fixed-effect model for subgroup differences [17]. Mortality was also assessed after exclusion of outliers and after exclusion of studies with COVID-19-related ARDS.

Heterogeneity was assessed graphically through L’Abbé plot [18]. Data were pooled and analyzed using R 4.1.0 (The R Foundation for Statistical Computing, Vienna, Austria).

Results
Studies
The overall flow of studies across the reviews is reported in the PRISMA flow diagram in Fig. 1. The electronic database searches identified a total of 5513 citations which were screened on the basis of title and abstract. At this stage, a total of 5786 articles were excluded, and 423 were deemed to be potentially relevant. These citations were retrieved for full publication review. Upon review of the full publications, a further 345 articles were excluded. Hand searching yielded eleven additional relevant papers, resulting in a total of 89 relevant publications from which 29 met the eligibility criteria of the review after the third pass. We, therefore, selected these 29 studies (10,101 patients) reporting the clinical consequences of hypercapnia in adults with ARDS for the present review [5, 11, 19–45]. All included studies were published as full publication. The sample size among the included studies varied from $N=4$ [34] to $N=3642$ [44]. An overview of all included studies is presented in Table 1. Two studies shared some patients [19, 20]: hemodynamic data were extracted from Amato 1995 [19], and mortality data from Amato 1998 [20]. Results from quality assessment checklist for included studies are presented in Table 2: for observational studies, 15 studies had overall weak rating (high risk of bias), eight had moderate rating and three had strong rating (low risk of bias). For RCTs, two studies had overall concerns, and one had low overall risk of bias. These bias are reported in Table 2. Due to the small number of studies, statistical tests to investigate for the presence of publication bias were not conducted.

Hypercapnia and tidal volumes
Definition of hypercapnia and $V_T$ used among the included studies have been captured in Table 1. A clear threshold for hypercapnia was reported in 11/29 of the included studies, that was defined as PaCO₂ $\geq 38$ mmHg [19], PaCO₂ $\geq 45$ mmHg [11, 25, 41], $\geq 48$ mmHg [23], $\geq 50$ mmHg [5, 28, 33, 35, 44] or $\geq 55$ mmHg[34]. Information regarding $V_T$ were reported in all but three studies [5, 26, 27]. Permissive hypercapnia, imposed hypercapnia under PV, and
Fig. 1 Study flowchart; *primary search from 2011 to 2018 and second search updated in November 2021
Table 1  Overview of all studies included in the review

| Study                        | Study design, sample size | Definition of hypercapnia, \(\text{PaCO}_2\) mmHg | Tidal volume used | Type of mechanical ventilation | Hospital deaths |
|------------------------------|---------------------------|-----------------------------------------------|-------------------|--------------------------------|-----------------|
| Kiegenow et al. (2006) [11]  | Secondary analysis of RCTs (NPV) \((N=369)\) | Definition: \(\geq 45\) mmHg Mean (SD) hypercapnia group: 52.5 (5) mmHg, normocapnia group: 34.7 (7) mmHg | Mean (SD): hypercapnia group: 10.8 (2.0) ml/kg, normocapnia group: 11.8 (0.9) ml/kg | Hypercapnia: NPV versus NPV | 4/13 142/356 |
| Aguirre-Bermeo et al. (2016) [30] | Observational (Cross over, not randomized) \((N=13)\) | Definition: NA mean (SD) hypercapnia group: 54±9 mmHg, mean (SD) normocapnia group: 50 (8) mmHg | Mean (SD) hypercapnia group: 6.3±0.8 ml/kg | Hypercapnia: PV versus control: PV+ End-inspiratory pause prolongation | NA NA |
| Bellani et al. (2016) [21] | Observational \((N=2377)\) | Definition: NA Mean (95% CI), mild & moderate ARDS: 41.5 [40.7–42.2] & 45.8 [44.9–46.6], respectively Mean (95% CI), severe ARDS: 52.2 [50.7–53.7] | Mean (85% CI) day-1, mild & moderate ARDS: 7.8 [7.6–7.9] & 7.6 [7.5–7.7] ml/kg, respectively | Hypercapnia: PV versus PV | 257/557 695/1820 |
| COVID_ICU (2021) [44]d | Observational \((N=3642)\) | Definition: \(\geq 50\) mmHg, mean (SD) hypercapnia group: 59.1 (8.5) mmHg, mean (SD) normocapnia group: 41.3 (5.8) mmHg | Mean (SD) hypercapnia group: 412.3 (90)ml, mean (SD) normocapnia group: 423.3 (115.2)ml | Hypercapnia: PV versus PV | 409/869 663/2319 |
| Ding et al. (2021) [33]d | Observational (Cross over, not randomized) \((N=12)\) | Definition: \(\geq 50\) mmHg median (IQR) hypercapnia group 64.5 [56–88.75] mmHg | Mean (SD) hypercapnia group: 5.94±0.18 ml/kg | Hypercapnia: PV versus control: PV+ extracorporeal CO\(_2\) removal | 8/12 - |
| Hickling et al. (1990) [26] | Observational \((N=70)\) | Definition: NA Mean (SD) hypercapnia group: 60.2 (20) mmHg | Down to 350 ml (5 ml/kg) | PV | 13/70 NA |
| Hickling et al. (1994) [27] | Observational \((N=64)\) | Definition: NA Mean 66.5 torr (range 38–158) | PV: around 7 ml/kg | PV | 17/64 NA |
| Husain-Syed et al. (2020) [34]d | Observational (Cross over, not randomized) \((N=4)\) | Definition: \(\geq 55\) mmHg, mean (SD) hypercapnia group: 60.7 mmHg | Mean (SD) hypercapnia group: 6.6 ml/kg | Hypercapnia: PV versus control: PV+ extracorporeal CO\(_2\) removal | NA NA |
| Kahl et al. (2021) [35] | Observational \((N=66)\) | Definition: \(\geq 50\) mmHg, mean (SD) hypercapnia group: 47.7 (6.6) mmHg, mean (SD) normocapnia group: 45.2 (11.1) mmHg | Mean (SD) hypercapnia group: 395 (133)ml, mean (SD) normocapnia group: 434 (185)ml | Hypercapnia: PV versus control: PV± extracorporeal CO\(_2\) removal | NA NA |
| Study | Study design, sample size | Definition of hypercapnia, \( \text{PaCO}_2 \ \text{mmHg} \) | Tidal volume used | Type of mechanical ventilation | Hospital deaths |
|-------|--------------------------|---------------------------------|-----------------|-------------------------------|----------------|
| Kalfon et al. (1997) [28] (PV to PV + EWO) | Observational (Cross over, not randomized) (\( N = 7 \)) | \( \geq 50 \) mmHg, mean (SD) hypercapnia group: 76.4 (4) mmHg, mean (SD) normocapnia group: 53 (3) mmHg | Mean (SD) hypercapnia group: 414 (27) ml, mean (SD) normocapnia group: 414 (27) ml | Hypercapnia: PV versus control: PV + expiratory washout | Hospital deaths |
| Kregenow et al. (2006) [11] (PV) | Secondary analysis of RCTs, (\( N = 351 \)) | \( \geq 45 \) mmHg | Mean (SD) hypercapnia group: 6.0 (0.9) ml/kg, mean (SD) normocapnia group: 6.3 (0.9) ml/kg | Hypercapnia: PV versus PV | Hospital deaths |
| Liu et al. (2020) [36] | Observational (\( N = 8 \)) | NA | Mean (SD) hypercapnia group: 7.0 (0.6) ml/kg, mean (SD) normocapnia group: 7.5 (0.6) ml/kg | Hypercapnia: PV versus NPV | Hospital deaths |
| Lotz et al. (2021) [37] | Observational (\( N = 7 \)) | NA | Median (IQR): 424 [390.5–467] ml | Hypercapnia: PV + NO | Hospital deaths |
| Mekontso Dessap et al. (2009) [22] | Observational (Cross over, randomized) (\( N = 11 \)) | NA | Mean (SD) hypercapnia group: 71 (60–94) mmHg, mean (SD) normocapnia group: 52 (43–68) mmHg | Hypercapnia: PV versus PV | Hospital deaths |
| Mekontso Dessap et al. (2016) [23] | Observational, (\( N = 752 \)) | \( \geq 48 \) mmHg, mean (SD) hypercapnia group: 58.1 (10.6) mmHg, mean (SD) normocapnia group: 39.1 (5.5) mmHg | Mean (SD) hypercapnia group: 6.6 (1.3) ml/kg, mean (SD) normocapnia group: 7.0 (1.2) ml/kg | Hypercapnia: PV versus PV | Hospital deaths |
| Nin et al. (2017) [5] | Secondary analysis of observational (\( N = 1899 \)) | \( \geq 50 \) mmHg, mean (SD) hypercapnia group: 606 (11.3) mmHg, mean (SD) normocapnia group: 387 (6.1) mmHg | \~ 90% of patients received between 6 and 8 ml/kg | Hypercapnia: PV versus PV | Hospital deaths |
| Pan et al. (2020) [38] | Observational (Cross over, not randomized) (\( N = 12 \)) | NA | Mean (SD) hypercapnia group: 375 (65) ml | Hypercapnia: PV versus control: PV ± extracorporeal CO2 removal | Hospital deaths |
| Retran et al. (2020) [39] | Observational (Cross over, not randomized) (\( N = 73 \)) | NA | Mean (SD) hypercapnia group: 4.8 (1.6) ml/kg, mean (SD) normocapnia group: 4.4 (1.5) ml/kg | Hypercapnia: PV versus control: PV + extracorporeal CO2 removal | Hospital deaths |
| Study                        | Study design, sample size | Definition of hypercapnia, PaCO₂ mmHg | Tidal volume used | Type of mechanical ventilation | Hospital deaths |
|------------------------------|---------------------------|---------------------------------------|-------------------|--------------------------------|----------------|
| Pereira Romano et al. (2020) | RCT (N=31)                | Definition: NA mean (SD) hypercapnia group: 59.5 mmHg, mean (SD) normocapnia group: 49.1 mmHg | Mean (SD) hypercapnia group: 4.3 (0.5) ml/kg, mean (SD) normocapnia group: 5.8 (0.5) ml/kg | Hypercapnia: PV versus PV + reduced driving pressure | 7/16 8/15       |
| Schmidt et al. (2020) [40]   | Observational (N=83)      | Definition: NA mean (SD) hypercapnia group: 57 (50–68) mmHg | Mean (SD) hypercapnia group: 6:0 (5:7–6:4) ml/kg | Hypercapnia: PV versus control: PV + extracorporeal CO2 removal | 30/83 NA        |
| Shimoda et al. (2021) [41]   | Observational (Cross over, not randomized) (N=6) | Definition: ≥ 45 mmHg, mean (SD) hypercapnia group: 55.9±7.9 mmHg, mean (SD) normocapnia group: 46.3±6.8 mmHg | Mean (SD) hypercapnia group: 6.8±1.2 ml/kg, mean (SD) normocapnia group: 6.6±1.3 ml/kg | Hypercapnia: PV versus control: PV + removal of catheter mount and heat-and-moisture exchanger | 6/21 NA |
| Winiszewski et al. (2018) [42] | Observational (Cross over, not randomized) (N=16) | Definition: Median (IQR) hypercapnia group: 50.3 [45.8—56.3] mmHg, median (IQR) normocapnia group: 42.0 [36.0–57] mmHg | Mean (SD) hypercapnia group: 5.3 [4.4–5.9] ml/kg, mean (SD) normocapnia group: 3.9 [3.5–4.2] ml/kg | Hypercapnia: PV versus control: PV + extracorporeal CO2 removal | 5/16 NA |

**Permissive hypercapnia**

| Study                        | Study design, sample size | Definition of hypercapnia, PaCO₂ mmHg | Tidal volume used | Type of mechanical ventilation | Hospital deaths |
|------------------------------|---------------------------|---------------------------------------|-------------------|--------------------------------|----------------|
| Amato et al. (1995) [19]     | RCT (N=28)                | Definition: ≥ 38 mmHg, mean (SD) hypercapnia group: 53 (3) mmHg, mean (SD) normocapnia group: 34 (2) mmHg | Mean (SD) hypercapnia group: 311 (23) ml, mean (SD) normocapnia group: 781 (27) ml | Hypercapnia: PV versus NPV | 5/15 7/13       |
| Amato et al. (1998) [20]     | RCT (N=53)                | Definition: NA mean (SD) hypercapnia group: 58.2 (33) mmHg, mean (SD) normocapnia group: 35.7 (17) mmHg | Mean (SD) hypercapnia group: 362 (11) ml, mean (SD) normocapnia group: 763 (26) ml | Hypercapnia: PV versus NPV | 13/29 17/24     |
| Feihl et al. (2000) [24]     | Observational (N=8)       | Definition: NA mean (SD) hypercapnia group: 67 (4) mmHg, normocapnia group: 45 (3) mmHg | Mean (SD) Hypercapnia group: 6.5 (1.2) ml/kg, normocapnia group: 10.3 (1.9) ml/kg | Hypercapnia: PV versus NPV in cross-over | NA NA |
| Gentilello et al. (1995) [25] | Observational (N=39)     | Definition: ≥ 45 mmHg, mean (SD) hypercapnia group: 63 (5.8) mmHg, mean (SD) normocapnia group: 41 (15) mmHg | Mean (SD), NPV at ARDS onset: 927 (11) ml, Mean (SD), PV at PV onset: 845 (180) ml | Hypercapnia: PV versus NPV | 1/11 12/23   |
### Table 1 (continued)

| Study                     | Study design, sample size | Definition of hypercapnia, \(\text{PaCO}_2\) mmHg | Tidal volume used | Type of mechanical ventilation | Hospital deaths |
|---------------------------|---------------------------|--------------------------------------------------|-------------------|--------------------------------|------------------|
|                           |                           | Mean (SD) hypercapnia group: 51 (10) mmHg, mean (SD) normocapnia group: 36 (6) mmHg | Mean (SD) hypercapnia group: 9 (2) ml/kg, mean (SD) normocapnia group: 13 (2) ml/kg | Hypercapnia: PV versus NPV | 12/37 21/33 |
| Jardin et al. (1999) [45] | Observational (\(N=70\)) | Definition: ≥ 50 mmHg, mean (SD) hypercapnia group: 76.4 (4) mmHg, mean (SD) normocapnia group: 45 (1) mmHg | Mean (SD) hypercapnia group: 414 (27) ml, mean (SD) normocapnia group: 679 (51) ml | Hypercapnia: PV versus NPV | 4/7 NA |
| Kalfon et al. (1997) [28] | Observational (Cross over, not randomized) (\(N=7\)) | Definition: NA | Mean (SD) hypercapnia group: 7.7 (0.5) ml/kg, mean (SD) normocapnia group: 9.9 (0.5) ml/kg | Hypercapnia: PV versus NPV | NA NA |
| McIntyre et al. (1994) [29] | Observational (Cross over, not randomized) (\(N=15\)) | Definition: NA | Mean (SD) hypercapnia group: 61 (12) mmHg, mean (SD) normocapnia group: 38 (6) mmHg | Hypercapnia: PV versus NPV | 9/12 NA |
| Pfeiffer et al. (2002) [31] (with shock) | Observational (Cross over, not randomized) (\(N=12\)) | Definition: NA | Mean (SD) hypercapnia group: 7.3 (0.6) ml/kg, mean (SD) normocapnia group: 10.5 (0.6) ml/kg | Hypercapnia: PV versus NPV | 5/10 NA |
| Pfeiffer et al. (2002) [31] (without shock) | Observational (Cross over, not randomized) (\(N=10\)) | Definition: NA | Mean (SD) hypercapnia group: 63 (11) mmHg, mean (SD) normocapnia group: 38 (6) mmHg | Hypercapnia: PV versus NPV | NA NA |
| Thorens et al. (1996) [32] | Observational (Cross over, not randomized) (\(N=11\)) | Definition: NA | Mean (SD) hypercapnia group: 8.2 + 4.1 ml/kg, mean (SD) normocapnia group: 13.5 + 6.1 ml/kg | Hypercapnia: PV versus NPV | NA NA |

CI confidence interval, HP high positive end-expiratory pressure, HR high respiratory rate, IQR interquartile range, LP low positive end-expiratory pressure, LR low respiratory rate, PV lung protective ventilation, NPV non-protective ventilation, NR not reported, Q quality of life data, RCT randomized controlled trial, PO prospective observational, SD standard deviation, SE standard error, TI thiopental and isoflurane, VT tidal volume, USA United States of America, UK United Kingdom

*a* This study was excluded from the meta-analysis for mortality because among 13 patients with hypercapnia at day-1, most (10) had transient hypercapnia, with only three patients (< 1%) with sustained hypercapnia at day-3; no other study reported data on imposed hypercapnia in patients with NPV, precluding any further analysis of imposed hypercapnia under NPV

*b* NPV data were not considered for the meta-analysis because they were obtained at zero end-expiratory pressure, followed by a pressure-volume curve

*c* Nine missing values for PaCO₂

*d* Studies of patients with COVID19-related ARDS
| (1) Author and year          | D1 Risk of bias arising from the randomization process | D2 Risk of bias due to deviations from the intended interventions | D3 Missing outcome data | D4 Risk of bias in measurement of the outcome | D5 Risk of bias in selection of the reported result | Overall |
|------------------------------|------------------------------------------------------|---------------------------------------------------------------|-------------------------|---------------------------------------------|-------------------------------------------------|---------|
| Amato et al. (1995) [19]     | High                                                 | Some concerns                                                 | Some concerns           | Some concerns                               | Some concerns                                   | Some concerns                                 |
| Amato et al. (1998) [20]     | Some concerns                                        | Some concerns                                                 | Some concerns           | Some concerns                               | Some concerns                                   | Some concerns                                 |
| Pereira Romano et al. (2020) [43] | Low                                                 | Low                                                           | Some concerns           | Low                                         | Low                                             | Low                                             |

| (2) Author and year          | D1 Risk of bias arising from the randomization process | D5 Risk of bias arising from period and carryover effects | D2 Risk of bias due to deviations from the intended interventions | D3 Risk of bias due to missing outcome data | D4 Risk of bias in measurement of the outcome | D5 Risk of bias in selection of the reported result | Overall |
|------------------------------|------------------------------------------------------|----------------------------------------------------------|---------------------------------------------------------------|---------------------------------------------|---------------------------------------------|-------------------------------------------------|---------|
| Mekontso Dessap et al. (2009) [22] | Low                                                 | Low                                                      | Some concerns                                                 | Low                                         | Some concerns                               | Low                                             | Low                                             |

| (3) Author and year          | Selection bias                                       | Judgment Study design                                      | Judgment Confounders                                           | Judgment Blinding                          | Judgment Data collection                      | Judgment Withdrawals                           | Judgment Global rating                         | Judgment Withdrawals                            | Judgment Overall                               |
|------------------------------|------------------------------------------------------|----------------------------------------------------------|---------------------------------------------------------------|---------------------------------------------|---------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|
| Aguirre-Bermudez et al. (2016) [30] | Moderate                                             | Strong                                                   | Strong                                                         | Moderate                                    | None                                        | Strong                                         | Moderate                                        | One withdrawal                                 | One "Weak" rating                              |
| Bellani et al. (2016) [21]   | Moderate                                             | Weak                                                     | Uncontrolled study                                             | Moderate                                    | Not described                               | Strong                                         | Moderate                                        | Withdrowals not reported                        | Strong                                         |
| COVID-ICU (2021) [44]        | Strong                                               | Strong                                                   | Strong                                                         | Moderate                                    | None                                        | Strong                                         | Moderate                                        | 399 withdrawal                                 | One "Weak" rating                              |
| Ding et al. (2021) [33]      | Strong                                               | Weak                                                     | Uncontrolled study                                             | Moderate                                    | None                                        | Strong                                         | Moderate                                        | Withdrowals not reported                        | Weak                                           |

Two "weak" ratings
| (3) Author and year | Selection bias | Judgement | Study design | Confounders | Judgement | Blinding | Judgement | Data collection | Withdrawals | Judgment | Global rating | Judgement |
|---------------------|----------------|-----------|--------------|-------------|-----------|----------|-----------|----------------|-------------|----------|--------------|-----------|
| Feihl et al. (2000) [24] | Strong | Participants are representative of the target population | Weak | Uncontrolled study | Weak | Control of confounders was not described | Moderate | Not described | Strong | Data collection tools are valid and reliable | Moderate | Withdrawals not reported | Weak | Two 'weak' ratings |
| Gentiliello et al. (1995) [25] | Strong | Participants are representative of the target population | Strong | controlled study | Strong | Control of confounders was described | Moderate | Not described | Strong | Data collection tools are valid and reliable | Moderate | Withdrawals not reported | Strong | No 'weak' rating |
| Hickling et al. (1990) [26] | Strong | Participants are representative of the target population | Weak | Uncontrolled study | Weak | Control of confounders was not described | Moderate | Not described | Strong | Data collection tools are valid and reliable | Moderate | Withdrawals not reported | Weak | Two 'weak' ratings |
| Hickling et al. (1994) [27] | Strong | Participants are representative of the target population | Weak | Uncontrolled study | Weak | Control of confounders was not described | Moderate | Not described | Strong | Data collection tools are valid and reliable | Moderate | Withdrawals not reported | Weak | Two 'weak' ratings |
| Husain-Syed et al. (2020) [34] | Moderate | Participants are likely to be representative of the target population | Moderate | Subject are their own controls | Weak | Control of confounders was not described | Moderate | None | Strong | Data collection tools are valid and reliable | Strong | No withdrawals | Weak | Two 'weak' ratings |
| Jardin et al. (1999) [45] | Strong | Participants are representative of the target population | Strong | controlled study | Weak | Control of confounders was not described | Moderate | Not described | Strong | Data collection tools are valid and reliable | Moderate | Withdrawals not reported | Moderate | One 'weak' rating |
| Kahl et al. (2021) [35] | Strong | Participants are representative of the target population | Strong | controlled study | Strong | Control of confounders was described | Moderate | Not described | Strong | Data collection tools are valid and reliable | Moderate | Four withdrawals | Strong | No 'weak' ratings |
| Kalfon et al. (1997) [28] | Strong | Participants are representative of the target population | Weak | Uncontrolled study | Weak | Control of confounders was not described | Moderate | Not described | Strong | Data collection tools are valid and reliable | Moderate | Withdrawals not reported | Weak | Two 'weak' ratings |
| Author and year         | Selection bias | Study design | Judgment Confounders | Blinding | Data collection | Judgment Withdrawals | Judgment Global rating | Judgment |
|------------------------|----------------|--------------|----------------------|----------|----------------|----------------------|------------------------|----------|
| Kregenow et al. (2006) | Strong         | Strong       | Strong               | Control of confounders was described | Moderate | Strong         | Data collection tools are valid and reliable | Strong   |
| Liu et al. (2020)      | Moderate       | Weak         | Uncontrolled study   | Control of confounders was not described | Moderate | Blinding none  | Data collection tools are valid and reliable | Strong   |
| Lotz et al. (2021)     | Moderate       | Weak         | Subject are their own controls | Control of confounders was not described | Moderate | Blinding none  | Data collection tools are valid and reliable | Strong   |
| McIntyre et al. (1994) | Strong         | Weak         | Uncontrolled study   | Control of confounders was not described | Moderate | Blinding is not described | Data collection tools are valid and reliable | Strong   |
| Mekontso Dessap et al. (2016) | Strong | Weak       | Uncontrolled study   | Control of confounders was described | Moderate | Blinding is not described | Data collection tools are valid and reliable | Strong   |
| Nin et al. (2017)      | Strong         | Weak         | Uncontrolled study   | Control of confounders was described | Moderate | Blinding is not described | Data collection tools are valid and reliable | Moderate |
| Pan et al. (2020)      | Moderate       | Weak         | Uncontrolled study   | Control of confounders was not described | Moderate | Blinding is not described | Data collection tools are valid and reliable | Moderate |
| Petran et al. (2020)   | Moderate       | Weak         | Uncontrolled study   | Control of confounders was described | Moderate | Blinding none  | Data collection tools are valid and reliable | Moderate |
| (3) Author and year | Selection bias | Judgment Study design | Judgment Confounders | Judgment Blinding | Judgment Data collection | Judgment Withdrawals | Judgment Global rating | Judgment |
|---------------------|----------------|-----------------------|---------------------|-------------------|-------------------------|----------------------|-----------------------|---------|
| Pfeiffer et al. (2002) [31] | Strong | Participants are representative of the target population | Weak | Uncontrolled study | Weak | Control of confounders was not described | Moderate | Blinding is not described | Strong | Data collection tools are valid and reliable | Moderate | Withdrawals not reported | Weak | Two ‘weak’ ratings |
| Schmidt et al. (2020) [40] | Strong | Participants are representative of the target population | Weak | Uncontrolled study | Strong | Control of confounders was described | Moderate | Blinding is not described | Strong | Data collection tools are valid and reliable | Moderate | Withdrawals not reported | Moderate | One ‘Weak’ rating |
| Shimoda et al. (2021) [41] | Moderate | Participants are likely to be representative of the target population | Weak | Subject are their own controls | Weak | Control of confounders was not described | Moderate | Blinding is not described | Strong | Data collection tools are valid and reliable | Moderate | Four withdrawals | Weak | Two ‘weak’ ratings |
| Thorens et al. (1996) [32] | Strong | Participants are representative of the target population | Weak | Uncontrolled study | Weak | Control of confounders was not described | Moderate | Blinding is not described | Strong | Data collection tools are valid and reliable | Moderate | Withdrawals not reported | Weak | Two ‘weak’ ratings |
| Winiszewski et al. (2018) [42] | Moderate | Participants are likely to be representative of the target population | Weak | Uncontrolled study | Weak | Control of confounders was not described | Moderate | Blinding none | Strong | Data collection tools are valid and reliable | Moderate | Withdrawals not reported | Weak | Two ‘weak’ ratings |

D1 Domain 1; D2 Domain 2; D3 Domain 3; D4 Domain 4; D5 Domain 5; DS Domain S
imposed hypercapnia under NPV were reported in eight studies (218 patients) [19, 20, 22, 24, 25, 29, 31, 32], 21 studies (9514 patients) [5, 11, 21–23, 26–28, 30, 33–44] and one (369 patients) [11] study, respectively. The latter study [11] was unique for imposed hypercapnia in NPV and reported <1% (3/369) patients with sustained PaCO₂ > 45 mmHg, precluding any further analysis of imposed hypercapnia under NPV.

Clinical consequences of acute hypercapnia

Mortality

Data for mortality were reported for hypercapnic and non-hypercapnic groups in three studies with permissive hypercapnia (157 patients) [19, 25, 45], and six others with imposed hypercapnia under PV (9,096 patients) [5, 11, 21, 23, 43, 44]. Studies testing permissive hypercapnia reported a lower mortality in hypercapnic patients receiving PV compared to non-hypercapnic patients receiving NPV (OR for random effect model = 0.26, 95% CI [0.07–0.89]). By contrast, studies reporting imposed hypercapnia under PV reported increased mortality in hypercapnic patients receiving PV as compared to non-hypercapnic patients receiving PV (OR for random effect model = 1.54, 95% CI [1.15–2.07]).

Hemodynamics

The impact of hypercapnia on hemodynamic parameters was reported in seven studies [19, 22, 24, 28, 29, 31, 32] involving 102 patients (see Fig. 4). Permissive hypercapnia induced an increase in cardiac index/output [19, 24, 31, 32], which could be due to increased systemic vasodilation as evidenced by a decrease in systemic vascular resistances [29, 31, 32]. This increased cardiac index was associated with: (i) an increase in pulmonary shunt [24, 28, 31] (see Fig. 4), with deterioration in gas exchange [24, 28] in all but one [19] study reporting shunt data; (ii) increased pulmonary pressures [19, 24, 31, 32], but no significant change in pulmonary vascular resistances [24, 29, 31, 32]. During PV, imposed hypercapnia was associated with conflicting effects on cardiac index [22, 28] and worsened pulmonary vascular function [22, 28].

Discussion

To the best of our knowledge, we herein report the first review of the literature with meta-analysis on the clinical consequences of hypercapnia in adult patients with ARDS, with the following findings: (i) the clinical effects of hypercapnia were conflicting depending on the mechanism of hypercapnia; (ii) permissive hypercapnia was associated with improved survival whereas imposed hypercapnia under PV worsened mortality, suggesting a major role of the PV strategy on the outcome and indicating imposed hypercapnia as a marker of ARDS severity; (iii) permissive hypercapnia was associated with increased cardiac index whereas imposed hypercapnia yielded conflicting results with worsened lung vascular function.

Conflicting role of hypercapnia

Complex findings were observed across literature. From these findings, it appeared that hypercapnia is protective when driven by lower VT, but is associated with increased mortality when imposed at lower VT (targeting 6 ml/kg predicted body weight). Overall, PV is probably driving the protective effect of permissive hypercapnia, in accordance with observational cohorts [5], randomized trials [1] and recommendations [46]. By contrast, the association of imposed hypercapnia under PV with increased mortality indicates it could be a marker of ARDS severity and/or have own detrimental effects. The former point is in accordance with studies suggesting pulmonary dead space as a strong prognostic factor in ARDS [47]. The latter point is corroborated by the finding of more renal and cardiac failure in patients with imposed hypercapnia under PV [5]. The main hemodynamic effect of imposed hypercapnia under PV relates to pulmonary vascular dysfunction, with pulmonary hypertension and RV dysfunction, which could trigger or worsen renal failure via a decreased cardiac output and/or an increased congestion [48]. This pulmonary vasoconstrictive effect of hypercapnia is in accordance with previous data in critically ill patients with [49] or without [50] ARDS.

Altogether, our findings suggest that, in the clinical setting, (i) permissive hypercapnia to achieve PV should be preferred to normocapnia under NPV; (ii) normocapnia under PV could be preferred to imposed hypercapnia.
under PV. However, we are still lacking randomized trials to assess if mitigating imposed hypercapnia under PV via reduced CO₂ production (e.g., hypothermia) or increased elimination (e.g., increased respiratory rate, and/or decreased instrumental dead space) alters clinical outcomes. Whether the use of extracorporeal CO₂ removal for imposed hypercapnia under PV may improve outcomes [51] also require further studies.

Future studies are similarly necessary to scrutinize the prognostic role of increased PaCO₂ generated by ultra-protective ventilation (UPV i.e. \( V_T \) targeting 3–4 ml/kg of predicted body weight), as compared to PV (i.e. \( V_T \) targeting 6 ml/kg of predicted body weight), and its potential mitigation by extracorporeal CO₂ removal [52].

In the recent REST randomized clinical trial, the use of extracorporeal CO₂ removal to facilitate UPV, compared with PV, did not significantly reduce 90-day mortality and was associated with more serious adverse events [53].

### Strengths and limitations

Strengths of our study include the wide period of assessment and selection process. Our search ended in 2021, and little new information has been published since on this topic, including for COVID-19-related ARDS. One limitation is the lack of standardization in the definition and duration of hypercapnia. However, we performed a subgroup analysis to scrutinize the respective roles of permissive and imposed hypercapnia. We cannot exclude that some part of the permissive...
hypercapnia in studies of PV is due to ARDS severity. There was heterogeneity among studies concerning their design (prospective or retrospective), tidal volume under PV (especially in observational cohorts), reporting of tidal volume related to predicted body weight, and hypercapnia definition. In addition, other potential confounding factors that might be associated with both hypercapnia and mortality were not taken into account. Last, we used the Berlin definition for ARDS, which was published after many studies included in the meta-analysis. However, included patients with acute lung injury before the Berlin definition were considered as having mild ARDS.

**Conclusion**

We performed a systematic review and meta-analysis of a wide population of adult patients with ARDS, and found conflicting clinical effects of hypercapnia depending on its mechanism. The favorable effects of permissive hypercapnia seemed driven by the associated PV, with improved hemodynamics. On the contrary, imposed hypercapnia under PV was associated with a worse outcome.
### A) Cardiac index (L/mm²/m²)

| Study   | PA/Pm, Hypocapnia Total Mean | SD | Mean Difference | MD  | 95% CI  |
|---------|-------------------------------|----|----------------|-----|--------|
| Group 1 permissive | 15 5.73 0.4700 | 13 4.80 0.4300 | 0.93 [0.60; 1.26] |
| Feihi 2000 | 8 5.10 0.5000 | 6 3.70 0.4000 | 1.40 [0.95; 1.84] |
| Pfeiffer 2002 (without shock) | 10 5.40 1.0000 | 10 3.50 0.9000 | 1.50 [0.97; 2.32] |
| Pfeiffer 2002 (with shock) | 12 6.00 1.0000 | 12 5.40 1.0000 | 0.60 [-0.33; 1.35] |
| Thonias 1996 | 11 4.70 2.7000 | 11 4.00 2.4000 | 0.70 [-1.43; 2.83] |
| Random effects model | 56 54 | 54 | 1.11 [0.56; 1.55] |

**Heterogeneity:** $I^2 = 10\%$, $Q = 0.0562$, $p = 0.30$

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### B) Pulmonary artery pressure, mean (mmHg)

| Study                     | PA/Pm, Hypocapnia Total Mean | SD | Mean Difference | MD  | 95% CI  |
|---------------------------|-------------------------------|----|----------------|-----|--------|
| Group 1 permissive        | 15 30.10 1.3000 | 13 27.40 2.2000 | 2.70 [1.34; 4.06] |
| Feihi 2000                | 8 32.00 4.0000 | 6 28.00 4.0000 | 4.00 [2.80; 5.20] |
| Pfeiffer 2002 (without shock) | 10 31.00 4.0000 | 10 25.00 4.0000 | 4.00 [2.80; 5.20] |
| Pfeiffer 2002 (with shock) | 12 32.00 7.0000 | 12 28.00 7.0000 | 4.00 [2.80; 5.20] |
| Thonias 1996              | 11 32.00 6.0000 | 11 29.00 5.0000 | 2.00 [2.30; 3.54] |

**Heterogeneity:** $I^2 = 0\%$, $Q = 0.0351$, $p = 0.97$

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### C) Pulmonary vascular resistance, mean (dynes.s.cm⁻²)

| Study                     | PVG, Hypocapnia Total Mean | SD | Mean Difference | MD  | 95% CI  |
|---------------------------|-------------------------------|----|----------------|-----|--------|
| Group 1 permissive        | 8 311.00 46.0000 | 8 344.00 39.0000 | -23.00 [-37.49; 7.89] |
| Feihi 2000                | 15 228.00 36.0000 | 15 276.00 39.0000 | -48.00 [-74.86; -21.14] |
| Pfeiffer 2002 (without shock) | 10 171.00 59.0000 | 10 152.00 56.0000 | -21.00 [-72.38; 30.32] |
| Pfeiffer 2002 (with shock) | 12 130.00 48.0000 | 12 133.00 56.0000 | 6.00 [-33.15; 47.73] |
| Thonias 1996              | 11 209.00 114.0000 | 11 208.00 115.0000 | 1.00 [94.69; 95.69] |

**Heterogeneity:** $I^2 = 22\%$, $Q = 2.389.5472$, $p = 0.27$

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### D) Pulmonary shunt

**Qs/Qt (%): fraction of total cardiac output flowing through the shunt**

| Study                     | Qs/Qt (%), Hypocapnia Total Mean | SD | Mean Difference | MD  | 95% CI  |
|---------------------------|-------------------------------|----|----------------|-----|--------|
| Group 1 permissive        | 8 48.00 5.0000 | 8 32.00 6.0000 | 16.00 [10.59; 21.41] |
| Feihi 2000                | 10 34.00 10.0000 | 10 24.00 6.0000 | 10.00 [-1.86; 21.86] |
| Pfeiffer 2002 (without shock) | 12 36.00 17.0000 | 12 28.00 16.0000 | 13.37 [3.84; 24.70] |
| Pfeiffer 2002 (with shock) | 30 30 | 30 | 8.00 [-5.21; 21.21] |
| Thonias 1996              | 48 | 48 | 13.37 [-3.75; 30.44] |

**Heterogeneity:** $I^2 = 0\%$, $Q = 6.3901$, $p = 0.41$

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### E) Systemic vascular resistance, mean (dynes.s.cm⁻²)

| Study                     | SVR, Hypocapnia Total Mean | SD | Mean Difference | MD  | 95% CI  |
|---------------------------|-------------------------------|----|----------------|-----|--------|
| Group 1 permissive        | 15 759.00 70.0000 | 15 879.00 53.0000 | -110.00 [-170.78; -49.22] |
| Feihi 2000                | 15 566.00 138.0000 | 15 737.00 256.0000 | -231.00 [-399.41; -42.62] |
| Pfeiffer 2002 (without shock) | 15 446.00 172.0000 | 15 520.00 136.0000 | -84.00 [-208.06; 36.06] |
| Pfeiffer 2002 (with shock) | 12 685.00 265.0000 | 12 866.00 454.0000 | -217.00 [-527.66; 93.66] |
| Thonias 1996              | 48 | 48 | -125.00 [-247.32; 95.65] |

**Heterogeneity:** $I^2 = 0\%$, $Q = 0.84$
Supplementary Information
The online version contains supplementary material available at https://doi.org/10.1007/s00134-022-06640-1.

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Acknowledgements
We thank Baxter for support for data extraction and the Reva network and COVID-ICU investigators for data provision.

Author contributions
AMD and AVB designed the meta-analysis. SG, TP, GG and AMD searched for the articles, screened titles and abstracts and extracted data. SG, TP, GG and AMD performed statistical analysis and interpretation of data. SG, TP, GG and AMD drafted the manuscript, and all authors revised it for important intellectual content. Final approval of the version submitted for publication was obtained for all authors.

Declarations
Conflicts of interest
On behalf of all authors, the corresponding author states that there is no conflict of interest.

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Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Received: 1 October 2021   Accepted: 3 February 2022

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