Effect of Lower Tidal Volume Ventilation Facilitated by Extracorporeal Carbon Dioxide Removal vs Standard Care Ventilation on 90-Day Mortality in Patients With Acute Hypoxemic Respiratory Failure

Effect of lower tidal volume ventilation facilitated by extracorporeal carbon dioxide removal versus standard care ventilation on 90-day mortality in patients with acute hypoxemic respiratory failure

The REST Randomized Clinical Trial

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Running Head

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Key points

Question: In adults with acute hypoxemic respiratory failure receiving mechanical ventilation, does further reduction in tidal volumes, facilitated by extracorporeal carbon dioxide removal, improve 90-day mortality when compared to conventional low tidal volume ventilation?

Findings: In this randomized clinical trial that included 412 adults, 90-day mortality was 41.5% in the extracorporeal carbon dioxide removal group and 39.5% for standard care, a difference that was not statistically significant.

Meaning: Among patients with acute hypoxemic respiratory failure, the use of extracorporeal carbon dioxide removal to facilitate lower tidal volume ventilation, compared with conventional low tidal volume ventilation, did not significantly reduce 90-day mortality.

Abstract

Importance: In patients who require mechanical ventilation for acute hypoxemic respiratory failure, further reduction in tidal volumes compared to conventional low tidal volume ventilation may improve outcomes.

Objective: To determine whether lower tidal volume mechanical ventilation using extracorporeal carbon dioxide removal improves outcome in patients with acute hypoxemic respiratory failure.

Design, Settings and Participants: The trial was a multicentre, randomized, allocation concealed, open-label, pragmatic clinical trial. 412 adult patients receiving mechanical ventilation for acute hypoxemic respiratory failure out of a planned sample size of 1120 patients were enrolled between May 2016 and December 2019 from 51 intensive care units in the UK. Follow up continued until 11th March 2020.

Interventions: Participants were randomly assigned to receive lower tidal volume ventilation facilitated by extracorporeal carbon dioxide removal for at least 48 hours (n=202) or standard care with conventional low tidal volume ventilation (n=210).

Main Outcomes and Measures: The primary outcome was all cause mortality at 90 days after randomization. Prespecified secondary outcomes included ventilator-free days at 28 days and adverse event rates.

Results: Among 412 patients who were randomized (mean age, 59 years; 143 (35%) women), 405 (98%) completed the trial. The trial was stopped early because of futility and feasibility following recommendations from the Data Monitoring and Ethics Committee. The 90-day

mortality was 41.5% in the lower tidal volume ventilation with extracorporeal carbon dioxide removal group versus 39.5% in the standard care group (risk ratio 1.1; 95% confidence interval (CI) 0.8 to 1.3; difference 2.0%, 95% CI -7.6% to 11.5%; P=0.68). There were significantly fewer ventilator-free days in the extracorporeal carbon dioxide removal group compared with the standard care group (mean 7.1 95% CI 5.9 to 8.3 v 9.2 95% CI 7.9 to 10.4 days, mean difference -2.1; 95% CI -3.8 to -0.3; P=0.02).

Serious adverse events were reported for 62 (31%) patients in the extracorporeal carbon dioxide removal group and 18 (9%) in the standard care group, including intracranial hemorrhage in 9 (4.5%) vs 0 (0%) respectively, and bleeding at other sites in 6 (3.0%) vs 1 (0.5%) respectively. Overall, 21 patients experienced 22 serious adverse events related to the study device.

Conclusions and Relevance: Among patients with acute hypoxemic respiratory failure, the use of extracorporeal carbon dioxide removal to facilitate lower tidal volume mechanical ventilation, compared with conventional low tidal volume mechanical ventilation, did not significantly reduce 90-day mortality. However, due to the early termination the study may have been underpowered to detect a clinically important difference.

Trial Registration: ClinicalTrials.gov identifier NCT02654327

Introduction

Acute hypoxemic respiratory failure is a leading cause of admission to intensive care units (ICUs) and is associated with significant mortality and long-term morbidity for survivors, as well as considerable resource implications for healthcare systems.[1] A significant proportion of affected patients by acute hypoxemic respiratory failure will meet the diagnostic criteria for acute respiratory distress syndrome (ARDS).[2] Invasive mechanical ventilation following tracheal intubation is often used as a life-saving intervention to maintain adequate gas exchange but is known to contribute to the overall morbidity and mortality of this condition.[3]

One of the few interventions shown to reduce mortality in patients with acute hypoxemic respiratory failure and ARDS is ventilation with a lung-protective strategy aiming for a tidal volume of 6 mL/kg predicted body weight and a plateau pressure less than or equal to 30 cmH_2O in patients[4]. However, even when using lung-protective invasive mechanical ventilation, lung hyperinflation and injury can still occur.[5] Reducing tidal volumes further may result in respiratory acidosis which can cause further adverse effects such as pulmonary hypertension and altered cardiac function. Extracorporeal gas exchange, including extracorporeal carbon dioxide removal ($ECCO_2R$), can facilitate mechanical ventilation with even lower tidal volumes, as it supports the removal of carbon dioxide that accumulates in this setting.[6,7] The feasibility of $ECCO_2R$ in patients with acute hypoxemic respiratory failure due to ARDS has recently been demonstrated.[8]

The primary objective of the REST trial was to determine whether lower tidal volume ventilation facilitated by $ECCO_2R$ compared with standard care in patients with acute hypoxemic respiratory failure decreased mortality 90 days after randomization.[9]

Methods

Trial design and oversight

This was a multicentre, randomized, allocation concealed, open-label, pragmatic clinical trial. After randomization, patients, clinical care clinicians, and researchers were unblinded due to the complex nature of the intervention. The trial was coordinated by the Northern Ireland Clinical Trials Unit and was sponsored by Belfast Health and Social Care Trust. The study design has been published,[9] and the trial protocol and statistical analysis plan (SAP) are provided in supplement 1 and 2. The protocol was approved by research ethics committees in England, Wales and Northern Ireland (16/SC/089), and Scotland (16/SS/048). The National Institute for Health Research in the UK convened an independently chaired (and majority independent) Trial Steering Committee and an independent Data Monitoring and Ethics Committee (DMEC). The study was conducted in accordance with Good Clinical Practice guidelines, local regulations, and the ethical principles described in the Declaration of Helsinki. Written informed consent from patients or agreement from their surrogates was obtained in keeping with regional regulations.

Sites and patients

The trial was conducted in 51 adult, general ICUs within the National Health Service across the United Kingdom. Patients aged at least 16 years and admitted to a participating ICU were eligible for inclusion if: they had an acute and potentially reversible cause of moderate to severe hypoxemic respiratory; were receiving invasive mechanical ventilation using at least 5 cmH_2O of positive end-expiratory pressure (PEEP) and were within 48 hours of onset of hypoxemia defined as a ratio of the partial pressure of oxygen in arterial blood to the fractional inspired concentration of oxygen ratio (PaO_2/FiO_2) of less than 150 mmHg. Exclusion criteria included invasive mechanical ventilation greater than 7 days, contraindication to limited systemic anticoagulation with heparin, untreated pulmonary embolism, pleural effusion or pneumothorax or acute respiratory failure fully explained by

left ventricular failure or fluid overload. Other reasons for exclusion are detailed in the trial protocol in supplement 1.

Randomization

After obtaining consent eligible patients were randomized. Allocation concealment was achieved by use of an automated online or telephone centralised 24-hour randomization facility. Patients were allocated to lower tidal volume ventilation with $ECCO_2R$ or lung protective ventilation alone in a 1:1 randomization ratio using a computer-generated schedule with a variable block size of 4, 6 and 8 stratified by recruitment centre. If allocated to $ECCO_2R$, this was recommended to commence within 8 hours of randomization.

Interventions

In patients assigned to $ECCO_2R$, a dual-lumen catheter was inserted percutaneously into a central vein using ultrasound guidance. Veno-venous $ECCO_2R$ was then commenced using intravenous heparin as systemic anticoagulation to prevent circuit thrombosis. The pump speed was increased to achieve the maximum possible blood flow (typically 350-450mL/min) and sweep gas flow was increased to 10 L/min to maximise carbon dioxide removal and concomitantly tidal volumes were reduced incrementally aiming for a tidal volume less than or equal to 3 mL/kg predicted body weight. The intervention was continued for at least 48 hours after which patients were weaned off $ECCO_2R$ as per the trial manual, provided in supplement 3, when patients demonstrated signs of clinical improvement and improvement in the degree of hypoxemia. $ECCO_2R$ was to be used for a maximum of seven days as part of the study protocol. An online educational package for catheter insertion and device management was provided to all sites.

For patients randomized to standard care, it was recommended that patients were mechanically ventilated using a tidal volume of 6 mL/kg predicted body weight with PEEP

set based on the ARDSNetwork trial.[4] In addition, in keeping with UK guidelines,[10] patients in both the intervention and control groups could receive neuromuscular blocking drugs (NMBD),[11] prone positioning[12] or referral for consideration of extracorporeal membrane oxygenation (ECMO).[13]

Outcome measures

The primary outcome was all-cause mortality at 90 days after randomization. Secondary clinical outcome measures were tidal volume at day 2 and day 3, ventilator-free days at 28 days, duration of invasive mechanical ventilation in survivors, need for ECMO up to day 7, mortality at 28 days and adverse event rate. All outcomes were reported from time of randomization. Pre-specified clinical outcome measures are listed in Table S1. The additional outcomes not reported will be reported separately. A cost-effectiveness analysis is also planned as described in the protocol in supplement 1. Duration of critical care and hospital length of stay were defined as outcomes for the cost-effectiveness analysis. Data on physiological parameters by treatment group were also collected up to day 7.

Statistical analysis

A sample size of 1120 patients was determined to provide power of 90% to show an absolute difference of 9% in 90-day mortality assuming a control group mortality of 41%.[14] This postulated effect size was estimated from a previous trial on the use of lung protective ventilation[4] which demonstrated a 9% reduction in mortality in patients with hypoxaemic respiratory failure secondary to ARDS with a 50% reduction in tidal volume (from 12 to 6 mL/kg predicted body weight).[15] Therefore we hypothesised that a similar relative reduction in tidal volume would result in a 9% difference in mortality. The sample-size calculation did not take a group-sequential trial design into account.

Patients were analyzed according to their randomization group. For the primary outcome and other dichotomous outcomes, risk ratios and % point differences with 95% confidence intervals (CI) were calculated. The primary outcome of 90-day mortality was analyzed using a chi-square test and a secondary analysis using a log-binomial regression adjusted for age, sequential organ failure assessment (SOFA)[16] score and baseline PaO_2/FiO_2 ratio was also carried out. Plateau pressure was planned to be included as a variable in the adjusted analysis, however as it was missing in a substantial number of patients this was not possible. A post hoc sensitivity analysis using generalized estimating equations was used to account for possible clustering of observations within participating centers. There was no imputation for missing data. Continuous outcomes were compared between the two groups using analysis of variance/analysis of covariance adjusting for other covariates where appropriate. Time-to-event outcomes were analysed by survival methods and reported as hazard ratios with 95% CI. The proportionality assumption was tested using the Schoenfeld test. Length of stay outcomes were compared using the Wilcoxon rank sum test. A pre-specified sensitivity analysis was also performed for the primary outcome excluding the first two intervention group patients at each site in order to address potential learning effects. A per protocol analysis was carried out for the secondary outcome of tidal volume at days 2 and 3, i.e. including those who were receiving $ECCO_2R$ on day 2 and 3 in the intervention group. We performed pre-specified subgroup analyses using 99% confidence intervals. Log-binomial regression was used with interaction terms (treatment group by subgroup).

One interim analysis for the primary outcome was planned before the recruitment of 560 patients. A post hoc conditional power analysis was carried out estimating the power given the observed data up to termination and then assuming varying differences between 2% and 10% for the remainder of the data that was to be observed. Because of the potential for type 1 error due to multiple comparisons, findings for analyses of secondary endpoints should be interpreted as exploratory. Analysis was conducted using Stata®/SE Version 15.1 (StataCorp

LP, College Station, TX, USA). Statistical significance was defined using a 2-sided test with $\alpha = .05$.

Trial Termination

During a recruitment pause for investigation of a serious adverse event (SAE) (fatal intracranial hemorrhage), the planned interim analysis was undertaken and the independent DMEC recommended that the trial be stopped due to futility (given that even under optimistic assumptions the trial was unlikely to demonstrate a significant benefit for the intervention) and subsequent feasibility to continue the trial. There were no formal stopping rules for futility and the decision to stop the study was not based on a formal calculation of futility. The decision to stop was based on the opinion of the DMEC based on all available information including data from the interim analysis, feasibility of future recruitment and a conditional power analysis. The conditional power analysis to detect a difference between the groups, assuming the patients remaining to be recruited to achieve the planned sample size met the assumptions of the original sample size, was 44%. Safety was not cited by the DMEC as a reason for stopping the trial. This decision was accepted by the Trial Steering Committee and agreed by the study sponsor and the trial was stopped on 11th February 2020.

Results

Patients

From May 2016 to December 2019 a total of 7071 patients from 51 centres were screened for eligibility and after applying the exclusion criteria 412 (6%) participants were recruited (Table S2). The patients were followed up until 11th March 2020. One patient was randomized twice in error, 2 patients were lost to follow up and 4 withdrew consent for confirmation of vital status. As a result, 405 participants (200 intervention, 205 standard care) were included in the final analysis of the primary outcome. (Figure 1). The commonest

reasons for exclusion were contraindication to systemic anticoagulation, a “do not resuscitate” order in place, imminent treatment withdrawal, and invasive mechanical ventilation for more than 7 days. 28% of patients screened were excluded for “other reasons” for which the most common reason was either the patient’s clinical condition rapidly improved or it deteriorated. The baseline characteristics of the 2 groups were well balanced prior to randomization and typical of patients with moderate to severe acute hypoxemic respiratory failure requiring ICU care (Table 1).

Primary Outcome

There was no significant difference in mortality between the groups. The 90-day mortality was 41.5% (83/200) in the intervention group and 39.5% (81/205) in the standard care group (risk ratio (RR) 1.1, 95% CI 0.8 to 1.3; % point difference 2.0, 95% CI -7.6 to 11.5) (Table 2 and Figure 2). The RR was similar after adjustment for age, SOFA score and PaO_2/FiO_2 ratio (RR 1.1, 95% CI 0.9 to 1.4) and in a per-protocol analysis for the primary outcome of the cohort who initiated $ECCO_2R$ (Table 2). In order to address a potential learning effect with the intervention, a sensitivity analysis was performed excluding the first 2 patients allocated to intervention at each site (Table 2). These findings were consistent with the primary analysis. Treatment-by-subgroup interactions were not significant with respect the presence of ARDS, requirement for vasopressors, severity of hypoxemia or hypercapnia, plateau and driving pressures, APACHE II score and volume of $ECCO_2R$ by site (Figure S1). The proportion of missing data for the primary analysis of the primary outcome was 1.7%.

Secondary Outcomes

The secondary outcomes are presented in Table 2. There were significantly fewer ventilator-free days at 28 days in the intervention group (7.1 95% CI 5.9 to 8.3 v 9.2 95% CI 7.9 to 10.4 days; mean difference -2.1 days (95% CI, -3.8 to -0.3); p = 0.02). There was no significant

between-group difference in duration of ventilation, need for ECMO at day 7, mortality at 28 days or duration of ICU or hospital stay.

Additional Secondary Outcomes and Intervention Fidelity

Of the 202 patients allocated to the intervention, 186 patients (92%) received $ECCO_2R$ after randomization with a mean (standard deviation) duration of $ECCO_2R$ of 4 (2) days. One patient in the standard care group received non-protocol $ECCO_2R$ for 2 days. $ECCO_2R$ was successfully weaned in 50 (28%) patients and was stopped due to seven days treatment in 33 (18%). It was discontinued for safety reasons in 14 (8%), need for ECMO in 12 (7%) and withdrawal of active medical treatment or death in 28 (16%) patients (Table S3).
Patients randomized to receive $ECCO_2R$ had a lower tidal volume at day 2 (4.5 95% CI 4.3 to 4.8 v 6.5 95% CI 6.3 to 6.7; mean difference 2.0 mL/kg (95% CI 1.7-2.3) and day 3 (4.4 95% CI 4.1 to 4.6 v 6.7 95% CI 6.4 to 7.0; mean difference 2.3 mL/kg (95% CI 2.0-2.7). In patients receiving $ECCO_2R$ on day 2 and 3, tidal volume was lower at day 2 (4.2 95% CI 4.0 to 4.4 v 6.5 95% CI 6.3 to 6.7; mean difference 2.4 mL/kg (95% CI 2.0-2.7) and day 3 (3.8 95% CI 3.6 to 4.0 v 6.7 95% CI 6.4 to 7.0; mean difference 2.9 mL/kg (95% CI 2.5-3.3) (Figure 3A and Table S4).

During day 2 and 3 following randomization, patients in the intervention group had a lower PaO_2/FiO_2 ratio (147.8 95% CI 140.4 to 155.1 v 161.1 95% CI 153.3 to 169.0; mean difference on day 2 was 13.3 mmHg (95% CI 2.6-24.1) and on day 3 was 147.9 95% CI 140.9 to 154.9 v 167.0 95% CI 158.6 to 175.4; mean difference 19.1 mmHg (95% CI 8.2-30.1), Figure S2A and Table S4). Patients in the intervention group had higher PEEP than patients in the control group (Figure 3B and Table S4). Plateau pressure was lower in the intervention group on days 2 and 4 following randomization, (23.5 95% CI 22.6 to 24.3 v 25.7 95% CI 24.9 to 26.6; mean difference on day 2 was 2.3 cmH_2O (95% CI 1.1-3.4) and on day 4 was

22.2 95% CI 21.2 to 23.1 v 23.7 95% CI 22.6 to 24.8; mean difference 1.6 cmH_2O (95% CI 0.1-3.0), Figure 3C and Table S4). Driving pressure was lower in the intervention group from day 2 to 5 following randomization (Figure 3D and Table S4). Total respiratory rate was higher in the intervention group from day 2 to 4 following randomization (26.6 95% CI 25.8 to 27.3 v 24.6 95% CI 23.9 to 25.3; mean difference on day 2 was 2.0 breaths per minute (95% CI 0.9 - 3.0), on day 3 was 27.8 95% CI 26.9 to 28.7 v 24.4 95% CI 23.6 to 25.2; mean difference 3.4 breaths per minute (95% CI 2.2 – 4.6) and on day 4 was 27.0 95% CI 26.0 to 28.1 v 24.4 95% CI 23.5 to 25.4; mean difference 2.6 breaths per minute (95% CI 1.2-4.0), Figure S2B and Table S4). Minute ventilation was lower in the intervention group from day 1 following randomization (Figure S2C and Table S4). $PaCO_2$ was higher from day 2 following randomization (Figure S2D and Table S4) and pH was lower in the intervention group following randomization (Figure S2E and Table S4). The rate of CO2 removal is shown in Table S4.

Patients in the intervention group were more likely to be ventilated with a mandatory mode of ventilation to day 7 (59(39.1%) v 32(18.9%); % point difference 20.1(10.4 to 29.9) on day 7), received more neuromuscular blockade from day 2 following randomization (110(55.6%) v 92(44.2%); % point difference 11.3(1.7 to 21.0) on day 2), and were ventilated less frequently in the prone position on days 1 and 2 following randomization (11(5.5%) v 29(13.9%); % point difference -8.4(-14.0 to -2.8) on day 1 and 18(9.1%) v 27(13.0%); % point difference -3.9(-10.0 to 2.2) on day 2) (Table S5).

Serious Adverse Events

Adverse event rates are presented in Table 3. Adverse events were more common in the intervention group. Eighty patients experienced SAEs, with 62 (31%) patients in the intervention group and 18 (9%) in the standard care group. Twenty one patients experienced 22 SAEs related to the study device (Table S6). There were 12 events defined as intracranial

haemorrhage, of which 9 were defined as SAEs, all of which occurred in the intervention group. Of these, 5 SAEs were considered by the site investigator to be at least possibly related to the intervention (3 patients suffered an intracerebral haemorrhage and 2 patients had a subarachnoid hemorrhage). An additional 4 SAEs were considered by the site investigator to be unlikely related to the intervention (1 patient suffered an intracerebral haemorrhage and 3 had hemorrhagic changes on brain imaging). There were 21 events defined as bleeding at other sites, of which 7 were defined as SAEs with 6 occurring in the intervention group and 1 in the control group. Of those in the intervention group, 4 SAEs were considered by the site investigator to be at least possibly related to the intervention (airway bleeding, hemothorax in a patient with chest trauma, bleeding from a venous haemodialysis catheter and a haematoma at an attempted vascular access site). The additional 2 SAEs were considered by the site investigator to be unlikely related to the intervention (upper gastrointestinal bleeding and pharyngeal bleeding following re-intubation). The event in the control group was an episode of rectal bleeding.

Conditional Power Analysis

Post hoc conditional power analysis for mortality showed a conditional power of 4% for an 2% effect size, 8% for an 4% effect size, 17% for an 6% effect size, 31% for an 8% effect size and 48% for a 10% effect size.

Discussion

In this UK multi-centre randomized clinical trial that was stopped early due to futility, tidal volume reduction during invasive mechanical ventilation facilitated by $ECCO_2R$, compared to standard care in patients with acute hypoxemic respiratory failure, did not reduce mortality at

90 days.

The aim of supportive care with invasive mechanical ventilation in patients with acute hypoxemic respiratory failure during the last 20 years has moved away from targeting normal gas exchange to limiting ventilator-induced lung injury.[3,4] A secondary analysis of the ARMA trial suggested there may be no safe threshold for tidal volumes with *in-vivo* data providing biological plausibility for the benefit of further reduction in tidal volumes.[15,17] In the study a reduction in mean tidal volumes of 2.0 and 2.3 mL/kg at day 2 and 3 were achieved respectively, from a pre-randomization tidal volume of 6.6 mL/kg with significant reduction in tidal volumes to day 7 which were associated with significant reductions in plateau and driving pressures. It was mandated that the intervention was applied for at least 48 hours to ensure an effective "dose" of lower tidal volumes although it is possible that a longer duration of $ECCO_2R$, with greater tidal volume reduction, may have been required to demonstrate an effect as higher intensities of invasive mechanical ventilation have been shown to be associated with increased risk of death in a time-dependent fashion.[18] Duration of $ECCO_2R$ in the study was limited to less than 7 days due to regulations associated with use of the device and the intervention was discontinued in 33 patients for this reason. It is unknown if the results would have changed had these 18% of intervention patients received longer $ECCO_2R$ treatment. The primary aim of the trial was to lower tidal volumes facilitated by extracorporeal carbon dioxide removal. Permissive hypercapnia was tolerated to enable tidal volume reduction.[19] There was a lower PaO_2/FiO_2 ratio, higher respiratory rate along with greater hypercapnia and respiratory acidosis in the intervention group, although these effects were modest. As a result, harmful effects associated with these physiological consequences could have contributed to the lack of clinical benefit. Furthermore, that the minute ventilation was reduced indicates that the increase in respiratory rate is unlikely to have offset the reduction in ventilator-induced lung injury achieved with tidal volume reduction. The effect

of a larger reduction in ventilator-induced lung injury on outcome remains unknown. Lung protective ventilation has also been demonstrated to improve outcomes in patients with acute hypoxemic respiratory failure without ARDS[20] so the aim was to include a broad cohort that would reflect the general population of critically ill patients who may benefit. A systematic review concluded that although evidence was limited, $ECCO_2R$ was feasible and had been shown to facilitate further reduction in tidal volumes with the potential to mitigate ventilator-induced lung injury and improve outcomes in more hypoxemic patients.[21] This work informed the use of a PaO_2/FiO_2 ratio of less than 150 mmHg as the qualifying level of hypoxemia for this study population.[22]

After adjustment for age, degree of hypoxia and organ dysfunction, the primary outcome was unchanged. Furthermore, subgroup analyses did not suggest that the effects of the intervention were modified by any of the variables investigated. Although sub-group analyses found other baseline characteristics associated with ventilator-induced lung injury did not have an effect on outcome, it remains unknown if a different population might benefit from $ECCO_2R$. Enrichment strategies to identify a population which may be more likely to benefit are needed for future trials of $ECCO_2R$.[23 24]

Five patients were reported to have intracranial haemorrhage related to the intervention. This incidence is comparable to data from previous trials of ECMO in severe acute respiratory failure [13 25]. A review of changes in $PaCO_2$, presence of thrombocytopenia or coagulopathy as well as the degree of therapeutic anticoagulation and blood pressure was undertaken in these patients but unfortunately it was not possible to identify a clear mechanism for these events. Patients with severe hypoxemic respiratory failure have an increased risk of intracranial haemorrhage, with recent data reporting a background rate of intracranial haemorrhage in patients with severe hypoxemic respiratory failure to be approximately 8-10%, although this

was substantially increased in those patients receiving ECMO.[26 27]

Limitations

The study has several limitations. First, only 6% of screened patients were randomized to the study which may limit the generalizability of the results. Second, 17 patients (8.4%) did not receive the intervention as allocated which could have diluted the effect in the intervention group, although a per protocol analysis of patients who received the intervention did not change the outcome. Third, most of the sites were naïve to the intervention before the study commenced. Although an extensive educational package and training programme addressing catheter insertion and maintenance of the device was put in place at all sites, it is possible that practical inexperience with the intervention may have negatively affected the outcomes in the intervention group. Volume-outcome relationships have been previously reported with ECMO.[28] In an attempt to address a potential learning effect, a sensitivity analysis excluding the first two intervention patients at each site was undertaken which showed no notable change to the primary outcome and additionally there was no significant difference in subgroup analysis between sites recruiting more or fewer than 10 patients to the trial. Fourth, other aspects of care were not standardized in each group as this was a pragmatic trial and clinicians were free to manage patients as they would normally. The use of the intervention was associated with longer use of neuromuscular blocking drugs and less prone positioning. Although the difference in the use of neuromuscular blocking drugs is unlikely to have modified outcome, the less frequent use of prone positioning could have affected the outcome in the intervention group, albeit the absolute difference in the use of prone positioning between the groups was relatively small.[11,12] Fifth, it is possible that the trial was underpowered to detect a clinically important difference, particularly as the trial was stopped before recruitment of the planned sample size was achieved. Sixth, due to the complexity of the intervention blinding to the clinicians or patients was not possible which could have

resulted in performance bias.

Conclusions

In patients requiring mechanical ventilation for acute hypoxemic respiratory failure, lower tidal volume ventilation facilitated by extracorporeal carbon dioxide removal, compared to standard care, did not result in a reduction in mortality at 90 days. However, due to the early termination the study may have been underpowered to detect a clinically important difference.

Author contributions

Dr McNamee, Prof McAuley and Clíona McDowell had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Conflict of Interest Disclosures

See submitted ICMJE forms for declared potential conflict of interests.

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Department of Health disclaimer

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Figure 1. Enrollment, randomization, and flow of patients in a study of lower tidal volume facilitated by extracorporeal carbon dioxide removal in patients with acute hypoxemic respiratory failure.

[a]Patients could meet more than 1 ineligibility criterion.
[b]'Other' was used when the reason for a patient's exclusion was not among those pre-defined in the protocol; the most commonly specified free-text explanations included rapid improvement or deterioration in clinical status
[c]Child Pugh >11
[d]Randomization was stratified by site
[e]This patient was re-randomized in error and was allocated to the same group.

Figure 2: Kaplan-Meier curve of the time to death by treatment group.
Median time to death in the $ECCO_2R$ group was 6 (IQR, 4-14) days and in the ventilation alone group was 9 (IQR, 5-16) days. The unadjusted hazard ratio for death at 90 days in the $ECCO_2R$ group was 1.1 (95%CI, 0.8, 1.5). The proportionality P = .40, suggesting that the proportionality assumption was met.

Figure 3: Physiological parameters by treatment group to day 7; Tidal Volume (A), Positive End-Expiratory Pressure (PEEP) (B), Plateau Pressure (C), Driving Pressure[a] (D).

[a]Driving Pressure = Plateau Pressure - PEEP

Table 1. Baseline characteristics[a]

	$ECCO_2R$ n = 202 (49%)	**Ventilation alone n = 210 (51%)**
Age (years) median[IQR]	60.2[50.6,69.0]	61.8[50.2,69.7]
Gender-Male Female	138 (68%) 64 (32%)	131 (62%) 79 (38%)
Dependency prior to hospital admission Able to live without assistance in daily activities Minor assistance with some daily activities Major assistance with majority of/all daily activities Total assistance with all daily activities	 152 (87%) 19 (11%) 2 (1%) 1 (1%)	 160 (88%) 19 (10%) 3 (2%) 0 (0%)
Predicted body weight (kg) median[IQR][b]	66.1[57.0,73.3]	66.0[56.9,71.5]
ICU admission diagnostic category[c] Respiratory Sepsis Cardiovascular Kidney Gastrointestinal Central Nervous System Other Toxicology Hematology Orthopedic	 175 (88%) 86 (43%) 45 (23%) 39 (20%) 27 (14%) 17 (9%) 14 (7%) 10 (5%) 7 (4%) 4 (2%)	 178 (85%) 102 (49%) 49 (23%) 42 (20%) 31 (15%) 14 (7%) 10 (5%) 10 (5%) 10 (5%) 8 (4%)
ARDS present at enrollment[d]	118/199 (59%)	130/207 (63%)
Aetiology of ARDS[c] Pneumonia Sepsis Gastric content aspiration Other Pancreatitis Thoracic trauma Smoke/toxin inhalation	n=118 96 (81%) 54 (46%) 8 (7%) 8 (7%) 5 (4%) 2 (2%) 2 (2%)	n=130 103 (80%) 66 (51%) 14 (11%) 10 (8%) 5 (4%) 3 (2%) 2 (2%)
APACHE II score at ICU Admission median[IQR][e]	19[15,23]	20[16,23]
SOFA Score median[IQR][f]	10[7,12] n=195	10[7,12] n=198
Mode of Ventilation Mandatory Mandatory and spontaneous breaths Spontaneous	 158 (78%) 37 (18%) 6 (3%)	 163 (78%) 31 (15%) 15 (7%)
Adjunctive ventilatory therapies		

Neuro-Muscular Blocking Drugs	103 (51%)	102 (49%)
Prone Positioning	22 (11%)	23 (11%)
Inhaled Nitric Oxide	6 (3%)	4 (2%)
Nebulized Epoprostenol	3 (1%)	5 (2%)
Tidal volume mL/kg PBW median[IQR]	6.3[5.8,7.0] n=201	6.4[5.8,7.1] n=208
Respiratory rate breaths/min median[IQR]	24[20,28] n=201	24[20,28] n=209
PEEP cmH_2O median[IQR]	10[8,12] n=200	10[8,12] n=208
Plateau pressure cmH_2O median[IQR]	26[23.5,30] n=160	26[23,30] n=163
Plateau pressure>28cmH_2O	50(31.3%)	58(35.6%)
Driving pressure cmH_2O median[IQR][g]	15[12,19] n=159	16[12.5,19] n=163
Driving pressure<15 cmH_2O	79(49.7%)	69(42.3%)
PaO_2/FiO_2 ratio mmHg median[IQR][h]	118.1[96.0,134.3] n=198	115.5[93.8,132.8] n=203
$PaCO_2$ mmHg median[IQR]	53.8[47.3,62.7] n=198	54.6[48.0,62.3] n=203
pH median[IQR]	7.30[7.25,7.37] n=198	7.30[7.24,7.37] n=202

Abbreviations: ARDS, Acute Respiratory Distress Syndrome; APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment; PEEP, positive end-expiratory pressure; FiO_2, fraction of inspired oxygen; PaO_2, partial pressure of arterial oxygen; $PaCO_2$, partial pressure of arterial carbon dioxide.

[a]Baseline clinical data were collected in the 24 hours prior to randomization unless stated otherwise. If more than one value was available for this 24-hour period, the value closest but prior to the time of randomization was recorded.

[b]The predicted body weight of male patients was calculated as equal to 50+0.91 (centimeters of height-152.4); that of female patients was calculated as equal to 45.5+0.91 (centimeters of height-152.4)

[c]Patients may have had more than one admission diagnostic category or cause of ARDS identified.

[d]The presence of ARDS was assessed by the treating physician.

[e]Scores on the Acute Physiology and Chronic Health Evaluation (APACHE) II range from 0 to 71, with higher scores indicating greater severity of illness.

[f]Scores on the Sequential Organ Failure Assessment (SOFA) scale range from 0 to 24, with higher scores indicating greater severity of disease.

[g]Driving Pressure = Plateau Pressure - PEEP

[h]Second qualifying PaO_2/FiO_2 ratio.

Table 2. Primary, secondary and other clinical outcomes

	$ECCO_2R$	**Ventilation alone**	**% Point or Mean Difference (95% CI)**	**Risk ratio (95% CI)**	**P-value**
Primary Outcome 90 day mortality n(%)	83(41.5)n=200	81(39.5)n=205	2.0 (-7.6, 11.5)	1.1 (0.8, 1.3)	0.68
Adjusted analysis[a]				1.1 (0.9, 1.4)	0.29
Sensitivity analysis to adjust for site effect[b]			1.8 (-7.7, 11.3)	1.0 (0.8, 1.3)	0.72
90 day mortality in cohort who initiated $ECCO_2R$[c] n(%)	80(43.5)n=184	80(39.2)n=204	4.3(-5.5, 14.1)	1.1 (0.9, 1.4)	0.39
90 day mortality excluding the first 2 patients at each site who initiated $ECCO_2R$[d] n(%)	48(37.8)n=127	81(39.5)n=205	-1.7(-12.5, 9.0)	1.0 (0.7, 1.3)	0.76
Secondary Outcomes					
Ventilator-free days, randomization to day 28[e]	7.1(8.8) n=199	9.2(9.3) n=206	-2.1(-3.8, 0.3)		0.02
Duration of ventilation in survivors (days)[fg]	18.0(13.6) n=121	17.4(31.3) n=137	0.7(-5.4, 6.7)		0.83
Need for ECMO to day 7 n(%)	12(6)n=202	6(3)n=210	3.1(-0.9, 7.0)	2.1 (0.8,5.4)	0.13
28 day mortality n(%)	76(38)n=200	74(36)n=207	2.3(-7.1, 11.6)	1.1(0.8,1.4)	0.64
ICU length of stay to death or discharge (days)[hi]	14[7,26] n=202	13[7,22]n=210			0.67
Hospital length of stay to death or discharge (days)[hi]	22[8,39] n=193	18[9,35]n=201			0.65

Abbreviations: ECMO, extracorporeal membrane oxygenation

[a]Adjusted for age, qualifying PaO_2/FiO_2 ratio and baseline SOFA (RR estimated from a log-binomial regression; model to estimate % point difference would not converge.

[b]Generalized estimating equations (GEE) used to account for possible clustering of observations within participating centers

[c]Per protocol analysis excludes the 17 patients who did not commence $ECCO_2R$ and the 1 patient who received $ECCO_2R$ in the standard care arm.

[d]Sensitivity analysis performed for the primary outcome excluding the first two intervention arm patients at each site in order to address potential learning effects.

[e]Ventilator-free days were defined as the number of days from the time of initiating unassisted breathing to day 28 after randomization (see the study protocol). Patients who died before day 28 were assigned 0 ventilator-free days.

[f]Mean (SD) for treatment arms and mean difference and 95% CI presented.

[g] Survivors were defined as patients who achieved unassisted breathing but could have subsequently died prior to day 90.

[h]Median[IQR] with P-value from Wilcoxon rank sum presented.

iLength of stay in ICU and hospital were not secondary outcomes.

Table 3. Adverse Events by treatment group

	$ECCO_2R$ no. events	**$ECCO_2R$ no. (%) patients n=202**	**Ventilation alone no. events**	**Ventilation alone no. (%) patients n=210**
AEs[a]	168	106(52.5%)	61	48(22.9%)
AEs related to study intervention[b]	65	51(25.3%)	0	0(0.0%)
SAEs[c,d]	70	62(30.7%)	20	18(8.6%)
SAEs related to study intervention[b]	22	21(10.4%)	0	0(0.0%)
AEs of specific interest				
Bleeding at other site (excluding intracranial hemorrhage)	18	17(8.4%)	3	3(1.4%)
Intracranial haemorrhage	10	10(5.0%)	2	2(1.0%)
Device failure causing AE	9	9(4.5%)	0	0(0.0%)
Bleeding at cannula site	8	8(4.0%)	0	0(0.0%)
Infectious complications[e]	7	7(3.5%)	1	1(0.5%)
Heparin induced thrombocytopenia	4	4(2.0%)	0	0(0.0%)
Haemolysis	3	3(1.5%)	0	0(0.0%)
Ischaemic stroke	1	1(0.5%)	3	3(1.4%)
SAEs of specific interest[f]				
Bleeding at other site (excluding intracranial hemorrhage)	6	6(3.0%)	1	1(0.5%)
Intracranial haemorrhage	9	9(4.5%)	0	0(0%)
Infectious complications[e]	5	5(2.5%)	0	0(0.0%)
Device failure causing SAE	2	2(1.0%)	0	0(0.0%)
Heparin induced thrombocytopenia	1	1(0.5%)	0	0(0.0%)
Ischaemic stroke	1	1(0.5%)	3	3(1.4%)

[a]AEs totals includes SAEs

[b]A list of AEs which were defined as related to the study intervention was provided in the study protocol. Events which were possibly, probably or definitely related to the study intervention (or were not assessable) were defined as related.

[c]SAEs defined by System Organ Class can be found in Table S7.

[d]A serious adverse event was defined as any adverse event that led to death or resulted in, a life threatening illness or injury, permanent impairment of a body structure or a body function, patient hospitalization or prolongation of existing hospitalization, medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or function, fetal distress, fetal death or a congenital abnormality or birth defect.

[e]Infectious complications were determined by the site investigator.

[f]There were no episodes of haemolysis or bleeding at canula site reported as serious adverse events.