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The Effect of Lower Tidal Volume Ventilation Facilitated by Extracorporeal Carbon Dioxide Removal Compared With Conventional Lung Protective Ventilation on Cardiac Function

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OBJECTIVES: Lower tidal volume ventilation (targeting 3 mL/kg predicted body weight, PBW) facilitated by extracorporeal carbon dioxide removal ($ECCO_2R$) has been investigated as a potential therapy for acute hypoxemic respiratory failure (AHRF) in the pRotective vEntilation with veno-venouS lung assisT in respiratory failure (REST) trial. We investigated the effect of this strategy on cardiac function, and in particular the right ventricle.

DESIGN: Substudy of the REST trial.

SETTING: Nine U.K. ICUs.

PATIENTS: Patients with AHRF ($Pao_2/Fio_2 < 150$ mm Hg [20 kPa]).

INTERVENTION: Transthoracic echocardiography and N-terminal pro-B-type natriuretic peptide (NT-proBNP) measurements were collected at baseline and postrandomization in patients randomized to $ECCO_2R$ or usual care.

MEASUREMENTS: The primary outcome measures were a difference in tricuspid annular plane systolic excursion (TAPSE) on postrandomization echocardiogram and difference in NT-proBNP postrandomization.

RESULTS: There were 21 patients included in the echocardiography cohort ($ECCO_2R$, $n = 13$; usual care, $n = 8$). Patient characteristics were similar in both groups at baseline. Median (interquartile range) tidal volumes were lower in the $ECCO_2R$ group compared with the usual care group postrandomization; 3.6 (3.1–4.2) mL/kg PBW versus 5.2 (4.9–5.7) mL/kg PBW, respectively ($p = 0.01$). There was no difference in the primary outcome measure of mean (SD) TAPSE in the $ECCO_2R$ and usual care groups postrandomization; 21.3 (5.4) mm versus 20.1 (3.2) mm, respectively ($p = 0.60$). There were 75 patients included in the NT-proBNP cohort ($ECCO_2R$, $n = 36$; usual care, $n = 39$). Patient characteristics were similar in both groups at baseline. Median (interquartile range [IQR]) tidal volumes were lower in the $ECCO_2R$ group than the usual care group postrandomization; 3.8 (3.3–4.2) mL/kg PBW versus 6.7 (5.8–8.1) mL/kg PBW, respectively ($p < 0.0001$). There was no difference in median (IQR) NT-proBNP postrandomization; 1121 (241–5370) pg/mL versus 1393 (723–4332) pg/mL in the $ECCO_2R$ and usual care groups, respectively ($p = 0.30$).

CONCLUSIONS: In patients with AHRF, a reduction in tidal volume facilitated by $ECCO_2R$, did not modify cardiac function.

KEYWORDS: acute hypoxemic respiratory failure; extracorporeal circulation; echocardiography; N-terminal pro-B-type natriuretic peptide; right ventricle

Acute hypoxemic respiratory failure (AHRF) affects one-third of patients receiving mechanical ventilation in intensive care (1). The majority of these patients meet the Berlin Definition criteria for acute respiratory

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KEY POINTS

Question: What is the effect of lower tidal volume ventilation facilitated by extracorporeal carbon dioxide removal ($ECCO_2R$) on cardiac function in patients with acute hypoxemic respiratory failure (AHRF)?

Findings: We conducted an echocardiography and biomarker substudy as part of the REST randomized controlled trial. Despite the $ECCO_2R$ group achieving a significant reduction in tidal volume, there was no difference in tricuspid annular plane systolic excursion or N-terminal pro-B-type natriuretic peptide levels between the $ECCO_2R$ and usual care groups.

Meanings: $ECCO_2R$ does not appear to affect cardiac, and in particular right ventricle (RV) function. Our findings do not support the use of $ECCO_2R$ to prevent or reverse RV dysfunction, acute cor pulmonale or pulmonary hypertension due to AHRF.

distress syndrome (ARDS) (1, 2). Protective lung ventilation using 6 mL/kg predicted body weight (PBW) has been shown to reduce mortality in ARDS (1, 3). It has been postulated that further reductions in tidal volume may reduce lung strain, reduce ventilator-induced lung injury, and improve outcomes (4–6). The pRotective vEntilation with veno-venouS lung assisT in respiratory failure (REST) trial (NCT02654327) examined whether lower tidal volume ventilation (aiming for 3 mL/kg PBW) facilitated by extracorporeal carbon dioxide removal ($ECCO_2R$) reduced mortality in patients with AHRF (4). The study was stopped early because of futility; however, no difference was found in mortality between the $ECCO_2R$ and usual care groups.

Mechanical ventilation in AHRF may particularly influence right ventricle (RV) function. High levels of positive end-expiratory pressure (PEEP) may cause regional alveolar over-distension with subsequent compression of intra-alveolar vessels increasing pulmonary vascular resistance (7, 8). High tidal volumes, plateau pressures, and driving pressures may expose the RV to increased afterload (9). Conversely, tidal volume ventilation below functional residual capacity increases pulmonary vascular resistance, which may be further exacerbated by permissive hypercapnia and acidosis (7, 8)

RV dysfunction or acute cor pulmonale (ACP) is present in 21–50% of patients mechanically ventilated for respiratory failure and is associated with increased mortality (8, 10, 11). Tidal volume is the primary determinant of RV afterload (9). Hence, lower tidal volume ventilation facilitated by $ECCO_2R$ has been suggested as a therapy for RV dysfunction in respiratory failure (12). Despite theoretical advantages, the effect of lower tidal volume ventilation facilitated by $ECCO_2R$ on the RV remains uncertain (8).

No consensus guidelines on the diagnosis of RV dysfunction in mechanically ventilated patients exist (11). Serial echocardiography likely represents the best diagnostic tool (13). Tricuspid annular plane systolic excursion (TAPSE) is a highly feasible measure of RV function in ventilated patients (obtainable in 96% of patients) (14). Reduced TAPSE is a strong predictor of short-term mortality in ARDS (15–17). TAPSE inversely correlates with systolic pulmonary artery pressure (sPAP) and, importantly, with tidal volume in patients on $ECCO_2R$ (18, 19). N-terminal pro-B-type natriuretic peptide (NT-proBNP) is a marker of cardiac dysfunction. Acute pulmonary hypertension and RV dilatation result in release of NT-proBNP (20, 21). NT-proBNP correlates with mean pulmonary artery pressure (mPAP) and predicts mortality in AHRF (22, 23).

We hypothesized that lower tidal volume ventilation facilitated by $ECCO_2R$ could modify cardiac, and in particular, RV function as measured by TAPSE and NT-proBNP.

MATERIALS AND METHODS

Study Design and Participants

The REST trial compared lower tidal volume ventilation (aiming for 3 mL/kg PBW) facilitated using $ECCO_2R$ group with conventional lung protective ventilation (usual care group) in patients with AHRF defined as a Pao_2/Fio_2 < 150 mm Hg (20 kPa). The REST trial was a randomized, open-label, pragmatic trial conducted in 51 ICUs in the United Kingdom. The inclusion and exclusion criteria have been described elsewhere (4, 24). Briefly, patients aged greater than or equal to 16 years with a potentially reversible cause of AHRF, who were receiving invasive mechanical ventilation using a minimum of 5 cm H_2O of PEEP were eligible, provided

they were within 48 hours of the onset of hypoxia. Exclusion criteria included mechanical ventilation of greater than 7 days duration, untreated pulmonary embolism, pleural effusion or pneumothorax, respiratory failure fully explained by left ventricular failure or a contraindication to systemic anticoagulation.

Ethical approval for the REST study (NCT02654327) was provided by the South Central—Berkshire Research Ethics Committee (REC) on February 24, 2016, for the United Kingdom, Wales, and Northern Ireland (16/SC/089), and by Scotland A REC on March 23, 2016 for Scotland (16/SS/048). Written informed consent was obtained from patients, or agreement was obtained from their surrogates in keeping with regional regulations. All study procedures were conducted in accordance with the ethical standards of the responsible committee on human experimentation (South Central—Berkshire REC and Scotland A REC) and with the Helsinki Declaration of 1975.

We investigated two cohorts: those who underwent serial echocardiography (echocardiography cohort) and those who participated in the biomarker substudy in which NT-proBNP was measured (NT-proBNP cohort).

Echocardiography Cohort

Echocardiograms were obtained from participating centers with sites selected based on their ability to perform critical care echocardiography following an expression of interest call. Studies were performed by trained echocardiographers. Echocardiograms performed as per trial protocol and those undertaken as part of clinical care were both eligible for inclusion. Echocardiograms performed up to two calendar days before randomization were taken as a baseline. In the usual care group, echocardiograms performed the calendar day after randomization could also be used as baseline. If multiple echocardiography studies were completed, the study closest but before randomization was used. Postrandomization echocardiograms could be taken up to five calendar days postrandomization. If multiple echocardiogram studies were completed, the study closest to the second calendar day postrandomization was used. For patients randomized to $ECCO_2R$, postrandomization echocardiograms must have been performed while still receiving lower tidal volume ventilation facilitated by $ECCO_2R$.

Images were reviewed by a single-blinded expert in critical care echocardiography (E.B.). Seventeen echocardiograms were independently reviewed by a second blinded expert in critical care echocardiography (S.O.) to check for reliability in measurement of TAPSE. TAPSE measurements were performed in the apical four chamber view using M-mode (mm) and measured between end diastole and peak systole (25). Three measurements were performed, and mean values were recorded. Where the angle of interrogation precluded accurate M-mode measurement, 2D measurements of TAPSE were performed (three studies) as previously described (26). All other measurements were performed in accordance with the American Society of Echocardiography and European Association of Cardiovascular Imaging guidelines (25).

In the echocardiography cohort, ventilator settings and arterial blood gas values are presented for baseline and the day of the postrandomization echocardiogram. Individual elements of the cardiovascular Sequential Organ Failure Assessment (SOFA) score are presented at baseline. However, these were not recorded at the time of postrandomization echocardiogram.

The a priori defined primary outcome measure was the difference in TAPSE postrandomization (4). Secondary outcome measures, including echocardiography measures of RV systolic function, RV size, RV afterload and LV function, are listed in **Supplementary Table 1** (http://links.lww.com/CCX/B293) (27) and further defined in **Supplementary Figure 1** (http://links.lww.com/CCX/B293) (28).

NT-proBNP Cohort

Plasma was collected at baseline and two calendar days postrandomization in an ethylene diamine tetraacetic acid tube and centrifuged before storage at –80°C. In the usual care group, plasma collected the calendar day after randomization could also be used as baseline. NT-proBNP measurements were performed using a commercially available enzyme-linked immunosorbent assay (SimpleStep ELISA, Abcam, Cambridge, United Kingdom) in accordance with manufacturer protocols.

In the NT-proBNP cohort, ventilator setting, arterial blood gases, and individual elements of the cardiovascular SOFA score are presented at baseline and two calendar days postrandomization.

The primary outcome measure was difference in NT-proBNP postrandomization. The secondary outcome measure was change in NT-proBNP from baseline.

Statistical Analysis

A sample of convenience was taken; therefore, no sample size calculation was performed. Categorical data are presented as frequency (%). Normally distributed quantitative data are presented as mean (SD), and non-normally distributed quantitative data are presented as median (interquartile range, IQR). Intraclass correlation coefficient for the primary outcome measure of TAPSE was calculated using a two-way random-effects model. Between group comparisons were made using *t*-test for normally distributed continuous data, Mann-Whitney *U* test for non-normally distributed continuous data and chi-square for categorical data. Wilcoxon Signed-Rank test was used for within group comparisons. *p* values of less than 0.05 were considered statistically significant. As an exploratory analysis, all results were considered hypothesis-generating generating and no adjustment was made for multiplicity.

We conducted a preplanned sensitivity analysis comparing TAPSE in those in the $ECCO_2R$ group who achieved a greater than or equal to 2 mL/kg PBW reduction in tidal volume to those managed with usual care.

RESULTS

Echocardiography Cohort

Six centers provided baseline and postrandomization echocardiograms for 21 patients ($ECCO_2R$, n = 13; usual care, n = 8). Baseline patient demographics and clinical outcomes are presented in **Table 1**. The two groups were similar at baseline. Respiratory pathology was the most common reason for admission to ICU (**Supplementary Table 2**, http://links.lww.com/CCX/B293). Ninety-day mortality was 15.4% and 25% in the $ECCO_2R$ and usual care groups, respectively.

Respiratory and Cardiovascular Characteristics

Respiratory and cardiovascular characteristics were similar at baseline, **Table 2**. In the $ECCO_2R$ group, median (IQR) tidal volume reduced from 6.4

TABLE 1.
Echocardiography Cohort: Baseline Characteristicsa

Characteristic	$ECCO_2R$ Group (n = 13)	Usual Care Group (n = 8)
Age, mean (SD), yr	52.7 (10.4)	56.0 (9.2)
Sex, *n* (%)		
Male	7 (53.8)	6 (75.0)
Female	6 (46.2)	2 (25.0)
Dependency before hospital admission, *n* (%)		
Able to live without assistance in daily activities	12 (92.3)	8 (100.0)
Minor assistance with some daily activities	1 (7.7)	0 (0.0)
Acute Physiology and Chronic Health Evaluation II score at ICU admission, mean (SD)[b]	17.2 (7.4)	20.6 (4.6)
Sequential Organ Failure Assessment score, mean (SD)[c]	9.1 (2.3)	11.4 (4.0)
28-d mortality, *n* (%)	2 (15.4)	2 (25.0)
90-d mortality, *n* (%)	2 (15.4)	2 (25.0)

[a]Baseline clinical data were collected in the 24 hours before randomization unless stated otherwise. If more than 1 value was available for this 24-hour period, the value closest, but prior, to the time of randomization was recorded.

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

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

TABLE 2.

Echocardiography Cohort: Ventilatory and Cardiovascular Characteristics at Baseline and Postrandomization

	Baseline		Postrandomization		
	$ECCO_2R$ Group ($n = 13$)	Usual care Group ($n = 8$)	$ECCO_2R$ Group ($n = 13$)	Usual care Group ($n = 8$)	*p*
Respiratory characteristics					
Mode of ventilation, *n* (%)					
Mandatory	10 (76.9)	6 (75.0)	11 (84.6)	8 (100.0)	0.51
Mandatory and spontaneous breaths	3 (23.1)	1 (12.5)	1 (7.7)	0 (0.0)	
Spontaneous	0 (0.0)	1 (12.5)	1 (7.7)	0 (0.0)	
Adjunctive ventilatory therapies, *n* (%)					
Neuromuscular-blocking drugs	10 (76.9)	5 (62.5)	7 (53.8)	6 (75.0)	0.33
Prone positioning	2 (15.4)	2 (25.0)	2 (15.4)	2 (25.0)	0.59
Pa_{O_2}/Fi_{O_2} ratio, median (IQR), mm Hg[a]	122.3 (117.0–137.3)	123.8 (84.0–127.1)	135.0 (123.0–197.3)	159.0 (129.8–182.6)	0.74
Positive end-expiratory pressure, median (IQR), cm H_2O	10.0 (10.0–12.0)	10.0 (9.0–12.0)	10.0 (8.0–12.0)	12.0 (11.0–13.0)	0.09
Tidal volume, median (IQR), mL/kg predicted body weight	6.4 (5.9–6.8)	5.7 (5.4–5.8)	3.6 (3.1–4.2)	5.2 (4.9–5.7)	0.01
Respiratory rate, mean (SD), breaths/min	22.8 (6.5)	24.1 (6.8)	27.7 (5.7)	27.9 (3.7)	0.94
Plateau pressure, mean (SD), cm H_2O	23.1 (4.3), $n = 7$	20.9 (2.9), $n = 4$	20.3 (6.1), $n = 7$	22.8 (1.8), $n = 5$	0.40
Driving pressure[b], mean (SD), cm H_2O	14.1 (3.7), $n = 7$	11.2 (2.2), $n = 4$	10.9 (5.1), $n = 7$	11.6 (2.0), $n = 5$	0.77
Compliance, mean (SD) mL/cm H_2O	34.7 (26.7), $n = 7$	38.2 (3.6), $n = 4$	24.7 (13.1), $n = 7$	35.9 (5.5), $n = 5$	0.10
Pa_{CO_2}, median (IQR), mm Hg	55.5 (51.0–62.3)	51.4 (46.5–58.1)	62.3 (58.4–75.0)	59.1 (52.5–63.4)	0.33
pH level, mean (SD)	7.33 (0.09)	7.32 (0.11)	7.32 (0.08)	7.31 (0.10)	0.80
Cardiovascular characteristics					
Heart rate, mean (SD)	88.4 (26.8), $n = 10$	90.7 (17.7), $n = 6$	87.8 (20.2), $n = 10$	94.5 (14.6), $n = 6$	0.49
Lowest mean arterial pressure, median (IQR), mm Hg	62 (62–65)	63.5 (60–65)			
Noradenaline, *n* (%)					
Yes	8 (61.5)	7 (87.5)			
No	5 (38.5)	1 (12.5)			
Highest Noradrenaline, median (IQR), µg/kg/min	0.07 (0–0.15)	0.17 (0.08–0.48)			

(*Continued*)

TABLE 2. (*Continued*)
Echocardiography Cohort: Ventilatory and Cardiovascular Characteristics at Baseline and Postrandomization

	Baseline		Postrandomization		
	$ECCO_2R$ Group (n = 13)	Usual care Group (n = 8)	$ECCO_2R$ Group (n = 13)	Usual care Group (n = 8)	p
Vasopressin, *n* (%)					
Yes	0 (0.0)	1 (12.5)			
No	13 (100.0)	7 (87.5)			
Milrinone, *n* (%)					
Yes	0 (0.0)	1 (12.5)			
No	13 (100.0)	7 (87.5)			

IQR = interquartile range.
[a]Second qualifying Pao_2/Fio_2 ratio.
[b]Driving pressure = plateau pressure−positive end-expiratory pressure.
p values from *t*-test where mean (SD) presented or Mann-Whitney *U* test where median (IQR) presented or chi-square for categorical data.

(5.9–6.8) mL/kg PBW at baseline to 3.6 (3.1–4.2) mL/kg PBW (p = 0.007) by the time of the postrandomization echocardiogram. In contrast, in the usual care group, there was no difference in median (IQR) tidal volume between baseline and postrandomization echocardiogram; 5.7 (5.4–5.8) mL/kg PBW versus 5.2 (4.9–5.7) mL/kg PBW (p = 0.23). At the time of the postrandomization echocardiogram, median (IQR) tidal volumes were significantly lower in the $ECCO_2R$ group than the usual care group; 3.6 (3.1–4.2) mL/kg PBW versus 5.2 (4.9–5.7) mL/kg PBW (p = 0.01).

There was no difference in plateau pressure, driving pressure, $Paco_2$, or pH between the two groups at the time of the postrandomization echocardiogram.

All patients were in sinus rhythm at the time of echocardiogram. Noradrenaline was the most commonly used vasoactive agent.

Primary and Secondary Echocardiography Outcome Measures

Echocardiography findings are presented in **Table 3**. and **Supplementary Table 3** (http://links.lww.com/CCX/B293). At baseline, measures of RV systolic function, size, and afterload were similar between groups. Postrandomization echocardiography was conducted with a median (IQR) of 1 (1–2) and 1 (1–1) days following randomization in the $ECCO_2R$ and usual care groups, respectively.

RV Systolic Function

The intraclass correlation (95% CI) for TAPSE between two observers was 0.93 (0.79–0.98), indicating good to excellent reliability. At baseline, mean (SD) TAPSE was 21.3 (3.7) mm and 19.5 (3.4) mm in the $ECCO_2R$ and usual care groups, respectively. There was no difference in the primary outcome measure of TAPSE on postrandomization echocardiogram; 21.3 (5.4) mm versus 20.1 (3.2) mm in the $ECCO_2R$ and usual care groups (p = 0.60). There was no difference in change from baseline in mean (SD) TAPSE; 0.58 (4.1) versus 0.61 (5.4) (p = 0.99) in the $ECCO_2R$ and usual care groups, respectively.

There was no difference in RV_{FAC} or right ventricular Tissue Doppler Imaging systolic excursion velocity (RV TDI S') on postrandomization echocardiogram. Right ventricular outflow tract velocity time integral (RVOT

TABLE 3.
Results of Baseline and Postrandomization Echocardiogram

	Normal Value	Baseline			Postrandomization		
		$ECCO_2R$ Group ($n = 13$)	Usual Care Group ($n = 8$)	p	$ECCO_2R$ Group ($n = 13$)	Usual Care Group ($n = 8$)	p
Primary outcome							
TAPSE, mean (SD), mm	≥ 17	21.3 (3.7)	19.5 (3.4)	0.29	21.3 (5.4), $n = 12$	20.1 (3.2), $n = 7$	0.60
Secondary outcome							
Measures of RV function							
Change in TAPSE, mean (SD), mm					0.58 (4.1), $n = 12$	0.61 (5.4), $n = 7$	0.99
RV fractional area change, mean (SD), %	≥ 35	44.9 (7.7), $n = 8$	41.3 (3.7), $n = 4$	0.40	44.8 (13.0), $n = 9$	45.3 (9.6), $n = 6$	0.93
Right ventricular Tissue Doppler Imaging systolic excursion velocity, mean (SD), cm/s	≥ 9.5	12.9 (2.0), $n = 7$	10.3 (0.6), $n = 3$	0.07	14.0 (3.7), $n = 9$	11.5 (1.3), $n = 4$	0.22
RVOT VTI, mean (SD), cm	≥ 19	16.4 (1.7), $n = 9$	16.0 $n = 1$	NA	17.9 (3.1), $n = 9$	11.8 (4.9), $n = 3$	0.027
Acute cor pulmonale, n (%)	Absent						
Absent		8 (80.0)	5 (83.3)	0.87	8 (72.7)	5 (71.4)	0.95
Present		2 (20.0)	1 (16.7)		3 (27.3)	2 (28.6)	
Measures of RV size							
RVEDA, mean (SD), cm^2	10–24	17.1 (3.2), $n = 8$	17.3 (3.1), $n = 4$	0.92	16.9 (2.9), $n = 8$	18.1 (4.8), $n = 6$	0.57
RVEDA/LVEDA, mean (SD)	< 0.6	0.60 (0.19), $n = 8$	0.53 (0.04), $n = 4$	0.52	0.60 (0.17), $n = 8$	0.57 (0.16), $n = 6$	0.78
Measures of RV afterload							
TR severity, n (%)	Absent						
Absent		1 (11.1)	4 (66.7)	0.08	1 (10.0)	2 (40.0)	0.39
Mild		7 (77.8)	2 (33.3)		6 (60.0)	2 (40.0)	
Moderate		1(11.1)	0 (0.0)		3 (30.0)	1 (20.0)	
Severe		0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
Tricuspid valve regurgitation velocity (maximum), mean (SD), m/s	≤ 2.8 or not measurable	2.7 (0.6), $n = 6$	$n = 0$		2.6 (0.8), $n = 6$	2.5 (0.4), $n = 3$	0.73
RVOT AT, mean (SD), ms	> 105	112.3 (15.5), $n = 7$	120.0 (14.1), $n = 2$	0.55	101.0 (25.3), $n = 9$	124.3 (14.0), $n = 3$	0.17

(*Continued*)

TABLE 3. (*Continued*)

Results of Baseline and Postrandomization Echocardiogram

	Normal Value	Baseline			Postrandomization		
		$ECCO_2R$ Group ($n = 13$)	Usual Care Group ($n = 8$)	*p*	$ECCO_2R$ Group ($n = 13$)	Usual Care Group ($n = 8$)	*p*
RVOT notching, *n* (%)	Absent						
Absent		7 (87.5)	1 (100.0)	0.71	7 (77.8)	3 (100.0)	0.37
Present		1 (12.5)	0 (0.0)		2 (22.2)	0 (0.0)	
Right atrium area, mean (SD), cm^2	≤ 18	14.6 (3.8), $n = 9$	15.1 (3.9), $n = 4$	0.83	15.3 (5.6), $n = 9$	14.3 (2.9), $n = 5$	0.70
Measures of LV function							
LV systolic function, *n* (%)							
Normal		7 (63.6)	2 (33.3)	0.08	8 (80.0)	3 (42.9)	0.10
Hyperdynamic		1 (9.1)	4 (66.7)		1 (10.0)	4 (57.1)	
Mildly impaired		2 (18.2)	0 (0.0)		1 (10.0)	0 (0.0)	
Moderately impaired		0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
Severely impaired		1 (9.1)	0 (0.0)		0 (0.0)	0 (0.0)	

LV = left ventricle, LVEDA = left ventricular end diastolic area, NA = not applicable, RV = right ventricle, RVEDA = right ventricular end diastolic area, RVOT = right ventricular outflow tract, RVOT AT = right ventricular outflow tract acceleration time, RVOT VTI = right ventricular outflow tract velocity time integral, TAPSE = tricuspid annular plane systolic excursion, TR = tricuspid regurgitation.

p values from *t*-test for continuous data or chi-square for categorical data.

VTI) was low at baseline in both groups. RVOT VTI was significantly lower in the usual care group on postrandomization echocardiogram. However, RVOT VTI could only be obtained in three patients on postrandomization echocardiogram in the usual care group.

Right ventricular dysfunction (RVD) was present in four patients (19.0%) at baseline and seven (33.3%) on postrandomization echocardiogram. Three patients (14.3%) had ACP at baseline (**Supplementary Table 4**, http://links.lww.com/CCX/B293). In the two patients with ACP at baseline in the $ECCO_2R$ group, ACP persisted in both postrandomization echocardiograms. Two further patients (one in each group) developed ACP between baseline and postrandomization echocardiogram.

RV Size

There was no between group difference in mean (SD) RVEDA/LVEDA ratio on postrandomization echocardiogram; 0.60 (0.17) versus 0.57 (0.16) in the $ECCO_2R$ and usual care groups, respectively ($p = 0.78$).

RV Afterload

Tricuspid regurgitation was either absent or mild in the majority of patients, limiting the ability to record maximum tricuspid valve regurgitation velocity (TRVmax). There was no difference in mean (SD) TRVmax between the two groups on postrandomization echocardiogram. There was no difference in right ventricular outflow tract acceleration time (RVOT AT), presence of RVOT notching, or right atrial area between the two groups.

Patients with pulmonary hypertension are shown in **Supplementary Table 5** (http://links.lww.com/CCX/B293). Criteria for intermediate probability of pulmonary hypertension were met by two patients at baseline, both in the $ECCO_2R$ group. In one, $ECCO_2R$ did not reverse pulmonary hypertension, in the other there was insufficient data on the postrandomization echocardiogram. One patient in the $ECCO_2R$ group met criteria for high probability of pulmonary hypertension at baseline, on postrandomization echocardiogram they met criteria for intermediate probability of pulmonary hypertension. A further three patients progressed from low to intermediate probability of pulmonary hypertension on the postrandomization echocardiogram (two in the $ECCO_2R$ group and one in the usual care group).

Sensitivity Analysis

A sensitivity analysis comparing those in the $ECCO_2R$ group ($n = 9$) who achieved a greater than or equal to 2 mL/kg PBW reduction in tidal volume to the usual care group produced similar results to the main analysis; mean (SD) TAPSE on postrandomization echocardiogram was 20.9 (6.0) mm versus 20.1 (3.2) mm, respectively ($p = 0.75$).

NT-proBNP Cohort

NT-proBNP results were available for 75 patients from nine centers ($ECCO_2R$, $n = 36$; usual care, $n = 39$). Baseline patient demographics and clinical outcomes are presented in **Supplementary Table 6** (http://links.lww.com/CCX/B293). The two groups were similar at baseline. Ninety-day mortality was 33.3% and 37.8% in the $ECCO_2R$ and usual care groups, respectively. Respiratory and cardiovascular characteristics were similar at baseline (**Supplementary Table 7**, http://links.lww.com/CCX/B293). Postrandomization, median (IQR) tidal volumes were lower in the $ECCO_2R$ group than the usual care group; 3.8 (3.3–4.2) mL/kg PBW versus 6.7 (5.8–8.1) mL/kg PBW, respectively ($p < 0.0001$). Driving pressure was lower in the $ECCO_2R$ compared with the usual care group; mean (SD) driving pressure was 10.0 (4.1) cm H_2O versus 16.2 (5.7) cm H_2O, respectively ($p < 0.0001$). Plateau pressure was also lower in the $ECCO_2R$ compared with the usual care group; mean (SD) plateau pressure was 19.8 (4.9) cm H_2O versus 25.0 (5.7) cm H_2O, respectively ($p = 0.0002$). There was no difference in $Paco_2$ or pH between the two groups postrandomization. In the $ECCO_2R$ group, 34 (94.4%) patients were still receiving $ECCO_2R$ support on the day of postrandomization NT-proBNP.

At baseline, median (IQR) NT-proBNP was 1328 (326–4524) pg/mL and 1030 (338–3320) pg/mL in the $ECCO_2R$ and usual care groups, respectively ($p = 0.93$). There was no difference in NT-proBNP postrandomization; 1121 (241–5370) pg/mL versus 1393 (723–4332) pg/ml in the $ECCO_2R$ and usual care groups, respectively ($p = 0.30$). There was no difference in change from baseline in median (IQR) NT-proBNP; –15 (–902 to 1532) pg/mL versus 278 (–315 to 1210) in the $ECCO_2R$ and usual care groups, respectively ($p = 0.32$).

DISCUSSION

This study reports the effect of lower tidal volume ventilation facilitated by $ECCO_2R$ on cardiac function in patients included in the REST trial who underwent serial echocardiography and NT-proBNP measurement. Despite achieving a reduction in tidal volume with $ECCO_2R$, we found no statistically significant difference in the primary outcome measures of TAPSE or NT-proBNP postrandomization, in comparison to usual care. The secondary echocardiography and NT-proBNP outcome measures were consistent with these findings.

In a nonrandomized study by Goursaud et al (18), patients with ARDS managed with $ECCO_2R$ underwent serial echocardiograms over 24 hours such that they acted as their own controls. Improvements in TAPSE and RV TDI S' wave velocity were seen with ventilation at 4 mL/kg PBW and $ECCO_2R$ (18). In our randomized sample, we found no statistically significant differences in TAPSE or RV TDI S'. Notably, driving pressure and $Paco_2$ were higher, and use of prone positioning (which is associated with improved RV function) was lower in our cohort (11, 18, 29). In both our study and that by Goursard e al (18), TAPSE and TDI S' were normal at baseline.

The prevalence of RVD, ACP, or pulmonary hypertension in our cohort was less than that seen in other studies (8). RV injury which includes both RVD and ACP occurs in 21–50% of patients with ARDS (8). A Pao_2/Fio_2 ratio less than 150 mm Hg (20 kPa) and $Paco_2$ greater than or equal to 48 mm Hg (6.4 kPa) are predictors of ACP (12). Despite the presence of these risk factors in our cohort, RVD (19.0%), ACP (14.3%) and pulmonary hypertension (14.3%) were infrequent at baseline. We found no evidence that $ECCO_2R$ reversed ACP or pulmonary hypertension when present at baseline, or prevented patients developing ACP or pulmonary hypertension (30). It is possible that we were underpowered to detect a difference given the relatively small sample size in the echocardiography cohort. However, in the larger NT-proBNP cohort, there was similarly no difference in NT-proBNP postrandomization between the two groups, although NT-proBNP is not specific for RV impairment.

NT-proBNP is frequently elevated in patients with respiratory failure and is an independent predictor of 90-day mortality (23, 31). NT-proBNP values in our cohort were lower to that seen in other studies of AHRF patients (20, 22, 23, 31). In patients with normal renal function, NT-proBNP is highly correlated with mPAP and pulmonary artery occlusion pressure (22). Therefore, the lower NT-proBNP levels seen in our cohort may reflect a lower incidence of RV and LV dysfunction. In our study, a reduction in tidal volume facilitated by $ECCO_2R$ did not result in a difference in postrandomization NT-proBNP between groups. Our findings are consistent with previous research, which demonstrated no difference in NT-proBNP in patients ventilated with 6 mL/kg PBW versus 10 mL/kg PBW (20). The reduction in tidal volume achieved in our patient cohort may have been insufficient to reduce myocardial stretch.

It has been postulated $ECCO_2R$ may benefit RV function through "metabolic control" of hypercapnia and acidosis (18). In the REST study, where the primary aim of the intervention was to limit injurious ventilation, the absence of a reduction in $Paco_2$ may explain our neutral result. The role of "mechanical offloading" should be considered. In our study, $ECCO_2R$ facilitated the use of lower tidal volumes. Reducing driving pressure has an important role in offloading the RV and is a primary mediator of survival benefits in lung protective ventilation (32). In our study, $ECCO_2R$ may have failed to sufficiently mechanically offload the RV.

Our study has a number of strengths. In comparison to usual care, the $ECCO_2R$ group achieved a statistically significant reduction in tidal volume in both the echocardiography and NT-proBNP cohorts. In a recent scoping review of RV-specific therapies in ARDS, the largest study of extracorporeal therapies included only 18 patients, and there were no randomized controlled trials (11). The presentation of baseline and postrandomization echocardiogram and NT-proBNP results provide additional information on temporal changes in cardiac, and in particular, RV function with $ECCO_2R$. Echocardiograms were independently assessed by blinded experienced critical care echocardiography clinicians.

Our study has several limitations. Patients included in the echocardiography substudy may not be representative of all patients in the REST trial. This is supported by the finding that the mortality in the echocardiography cohort was approximately half that of the main REST cohort (4). In contrast, the mortality in the NT-proBNP cohort was comparable to that seen

in the REST trial. The echocardiography cohort was a small sample of convenience of patients who had a baseline echocardiogram, some of which may have been clinically directed; this may have resulted in a biased cohort. Our study is likely to be underpowered to detect small changes in TAPSE. In addition, echocardiography has a sensitivity of only 60% (95% CI, 41–77%) in diagnosing RVD (33). Furthermore, the angle of interrogation may have impacted the accuracy of M-mode measurement of TAPSE in some patients. Indeed, 2D measurements of TAPSE were required in three studies (34). However, the NT-proBNP results give greater confidence the neutral result was not due to a type II error. Echocardiograms were performed at a median of 1 day, and NT-proBNP collected 2 days postrandomization; we cannot exclude that we missed transient changes in cardiac function at other time points. The technical challenges of critical care echocardiography meant our dataset was incomplete for some patients (10). However, the primary outcome measure (TAPSE) was obtained in all but two patients, and we present a number of measures of RV systolic function, size, and afterload, along with NT-proBNP results.((

Finally, we were unable to report levels of cardiovascular support at the time of the postrandomization echocardiogram as recommended in the Preferred Reporting Items for Critical Care Echocardiography statement, although detailed ventilator data were available, which is of greater importance in right heart studies (35). However, we report levels of cardiovascular support at baseline and postrandomization in the NT-proBNP cohort.

CONCLUSIONS

In a cohort of patients managed with lower tidal volume ventilation facilitated by $ECCO_2R$, we found no difference in our primary outcome measures of TAPSE or NT-proBNP, or secondary outcome measures of cardiac function. Our findings do not support the use of $ECCO_2R$ in RVD, ACP, or pulmonary hypertension due to AHRF.

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Orde, and Dr. McAuley were responsible for data curation. Dr. Bowcock and Dr. Orde analyzed the echocardiograms included in this investigation. Mr. Conlon conducted the N-terminal pro-B-type natriuretic peptide analysis included in this investigation. Dr. McGuigan, Dr. Bowcock, and Mr. McDowell were responsible for the formal analysis. Dr. McGuigan, Dr. Bowcock, Mr. McDowell were responsible for the statistical analysis plan. Mr. McDowell conducted the formal statistical analysis. Dr. McGuigan, Dr. Bowcock, Dr. Orde, and Mr. Conlon were responsible for the investigation. Dr. McGuigan, Dr. Bowcock, Dr. Orde, and Dr. McAuley were responsible for the methodology. Dr. McGuigan was responsible for the project administration. Dr. Blackwood, Dr. Orde, and Dr. McAuley were responsible for supervision. Dr. McGuigan wrote the original article draft. All authors undertook critical review and editing of the article for important intellectual content. All authors approved the final article. All authors are accountable for the accuracy and integrity of the work.

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