The role of low-flow $ECCO_2R$ in supporting LPV strategies

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How may mechanical ventilation adversely affect patient outcomes?

How may LPV reduce risk of VILI?

How may $ECCO_2R$ facilitate the use of LPV?

Abreviations: ALI, acute lung injury; ARDS, acute respiratory distress syndrome; CI, confidence interval; Crs, respiratory system compliance; $ECCO_2R$, extracorporeal carbon dioxide removal; FiO_2, fraction of inspired oxygen; ICU, intensive care unit; LPV, lung protective ventilation; MV, mechanical ventilation; OR, odds ratio; $PaCO_2$, arterial carbon dioxide partial pressure; PaO_2, arterial oxygen partial pressure; PBW, predicted body weight; PEEP, positive end-expiratory pressure; P_{plat}, plateau pressure; RR, relative risk; V_A/Q, alveolar ventilation to perfusion ratio; VILI, ventilator-induced lung injury; V_T, tidal volume; VV-ECMO, veno-venous extracorporeal membrane oxygenation; ΔP, driving pressure.

How may mechanical ventilation adversely affect patient outcomes?

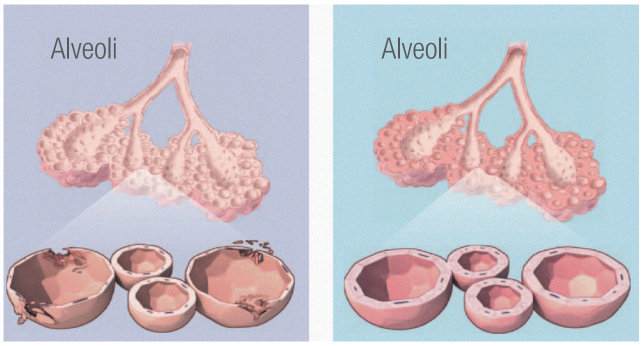
VILI is a potential complication of mechanical ventilation

- The goal of mechanical ventilation is to provide acceptable oxygenation and CO_2 removal while minimizing VILI[1]
- Complications of mechanical ventilation include volutrauma, barotrauma, atelectrauma, and biotrauma[2,3]

Complications of mechanical ventilation

Volutrauma (biophysical injury)	Over-distension of alveoli resulting from increased V_T
Barotrauma (biophysical injury)	Alveolar rupture and air leaks resulting from high pressure
Atelectrauma (biophysical injury)	Damage caused by repetitive opening and closing of collapsed lung parts
Biotrauma (biochemical injury)	Release of biological mediators and translocation into the circulation

Mechanisms of VILI



Extreme stress/strain
Volutrauma, barotrauma
Rupture

Moderate stress/strain
Atelectrauma
↓
Inflammatory mediators
↓
Full-blown inflammation

Biotrauma

Adapted from Gattinoni L, Protti A. *CMAJ* 2008;178:1174–6, with permission from Access Copyright.

- ARDS accounts for approximately 25% of patients requiring mechanical ventilation[4]
- As most patients with ARDS require invasive mechanical ventilation,[1] they are at risk of VILI

ARDS

- An acute inflammatory lung injury that leads to increased pulmonary vascular permeability, increased lung weight and loss of aerated lung tissue, resulting in hypoxemia and bilateral radiographic opacities[5]
- A serious condition that is common but often under-recognized in the ICU,[4] which may limit implementation of effective management
  - In the LUNG SAFE study, 35.8% of all cases were not recognized by physicians[4]
  - Less severe ARDS was more likely to be unrecognized (48.7% of mild cases vs 21.5% of severe cases)[4]

High incidence:[4]

- 1 in 10 of all ICU admissions*
- 1 in 4 of all patients requiring mechanical ventilation*

High mortality rate:[4]

- 40.0% hospital mortality*
- 35.3% ICU mortality*

Risk of multiple organ failure:

- 68.9–70.0% risk of failure of ≥ 2 organs[6]
- 30.0–31.1% risk of failure of ≥ 3 organs[6]
- High rates of renal failure (41–49%) and liver failure (13–34%)[7,8]

*As reported in LUNG SAFE; a large, international, prospective, cohort study (n = 2377).[4]

Evidence from animal studies suggests that VILI may contribute to the development of multiple organ failure

- A proposed mechanism for a relationship with multiple organ failure is based on the systemic release of inflammatory mediators resulting from VILI (biotrauma)[3,9]
- Multiple organ failure has been associated with increased risk of mortality in patients with ALI or ARDS; in one study, multiple organ failure was the cause of death in 16.7% of patients with ARDS[6]

Key points

- Mechanical ventilation is the cornerstone of treatment for patients with impaired lung function[1]
- However, VILI may complicate the management of mechanically ventilated patients,[1,2] particularly those with ARDS
- Evidence from animal studies suggests that VILI can contribute to poor outcomes, including multiple organ failure[3,9]

How may LPV reduce risk of VILI?

Lung protective ventilation strategies modify ventilation parameters to reduce the risk of VILI

Conventional MV	• V_T of 10–15 mL/kg PBW has been traditionally used to normalize $PaCO_2$, PaO_2 and pH[9] • May exacerbate or perpetuate lung injury[9]
Concept of LPV	• Utilizes lower V_T (~6 mL/kg PBW) than conventional MV[9] • Other components may include lower P_{plat}, higher PEEP, and lower ΔP[8,10,11] • Elevated $PaCO_2$ is either accepted (permissive hypercapnia) or may require measures to reduce CO_2 levels[12]
Concept of ultra LPV	• Utilizes even lower V_T ($\leq$ 3 mL/kg PBW) compared with LPV[13] • Other components may include lower P_{plat}, higher PEEP, and lower ΔP[14] • Greater elevations in $PaCO_2$ can occur compared with LPV and extracorporeal lung support is needed to reduce CO_2 levels[13]

Driving pressure

ΔP is defined as V_T normalized to Crs (V_T/Crs) or P_{plat} minus PEEP

$$\Delta P = P_{plat} - \text{PEEP}$$

LPV reduces duration of mechanical ventilation and mortality compared with conventional ventilation

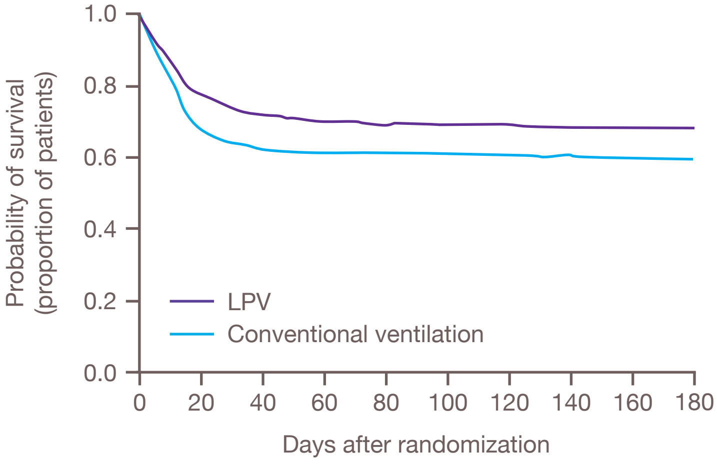
The landmark, randomized, controlled ARDS Network (ARDSNet) study compared conventional ventilation with LPV in 861 patients with ARDS[9]

- **Conventional ventilation:** initial V_T 12 mL/kg PBW and $P_{plat} \leq 50$ cmH_2O
- **LPV:** initial V_T 6 mL/kg PBW and $P_{plat} \leq 30$ cmH_2O

The LPV strategy was associated with:[9]

- Greater probability of survival over 180 days (69.0% vs 60.2%; $p = 0.007$)
- Greater number of ventilator-free days during the first 28 days (12 vs 10 days; $p = 0.007$)
- Greater number of non-pulmonary organ/system failure-free days during the first 28 days (15 vs 12 days; $p = 0.006$)

LPV with the ARDSNet protocol reduces mortality compared with conventional mechanical ventilation[9]

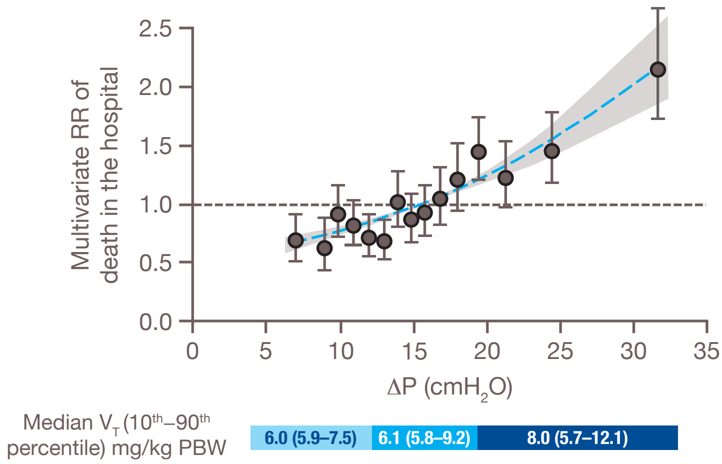


Mortality rate was reduced by 8.8 percentage points with the LPV protocol vs a conventional ventilation protocol

(31.0% vs 39.8%; $p = 0.007$)

Randomized controlled trial (ARDSNet): Clinical outcomes of patients with ALI or ARDS managed with a LPV protocol (initial V_T 6 mL/kg PBW and P_{plat} maintained between 25–30 cmH_2O) were compared with those managed with a conventional ventilation protocol (initial V_T 12 mL/kg PBW and $P_{plat} \leq 50$ cmH_2O). Adapted with permission from ARDS Network. *N Engl J Med* 2000;342:1301–8. Copyright © (2000) Massachusetts Medical Society.

Reducing driving pressure as part of an LPV strategy may improve survival[11]



- ΔP was strongly associated with mortality
  (RR 1.41; 95% CI 1.31–1.51, $p < 0.001$)
- This was true even in patients receiving 'protective' P_{plat} and V_T
  (RR 1.36; 95% CI 1.17–1.58, $p < 0.001$)
- Reductions in V_T or increases in PEEP were associated with better survival only if associated with reductions in ΔP

Randomized controlled trials: The relationship between different ventilation parameters and mortality was explored in a mediation analysis of data from 9 randomized controlled trials in patients with ARDS ($n = 3562$). Data shown as the increase in RR of hospital mortality as a function of ΔP after multivariate adjustment (95% CIs represented as grey shaded area). Adapted with permission from Amato MB, et al. *N Engl J Med* 2015;372:747–55. Copyright © (2015) Massachusetts Medical Society.

Key points

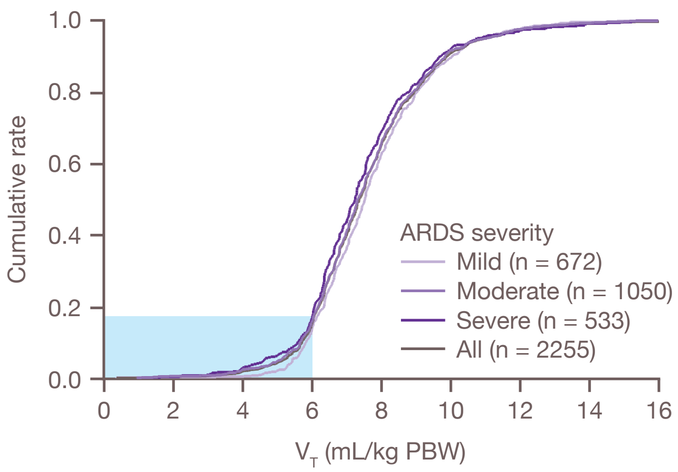
- LPV strategies modify ventilation parameters that have been shown to increase the risk of VILI[9]
- The ARDSNet LPV protocol, based on reduced V_T and P_{plat}, improves patient outcomes, including mortality[9,11] and duration of mechanical ventilation[9]
- More recent evidence shows that lower ΔP is associated with a reduced mortality risk in patients with ARDS[11]

How may low-flow $ECCO_2R$ facilitate the use of LPV?

Despite guidelines supporting the use of LPV,[15–18] V_T often exceeds 6 mL/kg PBW in clinical practice

- In a cross-sectional survey of 200 German ICUs (n = 152), only 2.6% of patients received low V_T ventilation despite the fact that perceived adherence by ICU directors was 79.9%[19]
- In the LUNG SAFE study (n = 2255), more than one-third of patients were mechanically ventilated with $V_T > 8$ mL/kg PBW[4]

Adherence to LPV is poor in clinical practice[4]



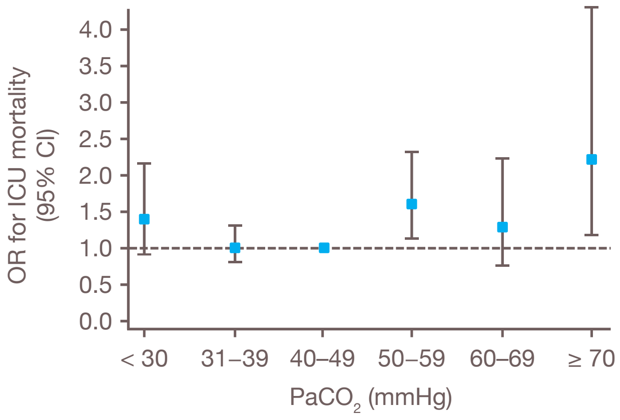
- $V_T \leq 6$ mL/kg PBW was used in only about 20% of patients with ARDS in the LUNG SAFE study
- Differences in mean V_T between patients with mild and severe ARDS were clinically modest

Prospective cohort study: Ventilatory management of patients with ARDS (Berlin definition; n = 2255) was assessed as a secondary endpoint in the LUNG SAFE study. Adapted with permission from Bellani G, et al. *JAMA* 2016;315:788–800. Copyright © (2016) American Medical Association. All rights reserved.

Major barriers to LPV adherence include concerns about hypercapnia and respiratory acidosis induced by V_T reduction[20–22]

- Hypercapnia is often regarded as an acceptable side effect, however, physiological effects may include pulmonary vasoconstriction, increased intracranial pressure, and decreased renal blood flow, among others[12]
- Recent evidence indicates that hypercapnia is associated with an increased risk of ICU mortality[23]

Severe hypercapnia is associated with an increased risk of ICU mortality[23]



$PaCO_2 \geq 50$ mmHg was independently associated with higher ICU mortality
(OR 2.40; 95% CI 1.67–3.46, $p < 0.001$)

Prospective observational studies: The relationship between hypercapnia and ICU mortality was assessed in a secondary analysis of 3 studies that included data from 1899 patients with moderate-to-severe ARDS. Results from a logistic regression model with adjustment for baseline variables are shown. Adapted with permission of Springer from Nin N, et al. *Intensive Care Med* 2017;43:200–8.

$ECCO_2R$ enhances CO_2 removal in patients receiving LPV

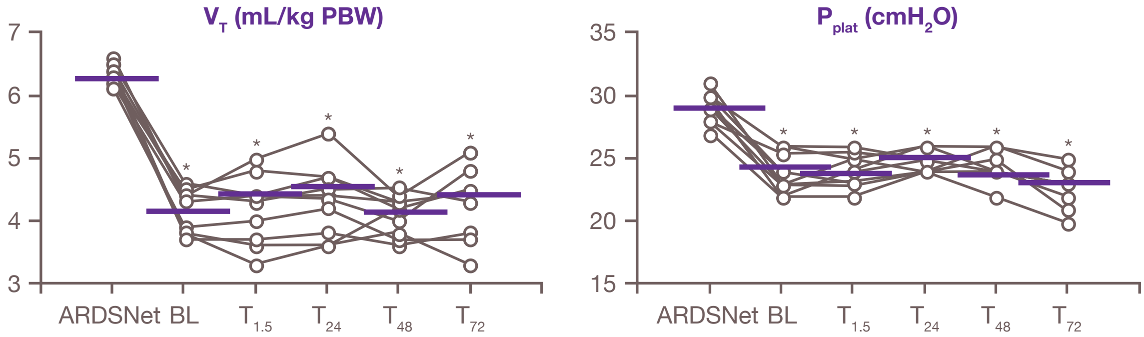
- Evidence shows that $ECCO_2R$ systems significantly reduce $PaCO_2$ levels, and may, therefore, facilitate LPV by allowing for a reduction in V_T[24]
- More specifically, low-flow $ECCO_2R$ devices using flow rates as low as 0.5 L/min should theoretically be sufficient to eliminate all CO_2 produced by the body[24]

1 L of blood with a $PaCO_2$ of 5 kPa contains around 500 mL of CO_2, or on average, two times more CO_2 than the body produces per minute

Low-flow $ECCO_2R$ enables use of LPV by reducing $PaCO_2$ levels and normalizing arterial pH

- The ability of low-flow $ECCO_2R$ to facilitate use of LPV has been demonstrated in a prospective study of patients with ARDS, 10 of whom had P_{plat} within the range of 28–30 cmH_2O while being treated with the ARDSNet protocol[25]

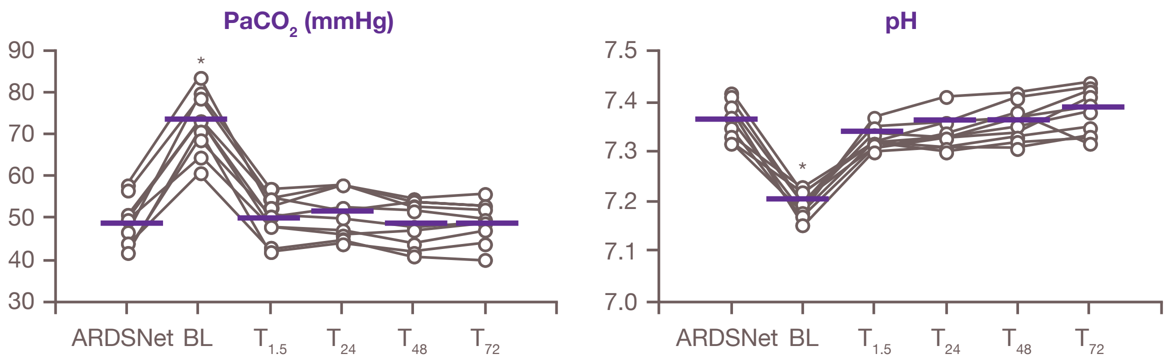
Low-flow $ECCO_2R$ allows for maintenance of V_T and P_{plat} in line with LPV strategies[25]



Prospective study: Data shown as individual and average (horizontal bars) values of V_T and P_{plat} during LPV with the ARDSNet protocol, after lowering V_T (BL), and at 1–1.5, 24, 48, and 72 hours after initiation of $ECCO_2R$ (n = 10 ICU patients with ARDS [American-European Consensus Conference definition]). *p < 0.001 vs ARDSNet ventilation. BL, baseline. Adapted with permission from Terragni PP, et al. *Anesthesiology* 2009;111:826–35.

- Patients received low-flow $ECCO_2R$ following a reduction in V_T to < 6 mL/kg PBW
- Low-flow $ECCO_2R$ allowed for maintenance of V_T < 6 mL/kg/PBW
- Low-flow $ECCO_2R$ allowed for maintenance of P_{plat} between 25–28 cmH_2O

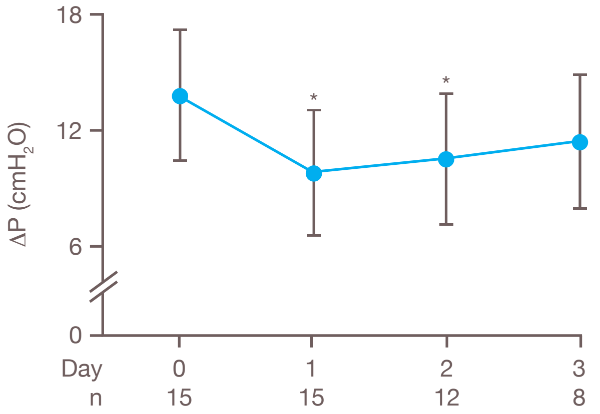
Low-flow $ECCO_2R$ reduces $PaCO_2$, thereby normalizing arterial pH[25]



Prospective study: Data shown as individual and average (horizontal bars) values of $PaCO_2$ and arterial pH during LPV with the ARDSNet protocol, after lowering V_T (BL), and at 1–1.5, 24, 48, and 72 hours after initiation of $ECCO_2R$ (n = 10 ICU patients with ARDS [American-European Consensus Conference definition]). *p < 0.001 vs ARDSNet ventilation. Adapted with permission from Terragni PP, et al. *Anesthesiology* 2009;111:826–35.

- Compared with baseline, $PaCO_2$ was significantly reduced and arterial pH was significantly increased after 1–1.5 hours of initiating low-flow $ECCO_2R$ (p < 0.001 for both)
- After 72 hours of low-flow $ECCO_2R$, the reduction in $PaCO_2$ was sufficient to normalize pH

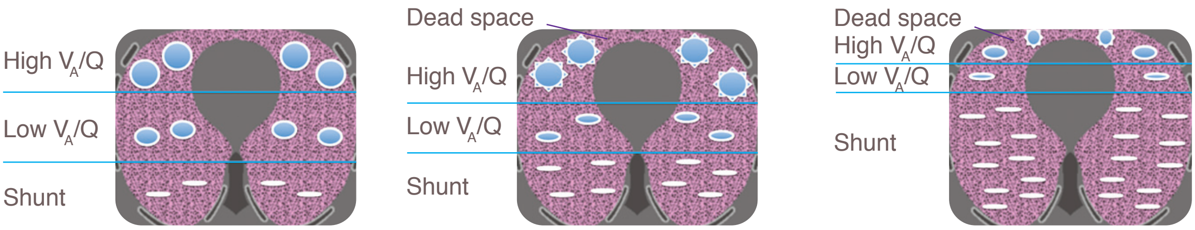
Ultraprotective ventilation facilitated by low-flow $ECCO_2R$ may reduce driving pressure[14]



- ΔP – an independent risk factor for hospital mortality[11] – was significantly reduced during the first two days of treatment vs baseline (13.9 vs 11.6 cmH_2O; $p < 0.05$)
- $PaCO_2$ and pH were corrected to within 10% of baseline values

Prospective study: The feasibility of very low V_T ventilation (4 mL/kg PBW) combined with low-flow $ECCO_2R$ was evaluated in patients with moderate ARDS (Berlin definition; n = 15). Adapted from Fanelli V, et al. *Crit Care* 2016;20:36.

$ECCO_2R$ may have a role in the management of patients with moderate to severe ARDS – an example algorithm[26]



Assuming: Optimum MV settings and application of adjunctive therapies		
Rare circumstances: $ECCO_2R$ may be considered to facilitate ultra LPV	**Consider $ECCO_2R$:** • pH < 7.25 for > 2 h • P_{plat} > 28 cmH_2O for > 2 h • Further reduction in risk of VILI (ultra LPV)	**Consider VV-ECMO to facilitate gas exchange during complete lung rest***
Mild ARDS	**Moderate ARDS**	**Severe ARDS**

Adapted from Del Sorbo L, et al. *Lancet Respir Med* 2014;2:154–64, with permission from Elsevier.

Note: This example algorithm is based on author opinion and is not a recognized guideline. Severity based on the Berlin definition.[5]
*$PaO_2/FiO_2 < 50$ with $FiO_2 > 0.8$ for > 3 h, or $PaO_2/FiO_2 < 80$ with $FiO_2 > 0.8$ for > 6 h.

Key points

- Despite evidence and guidelines in support of LPV, concerns about hypercapnia and respiratory acidosis resulting from LPV may limit its use[20–22]
- Recent evidence shows that severe hypercapnia is independently associated with increased ICU mortality[23]
- $ECCO_2R$ – even at low blood flow rates – enables use of LPV and ultra LPV by reducing $PaCO_2$ and thereby normalizing pH[25]

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