Advances in Mechanical Ventilation

permissive vs aggressive ventilation
Disclosures

• until January 2021 Xenios/Fresenius, Germany
• until January 2023 Hamilton Medical AG, Switzerland
Agenda

- permissive vs aggressive ventilation
- low $V_T$ ventilation
- lower or higher PEEP
- $\Delta P$ and MP
- prioritization of settings
Agenda

- permissive vs aggressive ventilation
- low $V_T$ ventilation
- lower or higher PEEP
- $\Delta P$ and MP
- prioritization of settings
**ventilator settings in critically ill patients—prioritize permissive over aggressive ventilation**

**Combining the settings**
Everchanging patient conditions mandate frequent refinements; automation could be helpful, also by reducing the ICU staff workloads associated with lung-protective ventilation.

**Integrate**
Refine settings further by incrementally adjusting $V_T$, PEEP, RR and FiO$_2$.

**Use low $V_T$**
Reduce the size of $V_T$; reductions might be more beneficial in patients with less compliant lungs.

**Do not use high PEEP by default**
Limit use of high PEEP to patients with severe hypoxemia, and only when lung lesions are recruitable; instead, consider prone positioning.

**Check ∆P and MP**
If high, consider reducing $V_T$ further; consider a change in other ventilator settings, like higher PEEP when lung lesions may be recruitable, or a longer inspiration time.

**Use O$_2$ wisely**
Do not target high O$_2$ levels; use high FiO$_2$ if a reduction in $V_T$ and use of low PEEP results in hypoxemia.

**Reduce the RR**
In an attempt to reduce MP, reduce RR; allow the CO$_2$ level to rise if MP remains high.

**Permissive hypercapnia**
RR is an important contributor to the amount of energy transferred to the lung; lowering RR reduces MP, but may induce hypercapnia.

**Chemotrauma**
Several studies have pointed at the side-effects of hyperoxia; some randomized clinical trials have shown benefit of restrictive O$_2$ use; a low O$_2$ target, though, might increase the risk of hypoxemia.

**Atelectrauma vs overdistension**
Randomized clinical trials could not confirm benefit from high PEEP, and observational studies even suggested harm; in some patients high PEEP could lead to overdistension rather than recruitment.

**Energytrauma**
Meta-analyses showed associations of higher ∆P and MP with relevant clinical outcomes; even short periods with high ∆P or high MP could be detrimental.

**Rational**
**Volutrauma**
Randomized clinical trials and observational studies have shown benefit from low $V_T$; ventilation with low $V_T$ might lead to hypoxemia; a compensatory increase in RR may be harmful.

Infographic on ventilation management by Marcus Schultz, Amsterdam UMC, Amsterdam, the Netherlands (1.1-240423)

$V_T$, tidal volume; PEEP, positive end-expiratory pressure; ∆P, driving pressure; MP, mechanical power of ventilation; RR, respiratory rate; FiO$_2$, fraction of inspired O$_2$.
**Rational**

**Volutrauma**
Randomized clinical trials and observational studies have shown benefit from low $V_T$; ventilation with low $V_T$ might lead to hypoxemia; a compensatory increase in RR may be harmful.

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Several studies have pointed at the side-effects of hyperoxia; some randomized clinical trials have shown benefit of restrictive $O_2$ use; a low $O_2$ target, though, might increase the risk of hypoxemia.

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RR is an important contributor to the amount of energy transferred to the lung; lowering RR reduces MP, but may induce hypercapnia.

**Integrate**
Refine settings further by incrementally adjusting $V_T$, PEEP, RR and $FiO_2$.

**Combining the settings**
Everchanging patient conditions mandate frequent refinements; automation could be helpful, also by reducing the ICU staff workloads associated with lung–protective ventilation.

**Use low $V_T$**
Reduce the size of $V_T$; reductions might be more beneficial in patients with less compliant lungs.

**Use $O_2$ wisely**
Do not target high $O_2$ levels; use high $FiO_2$ if a reduction in $V_T$ and use of low PEEP results in hypoxemia.

**Check $\Delta P$ and MP**
If high, consider reducing $V_T$ further; consider a change in other ventilator settings, like higher PEEP when lung lesions may be recruitable, or a longer inspiration time.

**Reduce the RR**
In an attempt to reduce MP, reduce RR; allow the $CO_2$ level to rise if MP remains high.

**Do not use high PEEP by default**
Limit use of high PEEP to patients with severe hypoxemia, and only when lung lesions are recruitable; instead, consider prone positioning.

**Energytrauma**
Meta–analyses showed associations of higher $\Delta P$ and MP with relevant clinical outcomes; even short periods with high $\Delta P$ or high MP could be detrimental.

**Rational**
Combining the settings
Everchanging patient conditions mandate frequent refinements; automation could be helpful, also by reducing the ICU staff workloads associated with lung–protective ventilation.
Traditionally–sized VT
VT of 10–15 ml/kg PBW improves oxygenation, and reduces the need for high RR.

Low VS high VT
Randomized clinical trials have shown benefit of low VT; realize, though, that these studies were mostly conducted in deeply sedated and often paralyzed patients.

Combining the settings
Low VT effects both oxygenation and decarboxylation, and thus may require the use of higher FiO₂, perhaps even increases in PEEP, and adjustments in RR—but keep ΔP and MP low.

In the early years of ICU
High VT was traditionally used in the operating room to prevent hypoxemia, also because PEEP was hardly used in this setting; and with high VT RR can stay low.

Ultralow VT
Interest has moved into using even lower VT; however, lower VT leads to hypercapnia, and so far ultralow VT has only been thoroughly tested under extracorporeal removal of CO₂.

Rational

Harm of low VT?
Re–analysis of preceding studies suggest that low VT could also be harmful; in patients with relative normal C₉S the use of low VT could cause harm if it triggers the use of higher RR.

Keep Vₜ low in selected cases
Low VT should be considered in deeply sedated and paralyzed patients, and in patients with a low Cₛₑ, even those without ARDS; low VT can decrease ΔP and MP in these patients as well.

Integrate
Refine the settings; keep in mind that the goal of ventilation is ‘lung–protection’, and not necessarily gas exchange.

Use even lower VT in selected cases
A further reduction of VT, to e.g., 4 ml/kg PBW, might be beneficial, for instance when ΔP and MP remain high, but it comes with a need for higher RR; extracorporeal removal of CO₂ might help to keep both VT and RR low.

Rational

Vₜ, tidal volume; PBW, predicted body weight; PEEP, positive end–expiratory pressure; ΔP, driving pressure; MP, mechanical power of ventilation; Cₛₑ, respiratory system compliance; RR, respiratory rate; FiO₂, fraction of inspired O₂
QUESTION Does the use of a lower tidal volume ($V_T$) with mechanical ventilation affect important clinical outcomes in ARDS patients?

CONCLUSION Ventilation with a lower $V_T$ than is traditionally used results in decreased mortality and increases the number of days without ventilator use.

### POPULATION

<table>
<thead>
<tr>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td>344</td>
<td>516</td>
</tr>
</tbody>
</table>

344 Women, 516 Men

Patients with ARDS

Mean age: 52 years

### LOCATION

ICUs in the USA

### VENTILATION STRATEGIES

- **861 patients** with mild, moderate or severe ARDS
- **432 patients** with lower $V_T$ (6 ml/kg) (~400 to 500 ml)
- **429 patients** with traditional $V_T$ (12 ml/kg) (~1000 to 1200 ml)

### (PRIMARY) OUTCOME

Hospital mortality and duration of invasive ventilation

### FINDINGS

QUESTION For patients in the ICU who are ventilated for reasons other than ARDS, is low tidal volume superior to intermediate tidal volume?

CONCLUSION Among ICU patients receiving invasive ventilation, a strategy with a low tidal volume was not superior to using intermediate tidal volume.

POPULATION

621 Men 340 Women
ICU patients without ARDS expected to be intubated for more than 24 hours
Median age: 68 years (IQR, 59-76)

LOCATIONS
6 ICUs in the Netherlands

INTERVENTIONS

961 Patients randomized
477 Randomized
475 Analyzed
484 Randomized
480 Analyzed

Low tidal volume
Started at tidal volume of 6 mL/kg; tidal volume then decreased in steps of 1 mL/kg predicted body weight

Intermediate tidal volume
Started at tidal volume of 10 mL/kg; if plateau pressure exceeded 25 cm H₂O, tidal volume was decreased in steps of 1 mL/kg predicted body weight

FINDINGS

PRIMARY OUTCOME
Number of ventilator-free days and alive at day 28

Writing Group for the PReVENT Investigators. Effect of a low vs intermediate tidal volume strategy on ventilator-free days in intensive care unit patients without ARDS: a randomized clinical trial [published online October 24, 2018]. JAMA. doi:10.1001/jama.2018.14280
QUESTION What is the impact of mechanical power on mortality in patients with ARDS as compared with that of primary ventilator variables such as the $\Delta P$, $V_T$, and RR?

CONCLUSION Mechanical power was associated with mortality during controlled mechanical ventilation in ARDS, but a simpler model using only the $\Delta P$ and RR was equivalent.

POPULATION

1728 Women  2821 Men

Patients with ARDS

Mean Age: 55 years

LOCATION

6 RCTs and 1 observational study

VENTILATION PARAMETERS

4549 patients with mild, moderate or severe ARDS

MP 0.32 J/min/kg

$\Delta P$ 15 cm H$_2$O

RR 26 breath/min

(FRIMARY) OUTCOME

Mortality at 28 or 60 days

FINDINGS

**ventilator settings in critically ill patients—prioritize permissive over aggressive ventilation**

**Combining the settings**
Ever-changing patient conditions mandate frequent refinements; automation could be helpful, also by reducing the ICU staff workloads associated with lung-protective ventilation.

**Integrate**
Refine settings further by incrementally adjusting $V_T$, PEEP, RR, and FiO$_2$.

**Use low $V_T$**
Reduce the size of $V_T$; reductions might be more beneficial in patients with less compliant lungs.

**Do not use high PEEP by default**
Limit use of high PEEP to patients with severe hypoxemia, and only when lung lesions are recruitable; instead, consider prone positioning.

**Chemotrauma**
Several studies have pointed at the side-effects of hyperoxia; some randomized clinical trials have shown benefit of restrictive O$_2$ use; a low O$_2$ target, though, might increase the risk of hypoxemia.

**Use O$_2$ wisely**
Do not target high O$_2$ levels; use high FiO$_2$ if a reduction in $V_T$ and use of low PEEP results in hypoxemia.

**Permissive hypercapnia**
RR is an important contributor to the amount of energy transferred to the lung; lowering RR reduces MP, but may induce hypercapnia.

**Reduce the RR**
In an attempt to reduce MP, reduce RR; allow the CO$_2$ level to rise if MP remains high.

**Check $\Delta P$ and MP**
If high, consider reducing $V_T$ further; consider a change in other ventilator settings, like higher PEEP when lung lesions may be recruitable, or a longer inspiration time.

**Volutrauma**
Randomized clinical trials and observational studies have shown benefit from low $V_T$; ventilation with low $V_T$ might lead to hypoxemia; a compensatory increase in RR may be harmful.

**Atelectrauma vs overdistension**
Randomized clinical trials could not confirm benefit from high PEEP, and observational studies even suggested harm; in some patients high PEEP could lead to overdistension rather than recruitment.

**Energytrauma**
Meta-analyses showed associations of higher $\Delta P$ and MP with relevant clinical outcomes; even short periods with high $\Delta P$ or high MP could be detrimental.

**Rational**
Combining the settings

**Rational**
Integrate

**Rational**
Use O$_2$ wisely

**Rational**
Permissive hypercapnia

**Rational**
Reduce the RR

**Rational**
Check $\Delta P$ and MP

**Rational**
Volutrauma

**Rational**
Atelectrauma vs overdistension

**Rational**
Energytrauma

$V_T$, tidal volume; PEEP, positive end-expiratory pressure; $\Delta P$, driving pressure; MP, mechanical power of ventilation; RR, respiratory rate; FiO$_2$, fraction of inspired O$_2$.

Infographic on ventilation management by Marcus Schultz, Amsterdam UMC, Amsterdam, the Netherlands (1.1–240423)
titration of PEEP in critically ill patients—prioritize clinical benefit over physiology

**Combining the settings**
Low PEEP may favor atelectases, but high PEEP increases the risk of overdistension; monitoring ∆P, and maybe also MP, could be helpful; note that (high) PEEP may have a negative effect on circulation.

**Integrate**
The goal of ventilation is ‘lung-protection’; do not chase physiology—instead, accept the pathophysiology; in the end, ventilation is not physiological at all.

**What is ‘Low’ PEEP?**
Not sure – but ever wondered why the ‘lowest’ PEEP is 5 cmH\textsubscript{2}O? There is no physiology behind this ‘magic’ number—it is the number of fingers on one hand.

**Do not use high PEEP by default**
Despite neutral, and even negative findings in studies, high PEEP remains popular to use; findings of meta-analyses, though, strongly argue against the use of high PEEP.

**Use a table to set PEEP (and FiO\textsubscript{2})**
Use a ‘low PEEP/high FiO\textsubscript{2}’ table, as use of a ‘high PEEP/low FiO\textsubscript{2}’ table has no advantages—it could even be harmful to use; currently, there are no valid arguments to use P\textsubscript{eso}, outside of a research setting.

**‘Physiology’ of PEEP**
PEEP can improve lung aeration; realize, though, that PEEP always causes lung overdistension as well.

**Rational**

**Patients without ARDS**
One randomized clinical trial showed low PEEP (to as low as 0 cmH\textsubscript{2}O) to be non—inferior to fixed high PEEP (of 8 cmH\textsubscript{2}O); as expected, more often hypoxemia occurred with low PEEP.

**PEEP vs FiO\textsubscript{2}**
So the ‘lowest’ PEEP can be 0 cmH\textsubscript{2}O, even if this means that higher FiO\textsubscript{2} is needed—at least in patients without ARDS the best PEEP may be the ‘lowest possible PEEP’ with which sufficient oxygenation is guaranteed.

**High PEEP**
Randomized clinical trials in patients with ARDS failed to show clinical benefit of high PEEP; one well–performed randomized clinical trial in patients with ARDS even showed harm of high PEEP.

**Rational**

**Heterogeneity**
There is heterogeneity of treatment effect; one Bayesian re–analysis suggest harm of high PEEP in patients with ARDS from pneumonia; one randomized clinical trial suggest harm from high PEEP if ARDS lesions are not recruitable.

**Individualize (high) PEEP**
High PEEP may still be beneficial, but probably only in ARDS patients with recruitable lung lesions, and only when the balance between recruitment and overdistension is acceptable. Monitoring changes in ∆P, and maybe also in MP, could be helpful herein.

**Titration of PEEP**
One approach is to use PEEP/FiO\textsubscript{2} tables; another way is to use P\textsubscript{eso}, but randomized clinical trials failed to show clinical benefit of this approach.

PEEP, positive end–expiratory pressure; ARDS, acute respiratory distress syndrome; P\textsubscript{eso}, esophagus pressure; ∆P, driving pressure; MP, mechanical power of ventilation; FiO\textsubscript{2}, fraction of inspired O\textsubscript{2}
QUESTION What is the association of higher vs lower PEEP with patient-important outcomes in adults with ARDS who are receiving ventilation with low tidal volumes?

CONCLUSION Higher levels of PEEP were associated with improved survival among patients with moderate to severe ARDS.

POPULATION

892 Women 1407 Men

patients with mild, moderate or severe ARDS (IPD metaanalysis)

Mean Age: 56 years

LOCATION

3 RCTs in 4 countries

VENTILATION STRATEGIES

2299 patients with mild, moderate or severe ARDS

1136 patients high PEEP (> 15 cm H₂O) with RM

1163 patients low PEEP (< 12 cm H₂O) without RM

(PRIMARY) OUTCOME

28–day mortality; length of ICU and hospital stay; VFD28; pneumothorax requiring drainage or barotrauma within 7 days

FINDINGS

benefit in moderate to severe ARDS, harm in mild ARDS

Briel M et al. Higher vs Lower Positive End-Expiratory Pressure in Patients With Acute Lung Injury and Acute Respiratory Distress Syndrome – Systematic Review and Meta-analysis [JAMA 2010; 303:865]
**QUESTION** Does use of a lung recruitment maneuver associated with PEEP titration according to the best respiratory-system compliance reduce 28-day mortality of patients with moderate to severe ARDS, compared with a conventional low–PEEP strategy?

**CONCLUSION** A strategy using a lung recruitment maneuver and titrated PEEP increased mortality of patients with moderate to severe ARDS.

**POPULATION**

<table>
<thead>
<tr>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td>379</td>
<td>631</td>
</tr>
</tbody>
</table>

Consecutive patients with moderate to severe ARDS

Mean Age: 51 years

**LOCATION**

120 ICUs from 9 countries

**VENTILATION STRATEGIES**

- **1010 patients with moderate or severe ARDS**
  - 501 patients titrated (high) PEEP [$>15$ cm $H_2O$] with RM
  - 509 patients standard (low) PEEP [$<12$ cm $H_2O$] without RM

**FINDINGS**

Lower $\Delta P$ (l), but more pneumothorax and barotrauma with high PEEP + RM

**PRIMARY OUTCOME**

28–day mortality; length of ICU and hospital stay; VFD28; pneumothorax requiring drainage or barotrauma within 7 days

Writing Group for the Alveolar Recruitment for Acute Respiratory Distress Syndrome Trial (ART) Investigators. Effect of Lung Recruitment and Titrated PEEP vs Low PEEP on Mortality in Patients With ARDS–A Randomized Clinical Trial [JAMA 2017; 318:1335]
**QUESTION** Do ventilation strategies using higher PEEP and/or RMs decrease mortality in patients with ARDS ventilated with low tidal volumes?

**CONCLUSION** In patients ventilated with low tidal volumes, the routine use of higher PEEP and/or RMs does not reduce mortality in unselected patients with ARDS.

**POPULATION**

- **1482** Women
- **2388** Men

Patients with moderate to severe ARDS (IPD metanalysis)

**LOCATION**

- **16** RCTs worldwide

**VEVENTRATION STRATEGIES**

- **3870** patients moderate or severe ARDS
- **1377** patients higher PEEP, no RM
- **2383** patients higher PEEP, RM
- **110** patients RM alone

**FINDINGS**

**Study**

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Events</th>
<th>Control</th>
<th>Events</th>
<th>Mortality</th>
<th>RR</th>
<th>95% CI</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Higher PEEP alone</td>
<td>276</td>
<td>68</td>
<td>273</td>
<td>1.11</td>
<td>[0.82; 1.46]</td>
<td>13.4%</td>
<td></td>
</tr>
<tr>
<td>Talbot 2006</td>
<td>12</td>
<td>0</td>
<td>12</td>
<td>0.89</td>
<td>[0.72; 1.11]</td>
<td>17.7%</td>
<td></td>
</tr>
<tr>
<td>Moris 2006</td>
<td>107</td>
<td>386</td>
<td>119</td>
<td>0.89</td>
<td>[0.72; 1.11]</td>
<td>17.7%</td>
<td></td>
</tr>
<tr>
<td>Subgroup</td>
<td>168</td>
<td>69</td>
<td>190</td>
<td>0.91</td>
<td>[0.66; 1.23]</td>
<td>33.1%</td>
<td></td>
</tr>
</tbody>
</table>

**Test for effect in subgroup:** $z = -0.60$ (p = 0.55)

**Higher PEEP and recruitment manoeuvres**

| Meade 2000 | 120 | 30 | 92 | 1.20 | [0.60; 2.39] | 3.3% |
| Huht 2009 | 12 | 3 | 9 | 1.50 | [0.30; 7.14] | 0.7% |
| Kacmarek 2001 | 22 | 9 | 21 | 0.93 | [0.31; 1.36] | 9.7% |
| Cavallero 2001 | 277 | 50 | 251 | 1.12 | [1.00; 1.26] | 27.5% |
| Hodgetts 2009 | 30 | 14 | 15 | 0.90 | [0.49; 1.72] | 3.9% |
| Subgroup | 463 | 1172 | 466 | 1211 | 1.01 | [0.80; 1.26] | 61.4% |

**Test for effect in subgroup:** $z = -0.20$ (p = 0.86)

**Recruitment manoeuvres**

| X1 2010 | 16 | 55 | 24 | 0.55 | [0.40; 1.11] | 5.5% |
| Subgroup | 16 | 55 | 24 | 0.67 | [0.40; 1.11] | 5.5% |

**Random effects model**

| Model 1918 | 691 | 1952 | 0.95 | [0.84; 1.09] | 100.0% |

**Test for overall effect:** $z = -0.08$ (p = 0.93)

**Test for subgroup differences:** $z = 3.65$ (p = 0.02)

**Fig. 2** Forest plot for mortality (collapsed at 28 days, ICU discharge, hospital discharge or 60-day survival). Studies are stratified according to whether higher PEEP and recruitment manoeuvres were used separately or as a bundle of interventions, ICU, intensive care unit; PEEP, positive end-expiratory pressure.

Ball L et al. Effects of higher PEEP and recruitment manoeuvres on mortality in patients with ARDS: a systematic review, meta-analysis, meta-regression and trial sequential analysis of randomized controlled trials [ICMx 2022; 205:865]
QUESTION What are the relative effects of different PEEP selection strategies on mortality in adult patients with moderate to severe Acute Respiratory Distress Syndrome?

CONCLUSION In adult patients with moderate to severe Acute Respiratory Distress Syndrome, higher PEEP without LRM is associated with a lower risk of death.

POPULATION

4646 Patients

patients with moderate to severe ARDS (IPD metanalysis)

Mean Age: 60 years

LOCATION

18 RCTs worldwide

STRATEGIES

2223 patients low PEEP

690 patients higher PEEP without RM

127 patients PES-guided

948 patients higher PEEP with prolonged RM

658 patients higher PEEP with short RM

(PRIMARY) OUTCOME

28–day mortality; various other ICU and hospital outcomes

[a network meta–analysis using a Bayesian framework]

FINDINGS

**QUESTION** In patients with COVID–19–related ARDS, is a higher PEEP strategy superior to a lower PEEP strategy with regard to the number of ventilator–free days (VFDs)?

**CONCLUSION** In patients with C–ARDS, use of higher PEEP may be associated with a lower number of VFDs, and may increase the incidence of AKI and need for RRT.

**PARTICIPANTS**

- **318 Women**
- **675 Men**

Studies in patients with C–ARDS

- Median age: 65 years

**LOCATION**

- **22 ICUs in the Netherlands**

**VENTILATION STRATEGIES**

- **993 patients with moderate to severe ARDS**
  - **674 patients** lower PEEP
  - **259 patients** higher PEEP

- **468 matched patients** lower PEEP
- **234 matched patients** higher PEEP

**FINDINGS**

- Number of VFDs, distant organ failures including AKI and use of RRT, and mortality

QUESTION Is there heterogeneity in treatment effects in patients enrolled in the ART, using a machine learning approach?

CONCLUSION Recruitment maneuvers and titrated PEEP may be harmful in ARDS patients with pneumonia or requiring vasopressor support. Driving pressure appears to modulate the association between the ART study intervention, etiology of ARDS, and mortality.

POPULATION

379 Women  631 Men

Consecutive patients with moderate to severe ARDS

Mean Age: 51 years

LOCATION

120 ICUs from 9 countries

VENTILATION STRATEGIES

1010 patients with moderate or severe ARDS

501 patients titrated (high) PEEP [>15 cm H₂O] with RM

509 patients standard (low) PEEP [<12 cm H₂O] without RM

FINDINGS

OUTCOME OF THE BAYESIAN ANALYSIS

28–day mortality

**QUESTION** Does a mechanical ventilation strategy that is personalized to individual patients' lung morphology improve the survival of patients with ARDS when compared with standard of care?

**CONCLUSION** Personalization of ventilation decreased mortality in patients with ARDS [in the posthoc analysis]; a ventilator strategy misaligned with lung morphology substantially increases mortality.

### POPULATION

<table>
<thead>
<tr>
<th>Gender</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women</td>
<td>114</td>
</tr>
<tr>
<td>Men</td>
<td>286</td>
</tr>
</tbody>
</table>

Patients with ARDS for less than 12 hours

Median Age: 62 years

### LOCATION

20 ICUs in France

### INTERVENTION

- **400 patients with moderate to severe ARDS**
  - **204 standard care**
    - $V_T$ 6 ml/kg PBW
    - low PEEP
  - **196 personalized care**
    - **non–focal**
      - $V_T$ 6 ml/kg PBW
      - high PEEP with RM
    - **focal**
      - $V_T$ 8 ml/kg PBW
      - low PEEP and prone positioning

### FINDINGS

- **mortality at day 90**; ventilator–free days, ARDS resolution; LOS in ICU; barotrauma

- **Medians** for ventilator–free days (in days):
  - Control group (n=204): 135
  - Personalised group (n=156): 160

- **LOS in ICU (in days):**
  - Control group (n=204): 129
  - Personalised group (n=156): 150

QUESTION Does a mechanical ventilation strategy that is personalized to individual patients’ lung morphology improve the survival of patients with ARDS when compared with standard of care?

CONCLUSION Personalization of ventilation decreased mortality in patients with ARDS [in the posthoc analysis]; a ventilator strategy misaligned with lung morphology substantially increases mortality.

POPULATION

114 Women  286 Men

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Median Age: 62 years

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400 patients with moderate to severe ARDS

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V_T 6 ml/kg PBW
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V_T 6 ml/kg PBW
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focal

V_T 8 ml/kg PBW
low PEEP and
prone positioning

(FRIMARY) OUTCOME

mortality at day 90; ventilator–free days,
ARDS resolution; LOS in ICU; barotrauma

FINDINGS

QUESTION In ICU patients who received invasive ventilation for reasons other than acute respiratory distress syndrome (ARDS), is a strategy with lower positive end-expiratory pressure (PEEP) noninferior to higher PEEP with respect to ventilator-free days at day 28?

CONCLUSION This clinical trial found that among ICU patients receiving invasive ventilation, a strategy with lower PEEP was noninferior to a strategy using higher PEEP for the outcome of ventilator-free days, supporting the use of lower PEEP in patients without ARDS.

POPULATION

623 Men  346 Women

Adults without ARDS expected not to be extubated within 24 hours of intubation

Median age: 66 years

LOCATIONS

8 ICUs in the Netherlands

INTERVENTION

980 Patients randomized
969 Patients analyzed

476 Lower PEEP strategy
Lowest level between 0-5 cm H₂O

493 Higher PEEP strategy
Lowest level of 8 cm H₂O

PRIMARY OUTCOME

Number of ventilator-free days by study day 28 (noninferiority margin of −10%)
Step 1: Use low V$_T$
- Reduce the size of V$_T$; reductions might be more beneficial in patients with less compliant lungs.

Step 2: Do not use PEEP by default
- Limit use of high PEEP to patients with severe hypoxemia, and only when lung lesions are recruitable; instead, consider prone positioning.

Step 3: Check ∆P and MP
- If high, consider reducing V$_T$ further; consider a change in other ventilator settings, like higher PEEP when lung lesions may be recruitable, or a longer inspiration time.

Step 4: Reduce the RR
- In an attempt to reduce MP, reduce RR; allow the CO$_2$ level to rise if MP remains high.

Step 5: Use O$_2$ wisely
- Do not target high O$_2$ levels; use high FiO$_2$ if a reduction in V$_T$ and use of low PEEP results in hypoxemia.

Step 6: Integrate
- Refine settings further by incrementally adjusting V$_T$, PEEP, RR and FiO$_2$.

Rational
- Volutrauma
  - Randomized clinical trials and observational studies have shown benefit from low V$_T$; ventilation with low V$_T$ might lead to hypoxemia; a compensatory increase in RR may be harmful.

Rational
- Atelectrauma vs overdistension
  - Randomized clinical trials could not confirm benefit from high PEEP, and observational studies even suggested harm; in some patients high PEEP could lead to overdistension rather than recruitment.

Rational
- Energytrauma
  - Meta-analyses showed associations of higher ∆P and MP with relevant clinical outcomes; even short periods with high ∆P or high MP could be detrimental.

Rational
- Chemotrauma
  - Several studies have pointed at the side-effects of hyperoxia; some randomized clinical trials have shown benefit of restrictive O$_2$ use; a low O$_2$ target, though, might increase the risk of hypoxemia.

Rational
- Permissive hypercapnia
  - RR is an important contributor to the amount of energy transferred to the lung; lowering RR reduces MP, but may induce hypercapnia.

Rational
- Combining the settings
  - Everchanging patient conditions mandate frequent refinements; automation could be helpful, also by reducing the ICU staff workloads associated with lung–protective ventilation.

Infographic on ventilation management by Marcus Schultz, Amsterdam UMC, Amsterdam, the Netherlands (1.1-240423)
What are ∆P and MP?

ΔP represents the ratio of V_T to C_RS; MP is a summary parameter that includes V_T, RR, and airway pressures including ΔP.

Calculate ∆P and MP

ΔP is the difference between Pplat (or Pmax) and PEEP in VCV (or PCV); MP can be calculated using simple power equations:

\[ 0.098 \times V_T \times RR \times (Ppeak - 0.5 \times \Delta P) \]  (or  
\[ 0.098 \times V_T \times RR \times (Pplat - 0.5 \times \Delta P) \]  ) in VCV (or PCV).

How to achieve low ∆P

A first logical and pragmatic step is to reduce V_T, higher PEEP may also decrease ∆P if it reduces atelectases; note that in one randomized clinical trial in patients with ARDS, high PEEP resulted in a lower ∆P but also higher mortality.

Safety cutoffs for ∆P

It is uncertain what is a safe ∆P; meta–analyses suggest, or use, 15 cmH₂O but it remains uncertain whether this is correct and useful in all patients categories.

How to achieve low MP

This is where the pain starts; which ventilation parameter to prioritize?; adjusting one setting that may lower MP may require a change in another setting that actually may rise MP—e.g., a decrease in V_T may require an increase in RR, but higher RR will increase MP.

Safety cutoffs for MP

The same is true for MP, it is uncertain what is a safe MP; meta–analyses suggest, or use, 17 J/min but it remains uncertain whether this is correct and useful in all patients categories.

Again, associations?

There is a discussion ongoing whether these two parameters are not just ‘biomarkers’; this may also explain the associations with outcomes—the sicker the lung, the higher ∆P and MP, but also the higher the chance of dying.

Enrichment

In this way, ∆P and MP could be used to compare patient cohorts, or maybe even for prognostic or predictive enrichment, e.g., by selecting only patients with high ∆P and MP for inclusion in a randomized clinical trial.

Integrate

The summary parameters ∆P and MP are dependent, in part on the way the ventilator is set; several settings can be adjusted if you want to lower the energy: V_T, RR, and PEEP.

Rational

Combining the settings

It may be advisable to regularly check ∆P and MP, and changes thereof over time; whether ventilation strategies that target low ∆P or MP really improve outcomes, however, still need to be studied.

Step 1

Step 2

Step 3

Step 4

Step 5

Step 6

Associations

Meta–analyses have shown associations of higher ∆P and MP with worse clinical outcomes, in patients with ARDS and also in patients without ARDS; even short periods with high ∆P or MP could be harmful.

Causal relations?

Despite the appealing associations of ∆P and MP with worse clinical outcomes, we should realize that there have been no randomized clinical trials yet that tested whether a ventilation strategy that targets either lower ∆P or less MP leads to better outcomes.

Rational

Safety cutoffs for ∆P

It is uncertain what is a safe ∆P; meta–analyses suggest, or use, 15 cmH₂O but it remains uncertain whether this is correct and useful in all patients categories.

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Safety cutoffs for ∆P

It is uncertain what is a safe ∆P; meta–analyses suggest, or use, 15 cmH₂O but it remains uncertain whether this is correct and useful in all patients categories.
QUESTION Is $\Delta P$ an index more strongly associated with survival than $V_T$ or PEEP in patients who are not actively breathing?

CONCLUSION $\Delta P$ is the ventilation variable that best stratified risk; decreases in $\Delta P$ owing to changes in ventilator settings may be strongly associated with increased survival.

POPULATION

$\sim40\%$ Women  $\sim60\%$ Men

patients with ARDS included in RCTs

Mean Age: from 34 to 60 years

SOURCE

9 trials worldwide

METHODS

multilevel mediation analysis of individual patient data from 3562 patients

prediction model

univariate
multivariate

mediation analysis

risk priority of $\Delta P$, $V_T$ and PEEP

PRIMARY) OUTCOME

60–day mortality

FINDINGS

QUESTION What is the association between mechanical power (MP) and mortality in critically ill patients receiving invasive ventilation for at least 48 hours?

CONCLUSION High MP of ventilation is independently associated with higher in-hospital mortality and several other outcomes in ICU patients receiving invasive ventilation for at least 48 hours.

POPULATION

3614 Women 4593 Men
patients with data stored in the databases of the MIMIC–III and eICU

Median Age: 63 years

LOCATION

2 databases from US

CLASSIFICATION

individual patient data from 8207 patients

3846 MIMIC–III database
4361 eICU database

(PRIMARY) OUTCOME

in–hospital mortality; MP in first 48 hours

FINDINGS

QUESTION What is the association between exposure to different intensities of mechanical ventilation over time and intensive care unit (ICU) mortality in patients with acute respiratory failure?

CONCLUSION Cumulative exposure to higher intensities of mechanical ventilation was harmful, even for short durations.

### POPULATION

5141 Women 8267 Men

patients receiving ventilation for 4 hours or more

Median Age: 62 years

### LOCATION

9 ICUs in Toronto, Canada

### FINDINGS

<table>
<thead>
<tr>
<th>Baseline variables</th>
<th>Exposure to high driving pressure</th>
<th>Exposure to high mechanical power</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR estimate (95% CI) p-value</td>
<td>HR estimate (95% CI) p-value</td>
</tr>
<tr>
<td>PaO2/FIO2, mm Hg</td>
<td>0.945 (0.896-0.994) 0.026</td>
<td>0.977 (0.930-1.031) 0.38</td>
</tr>
<tr>
<td>Age, years</td>
<td>1.008 (1.008-1.500) &lt;0.0001</td>
<td>1.987 (1.100-1.892) &lt;0.00001</td>
</tr>
<tr>
<td>APACHE III score</td>
<td>1.402 (1.256-1.880) &lt;0.0001</td>
<td>1.591 (1.524-1.669) &lt;0.0001</td>
</tr>
<tr>
<td>APACHE pH</td>
<td>0.832 (0.802-0.863) &lt;0.0001</td>
<td>0.840 (0.820-0.864) &lt;0.0001</td>
</tr>
</tbody>
</table>

Time-varying variables

<table>
<thead>
<tr>
<th>Days with driving pressure ≥55 cm H2O</th>
<th>HR estimate (95% CI) p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.051 (1.023-1.076) &lt;0.0001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Days with mechanical power ≥17/1 min</th>
<th>HR estimate (95% CI) p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.069 (1.043-1.093) &lt;0.0001</td>
</tr>
</tbody>
</table>

1622 (20.6%) of 7876 patients died; 64,281 daily observations were recorded. HRs were the adjusted HRs associated with a 1-SD increment in the given variable. Values higher than 1 indicate increased mortality. The values used for SDs were as follows: PaO2/FIO2, ratio 111; pH 0.1; age 17 years; and APACHE III score 29. The effects of the number of days with either driving pressure greater than or equal to 15 cm H2O or mechanical power greater than or equal to 17/1 min were estimated using Quasi-Poisson models in the joint model analyses. HR-hazard ratio; CI-credible interval. PaO2=partial pressure of oxygen. FIO2=fraction of inspired oxygen. APACHE-Acute Physiology and Chronic Health Evaluation.

Table 3: Cumulative effect on HRs of exposure to high intensities of mechanical ventilation for 7876 patients with available data

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QUESTION Does the intensity of ventilation, reflected by the mechanical power of ventilation (MP), has an association with outcome in invasively ventilated patients without ARDS.

CONCLUSION In ICU patients without ARDS, MP has an independent association with mortality. This finding suggests that MP holds an added predictive value over its individual components, making MP an attractive parameter to monitor and target in these patients.

POPULATION

1962 Patients

ICU patients without ARDS, expected to need invasive ventilation > 24 hours

Median Age: 67 years

LOCATION

8 ICUs in the Netherlands

van Meenen D, for the NEBULAE—, PReVENT— and RELAx—investigators. Effect of Intensity of Ventilation on Outcome in Invasively Ventilated ICU patients without ARDS—An IPD—analysis of Three Randomized Clinical Trials. [Eur J Anaesth 2022; Nov 21; doi:10.1097/EJA.0000000000001778]
Rational Volutrauma
Randomized clinical trials and observational studies have shown benefit from low VT; ventilation with low VT might lead to hypoxemia; a compensatory increase in RR may be harmful.

Rational Atelectrauma vs overdistension
Randomized clinical trials could not confirm benefit from high PEEP, and observational studies even suggested harm; in some patients high PEEP could lead to overdistension rather than recruitment.

Rational Energytrauma
Meta–analyses showed associations of higher ∆P and MP with relevant clinical outcomes; even short periods with high ∆P or high MP could be detrimental.

Rational Permissive hypercapnia
RR is an important contributor to the amount of energy transferred to the lung; lowering RR reduces MP, but may induce hypercapnia.

Rational Chemotrauma
Several studies have pointed at the side–effects of hyperoxia; some randomized clinical trials have shown benefit of restrictive O₂ use; a low O₂ target, though, might increase the risk of hypoxemia.

Combining the settings
Everchanging patient conditions mandate frequent refinements; automation could be helpful, also by reducing the ICU staff workloads associated with lung–protective ventilation.

Integrate
Refine settings further by incrementally adjusting VT, PEEP, RR and FiO₂.

Use low VT
Reduce the size of VT; reductions might be more beneficial in patients with less compliant lungs.

Use O₂ wisely
Do not target high O₂ levels; use high FiO₂ if a reduction in VT and use of low PEEP results in hypoxemia.

Do not use high PEEP by default
Limit use of high PEEP to patients with severe hypoxemia, and only when lung lesions are recruitable; instead, consider prone positioning.

Check ∆P and MP
If high, consider reducing VT further; consider a change in other ventilator settings, like higher PEEP when lung lesions may be recruitable, or a longer inspiration time.

Permissive hypercapnia
In an attempt to reduce MP, reduce RR; allow the CO₂ level to rise if MP remains high.

Reduce the RR
In an attempt to reduce MP, reduce RR; allow the CO₂ level to rise if MP remains high.

V̇̇T, tidal volume; PEEP, positive end–expiratory pressure; ∆P, driving pressure; MP, mechanical power of ventilation; RR, respiratory rate; FiO₂, fraction of inspired O₂

Infographic on ventilation management by Marcus Schultz, Amsterdam UMC, Amsterdam, the Netherlands (1.1–240423)
QUESTION What is the impact of mechanical power on mortality in patients with ARDS as compared with that of primary ventilator variables such as the ΔP, VT, and RR?

CONCLUSION Mechanical power was associated with mortality during controlled mechanical ventilation in ARDS, but a simpler model using only the ΔP and RR was equivalent.

POPULATION

1728 Women 2821 Men

Patients with ARDS

Mean Age: 55 years

LOCATION

6 RCTs and 1 observational study

VENTILATION PARAMETERS

4549 patients with mild, moderate or severe ARDS

ΔP 15 cm H₂O

MP 0.32 J/min/kg

RR 26 breath/min

(PRIMARY) OUTCOME

Mortality at 28 or 60 days

FINDINGS

**QUESTION** Is the amount of mechanical power of ventilation (MP) under adaptive support ventilation (ASV) different from that under nonautomated pressure–controlled ventilation?

**CONCLUSION** This study suggests ASV may have benefits compared with pressure–controlled ventilation with respect to the MP transferred from the ventilator to the respiratory system in passive invasively ventilated critically ill patients.

**POPULATION**

7 Women 15 Men

patients expected to need invasive ventilation for the next 24 hours

Median Age: 67 years

**LOCATION**

1 ICUs in The Netherlands

QUESTION In COVID–19 patients with ARDS, does INTELLiVENT–ASV reduce the driving pressure and mechanical power of ventilation compared with conventional ventilation?

CONCLUSION INTELLiVENT–ASV reduces the intensity of ventilation in COVID–19 patients with ARDS.

POPULATION

12 Women 39 Men

COVID–19 with moderate to severe ARDS

Median Age: 63 years

LOCATION

2 ICUs in the Netherlands

INTERVENTION

51 patients intubated in the ICU for acute hypoxemia

conventional ventilation  crossover  automated ventilation

(PRIMARY) OUTCOME

ΔP and MP before and after converting from conventional ventilation to INTELLiVENT–ASV

**QUESTION** Does INTELLiVENT–Adaptive Support Ventilation (ASV) reduce respiratory system and pulmonary driving pressure ($\Delta P_{RS}$ vs. $\Delta P_{TP}$) and mechanical power of ventilation ($MP_{RS}$ vs. $MP_{TP}$) in patients with moderate–to–severe ARDS that receive lung–protective ventilation?

**CONCLUSION** INTELLiVENT–ASV reduces $\Delta P_{TP}$ and $MP_{TP}$, in patients with moderate–to–severe ARDS that receive lung–protective ventilation.

**POPULATION**

13 passive patients

ICU patients with moderate to severe ARDS with a Peso in situ

Median Age: 67 years

**LOCATION**

1 ICU in the Netherlands

**INTERVENTION**

13 patients under invasive ventilation + Peso

4 hours conventional ventilation or closed–loop

4 hours conventional ventilation or closed–loop

**(PRIMARY) OUTCOME**

$\Delta P_{TP}$, $\Delta P_{RS}$, $V_t$, RR, PEEP, PIP$_{TP}$, $MP_{TP}$ and $MP_{RS}$

QUESTION Does a ventilatory strategy designed to minimize lung injuries reduce not only pulmonary complications but also mortality at 28 days in patients with ARDS?

CONCLUSION As compared with conventional ventilation, the protective strategy was associated with improved survival at 28 days, a higher rate of weaning, and a lower rate of barotrauma in patients with ARDS.

POPULATION

53 patients

patients with early (moderate to severe) ARDS

mean age: 35 years

LOCATION

2 ICUs in Brazil

VENTILATION STRATEGIES

53 patients with early (moderate to severe) ARDS

29 patients ‘protective’
low V\(_T\) (6 ml/kg) + permissive hypercapnia (CO\(_2\) up to 80 mmHg [10.7 kPa]) + P\(_{\text{flex}}\) for PEEP

24 patients ‘conservative’
high V\(_T\) (12 ml/kg) + normocapnia (CO\(_2\) up to 25 mmHg [3.3 kPa]) + incremental PEEP

FINDINGS

(PRIMARY) OUTCOME

Survival at day 28 (primary); duration of ventilation, barotrauma

QUESTION Which ventilator variable to prioritize when striving to achieve reduced MP levels?

CONCLUSION Increasing Pplat and increasing RR are most associated with a higher risk of high MP. When striving to achieve a lower MP, the RR seems to be the most attractive ventilator variable to adjust.

POPULATION

2885 Patients

ICU patients without ARDS, expected to need invasive ventilation > 24 hours

Median Age: 67 years

LOCATION

8 ICUs in the Netherlands

2885 patients randomized in the pooled dataset

1153 patients excluded
557 with spontaneous breathing activity
474 missing data for calculating MP
64 extubation before data collection
25 loss to follow-up
19 ARDS at start of ventilation
14 withdrew informed consent

1732 fully analyzable patients

NEBULAE–, PReVENT–, and RELAx–investigators (WizARDS). Associations of Mechanical Power of Ventilation with Separate Ventilation Variables in Patients without ARDS. In preparation.
**QUESTION** Which ventilator variable to prioritize when striving to achieve reduced MP levels?

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Median Age: 67 years

**LOCATION**

8 ICUs in the Netherlands
**QUESTION** Which ventilator variable to prioritize when striving to achieve reduced MP levels?

**CONCLUSION** Increasing Ppeak and increasing RR are most associated with a higher risk of high MP. When striving to achieve a lower MP, the RR seems to be the most attractive ventilator variable to adjust.

**POPULATION**

![Image](image.png)

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NEBULAE–, PReVENT–, and RELAx–investigators (WizARDS). Associations of Mechanical Power of Ventilation with Separate Ventilation Variables in Patients without ARDS. *In preparation.*
Conclusions

• from (too) aggressive to permissive
• from single variables to parameters
• from simple to complex settings
• \( \Delta P \) and MP —– \( V_T \), minute volume, RR, and maybe PEEP
• automation