Current utilization of HFO in adults

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Conflicts of interest

• None with respect to for-profit companies
• I am a co-investigator in OSCILLATE
Objectives

• Review HFO utilization in adults in the context of data from RCTs
• Illustrate differences in patient selection and outcomes between observational studies and trials
What do RCTs of HFO show?
HFO may reduce treatment failure in ARDS

<table>
<thead>
<tr>
<th>Study</th>
<th>High frequency oscillation</th>
<th>Conventional mechanical ventilation</th>
<th>Risk ratio (95% CI)</th>
<th>Weight (%)</th>
<th>Risk ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arnold 1994</td>
<td>11/29</td>
<td>19/29</td>
<td>0.58 (0.34 to 0.99)</td>
<td>52.1</td>
<td></td>
</tr>
<tr>
<td>Derder 2002</td>
<td>10/75</td>
<td>15/73</td>
<td>0.65 (0.31 to 1.35)</td>
<td>27.8</td>
<td></td>
</tr>
<tr>
<td>Bollen 2005</td>
<td>10/37</td>
<td>5/24</td>
<td>1.30 (0.51 to 3.33)</td>
<td>16.8</td>
<td></td>
</tr>
<tr>
<td>Mentzelopoulus 2007</td>
<td>0/27</td>
<td>2/27</td>
<td>0.20 (0.01 to 3.98)</td>
<td>1.7</td>
<td></td>
</tr>
<tr>
<td>Samransamruajkit 2005</td>
<td>0/6</td>
<td>1/10</td>
<td>0.52 (0.02 to 11.14)</td>
<td>1.6</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>31/174</td>
<td>42/163</td>
<td>0.67 (0.46 to 0.99)</td>
<td>100.0</td>
<td></td>
</tr>
</tbody>
</table>

Test for heterogeneity: $\tau^2=0.00$, $\chi^2=2.84$, df=4, P=0.59, $I^2=0\%$

Test for overall effect: $z=2.02$, P=0.04

**Fig 4** | Treatment failure in patients with acute lung injury/acute respiratory distress syndrome allocated to high frequency oscillation or conventional mechanical ventilation

**Treatment failure:** oxygenation, ventilation, hypotension, barotrauma

Sud et al, BMJ 2010;340:c2327
HFO does not increase complications

• Barotrauma
  – 8.5% (HFO) vs 14.2% (CV)

• Hypotension
  – 5% vs 3.2%

• ETT obstruction
  – 3.3% vs 2.4%

• Small numbers for each comparison

• No significant differences
HFO may reduce mortality in ARDS

Overall HFO mortality – 39%

Sud et al, BMJ 2010;340:c2327
Derdak et al (the largest RCT)

- $N=148$
- $P=0.078$ at 90 days
- Baseline P/F 112
- CV 2.7-4.4 d

![Graph showing survival over time for different treatments]
Caveats

• Few studies and patients
• Variable duration of ARDS before randomization: ~2 to 4.5 days
  – Patients did not have refractory hypoxemia
• Lack of current lung-protective approach in many control patients
• Ongoing large RCTs will be highly informative
Use of lung protective conventional ventilation may reduce HFO’s apparent effect

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No of trials</th>
<th>No of patients</th>
<th>Significance and heterogeneity</th>
<th>Pooled risk ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung protective ventilation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mandated</td>
<td>3</td>
<td>267</td>
<td>P=0.07, I^2=0%</td>
<td>0.67 (0.44 to 1.03)</td>
</tr>
<tr>
<td>Not mandated</td>
<td>3</td>
<td>98</td>
<td>P=0.28, I^2=13%</td>
<td>0.84 (0.61 to 1.16)</td>
</tr>
<tr>
<td>Interaction z test: P=0.41</td>
<td></td>
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<td></td>
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</table>

Sud et al, BMJ 2010;340:c2327
From past trials to current utilization

• Patient in past trials treated with HFO vs. conventional near the beginning of ARDS, not as rescue therapy
• Is this how HFO is actually used?
1st case series in adult ARDS

- N=17 failing IRV
- P/F 69 (22)
- 5.1 (4.3) d of CV
- N=14 improved oxygenation
- Complications:
  - Decr BP (3)
  - Mucus plus (1)
- N=9 died
Early Toronto cohort

- 156 adults, 1998 to Jan 2002
- All had ARDS
- Age 48 (18) yr
- APACHE II 24 (8)
- MV 5.6 (7.6) days before HFO
- PEEP 14 (3); Pplat 36 (6)
Oxygenation improved

Chest 126:518-27
Small hemodynamic effects

(A) Graph showing changes in systolic, diastolic blood pressure, and heart rate over time (0 to 72 hours) with markers indicating specific values at different time points.
Early Toronto cohort

• 156 adults, 1998 to Jan 2002
• 49% improved and weaned to CV after 6.1 (5.5) d
• 26% had HFO stopped due to oxygenation, ventilation or hemodynamics after median 19 h
• Other Rx
  – Paralysis 90%
  – NO 44%
  – Steroids 37%
  – Prone 6%
• 61% mortality

Chest 126:518-27
More recent Ontario cohort

• 190 adults, Jan 2007-Jan 2009, all 10 university-affiliated ICUs; 16 (11,26) per ICU
• Age 52 (17) yr
• APACHE II 28 (9)
• ETI 2 (1,8) d
• 90% ARDS
• 68% died in hospital
  – Associated with older age, higher APACHE II, higher PCO$_2$

Crit Care Med 39:2631-44
Patients on lung-protective CV with poor oxygenation

- Tidal volume 7.1 (2.2) mL/kg
- Pplat 35 (3) cmH$_2$O
- PEEP 14 (4) cmH$_2$O
- P/F 80 (42)
- FiO$_2$ 0.93 (0.11)
- OI 33 (13)
Variable oxygenation response at 2h

67.% - increase; 32.5% - decrease
62.5% met criteria for response
Mean increase 22 (14-31); 39% (26-52%)
No predictors found
Variable PCO₂ response

Mean change -4 (-7 to +1)

Crit Care Med 39:2631-44
Complications at 2h common

• Ventilatory 30.5%
  – ↓ pH to <7.25 or ↑ PCO₂ ≥10 mmHg
  – Associated with ↑ pH pre-HFO and ↑ Paw post-HFO

• Hemodynamic 27.5%
  – New pressors or ↓ MAP ≥10mmHg
  – Associated with ↑ MAP and no pressors pre-HFO and ↑ Paw post-HFO

• Barotrauma
  – 18% had chest tubes before HFO
  – 23.5% had barotrauma or new chest tubes after HFO
Adjunctive therapies common

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Patients Ever Receiving, N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuromuscular blockade</td>
<td>143/189 (75.6)</td>
</tr>
<tr>
<td>Vasopressors</td>
<td>173/190 (91.1)</td>
</tr>
<tr>
<td>Nitric oxide</td>
<td>51/150 (34.0)</td>
</tr>
<tr>
<td>Steroids</td>
<td>94/149 (63.1)</td>
</tr>
<tr>
<td>Recruitment maneuver</td>
<td>94/190 (49.5)</td>
</tr>
</tbody>
</table>

- NMB and pressors, median 100% of HFO days
Technical complications uncommon

<table>
<thead>
<tr>
<th>Problem</th>
<th>N/190 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanical dysfunction requiring new oscillator</td>
<td>3 (1.6)</td>
</tr>
<tr>
<td>Mechanical dysfunction requiring conventional ventilator</td>
<td>2 (1.1)</td>
</tr>
<tr>
<td>Humidifier problem</td>
<td>4 (2.1)</td>
</tr>
<tr>
<td>Leak</td>
<td>2 (1.1)</td>
</tr>
<tr>
<td>Ran dry</td>
<td>1 (0.53)</td>
</tr>
<tr>
<td>Cracking in water chamber</td>
<td>1 (0.53)</td>
</tr>
<tr>
<td>Mushroom valve leak (tear)</td>
<td>1 (0.53)</td>
</tr>
<tr>
<td>Endotracheal tube obstruction not requiring tube change</td>
<td>1 (0.53)</td>
</tr>
<tr>
<td>Unusual sound</td>
<td>1 (0.53)</td>
</tr>
<tr>
<td>Battery low</td>
<td>1 (0.53)</td>
</tr>
<tr>
<td>Overheating</td>
<td>1 (0.53)</td>
</tr>
</tbody>
</table>

Ten of 190 patients (5.3%) using high-frequency oscillation had at least one technical problem. Each patient could have more than one problem.
## Stopping HFO

<table>
<thead>
<tr>
<th>Reason for stopping HFO,(^a) n/189 (%)</th>
<th>Count (Percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death or withdrawal of life support</td>
<td>74 (39.1)</td>
</tr>
<tr>
<td>Significant improvement in respiratory failure</td>
<td>71 (37.6)</td>
</tr>
<tr>
<td>Inadequate improvement of respiratory failure</td>
<td>44 (23.3)</td>
</tr>
<tr>
<td>Hypercapnea alone</td>
<td>14 (7.4)</td>
</tr>
<tr>
<td>Hypoxemia alone</td>
<td>12 (6.3)</td>
</tr>
<tr>
<td>Both</td>
<td>13 (6.9)</td>
</tr>
<tr>
<td>Neither</td>
<td>5 (2.6)</td>
</tr>
<tr>
<td>Hemodynamic instability</td>
<td>6 (3.2)</td>
</tr>
<tr>
<td>Transportation out of intensive care unit and not restarted</td>
<td>4 (2.1)</td>
</tr>
<tr>
<td>Technical difficulties with HFO</td>
<td>2 (1.1)</td>
</tr>
<tr>
<td>Lack of humidification of inspired gas</td>
<td>2 (1.1)</td>
</tr>
<tr>
<td>Barotrauma</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>Other</td>
<td>2 (1.1)</td>
</tr>
</tbody>
</table>
Transition to CV in responders

- Paw 25 (4)
- P/F 220 (78); FiO$_2$ 0.45 (0.13)
- PCO$_2$ 43 (9)
- Paralysis 40%
- On CV, statistically significant changes in
  - FiO$_2$ 0.51 (0.13)
  - Paw 20 (5)
  - Paralysis 29%
  - P/F 202 (82) stable

Crit Care Med 39:2631-44
Use in selected other patient groups
HFO for patients with H1N1

- 20/168 (12%) patients in Canada
- 3/68 H1N1 patients later on ECMO in Aust/NZ
- 22 patients from Australia separately reported
  - 6 also received ECMO

HFO in burns with ARDS

N=25
42% (17%) TBSA
6.1 (5.8) d of HFO
Used in OR
28% mortality

Crit Care Med 33:S175-81
‘Extreme’ rescue therapy

**Conventional ILV**

RIGHT LUNG: $V_T$ 3 ml/kg, PEEP 15 cmH$_2$O, respiratory rate 20 b/min, FiO$_2$ 1

LEFT LUNG: $V_T$ 2 ml/kg, PEEP 18 cmH$_2$O, respiratory rate 20 b/min, FiO$_2$ 1

**HFO-ILV**

RIGHT LUNG: $V_T$ 3 ml/kg, PEEP 15 cmH$_2$O respiratory rate 20 b/min FiO$_2$ 1

LEFT LUNG: mean airway pressure 30 cmH$_2$O, oscillation frequency 8 Hz, bias flow 35 L/min, FiO$_2$ 1
Conclusions

• HFO in utilization reviews vs. trials
  – More complications reported
  – mortality higher
  – ...used in sicker patients
  – With other adjunctive treatments

• Unclear whether these patients would be more responsive if studied in trials vs. less severely hypoxemic patients