ALS 571 : Ventilation strategy post-ROSC

TFQO: Charles Deakin #329
EVREV 1: Asger Granfeldt  COI #63
EVREV 2: Bo Lofgren COI #363
Taskforce: ALS
Charles Deakin COI #329
- Commercial/industry
  - Director, Prometheus Medical
- Potential intellectual conflicts
  - Vice-chair, ALS, ERC
  - Executive Committee, Resuscitation Council (UK)
  - Editorial board, Resuscitation

Bo Lofgren COI #363
- Commercial/industry
  - None
- Potential intellectual conflicts
  - None

Asger Granfeldt COI #63
- Commercial/industry
  - None
- Potential intellectual conflicts
  - None
After restoration of circulation, routine hyperventilation leading to hypocapnia should be avoided in order to prevent additional cerebral ischemia.
Population: Among adults with ROSC after cardiac arrest in any setting

Intervention: ventilation to a specific PaCO2 goal

Comparison: compared with 1. no specific strategy or 2. a different PaCO2 goal

Outcomes:
- Survival with Favorable neurological/functional outcome at discharge, 30 days, 60 days, 180 days AND/OR 1 year (9-Critical)
- Survival only at discharge, 30 days, 60 days, 180 days AND/OR 1 year (8-Critical)
Inclusion/Exclusion & Articles Found

- **Inclusion**: All human studies.
- **Exclusion**: Animal studies.
- **No RCTs** were identified.
- The search yielded a total of 1,339 studies. No studies specifically targeted ventilation to a specific PaCO$_2$ goal.
- Of these, four observational studies were included for bias assessment.
No studies demonstrate better outcome with ventilation to a specific PaCO$_2$ in patients with ROSC.

We suggest maintaining PaCO$_2$ within a normal physiological range as part of a post-ROSC bundle of care (weak recommendation, very low quality evidence).
Hospital registry study (IHCA)
193 patients
1° outcome – CPC ≤ 2 at discharge

Hypocapnia (OR 2.43 (95% CI 1.04–5.65)) and hypercapnia (OR 2.20 (95% CI 1.03–4.71) were independently associated with poor neurological function.
Association between mean arterial blood gas tension and outcome in cardiac arrest patients treated with therapeutic hypothermia

Byung Kook Lee, MD, PhD a, Kyung Woon Jeung, MD, PhD a,*, Hyoung Youn Lee, MD b, Seung Joon Lee, MD c, Yong Hun Jung, MD a, Wang Ki Lee, MD a, Tag Heo, MD, PhD a, Yong Il Min, MD, PhD a


Hospital registry study (IHCA/OHCA)
213 patients
1° outcome – In-hospital mortality (survival)
2° outcome – CPC ≤ 2 at discharge

In multivariate analysis, hypocarbia was significantly associated with increased risk of in-hospital mortality (OR 2.522; 95% CI 1.18-5.37).

The mean PaCO₂ (hypercarbia) was significantly higher in survivors (5.2 kPa [4.9-5.5]) compared to non-survivors (5.0 kPa [4.6-5.5]), but the mean PaCO₂ was not associated with neurologic outcomes.
Hospital registry study (IHCA/OHCA)
213 patients
1° outcome – In-hospital mortality (survival)
2° outcome – CPC ≤ 2 at discharge

In multivariate analysis, hypocarbia was significantly associated with increased risk of in-hospital mortality (OR 2.522; 95% CI 1.18-5.37). The mean PaCO$_2$ (hypercarbia) was significantly higher in survivors (5.2 kPa [4.9-5.5]) compared to non-survivors (5.0 kPa [4.6-5.5]), but the mean PaCO$_2$ was not associated with neurologic outcomes.
Arterial carbon dioxide tension and outcome in patients admitted to the intensive care unit after cardiac arrest

Antoine G. Schneider\textsuperscript{a,b,1}, Glenn M. Eastwood\textsuperscript{a,1}, Rinaldo Bellomo\textsuperscript{a,b,*}, Michael Bailey\textsuperscript{b}, Miklos Lipcsey\textsuperscript{a,c}, David Pilcher\textsuperscript{d}, Paul Young\textsuperscript{e,f}, Peter Stow\textsuperscript{g}, John Santamaria\textsuperscript{h}, Edward Stachowski\textsuperscript{i}, Satoshi Suzuki\textsuperscript{a}, Nicholas C. Woinarski\textsuperscript{a}, Janine Pilcher\textsuperscript{f}

Resuscitation 84 (2013) 927–934

Hospital registry study (IHCA/OHCA)
16,542 patients
1° outcome – In-hospital mortality (survival)
2° outcome – Survival to discharge home

Patients with \textbf{hypocapnia} showed a trend toward greater mortality than those with normocapnia (OR 1.12 [95\% CI 1.00–1.24], \(p = 0.04\)).

No difference for in-hospital mortality between patients with \textbf{hypercapnia} and those with normocapnia (OR 1.07, [95\% CI 0.98–1.16], \(p = 0.13\)).
Arterial Blood Gas Tensions After Resuscitation From Out-of-Hospital Cardiac Arrest: Associations With Long-Term Neurologic Outcome*

Jukka Vaahersalo, MD¹; Stepani Bendel, MD, PhD²; Matti Reinikainen, MD, PhD³; Jouni Kurola, MD, PhD⁴; Marjaana Tiainen, MD, PhD⁵; Rahul Raj, BM¹; Ville Pettilä, MD, PhD¹; Tero Varpula, MD, PhD¹; Markus B. Skrifvars, MD, PhD, FCICM¹; for the FINNRESUSCI Study Group

*Crit Care Med 2014; 42:1463–1470*

Hospital registry study (OHCA)
409 patients
1° outcome – CPC ≤ 2 at 12 months

The mean 24 hours PaCO₂ level was an independent predictor of good outcome (OR 1.054; 95% CI 1.01–1.10)
With multivariate regression analysis, time spent in the PaCO₂ band higher than 6.0 kPa was associated with good outcome (OR 1.015; 95% CI 1.002–1.029)

No hypocapnia cohort
**Risk of Bias in non-RCTs**

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Design</th>
<th>Total Patients</th>
<th>Population</th>
<th>Industry Funding</th>
<th>Eligibility Criteria</th>
<th>Exposure/Outcome</th>
<th>Confounding</th>
<th>Follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Roberts</td>
<td>2013</td>
<td>Pro cohort</td>
<td>193</td>
<td>IHCA</td>
<td>No</td>
<td>High</td>
<td>High</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Lee</td>
<td>2014</td>
<td>Retro cohort</td>
<td>213</td>
<td>OHCA/IHCA</td>
<td>No</td>
<td>High</td>
<td>High</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Schneider</td>
<td>2013</td>
<td>Retro cohort</td>
<td>16,542</td>
<td>OHCA/IHCA</td>
<td>No</td>
<td>High</td>
<td>High</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Vaahtero</td>
<td>2014</td>
<td>Pro cohort</td>
<td>409</td>
<td>OHCA</td>
<td>Unclear</td>
<td>High</td>
<td>High</td>
<td>High</td>
<td>Low</td>
</tr>
</tbody>
</table>

**Notes:**

- Roberts: Timing of ABGs random so values outside normal range may be missed. Some patients had both hyper and hypocapnia. Random ABG timings so may miss outlying values.
- Lee: Excluded if data incomplete, lethal arrythmias or TH interrupted. Excluded if died during TH. Documented values across a range of PaO2 & PaCO2
- Schneider: Excluded if no ABGs (2.0%) or discharge status (2.9%) unknown. Random timing of ABGs
- Vaahtero: Timing of ABGs random, but time spent at each range was calculated. Temp correction of gases in 13/21 ICUs. 71% TTM, ABGs missing in 14.6% pts
## Evidence profile tables

**Hypocapnia**

<table>
<thead>
<tr>
<th>Quality assessment</th>
<th>Summary of findings</th>
<th>Effect</th>
<th>Quality</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nº of patients</td>
<td>Nº of patients</td>
<td>Relative (95% CI)</td>
<td>Absolute (95% CI)</td>
<td></td>
</tr>
<tr>
<td>Ventilation to a specific pCO₂ or pO₂ goal</td>
<td>1. no specific strategy or 2. a different pCO₂ or pO₂ goal</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Roberts 2013 - CO2 Hypocapnia (PaCO₂ <3.0kPa) (assessed with: CPC ≤2 at discharge)

<table>
<thead>
<tr>
<th>Nº of studies</th>
<th>Study design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other considerations</th>
<th>Nº of patients</th>
<th>Relative (95% CI)</th>
<th>Absolute (95% CI)</th>
<th>Quality</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>observational studies</td>
<td>very serious</td>
<td>not serious</td>
<td>not serious</td>
<td>very serious</td>
<td>none</td>
<td>52/112 (46.4%)</td>
<td>60/112 (53.6%)</td>
<td>OR 2.43 (1.04 to 5.65)</td>
<td>201 more per 1000 (from 10 more to 331 more)</td>
<td>⬤⬤⬤⬤</td>
</tr>
</tbody>
</table>

### Lee 2014 - CO2 Hypocapnia (PaCO₂ < 4.7kPa) (assessed with: CPC ≤2 at discharge)

<table>
<thead>
<tr>
<th>Nº of studies</th>
<th>Study design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other considerations</th>
<th>Nº of patients</th>
<th>Relative (95% CI)</th>
<th>Absolute (95% CI)</th>
<th>Quality</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>observational studies</td>
<td>very serious</td>
<td>not serious</td>
<td>serious</td>
<td>serious</td>
<td>none</td>
<td>-74/152</td>
<td>OR 2.4 (1.076 to 5.353)</td>
<td>208 more per 1000 (from 18 more to 350 more)</td>
<td>⬤⬤⬤⬤</td>
<td>CRITICAL</td>
</tr>
</tbody>
</table>

### Schneider 2013 - Hypocapnia (PaCO₂ <4.67kPa) (assessed with: Death or failure to be discharged home)

<table>
<thead>
<tr>
<th>Nº of studies</th>
<th>Study design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other considerations</th>
<th>Nº of patients</th>
<th>Relative (95% CI)</th>
<th>Absolute (95% CI)</th>
<th>Quality</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>observational studies</td>
<td>very serious</td>
<td>not serious</td>
<td>not serious</td>
<td>not serious</td>
<td>none</td>
<td>2282/6881 (33.2%)</td>
<td>4599/6881 (66.8%)</td>
<td>OR 1.23 (1.1 to 1.37)</td>
<td>44 more per 1000 (from 21 more to 66 more)</td>
<td>⬤⬤⬤⬤</td>
</tr>
</tbody>
</table>

### Roberts 2013 - CO2 Hypercapnia (PaCO₂ >6.7kPa) (assessed with: CPC ≤2 at discharge)

<table>
<thead>
<tr>
<th>Nº of studies</th>
<th>Study design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other considerations</th>
<th>Nº of patients</th>
<th>Relative (95% CI)</th>
<th>Absolute (95% CI)</th>
<th>Quality</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>observational studies</td>
<td>very serious</td>
<td>not serious</td>
<td>serious</td>
<td>very serious</td>
<td>none</td>
<td>63/123 (51.2%)</td>
<td>60/123 (48.8%)</td>
<td>OR 2.2 (1.03 to 4.71)</td>
<td>189 more per 1000 (from 7 more to 330 more)</td>
<td>⬤⬤⬤⬤</td>
</tr>
</tbody>
</table>

---

1. Some patients had both hypo and hypercapnia
2. Not ventilated to specific PaCO₂
3. 40%TTM, 8%PCI not controlled
4. Excluded if data incomplete, lethal arrhythmias or TH interrupted
5. Extremes of O₂/CO₂ not planned interventions
6. Excluded if no ABGs or unknown discharge status
7. No explanation was provided
8. Some patients in <15.6kPa group were hypoxic
9. <400 patients
# Hypercapnia

## Evidence profile tables

<table>
<thead>
<tr>
<th>Nº of studies</th>
<th>Study design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other considerations</th>
<th>Nº of patients</th>
<th>Summary of findings</th>
<th>Effect</th>
<th>Quality</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>observational studies</td>
<td>very serious 2.1</td>
<td>not serious</td>
<td>serious 4.8</td>
<td>very serious 1.8</td>
<td>none</td>
<td>63/123 (51.2%)</td>
<td>60/123 (48.8%)</td>
<td>OR 2.2 (1.05 to 4.71)</td>
<td>189 more per 1000 (from 7 more to 330 more)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Nº of patients</th>
<th>Summary of findings</th>
<th>Effect</th>
<th>Quality</th>
<th>Importance</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>63/123 (51.2%)</td>
<td>60/123 (48.8%)</td>
<td>OR 2.2 (1.05 to 4.71)</td>
<td>189 more per 1000 (from 7 more to 330 more)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Nº of patients</th>
<th>Summary of findings</th>
<th>Effect</th>
<th>Quality</th>
<th>Importance</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>321/850 (37.8%)</td>
<td>529/850 (62.2%)</td>
<td>OR 0.881 (0.318 to 2.444)</td>
<td>30 fewer per 1000 (from 179 more to 278 fewer)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Nº of patients</th>
<th>Summary of findings</th>
<th>Effect</th>
<th>Quality</th>
<th>Importance</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>4509/9108 (49.5%)</td>
<td>4599/9108 (50.5%)</td>
<td>OR 0.97 (0.89 to 1.06)</td>
<td>8 fewer per 1000 (from 15 more to 29 fewer)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Nº of patients</th>
<th>Summary of findings</th>
<th>Effect</th>
<th>Quality</th>
<th>Importance</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>OR 1.054 (1.006 to 1.104)</td>
<td>1 fewer per 1000 (from 0 fewer to 0 fewer)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---

1. Some patients had both hypo and hypercapnia
2. Not ventilated to specific PaCO2
3. 40%TTM, 8%PCI not controlled
4. Excluded if data incomplete, lethal arrhythmias or TH interrupted
5. Extremes of O2/C02 not planned interventions
6. Excluded if no ABGs or unknown discharge status
7. No explanation was provided
8. Some patients in <15.6kPa group were hypoxic
9. <400 patients
Proposed
Consensus on Science statements

Hypocapnia

- No studies have specifically randomised patients to ventilation to a specific PaCO₂ goal.

- For the critical outcome of neurologically intact survival, two very low quality cohort studies {Roberts 2013 2107, Lee 2014 55} with a total of 406 patients (downgraded for very serious concerns about risk of bias and imprecision) showed hypocapnia (<3.0 kPa & <4.7kPa respectively) was associated with a worse outcome.

- For the critical outcome of death (or failure to be discharged home), one very low quality cohort study {Schneider 2013 927} of 16,542 patients (downgraded for very serious concerns about risk of bias and imprecision) showed hypocapnia (<4.7kPa) was associated with a worse outcome.
Proposed Consensus on Science statements

Hypercapnia

No studies have specifically randomised patients to ventilation to a specific PaCO2 goal.

For the critical outcome of neurologically intact survival,

- One very low quality cohort study {Roberts 2013 2107} with a total of 193 patients (downgraded for very serious concerns about risk of bias and imprecision) showed worse outcome in patients ventilated to hypercapnia (>PaCO2 6.7kPa).
- One very low quality cohort study {Lee 2014 2107} with a total of 213 patients (downgraded for very serious concerns about risk of bias and imprecision) showed no difference in outcome for patients ventilated to hypercapnia (>PaCO2 6.0kPa).
- One very low quality cohort study {Verhaasalo 2014 1463} with a total of 409 patients (downgraded for very serious concerns about risk of bias and imprecision) showed better outcome for patients ventilated to hypercapnia (PaCO2 5.1-10.1 kPa).
Proposed
Consensus on Science statements

- **Hypercapnia**

  For the critical outcome of death (or failure to be discharged home),
  - One very low quality cohort study {Schneider 2013 927} with a total of 16,542 patients (downgraded for very serious concerns about risk of bias and imprecision) showed no difference in patients ventilated to hypercapnia (PaCO$_2$ >6.0kPa)
  - One very low quality cohort study {Lee 2014 2107} with a total of 213 patients (downgraded for very serious concerns about risk of bias and imprecision) showed a higher mean PaCO$_2$ in survivors.
We suggest maintaining PaCO\textsubscript{2} within a normal physiological range as part of a post-ROSC bundle of care (weak recommendation, very low quality evidence).

No studies demonstrate better outcome with ventilation to a specific PaCO\textsubscript{2} in patients with ROSC.

Hypocarbia is associated with worse outcome and we suggest should be avoided where possible (moderate recommendation, very low quality evidence).

The upper limit at which PaCO\textsubscript{2} becomes harmful is unknown, although mild hypercapnia may have some neuroprotective effect (weak recommendation, very low quality evidence).
Knowledge Gaps

*DO NOT USE FOR PLENARY*
- BREAKOUT ONLY

There are no prospective randomised studies addressing this topic.

Does mild hypercapnia offer a neuroprotective effect?