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| Question |
| **Carbon dioxide targets after return of spontaneous circulation (ROSC) in children with cardiac arrest** |
| **Population:** | Children in any setting (in-hospital or out-of-hospital) with cardiac arrest from any etiology who have attained ROSC |
| **Intervention:** | A strategy targeting a specific carbon dioxide range |
| **Comparison:** | A strategy targeting an alternative carbon dioxide range or no specific range. |
| **Main outcomes:** | Survival to hospital discharge, 3 months or longer; survival to hospital discharge, 3 months or longer with favorable neurologic outcome. |
| **Setting:** |  In the hospital setting |

# ASSESsment

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| ProblemIs the problem a priority? |
| Judgement | Research evidence | Additional considerations |
| ○ No○ Probably no○ Probably yes● Yes○ Varies○ Don't know | Pediatric cardiac arrest, both in the out-of-hospital and in-hospital setting, is relatively uncommon, but has a very high mortality, with neurologic injury as a common cause of death, particularly for out-of-the-hospital cardiac arrest (OHCA). Both hypocapnia and hypercapnia have been thought to possibly be associated with worse neurologic outcome in post-arrest patients previously. Hypocapnia can lead to cerebral vasoconstriction, which could lead to decreased perfusion in a brain already at risk for ischemic injury. Hypercapnia may increase cerebral blood flow. This has been posited as a possible way to mitigate hypoxic brain injury, but the effect of this when cerebral edema is present is not known. There are no randomized trials on this topic in children.  |  |
| Desirable EffectsHow substantial are the desirable anticipated effects? |
| Judgement | Research evidence | Additional considerations |
| ○ Trivial○ Small○ Moderate○ Large○ Varies● Don't know | There is no evidence for benefit associated with hypercapnia or hypocapnia after ROSC in children. The available evidence on the effect of hypercapnia or hypocapnia in adults is inconsistent, with the randomized trials done to-date showing no effect. Given the variability in results the effect is likely to be small, if any. However, the trials thus far are small and there is some data on the effect of carbon dioxide levels on cerebral perfusion, the clinical significance of which remains unknown.  |  |
| Undesirable EffectsHow substantial are the undesirable anticipated effects? |
| Judgement | Research evidence | Additional considerations |
| ○ Large○ Moderate○ Small○ Trivial○Varies● Don't know | The available evidence on the effect of hypercapnia or hypocapnia in children is limited to very low certainty evidence from one observational study. This study found that hypercapnia after ROSC was associated with worse survival. This association did not persist at 24 hours after ROSC. The same study failed to demonstrate an association between hypocapnia (compared to normocapnia) and outcome, but was limited by very small numbers in the hypocapnia group. **Question**: Hypercapnia after ROSC compared to normocapnia after ROSC for children after cardiac arrest

| **Certainty assessment** | **№ of patients** | **Effect** | **Certainty** | **Importance** |
| --- | --- | --- | --- | --- |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **hypercapnia after ROSC** | **normocapnia after ROSC** | **Relative(95% CI)** | **Absolute(95% CI)** |
| **Survival to hospital discharge-del Castillo** |
| 1  | observational studies  | very serious a | not serious  | serious b | not serious  | strong association  | 25/61 (41.0%)  | 87/130 (66.9%)  | **RR 0.61**(0.44 to 0.85)  | **261 fewer per 1,000**(from 375 fewer to 100 fewer)  | ⨁◯◯◯VERY LOW  | CRITICAL |

**Question**: Hypercapnia at 24 hours compared to normocapnia at 24 hours for children after cardiac arrest

| **Certainty assessment** | **№ of patients** | **Effect** | **Certainty** | **Importance** |
| --- | --- | --- | --- | --- |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **hypercapnia at 24 hours** | **normocapnia at 24 hours** | **Relative(95% CI)** | **Absolute(95% CI)** |
| **Survival to hospital discharge-del Castillo** |
| 1  | observational studies  | very serious a | not serious  | serious b | very serious c | strong association  | 17/25 (68.0%)  | 78/122 (63.9%)  | **RR 1.06**(0.79 to 1.44)  | **38 more per 1,000**(from 134 fewer to 281 more)  | ⨁◯◯◯VERY LOW  | CRITICAL  |

**Question**: Hypocapnia after ROSC compared to normocapnia after ROSC for children after cardiac arrest

| **Certainty assessment** | **№ of patients** | **Effect** | **Certainty** | **Importance** |
| --- | --- | --- | --- | --- |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **hypocapnia after ROSC** | **normocapnia after ROSC** | **Relative(95% CI)** | **Absolute(95% CI)** |
| **Survival to hospital discharge-del Castillo** |
| 1  | observational studies  | very serious a | not serious  | serious b | not serious  | none  | 15/30 (50.0%)  | 87/130 (66.9%)  | **RR 0.75**(0.51 to 1.09)  | **167 fewer per 1,000**(from 328 fewer to 60 more)  | ⨁◯◯◯VERY LOW  | CRITICAL  |

**Question**: Hypocapnia at 24 hours compared to normocapnia at 24 hours for children after cardiac arrest

| **Certainty assessment** | **№ of patients** | **Effect** | **Certainty** | **Importance** |
| --- | --- | --- | --- | --- |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **hypocapnia at 24 hours** | **normocapnia at 24 hours** | **Relative(95% CI)** | **Absolute(95% CI)** |
| **Survival to discharge-del Castillo** |
| 1  | observational studies  | very serious a | not serious  | serious b | very seriousc  | none  | 5/9 (55.6%)  | 79/118 (66.9%)  | **RR 0.83**(0.46 to 1.51)  | **114 fewer per 1,000**(from 362 fewer to 341 more)  | ⨁◯◯◯VERY LOW  | CRITICAL  |

The available evidence on the effect of hypercapnia or hypocapnia in adults is inconsistent, with the randomized trials done to-date showing no effect. Given the variability in results the effect is likely to be small, if any. However, the trials thus far are small and there is some data on the effect of carbon dioxide levels on cerebral perfusion, the clinical significance of which remains unknown.  |  |
| Certainty of evidenceWhat is the overall certainty of the evidence of effects? |
| Judgement | Research evidence | Additional considerations |
| ● Very low○ Low○ Moderate○ High○ No included studies |  The certainty of evidence from randomized trials is very low (see tables above). |  |
| ValuesIs there important uncertainty about or variability in how much people value the main outcomes? |
| Judgement | Research evidence | Additional considerations |
| ○ Important uncertainty or variability○ Possibly important uncertainty or variability● Probably no important uncertainty or variability○ No important uncertainty or variability | Survival with favorable neurologic outcome and survival are generally accepted as critical outcomes. |  |
| Balance of effectsDoes the balance between desirable and undesirable effects favor the intervention or the comparison? |
| Judgement | Research evidence | Additional considerations |
| ○ Favors the comparison○Probably favors the comparison○ Does not favor either the intervention or the comparison●Probably favors the intervention○ Favors the intervention○ Varies○ Don't know | For carbon dioxide, the balance of effects favors normocapnia.  |  |
| Resources requiredHow large are the resource requirements (costs)? |
| Judgement | Research evidence | Additional considerations |
| ○ Large costs○ Moderate costs○ Negligible costs and savings○ Moderate savings○ Large savings○ Varies● Don't know | We did not identify any studies evaluating the cost of a ventilation strategy targeting one carbon dioxide range over another, but a significant cost seems unlikely, except in settings where blood gas analysis is not available. |  |
| Certainty of evidence of required resourcesWhat is the certainty of the evidence of resource requirements (costs)? |
| Judgement | Research evidence | Additional considerations |
| ○ Very low○ Low○ Moderate○ High● No included studies | We did not identify any studies specifically comparing resources including costs between the two interventions.  |  |
| Cost effectivenessDoes the cost-effectiveness of the intervention favor the intervention or the comparison? |
| Judgement | Research evidence | Additional considerations |
| ○ Favors the comparison○ Probably favors the comparison○ Does not favor either the intervention or the comparison○ Probably favors the intervention○ Favors the intervention○ Varies● No included studies | We did not identify any studies addressing cost-effectiveness.  |  |
| EquityWhat would be the impact on health equity? |
| Judgement | Research evidence | Additional considerations |
| ○ Reduced○ Probably reduced○ Probably no impact○ Probably increased○ Increased○ Varies● Don't know | Targeting a specific carbon dioxide level may be difficult in settings where blood gas analysis is not available, but as this recommendation is not a change we do not think it will increase or decrease inequity that is already present.  |  |
| AcceptabilityIs the intervention acceptable to key stakeholders? |
| Judgement | Research evidence | Additional considerations |
| ○ No○ Probably no● Probably yes○ Yes○ Varies○ Don't know | We have not identified any research that assessed acceptability, but these TRs do not include any substantial changes compared to 2015. |  |
| FeasibilityIs the intervention feasible to implement? |
| Judgement | Research evidence | Additional considerations |
| ○ No○ Probably no● Probably yes○ Yes○ Varies○ Don't know | Feasibility was not specifically addressed by this review, but should be feasible in most settings given that this is not a change in recommendation.  |  |

# Summary of judgements

|  | **Judgement** |
| --- | --- |
| **Problem** | No | Probably no | Probably yes | **Yes** |  | Varies | Don't know |
| **Desirable Effects** | **Trivial** | **Small** | Moderate | Large |  | Varies | **Don't know** |
| **Undesirable Effects** | Large | **Moderate** | Small | Trivial |  | Varies | **Don't know** |
| **Certainty of evidence** | **Very low** | Low | Moderate | High |  |  | No included studies |
| **Values** | Important uncertainty or variability | Possibly important uncertainty or variability | **Probably no important uncertainty or variability** | No important uncertainty or variability |  |  |  |
| **Balance of effects** | Favors the comparison | **Probably favors the comparison** | Does not favor either the intervention or the comparison | Probably favors the intervention | Favors the intervention | Varies | Don't know |
| **Resources required** | Large costs | Moderate costs | Negligible costs and savings | Moderate savings | Large savings | Varies | **Don't know** |
| **Certainty of evidence of required resources** | Very low | Low | Moderate | High |  |  | **No included studies** |
| **Cost effectiveness** | Favors the comparison | Probably favors the comparison | Does not favor either the intervention or the comparison | Probably favors the intervention | Favors the intervention | Varies | **No included studies** |
| **Equity** | Reduced | Probably reduced | Probably no impact | Probably increased | Increased | Varies | **Don't know** |
| **Acceptability** | No | Probably no | **Probably yes** | Yes |  | Varies | Don't know |
| **Feasibility** | No | Probably no | **Probably yes** | Yes |  | Varies | Don't know |

# Type of recommendation

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Strong recommendation against the intervention | **Conditional recommendation against the intervention** | Conditional recommendation for either the intervention or the comparison | Conditional recommendation for the intervention | Strong recommendation for the intervention |
| ○  | **●**  | ○  | ○  | ○  |

# Conclusions

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| Recommendation |
| We suggest that rescuers measure PaCO2 after ROSC and target normocapnia (weak recommendation, very-low-certainty evidence). Consider adjustments to the target paCO2 for specific patient populations where normocapnia may not desirable (e.g. chronic lung disease with chronic hypercapnia, congenital heart disease with single ventricle physiology, increased intracranial pressure with impending herniation). |
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| Justification |
| Very low certainty evidence from one newer pediatric study suggests hypercapnia and hypocapnia may be associated with worse outcome, although this was only seen at the immediate post-ROSC time point, and this study has significant risk of bias. This evidence, combined with the limited and inconsistent evidence in adults, favors targeting normocapnia..Providers should consider adjustments to the target paCO2 for specific patient populations where normocapnia may not desirable (e.g. chronic lung disease with chronic hypercapnia, congenital heart disease with single ventricle physiology, increased intracranial pressure with impending herniation) |

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| Subgroup considerations |
| There is insufficient evidence to evaluate whether any particular subgroups should be treated with different PaCO2 targets, but expert consensus recommends considering different targets in the groups previously mentioned. |

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| Implementation considerations |
| This recommendation is not a significant change from 2015, so we do not anticipate any challenge with implementation.  |

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| Monitoring and evaluation |
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| Research priorities |
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