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| Question | |
| **Carbon dioxide targets after return of spontaneous circulation (ROSC) in adults with cardiac arrest** | |
| **Population:** | Adults in any setting (in-hospital or out-of-hospital) with cardiac arrest from any aetiology who have attained ROSC |
| **Intervention:** | A strategy targeting hypo- or hypercapnia |
| **Comparison:** | A strategy targeting normocapnia |
| **Main outcomes:** | Survival to hospital discharge, 3 months or longer; survival with favorable neurologic outcome at hospital discharge, 3 months or longer. |
| **Setting:** | Post-ROSC patients in the hospital setting |

# ASSESsment

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| Problem Is the problem a priority? | | |
| Judgement | Research evidence | Additional considerations |
| ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know | Cardiac arrest, both in the out-of-hospital and in-hospital setting, is relatively common and has a very high mortality, with neurologic injury as a common cause of death. Both hypocapnia and hypercapnia have previously been thought to be associated with worse neurologic outcome in post-arrest patients. 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, and thus has been posited as a possible way to mitigate hypoxic brain injury. However, the effect of hypercapnia when cerebral edema is present is not known. | A large randomized trial is currently underway investigating different CO2 targets in the first 24 hours of ICU admission in post-arrest patients (TAME trial, NCT03114033). |
| Desirable Effects How substantial are the desirable anticipated effects? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ● Don't know | The available evidence on the effects of both hypercapnia and hypocapnia is inconsistent, with the randomized trials done to-date showing no effect. Given the variability in results across the two trials and observational studies, the effect is likely to be small, if any. However, the trials thus far are small. There are some data on the effect of carbon dioxide values on cerebral perfusion but the clinical significance of this is unknown.   | **Certainty assessment** | | | | | | | **№ of patients** | | **Effect** | | **Certainty** | **Importance** | | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | | **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **Ventilation targeting mild hypercapnia** | **ventilation targeting normocapnia** | **Relative (95% CI)** | **Absolute (95% CI)** | | Survival to hospital discharge-Eastwood, Jakkula | | | | | | | | | | | | | | 2 | randomised trials | not serious | serious a | not serious | serious b | none | 67/101 (66.3%) | 72/102 (70.6%) | **RR 0.94** (0.78 to 1.14) | **42 fewer per 1,000** (from 155 fewer to 99 more) | ⨁⨁◯◯  LOW | CRITICAL | | Favorable neurologic outcome at 6 months (CPC 1-2, GOSE<6)-Eastwood, Jakkula | | | | | | | | | | | | | | 2 | randomised trials | not serious | serious a | not serious | serious b | none | 58/101 (57.4%) | 61/102 (59.8%) | **RR 0.96** (0.77 to 1.21) | **24 fewer per 1,000** (from 138 fewer to 126 more) | ⨁⨁◯◯ LOW | CRITICAL | | Ongoing trial as noted |
| Undesirable Effects How 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 is inconsistent, with the randomized trials done to-date showing no effect (see tables above). Given the variability in results the effect, if any, is likely to be small. However, the trials thus far are small. There are some preclinical data on the effect of carbon dioxide values on cerebral perfusion but the clinical significance of this is unknown. |  |
| Certainty of evidence What 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 low because the trials are small and the results are inconsistent. |  |
| Values Is 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 effects Does 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 | The balance of effects favors the comparison (normocapnia) when compared to hypocapnia. The balance of effects favors neither the comparison nor the intervention when comparing normocapnia to mild hypercapnia. |  |
| Resources required How 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 (see Equity). |  |
| Certainty of evidence of required resources What 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 effectiveness Does 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. |  |
| Equity What 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 value may be difficult in settings where blood gas analysis is not available. However, as measuring carbon dioxide values is not a change, we do not think that recommending a specific target will change existing equity or inequity. |  |
| Acceptability Is 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 treatment recommendations do not include any substantial changes compared to 2015. |  |
| Feasibility Is 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 significant change in recommendation. |  |

# Summary of judgements

|  | **Judgement** | | | | | | |
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| **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

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| 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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| Recommendations |
| **There is insufficient evidence to suggest for or against targeting mild hypercapnia compared with normocapnia in adults with ROSC after cardiac arrest.**  **We suggest against routinely targeting hypocapnia in adults with ROSC after cardiac arrest (weak recommendation, low-certainty evidence).** |
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| Justification |
| Evidence from existing randomized trials and observational studies is very inconsistent. Both randomized trials failed to show an effect of different CO2 targets (mild hypercapnia compared to normal or low-normal targets). Observational studies were evenly distributed in showing benefit, harm or no effect associated with hypercapnia. Hypocapnia results were also inconsistent, although no studies found an association with benefit. In light of the lack of evidence for benefit, and lack of consistent evidence for harm from CO2 levels higher than normal, the task force did not think there was sufficient evidence to suggest for or against targeting mild hypercapnia compared to normocapnia. An ongoing trial investigating this comparison may bring clarity to this issue. For hypocapnia, very limited evidence suggests either no benefit or harm, supporting the task force’s suggestion against targeting hypocapnia. As with all critically ill patients, there may be specific scenarios in which a patient’s CO2 level may need to be higher or lower than normal to accommodate or compensate for other illness (e.g. severe lung injury or metabolic acidosis). |

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| Subgroup considerations |
| Although the task force discussed whether patients with baseline chronic lung disease and chronic CO2 retention might respond differently to different CO2 targets, no evidence addressing this subgroup was found. The task force agreed it would be reasonable to adjust PaCO2 targets in patients with known chronic CO2 retention, but this is expert opinion only as no evidence was identified on this topic. |

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| Implementation considerations |
| The prior treatment recommendation (2015) was a suggestion to maintain normocapnia. The updated treatment recommendation supports this approach, while allowing that we do not currently know if an approach targeting mild hypercapnia is beneficial, harmful, or equal in comparison to targeting normocapnia. The task force discussed the possible complication of acidemia from hypercapnia. The presence or absence of metabolic acidosis is generally something that needs to be considered when choosing a ventilation strategy and PaCO2 target, and metabolic acidosis is common in post-arrest patients. The PaCO2 targets or ranges also differed somewhat between studies. The Eastwood et al trial used a target of 50-55mmHg for the hypercapnia group while the Jakkula trial used 5.8-6kPa (equivalent to 43-45mmHg), as an example of such a difference. For this reason, the task force chose not to define specific numeric targets as no optimal target or range has been made clear. Additionally, opinions vary on whether arterial blood gas analysis in patients receiving targeted temperature management should be adjusted for temperature. Once again trials differed in their approach, with the Eastwood trial using the alpha-stat method (values measured at a temperature of 37) while the Jakkula trial adjusted values to reflect the patient’s actual temperature at time of measurement. Approaches to blood gas interpretation regarding temperature also varied across the observational studies. These variations in methodology and in definitions of target ranges prohibit the task force from being able to recommend specific numbers or a specific method for blood gas analysis for systems implementing these recommendations. |

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| Monitoring and evaluation |
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| Research priorities |
| As the current evidence is inconsistent, primarily from observational studies and from only small RCTs, a large RCT to address the utility of this intervention will be useful, and is recruiting currently. |