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| Question |
| **Oxygenation strategy 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 specific oxygenation strategy |
| **Comparison:** | An alternative oxygenation strategy or no specific oxygenation strategy |
| **Main outcomes:** | Survival to hospital discharge, 3 months, or longer; survival to hospital discharge, 3 months, or longer with favorable neurologic outcome. |
| **Setting:** | Pre-hospital and ICU settings |

# 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 | Cardiac arrest, both in and out-of hospital, is relatively common and has a very high mortality. Previously, both hypoxemia and hyperoxia have been reported to be associated with worse outcome in patients who are post-cardiac arrest. Hypoxemia may worsen ischemic brain injury and injury to other organs, while hyperoxia may lead to increased oxidative stress and organ damage after reperfusion. Several new studies, both observational and randomized trials, have been published since this topic was last updated in 2015. There are three ongoing randomized trials investigating different oxygenation strategies (NCT03138005, NCT03653325, NCT03141099), demonstrating that this continues to be a topic of high interest.  | The ongoing trials are scheduled to complete enrollments in 2020-2021.  |
| Desirable EffectsHow substantial are the desirable anticipated effects? |
| Judgement | Research evidence | Additional considerations |
| ○ Trivial○ Small○ Moderate○ Large○ Varies● Don't know | The evidence on the effect of hyperoxia on survival and neurologic outcome is very mixed, with many inconsistencies across studies in both methodology and results. Randomized trials done to date are very small and the observational studies are all at serious or critical risk of bias. Within these limitations, studies have reported a mix of positive and negative results, leaving true uncertainty. Randomized trials and observational studies have generally found either no effect or a possible benefit from normoxia compared to hyperoxia. Trials done in a hospital/ICU setting are more suggestive of benefit from normoxia than trials done in the pre-hospital setting, but the pre-hospital trials are limited by very small sample size. A recent randomized trial {Mackle 2019 } that was an ICU intervention and included a subgroup of post-arrest patients (larger than any of the RCTs done previously) found a benefit in the conservative (lower) oxygen group. Although the certainty of this finding is limited by the fact that it was a subgroup analysis, it does support the possibility of a true benefit from conservative oxygen therapy in post-cardiac arrest patients. We divided the available trial data into interventions carried out in the pre-hospital setting and those carried out in the intensive care unit, as below.PRE-HOSPITAL INTERVENTION

| **№ of studies** | **Study design** | **Lower % oxygen pre-hospital** | **higher % oxygen pre-hospital** | **Relative(95% CI)** | **Absolute(95% CI)** | **Certainty** | **Importance** |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Survival to Discharge, O2 in pre-hospital setting - Kuisma, Bray** |
| 2  | randomised trials  | 29/51 (56.9%)  | 23/38 (60.5%)  | **RR 0.97**(0.68 to 1.37)  | **18 fewer per 1,000**(from 194 fewer to 224 more)  | ⨁⨁◯◯LOW  | CRITICAL  |
| **Survival to Discharge, O2 in pre-hospital setting -Thomas (cluster randomized by paramedic)** |
| 1  | randomised trial | 10/18 (55.6%)  | 3/17 (17.6%)  | **RR 3.15**(1.04 to 9.52)  | **379 more per 1,000**(from 7 more to 1,000 more)  | ⨁◯◯◯VERY LOW  | CRITICAL |
| **Favorable neurological outcome (OPC < 3) at discharge - Kuisma** |
| 1  | randomised trial | 8/14 (57.1%)  | 6/14 (42.9%)  | **RR 1.33**(0.63 to 2.84)  | **141 more per 1,000**(from 159 fewer to 789 more)  | ⨁⨁◯◯LOW  | CRITICAL |
| **Discharge to home-Young** |
| 1  | randomised trial | 2/8 (25.0%)  | 4/9 (44.4%)  | **RR 0.56**(0.14 to 2.29)  | **196 fewer per 1,000**(from 382 fewer to 573 more)  | ⨁◯◯◯VERY LOW  | CRITICAL |

ICU INTERVENTION

| **№ of studies** | **Study design** | **lower % oxygen** | **higher % oxygen** | **Relative(95% CI)** | **Absolute(95% CI)** | **Certainty** | **Importance** |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Survival to discharge -Young** |
| 1  | randomised trial  | 4/8 (50.0%)  | 4/9 (44.4%)  | **RR 1.13**(0.41 to 3.08)  | **58 more per 1,000**(from 262 fewer to 924 more)  | ⨁◯◯◯VERY LOW  | CRITICAL |
| **Survival to discharge - Jakkula** |
| 1  | randomised trial  | 43/61 (70.5%)  | 39/59 (66.1%)  | **RR 1.07**(0.84 to 1.36)  | **46 more per 1,000**(from 106 fewer to 238 more)  | ⨁⨁⨁◯MODERATE  | CRITICAL |
| **3 month survival - ICU-ROX** |
| 1  | randomised trial | 49/86 (57.0%)  | 32/78 (41.0%)  | **RR 1.39**(1.01 to 1.92)  | **160 more per 1,000**(from 4 more to 377 more)  | ⨁⨁◯◯LOW  | CRITICAL |
| **Discharge to home -Young**  |
| 1  | randomised trial  | 2/8 (25.0%)  | 4/9 (44.4%)  | **RR 0.56**(0.14 to 2.29)  | **196 fewer per 1,000**(from 382 fewer to 573 more)  | ⨁◯◯◯VERY LOW  | CRITICAL |
| **CPC 1-2 at 6 months - Jakkula** |
| 1  | randomised trial  | 42/61 (68.9%)  | 36/59 (61.0%)  | **RR 1.13**(0.87 to 1.47)  | **79 more per 1,000**(from 79 fewer to 287 more)  | ⨁⨁⨁◯MODERATE  | CRITICAL |
| **Favorable GOSE at 6 months - ICU-ROX** |
| 1  | randomised trial  | 35/78 (44.9%)  | 23/72 (31.9%)  | **RR 1.40**(0.93 to 2.13)  | **128 more per 1,000**(from 22 fewer to 361 more)  | ⨁◯◯◯VERY LOW  | CRITICAL |

  | Ongoing trials as noted |
| Undesirable EffectsHow substantial are the undesirable anticipated effects? |
| Judgement | Research evidence | Additional considerations |
| ○ Large○ Moderate○ Small○ Trivial● Varies○  Don't know | Although the evidence is of low certainty, it is likely that the undesirable effects of hypoxia are significant. The undesirable effects of hyperoxia on neurologic outcome are very uncertain due to inconsistency in study results, but a small negative effect on neurologic outcome and survival is possible based on limited existing evidence (see evidence tables above). |  |
| 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 varies across the included studies from very low to moderate (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. {Haywood 2018 e783}  |  |
| Balance of effects2018Does 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 hyperoxia, studies generally show either association with harm or no association, but do not generally show association with benefit. The balance of evidence therefore slightly favors a benefit from normoxia in comparison with hyperoxia. For hypoxemia, limited evidence favors avoiding hypoxemia, with a benefit from normoxia. |  |
| 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 an oxygen strategy targeting a specific/lower oxygen saturation. However, as it is the current standard of care to measure an oxygen saturation continuously in post-arrest, critically-ill patients, and since a titrated oxygen approach would lead to the same or decreased oxygen use, it is likely that an intervention to avoid hyperoxia would not incur significant cost.  | In lower resource settings where pulse oximetry and arterial blood gas analysis are not routinely available, titration of oxygen may be less feasible (see Equity section).  |
| 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 | We did not identify any studies addressing the effect of titration of oxygen to specific targets on health equity in post-arrest patients. In resource-poor settings where ICU equipment and oxygen may be of limited supply, titrating to the minimum amount of oxygen needed to maintain a saturation in the normal range could increase equity by reserving oxygen for other patients. {Sutherland 2019 1138}  |  |
| 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 treatment recommendations do not include any substantial changes compared to 2015. | Although we did not identify any studies addressing acceptability, it is common practice to decrease FiO2 for other critically ill patients once reliable monitoring of oxygenation is available.  |
| 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. However, avoiding hyperoxia should be feasible in most ICU settings where patients are continually monitored. Decreasing FiO2 in the pre-hospital setting or in the immediate post-arrest period may be less feasible as oxygen saturations may be hard to obtain reliably. Some pre-hospital systems utilize transport ventilators that do not have the capacity to adjust the fraction of inspired oxygen, which may also limit feasibility in the pre-hospital setting. There may be significant limitations to feasibility for many aspects of post-arrest care in resource-poor settings, but this is not specific to oxygen titration.  |  |

# 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

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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 |
| **We recommend avoiding hypoxemia in adults with ROSC after cardiac arrest in any setting (strong recommendation, very low certainty evidence).** **We suggest avoiding hyperoxia in adults with ROSC after cardiac arrest in any setting (weak recommendation, low certainty evidence).** **We suggest the use of 100% inspired oxygen until the arterial oxygen saturation or the partial pressure of arterial oxygen can be measured reliably in adults with ROSC after cardiac arrest in any setting (weak recommendation, very low certainty evidence).** |
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| Justification |
|  In making the recommendation to avoid hypoxemia, the task force acknowledges that the evidence is of very low certainty. The task force concluded that the physiologic basis for hypoxia being harmful justifies its avoidance, and detection of hypoxemia may be the best surrogate for true hypoxia. The suggestion to avoid hyperoxia is based on low to moderate certainty evidence that showed either harm or no benefit from hyperoxia. In light of the possible benefit and lack of evidence for harm, the task force suggests targeting normoxia and avoiding hyperoxia. The task force acknowledges that the primary randomized trial evidence suggesting benefit from avoiding hyperoxia is from a subgroup analysis only, and more trials (three currently recruiting) will be helpful. It is also important to consider that the trials generally compare a strategy of more conservative (lower) oxygen administration strategy to a higher oxygen administration strategy. The “higher” arm varies across trials from being usual care (as determined by clinical teams) to a defined intervention of 100% oxygen. Observational studies, which compare oxygen levels rather than strategies, generally defined the hyperoxia group as those with PaO2 ≥300mmHg, a level above what many would consider usual care. The trials enrolling currently will shed much-needed light on this question. The task force felt that titration of oxygen should not be attempted until oxygen levels (peripheral oxygen saturation or partial pressure of oxygen in arterial blood) could be measured reliably. This is most likely to be an important consideration in the pre-hospital setting where arterial blood gas analysis is rarely available and peripheral oxygen saturation may be difficult to obtain. Some of the randomized trials done in the pre-hospital setting, although very small, reported more desaturation in the lower oxygen group, which reinforces the task force suggestion to administer 100% oxygen until reliable measurement of oxygen level is possible. This is likely to be more important in the pre-hospital setting. |

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| Subgroup considerations |
|  The studies available have included both IHCA and OHCA, and generally have not analyzed patients separately. No evidence suggesting a differential effect was found.  |

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| Implementation considerations |
| These recommendations have not changed significantly compared to 2015, so the task force did not think implementation would be a challenge.  |

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| Monitoring and evaluation |
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| Research priorities |
| The evidence regarding the effect of targeting different levels of oxygenation in post-arrest patients remains very limited. As noted above there are three trials ongoing which are likely to clarify this question.  |

1. Mackle D, Bellomo R, Bailey M, Beasley R, Deane A, Eastwood G, Finfer S, Freebairn R, King V, Linke N, Litton E, McArthur C, McGuinness S, Panwar R, Young P and Group I-RIatAaNZICSCT. Conservative Oxygen Therapy during Mechanical Ventilation in the ICU. *N Engl J Med*. 2019.

2. Haywood K, Whitehead L, Nadkarni VM, Achana F, Beesems S, Böttiger BW, Brooks A, Castrén M, Ong ME, Hazinski MF, Koster RW, Lilja G, Long J, Monsieurs KG, Morley PT, Morrison L, Nichol G, Oriolo V, Saposnik G, Smyth M, Spearpoint K, Williams B, Perkins GD and Collaborators C. COSCA (Core Outcome Set for Cardiac Arrest) in Adults: An Advisory Statement From the International Liaison Committee on Resuscitation. *Circulation*. 2018;137:e783-e801.

3. Sutherland T, Moriau V, Niyonzima JM, Mueller A, Kabeja L, Twagirumugabe T, Rosenberg N, Umuhire OF, Talmor DS and Riviello ED. The "Just Right" Amount of Oxygen. Improving Oxygen Use in a Rwandan Emergency Department. *Ann Am Thorac Soc*. 2019;16:1138-1142.