Original Article

Near-Infrared Spectroscopy in Adult Cardiac Surgery Patients: A Systematic Review and Meta-Analysis

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Objectives: To identify the normal baseline preoperative range of cerebral tissue oxygen saturation (SctO2) derived using near-infrared spectroscopy (NIRS) and the efficacy of perioperative interventions designed to modulate SctO2 in cardiac surgical patients.

Design: Systematic review and meta-analysis of relevant randomized controlled trials (RCTs) extracted from the Medline, Embase, and Cochrane Central Register of Controlled Trials databases.

Setting: Hospitals performing cardiac surgery.

Participants: The study comprised 953 participants from 11 RCTs.

Interventions: Interventions included the following: (1) SctO2 monitoring protocol compared with no monitoring; (2) use of cardiopulmonary bypass (CPB) compared with no CPB; (3) normothermic CPB compared with hypothermic CPB; (4) glyceryl trinitrate during surgery compared with placebo; (5) midazolam during induction of anesthesia compared with propofol; (6) sevoflurane anesthesia compared with total intravenous anesthesia; (7) sevoflurane anesthesia compared with propofol-based anesthesia; and (8) norepinephrine during CPB compared with phenylephrine.

Measurements and Main Results: Eleven RCTs with 953 participants measured baseline preoperative SctO2 using NIRS. The pooled mean baseline SctO2 was 66.4% (95% CI 65.0-67.7), generating a reference range of 51.0% to 81.8%. Four interventions (1, 3, 4, and 6 described in the Interventions section above) increased intraoperative SctO2 across the majority of reported time points. Postoperative follow-up of SctO2 occurred in only 1 study, and postoperative cognitive assessment correlating SctO2 with cognitive function was applied in only 4 studies using variable methodology.

Conclusions: The authors have established that reference values for baseline NIRS-derived SctO2 in cardiac surgery patients are varied and have identified interventions that modulate SctO2. This information opens the door to standardized research and interventional studies in this field.

Key Words: cardiac surgery; near-infrared spectroscopy; cerebral oxygenation; cerebral tissue oxygen saturation; postoperative cognitive dysfunction; meta-analysis

# NEAR-INFRARED SPECTROSCOPY (NIRS) can be used to estimate regional cerebral tissue oxygen saturation (SctO2) noninvasively in cardiac surgical patients during and after cardiopulmonary bypass (CPB). NIRS calculates this estimate from the differential absorbance of light by oxygenated and
total hemoglobin in frontal lobe cerebral tissues after subtracting the signal from superficial vessels. This SctO₂ reading principally reflects venous oxygenation, given the proportionally greater volume of the venous system. Thus, NIRS provides potential estimates of the balance between bifrontal oxygen supply and demand. From such information, inferences can be made about global SctO₂ and cerebral oxygenation. Importantly, NIRS differs from pulse oximetry in that it does not limit its signal to that from pulsing blood alone and therefore can be used when there is nonpulsatile cerebral blood flow, as in CPB. Given its potential usefulness, a number of commercial NIRS devices are now available, producing differing results. To date, there has never been a systematic assessment of average values of SctO₂, the variability of this value, and the associated effect of intraoperative interventions on this value in this cohort of cardiac surgery patients in the literature, despite its potential importance in establishing what is normal. In particular, it may be important to appreciate the relationship, or lack thereof, between intraoperative and postoperative NIRS-derived cerebral oxygen desaturation (COD) and postoperative cognitive dysfunction (POCD).

Accordingly, the authors aimed to identify the normal baseline range of SctO₂ values in cardiac surgical patients, as estimated using NIRS, and the nature and efficacy of interventions seeking to modulate SctO₂. The authors also aimed to synthesize available data on postoperative SctO₂, mortality, and POCD.

**Methods**

A protocol for this review was registered prospectively and published as part of the PROSPERO International Prospective Register of Systematic Reviews (CRD42016038410). Medline, Embase, and the Cochrane Central Registry of Controlled Trials were searched through April 15, 2016 for randomized controlled trials (RCTs) that included the evaluation of baseline preoperative SctO₂ with NIRS in adult cardiac surgery patients, using "brain," "oxygenation," and "cardiac surgery" as initial search terms (Appendix 1, Electronic Supplemental Material [ESM]). RCTs in languages other than English, on children, without baseline NIRS readings reported, without SctO₂ reported as a raw percentage, and published as abstracts without full text were excluded. ClinicalTrials.gov also was searched for current trials underway as of April 15, 2016, yielding 3 relevant active or recruiting trials. However, data for these trials have not been published and therefore could not be considered for this meta-analysis.

A 2-stage process was used for study selection. Two review authors (M.J.C and T.C.) independently screened the titles and abstracts of search results and then assessed the eligibility of each full-text trial report using a standardized pre-piloted form outlining the inclusion and exclusion criteria. A third reviewer (N.J.G.) resolved any disagreements. Data collection and bias assessment then were performed by 2 review authors (M.J.C and T.C.) using a pre-piloted form appropriately modified from the Cochrane Collaboration’s standardized form as per protocol. The primary outcome measure was baseline preoperative SctO₂, as measured at any point before induction of anesthesia. Intraoperative SctO₂, whenever measured between induction of anesthesia and closure of the skin; postoperative SctO₂, whenever measured between closure of the skin and discharge from hospital; mortality; and POCD as reported in the studies were collected as secondary outcomes. Missing data were entered as reported without imputation.

Measures of central tendency and variance were recorded for continuous variables, with medians and interquartile ranges converted into parametric estimates with the assumption that the distribution of SctO₂ data is similar to a normal distribution. Where multiple values could be compared, pooled measurements of central tendency, standard error, variance, 95% confidence intervals (95% CIs), and theoretical reference ranges (2.5% quantile to 97.5% quantile) then were calculated. Student t-test was used, as appropriate, on parametric continuous variables to calculate and evaluate the effect size of interventions. Publication bias was assessed formally with a funnel plot analysis, and Egger’s test was used to test the symmetry of the funnel plot. The Cochran Q statistic and study inconsistency (I², the percentage of total variance across studies attributable to heterogeneity rather than chance) were calculated. They were used to determine heterogeneity of studies in the primary outcome and for each sensitivity analysis, with I² = 0% to 40% being no, 40% to 60% being moderate, 60% to 80% being substantial, and 80% to 100% being considerable heterogeneity. Sensitivity analysis included limiting the analysis to measurements of each
<table>
<thead>
<tr>
<th>Study Authors</th>
<th>Year</th>
<th>Number Randomized</th>
<th>Country of Study</th>
<th>NIRS Machine Used</th>
<th>Study Population and Comorbidities</th>
<th>Study Primary Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brassard et al</td>
<td>2014</td>
<td>31</td>
<td>Canada</td>
<td>INVOS* (Somanetics, Troy, MI)</td>
<td>Any cardiac surgery</td>
<td>Administration of norepinephrine to restore MAP during CPB in diabetic patients associated with reduction in cerebral oxygen saturation (not in patients without diabetes); administration of phenylephrine associated with trend toward greater reduction in diabetic patients</td>
</tr>
<tr>
<td>Guclu et al</td>
<td>2014</td>
<td>80 (only 37 reported)</td>
<td>Turkey</td>
<td>INVOS 3100</td>
<td>CABG (elective)</td>
<td>Higher cerebral oxygen saturation in patients with sevoflurane anesthesia maintenance compared with total intravenous anesthesia</td>
</tr>
<tr>
<td>Kim et al</td>
<td>2009</td>
<td>60</td>
<td>Korea</td>
<td>INVOS 5100</td>
<td>CABG without CPB</td>
<td>Single-dose midazolam during induction of anesthesia preserves cerebral oxygen saturation to a similar degree as propofol</td>
</tr>
<tr>
<td>Kok et al</td>
<td>2014</td>
<td>60 (1 exclusion)</td>
<td>Netherlands</td>
<td>INVOS 5100C</td>
<td>CABG (with or without CPB)</td>
<td>Incidence of cerebral oxygen desaturation is uncommon in low-risk patients and not different between CPB and non-CPB patients</td>
</tr>
<tr>
<td>Lenkin et al</td>
<td>2013</td>
<td>40</td>
<td>Russia</td>
<td>FORE-SIGHT* (CAS Medical Systems, Branford, CT)</td>
<td>Multiple valve repairs/replacements (high risk)</td>
<td>Normothermic CPB patients have higher cerebral oxygen saturation during combined valve surgery compared with hypothermic CPB</td>
</tr>
<tr>
<td>Mohandas et al</td>
<td>2013</td>
<td>100</td>
<td>India</td>
<td>EQUANOX 7600 (Nonin, Plymouth, MN)</td>
<td>Any cardiac surgery with CPB</td>
<td>Intraoperative cerebral oxygen saturation monitoring decreases the incidence of POCD</td>
</tr>
<tr>
<td>Murkin et al</td>
<td>2007</td>
<td>200 (6 exclusions)</td>
<td>Canada</td>
<td>INVOS 5100</td>
<td>CABG with CPB (elective)</td>
<td>Intraoperative cerebral oxygen saturation monitoring decreases the incidence of major organ morbidity and mortality</td>
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<td>Negargar et al</td>
<td>2007</td>
<td>72</td>
<td>Iran</td>
<td>INVOS 4100</td>
<td>Any cardiac surgery (elective)</td>
<td>Cerebral oxygen desaturation may help to predict neurologic complications, although not statistically significant</td>
</tr>
<tr>
<td>Piquette et al</td>
<td>2007</td>
<td>32 (2 exclusions)</td>
<td>Canada</td>
<td>INVOS 4100</td>
<td>Any cardiac surgery with CPB (elective, Parsonnet score &gt; 15 = high risk)</td>
<td>Intravenous nitroglycerin infusion before/during CPB helps to maintain cerebral oxygen saturation during CPB in high-risk patients</td>
</tr>
<tr>
<td>Schoen et al</td>
<td>2011</td>
<td>128 (18 exclusions)</td>
<td>Germany</td>
<td>INVOS 5100</td>
<td>Any cardiac surgery with CPB</td>
<td>Intraoperative cerebral oxygen desaturation associated with worse early cognitive outcomes; sevoflurane-based anesthesia may be associated with better postoperative cognitive function compared with propofol-based anesthesia</td>
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cerebral hemisphere, removal of studies with varying NIRS machines, removal of studies with high risk of bias, and removal of studies with high-risk patient groups, in which there was a severity of disease inclusion criteria, such as surgery for complex cardiac disease or a high presurgical risk score. Data were pooled and analyzed using RevMan, version 5.3 (Cochrane, London, United Kingdom); Comprehensive Meta-Analysis, version 3.0 (Biostat, Englewood, NJ); and R, version 3.3.0 (R Foundation for Statistical Computing, Vienna, Austria). Two-tailed p values \( < 0.05 \) were considered to be statistically significant.

**Results**

The search strategy identified 601 reports for review: 140 in Medline, 256 in Embase, and 205 in Cochrane Central Registry of Controlled Trials. Of these, 11 RCTs with 953 randomized participants were included in the review (Fig 1). Characteristics of the included studies are shown in Table 1.\(^1\),\(^1\)\(^,\)\(^9\)\(^,\)\(^1\)\(^9\)\(^,\)\(^1\)\(^9\) There was a wide variation in methodologic quality of the included studies, with only 1 RCT\(^1\)\(^2\) satisfying a low risk of bias in all domains. Five RCTs were deemed to be at particularly high risk of bias (Figs E1 and E2 in Appendix 2 [ESM]).

All baseline preoperative \( \text{SctO}_2 \) data reported were recorded and used to calculate an overall pooled mean and standard deviation across all 11 RCTs of 66.4% \( \pm \) 7.8% (standard error 0.65; 95% CI 65.0-67.7) (Table 2). A 95% reference range for \( \text{SctO}_2 \) in cardiac surgical patients was calculated for this figure as 51.0% to 81.8%. Considerable statistical heterogeneity was found among studies, with a Cochran \( Q \) statistic of 258.9 (\( p < 0.001 \)) and an \( I^2 \) statistic of 88.8% (Fig 2). Sensitivity analyses did not demonstrate a significant difference on visual inspection of the data (Table 2; Figs E3-8 in Appendix 2 [ESM]).

Pooled data on \( \text{SctO}_2 \) for the left hemisphere only and right hemisphere only were 65.4% \( \pm \) 8.8% and 64.7% \( \pm \) 8.7%, respectively. The funnel plot of all studies and subgroups was asymmetrical (\( p = 0.017 \)) (Fig E9 in Appendix 2 [ESM]). Only 2 studies quoted a normal range for \( \text{SctO}_2 \); one\(^1\)\(^4\) with an unreferenced statement of 65% to 75%, and another\(^1\)\(^7\) with figures of 55% to 75% from a reference that actually did not contain such information.

Intraoperative \( \text{SctO}_2 \) was measured in 7 RCTs, each trialing different interventions (Table 3). On visual inspection, 4 of these interventions (\( \text{SctO}_2 \) monitoring protocol compared with no monitoring; normothermic CPB compared with hypothermic CPB; administration of glyceryl trinitrate during surgery compared with placebo; and sevoflurane anesthesia compared with total intravenous anesthesia) had a positive mean effect size of significance in the majority of measured time points. These ranged from a minimum significant effect size of 1.6% (\( p < 0.001 \)) throughout CPB, with an \( \text{SctO}_2 \) monitoring protocol in 1 RCT\(^1\)\(^6\) to a maximum significant effect size of 15% (\( p < 0.001 \)) at the end of CPB on the right hemisphere with glyceryl trinitrate in another.\(^1\) Assessing only the control groups of these studies, intraoperative COD was determined in 8 out of 8 studies (100%) reporting intraoperative \( \text{SctO}_2 \) or...
<table>
<thead>
<tr>
<th>Study</th>
<th>Study Arm/Interventions</th>
<th>Study Subgroup</th>
<th>Hemisphere</th>
<th>Number of Patients</th>
<th>Mean ± Standard Deviation</th>
<th>95% CI</th>
<th>Normal Range Quoted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brassard 2014 et al</td>
<td>Norepinephrine (to keep MAP &gt; 60 mmHg)</td>
<td>Diabetics</td>
<td>—</td>
<td>6</td>
<td>60 ± 11</td>
<td>51.2-68.8</td>
<td>None stated</td>
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<td></td>
<td>Phenylephrine (to keep MAP &gt; 60 mmHg)</td>
<td>Diabetics</td>
<td>—</td>
<td>8</td>
<td>61 ± 9</td>
<td>54.8-67.2</td>
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<tr>
<td></td>
<td></td>
<td>Non-diabetics</td>
<td>—</td>
<td>8</td>
<td>63 ± 3</td>
<td>60.9-65.1</td>
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<tr>
<td>Guclu 2014 et al</td>
<td>Sevoflurane (for anesthesia maintenance)</td>
<td>Diabetics</td>
<td>L</td>
<td>16</td>
<td>66.4 ± 7.7</td>
<td>62.6-70.2</td>
<td>None stated</td>
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<td></td>
<td></td>
<td>Non-diabetics</td>
<td>R</td>
<td>16</td>
<td>64.5 ± 7.1</td>
<td>61.0-68.0</td>
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<tr>
<td></td>
<td>Total intravenous anesthesia</td>
<td>Diabetics</td>
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<td>86</td>
<td>60.9-65.1</td>
<td>61.1-68.9</td>
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<tr>
<td></td>
<td></td>
<td>Non-diabetics</td>
<td>—</td>
<td>91</td>
<td>61.1-68.9</td>
<td>61.1-68.9</td>
<td></td>
</tr>
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<td>Kim et al 2009</td>
<td>Midazolam (induction of anesthesia)</td>
<td>Diabetics</td>
<td>L</td>
<td>30</td>
<td>65 ± 7</td>
<td>61.8-68.2</td>
<td>None stated</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Non-diabetics</td>
<td>R</td>
<td>30</td>
<td>64 ± 10</td>
<td>60.4-67.6</td>
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<td>Propofol (induction of anesthesia)</td>
<td>Diabetics</td>
<td>—</td>
<td>30</td>
<td>66 ± 7</td>
<td>63.5-68.5</td>
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<td></td>
<td></td>
<td>Non-diabetics</td>
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<td>67 ± 7</td>
<td>63.5-68.5</td>
<td></td>
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<tr>
<td>Kok et al 2014</td>
<td>Overall</td>
<td>—</td>
<td>59</td>
<td>67.1 ± 9.4</td>
<td>64.7-69.5</td>
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<td>With CPB</td>
<td>—</td>
<td>29</td>
<td>67.2 ± 10.1</td>
<td>63.5-70.9</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Without CPB</td>
<td>—</td>
<td>30</td>
<td>67 ± 8.8</td>
<td>63.9-70.1</td>
<td></td>
<td></td>
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<tr>
<td>Lenkin et al 2013</td>
<td>Normothermic CPB</td>
<td>—</td>
<td>20</td>
<td>65 ± 8</td>
<td>61.5-68.5</td>
<td>65%-75% (no study referenced)</td>
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<td>Hypothermic CPB</td>
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<td>20</td>
<td>64 ± 6</td>
<td>61.4-66.6</td>
<td></td>
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<td>Mohandas et al 2013</td>
<td>Cerebral oxygenation monitoring</td>
<td>—</td>
<td>50</td>
<td>66.32</td>
<td>—</td>
<td>None stated</td>
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<tr>
<td></td>
<td>No monitoring</td>
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<td>50</td>
<td>65.78</td>
<td>—</td>
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<td></td>
<td>Cerebral oxygenation monitoring</td>
<td>—</td>
<td>50</td>
<td>66.38</td>
<td>—</td>
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<td>50</td>
<td>65.42</td>
<td>—</td>
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<td>Murkin et al 2007</td>
<td>Cerebral oxygenation monitoring</td>
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<td>100</td>
<td>68.9 ± 7.2</td>
<td>67.5-70.3</td>
<td>None stated</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No monitoring</td>
<td>—</td>
<td>100</td>
<td>70.3 ± 7.1</td>
<td>68.9-71.7</td>
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<td></td>
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<tr>
<td>Negargar et al 2007</td>
<td>CABG with CPB</td>
<td>—</td>
<td>24</td>
<td>77.3 ± 8.3</td>
<td>74.0-80.6</td>
<td>55%-75% (Paula MB et al 2001 referenced)</td>
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<tr>
<td></td>
<td>CABG without CPB</td>
<td>—</td>
<td>24</td>
<td>75.6 ± 7.9</td>
<td>72.4-78.8</td>
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<tr>
<td></td>
<td>Valve surgery</td>
<td>—</td>
<td>24</td>
<td>70.8 ± 9.6</td>
<td>67.0-74.6</td>
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<tr>
<td>Piquette et al 2007</td>
<td>Glyceryl trinitrate</td>
<td>—</td>
<td>15</td>
<td>54 ± 11</td>
<td>48.4-59.6</td>
<td>Not stated</td>
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<tr>
<td></td>
<td>Control</td>
<td>—</td>
<td>15</td>
<td>51 ± 8</td>
<td>47.0-55.0</td>
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<tr>
<td></td>
<td></td>
<td>—</td>
<td>15</td>
<td>63 ± 8</td>
<td>59.0-67.0</td>
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<td></td>
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<td>—</td>
<td>15</td>
<td>59 ± 11</td>
<td>53.4-64.6</td>
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<tr>
<td>Schoen et al 2011</td>
<td>Sevoflurane</td>
<td>—</td>
<td>42</td>
<td>66.2 ± 6</td>
<td>64.4-68.0</td>
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<tr>
<td></td>
<td></td>
<td>Desaturations</td>
<td>—</td>
<td>14</td>
<td>60.2 ± 7.8</td>
<td>56.1-64.3</td>
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<tr>
<td></td>
<td></td>
<td>Propofol</td>
<td>—</td>
<td>34</td>
<td>66 ± 4.6</td>
<td>64.5-67.5</td>
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<tr>
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<td>Desaturations</td>
<td>—</td>
<td>20</td>
<td>57.6 ± 8.6</td>
<td>53.8-61.4</td>
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<tr>
<td>Vretzakis et al 2013</td>
<td>Cerebral oxygenation monitoring</td>
<td>—</td>
<td>75</td>
<td>66.29 ± 7.48</td>
<td>64.6-68.0</td>
<td>Not stated</td>
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</table>
other measures of COD (Table 4). Only 1 RCT reported postoperative SctO₂, with no COD determined in either patient group (Table 4).

Mortality was low in these studies when reported (3 studies), with no intervention demonstrating a statistically significant difference in outcome. POCD also was uncommonly reported (4 studies), with a wide variety of tests and test outcomes being used for assessment (see Table 3).

Discussion

Key Findings

The authors conducted a systematic review of all RCTs of interventions measuring and designed to modify NIRS-derived SctO₂ during CPB in adult patients and identified 11 RCTs that reported relevant information. From these studies, the pooled mean baseline preoperative SctO₂ of this clinically heterogeneous cohort of cardiac surgical patients was found to be approximately 66%, with a wide reference range. Moreover, the following 4 interventions were observed to possibly improve intraoperative SctO₂, as supported by 1 RCT each: (1) an SctO₂ monitoring protocol, (2) normothermic CPB compared with hypothermic CPB, (3) glyceryl trinitrate during surgery compared with placebo, and (4) sevoflurane anesthesia compared with total intravenous anesthesia. Finally, follow-up of postoperative SctO₂, mortality, and POCD was found to be rare among studies involving SctO₂.

Relationship With Previous Literature

These results were comparable with those reported in a prospective, observational study of 1,178 German adult cardiac surgery patients requiring CPB. In these patients, investigators reported a median baseline SctO₂ on room air of 62% (57%-67%) on the left and 62% (56%-67%) on the right, and a median minimal preoperative oxygen-supplemented SctO₂ of 64% (range: 15%-92%) using the INVOS (Medtronic, Minneapolis, MN) system. Another prospective, observational study of 101 cardiac surgery patients requiring CPB also using the INVOS system found mean baseline SctO₂ values of 58.6% ± 10.2%. These comparatively lower values may be explained by the study protocol, which involved collection of the lower SctO₂ value of the hemispheres for a single reading at each time point.

An early systematic review of the use of NIRS monitoring in cardiac surgery returned only 1 small randomized study and did not discuss baseline preoperative SctO₂ values. A more recent comparison of different NIRS devices in cardiac surgery did not seek to define a normal baseline preoperative SctO₂ range and did not assess the effect of intraoperative interventions on SctO₂. Even though there were some inconsistencies in the classification of level of evidence compared with the review presented here, there were similar findings regarding the paucity of large randomized research performed in this field, the variety in measurement of POCD, and the predominance of the use of the INVOS system in the literature. Finally,
a systematic review by Zheng et al found that only low-level evidence supported the association between low SctO2 and POCD and that few interventions modulating SctO2 have been shown to improve such neurologic outcomes.24

Study Implications

The results of the study presented here provided the first RCT-based comprehensive estimate of normal baseline values for SctO2 in adult cardiac surgery patients, implying that this information likely provided the most robust dataset to date for future comparisons and interventions. Furthermore, these findings suggested that a variety of interventions may increase SctO2 during CPB significantly, implying that it is possible to manipulate SctO2 during CPB. However, they also showed that there is almost no knowledge of postoperative changes in SctO2 and of the link between SctO2 changes and POCD. It remains possible that this lack of information about postoperative SctO2 is a major confounder in studies comparing intraoperative COD with POCD, implying that more work is needed to understand these changes and their clinical consequences. This study was not able to provide data comparing different NIRS technologies due to the predominant use of the INVOS system in reviewed studies.

Strengths and Limitations

To the authors’ knowledge, this review was the first to meta-analyze and describe baseline SctO2 in this patient cohort using data from RCTs. The search strategy was systematic and unlikely to introduce bias. It also provided the most up-to-date review of the literature on the use of NIRS in cardiac surgery patients. The findings extended the understanding of baseline SctO2 and trends during cardiac surgery despite the significant clinical and methodologic heterogeneity in the included studies.

However, this review had several limitations. The choice of including only outcome data presented as percentage saturation may have limited the inclusion of some studies with relevant findings; however, this was an unavoidable limitation, given the wide range of definitions in each study for other

Fig 2. Baseline SctO2: forest plot of point estimates and confidence intervals of all studies and subgroups.

<table>
<thead>
<tr>
<th>Study</th>
<th>Subgroup</th>
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<tbody>
<tr>
<td>Brassard2014</td>
<td>Norepinephrine (Diabetics)</td>
</tr>
<tr>
<td>Brassard2014</td>
<td>Norepinephrine (Nondiabetics)</td>
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<td>Brassard2014</td>
<td>Phenytoin (Diabetics)</td>
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<td>Brassard2014</td>
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<td>Gudel14</td>
<td>Sevoflurane (L)</td>
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<tr>
<td>Gudel14</td>
<td>Sevoflurane (R)</td>
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<tr>
<td>Gudel14</td>
<td>Total intravenous anaesthesia (L)</td>
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<td>Gudel14</td>
<td>Total intravenous anaesthesia (R)</td>
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<tr>
<td>Kim13 2009</td>
<td>Midazolam (L)</td>
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<td>Kim13 2009</td>
<td>Midazolam (R)</td>
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<tr>
<td>Kim13 2009</td>
<td>Propofol (L)</td>
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<td>Kim13 2009</td>
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<td>Kok13 2014</td>
<td>All patients</td>
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<tr>
<td>Lenkin 2013</td>
<td>Normothermic CPB</td>
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<td>Lenkin 2013</td>
<td>Hypothermic CPB</td>
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<td>Murkin13 2007</td>
<td>SctO2 monitoring</td>
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<td>Murkin13 2007</td>
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<tr>
<td>Negarg13 2007</td>
<td>CABG with CPB</td>
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<td>Negarg13 2007</td>
<td>CABG without CPB</td>
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<td>Valve surgery</td>
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<td>Piquette1 2007</td>
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<td>Piquette1 2007</td>
<td>Control (L)</td>
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<td>Control (R)</td>
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<td>Schoen15 2011</td>
<td>Sevoflurane (No desaturations)</td>
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<tr>
<td>Schoen15 2011</td>
<td>Sevoflurane (Desaturations)</td>
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<tr>
<td>Schoen15 2011</td>
<td>Propofol (No desaturations)</td>
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<td>Schoen15 2011</td>
<td>Propofol (Desaturations)</td>
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<td>Vretzakis10 2013</td>
<td>SctO2 monitoring (L)</td>
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<tr>
<td>Vretzakis10 2013</td>
<td>SctO2 monitoring (L)</td>
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</tbody>
</table>

Summary

Heterogeneity: Cochran Q = 258.95 (P < 0.001), df = 29, I² = 88.80
<table>
<thead>
<tr>
<th>Intervention</th>
<th>Studies Tested and Reported</th>
<th>Time Points Reported /Subgroups</th>
<th>Hemisphere</th>
<th>Number of Participants (Control v Intervention)</th>
<th>Control Mean Difference (Compared with Baseline)</th>
<th>Intervention Mean Difference (Compared with Baseline)</th>
<th>Mean Effect Size and Standard Error</th>
<th>95% CI</th>
<th>p Value</th>
<th>Mortality (Control v Intervention)</th>
<th>POCD (Control v Intervention)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebral oxygenation monitoring v no monitoring</td>
<td>Murkin et al 2007\cite{16}</td>
<td>Mean throughout surgery</td>
<td>—</td>
<td>100 v 100</td>
<td>-6.9 ± 1.0</td>
<td>-5.3 ± 1.0</td>
<td>1.6 ± 0.16</td>
<td>1.32-1.88</td>
<td>&lt;0.001</td>
<td>1% v 0% (ITT analysis: p = 0.50)</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Mohandas et al 2013\cite{15}</td>
<td>—</td>
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<tr>
<td></td>
<td>Vretzakis 2013\cite{9}</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>1.3% v 1.3% (p = 1.0)</td>
<td>—</td>
</tr>
<tr>
<td>CABG with CPB v without CPB</td>
<td>Negargar 2007\cite{17}</td>
<td>1st h of surgery</td>
<td>—</td>
<td>24 v 24</td>
<td>-4.8 ± 2.3</td>
<td>-3.8 ± 2.6</td>
<td>1.0 ± 0.7</td>
<td>-0.43 to 2.43</td>
<td>0.165</td>
<td>—</td>
<td>4% v 4% (p = 1.0); measured with MMSE (decrease &gt; 20% and 1 SD)</td>
</tr>
<tr>
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<td>2nd h of surgery</td>
<td>—</td>
<td>—</td>
<td>-6.5 ± 2.3</td>
<td>-5.6 ± 2.4</td>
<td>0.9 ± 0.6</td>
<td>-0.47 to 2.27</td>
<td>0.191</td>
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<tr>
<td></td>
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<td>3rd h of surgery</td>
<td>—</td>
<td>—</td>
<td>-8.1 ± 2.3</td>
<td>-11.4 ± 2.8</td>
<td>-3.3 ± 0.7</td>
<td>-4.79 to -1.81</td>
<td>&lt;0.001</td>
<td>—</td>
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<tr>
<td></td>
<td></td>
<td>4th h of surgery</td>
<td>—</td>
<td>—</td>
<td>-9.8 ± 2.5</td>
<td>-9.8 ± 1.7</td>
<td>0 ± 0.61</td>
<td>-1.24 to 1.24</td>
<td>1.000</td>
<td>—</td>
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<tr>
<td></td>
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<td>5th h of surgery</td>
<td>—</td>
<td>—</td>
<td>-13.1 ± 2.2</td>
<td>-6.9 ± 3.1</td>
<td>6.2 ± 0.7</td>
<td>4.64-7.76</td>
<td>&lt;0.001</td>
<td>—</td>
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<tr>
<td>Normothermic CPB v hypothermic CPB</td>
<td>Lenkin et al 2013\cite{14}</td>
<td>Start of CPB</td>
<td>—</td>
<td>20 v 20</td>
<td>-1.0 ± 1.8</td>
<td>1.0 ± 2.1</td>
<td>2.0 ± 0.62</td>
<td>0.75 to 3.25</td>
<td>0.003</td>
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<tr>
<td></td>
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<td>30 min into CPB</td>
<td>—</td>
<td>—</td>
<td>5.0 ± 1.8</td>
<td>6.0 ± 2.0</td>
<td>1.0 ± 0.61</td>
<td>-0.23 to 2.23</td>
<td>0.107</td>
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<tr>
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<td>—</td>
<td>—</td>
<td>3.0 ± 2.3</td>
<td>6.0 ± 2.0</td>
<td>3.0 ± 0.68</td>
<td>1.26 to 4.74</td>
<td>0.001</td>
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<td>90 min into CPB</td>
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<td>3.0 ± 2.1</td>
<td>8.0 ± 2.0</td>
<td>5.0 ± 0.66</td>
<td>3.66 to 6.34</td>
<td>&lt;0.001</td>
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<td></td>
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<td>120 min into CPB</td>
<td>—</td>
<td>—</td>
<td>0 ± 1.8</td>
<td>9.0 ± 2.2</td>
<td>9.0 ± 0.64</td>
<td>7.71 to 10.29</td>
<td>&lt;0.001</td>
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<tr>
<td>Glyceryl trinitrate during pre-CPB and CPB v placebo</td>
<td>Piquette et al 2007\cite{1}</td>
<td>Start of CPB</td>
<td>R</td>
<td>15 v 15</td>
<td>-3.0 ± 4.6</td>
<td>2.0 ± 3.5</td>
<td>5.0 ± 1.49</td>
<td>1.94-8.06</td>
<td>0.002</td>
<td>(p value) 13%</td>
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<tr>
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<td>End of CPB</td>
<td>L</td>
<td>—</td>
<td>-11 ± 4.2</td>
<td>2.0 ± 3.4</td>
<td>13.0 ± 1.40</td>
<td>10.14-15.86</td>
<td>&lt;0.001</td>
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<td></td>
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<td>—</td>
<td>R</td>
<td>—</td>
<td>-13 ± 4.6</td>
<td>2.0 ± 2.7</td>
<td>15.0 ± 1.38</td>
<td>12.18-17.82</td>
<td>&lt;0.001</td>
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<tr>
<td>Midazolam as part of induction of anesthesia v propofol</td>
<td>Kim et al 2009\cite{12}</td>
<td>5 min after administration</td>
<td>L</td>
<td>30 v 30</td>
<td>8.0 ± 1.9</td>
<td>9.0 ± 2.3</td>
<td>1.0 ± 0.55</td>
<td>-0.09 to 2.09</td>
<td>0.071</td>
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<td>R</td>
<td>8.0 ± 1.9</td>
<td>9.0 ± 2.5</td>
<td>1.0 ± 0.57</td>
<td>-0.15 to 2.15</td>
<td>0.086</td>
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<tr>
<td>Sevoflurane anesthesia v total intravenous anesthesia</td>
<td>Guclu et al 2014\cite{11}</td>
<td>Intubation</td>
<td>L</td>
<td>16 v 16</td>
<td>4.3 ± 3.8</td>
<td>7.1 ± 3.2</td>
<td>2.8 ± 1.24</td>
<td>0.26 to 5.34</td>
<td>0.032</td>
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<td>R</td>
<td>—</td>
<td>5.2 ± 3.1</td>
<td>6.9 ± 2.6</td>
<td>1.7 ± 1.01</td>
<td>-0.37 to 3.77</td>
<td>0.103</td>
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<td>L</td>
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<td>-1.9 ± 2.5</td>
<td>-1.4 ± 3.1</td>
<td>0.5 ± 1.17</td>
<td>-1.89 to 2.89</td>
<td>0.672</td>
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<td>R</td>
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<td>-2.5 ± 2.8</td>
<td>-2.9 ± 2.6</td>
<td>-0.4 ± 0.96</td>
<td>-2.35 to 1.55</td>
<td>0.678</td>
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<td></td>
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<td></td>
<td>R</td>
<td>—</td>
<td>-10.6 ± 3.1</td>
<td>-1.8 ± 3.4</td>
<td>8.8 ± 1.15</td>
<td>6.45 to 11.15</td>
<td>&lt;0.001</td>
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<td>L</td>
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<td>-7.6 ± 2.9</td>
<td>-4.7 ± 2.9</td>
<td>2.9 ± 1.03</td>
<td>0.81 to 4.99</td>
<td>0.008</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>L</td>
<td>—</td>
<td>-11.7 ± 3.5</td>
<td>-4.1 ± 3.5</td>
<td>7.6 ± 1.24</td>
<td>5.07 to 10.13</td>
<td>&lt;0.001</td>
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<td>R</td>
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<td>-12.0 ± 3.5</td>
<td>-5.3 ± 2.6</td>
<td>6.7 ± 1.09</td>
<td>4.47 to 8.93</td>
<td>&lt;0.001</td>
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At CPB lowest temperature

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<td>–17.8 ± 3.4</td>
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<td>–4.0 ± 3.2</td>
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<td>13.8 ± 1.17</td>
<td>9.6 ± 0.99</td>
<td>7.4 ± 1.10</td>
<td>8.2 ± 0.99</td>
<td>11.42 to 16.18</td>
<td>5.16 to 9.64</td>
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<td>&lt; 0.001</td>
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Rewarming to 36°C

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<td>–9.7 ± 2.5</td>
<td>–7.8 ± 3.0</td>
<td>–9.7 ± 2.5</td>
<td>–0.4 ± 3.2</td>
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<tr>
<td></td>
<td>7.4 ± 1.10</td>
<td>3.9 ± 0.94</td>
<td>5.16 to 9.64</td>
<td>1.98 to 5.82</td>
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<td>5.16 to 9.64</td>
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Post-CPB

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<tr>
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<td>–4.7 ± 3.0</td>
<td>–5.5 ± 2.6</td>
<td>–4.7 ± 3.0</td>
<td>–5.5 ± 2.6</td>
<td>1.4 ± 2.8</td>
<td>–2.0 ± 3.1</td>
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<td>6.1 ± 1.03</td>
<td>3.5 ± 1.01</td>
<td>4.00 to 8.20</td>
<td>1.43 to 5.57</td>
<td>11.42 to 16.18</td>
<td>5.16 to 9.64</td>
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<td>&lt; 0.001</td>
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Skin closure

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<tbody>
<tr>
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<td>–3.5 ± 3.8</td>
<td>–6.1 ± 2.9</td>
<td>–3.5 ± 3.8</td>
<td>–6.1 ± 2.9</td>
<td>1.4 ± 3.2</td>
<td>–0.1 ± 3.3</td>
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<tr>
<td></td>
<td>4.9 ± 1.24</td>
<td>6.0 ± 1.10</td>
<td>2.36 to 7.44</td>
<td>3.76 to 8.24</td>
<td>11.42 to 16.18</td>
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Sevoflurane-based anesthesia vs propofol-based anesthesia

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<th>Propofol-based anesthesia</th>
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<tr>
<td></td>
<td>Schoen et al 2011</td>
<td>—</td>
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Test values directly compared; Measured with AMT, Stroop test, TMT, WL-N

Norepinephrine during CPB vs phenylephrine

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<th>Norepinephrine during CPB</th>
<th>Phenylephrine</th>
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<tbody>
<tr>
<td></td>
<td>Brassard et al 2014</td>
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</table>

Mean throughout CPB Diabetics Nondiabetics

<table>
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<th></th>
<th>Diabetics</th>
<th>Nondiabetics</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>8 v 6</td>
<td>9 v 8</td>
</tr>
</tbody>
</table>

8.0 ± 2.4 4.0 ± 2.8
8.0 ± 6.6 1.0 ± 4.3
0 ± 2.50 5.0 ± 1.74
–5.48 to 5.48 1.29 to 8.71
1.000 0.012

NOTE. All values listed as percentage (%).

Abbreviations: —, unclear/not reported; AMT, Abbreviated Mental Test; ASEM, antisaccadic eye movement test; CABG, coronary artery bypass graft surgery; Cl, confidence interval; CPB, cardiopulmonary bypass; ITT, intention-to-treat; L, left; MMSE, Mini-Mental State Examination; POCD, postoperative cognitive dysfunction; R, right; cerebral tissue oxygen saturation; SD, standard deviation; TMT, Trail-Making Test; WL-N, word list recall test.

*Mohandas et al: only means reported (no measure of variance); Vretzakis et al: no control data; Kok et al and Schoen et al: no intraoperative ScrO2 data.

†Difference between groups statistically significant (p < 0.05).

‡Lenkin et al data were reported as median (interquartile range); mean and standard variation estimated.
outcome measures. Only RCTs were considered for inclusion in this review, limiting the pool of studies and patients. However, the authors considered that RCTs would provide the most robust dataset for such assessment. Furthermore, English was a requirement of the search strategy and several studies were excluded on the basis of being published in a non-English language. However, neither of these strategies was likely to add bias to the review. The study findings were limited by the significant clinical heterogeneity and varying methodologic quality of the included studies. This heterogeneity likely was the cause of the funnel plot asymmetry, rather than publication bias, in this setting. In addition, the authors are unable to comment on the potential reasons for the observed wide interindividual variability in baseline ScO₂ due to the limited information available. This lack of information highlights the need for additional study into the effects of patient demographic and physiologic variables on ScO₂ because factors such as patient age, sex, presence of cerebral vascular disease, hemoglobin, and hemodynamic parameters are likely to influence ScO₂. This study also was not able to provide evidence to suggest that either avoiding intraoperative COD or applying the interventions discussed is beneficial to postoperative patient outcomes.

Conclusions

This systematic review showed that the normal baseline ScO₂ of cardiac surgery patients from 11 identified RCTs was approximately 66%, with a wide reference range. Moreover, this review suggested that intraoperative ScO₂ may be modulated by particular interventions and confirmed there is a paucity of data on postoperative ScO₂. Finally, the review demonstrated that there is very little or no RCT-derived information on any association between changes in intraoperative or postoperative ScO₂ and POCD. Additional standardized research is indicated to relate intraoperative ScO₂ to normal preoperative values and to identify whether intraoperative and postoperative modulation of ScO₂ is associated with changes in POCD.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1053/j.jvca.2017.02.187.

References


Table 4

Intraoperative and Postoperative ScO₂ Desaturation in Control Groups

<table>
<thead>
<tr>
<th>Study</th>
<th>Measure of COD</th>
<th>COD at Start of Early CPB</th>
<th>COD During CPB</th>
<th>COD at End of/Late CPB</th>
<th>COD Postoperatively</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brassard et al 2014&lt;sup&gt;10&lt;/sup&gt;</td>
<td>Absolute % reduction from baseline</td>
<td>–</td>
<td>Y</td>
<td>–</td>
<td>Not tested</td>
</tr>
<tr>
<td>Guclu et al 2014&lt;sup&gt;11&lt;/sup&gt;</td>
<td>Absolute % reduction from baseline</td>
<td>–</td>
<td>Y</td>
<td>Y</td>
<td>Not tested</td>
</tr>
<tr>
<td>Kok et al 2014&lt;sup&gt;12,13&lt;/sup&gt;</td>
<td>COD = drop &gt; 30% from baseline at any time</td>
<td>–</td>
<td>Y</td>
<td>–</td>
<td>Not tested</td>
</tr>
<tr>
<td>Lenkin et al 2013&lt;sup&gt;14&lt;/sup&gt;</td>
<td>Absolute % reduction from baseline</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Mohandas et al 2013&lt;sup&gt;15&lt;/sup&gt;</td>
<td>Absolute % reduction from baseline</td>
<td>–</td>
<td>Y</td>
<td>–</td>
<td>Not tested</td>
</tr>
<tr>
<td>Murkin et al 2007&lt;sup&gt;16&lt;/sup&gt;</td>
<td>Absolute % reduction from baseline</td>
<td>–</td>
<td>Y</td>
<td>–</td>
<td>Not tested</td>
</tr>
<tr>
<td>Negargar et al 2007&lt;sup&gt;17&lt;/sup&gt;</td>
<td>Absolute % reduction from baseline</td>
<td>Y</td>
<td>–</td>
<td>–</td>
<td>Not tested</td>
</tr>
<tr>
<td>Piquette et al 2007&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Absolute % reduction from baseline</td>
<td>Y</td>
<td>–</td>
<td>Y</td>
<td>Not tested</td>
</tr>
</tbody>
</table>

Abbreviations: –, unclear/not reported; CABG, coronary artery bypass grafting; COD, cerebral oxygen desaturation; cerebral tissue oxygen saturation.


