Published in final edited form as:
Perfusion. ; : 2676591251380659. doi:10.1177/02676591251380659.

Delivery of oxygen during cardiopulmonary bypass and associated clinical outcomes among adult cardiac surgery patients: A systematic review

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Abstract

Purpose: Oxygen delivery (DO_2) during cardiopulmonary bypass (CPB) is critical in preventing postoperative complications in adult cardiac surgery. This systematic review aimed to assess the relationship between intraoperative DO_2 during CPB, particularly within Goal-directed Perfusion (GDP) strategies, and associated clinical outcomes.

Methods: A systematic search of MEDLINE, Embase, Web of Science, PsycINFO, CINAHL, PROSPERO, and Cochrane was conducted from database inception through December 2024, adhering to PRISMA 2020 guidelines. Studies reported intraoperative DO_2 measurements and their relationship with clinical outcomes among adults undergoing cardiac surgery with CPB. Data extraction and quality assessment were performed independently by two reviewers.

Results: Thirty-nine studies (71,050 patients) were included, with acute kidney injury (AKI) being the most frequently studied outcome (84.6% of studies). A consistent association was found

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Declaration of conflicting interests
The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

between lower intraoperative DO_2 and increased risk of AKI, intraoperative lactate elevations, and prolonged mechanical ventilation. Five randomized controlled trials (RCTs) demonstrated that maintaining DO_2 levels, indexed to body surface area (iDO_2), above a threshold of 270–300 mL/min/m^2 significantly reduced the risk of postoperative AKI. However, evidence linking DO_2 management directly to reductions in mortality or neurologic complications remains limited, as well as studies reporting compliance with GDP strategies.

Conclusion: Maintaining adequate iDO_2 during CPB significantly reduces postoperative complications, especially AKI. These findings underscore the clinical relevance of GDP strategies, highlighting the importance of individualized perfusion management to optimize outcomes. Further large-scale RCTs are needed to confirm these benefits, standardize specific iDO_2 threshold levels that are beneficial, and to explore strategies that impact mortality and neurologic outcomes, as well as investigate the role that temperature management plays in DO_2 threshold determination.

Keywords

cardiopulmonary bypass; oxygen delivery; acute kidney injury; goal-directed perfusion; cardiac surgery

Introduction

Cardiopulmonary bypass (CPB) is an indispensable component of adult cardiac surgery. However, CPB's inherent need for at least some degree of hemodilution, combined with variable pump flow, may compromise oxygen delivery (DO_2) to tissues, leading to metabolic acidosis.[1] DO_2 – typically indexed to body surface area (iDO_2) – is the product of pump flow and arterial oxygen content and represents the volume of oxygen delivered to the tissues per minute. Maintaining adequate DO_2 during CPB is physiologically paramount because, once DO_2 falls below a critical threshold, oxygen consumption becomes supply-dependent, leading to tissue dysoxia. Under such conditions, anaerobic metabolism ensues with increased lactate production and cellular injury.[2] Ensuring sufficient DO_2 on bypass is therefore crucial to prevent hypoxic organ damage during cardiac surgery, and strategies to optimize DO_2 are known as Goal-Directed Perfusion (GDP).[3]

Mounting evidence indicates that even relatively short episodes of low DO_2 during CPB are strongly associated with adverse postoperative outcomes, particularly acute kidney injury (AKI).[1] In one seminal study, Ranucci et al. reported that a nadir iDO_2 below 272 mL/min/m^2 was the single strongest independent predictor of acute renal failure after coronary artery bypass grafting (CABG) procedures.[4] Numerous subsequent investigations have corroborated the link between inadequate CPB perfusion and renal injury, with critical iDO_2i thresholds in the range of roughly 225–300 mL/min/m^2 identified across multiple studies.[5] For example, when iDO_2 falls below ~260 mL/min/m^2, a sharp rise in intraoperative lactate has been observed, reflecting a shift to anaerobic metabolism at the tissue level.[1] Clinically, patients who experience prolonged low-DO_2 states on bypass are at heightened risk not only for AKI but also for other organ dysfunction, such as neurological and respiratory issues.[6–8] Severe AKI itself carries a grave prognosis—mortality climbs to 30–50% in patients who require dialysis after cardiac surgery.[2] Encouragingly, recent interventional data support a causal role of DO_2: a randomized trial demonstrated that using a goal-directed perfusion strategy to maintain iDO_2 ≥280 mL/min/m^2 significantly reduced the incidence of postoperative AKI.[9] These findings underscore the concept that oxygen delivery during CPB is a key determinant of patient outcomes.

Despite growing recognition of the importance of DO_2 during bypass, there is substantial variability in the literature and in practice regarding specific DO_2 thresholds and monitoring strategies.[10] Investigators have used disparate cutoff values for "critical" iDO_2, with early studies suggesting injury occurs below ~250 mL/min/m^2, whereas more recent data advocate for maintaining iDO_2 above 300 mL/min/m^2 for optimal outcomes.[5] Some, but not all, of this variation is related to differences in temperature management during CPB, i.e., the warmer the patient temperature, the more likely a higher iDO_2 is required. Indeed, some authors acknowledge that while a iDO_2 around 260 mL/min/m^2 is often cited as critical, supporting data for a universal threshold remain limited.[1] Moreover, there is no consensus on how best to measure or augment oxygen delivery during CPB. Some centers do not continuously monitor DO_2 at all,[2] and others rely on surrogate metrics such as the ratio of DO_2 to carbon dioxide production (DO_2/VCO_2) to assess perfusion adequacy.[1] Strategies to avoid critical DO_2 drops also vary, ranging from increasing pump flow to transfusing red blood cells to raise oxygen carrying capacity. This heterogeneity in definitions and management of "adequate" DO_2 highlights a significant gap in guideline guidance, and what remains to be well understood is what DO_2 threshold clinicians should target, as well as what evidence supports that target to improve outcomes. Currently, no universal standard exists, and practice patterns remain inconsistent.[11] Given the clinical stakes and the variability in current practice, a comprehensive review of the evidence is warranted.

This study aimed to systematically review scientific literature and synthesize the findings from peer-reviewed studies investigating the relationship between DO_2 during CPB and clinical outcomes among adult cardiac surgery patients.

Methods

To design the present study and report the review findings, we followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines.[12] Study selection, quality assessment, and data management were conducted using Covidence (*Veritas Health Innovation Ltda*, Melbourne, Australia), a web-based systematic review platform.

Search strategy and data sources

A literature search was conducted in January 2025 using MEDLINE (PubMed), Embase (embase.com), Web of Science (Core Collection), PsycINFO (EBSCO), Cumulative Index to Nursing and Allied Health Literature (CINAHL), International Prospective Register of Systematic Reviews (PROSPERO), and Cochrane Database of Systematic Reviews (EBSCO) databases. All studies published from database inception to December 31, 2024, were considered, and no language or study design restriction was imposed. A representative MEDLINE search strategy included a combination of Medical Subject Headings (MeSH) and keywords targeting the concepts of cardiopulmonary bypass (e.g., "cardiopulmonary bypass", "heart-lung machine"), cardiac surgery (e.g., "cardiac surgical procedures”, “coronary artery bypass”, “valve replacement”), and oxygen delivery (e.g., “oxygen delivery”, “DO_2”, “goal-directed perfusion”). These terms were combined using Boolean operators (AND/OR) to ensure comprehensive coverage. The complete MEDLINE strategy is available in Supplementary Table S1. The MEDLINE search strategy was adapted to other databases according to the specific syntax required. In addition, a hand search of references cited in the studies and reviews was conducted to ensure literature saturation.

Selection process and data extraction

Only original peer-reviewed studies were considered, using the following eligibility criteria. Inclusion Criteria: (a) Only peer-reviewed original publications (includes peer-reviewed conference papers and full-paper proceedings but does not include dissertations, editorials, reviews, and commentaries); (b) Any language; (c) Population: adult patients undergoing any type of cardiac surgery; (d) Exposure: any measurement of DO_2 during CPB; (e) Comparison: any relationship between DO_2 and clinical outcome measures; (f) Outcomes: any clinical outcomes (intraoperative and/or postoperative).

Exclusion Criteria: (a) Studies conducted outside the OR (e.g., intensive care units); (b) Patients on Extra-corporeal Membrane Oxygenation (ECMO); (c) Off-pump procedures; (d) Pediatric population; (e) No measure of the DO_2 in the intraoperative; (f) Animal models; (g) Heart transplant.

Two investigators independently screened the titles and abstracts of all search results and identified relevant articles based on the eligibility criteria. For these screened articles, the full text was reviewed by two investigators, independently, who then decided whether the study met the inclusion criteria for the systematic review. The reason for excluding articles after full-text review was registered. When there was a disagreement in the inclusion/exclusion decision and/or reason for exclusion between the two reviewers, a third investigator made a final consensus determination. Figure 1 displays the PRISMA flowchart showing identification, screening, and inclusion/exclusion metrics. Using a structured extraction form, two authors extracted specific data fields from each study included in the systematic review, discussing any discrepancies and reaching a final consensus.

Data synthesis and quality assessment

This systematic review included mostly observational cohorts and cross-sectional studies. Therefore, the assessment of the methodological quality of the studies was conducted using the National Institutes of Health/National Heart, Lung and Blood Institute (NHLBI) quality assessment tool.[13] Two reviewers independently assessed the study quality and completed the NHLBI quality assessment tool in Covidence. A third reviewer provided consensus among the two initial assessments. After answering the 14 quality assessment questions, each study was rated as poor (0–4 out of 14 questions), fair (5–10 out of 14 questions), or good (11–14 out of 14 questions).

Results

A total of 1546 studies were initially identified across 6 databases and screened for eligibility. After title/abstract screening and full-text review, the systematic review process retrieved 39 studies for final inclusion (Figure 1). Most studies (*N* = 22, 56.4%) were published in the past 5 years, as shown in Figure 2.

Patient characteristics

The median number of participants included across all studies was 246 (1st IQ: 113 – 3rd IQ: 492), ranging between a minimum of 28 and a maximum of 30,145 patients. The median patient's age was 66.5 years (1st IQ: 64 – 3rd IQ: 68), and the median percentage of male patients was 64.2% (1st IQ: 69 – 3rd IQ: 78). Table 1 shows the different cardiac surgery procedures included across all studies.

Study designs and settings: Observational studies were the most frequent (*N* = 33, 84.6%), and only 6 studies (15.4%) investigated DO_2-related interventions through randomized controlled trials (Table 2). Three retrospective studies conducted a propensity score matching to compare groups, and 3 studies involved a retrospective analysis from previous prospective cohorts. Only 5 studies (12.8%) were multicenter, involving either 2 or 9 centers, and 2 of these studies were based on the same registry database, the Australian and New Zealand Collaborative Perfusion Registry (ANZCPR).

DO_2 measurement: There was considerable heterogeneity across the 39 included studies in how DO_2 was measured during CPB. With respect to measurement methods, 10 studies (25.6%) reported continuous DO_2 monitoring throughout CPB. Fourteen studies (35.9%) calculated DO_2 from interval-based sampling, while the remaining 15 studies (38.5% did not specify the timing or method of DO_2 measurement.

Regarding the equipment used for DO_2 quantification, the Terumo CDI-550 was the most frequently used device, appearing in 7 studies. The LivaNova Connect system was employed in 5 studies, followed by Spectrum Medical systems in 2 studies, and Eurosets systems in 3 studies. Maquet and Microsoft Excel-based solutions were each used in 1 study. However, nearly half of the studies (16 in total) either used manual methods or did not report the device used. An additional 4 studies utilized various other devices.

In terms of the formulas used to compute DO_2, the majority of studies (30 in total) used custom or partially documented equations derived from the ”standard” formula, incorporating pump flow, hemoglobin (Hb), arterial oxygen saturation (SaO_2), and arterial oxygen tension (PaO_2). Only 2 studies used a simplified version of the formula, omitting PaO_2. Seven studies did not report a formula at all.

Temperature management: Temperature management strategies during CPB were heterogeneous across the 39 included studies. The majority (17 studies, 43.6%) employed mild hypothermia (32–35°C), consistent with conventional adult cardiac surgery practice. Normothermia (≥36°C) was used in 10 studies (25.6%), while moderate hypothermia (28–31°C) and deep hypothermia (<28°C) were used in 2 (5.1%) and 1 (2.6%) studies, respectively. Additionally, 6 studies (15.4%) used mixed temperature ranges that spanned multiple classifications (e.g., mild hypothermia to normothermia or moderate to mild hypothermia), and 3 studies (7.7%) did not report sufficient temperature information for classification. This variation in thermal strategies is important context for interpreting

DO_2 thresholds, which are highly dependent on metabolic oxygen demand modulated by temperature.

Clinical outcomes: The most frequent outcomes investigated in regards to its relationship with DO_2 were AKI (33 studies, 85.6%), followed by intraoperative red blood cell (RBC) transfusion (19 studies, 48.7%), new onset dialysis (16 studies, 41.0%), and mortality (13 studies, 33.3%). Most of the studies investigating AKI (27 studies), time on mechanical ventilation (7 studies), and intraoperative lactate (5 studies) found a statistically significant relationship between DO_2 levels and these outcomes. Nine of the included studies (23.1%) assessed neurologic outcomes such as stroke, delirium, cerebral injury biomarker or postoperative cognitive dysfunction. However, only one study employed intraoperative brain-specific monitoring -Magruder et al. (2017), which used near-infrared spectroscopy (NIRS) to guide goal-directed perfusion with cerebral oxygenation as a key parameter. The other studies reported neurologic complications as clinical outcomes, but did not include any cerebral monitoring tool. Other clinical outcomes found to be significantly associated with DO_2 were neurocognitive preservation and intra- and postoperative use of vasopressors. All included studies reported short-term outcomes, most commonly in-hospital or 30-day postoperative endpoints. No study provided data on long-term follow-up (e.g., renal function beyond hospital discharge, long-term cognitive outcomes, or neurologic disability). Table 3 shows a summary of the most commonly investigated clinical outcomes across the 39 included studies.

Study quality appraisal: The study quality ratings based on the NHLBI quality assessment tool showed that 19 (48.7%) studies presented a fair methodological quality, while 20 (51.3%) presented a good quality.

The median quality score across all studies was 11 points (1st IQ: 9 – 3rd IQ: 11.5), ranging between a minimum of 6 and a maximum of 13 points.

Table S2 (supplementary material) displays the summarized data extracted from each of the 39 studies included in this systematic review.

Discussion

This systematic review found that DO_2 during CPB is a critical determinant of intraoperative and postoperative outcomes in adult cardiac surgery. Across the included studies, lower intraoperative DO_2—particularly when falling below a certain indexed threshold—was consistently associated with higher rates of organ injury, most notably acute kidney injury (AKI). By contrast, patients maintained above the critical DO_2 threshold experienced fewer complications. These findings directly support the study aim of synthesizing the existing literature on the relationship between CPB oxygen delivery and clinical outcomes: inadequate DO_2 during bypass emerged as a key driver of poor outcomes, whereas interventions to preserve DO_2 translated into improved patient outcomes. The strongest evidence of negative outcomes with low DO_2 relates to AKI, longer length of stay in the ICU, and prolonged mechanical ventilation, whereas effects on mortality and neurologic injury were less evident in the current literature.

Comparison with prior studies and interpretation

These systematic review findings align with a growing body of studies, identifying nadir DO_2 on CPB as a potent predictor of postoperative organ dysfunction. *Ranucci et al.* (2005) first demonstrated this link in a large prospective study, showing that the lowest DO_2 index during CPB was the strongest predictor of AKI and postoperative creatinine rise, with a critical DO_2 value around 272 $mL/min/m^2$.[4] In that study, extreme hemodilution (i.e., nadir hematocrit ~26%) was also associated with AKI, but, after accounting for transfusions, only DO_2 remained an independent risk factor. This study suggested that it is the combined effect of pump flow and oxygen-carrying capacity (reflected by DO_2) rather than anemia alone that jeopardizes renal perfusion. Subsequent investigations reinforced these findings. For example, a recent analysis of 19,410 patients by *Newland et al. (2019)* identified an optimal iDO_2 threshold of ~270 $mL/min/m^2$ for avoiding AKI; dropping below this threshold was associated with a 52% increase in the odds of postoperative AKI (odds ratio ~1.52).[14] Similarly, several studies have linked episodes of low DO_2 to surrogates of inadequate perfusion, such as intraoperative hyperlactatemia, which in turn correlates with higher risks of renal injury, prolonged ventilation, and even mortality.[15] These convergent data from diverse centers underscore that a minimum DO_2 in the range of roughly 250–300 $mL/min/m^2$ represents a physiologic tipping point, below which tissue oxygen debt accumulates and organ dysfunction becomes more likely.

Critically, emerging interventional studies have gone beyond association and tested whether actively guiding perfusion to maintain DO_2 above such a threshold (Goal-Directed Perfusion) can improve outcomes. The Goal-Directed Perfusion (GDP) Trial by *Ranucci et al.* (2018) was a multicenter randomized study that targeted a $iDO_2 \geq 280$ $mL/min/m^2$ during CPB.[9] That trial demonstrated a significant reduction in AKI, specifically, a ~55% relative decrease in mild AKI (AKIN Stage 1) in the DO_2-targeted group. Although rates of more severe AKI (Stages 2–3) did not differ, this was likely due to limited power given the low incidence of advanced AKI. More recently, *Mukaida et al. (2023)* reported a randomized controlled trial in which perfusionists adjusted pump flow to keep DO_2 > 300 $mL/min/m^2$, as opposed to conventional flow management, in patients maintained at a relatively warm temperature of 35°C. The results were striking: the DO_2-guided strategy halved the incidence of postoperative AKI (14.6% vs 30.4%).[16] Importantly, the trial confirmed a relative risk of 0.5 for AKI with DO_2-guided perfusion, validating the causal role of inadequate DO_2 in precipitating renal injury. These high-quality trials support the interpretation that the association between low DO_2 and organ injury is not merely correlational; rather, there is a modifiable, cause-and-effect relationship. At the same time, both Ranucci et al.[9] and Mukaida et al.[16] reported no significant differences in short-term mortality with DO_2-guided perfusion, and no trial to date has shown a clear impact on neurologic complications such as stroke. This is consistent with our review's findings that DO_2 management mainly influences perioperative morbidity, such as AKI, new onset dialysis, prolonged mechanical ventilation, and length of stay, whereas effects on infrequent endpoints (e.g., stroke, death) are harder to demonstrate, possibly due to sample size limitations or multifactorial etiologies for those outcomes. Nonetheless, the reduction in morbidity is clinically consequential: for example, a recent meta-analysis[17] of interventional trials noted that goal-directed perfusion was associated with a 57% reduction in the odds of postoperative complications overall, including shorter ICU and hospital stays, even though mortality was unchanged. Moreover, real-world perfusion protocol changes have yielded tangible improvements. *Magruder et al.* reported that implementing a multifaceted GDP protocol (maintaining DO_2 > 300 mL/min/m^2, along with mean arterial pressure >70 mmHg and proactive ultrafiltration) was associated with a drop in AKI incidence from 23.9% to 9.1% (p = .008).[18]

Temperature significantly influences oxygen metabolism during cardiopulmonary bypass (CPB), affecting the critical DO_2 threshold needed to avoid tissue hypoxia. For each 1°C drop in core temperature, metabolic oxygen consumption (VO_2) decreases by 5–7%, allowing lower DO_2 levels to suffice under hypothermic conditions. For example, *Ranucci et al.* (2005) found that a DO_2 threshold of ~272 mL/min/m^2 predicted AKI during mild hypothermia,[4] while *de Somer et al.* (2011) reported a similar threshold (~262 mL/min/m^2) under comparable conditions.[2] In contrast, normothermic strategies require higher oxygen delivery. In a randomized controlled trial using near-normothermic CPB (~35–36°C), *Mukaida et al.* (2023) showed that maintaining DO_2 above 300 mL/min/m^2 halved the incidence of AKI compared to standard perfusion.[16] These findings highlight the need to tailor DO_2 targets to thermal strategy - lower thresholds may be adequate with hypothermia, but normothermia demands higher DO_2 to preserve aerobic metabolism and reduce organ injury.

A further limitation of the current literature is the lack of long-term follow-up data. None of the studies included in this review assessed persistent renal dysfunction, long-term neurologic deficits, or quality-of-life outcomes following DO_2-guided CPB. As such, it remains unclear whether optimizing DO_2 intraoperatively confers sustained organ protection beyond the immediate postoperative period. Future research should in-corporate longitudinal outcome tracking to determine whether intraoperative DO_2 management translates into durable clinical benefits.

Clinical implications for perfusion practice

The consistent relationship between CPB iDO_2 and patient outcomes has important clinical implications for cardiac surgery. First and foremost, perfusionists and the surgical team should view oxygen delivery as a key perfusion metric to monitor continuously during CPB, analogous to vital signs. Our review supports adopting an indexed DO_2 “safety threshold” in the range of approximately 270–300 mL/min/m^2. Practically, this means that pump flow rate and hematocrit should be managed to prevent iDO_2 from dropping below this level at any point on bypass. In patients with chronic anemia, smaller patients, and patients maintained at warmer temperatures during CPB may require a higher pump flow or earlier transfusion when hemodilution is unavoidable.[4] In fact, strategies for goal-directed perfusion (GDP) have emerged: rather than using fixed pump flows for all, the perfusion flow is individualized to the patient’s metabolic needs. This need is typically assessed by DO_2 or mixed venous oxygen saturation. If iDO_2 approaches the critical threshold, the team can respond by increasing flow, raising arterial oxygen content (e.g., administering blood to increase hematocrit), or adjusting other parameters (temperature or oxygen fraction) to improve tissue oxygenation. This proactive approach is a departure from historically relying solely on mean arterial pressure or generalized flow indices, and it represents a shift toward *patient-specific perfusion*. Our findings lend weight to this strategy: by maintaining adequate DO_2, clinicians can potentially avert downstream complications like AKI, which in turn may shorten ICU stay and resource utilization. Importantly, the benefit of DO_2-guided perfusion was observed without a concomitant increase in transfusion requirements in several studies,[17] suggesting that optimizing pump flow and circuit management can often maintain DO_2 without excessive blood product use. This has positive implications for patient blood management and overall recovery.

Another implication is the need to standardize monitoring techniques for oxygen delivery. Many modern heart-lung machines or perfusion monitoring systems can calculate DO_2 continuously from pump flow, hemoglobin, and oxygen saturation. Where such capability is available, our review would advocate for integrating DO_2 readouts into routine intraoperative monitoring. Centers that do not have continuous DO_2 displays should use surrogate measures to ensure perfusion adequacy. For instance, trends in venous oxygen saturation (SvO_2) or serial lactate levels can alert the team to inadequate oxygen delivery.[1,19] A previous study has developed a quick reference tool for GDP that allows perfusionists to quickly determine the lowest acceptable blood flow needed to provide a patient of any BSA with a satisfactory DO_2 without the need for additional dedicated technology.[3] However, relying on such indirect signs means the onset of oxygen debt is already underway; by contrast, direct DO_2 monitoring allows perfusionists to preemptively adjust flows before tissue hypoxia occurs. By incorporating these evidence-based thresholds, perfusionists can make real-time, goal-directed decisions to safeguard end-organ perfusion. Indeed, the European Association for Cardio-Thoracic Surgery now endorses goal-directed perfusion in guidelines (Class I recommendation, Level of Evidence A)[20] as a means to reduce postoperative complications, and the American Society of Extra Corporeal Technology (AmSECT) 2023 Standards and Guidelines recommends the utilization of indexed oxygen delivery (iDO_2) and consumption calculations to evaluate and optimize gas exchange during CPB, reflecting the maturity of this evidence. The clinical message is clear: maintaining adequate oxygen delivery during CPB is a modifiable factor that should be prioritized alongside temperature, pressure, and other perfusion parameters to improve patient outcomes.

A key limitation across the included studies is the lack of consistent documentation of adherence to GDP protocols. While many studies specified DO_2 thresholds (e.g., 260 or 280 $mL/min/m^2$), only a minority reported whether these targets were maintained throughout CPB or how compliance was measured. In some studies, thresholds were used retrospectively to stratify outcomes rather than as active targets during perfusion. This limits causal inference and undermines the interpretation of GDP efficacy. Furthermore, the absence of standardized methods for DO_2 monitoring and intervention thresholds across studies adds to the heterogeneity. For GDP to be meaningfully implemented in clinical practice, future studies must include prospective designs with explicit compliance metrics, real-time DO_2 monitoring, and standardized intervention protocols when thresholds are breached.[21]

Study limitations

Several limitations of the present review and the underlying literature should be acknowledged. First, although we included the best available studies, much of the evidence base consists of observational cohorts. These studies are inherently subject to confounding: patients who experienced low DO_2 on CPB often had other high-risk features (longer bypass times, more complex surgeries, etc.) that themselves contribute to worse outcomes. While many analyses adjusted for such variables and still found DO_2 to be an independent predictor, the possibility of residual confounding cannot be eliminated. Second, there was notable methodological heterogeneity across studies. Different investigators used different DO_2 cutoff values to define “low” oxygen delivery – for example, some defined it as <250 mL/min/m^2, others used <300 mL/min/m^2 – and the AKI outcome was not uniform (variously defined by RIFLE, AKIN, or KDIGO criteria). We also observed variability in perfusion techniques (e.g., degree of hypothermia, use of ultrafiltration, targets for perfusion pressure) that could influence outcomes independently of iDO_2. Consequently, when interpreting aggregate results, one should be cautious – the exact “critical” iDO_2 value may not be identical for every patient or scenario. Third, the randomized trials to date, while enormously informative, have been relatively small (hundreds of patients) and often single-center. These sample sizes may be underpowered to detect differences in rare outcomes like stroke or mortality, leading to neutral findings on those endpoints even if true differences exist. Additionally, blinding in perfusion trials is essentially impossible – the perfusionist must know the strategy, which means there is some risk of bias in how outcomes were managed or reported (though objective endpoints like serum creatinine mitigate this concern to an extent). As with any systematic review, our analysis is also limited by the quality of the included studies; publication bias is possible if negative or contrary studies were less likely to be reported. We attempted to minimize bias through a comprehensive search and inclusion of all study designs, but the conclusions rely on the assumption that the published data are representative. Lastly, while our review focused primarily on DO_2 as the most commonly studied GDP parameter, we acknowledge that other perfusion metrics play important roles in optimizing outcomes. The heterogeneity in which additional parameters were monitored and reported across studies limited our ability to perform detailed comparative analyses of their relative importance.

Future directions

This review highlights several avenues for future research and quality improvement. A priority is the conduct of larger multicenter randomized trials to definitively establish whether goal-directed perfusion improves hard clinical outcomes. While existing RCTs show reductions in AKI, a sufficiently powered trial could assess effects on outcomes like severe AKI requiring dialysis, stroke, or survival, which individual studies have not yet shown conclusively. Such trials should also examine longer-term outcomes: for instance, does preventing AKI during cardiac surgery translate into lower rates of chronic kidney disease or better long-term survival? This question is pertinent given evidence that even transient postoperative AKI can accelerate long-term renal decline and increase mortality. Future studies might also refine what the optimal DO_2 target should be for different patient subgroups. It remains unknown whether a “one-size-fits-all” threshold (e.g., 280 mL/min/m^2 for all patients) is ideal. Patients with preexisting renal dysfunction, advanced age, or other comorbidities might benefit from an even higher DO_2 margin of safety. On the other hand, excessively high flows to achieve very high DO_2 could have downsides (e.g., shear stress, edema, emboli), so research is needed to balance *how high* is high enough. Technological advancements may facilitate some of this research: emerging perfusion monitors that can track real-time oxygen consumption (VO_2) or tissue oxygenation (such as cerebral or renal oximetry) could allow a more nuanced, patient-specific perfusion strategy. Finally, from a broader perspective, future work should focus on implementation science – how to translate these findings into widespread practice. This could include developing perfusion checklists or training curricula that emphasize iDO_2 management, as well as leveraging machine learning and artificial intelligence for real-time clinical decision support during CPB to optimize iDO_2, and even predicting moments of low iDO_2 before its occurrence, allowing proactive perfusion management.

Conclusion

In conclusion, our review solidifies oxygen delivery as a central focus for quality improvement in cardiac surgery using CPB. Moving forward, a concerted effort by clinicians and researchers to fine-tune iDO_2 thresholds, personalize perfusion, and systematically monitor outcomes will help ensure that patients benefit from the best evidence-based care during cardiopulmonary bypass. By preventing avoidable organ injury in the intraoperative period, we can ultimately improve both the immediate and long-term health of patients undergoing cardiac surgery.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

This work was supported by the National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health (NIH) [Grant Numbers: R01HL126896, R01HL157457]. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by the National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health (NIH) [Grant Numbers: R01HL126896, R01HL157457].

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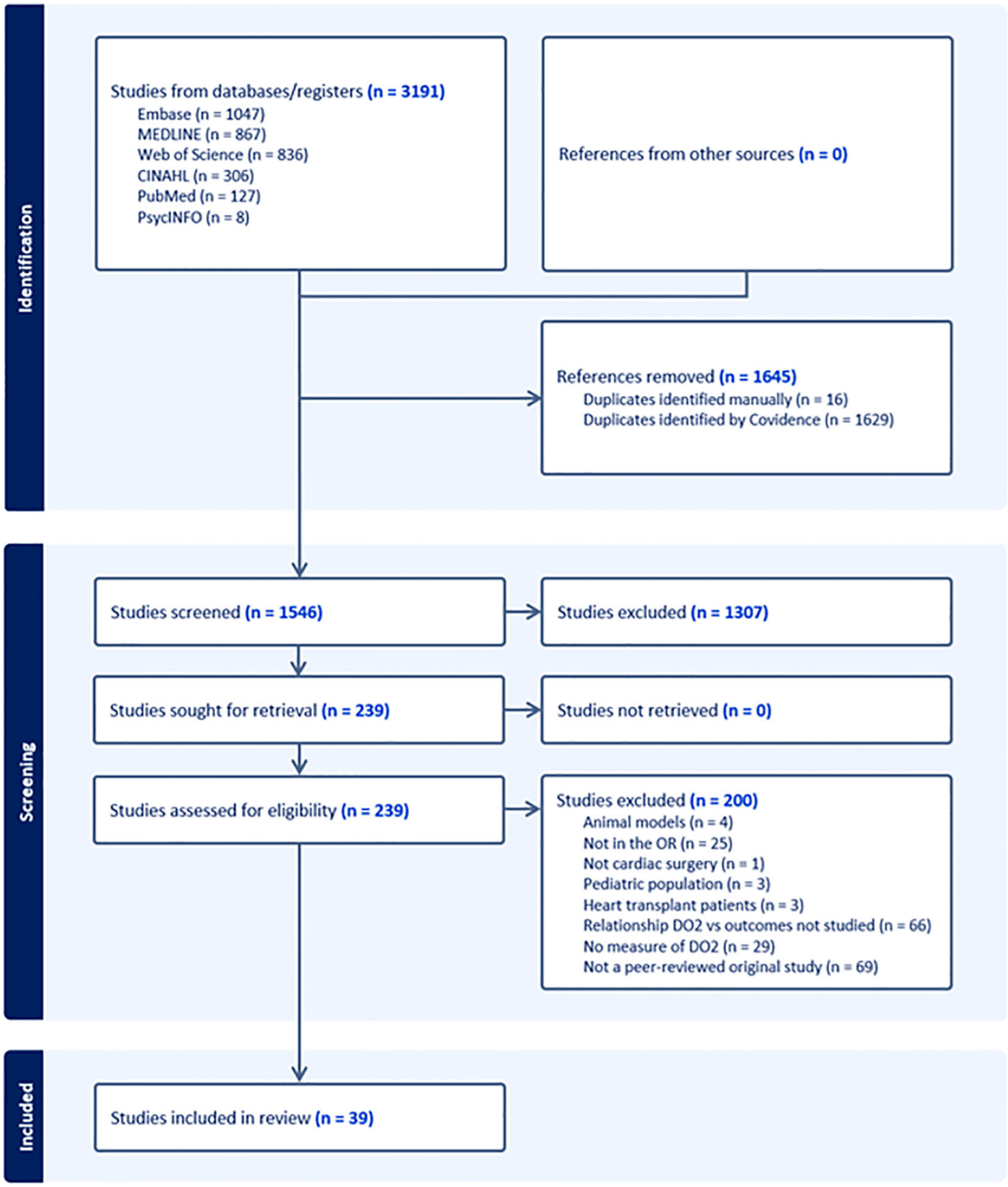

Figure 1.

PRISMA flowchart showing identification, screening, and inclusion metrics.

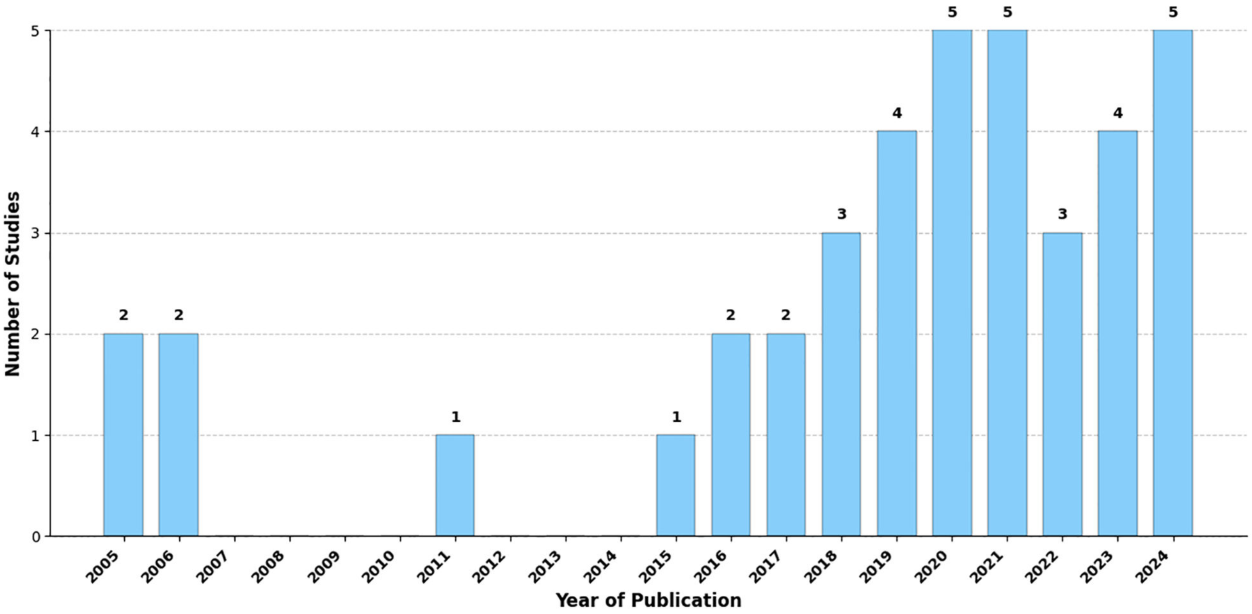

Figure 2.

Number of studies by year of publication.

Table 1.

Distribution of publications based on the type of procedure.

Cardiac surgery procedure	***N* (%)**
CABG and valve (isolated and combined)	26 (66.7)
CABG isolated	12 (30.8)
Aorta procedure	10 (25.6)
Other cardiac procedures	6 (15.4)
Adult congenital procedures	4 (10.3)
Cardiac tumor removal	3 (7.7)
Atrial fibrillation procedure	2 (5.1)
Valve (isolated and combined)	1 (2.6)

Table 2.

Distribution of publications based on the study design.

Study design	***N*** **(%)**
Retrospective cohort study	24 (61.5)
Prospective cohort study	9 (23.1)[a]
Randomized controlled trial	6 (15.4)[a]
Retrospective case-control	1 (2.6)

[a] one study reported the findings from a prospective cohort and a randomized controlled trial.

Table 3.

Association between patient DO_2 levels during CPB and Intraoperative and Postoperative Outcome Measures.

Outcome measures	**Number of studies (% from all studies)**	**Statistically significant association (% from outcome-specific studies)**
Intraoperative		
RBC transfusion	19 (48.7%)	9 (47.4%)
Lactate	9 (23.1%)	5 (55.6%)
Postoperative		
Acute kidney injury	33 (84.6%)	27 (81.8%)
Dialysis (new onset)	16 (41.0%)	8 (50.0%)
Hospital or 30-day mortality	13 (33.3%)	2 (15.4%)
Length of ICU stay	11 (28.2%)	5 (45.5%)
Time on MV	11 (28.2%)	7 (63.6%)
Length of hospital stay	8 (20.5%)	3 (37.5%)
RBC transfusion	7 (17.9%)	3 (42.9%)
Stroke	6 (15.4%)	0 (0.0%)
Delirium	3 (7.7%)	2 (66.7%)
Cerebral injury biomarker	2 (5.1%)	2 (100.0%)

DO_2: delivery of oxygen; CPB: cardiopulmonary bypass; RBC: red blood cells; ICU: intensive care unit; MV: mechanical ventilation.