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Mini-Compendium on Goal-Directed Perfusion (GDP) Based on a Narrative Review

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Abstract

Background: Goal-Directed Perfusion represents an evolving physiological framework for the management of cardiopulmonary bypass, designed to preserve tissue oxygenation and protect organ function through the integration of hemodynamic and metabolic control. This mini-compendium expands the concept by including all variables that directly or indirectly affect oxygen delivery, offering a holistic and quantitative view of perfusion adequacy. Traditional approaches based only on flow or arterial pressure fail to consider the complex interdependence between oxygen transport, utilization, and pressure-dependent microcirculation. Goal-Directed Perfusion integrates these dimensions into a single, physiology-based model that combines indexed oxygen delivery, oxygen consumption, carbon dioxide production, oxygen extraction ratio, and mean arterial pressure, together with composite indicators such as the oxygen delivery to carbon dioxide production ratio and the oxygen delivery to oxygen extraction ratio, as well as time–dose response analysis for oxygen delivery and arterial pressure.

Materials and methods: A narrative review was conducted to synthesize physiological principles, mathematical formulations, and clinical implications of these interrelated variables. Electronic searches in PubMed, Scopus, and Web of Science (2011–2025) identified studies analyzing oxygen and pressure-derived metrics during cardiopulmonary bypass.

Results: Twenty-six studies met inclusion criteria. Evidence confirms that indexed oxygen delivery remains the primary determinant of aerobic metabolism, while metabolic coupling ratios refine early detection of oxygen debt and the transition to anaerobic metabolism. The integration of time–dose models for oxygen delivery and arterial pressure quantifies cumulative deficits in perfusion, linking hemodynamic and metabolic domains into a unified assessment. Together, these variables define a multidimensional, predictive

system for individualized perfusion management that aligns oxygen transport, metabolic demand, and perfusion pressure in real time.

Conclusions: This mini-compendium redefines Goal-Directed Perfusion as an inclusive and integrative approach that unites hemodynamic, metabolic, and temporal determinants of oxygen delivery into a single conceptual continuum. By encompassing all variables influencing oxygen transport, directly or indirectly, this model evolves from a collection of isolated indicators to a holistic, data-driven strategy for optimizing perfusion, minimizing oxygen debt, and preventing postoperative organ dysfunction. Such integration transforms perfusion from a static, flow-based practice into a dynamic and predictive physiology, establishing the foundation for a standardized, patient-specific model of care in contemporary extracorporeal management.

Keywords: *Goal-Directed Perfusion; Cardiopulmonary Bypass; Oxygen Delivery; Oxygen Extraction Ratio; Mean Arterial Pressure; Time Dose Response.*

Introduction

Cardiopulmonary bypass (CPB) allows cardiac surgery to be performed under controlled and bloodless conditions but exposes the patient to a non-physiological state in which perfusion and oxygen transport are entirely dependent on the extracorporeal circuit. Despite significant technological progress, traditional perfusion management remains largely based on standardized flow and mean arterial pressure (MAP) targets, without fully considering the dynamic balance between oxygen delivery and metabolic demand. This limitation contributes to tissue hypoxia, hyperlactatemia, and postoperative organ dysfunction, including acute kidney injury (AKI) [1–4, 22]. Goal-Directed Perfusion (GDP) has emerged as a physiology-based strategy designed to maintain adequate tissue oxygenation and organ perfusion during CPB through continuous, patient-specific monitoring of hemodynamic and metabolic parameters [2, 5–7]. The concept aims to ensure that oxygen delivery meets cellular metabolic needs, thereby preventing oxygen debt accumulation and its downstream consequences. GDP integrates several physiological variables into a unified monitoring framework: indexed oxygen delivery (DO_2i), oxygen consumption (VO_2i), carbon dioxide production (VCO_2i), indexed oxygen

extraction ratio (O_2ERi), the DO_2/VCO_2 ratio, and mean arterial pressure (MAP) [5, 8–10]. Each variable provides a distinct dimension of information regarding the adequacy of systemic perfusion and the balance between oxygen supply and demand. Among these, DO_2i has been consistently identified as a critical determinant of aerobic metabolism, with threshold values around 260–280 $mL \cdot min^{-1} \cdot m^{-2}$ below which anaerobic metabolism and organ injury are likely to occur [1–3, 14, 18]. VO_2i and VCO_2i reflect tissue metabolic activity and can indicate the transition to anaerobic metabolism, while O_2ERi expresses the efficiency of oxygen extraction at the cellular level. The DO_2/VCO_2 ratio has recently gained attention as an integrated marker of metabolic adequacy, linking oxygen delivery to CO_2 kinetics [5, 9, 10]. Meanwhile, MAP remains the hemodynamic foundation of perfusion, ensuring that adequate flow translates into effective tissue perfusion pressure [11, 12]. More recently, the **t**ime–dose response concept has been introduced to describe the cumulative exposure to suboptimal oxygen delivery or perfusion pressure over time, integrating both the magnitude and duration of perfusion deficits [17–19]. This approach, derived from studies of oxygen debt physiology, allows clinicians to quantify the total “dose” of hypoperfusion, rather than relying solely on nadir or mean values, and has shown strong associations with postoperative AKI and neurological complications. This review aims to provide a didactic and comprehensive overview of the physiological foundations, mathematical expressions, and clinical relevance of GDP variables. Each parameter will be discussed in relation to its role in maintaining metabolic homeostasis during CPB, highlighting how integrated monitoring of DO_2i, VO_2i, VCO_2i, O_2ERi, and MAP supports individualized perfusion management. In addition, the review will explore the conceptual and clinical implications of the time dose response model for DO_2 and MAP as a framework for predictive, physiology-driven perfusion. This narrative synthesis intends to serve as both an educational reference for clinicians and perfusionists and a scientific foundation for the future evolution of precision perfusion, in which real-time, data-driven control of oxygen delivery and pressure will guide extracorporeal circulation toward improved organ protection and outcomes.

Materials and methods

This study was conceived as a narrative review with a didactic and integrative purpose, aimed at synthesizing the physiological principles, mathematical formulations, and clinical implications of Goal-Directed Perfusion (GDP) during cardiopulmonary bypass (CPB). In accordance with established standards for narrative reviews, the primary objective was conceptual clarity and physiological coherence rather than quantitative effect estimation or formal grading of evidence quality. A comprehensive electronic literature search was conducted in PubMed, Scopus, and Web of Science databases, covering publications from January 2011 to October 2025. The search strategy combined MeSH terms and free-text keywords using Boolean operators, including: “Goal-Directed Perfusion”, “Cardiopulmonary Bypass”, “Oxygen Delivery”, “Oxygen Consumption”, “Carbon Dioxide Production”, “Oxygen Extraction Ratio”, “Mean Arterial Pressure”, “Time–Dose Response”, and “Acute Kidney Injury”.

Studies were eligible for inclusion if they fulfilled all of the following criteria:

1) adult patients undergoing cardiopulmonary bypass;

2) reporting at least one GDP-related variable (indexed oxygen delivery (DO_2i), indexed oxygen consumption (VO_2i), indexed carbon dioxide production (VCO_2i), indexed oxygen extraction ratio (O_2Eri), DO_2/VCO_2 ratio, DO_2/O_2ERi ratio, or mean arterial pressure (MAP);

3) description of the underlying physiological rationale;

4) presentation of the mathematical formulation or computational approach; and

5) correlation of the variable with perfusion adequacy or postoperative clinical outcomes.

Randomized controlled trials, observational studies, and systematic reviews or meta-analyses were considered eligible. Exclusion criteria included animal or in vitro studies, publications focused exclusively on pharmacological interventions, conference abstracts, editorials, and reports lacking sufficient

methodological detail. The initial search identified approximately 145 records. After title and abstract screening, 37 articles underwent full-text assessment. Of these, 26 studies met all inclusion criteria and were retained for narrative synthesis. Although this work was not designed as a systematic review, the study selection process is summarized using a PRISMA-style flow diagram to enhance transparency. A PRISMA-style flow diagram illustrating the literature selection process (145 records identified, 37 full texts assessed, and 26 studies included) is provided to improve methodological transparency (Figure 1).

Results

Studies addressing time–dose response models for DO_2 and MAP were also included, as they represent an advanced approach to quantify the cumulative burden of perfusion deficits over time. Randomized controlled trials, observational studies, and systematic reviews or meta-analyses were all eligible if they met these inclusion criteria. Exclusion criteria comprised studies conducted exclusively in animal or in vitro models, those focused purely on pharmacologic interventions, and reports lacking sufficient methodological detail such as conference abstracts or editorials. The initial search identified approximately 145 articles, of which 37 were assessed in full text. After detailed evaluation, 26 studies met all inclusion criteria and were retained for synthesis [1–23]. These publications collectively describe the formulas, physiological foundations, and clinical relevance of GDP variables in the context of cardiac surgery. Data extraction was qualitative and centered on identifying physiological thresholds, analytical equations, and clinical correlations with postoperative outcomes, including acute kidney injury, hyperlactatemia, and organ dysfunction. Given the educational intent of this review, data were narratively integrated to illustrate how oxygen- and pressure-derived indices can be applied synergistically in a GDP framework. This synthesis aims to consolidate current knowledge into a clear, practical, and conceptually coherent model of precision perfusion, bridging physiological understanding with clinical application. A total of 26 peer-reviewed studies published between 2011 and 2025 were included in this review. Collectively, these investigations

delineate the physiological rationale, computational framework, and clinical significance of Goal-Directed Perfusion (GDP) as a structured approach to cardiopulmonary bypass (CPB) management. The selected literature spans randomized clinical trials, observational studies, and meta-analyses addressing the relationship between oxygen delivery, metabolic efficiency, and end-organ protection. Together, these works highlight how GDP represents a paradigm shift from traditional flow- or pressure-based perfusion toward a quantitative, physiology-driven model, in which oxygen transport and utilization are continuously balanced and individualized in real time. Each variable within the GDP framework indexed oxygen delivery (DO_2i), oxygen consumption (VO_2i), carbon dioxide production (VCO_2i), indexed oxygen extraction ratio (O_2ERi), the DO_2/VCO_2 ratio, and mean arterial pressure (MAP) acts as a measurable indicator of tissue oxygenation and metabolic adequacy.

1) Clinical Interpretation of Indexed Oxygen Delivery (DO_2i)

The concept of oxygen delivery (DO_2) originates from classical cardiovascular physiology, derived from Fick's principle describing the relationship between oxygen transport, blood flow, and metabolic consumption. Its indexed form (DO_2i), normalized to body surface area, was introduced in perfusion science during the 1980s to provide a quantitative assessment of tissue oxygenation during cardiopulmonary bypass (CPB). Over the years, DO_2i has evolved from a theoretical construct into the cornerstone of Goal-Directed Perfusion (GDP), serving as a measurable determinant of aerobic metabolism and organ protection during extracorporeal circulation. Mathematically, DO_2i quantifies the convective rate of oxygen delivery per unit body surface area:

$$DO_2i = \frac{Flow \times (1.34 \times Hb \times SaO_2 + 0.003 \times PaO_2)}{BSA}$$

Each variable in this equation holds distinct physiological relevance. Pump flow (L/min) represents the mechanical driver of perfusion and can be directly modulated by the perfusionist. Hemoglobin concentration (Hb) determines the oxygen-carrying capacity, with every gram of Hb binding 1.34 mL of oxygen. Arterial oxygen saturation (SaO_2) and arterial oxygen tension (PaO_2) represent the gas exchange efficiency across the oxygenator. These parameters integrate hydraulic, hematologic, and respiratory components into a single quantitative indicator of oxygen transport adequacy. Historically, perfusion management relied on fixed flow settings (e.g., 2.4 L/min/m²), assuming they guaranteed adequate oxygenation. However, accumulating evidence showed that this “one-size-fits-all” approach could result in unrecognized tissue hypoxia, particularly in anemic or hypothermic patients. The paradigm shifted with the work of de Somer et al. (2011) [2], who demonstrated that oxygen delivery below 262 mL/min/m² during CPB was associated with a threefold increase in postoperative acute kidney injury (AKI). This finding established DO_2i as the critical determinant of end-organ protection. Subsequent studies, including Ranucci et al. (2018) [3] and Carrasco-Serrano et al. (2022) [4], corroborated these results, linking cumulative oxygen delivery deficits to postoperative hyperlactatemia and renal dysfunction. Clinically, this means that brief, isolated reductions in DO_2i (for instance, during cannulation or cross-clamping) are usually well tolerated, while prolonged or repetitive subthreshold periods accumulate measurable oxygen debt that manifests as rising lactate and declining organ perfusion markers. A critical refinement of this model was proposed by El Dsouki & Condello (2025) [23], who demonstrated that the critical DO_2i threshold is not static but temperature-dependent**.** Their temperature-adjusted algorithm corrects DO_2i targets according to metabolic rate, decreasing the critical value by approximately 7 mL/min/m² per °C decrease in core temperature. This adjustment recognizes that hypothermia reduces oxygen consumption by 20–25% for every 5 °C decrease, allowing a lower DO_2i to remain physiologically safe. Conversely, during rewarming when metabolic demand rises exponentially the same DO_2i that was adequate at 30

°C may become critically low at 36 °C, thus increasing the AUC–DO_2 and the risk of tissue hypoxia. Integrating this temperature dependency transforms the AUC–DO_2 concept from a static numeric threshold into a dynamic, patient-specific physiologic model**.** It enables clinicians to assess real-time oxygen debt in the context of metabolic demand, rather than relying on fixed cutoffs. As a result, temperature-adjusted AUC–DO_2 monitoring provides a more precise, individualized risk stratification tool for predicting organ injury, ensuring that both the *duration* and *context* of oxygen underdelivery are accurately represented within Goal-Directed Perfusion management

Clinical case illustrations

1) *Clinical Example 1 (Low Hemoglobin Scenario):*

Consider a 75-year-old patient undergoing valve replacement with hemodilution to Hb 7.0 g/dL. Even with a pump flow of 2.4 L/min/m^2 and SaO_2 100%, the resulting DO_2i is approximately 225 mL/min/m^2, falling below the critical threshold. Studies have shown that such levels lead to increased lactate production and renal dysfunction [2,3]. Raising Hb to 9.0 g/dL or increasing flow by 0.3 L·min^{-1}·m^{-2} typically restores DO_2i to 290–300 mL/min/m^2, preventing oxygen debt.

2) *Clinical Example 2 (Low Flow State):*

In a 65-year-old patient with low systemic vascular resistance following aortic surgery, perfusion flow may be reduced to 1.8 L/min/m^2 to maintain MAP. Despite adequate Hb (10 g/dL), DO_2i drops to 230 mL/min/m^2. Restoring target flow to ≥2.3 L·min^{-1}·m^{-2} immediately improves mixed venous oxygen saturation (SvO_2) and decreases lactate accumulation. This illustrates how mechanical adjustments, not pharmacologic interventions, are often the first corrective step.

3) *Clinical Example 3 (Oxygenator Dysfunction):*

When SaO_2 falls to 88–90% due to inadequate oxygenator performance or flow–sweep matching, DO_2i can rapidly decline even if flow and Hb are apparently adequate. For example, in a 68-year-old patient with Hb = 9 g/dL, flow = 2.4

L/min/m², and SaO_2 = 89%, the resulting DO_2i is only 257 mL/min/m², crossing below the critical limit associated with increased risk of postoperative hyperlactatemia and renal injury [2–4]. Correcting sweep gas flow and FiO_2 to restore SaO_2 > 95% can increase DO_2i to 275–285 mL/min/m² within minutes, normalizing tissue perfusion indices. These examples illustrate that *any reduction* in one of the three main determinants flow, hemoglobin, or oxygenation may compromise total oxygen transport, even when others remain within nominal ranges. Hence, GDP requires a dynamic and integrative approach, adjusting parameters interactively rather than in isolation.

2) Clinical Interpretation of the AUC–DO_2 Concept

The physiological aim of maintaining adequate DO_{2i} is to sustain aerobic metabolism and prevent the transition to anaerobic glycolysis, which manifests as rising lactate levels and base deficit. Once the critical DO_2i threshold (300 mL/min/m²) is crossed, oxygen consumption (VO_2) becomes supply-dependent, marking the onset of *oxygen debt*. Mukaida et al. (2019) [18] expanded this concept by introducing the *time–dose response model*, quantifying the cumulative effect of low oxygen delivery through the Area Under the Curve (AUC–DO_2) below the critical DO_2i threshold. The *time–dose response model*, expressed as the Area Under the Curve of DO_2i below the critical threshold (AUC–DO_2):

$$\text{AUC–DO}_2 = \int_{t_1}^{t_2} (\text{DO}_{2\text{crit}} - \text{DO}_2\text{i})\, dt$$

In their prospective cohort of 112 adults undergoing CPB, patients who developed postoperative AKI had:

- Mean cumulative duration of DO_2i < 300 mL/min/m² = 34.7 ± 26 min vs 15.3 ± 17 min in non-AKI;
- AUC–DO_2 values averaging 1,581 vs 632 ($p < 0.01$).

These data established AUC–DO_2 as a superior predictor of postoperative renal dysfunction compared to nadir DO_2i alone. Subsequent studies (Ranucci et al. 2018 [3], Carrasco-Serrano et al. 2022 [4]) confirmed this relationship, linking cumulative DO_2 deficits with both AKI and hyperlactatemia.These findings confirmed that *both duration and intensity* of oxygen underdelivery predict postoperative AKI more accurately than the nadir DO_{2i} alone. In clinical terms, transient DO_{2i} drops (e.g., a few minutes during cannulation) are usually well tolerated, while prolonged or repetitive subthreshold periods accumulate into a measurable oxygen debt. The AUC–DO_2 framework thus allows clinicians to quantify this cumulative burden, integrating physiology, perfusion practice, and outcome prediction.

Clinical Case Illustrations

To appreciate how the indexed oxygen delivery (DO_2i) interacts with patient physiology, the following representative cases illustrate typical intraoperative scenarios encountered during cardiopulmonary bypass (CPB). Each example integrates perfusion parameters, clinical context, and the *time–dose response* concept to explain the onset or prevention of oxygen debt.

Case 1, Transient DO_2i Reduction During Aortic Cross-Clamping (Physiological Compensation)

A 66-year-old man undergoing elective CABG is perfused at 2.4 $L \cdot min^{-1} \cdot m^{-2}$, with Hb 8.2 g/dL and arterial oxygen saturation (SaO_2) = 98%. At cross-clamp onset, venous return transiently decreases, causing a 10% flow reduction. DO_2i briefly falls from 300 to 250 $mL/min/m^2$ for =5 minutes. The calculated AUC–DO_2 is roughly 250 $mL/min/m^2 \cdot min$, far below the risk range identified by Mukaida et al. [18]. Lactate remains stable (1.6 mmol/L), and SvO_2 stays > 70%. This short, mild deficit remains within the physiological reserve of tissue oxygen extraction. The patient maintains full aerobic metabolism, demonstrating that isolated, transient dips in DO_2i are usually benign if promptly self-corrected.

Case 2, Hemodilution-Induced Deficit With Subclinical Metabolic Stress

A 70-year-old female patient undergoing mitral valve repair has progressive hemodilution (Hb 6.9 g/dL) during normothermic CPB. Despite maintaining a flow of 2.2 L/min/m², DO_2i stabilizes around 260 mL/min/m² (= 40 below the critical threshold) for = 60 minutes. This results in an AUC–DO_2 of 2,400 mL/min/m²/min, corresponding to a moderate cumulative oxygen debt. Lactate slowly increases to 2.5 mmol/L, returning to baseline after correction of Hb > 7.5 g/dL and slight flow augmentation. This condition reflects a supply demand mismatch secondary to anemia rather than perfusion failure. The body partially compensates through increased oxygen extraction (O_2ERi ↑), but prolonged exposure approaches the limit of metabolic tolerance.
The case highlights the importance of hemoglobin optimization and individualized perfusion flow adjustment core principles of Goal-Directed Perfusion (GDP).

Case 3, Combined Flow and Oxygenation Deficit Leading to Renal Injury

A 73-year-old woman with pre-existing hypertension undergoes valve + CABG surgery under mild hypothermia (32 °C). Low systemic flow (2.0 L/min/m²), Hb 6.8 g/dL, and partial membrane oxygenator dysfunction cause a sustained DO_2i of =230 mL/min/m² for 30 minutes.
Two additional minor dips to =250 mL/min/m² (10–20 min each) occur during rewarming. The cumulative exposure yields an AUC–DO_2 = 3,400 mL/min/m²/min, within the high-risk range reported for postoperative AKI [18]. Lactate peaks at 3.8 mmol/L; urine output falls; creatinine rises +0.6 mg/dL within 24 h (KDIGO Stage 1). This case demonstrates the combined effect of low Hb and inadequate pump flow, which synergistically depress DO_2i. Despite moderate MAP (65 mmHg), oxygen consumption (VO_2i) becomes supply-dependent, leading to renal hypoxia. Early recognition through continuous DO_2i and O_2ERi monitoring would have enabled pre-emptive correction before irreversible tissue injury developed.

Case 4, Preventive Optimization Guided by GDP Principles

A 58-year-old male patient undergoing aortic valve replacement experiences a gradual drop in DO_2i to =240 mL/min/m² for 10 minutes during cooling to 30 °C. Prompt detection via perfusion monitoring triggers an increase in flow (to 2.6 $L \cdot min^{-1} \cdot m^{-2}$) and transfusion (Hb 8.0 g/dL). DO_2i rapidly normalizes to > 300 mL/min/m², limiting total AUC–DO_2 = 600 mL/min/m²/min consistent with the non-AKI cohort in Mukaida et al. [18]. This case typifies the preventive power of real-time GDP monitoring. By promptly correcting underdelivery, cumulative oxygen debt remains minimal. Lactate stays < 2 mmol/L; renal and neurologic outcomes are preserved. The physiologic principle mirrors the *"time–dose sparing effect"* short exposures below threshold have little clinical consequence if rapidly reversed.

Case 5, Temperature-Adjusted Prediction and Adaptive Perfusion Control

In a recent pilot analysis by El Dsouki and Condello (2025), an algorithm incorporating blood temperature predicted critical DO_2i thresholds varying between 270–310 mL/min/m², accounting for altered metabolic demand. A 64-year-old patient under moderate hypothermia (28 °C) would thus tolerate a transient DO_2i of =250 mL/min/m² without riskwhereas the same value at 36 °C might fall below the safe limit.This adaptive approach refines perfusion targets based on physiologic temperature correction, aligning DO_2i goals with the real metabolic rate and reinforcing the evolution toward personalized perfusion medicine (**Table 1**).

3) DO_2/VCO_2 and DO_2/O_2ERi Ratios: Integrative Markers of Perfusion–Metabolism Coupling

The integration of oxygen delivery (DO_2i) and carbon dioxide production (VCO_2i) into derived ratios represents one of the most meaningful evolutions in Goal-Directed Perfusion (GDP) strategy. These indices allow continuous assessment of the balance between tissue oxygen supply and metabolic demand, transforming perfusion from a static flow paradigm into a dynamic, physiology-driven process. Whereas DO_2i quantifies oxygen transport capacity, VCO_2i reflects the rate of carbon dioxide generation from aerobic and anaerobic metabolism. Their ratio (DO_2/VCO_2) therefore acts as a composite indicator of

metabolic efficiency and perfusion adequacy linking oxygen transport to substrate utilization and acid–base homeostasis in real time. Under normal aerobic conditions, VCO_2i is proportional to VO_2i according to the respiratory quotient (RQ=0.8). When oxygen delivery becomes insufficient, tissues switch partially to anaerobic glycolysis, generating lactate and excess CO_2 via bicarbonate buffering. This leads to a disproportionate increase in VCO_2i relative to VO_2i, and consequently, a drop in the DO_2/VCO_2 ratio. This decline precedes overt lactate accumulation, providing an early metabolic warning of tissue hypoxia. The first formal description of this phenomenon was provided by de Somer et al. (2011) [2], who demonstrated that combined monitoring of DO_2i and VCO_2i during cardiopulmonary bypass (CPB) improved detection of early oxygen debt. The study introduced the concept of *metabolic coupling* between oxygen and carbon dioxide kinetics as a real-time guide for perfusion adequacy.

Mathematical Framework:

$$\mathrm{DO_2/VCO_2\ ratio} = \frac{\text{Indexed Oxygen Delivery } (\mathrm{DO_2i})}{\text{Indexed } \mathrm{CO_2} \text{ Production } (\mathrm{VCO_2i})}$$

$$VCO_2i = (\dot{V}_{gas}) \times (F_{CO_2,out} - F_{CO_2,in})$$

Both parameters are expressed in mL/min/m², with VCO_2i derived from gas analysis of the oxygenator exhaust. Under normothermic CPB, a DO_2/VCO_2 ratio ≥ 5.3 indicates preserved aerobic metabolism, whereas values < 4 signal metabolic stress and early anaerobic transition (Zhang & Zhou, 2022 [5]; Gerritse et al., 2023 [9]).

Clinical Case Illustrations, DO_2/VCO_2 Ratio

The DO_2/VCO_2 ratio provides a dynamic, integrative measure of the metabolic balance between oxygen delivery and carbon dioxide production. Unlike single-

point variables, it reflects *both the adequacy of tissue perfusion and the metabolic cost of oxygen utilization*. The following clinical examples illustrate its application across a spectrum of perfusion states.

Example 1, Normoperfusion (Optimal Metabolic Balance)

A 62-year-old male undergoing CABG at 36 °C demonstrates:
• DO_2i = 310 mL/min/m²
• VCO_2i = 55 mL/min/m² → DO_2/VCO_2 = 5.6
• Lactate = 1.3 mmol/L, SvO_2 = 74%, O_2ERi = 26%

All parameters fall within the aerobic range, confirming efficient oxygen transport and normal metabolic coupling.
Interpretation: DO_2/VCO_2 > 5 indicates preserved aerobic metabolism and adequate perfusion reserve. No intervention required.
(*Consistent with de Somer 2011 [2] and Condello 2020 [23]*)

Example 2, Early Oxygen Debt (Subclinical Stress)

A 70-year-old aortic valve patient presents with anemia (Hb = 7.0 g/dL) and low flow (2.2 L/min/m²):
• DO_2i = 260 mL/min/m²
• VCO_2i = 70 mL/min/m² → DO_2/VCO_2 = 3.7
• Lactate = 2.1 mmol/L, O_2ERi = 44%, SvO_2 = 65%

The ratio below 4 reveals early imbalance between oxygen supply and CO_2 clearance, even before significant lactate accumulation.
Interpretation: This pattern indicates *incipient anaerobic metabolism* and reversible oxygen debt. Corrective action (↑ pump flow, ↑ Hb) promptly restores the ratio to >5, normalizing metabolism.
(*In agreement with de Somer 2011 [2] and Ranucci 2018 [3]*)

Example 3, Overt Anaerobic Metabolism

During prolonged CPB (90 min, 36 °C), a 68-year-old with preoperative anemia develops:

• DO_2i = 240 mL/min/m²
• VCO_2i = 80 mL/min/m² → DO_2/VCO_2 = 3.0
• Lactate = 3.8 mmol/L, O_2ERi = 52%, SvO_2 = 60%

The low ratio confirms severe metabolic distress and onset of anaerobiosis. Excess CO_2 generation from bicarbonate buffering produces a marked rise in VCO_2i.

Interpretation: Sustained DO_2/VCO_2 < 4 indicates uncompensated oxygen debt and correlates with postoperative hyperlactatemia and AKI risk. Immediate optimization of perfusion flow and oxygen content is mandatory.

(*Consistent with Ranucci 2018 [3] and Condello 2020 [23]*)

Example 4, Hypothermic Perfusion (Temperature-Adjusted Equilibrium)

A 60-year-old patient during mild hypothermia (30 °C):

• DO_2i = 250 mL/min/m²
• VCO_2i = 45 mL/min/m² → DO_2/VCO_2 = 5.5
• Lactate = 1.4 mmol/L, O_2ERi = 34%

Despite lower DO_2i, the metabolic ratio remains within the aerobic range due to decreased cellular oxygen consumption and CO_2 production.

Interpretation: Under hypothermia, the critical ratio thresholds shift upward (safe range = 5–6). Adjusting DO_2/VCO_2 interpretation for temperature improves accuracy of perfusion management.

(*As refined by El Dsouki & Condello 2025 [24]*)

4) DO_2/O_2ERi Ratio: A Composite Index of Oxygen Delivery

The DO_2/O_2ERi ratio integrates the concepts of oxygen delivery and extraction into a single quantitative marker of metabolic adequacy. While DO_2i measures the total oxygen transported per unit surface area, and O_2ERi expresses the proportion extracted by tissues, their ratio reflects the functional balance between oxygen supply and utilization. It transforms two interdependent physiological variables into a dimensionless index that directly correlates with tissue oxygenation reserve.

Physiological Rationale

Under stable aerobic conditions, oxygen extraction efficiency remains constant, and thus, the DO_2/O_2ERi ratio maintains a wide safety margin. When oxygen delivery declines due to anemia, reduced flow, or desaturation, the body compensates by increasing extraction decreasing the ratio. This fall in DO_2/O_2ERi precedes the onset of anaerobic metabolism and acts as an integrated warning signal that combines hemodynamic, hematologic, and metabolic data. Ranucci et al. (2018) [3] first proposed that this combined ratio could serve as a real-time index of perfusion adequacy during cardiopulmonary bypass (CPB), with declining values paralleling lactate rise and postoperative organ dysfunction. Later, Condello et al. (2020) [23] confirmed that simultaneous reduction in DO_2i and elevation of O_2ERi (>45%) corresponded to a critical imbalance between oxygen transport and demand, preceding hyperlactatemia and renal impairment.
More recently, El Dsouki & Condello (2025) [24] introduced temperature-adjusted thresholds, demonstrating that this ratio dynamically scales with metabolic rate maintaining predictive value across thermal conditions.

Mathematical formula:

$$\mathrm{DO_2/O_2ERi\ ratio} = \frac{\mathrm{Indexed\ Oxygen\ Delivery\ (DO_2i)}}{\mathrm{Indexed\ Oxygen\ Extraction\ Ratio\ (O_2ERi)}}$$

$$O_2ERi = \frac{CaO_2 - CvO_2}{CaO_2} \times 100$$

Typical clinical ranges under normothermia (36 °C) are:

- Normal / Optimal: $DO_2/O_2ERi \geq 8$
- Compensated: 6–8
- Critical: < 6

At hypothermic conditions (30–32 °C), due to reduced VO_2 and extraction, safe values shift slightly lower (7–9 optimal range) [24]. The DO_2/O_2ERi ratio functions as a *global marker of oxygen delivery adequacy relative to tissue demand*. A low ratio indicates that the system is consuming a high fraction of delivered oxygen, reflecting limited reserve and emerging oxygen debt. Conversely, a high ratio denotes sufficient delivery and preserved extraction margin. Condello et al. (2020) [23] demonstrated that patients with DO_2/O_2ERi < 6 during CPB had markedly higher incidence of hyperlactatemia (38% vs. 11%, $p < 0.01$) and postoperative renal dysfunction, independent of flow or temperature. These data highlight that monitoring this ratio provides integrated insight into both supply and utilization components of perfusion (**Table 2**).

5) Mean Arterial Pressure (MAP): Hemodynamic Driver of Perfusion Adequacy

Mean Arterial Pressure (MAP) represents the primary hemodynamic determinant of organ perfusion during cardiopulmonary bypass (CPB). It reflects the balance between systemic vascular resistance (SVR) and pump flow, defining the driving pressure for microcirculatory blood flow and tissue oxygen delivery. In the context of Goal-Directed Perfusion (GDP), MAP complements metabolic parameters (DO_2i, VO_2i, VCO_2i, O_2ERi) by quantifying the *pressure component* of tissue oxygenation. During CPB, autoregulation of flow in vital organs especially brain and kidney is pressure-dependent. Below the lower limit of autoregulation (typically 50–60 mmHg in adults), organ perfusion becomes linearly dependent on MAP, rendering tissues vulnerable to hypoxia even when global DO_2i appears adequate. Conversely, excessive MAP (>80–90 mmHg) increases afterload and microvascular shunting, impairing capillary exchange and elevating myocardial oxygen demand. Thus, MAP must be maintained within the individualized autoregulatory plateau to ensure optimal flow–pressure coupling.

Mathematical formula during CPB

$$\mathrm{MAP} = \mathrm{CO} \times \mathrm{SVR} + \mathrm{CVP}$$

where:

- CO = cardiac output (approximated by pump flow during CPB)
- SVR = systemic vascular resistance
- CVP = central venous pressure (usually negligible under CPB conditions)

MAP serves as the *pressure analogue* to DO_2i: both define essential boundaries for oxygen delivery—DO_2i describing transport capacity, MAP ensuring delivery pressure. When analyzed together, they delineate the global perfusion envelope. Recent studies emphasize the independent role of MAP in organ protection during CPB: Schreiber et al. (2024) [24] demonstrated that each 5 mmHg decrease below 65 mmHg increased the risk of postoperative acute kidney injury (AKI) by 12%, even when DO_2i was adequate. Badin et al. (2011) [25] correlated renal dysfunction with the cumulative duration of MAP below 65 mmHg, introducing the concept of *time–dose hypotension exposure* analogous to AUC–DO_2. Since CVP = 0, MAP depends primarily on pump flow and systemic vascular resistance (SVR).
Thus, low MAP can arise from:

1. Low flow (reduced DO_2i, hypovolemia),
2. Low SVR (vasoplegia, hemodilution),
3. Low viscosity (anemia).

Each mechanism requires a specific intervention increase flow for convective deficit, restore tone for vasoplegia, correct hematocrit for hemodilution.

The MAP Time Dose Response Model

In parallel to the AUC–DO_2 concept, the MAP Time–Dose Response Model quantifies the cumulative burden of hypotension during CPB, integrating both *intensity* and *duration* of pressure drops.

$$AUC\text{–MAP} = \int_{t_1}^{t_2} (MAP_{crit} - MAP)\, dt$$

- Unit: mmHg·min
- $MAP_{(crit)}$: autoregulatory threshold, typically 65 mmHg.
- The larger the AUC–MAP, the greater the cumulative ischemic pressure deficit and AKI risk.

This concept was first applied by Badin et al. (2011) [25]**,** who showed that both *severity* and *duration* of MAP <65 mmHg predicted renal injury in shock patients. Later, Schreiber et al. (2024) [24] extended this principle to cardiac surgery, introducing the Time-Weighted Average MAP (TWA–MAP) a quantitative index that expresses the average depth of hypotension during CPB, normalized for bypass time. In the largest analysis to date (n = 2,352), Schreiber and colleagues [24] used the INSPIRE open dataset to examine the association between TWA–MAP <65 mmHg and cardiac-surgery-associated AKI (CSA-AKI) (**Table 3**).

Case 1, Optimal Pressure Maintenance (Physiologic Equilibrium)

A 62-year-old male undergoing CABG under normothermic CPB (36 °C) demonstrates:

- MAP = 72 mmHg,
- DO_2i = 310 mL/min/m²,
- O_2ERi = 28%,
- Lactate = 1.3 mmol/L.

Calculated AUC–MAP ≈ 0 mmHg·min, TWA–MAP < 65 = 0 mmHg.

This represents a fully preserved autoregulatory state with zero pressure debt. Continuous arterial line monitoring (radial artery) confirms stable waveform and flow–pressure coupling.

Interpretation: Adequate perfusion pressure ensures normal renal and cerebral autoregulation. No metabolic stress is observed.

Case 2, Transient Subcritical MAP (Moderate Exposure)

During temperature stabilization, a transient pressure drop occurs:

- MAP = 60 mmHg for 10 minutes,
- DO_2i = 285 mL/min/m^2,

AUC–MAP = (65 – 60) × 10 = 50 mmHg·min, TWA–MAP = 1.2 mmHg.

Despite crossing the autoregulatory threshold briefly, the low cumulative exposure yields negligible ischemic burden. Lactate remains <2.0 mmol/L, and postoperative renal function is normal.
Interpretation: Short-lived MAP reductions are well tolerated when global flow and DO_2i remain adequate. Observation suffices without pharmacologic correction.

Case 3, Prolonged Hypotension (High-Risk Scenario)

A 70-year-old valve patient with hemodilution (Hb 7.5 g/dL) presents with:

- MAP = 55 mmHg for 40 minutes,
- DO_2i = 260 mL/min/m^2,
- Lactate = 3.5 mmol/L,
- Creatinine +0.8 mg/dL (KDIGO 1).

AUC–MAP = (65 – 55) × 40 = 400 mmHg·min, TWA–MAP = 5 mmHg.

This cumulative hypotensive load aligns with the high-risk range described by Schreiber et al. (2024) [24], where each +1 mmHg increase in TWA–MAP <65 correlates with a 7% increase in AKI risk. The prolonged subthreshold exposure indicates progressive loss of renal autoregulation and oxygen debt accrual,

even though DO_2i remains marginally acceptable. Interpretation: Sustained hypotension amplifies microcirculatory shear stress and renal medullary hypoxia. Corrective actions include augmenting pump flow, increasing hematocrit, and titrating vasopressors to restore SVR.

Case 4, Preventive Perfusion Strategy (Nasso 2023 Protocol)

Following the Nasso et al. (2023) [26] protocol, a 58-year-old CABG patient receives:

- Retrograde Autologous Priming (RAP),
- Stepwise CPB initiation (3 minutes), and
- Pulsatile pump flow.

MAP is maintained ≥70 mmHg throughout CPB with stable SVR and DO_2i >300 mL/min/m^2.
AUC–MAP ≈ 0 mmHg·min; TWA–MAP <65 = 0 mmHg.

Discussion

Goal-Directed Perfusion can be conceptualized according to four interdependent physiological pillars: Model, Mission, Means, and Monitoring.

1) The Model is represented by cardiopulmonary bypass as a fully extracorporeal system in which native cardiac, pulmonary, and autonomic regulatory mechanisms are suspended. In this setting, oxygen transport, carbon dioxide clearance, and perfusion pressure are entirely determined by mechanical and physicochemical variables.

2) The Mission of GDP is not the achievement of fixed, group-defined targets, but the preservation of metabolic coherence, ensuring that oxygen delivery adequately meets individual tissue oxygen consumption. The physiological objective is to prevent oxygen supply dependency and cumulative oxygen debt rather than to adhere rigidly to predefined flow or pressure values.
3) The Means available to accomplish this mission include pump flow, hemoglobin concentration, arterial oxygen saturation, temperature management, and vascular tone. These variables directly modulate convective oxygen transport and can be dynamically adjusted in real time.

Monitoring integrates these components through continuous assessment of DO_2i, VO_2i, VCO_2i, O_2ERi, derived metabolic ratios (DO_2/VCO_2 and DO_2/O_2ERi), and mean arterial pressure, as well as their time–dose responses. Within this framework, indexed thresholds should be interpreted as physiological guardrails rather than rigid targets, supporting individualized perfusion strategies tailored to patient-specific metabolic demand**.** This proactive, physiology-based approach virtually eliminates hypotensive events (mean 3 ± 1 vs 8 ± 2 in control, $p = 0.019$) and reduces vasopressor demand, confirming the synergistic effect between pressure management and oxygen delivery. Interpretation: Stepwise initiation and pulsatile perfusion prevent early vasoplegia, preserve endothelial tone, and ensure continuous pressure–flow coherence hallmarks of goal-directed perfusion. Goal-Directed Perfusion (GDP) redefines perfusion management by integrating hemodynamic and metabolic parameters into a cohesive framework that quantifies the adequacy of oxygen transport and utilization during CPB. Traditional perfusion relied on fixed flow and pressure targets, often ignoring interpatient variability and the dynamic relationship between oxygen delivery (DO_2i) and tissue metabolic demand. GDP bridges this gap by continuously monitoring DO_2i, VO_2i, VCO_2i, O_2ERi, DO_2/VCO_2, DO_2/O_2ERi**,** and MAP**,** each representing a complementary dimension of systemic oxygenation and perfusion. Indexed oxygen delivery (DO_2i) serves as the cornerstone of this concept, expressing the convective transport of oxygen to tissues. Empirical and prospective data (de Somer 2011 [2]; Ranucci 2018 [3]; Magruder 2017 [6]) established that maintaining $DO_2i \geq 260–280$ $mL \cdot min^{-1} \cdot m^{-2}$ prevents oxygen-supply dependence and postoperative

organ injury. Below this critical threshold, oxygen consumption (VO_2i) becomes supply-limited, triggering anaerobic metabolism and lactate accumulation. The time–dose response model developed by *Mukaida et al.* (2019) [18] introduced the AUC–DO_2 index, quantifying both depth and duration of oxygen underdelivery. Later analyses (*Carrasco-Serrano 2022* [4]) confirmed that AUC–DO_2 > 2 500 $mL \cdot min^{-1} \cdot m^{-2} \cdot min$ strongly predicts acute kidney injury (AKI), outperforming nadir DO_2i alone. Temperature-adjusted algorithms further refined this metric, demonstrating that critical thresholds vary with metabolic rate (*El Dsouki & Condello 2025* [23]). Beyond single-parameter analysis, metabolic coupling ratios particularly DO_2/VCO_2 and DO_2/O_2Eri extend GDP into integrative physiology. Under aerobic conditions, VCO_2i scales proportionally to VO_2i (RQ ≈ 0.8); when DO_2i declines, CO_2 generation rises disproportionately through bicarbonate buffering, reducing DO_2/VCO_2 below 5.3 (*de Somer 2011* [2]; Zhang & Zhou 2022 [5]). This drop precedes lactate elevation, marking the earliest transition to anaerobic metabolism. Similarly, the DO_2/O_2ERi ratio reflects the system's extraction reserve: values < 6 indicate exhausted compensatory capacity and correlate with hyperlactatemia and renal dysfunction (*Condello 2020* [14]). These ratios embody the principle of GDP as a real-time, quantitative integration of flow, gas exchange, and tissue metabolism. While oxygen delivery ensures convective transport, Mean Arterial Pressure (MAP) governs the pressure-dependent transmission of flow to the microcirculation. The balance between DO_2i and MAP defines the physiologic perfusion envelope where convective and hydraulic adequacy coexist. During CPB, autoregulation of cerebral and renal flow persists only above a MAP ≈ 65–70 mmHg; below this, perfusion becomes linearly pressure-dependent (*Badin 2011* [25]; Schreiber 2024* [24]). The MAP time–dose model (AUC–MAP, TWA–MAP) parallels AUC–DO_2 by quantifying cumulative hypotensive burden. *Schreiber et al.* (2024) [24] demonstrated that each +1 mmHg rise in TWA–MAP < 65 mmHg increased AKI risk by 7%, underscoring that even transient hypotension can induce pressure-related oxygen debt. Preventive strategies described by *Nasso et al.* (2023) [26] retrograde autologous priming, stepwise CPB initiation, and pulsatile flow maintain MAP ≥ 70 mmHg, reduce vasopressor use, and stabilize DO_2i and O_2ERi, highlighting the synergy between hydraulic and metabolic control. The integration of oxygen- and

pressure-derived metrics thus constructs a multidimensional map of perfusion adequacy. GDP shifts practice from reactive correction to predictive physiology: DO_2i quantifies oxygen transport; VCO_2i and lactate reveal metabolic response; O_2ERi measures extraction efficiency; and MAP sustains the hydraulic gradient required for capillary exchange. Time–dose indices (AUC–DO_2, AUC–MAP) translate these instantaneous measures into cumulative "debt accounting," enabling clinicians to quantify the physiological cost of suboptimal perfusion. The Mini-Compendium on GDP, presented here as a synthesis of available evidence, fills a critical gap in perfusion literature. It serves not as a guideline but as a foundational reference integrating quantitative physiology, mathematical modeling, and clinical thresholds into a single framework. By providing definable cut-offs $DO_2i \geq 280$ mL·min^{-1}·m^{-2}, $DO_2/VCO_2 \geq 5.3$, $DO_2/O_2ERi \geq 6$, MAP ≥ 70 mmHg and by incorporating time-dose parameters (AUC–DO_2 < 1 000; AUC–MAP < 300 mmHg·min), the Compendium translates complex perfusion physiology into actionable, bedside targets. Ultimately, GDP transforms CPB from a mechanical procedure into **a** quantitative, organ-protective discipline**.** Through continuous monitoring, dynamic feedback, and integration of oxygen transport and pressure variables, perfusion becomes predictive rather than reactive. The ongoing development of automated dashboards and AI-supported algorithms may soon operationalize this framework, enabling fully individualized perfusion strategies across adult, pediatric, and extracorporeal support contexts. By consolidating physiological theory and clinical application, this Mini-Compendium provides the conceptual groundwork for establishing GDP as a reproducible, data-driven standard of care.

Limitations

Importantly, the principles of Goal-Directed Perfusion are not restricted to centers equipped with advanced real-time metabolic monitoring systems. In resource-limited settings, indexed oxygen delivery can be calculated using routinely available variables such as pump flow, hemoglobin concentration, and arterial oxygen saturation. Intermittent mixed venous oxygen saturation measurements, lactate trends, and mean arterial pressure can serve as clinically meaningful surrogate indicators of metabolic adequacy. Even in the

absence of continuous VCO_2 monitoring, maintaining DO_2i above physiologically safe thresholds and avoiding prolonged hypotension allows practical implementation of GDP principles using standard perfusion technology.

Conclusions

The Mini-Compendium on Goal-Directed Perfusion (GDP) provides the first structured synthesis of physiological principles for individualized perfusion management during cardiopulmonary bypass. By integrating oxygen delivery (DO_2i), metabolic coupling ratios (DO_2/VCO_2, DO_2/O_2ERi), and perfusion pressure metrics (MAP, AUC–MAP), GDP establishes a unified, quantitative framework to assess and maintain tissue oxygenation in real time. This approach moves beyond static flow targets, defining perfusion as a dynamic equilibrium between oxygen transport, utilization, and driving pressure. Maintaining $DO_2i \geq 280$ mL/min/m², $DO_2/VCO_2 \geq 5.3$, and MAP ≥ 70 mmHg minimizes cumulative oxygen and pressure debt and reduces organ injury risk. GDP thus transforms perfusion from a mechanical process into predictive physiology, enabling early recognition and correction of metabolic imbalance. As a novel conceptual and practical guide not yet present in current literaturethe Mini-Compendium outlines the foundations for a standardized, data-driven, and patient-specific perfusion strategy aimed at improving safety and outcomes in cardiac surgery.

List of Abbreviations

- **AUC–DO_2**, Area Under the Curve of Indexed Oxygen Delivery below the critical threshold
- **AUC–MAP**,Area Under the Curve of Mean Arterial Pressure below the critical threshold
- **CPB**,Cardiopulmonary Bypass
- **DO_2**,Oxygen Delivery
- **DO_2i**, Indexed Oxygen Delivery (oxygen delivery normalized to body surface area)
- **DO_2/O_2Eri**,Ratio of Indexed Oxygen Delivery to Indexed Oxygen Extraction Ratio
- **DO_2/VCO_2**, Ratio of Indexed Oxygen Delivery to Indexed Carbon Dioxide Production
- **GDP** – Goal-Directed Perfusion
- **Hb**, Hemoglobin
- **MAP**, Mean Arterial Pressure
- **O_2Eri**, Indexed Oxygen Extraction Ratio (fraction of delivered oxygen extracted by tissues)
- **PaO_2**, Arterial Oxygen Partial Pressure
- **SaO_2**, Arterial Oxygen Saturation
- **SvO_2**, Mixed Venous Oxygen Saturation
- **TWA–MAP**, Time-Weighted Average of Mean Arterial Pressure below 65 mmHg

- **VCO_2**, Carbon Dioxide Production
- **VCO_2i**, Indexed Carbon Dioxide Production
- **VO_2**, Oxygen Consumption
- **VO_2i**, Indexed Oxygen Consumption

Declarations

Clinical trial number: not applicable.

Ethics approval and consent to participate: Not applicable. This study is a narrative review of previously published literature and did not involve any human participants, animal experiments, or patient data requiring ethical approval.

Consent for publication: Not applicable. The manuscript does not include any individual patient data, images, or other personal information requiring consent for publication.

Availability of data and materials: All data supporting the findings of this review are derived from publicly available studies indexed in PubMed, Scopus, and Web of Science, as detailed in the reference list. Additional information is available from the corresponding author upon reasonable request.

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Figure legends

Graphical Abstract. Mini-Compendium on Goal-Directed Perfusion (GDP)

Figure 1. PRISMA-style flow diagram of study selection.

Table Legends

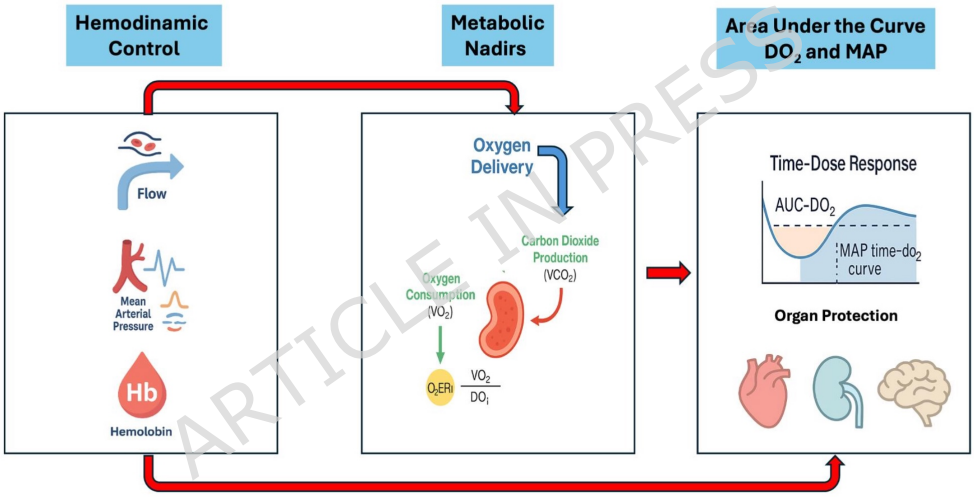
Table 1. Quantitative Risk Stratification Based on Indexed Oxygen Delivery (DO_2i) and Cumulative Oxygen Deficit (AUC–DO_2) Parameters.

Table 2. Integrative Perfusion–Metabolism Ratios: DO_2/VCO_2 and DO_2/O_2Eri.

Table 3. Time–Dose Categories and Clinical Thresholds.

Mini-Compendium on Goal-Directed Perfusion (GDP)

Integrating Hemodynamic and Metabolic Determinants of Oxygen Delivery (DO_2)



«This mini-compendium redefines Goal-Directed Perfusion as an inclusive and integrative approach that unites hemodynamic, metabolic, and temporal determinants of oxygen delivery into a single conceptual continuum.»