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Research paper

Can utilization of the venous-to-arterial carbon dioxide difference improve patient outcomes in cardiogenic shock? A narrative review☆

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ABSTRACT

Cardiogenic shock (CS) is a critical condition with high mortality, characterized by reduced cardiac output (CO) and tissue hypoperfusion, despite advancements in treatment. Traditional hemodynamic markers like CO measurements, monitoring of mixed venous oxygen saturation (SvO_2) and lactate levels have limitations, particularly in detecting microcirculatory dysfunction. The venous-to-arterial carbon dioxide tension difference (V-A PCO_2 gap, also known as P(V-A)CO_2 and delta PCO_2 or ΔPCO_2) has been established as a sensitive marker of tissue perfusion and CO adequacy in septic shock but lacks extensive exploration in CS.

This narrative review evaluates the possible uses of V-A PCO_2 gap in contemporary management of CS. Based on the available literature, it elucidates how the V-A PCO_2 gap may offer valuable insight into tissue perfusion and CO adequacy in patients with CS. Elevated V-A PCO_2 gaps may reflect impaired clearance of CO_2 due to reduced CO and tissue hypoxia, serving as a reliable early indicator of circulatory failure. Integrating V-A PCO_2 gap monitoring into contemporary hemodynamic assessments holds potential to improve clinical decision-making, enabling more timely interventions and better stratification of patients at risk of deterioration.

The sparse evidence suggests an association between elevated V-A PCO_2 gaps and poor outcomes in cardiac patients, including increased mortality and prolonged ventilation needs. Further research is needed to validate the use of this marker in CS and explore its potential to enhance treatment protocols by providing a more nuanced understanding of tissue-level perfusion, especially when macrocirculatory function appears normalized.

1. Background

Cardiogenic shock (CS) is a life-threatening condition characterized by the inability of the heart to deliver sufficient blood to meet the metabolic demands of the body, resulting in systemic hypoperfusion and multiorgan dysfunction. Ischemic left ventricular (LV) dysfunction, often secondary to acute myocardial infarction, is a leading cause of cardiogenic shock (AMI-CS) and is associated with persistently high mortality rates despite significant advancements in therapeutic interventions [1–4].

Traditionally, the mixed venous oxygen saturation (SvO_2) has been utilized as a key parameter in cardiovascular monitoring due to its correlation with cardiac output (CO) [5]. However, a normal SvO_2 does not rule out local hypoperfusion and damaged microcirculation [6,7]. Also, circulating levels of lactate have been utilized in prognostication of AMI-CS patients [8,9]. Notably, a high proportion of patients with CS die despite a restored macrocirculatory function with normalized CO. Hence, peripheral and microcirculatory parameters may better predict patient outcomes [10–12].

Recent evidence has suggested that the venous-to-arterial carbon dioxide tension difference (V-A PCO_2 gap, also known as P(v-a)CO_2 and delta PCO_2) may serve as an additional marker in the critical care setting and has been evaluated thoroughly in septic shock where it has been proposed as a valuable measurement able to guide therapy [13–19]. The V-A PCO_2 gap offers an indirect measure of tissue perfusion and the adequacy of CO, reflecting the balance between oxygen delivery and consumption at the microcirculatory, cellular level. Still, the use of the V-A PCO_2 gap in CS remains to be fully elucidated, though utilization of the V-A PCO_2 gap may enhance the treatment and early detection of hypoperfusion in CS patients.

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2. Purpose of this review

This narrative review explores the possibility that integrating the V-A PCO_2 gap into current hemodynamic monitoring may improve the early identification of patients at risk for poor outcomes. In CS reduced CO impairs the clearance of CO_2 from tissues, leading to an elevated V-A PCO_2 gap. As this gap reflects impaired tissue perfusion and correlates inversely with CO, it may serve as a more precise indicator of circulatory insufficiency compared to traditional measures. Evidence from septic shock demonstrates that the V-A PCO_2 gap can effectively guide resuscitation strategies, suggesting its potential utility in CS as well. Incorporating this parameter into existing monitoring frameworks could enhance clinical decision-making by providing earlier detection of hemodynamic deterioration, enabling timely and targeted interventions. This approach adds to the current guidelines, as the V-A PCO_2 gap is not included in the Society for Cardiovascular Angiography and Interventions (SCAI) classification of cardiogenic shock.

3. Microcirculatory dysfunction in cardiogenic shock

CS is characterized by a significant decline in CO, leading to systemic hypoperfusion and tissue hypoxia. Beyond these systemic, macrocirculatory, effects, CS profoundly disrupts the microcirculation which is the network of small blood vessels responsible for delivering oxygen and nutrients at the tissue level. This microcirculatory dysfunction is a critical factor in the progression of organ failure and is strongly associated with adverse outcomes in CS patients [49].

In CS, reduced perfusion pressure compromises blood flow within the microvasculature. This leads to heterogeneous blood flow distribution, with some capillary networks becoming underperfused while others may experience stasis [20]. Such irregularities cause regional hypoxia, triggering inflammatory responses and endothelial cell activation. Activated endothelial cells can promote leukocyte adhesion and microvascular thrombosis, which further obstructs blood flow [21,22]. These microcirculatory disturbances create a vicious cycle of worsening tissue hypoxia and inflammation, contributing to the development of multiple organ failure. Importantly, these microvascular alterations may persist even after systemic hemodynamic parameters, such as blood pressure and CO, have been stabilized – a phenomenon referred to as "loss of hemodynamic coherence" [12]. Notably, while restoration of CO in patients with CS remains a primary treatment goal, this may not always improve outcomes as a significant proportion of these patients die despite a normalized macrocirculatory function [10,11].

In this context the V-A PCO_2 gap has emerged as a valuable marker in critical care for assessing tissue perfusion and CO already well-studied in septic shock [13–19,23]. Physiologically this makes sense, as according to modified Fick equation, the V-A PCO_2 gap is directly related to CO_2 production and inversely related to CO. When CO is sufficient, CO_2 is efficiently cleared, preventing rises in the V-A PCO_2 gap. A reduction in CO, however, results in prolonged transit times in the microvasculature, allowing for CO_2 accumulation in venous blood resulting in elevated V-A PCO_2 gap [24–26].In critical care settings, this marker becomes particularly useful for identifying hypoperfusion and potential tissue hypoxia. In cases of reduced CO, as seen in sepsis or other low-flow states such as CS, the V-A PCO_2 gap rises as CO_2 clearance diminishes, reflecting impaired perfusion. This relationship holds under aerobic conditions, but in situations where oxygen delivery is critically reduced, anaerobic metabolism may commence, leading to additional CO_2 production and lactate accumulation [27] (Fig. 1). The V-A PCO_2 gap increases further, thus indicating severe tissue dysoxia and hypoperfusion. In this regard, the V-A PCO_2 gap might serve as a sensitive marker, which can provide critical insight into the adequacy of tissue perfusion both in the early and late states of circulatory failure.

4. V-A PCO_2 gap in cardiac disease

While extensively studied in sepsis the value V-A PCO_2 have not been assessed thoroughly in CS. It is important to note that the pathophysiological mechanisms underlying septic shock differ significantly from those seen in cardiogenic shock, particularly regarding vascular tone, CO, and metabolic demands [28]. As a result, extrapolating findings from septic shock to AMI-CS without direct evidence may lead to inaccurate conclusions and suboptimal patient management.

Some evidence, however, supports the role of the V-A PCO_2 gap in management and monitoring of cardiac patients (Table 1). In 1998 Teboul et al. studied 10 patients with low CO but with no signs of clinical shock according to the criteria of the time. They found that V-A PCO_2 gap was a reliable marker of adequacy of CO [29]. In present time, a study from López-Sobrino et al. (2023) in 50 patients with CS found that an elevated V-A PCO_2 gap at admission was associated with cardiovascular mortality, as was lactate values and central venous oxygen saturation [30,31]. Merdji et al. (2022) assessed 61 patients with CS. They examined whether an increased capillary refill time (CRT) was associated with the need for treatment with veno-arterial extracorporeal membrane oxygenation (VA ECMO) and 90 day mortality. They concluded that an increased CRT was associated with early prediction of 90-day mortality or need for VA ECMO. Also, VA PCO_2 gap was correlated with CRT, pointing to a predictive ability of VA PCO_2 gap as well [32]. Other studies provide more uncertain evidence regarding the use of the V-A PCO_2 gap in CS. A small study by Güven et al. (2022) in 22 CS patients, found that the V-A PCO_2 gap alone was not associated with increased mortality. However, integration of the V-A PCO_2 gap together with arterial to venous oxygen content, revealed a significant association with mortality [33]. Notably, conflicting results were proposed by Markota et al. (2012) in 30 patients with AMI-CS, where low V-A PCO_2 gap was associated with excess mortality even in patients with normal central venous oxygen saturation. The authors speculated that this was due to the non-survivors being severely and irreversibly shocked with a low CO_2 production [34]. Together, these results suggest that the utilization of the V-A PCO_2 gap might enhance the prediction of risk of mortality and other adverse events in CS and heart failure patients. However, none of these studies were controlled randomized trials and the results are somewhat conflicting. Also, additional factors including the oxygen saturation of hemoglobin (Haldane effect), metabolic shifts of pH, temperature and hemoglobin concentration must be taken into consideration when interpreting the V-A PCO_2 gap [50]. Hence, to validate V-A PCO_2 gap in the setting of CS monitoring and prediction of outcome further studies are needed.

Utilization of the V-A PCO_2 gap have also been suggested as a viable marker able to predict successful outcomes following mechanical circulatory support (MCS). Liang et al. (2023) hypothesized that a lower V-A PCO_2 gap following implantation of an Impella device was predictive of successful extubation in 40 patients. The results suggested that the V-A PCO_2 gap has the potential to be used as a predictor of successful extubation [35]. Another study by McDonald et al. (2021) reviewed 31 CS patients requiring VA ECMO support. The study found that the V-A PCO_2 gap were significantly elevated in non-survivors and evaluated the optimum cut-point for mortality prediction of 6 mmHg for the V-A PCO_2 gap [36], which is strikingly similar to cut-points found in sepsis [37,38].

Enhanced predictive performance has also been found in other cardiac diseases. Kanzariya et al. (2020) did a study in 65 off-pump coronary artery bypass grafting patients, all with a central venous oxygen saturation > 70 %, and found that patients with a V-A PCO_2 gap >8 mmHg had a prolonged need for mechanical ventilation and hospital stay, with no overall rate of post-operative complications between the groups [39]. Similar results have been identified by Habicher et al.

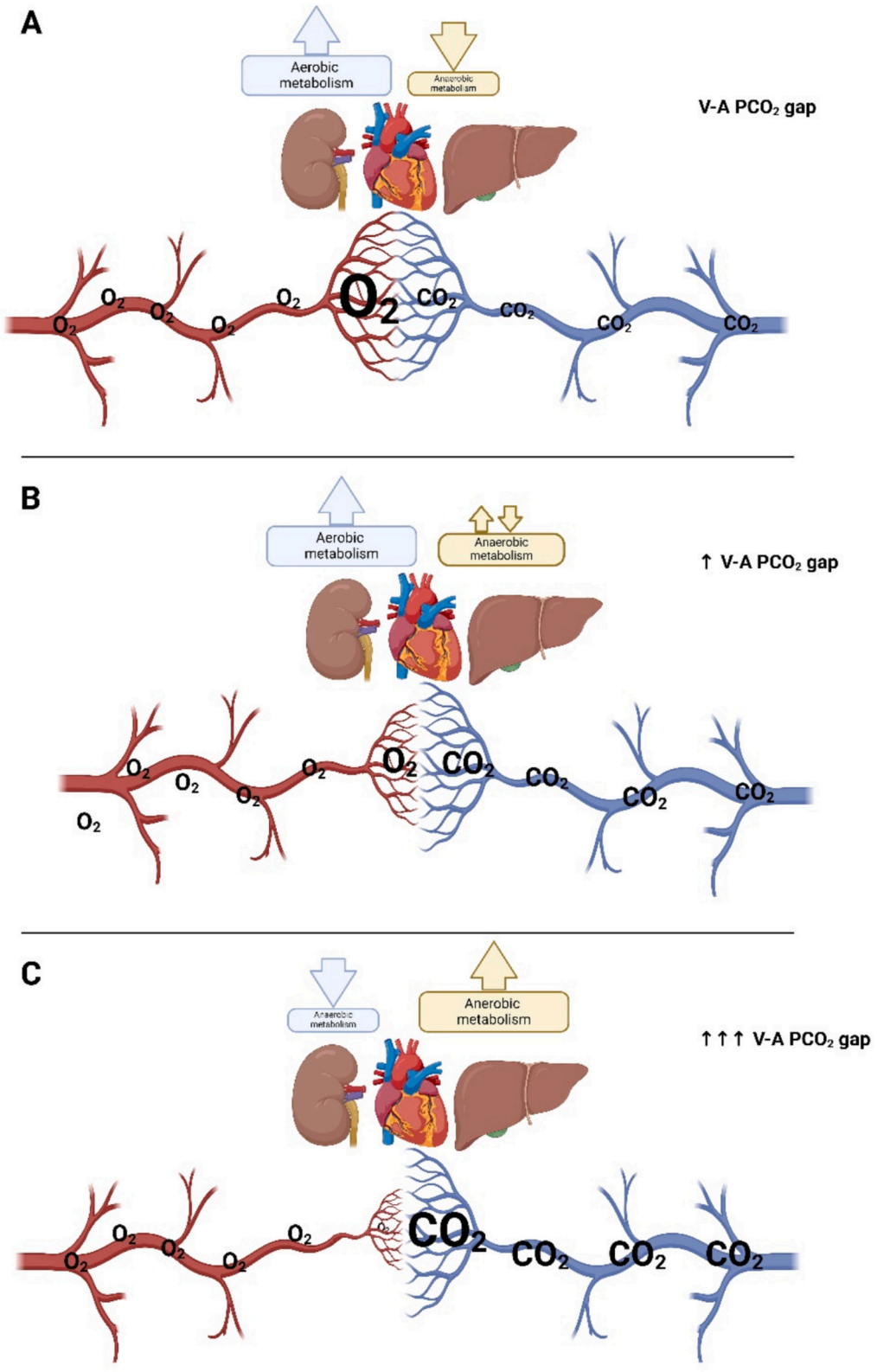

Fig. 1. Venous-to-Arterial PCO_2 gap
During normal aerobic states with normal microvascular function, oxygen is supplied to organs, which by aerobic metabolism produces ATP and CO_2. Clearence of CO_2 is ensured by sufficient cardiac output and venous flow (A). When CO decreases, the V-A PCO_2 gap increases demonstrating a negative correlation, due to inadequate blood flow to clear the formed CO_2, thus resulting in venous CO_2 accumulation (B). In case of severe micro- or macrovascular dysfunction oxygen deficiency occurs in peripheral tissue, and in response to tissue hypoxia anaerobic metabolism occurs resulting in further CO_2 production through the H^+ and bicarbonate buffer system. This, together with increasingly lowered venous blood flow results in markedly elevated V-A PCO_2.

Table 1
Overview of studies investigating the V-A PCO2 gap in cardiac disease in order of appearance in main text.

Author and year	Study population	Objective	Main findings
Teboul et al. (1998) [29]	10 patients with congestive heart failure but no clinical signs of shock and normal blood lactate level.	To test the value of V-A PCO_2 gap to reflect the adequacy of cardiac output (CO) to oxygen demand in patients submitted to rapid changes of CO and oxygen demand.	V-A PCO_2 gap was a reliable marker of adequacy of CO and particularly for detecting changes in oxygen demand.
López-Sobrino et al. (2024) [31]	50 patients with cardiogenic shock admitted to a cardiac intensive care unit (ICU).	To describe the changes in V-A PCO_2 gap during the 48 h after hospital admission.	Low V-A PCO_2 gap between 12 and 24 h after admission may identify patients at low risk of death due to CVD or refractory cardiogenic shock.
Merdji et al. (2022) [32]	61 patients with cardiogenic shock admitted to an ICU.	To assess the correlation of capillary refill time (CRT) values with 90-day mortality in cardiogenic shock patients or the need for VA-ECMO support. Also to assess the correlation between capillary refill time and hemodynamic parameters.	A high V-A PCO_2 gap was correlated with a prolonged CRT >3 s. This was associated with an early prediction of 90-day mortality or the need for VA-ECMO support.
Güven et al. (2022) [33]	46 patients with shock, hereof 22 with cardiogenic shock admitted to an ICU.	To test V-A PCO2 gap to A-V PO_2 content ratio in different shock types and correlation with hypoxia indicators.	The V-A PCO_2 gap to A-V PO_2 content ratio is a valuable hypoxia indicator in states of shock associated with mortality. The V-A PCO_2 gap alone was not associated with mortality.
Markota et al. (2012) [34]	30 patients with acute myocardial infarction and cardiogenic shock.	To test if patients with higher central V-A PCO_2 gap on admission would have higher mortality.	A lowered V-A PCO_2 gap was associated with excess mortality.
Liang et al. (2023) [35]	46 patients with cardiogenic shock treated with Impella 5.5	To test if a low V-A PCO_2 gap at 5 days post Impella 5.5 implantation is predictive of successful extubation.	V-A PCO_2 at 5 days post Impella 5.5 implantation has the potential to be used as a predictor of successful extubation,
McDonald et al. (2021) [36]	21 patients with cardiogenic shock treated with VA ECMO	To test if V-A PCO_2 gap would be an early indicator of microcirculatory status and useful parameters for outcome prediction during ECMO support.	V-A PCO_2 gap after 24 h of VA ECMO treatment was significantly higher in non-survivors. Increased V-A PCO_2 gap was associated with increased mortality.
Kanzariya et al. (2020) [39]	65 off pump coronary artery bypass grafting patients.	To test if monitoring central central V-A PCO2 gap could serve as a marker in detecting hypoperfusion in cardiac surgery patients.	Elevated central V-A PCO_2 gap was associated increased oxygen extraction ratio, longer need for mechanical ventilation and longer ICU stay.
Habicher et al. (2015) [40]	60 patients undergoing surgery with cardiopulmonary bypass.	To test if central V-A PCO_2 gap could serve as a parameter to evaluate the adequacy of perfusion in cardiac surgery patients.	Elevated central V-A PCO_2 gap was associated with increased post-operative lactate levels, decreased splanchnic function, prolonged need for mechanical ventilation and longer ICU stay.
Robin et al. (2015) [41]	115 patients undergoing high-risk surgery.	To test if central V-A PCO_2 gap could serve as a parameter to identify patients requiring hemodynamic optimization at ICU admission following surgery.	Elevated central V-A PCO_2 gap at admission in the postoperative ICU was significantly associated with increased postoperative complications.
Siuba et al. (2023) [42]	186 patients with pulmonary hypertension.	To test if V-A PCO_2 gap is a reliable surrogate for Fick cardiac index (CI) in patients with pulmonary hypertension.	V-A PCO_2 gap was moderately correlated with Fick CI. Central venous PCO_2 overestimated mixed venous values.
Yuriditsky et al. (2024) [43]	107 patients with pulmonary embolism (PE) undergoing mechanical thrombectomy.	To describe V-A PCO_2 gap as a surrogate of perfusion adequacy, among patients with acute PE undergoing mechanical thrombectomy.	The V-A PCO_2 gap was abnormal in nearly 50 % of patients and inversely related to the CI.

V-A PCO_2 gap = The venous-to-arterial carbon dioxide tension difference, CI = cardiac index, CO = cardiac output, ICU = intensive care unit.

(2015) who also demonstrated increased levels of proinflammatory cytokines with elevated V-A PCO_2 gap [40]. Robin et al. (2015) evaluated the clinical relevance of the V-A PCO_2 gap in 115 high-risk surgical patients admitted to postoperative care at the intensive care unit (ICU). The study found that a high V-A PCO_2 gap at admission in the post-operative ICU was significantly associated with increased postoperative complications showing superior diagnostic performances compared with lactate levels and troponin [41]. Finally, associations between the V-A PCO_2 gap and macrocirculatory function have been established in pulmonary hypertension [42] and pulmonary embolism [43].

To sum up, utilization of the V-A PCO_2 gap have been promising in cardiac patients. Elevated V-A PCO_2 gap levels have been associated with adverse outcomes, including increased mortality in CS patients, prolonged ventilation needs, and hospital stays in cardiac surgery patients. On the other hand, lower values have been predictive of positive outcomes in patients treated with MCS and following surgery. While its use in septic shock is well-established, this emerging evidence suggests a potential clinical relevance in managing CS. Still, however, the current evidence in CS is sparse, somewhat conflicting, and based on smaller single center studies.

5. Future directions

Despite the existence of CS guidelines, risk-stratisfying patients with CS remains a major unresolved challenge, and the SCAI criteria lacks uniform criteria defining each stage [44]. Based on the existing evidence incorporating the V-A PCO_2 gap into contemporary clinical practice holds potential to represent a reasonable addition to the contemporary CS guidelines [45] for the characterization, risk stratification, and treatment of CS. Notably, the majority of the studies are small scale single center studies. Hence, larger scaled studies are warranted in order to fully clarify and justify the use of V-A PCO_2 in CS monitoring. Notably, CS etiologies may vary significantly, and the usability of the V-A PCO_2 gap in the monitoring and prognostication might also vary between these etiologies. Furthermore, the role of V-A PCO_2 gap in mixed CS, where various elements of cardiac dysfunction, etiologies, volume status, inflammation and vascular resistance are present have yet to be explored [46].

Nonetheless, the findings in the evaluated studies are intriguing and points to that incorporation of the V-A PCO_2 gap in contemporary guidelines may improve prognostication of treatment and even survival. Today, the SCAI shock stages are primarily based on clinical, hemodynamic, and biochemical markers such as CO, lactate levels, and blood pressure. However, these markers focus largely on macrocirculatory function. This introduces a risk of missing the nuanced dynamics of microcirculatory perfusion and tissue oxygenation. In this context the V-A PCO_2 gap may provide additional insight by serving as an indirect marker of tissue hypoxia and CO_2 clearance, potentially capturing early signs of microcirculatory failure that might be missed by standard measures [23]. Notably, complementing lactate assessment with central venous V-A PCO_2 gap during early stages of sepsis resuscitation leads to improved identification of patients with risk of adverse outcomes [47,48]. This points to that integration of V-A PCO_2 gap in existing guidelines with already used parameters may improve risk stratification and clinical patient outcomes. The V-A PCO_2 gap may provide more tailored treatment approaches. In current practice, restoration of CO and blood pressure is the primary focus of treatment in CS, often by inotropes, vasopressors, or MCS devices like Impella or VA ECMO [1–4]. However, these interventions do not always lead to improved outcomes, as macrocirculatory normalization does not guarantee tissue-level recovery [11,12]. Monitoring the V-A PCO_2 gap could guide clinicians in optimizing therapies aimed at restoring microcirculatory perfusion [12,23]. For instance, in cases where the V-A PCO_2 gap remains elevated despite normalized CO, clinicians might reconsider vasopressor strategies or escalate MCS support earlier to improve microcirculatory function. Regardless, however, further research is warrented to understand and address the pitfalls in obtaining and interpretation of V-A PCO_2 gap and factors able to influence its accuracy and reliability in CS [50].

Ultimately, integrating the V-A PCO_2 gap into CS staging and treatment protocols could lead to a more comprehensive assessment of CS, focusing not just on restoring macro-level circulatory function but also on ensuring adequate tissue perfusion. This may hold potential to introduce more individualized care plans, potentially improving outcomes by targeting both cardiac performance and tissue oxygenation in tandem.

CRediT authorship contribution statement

Oskar Kjærgaard Hørsdal: Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Resources, Project administration, Methodology, Investigation, Conceptualization.

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Declaration of competing interest

Nothing to declare.

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