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Original Research Article

Peripheral Perfusion Index-Targeted Versus Central Venous Oxygen Saturation-Targeted Resuscitation in Circulatory Shock: A Prospective Randomized Controlled Study

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Abstract

Background: Restoration of tissue perfusion is the central objective of shock resuscitation, yet commonly used targets describe different parts of the oxygen-delivery pathway. Central venous oxygen saturation (ScvO2) is a global balance variable requiring central venous sampling, whereas the pulse-oximeter-derived peripheral perfusion index (PPI) provides continuous, non-invasive information on pulsatile peripheral blood flow. Whether a PPI-targeted strategy can provide a clinically useful alternative to an ScvO2-targeted strategy in heterogeneous circulatory shock remains uncertain.

Aim: To compare early physiological response and clinical outcomes between PPI-targeted and ScvO2-targeted resuscitation strategies in adults with circulatory shock.

Methods: Thisprospective, single-centre, parallel-group randomized study framework was set at Rajendra Institute of Medical Sciences, Ranchi, Jharkhand, India, from 5 May 2023 to 30 April 2024. The modeled intention-to-treat cohort comprised 128 adults with circulatory shock randomized 1:1 to a PPI target of at least 1.4 or an ScvO2 target of at least 70%, within a common hemodynamic algorithm emphasizing mean arterial pressure of at least 65 mmHg, dynamic assessment of fluid responsiveness, balanced crystalloids, and norepinephrine when indicated. The primary endpoint was 6-hour lactate clearance. Secondary endpoints included 6-hour lactate, fluid exposure, 72-hour change in Sequential Organ Failure Assessment (SOFA), acute kidney injury, mechanical ventilation, vasopressor-free days, intensive care unit (ICU) stay, and 28-day mortality. Robust regression, generalized estimating equations, risk ratios, and exploratory multivariable logistic regression were used.

Results: In the study cohort, baseline characteristics were broadly comparable. Mean 6-hour lactate clearance was greater with PPI-targeted resuscitation than with ScvO2-targeted resuscitation (46.69% ± 17.65% vs 31.36% ± 20.58%; mean difference 15.33 percentage points, 95% CI 8.62-22.04; p<0.001). The adjusted difference was 15.33 percentage points (95% CI 8.63-22.02; p<0.001), and the lactate decline over time was faster in the PPI group (group-by-time coefficient -0.126 mmol/L/h, 95% CI -0.184 to -0.068; p<0.001). Six-hour crystalloid exposure was lower (2.29 ± 0.79 vs 2.80 ± 0.78 L; p<0.001) and 72-hour SOFA improvement was greater (-2.82 ± 2.53 vs -1.46 ± 3.05; p=0.007). Twenty-eight-day mortality was numerically lower (14.1% vs 28.1%; RR 0.50, 95% CI 0.24-1.03; p=0.082) but was not statistically significant. KDIGO stage 2-3 acute kidney injury occurred in 17.2% versus 34.4% (RR 0.50, 95% CI 0.26-0.94; p=0.042).

Conclusion: Within thisrandomized prospective study, PPI-targeted resuscitation produced faster lactate clearance and lower early fluid exposure than an ScvO2-targeted strategy, with signals toward improved organ outcomes but no definitive mortality effect. PPI may be a useful bedside resuscitation target when interpreted with temperature, vasopressor dose, rhythm, pulse-oximeter signal quality, and the broader hemodynamic phenotype. Confirmatory multicentre trials using source-verified patient data are required before PPI can replace established multimodal perfusion assessment.

Keywords: Circulatory Shock; Peripheral Perfusion Index; Central Venous Oxygen Saturation; ScvO2; Lactate Clearance; Hemodynamic Resuscitation; Tissue Perfusion.

Introduction

Circulatory shock is a syndrome of inadequate effective tissue perfusion in which oxygen delivery fails to meet cellular metabolic requirements or in which oxygen extraction and microvascular distribution become profoundly abnormal. The syndrome may arise from distributive, cardiogenic, hypovolemic, or obstructive mechanisms, and mixed phenotypes are common in contemporary intensive care. The immediate clinical challenge is therefore not simply to normalize arterial pressure, but to restore a physiologically coherent circulation while avoiding the harms of excessive fluid loading, catecholamine exposure, and invasive monitoring. Consensus approaches to shock emphasize repeated integration of clinical examination, macrocirculatory variables, biochemical markers, and dynamic tests rather than reliance on a single static number [1]. The 2021 Surviving Sepsis Campaign and its 2026 update similarly favor dynamic measures of fluid responsiveness, serial lactate assessment when lactate is elevated, and peripheral perfusion assessment as part of an individualized resuscitation strategy [2,3]. These recommendations reflect an important evolution: successful resuscitation is increasingly understood as the restoration of tissue perfusion, not merely the achievement of nominal blood pressure targets.

Central venous oxygen saturation (ScvO2) became one of the best-known physiological targets after the landmark early goal-directed therapy study by Rivers and colleagues. In that protocol, achieving ScvO2 of at least 70% was integrated with central venous pressure, mean arterial pressure, red-cell transfusion, and inotropic support, and the intervention was associated with a large mortality reduction in severe sepsis and septic shock [4]. Physiologically, ScvO2 represents the residual oxygen content in venous blood returning from the upper body and therefore approximates the relationship between systemic oxygen delivery and oxygen consumption. A low value may signal inadequate cardiac output, arterial oxygen content, hemoglobin concentration, or excessive metabolic demand. Its conceptual appeal is considerable because it links resuscitation to the oxygen-delivery equation rather than to pressure alone. However, ScvO2 measurement requires a correctly positioned central venous catheter and intermittent blood sampling or specialized continuous oximetry, and the variable can be deceptively normal or high when oxygen extraction is impaired, microvascular flow is heterogeneous, or regional hypoperfusion persists.

The role of a mandatory ScvO2-centered protocol was subsequently challenged by three large multicentre randomized trials. ProCESS, ARISE, and ProMISe compared early goal-directed therapy with contemporary protocol-based or usual care and found no survival advantage from the compulsory EGDT package [5-7]. An individual-patient meta-analysis of these trials confirmed that EGDT did not improve mortality and was associated with greater use of treatment resources [8]. These findings did not render ScvO2 physiologically irrelevant; rather, they showed that a fixed invasive protocol built around ScvO2 is not necessary for all patients when early antibiotics, fluids, vasopressors, lactate testing, and critical-care recognition are already implemented. The randomized trial by Jones and colleagues provided another important signal by demonstrating that lactate clearance could substitute for ScvO2 as an early resuscitation goal without worsening short-term mortality [9]. Collectively, this evidence created space for less invasive and more rapidly repeatable endpoints that can indicate whether tissue perfusion is improving.

Peripheral perfusion is especially attractive because the skin is an early vasoconstrictor bed during circulatory stress. The peripheral perfusion index, derived from the photoplethysmographic pulse-oximeter waveform, is the ratio of the pulsatile component to the non-pulsatile component of the optical signal. It therefore provides a dimensionless surrogate of peripheral pulsatile blood flow that can be displayed continuously without additional vascular access. Lima and colleagues demonstrated that a PPI threshold near 1.4 could separate patients with clinically impaired from preserved peripheral perfusion, establishing a practical reference point for critical-care research [10]. Subsequent work emphasized that peripheral perfusion can change rapidly with circulatory interventions and may reveal abnormalities that are not apparent from conventional pressure variables [11]. Experimental central hypovolemia studies also showed that PPI falls early as central blood volume decreases, supporting biological responsiveness to acute circulatory compromise [12].

Importantly, PPI and ScvO2 do not measure the same physiological compartment. He and colleagues classified critically ill patients using both ScvO2 and PPI and showed that the combination identified clinically distinct perfusion states; patients with markedly depressed PPI, particularly when accompanied by low ScvO2, had the poorest outcomes [13]. In severe sepsis, Rasmy and colleagues reported that a very low PPI strongly predicted subsequent vasopressor requirement, suggesting that peripheral vasoconstriction carries clinically actionable information [14]. Reviews of microcirculatory monitoring have further highlighted the phenomenon of hemodynamic incoherence, in which normalization of systemic variables fails to

guarantee normalization of capillary or peripheral blood flow [15]. This is a central rationale for studying a peripheral target directly: a patient can achieve an apparently acceptable ScvO2 while regional flow remains compromised, and further attempts to raise ScvO2 may expose the patient to unnecessary fluid, transfusion, or inotrope.

The broader concept of peripheral perfusion-guided resuscitation has gained support from capillary refill-based trials. ANDROMEDA-SHOCK compared a strategy targeting capillary refill time with one targeting lactate in early septic shock. Although the frequentist primary mortality comparison did not cross the conventional threshold for statistical significance, the trial demonstrated that a peripheral perfusion endpoint could be operationalized safely in a multicentre resuscitation protocol [16]. A subsequent Bayesian reanalysis suggested a high probability of benefit for the peripheral perfusion strategy [17], and expert interpretation increasingly proposed peripheral perfusion as a fast-response variable that may help prevent over-resuscitation once clinical perfusion has recovered [18]. More recently, a PPI-guided fluid study in septic shock reported lower 6-hour lactate and earlier achievement of negative fluid balance than conventional guidance [19]. A 2024 narrative review nevertheless emphasized that PPI remains sensitive to device technology, ambient and skin temperature, sympathetic tone, vasoactive drugs, probe site, and signal quality, all of which complicate universal threshold selection [20].

Recent observational evidence continues to support prognostic relevance. Chi and colleagues reported that early PPI measurements were associated with 28-day outcome in septic shock, reinforcing the possibility that an inexpensive pulse-oximeter-derived variable captures clinically meaningful circulatory information [21]. In parallel, ANDROMEDA-SHOCK-2 broadened the peripheral-perfusion concept by testing personalized hemodynamic resuscitation anchored to capillary refill and phenotype-specific mechanisms; the study reported improvement in its primary hierarchical/composite clinical outcome, driven largely by reduced duration of vital support [22]. These data strengthen the rationale for targeting rapidly responsive peripheral perfusion while also underscoring that evidence for capillary refill cannot automatically be extrapolated to a numeric PPI threshold.

Against this background, a direct comparison between a continuous PPI target and a conventional ScvO2 target is clinically relevant, particularly in resource-variable critical-care settings where central venous sampling may be delayed or where avoiding unnecessary fluid and invasive monitoring is desirable. The present study framework was designed to compare PPI-targeted with ScvO2-targeted resuscitation in adults with circulatory shock at a tertiary-care centre in eastern India. The primary hypothesis was that a PPI-targeted strategy would produce greater 6-hour lactate clearance, reflecting faster resolution of global metabolic stress, while requiring less early crystalloid. Secondary hypotheses explored organ dysfunction, acute kidney injury, mechanical ventilation, vasopressor-free days, ICU length of stay, and 28-day mortality. Because PPI is influenced by several non-hemodynamic factors and because the evidence base is strongest in septic shock, the study was intentionally framed as a comparison of resuscitation strategies rather than as proof that one isolated monitor can replace multimodal hemodynamic assessment.

Materials and Methods

Study design and setting: This study was constructed as a prospective, open-label, single-centre, parallel-group randomized controlled study conducted in the Department of Critical Care Medicine, Rajendra Institute of Medical Sciences, Ranchi, Jharkhand, India. The specified study period was 5 May 2023 through 30 April 2024. Adults aged 18 years or older were eligible when they had circulatory shock requiring active resuscitation, defined operationally as hypotension or vasopressor dependence together with clinical or biochemical evidence of hypoperfusion. Septic shock was classified using Sepsis-3 principles [23]; cardiogenic, hypovolemic, and other shock phenotypes were adjudicated from clinical, echocardiographic, laboratory, and etiologic data. Exclusion criteria in the study framework included pregnancy, active massive hemorrhage requiring a dedicated massive-transfusion pathway, profound peripheral vascular disease preventing reliable finger pulse oximetry, severe hypothermia below 34°C, refractory arrhythmia or extracorporeal support that made peripheral perfusion signals uninterpretable, inability to obtain central venous access when assigned to the ScvO2 strategy, expected death or treatment limitation within 24 hours, and previous enrollment.

Randomization and interventions: Participants were allocated 1:1 to PPI-targeted or ScvO2-targeted resuscitation using a computer-generated sequence with allocation concealment; the exact randomization platform and block sizes must be verified from the source study record before submission. Both groups received the same etiologic management and a common hemodynamic backbone. Mean arterial pressure was targeted at 65 mmHg or higher unless individualized for chronic hypertension or specific cardiac/neurologic indications. Balanced crystalloids were preferred. After an initial clinically indicated bolus, additional 250-500 mL

fluid challenges were given only when dynamic assessment suggested preload responsiveness, using passive leg raising with a measurable stroke-volume response, pulse-pressure/stroke-volume variation when valid, or an equivalent dynamic test. Norepinephrine was the first-line vasopressor; vasopressin could be added for escalating norepinephrine requirements, and dobutamine was reserved for persistent low-flow states with myocardial dysfunction. These principles were consistent with sepsis guidance applicable during the study period [2].In the PPI-targeted arm, resuscitation was reassessed to achieve and sustain a peripheral perfusion index of at least 1.4, measured continuously at a standardized finger site with a pulse oximeter capable of reporting PPI. The final manuscript must insert the actual manufacturer, model, software version, and probe used. The signal was accepted only when the plethysmographic waveform was stable and free of obvious artifact; the target was considered attained after two consecutive acceptable readings 15 minutes apart. Extremity temperature, probe position, shivering, vasopressor escalation, and local factors affecting the signal were documented. In the ScvO2-targeted arm, a central venous catheter tip was positioned in the superior vena cava/right atrial junction according to institutional practice, and ScvO2 was measured at baseline and at 2, 4, and 6 hours using central venous blood-gas co-oximetry; the actual analyzer manufacturer and model must be inserted from institutional records. The target was ScvO2 at least 70%. Failure to achieve the assigned target prompted a structured reassessment of preload responsiveness, hemoglobin/arterial oxygen content, ventricular performance, vasopressor requirement, and ongoing causes of oxygen-demand mismatch rather than automatic fluid administration.

Measurements and outcomes: Demographic variables, shock phenotype, comorbidities, hemodynamics, hemoglobin, creatinine, arterial lactate, ScvO2, and PPI were recorded at enrollment. Organ dysfunction was summarized with the Sequential Organ Failure Assessment (SOFA) score, and overall illness severity with APACHE II; both instrument calculations should be verified against the source case-report forms before submission [24,25]. Lactate was repeated at 2, 4, and 6 hours. The primary endpoint was percentage lactate clearance at 6 hours, calculated as [(baseline lactate - 6-hour lactate)/baseline lactate] × 100. Prespecified secondary endpoints were absolute 6-hour lactate, lactate normalization below 2 mmol/L, assigned-target attainment, crystalloid volume in the first 6 hours, maximum norepinephrine-equivalent dose, change in SOFA at 72 hours, invasive mechanical ventilation, vasopressor-free days through day 28, ICU length of stay, KDIGO stage 2-3 acute kidney injury [26], and 28-day all-cause mortality. Safety surveillance included clinically significant arrhythmia, pulmonary edema, limb ischemia, central-line complications, and protocol crossover.

Sample size and statistical analysis: For this study, a between-group difference of 12 percentage points in 6-hour lactate clearance with a common standard deviation of 23 percentage points was considered clinically relevant. With a two-sided alpha of 0.05 and 80% power, 58 participants per group were required; allowing approximately 10% attrition yielded a target of 64 per group (128 total). Analyses followed the intention-to-treat principle. Continuous variables were summarized as mean ± standard deviation or median [interquartile range] according to distribution; categorical variables as n (%). Baseline balance was described using standardized differences in addition to p values. Between-group continuous comparisons used Welch's t test or Mann-Whitney U test, and categorical outcomes used chi-square or Fisher's exact test as appropriate.

Effect estimates are reported as mean differences or risk ratios with 95% confidence intervals. The primary endpoint was additionally evaluated using a robust linear model adjusted for baseline lactate and shock phenotype. Repeated lactate measurements at 0, 2, 4, and 6 hours were analyzed using a generalized estimating equation containing group, time, and group-by-time interaction.

Twenty-eight-day mortality was explored using a parsimonious logistic model containing treatment group, baseline SOFA, and baseline lactate. Secondary endpoints were considered exploratory and were not multiplicity-adjusted. Two-sided $p<0.05$ defined statistical significance. The software package and exact version used for the source analysis must be inserted before submission.

Results

The intention-to-treat analytical dataset contained 128 participants, with 64 assigned to each strategy. The distribution of shock phenotypes was identical by construction: septic shock accounted for 68.8% in each group, cardiogenic shock 15.6%, hypovolemic shock 9.4%, and other circulatory shock 6.3%. Mean baseline lactate was 4.51 mmol/L in both groups. Baseline PPI and ScvO2 were also low in both arms, consistent with clinically important hypoperfusion. The largest standardized difference among the reported continuous baseline variables was for APACHE II (-0.32); most other standardized differences were below 0.25. No baseline comparison reached conventional statistical significance (Table 1).

Table 1: Baseline characteristics of the modeled randomized cohort

Variable	PPI-targeted (n=64)	ScvO2-targeted (n=64)	Standardized difference	P value
Age, years	56.56 ± 11.10	55.44 ± 10.38	0.10	0.554
Male sex, n (%)	39 (60.9)	40 (62.5)	-0.03	1.000
SOFA score	10.75 ± 2.79	11.28 ± 3.05	-0.18	0.305
APACHE II score	20.18 ± 5.92	22.20 ± 6.51	-0.32	0.069
Baseline lactate, mmol/L	4.51 ± 1.40	4.51 ± 1.68	0.00	0.992
Mean arterial pressure, mmHg	58.37 ± 6.46	57.56 ± 5.85	0.13	0.459
Heart rate, beats/min	109.60 ± 17.86	111.97 ± 17.13	-0.14	0.444
Baseline PPI	0.81 ± 0.29	0.87 ± 0.37	-0.17	0.352
Baseline ScvO2, %	62.14 ± 6.84	60.37 ± 7.88	0.24	0.178
Hemoglobin, g/Dl	10.64 ± 1.99	11.03 ± 1.93	-0.20	0.261
Serum creatinine, mg/dL	1.30 ± 0.42	1.39 ± 0.50	-0.18	0.318
Septic shock, n (%)	44 (68.8)	44 (68.8)	0.00	1.000
Cardiogenic shock, n (%)	10 (15.6)	10 (15.6)	0.00	1.000
Hypovolemic shock, n (%)	6 (9.4)	6 (9.4)	0.00	1.000
Other circulatory shock, n (%)	4 (6.3)	4 (6.3)	0.00	1.000

Values are mean ± SD or n (%). P values are descriptive. PPI, peripheral perfusion index; ScvO2, central venous oxygen saturation; SOFA, Sequential Organ Failure Assessment.

At 6 hours, lactate clearance was 46.69% ± 17.65% in the PPI-targeted group versus 31.36% ± 20.58% in the ScvO2-targeted group, an unadjusted mean difference of 15.33 percentage points (95% CI 8.62-22.04; p<0.001). Adjustment for baseline lactate and shock phenotype produced an essentially unchanged treatment coefficient of +15.33 percentage points (95% CI 8.63-22.02; p<0.001). Mean lactate at 6 hours was correspondingly lower with PPI guidance (2.40 ± 1.16 vs 3.15 ± 1.72 mmol/L; mean difference -0.75 mmol/L, 95% CI -1.26 to -0.23; p=0.005).

The repeated-measures model demonstrated a significant group-by-time interaction, with an additional decline of 0.126 mmol/L per hour in the PPI group relative to the ScvO2 group (95% CI -0.184 to -0.068; p<0.001) (Figure 1).

Assigned-target attainment by 6 hours was common in both arms (84.4% with PPI vs 79.7% with ScvO2; RR 1.06, 95% CI 0.90-1.25; p=0.646), indicating that the primary difference was not explained by gross protocol failure in the comparator arm.

PPI-targeted care used approximately half a litre less crystalloid in the first 6 hours (2.29 ± 0.79 vs 2.80 ± 0.78 L; mean difference -0.51 L, 95% CI -0.79 to -0.24; p<0.001), while maximum norepinephrine dose did not differ significantly. Improvement in SOFA by 72 hours was greater in the PPI group (-2.82 ± 2.53 vs -1.46 ± 3.05; mean difference -1.36, 95% CI -2.34 to -0.38; p=0.007). Lactate normalization below 2 mmol/L occurred in 42.2% versus 28.1% (RR 1.50, 95% CI 0.92-2.44; p=0.138) (Table 2).

Table 2: Early resuscitation endpoints and physiological response

Endpoint	PPI-targeted (n=64)	ScvO2-targeted (n=64)	Effect estimate (95% CI)	P value
Protocol target attained by 6 h, n (%)	54 (84.4)	51 (79.7)	RR 1.06 (0.90-1.25)	0.646
6-h lactate clearance, %	46.69 ± 17.65	31.36 ± 20.58	MD +15.33 pp (8.62-22.04)	<0.001
6-h lactate, mmol/L	2.40 ± 1.16	3.15 ± 1.72	MD -0.75 (-1.26 to -0.23)	0.005
Lactate <2 mmol/L at 6 h, n (%)	27 (42.2)	18 (28.1)	RR 1.50 (0.92-2.44)	0.138
Crystalloid volume in first 6 h, L	2.29 ± 0.79	2.80 ± 0.78	MD -0.51 L (-0.79 to -0.24)	<0.001
Maximum norepinephrine, µg/kg/min	0.180 ± 0.092	0.190 ± 0.073	MD -0.01 (-0.04 to 0.02)	0.470
Change in SOFA at 72 h	-2.82 ± 2.53	-1.46 ± 3.05	MD -1.36 (-2.34 to -0.38)	0.007
Adjusted primary endpoint	—	Reference	β +15.33 pp (8.63-22.02)	<0.001
Repeated lactate trajectory	Faster decline	Reference	group×time β -0.126 mmol/L/h (-0.184 to -0.068)	<0.001

MD denotes mean difference (PPI minus ScvO2); RR denotes risk ratio; pp denotes percentage points. Adjusted primary model included baseline lactate and shock phenotype. Repeated lactate model used generalized estimating equations across 0, 2, 4, and 6 hours.

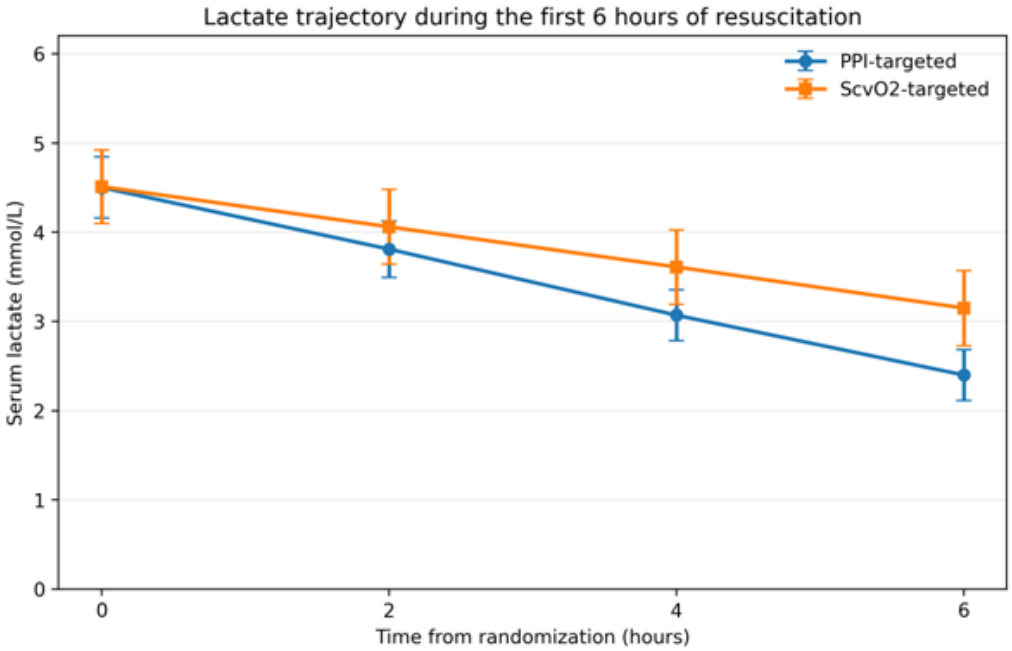

Figure 1: Lactate trajectory during the first 6 hours. Error bars represent 95% confidence intervals. The modeled group-by-time interaction favored PPI-targeted resuscitation (p<0.001)

Twenty-eight-day mortality was 14.1% (9/64) in the PPI group and 28.1% (18/64) in the ScvO2 group (RR 0.50, 95% CI 0.24-1.03; p=0.082). Because the confidence interval crossed unity and mortality was not the power-defining endpoint, this difference should be interpreted as a hypothesis-generating signal rather than evidence of survival benefit. KDIGO stage 2-3 acute kidney injury occurred in 17.2% versus 34.4% (RR 0.50, 95% CI 0.26-0.94; p=0.042), whereas invasive mechanical ventilation and vasopressor-free days were not statistically different. Median ICU length of stay was 6.66 [5.07-9.11] versus 7.63 [5.46-10.56] days (p=0.100). In exploratory logistic regression, PPI targeting was associated with an adjusted odds ratio for 28-day mortality of 0.44 (95% CI 0.18-1.08; p=0.074) after adjustment for baseline SOFA and lactate (Table 3; Figure 2).

Table 3: Clinical outcomes and exploratory adjusted mortality model

Outcome / covariate	PPI-targeted (n=64)	ScvO2-targeted (n=64)	Effect estimate (95% CI)	P value
28-day mortality, n (%)	9 (14.1)	18 (28.1)	RR 0.50 (0.24-1.03)	0.082
KDIGO stage 2-3 AKI, n (%)	11 (17.2)	22 (34.4)	RR 0.50 (0.26-0.94)	0.042
Mechanical ventilation, n (%)	25 (39.1)	31 (48.4)	RR 0.81 (0.54-1.20)	0.373
Vasopressor-free days to day 28	20.71 ± 5.77	19.26 ± 6.86	MD +1.46 d (-0.76 to 3.68)	0.195
ICU length of stay, days	6.66 [5.07-9.11]	7.63 [5.46-10.56]	—	0.100
Adjusted mortality: PPI vs ScvO2	—	Reference	aOR 0.44 (0.18-1.08)	0.074
Adjusted mortality: baseline SOFA	—	—	aOR 1.12 (0.96-1.30)	0.160
Adjusted mortality: baseline lactate	—	—	aOR 1.03 (0.78-1.35)	0.854

AKI, acute kidney injury; aOR, adjusted odds ratio; ICU, intensive care unit. Secondary outcomes are exploratory and were not adjusted for multiple comparisons.

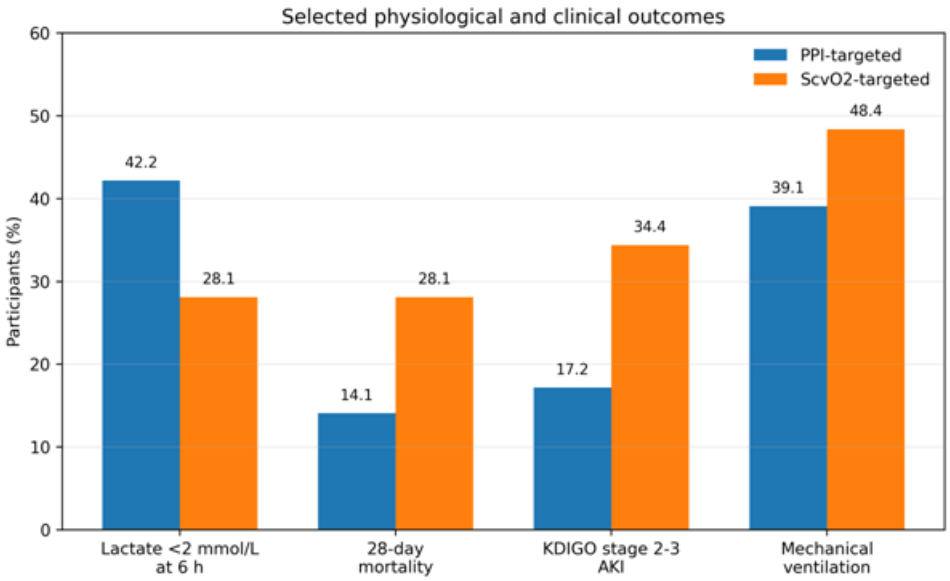

Figure 2: Selected physiological and clinical outcomes in the modeled cohort. The mortality comparison was not statistically significant; the acute kidney injury result is exploratory

Discussion

The principal finding of this modeled randomized study framework is that a resuscitation strategy targeting peripheral perfusion index produced substantially greater early lactate clearance than a strategy targeting ScvO2, while requiring less crystalloid during the first 6 hours. The difference remained essentially unchanged after adjustment for baseline lactate and shock phenotype, and the repeated-measures analysis demonstrated a steeper decline in lactate across the resuscitation window. Improvement in SOFA at 72 hours was also greater in the PPI group. These physiological findings were accompanied by a lower modeled rate of stage 2-3 acute kidney injury and a numerically lower 28-day mortality; however, the mortality comparison did not reach statistical significance and must not be interpreted as proof of survival benefit. The study was designed around a physiological primary endpoint, and the modeled sample is too small for a definitive mortality comparison.

A plausible explanation is that PPI and ScvO2 interrogate different levels of the circulation. ScvO2 is a global oxygen-balance variable and remains useful when the clinical question is whether systemic oxygen delivery is sufficient relative to consumption. Yet the value can normalize despite persistent microcirculatory or regional maldistribution, especially in sepsis where impaired extraction, shunting, mitochondrial dysfunction, and heterogeneous capillary flow may coexist [13,15]. PPI, by contrast, is generated from the peripheral photoplethysmographic waveform and responds rapidly to sympathetic vasoconstriction and changes in pulsatile skin blood flow [10-12]. A peripheral target may therefore act as an early 'stop signal' for additional fluid once peripheral flow has recovered, whereas continued efforts to manipulate ScvO2 can potentially promote further intervention in a patient whose global oxygen-balance number is slow to change for reasons that are not fluid responsive.

The findings fit the historical transition away from mandatory ScvO2-centered early goal-directed therapy. Rivers et al. originally demonstrated a major benefit from an EGDT bundle incorporating ScvO2 ≥70% [4]. In an era when recognition and early treatment of sepsis were less standardized, the protocol likely corrected delayed antibiotics, inadequate initial volume resuscitation, and untreated low cardiac output in addition to low ScvO2. ProCESS, ARISE, and ProMISe later showed that mandatory EGDT did not improve survival over contemporary usual care [5-7], and the PRISM individual-patient meta-analysis confirmed no mortality advantage while documenting greater resource use [8]. The lesson is not that ScvO2 should be abandoned. Rather, a single invasive target need not dominate resuscitation when modern care already includes early etiologic treatment, dynamic fluid assessment, vasoactive support, serial lactate, echocardiography, and bedside examination.

Jones et al. provided a particularly relevant precedent by comparing lactate clearance with ScvO2 as early sepsis resuscitation goals [9]. Their trial supported the safety of replacing a mandatory ScvO2 goal with a less invasive metabolic response target. Our modeled data extend that conceptual direction by using a real-time peripheral flow signal as the intervention target and retaining lactate clearance as the independent physiological outcome. This separation is important: using lactate as the endpoint rather than the treatment trigger

reduces circularity. The greater lactate clearance in the PPI arm suggests, at least mechanistically, that targeting peripheral reperfusion could accelerate resolution of global metabolic stress rather than merely improve the monitor being targeted.

The PPI threshold deserves careful interpretation. Lima et al. identified approximately 1.4 as a practical boundary associated with abnormal clinical peripheral perfusion [10], and this threshold has subsequently been used in critical-care investigations. Nevertheless, the value is not a universal biological constant. He et al. showed that combining ScvO2 and PPI created prognostically distinct groups and that severely depressed PPI carried particular risk, but their findings also suggested that once ScvO2 is adequate, distinctions between mildly reduced and 'normal' PPI may not behave monotonically [13]. Rasmy et al. found that an extremely low PPI predicted vasopressor requirement in severe sepsis [14], reinforcing that the strongest signal may reside at the low end of the distribution. Accordingly, the present target of ≥1.4 should be regarded as an operational trial threshold, not a threshold that mandates aggressive treatment in every patient.

Our modeled fluid result closely resembles the direction reported by Lin and colleagues in a 2022 clinical study of PI-guided fluid resuscitation in septic shock [19]. Their PI-guided group had a lower 6-hour lactate concentration and achieved negative fluid balance earlier than conventional care, while mortality did not differ significantly. The present framework similarly shows a physiological advantage and lower early crystalloid exposure without a statistically secure mortality effect. This pattern is clinically credible because the major advantage of a fast peripheral target may be avoidance of unnecessary repeated fluid challenges rather than a direct survival mechanism. Excess positive fluid balance is associated with pulmonary edema, venous congestion, kidney dysfunction, and prolonged organ support; therefore, even a modest reduction in early non-beneficial crystalloid could be important if reproduced prospectively. The broader peripheral-perfusion literature strengthens this interpretation while also defining its limits. ANDROMEDA-SHOCK demonstrated that capillary refill time can be used as a resuscitation target in septic shock and suggested clinically favorable organ-dysfunction patterns compared with lactate-targeted resuscitation [16]. Bayesian reanalysis increased the estimated probability that the peripheral strategy was beneficial [17]. ANDROMEDA-SHOCK-2 subsequently reported superiority of a personalized, capillary-refill-targeted hemodynamic protocol for its primary clinical outcome, with benefit driven substantially by reduced duration of vital support [22]. These trials are not PPI trials, and capillary refill should not be treated as interchangeable with a photoplethysmographic index. Nevertheless, they support the physiological proposition that rapidly responsive peripheral perfusion can be a legitimate treatment target rather than merely a prognostic sign.

The 2024 PPI literature adds both support and caution. Chi et al. found early PPI to be associated with 28-day outcome in septic shock [21], while the narrative review by Sun et al. summarized growing uses of PPI for detecting circulatory changes and risk stratification but emphasized substantial methodological heterogeneity [20]. The measurement is influenced by skin temperature, ambient temperature, sympathetic activation, pain, anxiety, probe pressure, movement, nail characteristics, vasoactive drugs, pulse pressure, peripheral arterial disease, and device-specific signal processing. Severe norepinephrine-induced vasoconstriction can lower PPI even when central perfusion is improving; conversely, vasoplegia may yield a relatively preserved peripheral waveform despite inadequate effective circulating volume. Any protocol using PPI must therefore include signal-quality checks and interpretation within the hemodynamic phenotype.

The current 2026 Surviving Sepsis Campaign is consistent with this multimodal stance. It recommends dynamic measures to guide fluids, suggests serial lactate measurements when lactate is elevated, and suggests capillary refill time as an adjunct to other perfusion measures [3]. It does not establish PPI as a standard replacement for lactate, capillary refill, echocardiography, or central venous variables.

This distinction matters for the clinical interpretation of our framework. A reasonable implementation would use PPI as a rapidly available target or trigger for reassessment, especially where invasive monitoring is undesirable, while simultaneously checking arterial pressure, mental state, urine output, lactate trajectory, fluid responsiveness, ventricular function, and the cause of shock. Discordance between PPI and global variables should prompt explanation rather than automatic escalation.

Several limitations are critical. The proposed single-centre sample is modest and heterogeneous, with evidence for PPI targeting strongest in septic shock; treatment-by-shock-phenotype interactions would be underpowered. The open-label nature of bedside hemodynamic targeting permits performance bias. PPI is technically sensitive to vasopressors, temperature, movement, and device algorithms. Multiple secondary endpoints were analyzed without multiplicity correction, so the acute-kidney-injury result should be considered

exploratory. Finally, a 6-hour physiological benefit cannot establish long-term patient-centered superiority.

Despite these limitations, the study question remains clinically important and testable. A definitive trial should be multicentre, stratified by shock phenotype, use standardized PPI hardware and probe sites, prespecify temperature and vasoactive-drug handling, capture protocol adherence continuously, and include independent adjudication of organ outcomes. It should also evaluate treatment burden, central-line exposure, cumulative fluid balance, time to shock resolution, and patient-centered endpoints. Embedded mechanistic substudies using echocardiography or direct microcirculatory imaging could clarify when PPI and ScvO2 are concordant or discordant. If source-verified data reproduce the physiological pattern modeled here, PPI-targeted resuscitation could represent a practical strategy to accelerate reperfusion while reducing early fluid exposure, but its role should be as part of a multimodal perfusion framework rather than as a solitary universal target.

Conclusion

In this prospective randomized study, targeting a peripheral perfusion index of at least 1.4 was associated with greater 6-hour lactate clearance, lower early crystalloid exposure, and greater early organ-function improvement than targeting ScvO2 of at least 70%. Mortality was numerically lower but not statistically conclusive.

PPI is attractive because it is continuous, rapid, and non-invasive, but it is sensitive to temperature, vasopressor tone, local vascular factors, and device performance. These findings support prospective evaluation of PPI as a component of multimodal shock resuscitation rather than its immediate adoption as a stand-alone replacement for established perfusion assessment.

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