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RAPID IL-6 REDUCTION AS A POTENTIAL PHENOTYPE FOR EARLY HEMODYNAMIC IMPROVEMENT DURING COMBINED OXIRIS AND HA330 HEMOADSORPTION IN SEPTIC SHOCK

Le Duc Nhan[1*], Hoang Huu Hieu[1], Pham Minh An[1], Doan Hieu Trung[2]

[1]*Department of Intensive Care and Toxicology, Da Nang Hospital - Da Nang, Vietnam*
[2]*Department of Geriatrics, Da Nang Hospital - Da Nang, Vietnam*

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ABSTRACT

Objective: To describe early hemodynamic, metabolic, inflammatory, and organ dysfunction trajectories during the first 48 hours of combined oXiris-HA330 hemoadsorption in septic shock patients requiring continuous renal replacement therapy (CRRT), and to explore whether rapid interleukin-6 (IL-6) reduction may identify a potential responder phenotype.

Subjects and Methods: This prospective single-center observational study included 31 adult patients with septic shock requiring CRRT who received combined oXiris-HA330 hemoadsorption. Clinical and laboratory variables were collected at baseline, 24 hours, and 48 hours after treatment initiation. Rapid IL-6 response was defined as a ≥50% reduction at 24 hours compared with baseline.

Results: Thirty-one patients with septic shock requiring CRRT received combined oXiris-HA330 hemoadsorption. During the first 48 hours, mean arterial pressure increased, while vasoactive-inotropic score decreased significantly. Lactate, base excess, IL-6, and procalcitonin also improved over time (all $p < 0.01$). Patients with rapid IL-6 reduction were more likely to receive treatment within 12 hours after septic shock diagnosis (61.1% vs. 23.1%, $p = 0.036$) and showed lower vasoactive requirements and lower observed 28-day mortality than non-responders (5.6% vs. 69.2%, $p < 0.001$).

Conclusion: Combined oXiris-HA330 hemoadsorption was associated with favorable early hemodynamic and inflammatory trajectories in septic shock patients requiring CRRT. Rapid IL-6 reduction may represent a potential biological responder phenotype associated with more favorable clinical trajectories. These exploratory findings require validation in larger controlled studies.

Keywords: Septic shock; CRRT; blood purification; cytokine adsorption; oXiris membrane; HA330 hemoadsorption.

1. INTRODUCTION

Septic shock remains a major challenge in intensive care units, characterized by high mortality, refractory hemodynamic instability, dysregulated inflammation, endothelial dysfunction, microcirculatory impairment, and multiple organ dysfunction [1]. Extracorporeal blood purification has been investigated as an adjunctive strategy in septic shock, particularly in patients with hyperinflammation and organ failure requiring CRRT. The oXiris membrane is a modified AN69-based hemofilter that combines renal support, endotoxin removal, and cytokine adsorption, whereas the HA330 resin cartridge provides additional adsorptive capacity for medium-sized inflammatory mediators, including pro-inflammatory cytokines [2,3]. Therefore, combining oXiris with HA330 may offer complementary mechanisms, with oXiris providing CRRT and endotoxin adsorption and HA330 enhancing cytokine removal. However, the clinical benefit of blood purification in septic shock remains uncertain because of heterogeneity in patient selection, timing, device configuration, treatment duration, and outcome definitions. Accordingly, the 2026 Surviving Sepsis Campaign guidelines emphasize the need to identify specific phenotypes that may benefit from these interventions, including patients with endotoxin activity or inflammatory biomarker-defined profiles [4]. Clinical data on the combined use of oXiris and HA330 remain limited. It is unclear whether this combined approach is associated with early improvement in vasopressor requirement, organ dysfunction, metabolic status, and inflammatory markers during the first 24-48 hours of treatment. Therefore, this single-arm observational study evaluated early clinical and biological trajectories during the first 48 hours of combined oXiris and HA330 therapy in patients with septic shock requiring CRRT.

2. MATERIALS AND METHODS

2.1. Study design and setting

This was a prospective single-center observational longitudinal study conducted at the Department of Intensive Care and Toxicology, Da Nang Hospital, Vietnam, between January 2026 and April 2026. The study included adult patients with septic shock requiring CRRT who received combined oXiris-HA330 hemoadsorption therapy.

2.2. Study population

*Corresponding author
Email: drnhandanang@gmail.com **Phone:** (+84) xxx **Https:**//doi.org/10.52163/yhc.v67iE1.5278

Patients were eligible for inclusion if they: (1) were aged ≥18 years; (2) met the Sepsis-3 criteria for septic shock; (3) required CRRT and (4) initiated combined oXiris-HA330 therapy within 24 hours of septic shock diagnosis. Septic shock was defined as suspected or confirmed infection requiring vasopressors to maintain a mean arterial pressure (MAP) ≥65 mmHg and a serum lactate level >2 mmol/L despite adequate fluid resuscitation. Exclusion criteria included shock primarily due to non-septic causes, initiation of combined therapy >24 hours after septic shock diagnosis; incomplete baseline or 24-hour follow-up data; or unavailable 28-day survival status. The decision to initiate CRRT and combined hemoadsorption was made by the attending intensivists according to clinical judgment and institutional practice.

2.3. Sample size

All consecutive eligible patients with complete data during the study period were included. Based on precision estimation, 30 patients would allow estimation of a 50% rapid hemodynamic responder rate with approximately ±18% precision at the 95% confidence level; therefore, the available sample of 31 patients was considered acceptable for this exploratory study.

2.4. Hemoadsorption and CRRT protocol

CRRT was performed using the Prismaflex system (Baxter, USA). The oXiris membrane served as the primary hemofilter, with the HA330 cartridge connected in series before the oXiris membrane within the extracorporeal circuit. Blood flow was titrated based on hemodynamic tolerance and circuit performance, with a prescribed CRRT dose typically targeted at 30-35 mL/kg/h. Anticoagulation, using systemic heparin, was administered unless contraindicated.

During the initial 48 hours, patients underwent two sessions of combined oXiris-HA330 therapy. Each HA330 session lasted approximately 240-360 minutes. Upon completion of each HA330 session, the cartridge was removed, while CRRT continued using the oXiris membrane. All patients received standard-of-care sepsis management.

2.5. Data collection and variables

Baseline data (T0) included demographics, comorbidities, infection source, and APACHE II score. Hemodynamic variables, including MAP, heart rate, vasopressor doses, and Vasoactive-Inotropic Score (VIS), metabolic variables and inflammatory markers were recorded. Clinical and laboratory data were collected at three predefined time points. (T0): Immediately before initiation of the first combined oXiris-HA330 hemoadsorption session. (T24) and (T48) defined as 24 and 48 hours after initiation of the first combined hemoadsorption session, respectively. Rapid IL-6 response was defined as a ≥50% reduction in IL-6 at T24 compared with T0. Early initiation was defined as therapy starting within 12 hours of septic shock diagnosis.

2.6. Outcomes

The primary outcome was the trajectory of hemodynamic, metabolic, inflammatory, and organ dysfunction variables during the first 48 hours after combined therapy.

Secondary exploratory outcomes included: Comparison between rapid IL-6 responders and non-responders, early hemodynamic recovery and observed 28-day mortality.

2.7. Statistical analysis

Statistical analysis was performed using SPSS version 27.0. Continuous variables were expressed as mean ± standard deviation (SD) or median (interquartile range [IQR]) according to data distribution assessed using the Shapiro-Wilk test. Categorical variables were expressed as frequencies and percentages. Changes over time were analyzed using repeated-measures ANOVA or the Friedman test, as appropriate. Comparisons between groups were performed using the Student's t-test, Mann-Whitney U test, chi-square test, or Fisher's exact test where appropriate. A two-sided p-value <0.05 was considered statistically significant.

2.8. Ethical considerations

The study was approved by the Institutional Ethics Committee of Da Nang Hospital (Approval No. 1309/BVĐN-HĐĐĐ, May 8, 2026) and was conducted in accordance with the principles of the Declaration of Helsinki. All patient data were anonymized to ensure confidentiality.

3. RESULTS

3.1. Baseline characteristics of the study population

A total of 31 patients with septic shock receiving combined oXiris-HA330 hemoadsorption were included in the analysis. Compared with survivors, non-survivors had significantly higher baseline APACHE II scores, whereas other baseline demographic, clinical, hemodynamic, and inflammatory variables were generally comparable between groups (Table 1).

Table 1. Baseline Clinical Characteristics of Patients with Septic Shock Treated with Combined oXiris and HA330 Hemoadsorption

Variable	Overall n = 31	Survivors n =21	Non-survivors n =10	p-value
Demographic characteristics				
Age (years)	73.0 (23.0)	72 (24)	75.0 (19.0)	0.735
Male sex, n(%)	16 (51.6)	9 (42.9)	7 (70.0)	0.252
Comorbidities				
Diabetes mellitus, n(%)	9 (29.0)	5 (23.8)	4 (40.0)	0.417
Hypertension, n(%)	11 (35.5)	7 (33.3)	4 (40.0)	1.000
Coronary disease, n(%)	5 (16.1)	2 (9.5)	3 (30.0)	0.296
Chronic kidney disease, n(%)	5 (16.1)	3 (14.3)	2 (20.0)	1.000
Cancer, n(%)	7 (22.6)	4 (19.0)	3 (30.0)	0.652
Source of infection				
Pneumonia, n(%)	9 (29.0)	6 (28.6)	3 (30.0)	
Intra-abdominal infection, n(%)	15 (48.4)	10 (47.6)	5 (50.0)	
Urinary tract infection, n(%)	4 (12.9)	3 (14.3)	1 (10.0)	
Skin/ soft tissue infection, n(%)	1 (3.2)	0 (0.0)	1 (10.0)	

Variable	Overall n = 31	Survivors n =21	Non-survivors n =10	p-value
Unknown source, n(%)	2 (6.5)	2 (9.5)	0 (0.0)	
Positive culture, n(%)	15 (48.4)	11 (52.4)	4 (40.0)	
Severity of illness at baseline				
APACHE II score	20.3±7.5	18.3±6.2	24.7±8.4	0.025
Lactate, mmol/L	4.9 (4.4)	4.9 (4.1)	5.5 (5.9)	0.983
IL-6, pg/mL	1246 (4584.0)	1180 (3500.0)	1409 (4627.3)	0.603
Procalcitonin, ng/mL	34.7 (88.4)	41.8 (85.8)	29.1 (94.1)	0.492
Ferritin, ng/mL	1680 (2523.0)	1810 (2167.0)	1104 (3894.0)	0.546
Heart rate, bpm	99.6 (20.7)	100.2 (19.6)	98.5 (23.7)	0.831
Mean arterial pressure, mmHg	71.5 (12.0)	71.9 (11.6)	70.7 (13.5)	0.792
VIS, points	35.8 (62.0)	35.8 (54.9)	33.7 (146.1)	0.735
Mechanical ventilation, n(%)	23 (74.2)	15 (71.4)	8 (80.0)	1.000

APACHE II: Acute Physiology and Chronic Health Evaluation II, IL-6: Interleukin-6, VIS: Vasoactive-Inotropic Score, N/A: no tested.

3.2. Early changes during the first 48 hours after combined oXiris-HA330 therapy

During the first 48 hours (Table 2), vasopressor requirement decreased progressively, while MAP increased over time. Lactate levels and base excess improved significantly, suggesting partial reversal of tissue hypoperfusion and metabolic acidosis. Inflammatory markers also declined early after therapy. IL-6 showed a marked reduction from baseline to 24 and 48 hours, and procalcitonin decreased significantly during the same period. Overall physiological severity improved, with a significant reduction in APACHE II score by 48 hours. In contrast, platelet count decreased significantly during follow-up.

Table 2. Changes in Hemodynamic, Metabolic, and Organ Dysfunction Parameters During the First 48 Hours of Combined HA330 and oXiris Treatment

Variable	T0	T24	T48	Overall p-value
Hemodynamic parameters				
Heart rate, bpm	99.2±21.3	92.3±18.0	92.5±18.7	0.082
MAP, mmHg	71.1±12.1	75.6±11.4	78.9±18.2	0.030
VIS	36.2 (72.4)	34.8 (49.5)	18.4 (59.5)	<0.001
Metabolic parameters				
Lactate, mmol/L	4.8 (4.9)	3.6 (4.0)	2.8 (3.1)	0.004
BE, mmol/L	-7.7 (7.2)	-4.6 (4.9)	-1.6 (5.9)	<0.001
Albumin, g/L	27.8 (4.8)	26.9 (4.6)	27.5 (4.0)	0.449
Inflammatory parameters				
IL-6, pg/mL	1220 (4577)	243.5 (628)	177.0 (904.4)	<0.001
Procalcitonin, ng/mL	39.6 (80.8)	31.2 (82.2)	19.3 (50.7)	<0.001
Ferritin, ng/mL	1721 (3161)	1692 (4163)	1454 (5140)	0.576
Organ dysfunction				
Platelets, G/L	117.6±68.4	77.0±47.3	76.3±41.8	<0.001
PaO_2/FiO_2	220.3±109.1	270.9±102.5	273.8±130.6	0.071
Bilirubin total, µmol/L	24.8 (36.4)	22. (32.8)	20.1 (49.4)	0.430
APACHE II score	20.3 (7.5)		13.0 (8.0)	0.003

APACHE II: Acute Physiology and Chronic Health Evaluation II, BE: Base Excess, IL-6: Interleukin-6, MAP: Mean Arterial Pressure, VIS: Vasoactive-Inotropic Score

3.3. Rapid IL-6 response phenotype

Patients with rapid IL-6 reduction were more likely to have received combined oXiris-HA330 therapy within 12 hours after septic shock diagnosis. Baseline APACHE II score, IL-6, VIS, and lactate were not significantly different between groups, although APACHE II score tended to be lower among rapid responders. Rapid IL-6 responders demonstrated more favorable early hemodynamic trajectories, with significantly lower VIS at 48 hours and greater VIS reduction compared with non-responders. APACHE II score at 48 hours was also significantly lower in rapid responders. The 28-day mortality rate was markedly lower in the rapid IL-6 responder group (Table 3).

Table 3. Comparison of Early Hemodynamic Responders and Non-Responders After Combined oXiris and HA330 Hemoadsorption Treatment

Variable	Rapid IL-6 responders n =18	Non-rapid IL-6 responders n =13	p-value
Baseline status			
APACHE II score	18.3±6.0	23.2±8.6	0.073
IL-6 at T0, pg/mL	1479.0 (4618.0)	686.0 (3381.0)	0.952

Variable	Rapid IL-6 responders n =18	Non-rapid IL-6 responders n =13	p-value
VIS at T0, points	31.8 (35.3)	38.8 (145.8)	0.378
Lactate at T0, mmol/L	4.2 (3.2)	6.9 (6.2)	0.118
Early initiation ≤12 h, n (%)	11 (61.1)	3 (23.1)	0.036
Subsequent hemodynamic response			
VIS at T24, points	16.3 (21.9)	73.3 (109.4)	0.085
VIS at T48, points	14.7 (21.7)	70.7 (187.4)	0.008
VIS reduction at T48, %	66.2 (50.3)	-55.4 (299.6)	0.01
MAP at T48, mmHg	81.0±15.0	69.5±18.1	0.053
Perfusion and organ dysfunction response			
Lactate clearance at T48, %	49.9 (49.9)	12.3 (56.2)	0.500
APACHE II at T48	11 (6)	21 (18)	0.003
Clinical outcomes			
28-day mortality, n (%)	1 (5.6)	9 (69.2)	< 0.001

APACHE II: Acute Physiology and Chronic Health Evaluation II, IL-6: Interleukin-6, MAP: Mean Arterial Pressure, VIS: Vasoactive-Inotropic Score

4. DISCUSSION

In this single-arm observational study of patients with septic shock treated with combined oXiris-HA330 hemoadsorption during CRRT, combined therapy was associated with favorable early clinical and biological trajectories during the first 48 hours. As shown in Table 2, vasopressor requirement progressively decreased while mean arterial pressure was maintained or improved, accompanied by reductions in lactate, base excess, IL-6, procalcitonin, and overall physiological severity. In addition, a rapid IL-6 reduction phenotype was observed. Patients who achieved at least 50% reduction in IL-6 at 24 hours appeared to demonstrate more favorable subsequent hemodynamic and clinical trajectories than non-responders, including lower VIS at 48 hours and lower observed 28-day mortality (Table 3). These findings suggest that early biomarker kinetics may potentially help characterize biological responsiveness to extracorporeal blood purification in selected patients with septic shock [5].

The reduction in vasoactive support is clinically relevant because persistent vasopressor dependence reflects ongoing vasoplegia and circulatory failure in septic shock. In our study, VIS progressively decreased over time while MAP remained within conventional resuscitation targets (Table 2), suggesting a potentially favorable early hemodynamic trajectory. Improvements in lactate and base excess were also observed during follow-up, which may reflect partial reversal of tissue hypoperfusion and metabolic disturbances. However, because the study lacked a control group, causality cannot be inferred. The observed changes may also have been influenced by concurrent standard care, including antimicrobial therapy, source control, fluid management, corticosteroids, vasopressor titration, and CRRT itself. Therefore, these findings should be interpreted primarily as descriptive early clinical trajectories rather than definitive evidence of treatment efficacy.

A key finding of this study was the identification of rapid IL-6 responders. IL-6 is a central inflammatory biomarker in sepsis, and rapid reduction within 24 hours may represent a potential biological response phenotype [6]. In our cohort, rapid IL-6 responders were more likely to have received combined oXiris-HA330 therapy within 12 hours after septic shock diagnosis (Table 3), suggesting that therapeutic timing may influence biological responsiveness. Patients in this subgroup also demonstrated lower vasoactive requirements and lower APACHE II scores at 48 hours. These observations may support the concept of a potential early therapeutic window during the hyperinflammatory phase of septic shock, when extracorporeal mediator removal might be more biologically plausible before inflammatory injury and vasoplegia become less reversible. Nevertheless, rapid IL-6 reduction may also identify patients with more reversible shock, more effective source control, or lower unmeasured disease burden. In addition, baseline APACHE II scores tended to be lower among rapid responders, although the difference did not reach statistical significance. Therefore, this phenotype should be considered exploratory and hypothesis-generating rather than confirmatory [7].

These findings should also be interpreted within the current uncertainty surrounding blood purification in sepsis. Contemporary guidelines do not recommend routine blood purification for all patients with sepsis or septic shock because existing evidence remains heterogeneous and of low certainty [4]. However, this does not exclude the possibility that selected phenotypes may derive benefit from extracorporeal therapies. The variability among prior studies highlights the importance of phenotype-enriched approaches based on inflammatory burden, endotoxin activity, vasopressor-refractory shock, and clear CRRT indications. In this context, the rapid IL-6 responder phenotype observed in our study may provide a potentially useful framework for future biomarker-guided investigation rather than supporting indiscriminate use of combined hemoadsorption.

The combined use of oXiris and HA330 may increase circuit complexity and raise safety concerns. Notably, platelet count decreased significantly during the first 48 hours (Table 2). Several mechanisms may contribute to thrombocytopenia during extracorporeal therapies, including circuit-related platelet activation, membrane interaction, anticoagulation exposure, sepsis-associated coagulopathy, and consumptive processes. Although the exact mechanism cannot be determined from this study, this finding underscores the importance of close monitoring of platelet count and coagulation parameters during combined oXiris-HA330 therapy.

This study has several important limitations. First, its single-arm observational design precludes causal inference, and the small sample size limits statistical power, particularly for subgroup analyses. Second, the absence of a control group receiving standard CRRT alone limits interpretation regarding the incremental effect of combined hemoadsorption. Third, confounding

by indication is likely because treatment decisions were based on clinical judgment. Co-interventions such as antibiotics, source control, corticosteroids, fluid strategy, vasopressor titration, transfusion, albumin use, and CRRT prescription may also have influenced outcomes. In addition, survivorship bias may have affected longitudinal analyses because repeated measurements were only available in patients surviving long enough for follow-up assessments. IL-6 kinetics may also be influenced by biological variability and sampling timing. Although observed 28-day mortality differed substantially between rapid IL-6 responders and non-responders (Table 3), the study was not designed to determine survival benefit. Finally, the ≥50% IL-6 reduction threshold used to define rapid responders was exploratory and should not be interpreted as a validated biomarker cutoff. Future studies should include multicenter cohorts, control groups or propensity-score matching, prespecified responder definitions, and clinically meaningful outcomes such as shock reversal, vasopressor-free days, CRRT-free days, ICU mortality, and 28-day mortality.

5. CONCLUSION

Combined oXiris-HA330 hemoadsorption was associated with favorable early hemodynamic and inflammatory trajectories in septic shock patients requiring CRRT. Rapid IL-6 reduction may represent a potential biological responder phenotype associated with more favorable clinical trajectories and lower observed 28-day mortality. Although promising, these preliminary findings remain exploratory and require validation in larger controlled studies before definitive conclusions regarding clinical efficacy can be established.

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