



CASE REPORT

RDW and Immature Granulocytes as Predictors of Hemolysis and Immune Dysfunction in VV-ECMO Patients

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ABSTRACT

Shear stress can cause severe blood trauma during venovenous (VV) extracorporeal membrane oxygenation (ECMO), primarily because of high-flow rates and contact with foreign surfaces. Therefore, optimizing the timing of oxygenator exchange is critical for mitigating these hematological complications. Herein, we present the case of a patient who required VV-ECMO for refractory acute respiratory distress syndrome and septic shock following emergency coronary artery bypass grafting. During ECMO support, C-reactive protein, red cell distribution width, and immature granulocytes served as important biomarkers. These markers facilitated early detection of filter dysfunction, guided oxygenator exchange, and enabled monitoring of shear stress. Ultimately, monitoring these biomarkers may help optimize the management of complications associated with high-flow ECMO and provide a basis for further clinical research.

Keywords: VV-ECMO, mechanical hemolysis, red cell distribution width (RDW), immature granulocytes, shear stress, disseminated intravascular coagulation (DIC)

INTRODUCTION

Left main coronary artery (LMCA) disease with active pneumonia can severely complicate cardiovascular surgery and contribute to substantial perioperative morbidity. Emergency coronary artery bypass grafting (CABG) under these critical conditions may trigger severe postoperative complications, such as refractory acute respiratory distress syndrome (ARDS) and fulminant septic shock.

For patients progressing to these advanced stages of respiratory failure, venovenous (VV) extracorporeal membrane oxygenation (VV-ECMO) emerges as a definitive life-sustaining intervention. To accommodate the hypermetabolic state associated with sepsis, the implementation of high-flow perfusion strategies may become clinically necessary. Consequently, the extracorporeal circuit subjects circulating blood elements to elevated levels of shear stress. This supraphysiologic mechanical force can induce profound hemotrauma, contributing to intravascular hemolysis, systemic immune dysfunction, and disseminated intravascular coagulation (DIC).^{1,2}

Reducing this cascade of severe complications relies heavily on the timely recognition of filter dysfunction and the appropriate

optimization of oxygenator exchanges. As conventional monitoring parameters may frequently fail to indicate imminent mechanical and immunological complications, novel prognostic markers are needed. Herein, we delineate the precipitous and ultimately fatal clinical course of a patient managed with high-flow VV-ECMO following emergency CABG. Furthermore, we critically evaluate the prognostic value of C-reactive protein (CRP), red cell distribution width (RDW), and immature granulocyte (IG) indices. By elucidating their capacity to reflect shear stress-induced hemotrauma and anticipate early oxygenator failure, we propose that these biomarkers may provide important clinical guidance in the management of high-risk extracorporeal life support (ECLS).

CASE REPORT

A 64-year-old man with a history of essential hypertension, insulin-dependent diabetes, chronic obstructive pulmonary disease (COPD), and prior coronary stenting presented with progressive chest pain. Angiographic evaluation revealed LMCA in-stent restenosis, total occlusion of the obtuse marginal branches, and 85% right coronary artery stenosis. This severe coronary disease necessitated an urgent

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surgical plan. Preoperatively, the patient developed a purulent cough, and subsequent chest computed tomography revealed active pneumonia characterized by ground-glass opacities and consolidation. Following 5 days of targeted piperacillin-tazobactam therapy, the patient's CRP level decreased from 232 mg/L to 64.1 mg/L. A multidisciplinary Heart Team consensus deemed the patient eligible for urgent surgery. Following informed consent, the patient underwent the emergency procedure.

Under general anesthesia, a median sternotomy was performed. The left internal mammary artery (LIMA) and greater saphenous vein were harvested. Following systemic heparinization, cardiopulmonary bypass (CPB) was established via ascending aortic and right atrial cannulation. The aorta was cross-clamped, and myocardial protection was maintained with intermittent antegrade blood cardioplegia. Saphenous vein grafts were anastomosed to the first diagonal, second obtuse marginal, and posterior descending artery. The LIMA was grafted to the left anterior descending artery. Proximal anastomoses were secured to the aorta. The patient was successfully weaned from CPB, and the procedure concluded without intraoperative complications.

The patient was extubated on postoperative day 1. However, his clinical course rapidly deteriorated. Serial arterial blood gas analyses revealed a progressive decline in oxygenation. Despite escalating noninvasive respiratory support with high-flow nasal cannula and continuous positive airway pressure, the patient developed severe ARDS. Worsening respiratory failure and profound sudden desaturation (SpO₂, 89%) necessitated reintubation on postoperative day 3. Ultimately, refractory hypoxemia necessitated prompt initiation of VV-ECMO support.

The ECLS course encompassed two distinct oxygenator phases. Initial support utilized a Sorin oxygenator; however, recurrent thrombus formation and severe coagulopathy necessitated frequent partial circuit exchanges at approximately 5-day intervals. These interventions were prompted by critical elevations in the transmembrane pressure (TMP) gradient (>150 mmHg), which led to sudden and unpredictable decreases in oxygenator efficiency. During this initial phase, RDW-SD values remained relatively stable (50-55 fL). To mitigate these persistent device-induced coagulation issues and enhance biocompatibility, the circuit was completely transitioned to a Maquet Quadrox system. This strategy is consistent with current literature demonstrating the advantages of the Quadrox polymethylpentene (PMP) membrane in adults, notably its reduced flow resistance, lower heparin requirements, and superior long-term stability.^{1,2}

Following clinical improvement and achievement of a PaO₂/FiO₂ ratio exceeding 200 mmHg, ECMO flow was reduced to 1 L/min to initiate a weaning trial. During awake positional therapy (16 hours prone, 8 hours supine), patient agitation culminated in unexpected self-extubation. This event rapidly compromised the patient's respiratory status by precipitating extensive atelectasis within the fragile pulmonary parenchyma. This mechanical setback, compounded by persistent ARDS progression despite aggressive medical management, led to profound respiratory deterioration. Guided by deteriorating serial arterial blood gas values, adverse laboratory markers, and mechanical circuit indicators, the transition between ECMO systems

was managed progressively. To ensure immediate stabilization during this acute decompensation, ECMO flow was promptly increased to 4.0-4.5 L/min.

Following a total ECMO support duration of approximately 2 months (8 weeks), dramatic changes were observed in laboratory parameters during the final 2 weeks of high-flow perfusion. Mechanical hemolysis occurred as shear stress caused RDW-SD values to peak at 77.7 fL. Immune dysfunction was evidenced by IG counts decreasing to 0.05 during an inflammatory storm in which CRP peaked at 206 mg/L. Finally, consumption coagulopathy resulted in a platelet count of 35,000/μL before the terminal stage.

As the patient progressed toward multiorgan failure (MOF), severe hepatic dysfunction developed. This was characterized not only by extreme hyperbilirubinemia (total bilirubin, 33.2 mg/dL) but also by a dramatic acute surge in transaminases (AST, 3450 U/L; ALT, 2800 U/L) and LDH (1850 U/L). This profound hepatocellular injury closely followed documented periods of systemic hypotension and severe low-flow perfusion. Concurrently, worsening renal function and anuria mandated the initiation of renal replacement therapy via continuous venovenous hemodiafiltration (CVVHDF) to manage fluid overload, severe electrolyte imbalances, and metabolic waste clearance. A fatal DIC state, characterized by collapse of the coagulation cascade (INR, 3.9), manifested clinically with severe perfusion and microvascular impairments. These complications resulted in significant nutritional and ischemic perfusion deficits in the extremities, uncontrollable massive mucosal hemorrhages, and melena. Finally, the patient, presenting with profound refractory metabolic acidosis (pH 6.60, lactate 10 mmol/L), suffered a bradycardic arrest and expired after failing to respond to cardiopulmonary resuscitation.

DISCUSSION

Surgical timing in the presence of critical LMCA stenosis represents a delicate balance between the risk of an acute coronary event and postoperative morbidity caused by systemic infection.³ In the literature, a CRP value below 10 mg/L or complete clinical or radiological resolution of infection is considered ideal for elective surgical interventions.⁴ However, in critical arterial stenosis with a high-risk of mortality, such as LMCA in-stent restenosis, the risk of sudden cardiac arrest increases when the stabilization process is prolonged.⁵ Therefore, the literature suggests that in the presence of unstable symptomatic LMCA stenosis, complete normalization of CRP may not be feasible, yet a substantial decline may be acceptable based on a risk-benefit analysis.^{4,6}

In our case, the decrease in CRP from 232 mg/L to 64.1 mg/L following broad-spectrum antibiotic therapy was considered laboratory evidence that the infection was under control. At this point, a multidisciplinary team comprising specialists in Cardiology, Cardiovascular Surgery, and Anesthesiology reached a consensus that delaying surgery would result in "life-threatening ischemia" and that the downward trend in CRP provided the optimal time to perform surgery.

Despite this strategic decision, the patient's progression to refractory ARDS in the postoperative period may be explained by an immunological "priming" process. Due to preoperative pneumonia,

the lung parenchyma had already been exposed to a proinflammatory stimulus. Subsequent CPB may have triggered an inflammatory cascade through complement activation and leukocyte degranulation.⁷

This pathophysiological sequence exemplifies the “second hit” phenomenon described in the literature. The baseline damage to the alveolocapillary membrane, compounded by CPB-induced systemic inflammatory response syndrome, ultimately precipitated severe, irreversible ARDS. Consequently, although the surgical risk accepted by the multidisciplinary team was necessary given the critical stenosis, the patient’s underlying COPD and preoperative pneumonia may have significantly compromised the baseline pulmonary reserve, rendering it insufficient to withstand this second insult.⁸

The gas exchange capacity of the Maquet (Quadrox-i) ECMO oxygenator system remained clinically adequate during the 14-day usage period. However, this may have created a “false sense of security” regarding the biological integrity of the circuit. Literature suggests that the long-term gas exchange performance of PMP membranes can mask microscopic fibrin deposits and protein adsorption (Vroman effect).⁹ Even without impaired gas exchange, microthrombi accumulation can narrow flow channels, increasing local turbulence and shear stress. A direct, case-specific comparison at identical high-flow rates (e.g., 4.5 L/min) was not feasible in this patient because high-flow perfusion was initiated only during the Maquet phase. However, established literature confirms that the hemolysis index is not solely dependent on the device brand but is fundamentally determined by operational parameters, including flow velocity, revolutions per minute, levitation pump design, and circuit fluid dynamics.¹⁰ In this case, while the Maquet system demonstrated superior long-term mechanical durability by maintaining stable gas exchange without requiring replacement, the

sustained high-flow rate of 4.5 L/min directly increased mechanical shear stress. This mechanical trauma is reflected by the progressive elevation in RDW and CRP values, highlighting that achieving adequate systemic oxygenation does not guarantee preservation of cellular blood components. Consequently, despite optimal clinical oxygenation, we performed a preemptive oxygenator exchange guided strictly by these adverse RDW and CRP trajectories, deliberately choosing not to wait for traditional mechanical warning signs such as overt TMP gradient alterations (Table 1).

Given the single-patient design of this case report, traditional inferential statistics (such as receiver operating characteristic curve analysis) are not applicable. Instead, a longitudinal descriptive analysis of erythrocyte kinetics was performed. We evaluated the observational trend (increase over time) in RDW-SD and RDW-CV during the 48-72-hour window preceding each critical TMP spike (>150 mmHg). Our longitudinal data revealed a consistent descriptive acceleration in erythrocyte size variation preceding macroscopic circuit occlusion. During the initial support phase, repeated oxygenator failures consistently coincided with RDW-CV peaks approaching the 18.0-19.0% threshold. Furthermore, leading up to the massive mechanical failure culminating in the Maquet transition, RDW-CV (11.1-15%) increased to an extreme value of 25.8%, and RDW-SD (37-54 fL) peaked at 77.7 fL. Although limited to a single case, this distinct temporal pattern suggests that monitoring the continuous upward trend in RDW indices may provide a useful observational window into subclinical hemotrauma, often preceding traditional pressure-based alarms (Figure 1).

The hypothesis of mechanical hemolysis was objectively supported by a triad of severe anemia, rising hemolytic markers, and compensatory erythropoiesis. The patient’s initial hemoglobin level of 13.3 g/dL

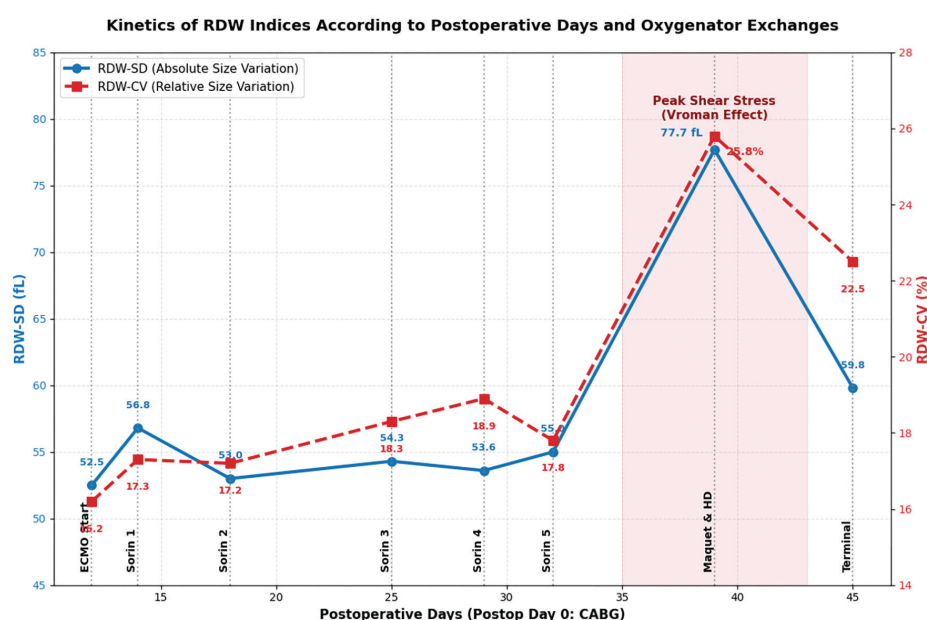


Figure 1. Longitudinal kinetics of red cell distribution width indices (RDW-SD and RDW-CV) across postoperative days, indicating the exact timing of sequential ECMO oxygenator filter exchanges

CABG: Coronary artery bypass grafting, RDW-SD: Red cell distribution width standard deviation, RDW-CV: Red cell distribution width coefficient of variation

Table 1. Kinetics of RDW indices preceding oxygenator exchanges in high-flow VV-ECMO

Clinical event (filter exchange)	Date (time window)	RDW-SD (fL)	RDW-CV (%)	Clinical and hematological observation (Δ trend)
Event 1: ECMO initiation and 1 st exchange	T (-2)	52.5	16.2	Initial mechanical exposure.
	T (-1)	53.6	15.9	Fluctuating baseline course.
	T (0)	56.8	17.3	Sudden and sharp elevation concurrent with macroscopic occlusion.
Event 2: 2 nd sorin filter exchange	T (-2)	57.5	18.1	Residual shear stress and fragmentation from the previous circuit.
	T (-1)	55.1	17.3	Slight regression of hemotrauma indices.
	T (0)	53.0	17.2	Attempted stabilization following the second exchange.
Event 3: 3 rd sorin filter exchange	T (-3)	48.1	16.4	Return to relative baseline levels.
	T (-1)	51.0	17.6	Onset of pre-occlusion mechanical stress and marker acceleration.
	T (0)	54.3	18.3	Marked upward trajectory in the 48 hours prior to exchange.
Event 4: 4 th sorin filter exchange	T (-2)	53.2	18.7	Gradual increase indicating subclinical thrombosis.
	T (-1)	54.4	19.3	Formation of a distinct peak prior to filter exchange
	T (0)	53.6	18.9	Plateauing of values concurrent with circuit failure.
Event 5: 5 th sorin filter exchange	T (-2)	54.5	18.3	Persistent mechanical damage markers.
	T (-1)	53.9	17.7	High baseline maintenance.
	T (0)	55.0	17.8	Reflection of a recurrent microthrombi shower and turbulence.
Event 6: Maquet transition (mechanical collapse)	T (-2)	69.2	22.3	Uncontrolled mechanical fragmentation.
	T (-1)	73.4	23.8	Massive schistocyte formation and pronounced Vroman effect.
	T (0)	77.7	25.8	Complete circuit collapse; the absolute peak of RDW indices.

Note: T=0 represents the day of mandatory oxygenator exchange triggered by traditional macroscopic parameters (e.g., trans-membrane pressure gradient >150 mmHg). T-1, T-2, and T-3 represent the respective days preceding the exchange event. [RDW-SD (fL37-54), RDW-CV (11.1-15%)]. RDW-SD: Red cell distribution width standard deviation, RDW-CV: Red cell distribution width coefficient of variation, VV-ECMO: Venovenous extracorporeal membrane oxygenation

progressively decreased to as low as 6.4 g/dL and 6.5 g/dL during the ECMO course, necessitating recurrent blood transfusions. Paralleling the severe shear stress, LDH values increased proportionally, rising from 450 U/L to 1850 U/L. In response to this substantial peripheral destruction, the reticulocyte count demonstrated a continuous upward trajectory, peaking at 6.8%, reflecting an intense but ultimately overwhelmed bone marrow effort to restore red cell mass.

One of the greatest challenges in sepsis management is distinguishing between “sterile inflammation” induced by mechanical destruction and true “bacterial progression”.¹¹ The biomarker paradox observed in the terminal stage of our case constitutes the pathophysiological basis for this differentiation. The CRP level, which reached 206 mg/L during the patient’s terminal phase, was initially interpreted as antibiotic failure or an active focus of infection.¹² However, the decrease in IG counts to 0.05 during this process, reflecting the bone marrow response, is consistent with the condition described in the literature as “sepsis-associated immunosuppression” (immune paralysis).

While the initial phase of the extreme inflammatory response was heavily driven by sterile tissue destruction and mechanical “shear stress” from the high-flow circuit, distinguishing this from an active infectious exacerbation is complex.¹¹ In the terminal phase, the clinical picture evolved into a mixed pathophysiological state. Serial cultures obtained during the patient’s deterioration confirmed the superimposition of secondary nosocomial infections, characterized

by the growth of opportunistic pathogens, including *Acinetobacter baumannii* in respiratory secretions and *Candida albicans* fungemia. This infectious progression was corroborated by a simultaneous marked elevation in procalcitonin levels, which peaked at 18.4 ng/mL. Therefore, the terminal surge in CRP and the erratic fluctuations in IG% underscore a catastrophic dual insult: ongoing mechanical hemotrauma compounded by fulminant hospital-acquired septic shock, ultimately leading to unrecoverable MOF (IG%, 0.16-0.62).

The 10-day systemic steroid treatment for ARDS management further influenced this biomarker profile. Glucocorticoids are known to induce neutrophilia primarily by mobilizing the margined mature neutrophil pool and stimulating granulocyte release from the bone marrow.¹³ In our case, the paradoxical suppression of the IG count despite severe systemic inflammation and exogenous steroid stimulation indicates bone marrow exhaustion, in which the hematopoietic system is no longer capable of mobilizing immature myeloid precursors into the circulation (IG%, 0.16-0.62).

This indicates that terminally elevated CRP levels reflect sterile tissue destruction caused by massive atelectrauma following self-extubation and mechanical “shear stress” from the high-flow (4.5 L/min) ECMO circuit, rather than septic progression.^{10,13} Consequently, a low IG level during steroid therapy should be recognized as a potential precursor to “immune collapse” rather than infection.

In respiratory failure developing on a COPD background, the “Awake ECMO” strategy may help avoid complications of invasive mechanical ventilation and minimize ventilator-induced diaphragmatic dysfunction. Its success, however, is directly correlated with neurocognitive stability and patient cooperation.¹⁴

In our case, deep sedation was avoided to preserve diaphragmatic integrity; a combination of an alpha-2 agonist (dexmedetomidine) and an opioid (fentanyl) was preferred. Although dexmedetomidine reduces the incidence of delirium without suppressing respiratory drive,¹⁵ it may be insufficient alone in cases of hyperactive delirium following complex cardiac surgery. The uncontrolled agitation indicated that pharmacological management could not adequately suppress the metabolic and inflammatory stress response.

Self-extubation compromised airway safety and exposed the patient to a high work of breathing and patient self-induced lung injury.¹⁶ The resulting hypoxemia necessitated an aggressive increase in ECMO flow to 4.5 L/min, initiating the cycle of mechanical hemolysis and shear stress.

Current consensus (ELSO guidelines) suggests that the “Awake ECMO” strategy should be maintained only in selected cases with complete hemodynamic stability, patient cooperation, and strict airway safety protocols.¹⁷ In ARDS cases with a high-risk of hyperactive delirium and self-injury, the goal of preserving diaphragmatic function should not supersede systemic stabilization. Based on our clinical experience, when patient agitation becomes unmanageable, transitioning to deep sedation and neuromuscular blockade may be necessary. Although this approach carries an inherent risk of diaphragmatic atrophy, protecting the lung parenchyma from self-inflicted injury and ensuring the mechanical stability of the ECMO circuit should take clinical precedence.¹⁸

The patient’s clinical course concluded with terminal consumption coagulopathy (DIC), a severe complication of ECLS described in the literature as involving a combination of contact activation and mechanical trauma. This fatal condition resulted from a complex interplay in which mechanical, hematological, and metabolic factors combined.¹⁹

The integration of a CVVHDF circuit with high-flow (4.5 L/min) VV-ECMO perfusion dramatically increased the nonbiological surface area. This triggered the Vroman effect, involving the rapid adsorption of proteins to synthetic surfaces, leading to platelet adhesion and aggregation. High-flow perfusion exacerbated this surface interaction through shear stress, resulting in both quantitative platelet depletion and functional acquired storage pool deficiency.^{16,20}

Mechanical hemolysis released large amounts of free hemoglobin into the circulation, which bound nitric oxide with high affinity and led to nitric oxide scavenging. This depletion triggered uncontrolled vasoconstriction within the microvascular bed, worsening organ hypoperfusion.²¹ Simultaneously, the release of intracellular components such as ADP and DAMPs shifted the coagulation cascade toward a prothrombotic state, reinforcing microvascular thrombosis and the subsequent development of consumption coagulopathy.²²

The concurrent liver failure, marked by acute transaminitis (AST and ALT exceeding 2,000 U/L) and bilirubin peaking at 33.2 mg/dL following prolonged hypotensive episodes, is consistent with the pathology described in the literature as “ischemic hepatitis” or “shock liver”.²³ The increase in right ventricular afterload and systemic low-flow led to profound sinusoidal congestion and centrilobular necrosis. The collapse of the liver’s synthetic capacity halted the production of vitamin K-dependent clotting factors (factors II, VII, IX, and X), causing the INR to rise to 8.0 and substantially shifting the hemostatic balance toward hemorrhage.

In conclusion, the synergy between mechanical destruction (platelet consumption), hematological toxicity (free hemoglobin), and metabolic failure (loss of hepatic synthesis) resulted in uncontrollable massive hemorrhaging across the patient’s scleral and mucosal barriers. This condition is recognized in the literature not merely as an anticoagulation error but as terminal “coagulation failure,” in which extracorporeal support, sepsis, and MOF converge.²⁴

CONCLUSION

High-flow VV-ECMO perfusion can induce substantial mechanical shear stress. In septic patients, this physical trauma may contribute to increased morbidity and mortality. Monitoring RDW and CRP trends may facilitate the early detection of mechanical hemolysis and subsequent DIC. Concurrently, a decline in IG counts may serve as an indicator of bone marrow exhaustion and immune dysfunction. Clinicians should closely evaluate these hematological parameters during increases in flow rate. In conclusion, proactive oxygenator exchanges guided by RDW and CRP trends may be considered independently of the device’s duration of use, sustained clinical oxygenation, or stable TMP parameters.

Furthermore, implementing the “Awake ECMO” strategy in patients with COPD requires strict control of agitation to maintain circuit and patient safety.

Informed Consent: Following informed consent, the patient underwent the emergency procedure.

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