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Mircea R. Mihiu

Oklahoma State University Health Science Center, Mircea.Mihu@integrisok.com

Aly El-Banayosy

Oklahoma State University Health Science Center, Aly.ElBanayosy@integrisok.com

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2022 Symposium Presentation

Systemic Inflammatory Response Syndrome and Mechanical Circulatory Support Devices

Mircea R. Mihu,¹Aly El Banayosy²

¹Specialty Critical Care, Nazih Zuhdi Transplant Institute, Integris Baptist Medical Center, Oklahoma City, Oklahoma

²Department of Medicine/Cardiology, Oklahoma State University Health Science Center, Tulsa, OK, USA

Email: Aly.ElBanayosy@integrisok.com

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Abstract

Systemic inflammatory response syndrome is an increased inflammatory state affecting the whole body. Mechanical circulatory support (MCS) is a temporary or permanent form of extracorporeal support that may have an associated complication of an exacerbated inflammatory response to the extracorporeal circuit. This brief review will focus on understanding the complex pathophysiology of inflammatory response to MCS, factors that influence the extent of the inflammatory response, the inflammatory response and outcomes as well as potential therapeutic strategies.

Keywords: mechanical circulatory support, extracorporeal life support, systemic inflammatory response syndrome

Introduction

Systemic inflammatory response syndrome (SIRS) is an exacerbated response of the human body to harmful stressors like infections, pancreatitis, burns, surgery, trauma, ischemia, reperfusion, or the presence of mechanical circulatory support devices (MCS) as well as others.¹ The current SIRS criteria are based on changes in body temperature, heart rate, respiratory rate, and white blood cell count.² MCS devices can provide circulatory support for patients with acute hemodynamic compromise as well as chronic end-stage heart failure, acute respiratory failure, or chronic respiratory failure as a bridge to lung transplantation.³ These devices include veno-arterial (V-A) and veno-venous (V-V) extracorporeal membrane oxygenation (ECMO), percutaneous right ventricular assist device (pRVAD) as well as percutaneous temporary left ventricular assist devices (pLVAD), intra-aortic balloon pump (IABP), left ventricular assist devices (LVAD) and total artificial heart (TAH).

Pathophysiology of the Inflammatory Response to Mechanical Circulatory Support Devices

Extracorporeal Membrane Oxygenation

The pathophysiology of inflammation during ECMO is extremely complex and not fully understood. The commencement of extracorporeal life support is associated with an instantaneous inflammatory response similar to systemic inflammatory response syndrome secondary to contact between a patient's blood and the foreign surfaces of the ECMO circuit. The levels of proinflammatory cytokines and complement levels increase rapidly, which results in leukocyte activation.⁴ If the inflammatory response is severe and persistent without any compensatory anti-inflammatory response,⁵ it may lead to endothelial injury and end-organ failure.

The factors implicated in the complex immune and inflammatory response to ECMO include:

- The contact system—factor XII, factor XI, prekallikrein and high-molecular-weight kininogen. The activation of these factors leads to formation of kallikrein and bradykinin, which in turn will promote coagulation and inflammation.⁴
- Intrinsic coagulation is triggered by the contact system, and extrinsic coagulation is activated as well to a lesser degree, promoting subsequent clot formation.⁴
- Platelet activation—has two critically important roles, the first one in hemostasis and the second one in triggering inflammation through the release of their granular content.⁴
- The complement system plays a critical role in the innate immune response. While its response to cardiopulmonary bypass has been described earlier in the literature,⁶ the interaction between complement activation and ECMO requires additional investigations.
- Endothelial cell activation is another key element in the inflammatory response during ECMO. The inflammatory mediators triggered in response to ECMO, lead to activation of the endothelial cells, which further exacerbates the inflammatory response by producing proinflammatory cytokines and increases the expression of adhesion molecules, leading to the increased migration of leukocytes.⁴
- Furthermore, neutrophils are also activated by the extracorporeal circuit. Upon neutrophil activation, the cells degranulate, releasing cytotoxic enzymes, which further exacerbate the inflammation leading to end-organ damage.⁷
- Cytokines play an important role in the innate immune response. Upon ECMO initiation, proinflammatory, as well as anti-inflammatory cytokines, are produced. The most studied cytokines in relationship to ECMO are TNF- α , IL-6, IL-8, and IL-10.⁴ Their precise roles require further investigations.

Indications versus Contraindications for ECMO

Recommended indications for the use of ECMO include refractory hypoxemia, use of mechanical ventilation for <7 days, risk of death greater than 50%, severe air leak syndrome, and a diagnosis of severe myocarditis or cardiogenic shock.⁴

Absolute contraindications include significant comorbidities from which a patient cannot recover. These include severe immunosuppression, sepsis with bacteremia, contraindications to systemic anticoagulation, severe multiple organ failure, severe aortic dissection, acute intracerebral hemorrhage, irreversible severe brain injury, critical congenital heart defects, chronic lung disease, and lethal chromosomal anomalies.⁴ Relative contraindications also include an age of 65 years or older, a body mass index greater than 30, prolonged ventilatory support, frailty, allosensitization with prolonged waitlist time, and limitations in vascular access.⁴ During the early phase of the COVID-19 pandemic, the Extracorporeal Life Support Organization recommended prioritizing young, previously healthy patients with only a single organ failure for ECMO support, as they may derive the maximum benefit.⁵ As clinical experience continued to evolve, these priorities were relaxed based on program experience and increased access to health care resources.

The Inflammatory Response to Ventricular Assist Devices

Heart failure patients with reduced ejection fraction have a baseline proinflammatory state secondary to myocardial infarction, cardiogenic shock, or acute or chronic systolic heart failure.

The mechanism through which VAD impacts inflammation remains to be fully understood. The two key elements involved in the body's immune response are high levels of shear stress and the contact of blood with foreign materials.⁸ Leukocytes and platelets are continuously exposed to high shear stress resulting in their activation.⁹ Published data shows that neutrophils exposed to wall shear stress greater than 25 dyne/cm², lead to structural disruption.¹⁰ Moreover, the contact of leukocytes with foreign bodies leads to protein absorption, creating either an inert surface or a highly dynamic matrix, which can further promote cellular activation and adhesion.¹¹

Factors that Influence the Inflammatory Response

The factors that influence the extent of the inflammatory response include the etiology of shock, the patient's clinical status (the degree of shock), the hemocompatibility as well as the performance of the mechanical circulatory device applied (ECMO, percutaneous LVAD or RVAD, surgically implanted VAD). Another critical factor that can influence the inflammatory response includes the trauma and potential complications associated with the device insertion.

The Inflammatory Response and Outcomes

Diakos et al. retrospectively analyzed the neutrophil-to-lymphocyte ratio (NLR) among 111 patients with cardiogenic

shock supported by V-A ECMO or pLVAD/pRVAD and found that compared to nonsurvivors, the survivors had a lower NLR (7.4 ± 0.9 vs 14.4 ± 11 ; $P < .001$). Setiadi et al. investigated Oncostatin M (OSM), a member of the IL-6 family of cytokines, as a potential biomarker to predict outcomes in 30 patients with ARDS requiring V-V ECMO support (manuscript in progress). Preliminary data showed that the percentage of pre-ECMO decannulation plasma OSM levels as compared to pre-ECMO cannulation levels was significantly lower in the recovered patients compared to expired patients.

Furthermore, OSM was also used as a potential biomarker to predict infections in patients with LVADs. A study that included 41 patients showed that elevated plasma OSM pre-LVAD implantation was associated with an increased risk of developing infections postimplantation as compared to the control.¹²

Potential Therapeutic Strategies

At this point, there is no proven therapy to mitigate an exacerbated inflammatory response. Most strategies are currently experimental and primarily target cardiopulmonary bypass. Therapies that were or are under investigation include steroids, statins, protease inhibitors, milrinone, monoclonal antibodies, mesenchymal stromal cells (animal model only), and extracorporeal cytokine absorber therapy. An interesting method is the potential removal of inflammatory factors by extracorporeal methods. In a study by Gruda et al., hemoadsorption through porous polymer bead devices reduced the levels of a broad spectrum of cytokines, pathogen-associated molecular patterns, damage-associated molecular patterns, and mycotoxins by more than 50%.¹³

Summary

The pathophysiology of the inflammatory response to MCS is extremely complex and requires further studies to better understand the interaction between the two key components: the host and the extracorporeal support. Using MCS in patients with a certain degree of inflammation or systemic inflammatory response syndrome adds to the complexity and requires additional research to better understand the patient and device interaction and to help advance the technology as well as potential therapeutics.

How do These Concepts Impact Clinical Practice?

By better understanding the complex pathophysiology of the inflammatory response to MCS, we can help to develop therapeutics, improve the current forms of extracorporeal circulatory support to minimize an exacerbated immune inflammatory response to the foreign circuits and pumps, discover inflammatory markers to help predict outcomes, and eventually provide better and safer patient care.

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