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oXiris in severe cardiogenic shock with endotoxemia: interpreting the negative findings of the CLEAN-ECMO trial

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The recent article by Ko et al., entitled "The effects of extracorporeal blood purification (oXiris®) in patients with cardiogenic shock who require VA-ECMO (CLEAN ECMO): a prospective, open-label, randomized controlled pilot study," reported that extracorporeal blood purification with the oXiris membrane did not significantly reduce endotoxin levels or improve clinical outcomes in patients with cardiogenic shock requiring veno-arterial extracorporeal membrane oxygenation (VA-ECMO) [1]. While the authors should be commended for conducting a randomized pilot trial in this challenging population, several aspects of the interpretation of the negative findings merit further discussion.

Although the study focused on cardiogenic shock associated with circulating endotoxin [1], caution is warranted when drawing parallels with endotoxic septic shock. The endotoxin activity assay (EEA) threshold at which endotoxin absorption therapies, such as polymyxin B hemoperfusion (PMX) (Toray, Japan) or the oXiris membrane (Baxter, Meyzieu, France), should be initiated in this context remains uncertain. In septic shock, an EEA value ≥ 0.6 (Spectral Medical Inc., Toronto, ON, Canada) has been proposed as a potential threshold for intervention [2, 3]. Furthermore, the endotoxin-binding capacity of a PMX cartridge is finite [4]. When EEA values exceed approximately 0.9, adsorption capacity may become saturated, potentially rendering hemoperfusion ineffective in endotoxic septic shock [4].

In the intervention group receiving oXiris in the study by Ko et al., the baseline endotoxin level was reported as 1 [1]. An EEA value of 1 corresponds roughly to 12 ng/mL of circulating endotoxin and may reflect a total endotoxin burden of approximately 150 µg in the human body, potentially exceeding the adsorption capacity of both a PMX cartridges and oXiris filters [4]. However, endotoxin levels in the CLEAN-ECMO study were measured using a limulus amebocyte lysate chromogenic quantification assay (Pierce™ Chromogenic Endotoxin Quantitation Kit, Pierce Biotechnology, Rockford, IL, USA). Whether values obtained with this assay are directly comparable with those derived from the EEA (Spectral Medical Inc., Toronto, ON, Canada) remains uncertain [4]. This methodological difference complicates the interpretation

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of endotoxin levels and raises questions regarding the potential effectiveness, or possible futility, of endotoxin adsorption in this setting.

Interestingly, the reported endotoxin level in the control group was 0.8 [1]. Considering the methodological differences between endotoxin assays, this value might theoretically fall within a range amenable to endotoxin adsorption therapies such as PMX or oXiris [4]. This observation further underscores the complexity of interpreting endotoxin measurements across different assays and clinical contexts.

Disease severity should also be considered. In the study by Ko et al., the median Sequential Organ Failure Assessment (SOFA) score was numerically higher in the treated group (11.0) compared with the control group (8.0), although this difference did not reach statistical significance [1]. All patients required VA-ECMO support, yet the reported 30-day mortality was 35% in the treated arm and 20% in the control group [1]. These mortality rates are substantially lower than those reported in patients with severe endotoxic septic shock with EEA levels above 0.9, in whom mortality may exceed 70% [5]. This discrepancy suggests that endotoxemia in cardiogenic shock may not carry the same pathophysiological significance as in septic shock.

The authors further propose that endotoxemia in cardiogenic shock likely originates from gut barrier dysfunction, resulting in endotoxin translocation into the systemic circulation [6, 7]. While endotoxin exposure can indeed induce cardiovascular dysfunction resembling septic shock, including reduced ejection fraction, ventricular dilatation, and decreased systemic vascular resistance [7, 8], its direct myocardial impact in cardiogenic shock remains uncertain.

Supporting this concept, Peschel et al. demonstrated that endotoxin concentrations in cardiogenic shock were highest in the hepatic veins (> 0.6) and significantly lower in the left ventricle (< 0.5) (p = 0.02) [9]. This gradient likely reflects intestinal endotoxin translocation rather than myocardial production, as blood cultures were negative [6]. Moreover, similar levels of soluble CD14, tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) were observed in the hepatic veins, pulmonary artery, and left ventricle, suggesting the absence of a transmyocardial cytokine release and potentially a limited direct myocardial effect of endotoxin in cardiogenic shock.

These pathophysiological differences may partly explain the absence of clinical benefit observed with oXiris in the CLEAN-ECMO trial [1]. Despite its negative findings, the study by Ko et al. raises important questions regarding the role of endotoxin adsorption in cardiogenic shock. Differences in endotoxin burden, assay methodology, and the distinct pathophysiology of cardiogenic versus septic shock may all contribute to the observed lack of efficacy. Further exploratory studies are therefore warranted to better define the potential role of endotoxin removal therapies in cardiogenic shock associated with endotoxemia.

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