Mechanical Circulatory Support: A Computational Approach

Introduction

For a long time, the evidence base for the use of Mechanical Circulatory Support (MCS) in acute myocardial infarction cardiogenic shock (AMI-CS) has shown mixed results. Previous large-scale randomised control trials (RCT), *IABP-SHOCK II* and *ECLS-SHOCK,* demonstrated neutral results, leading to scepticism towards its use, but more recently, the *DanGer Shock* trial in 2024 revealed substantial mortality benefit. [1,2,3] Such disparity in results between high-quality RCTs was unexpected and led to a statistical controversy. Pooling heterogenous populations and devices in prior meta-analyses caused a dilution in the results for the specific treatments, and as a result the controversy remained unresolved.

The Methodological Controversy

Most early meta-analyses pooled all 'active MCS' into the same category, which compromised the clinical exchangeability by ignoring two important confounders:

1. **Physiological Mechanism:** The mechanisms of VA-ECMO and microaxial flow pumps like Impella have opposing effects. While VA-ECMO increases left ventricular (LV) afterload, microaxial flow pumps reduce it. Pooling two devices with contrasting mechanisms obscured the device-specific results.
2. **Competing Risks:** Several of the patients *ECLS-SHOCK* trial experienced cardiac arrest (approximately 78%).[2] The risk of hypoxic brain injury for this group is significant, and this means that the haemodynamic benefit from the device becomes irrelevant. *DanGer Shock* accounted for this successfully and excluded the comatose survivors from the study, thus highlighting the hemodynamic signal.[3]

Computational Resolution via MCS-Logic

To overcome these issues, the *MCS-Logic v4.1* dashboard synthesises evidence in a dynamic and interactive manner, rather than as a static publication in the form of a fixed PDF forest plot. *MCS-Logic v4.1*'s coding allows meta-analyses to be treated as a parametric function of clinical criteria.

There are three ways in which the Javascript code addresses the controversy:

1. **Dynamic Sensitivity Analysis:** `getFilteredTrials()` adds the feature of being able to toggle the exclusion criteria as desired. Clinicans can now use the `excludeHighArrest` state variable to see how the hazard ratio changes when "DanGer-like" populations are isolated from "ECLS-like" populations, revealing openly the effect of the cardiac arrest confounder.
2. **Physiological Guardrails:** `renderResults` contains a detection feature, where it alerts the user if they have chosen both `deviceClass:'ecmo'` (loading) and `deviceClass:'impella'` (unloading) and gives the warning of a Physiological Conflict". This ensures there is domain expertise in the analysis and prevents 'apple

and orange' errors.

3. **Automated GRADE Assessment:** The `renderGRADE()` is able to evaluate whether the I^2 (heterogeneity) exceeds 50% or if control groups are mixed (indirectness), and if these are the case, then lower the certainty of evidence automatically. It contextualises the results for the user, so that they don't only have a 'pooled HR' but can assess the statistical fragility of the results.

Conclusion

The *MCS-Logic* dashboard can encode trials as data objects with distinct physiological properties (`mechanism`, `arrestProp`). This has revealed that the statistical controversy regarding MCS devices is not to do with device failure, but to do with the selection of patients. By applying the relevant physiological and clinical filters using *MCS-Logic*, the benefit of MCS devices is drawn out from the heterogenous trial data.

References

1. Thiele H, Zeymer U, Neumann FJ, Ferenc M, Olbrich HG, Hausleiter J, et al. Intraaortic Balloon Support for Myocardial Infarction with Cardiogenic Shock. New England Journal of Medicine. 2012 Oct 4;367(14):1287–96. Available from: https://www.nejm.org/doi/full/10.1056/NEJMoa1208410

2. Thiele H, Uwe Zeymer, Akin I, Behnes M, Tienush Rassaf, Mahabadi AA, et al. Extracorporeal Life Support in Infarct-Related Cardiogenic Shock. The New England Journal of Medicine. 2023 Aug 26;389(14). Available from: https://www.nejm.org/doi/full/10.1056/NEJMoa2307227

3. Møller JE, Engstrøm T, Jensen LO, Eiskjær H, Mangner N, Polzin A, et al. Microaxial Flow Pump or Standard Care in Infarct-Related Cardiogenic Shock. The New England Journal of Medicine [Internet]. 2024 Apr 7;390(15). Available from: https://pubmed.ncbi.nlm.nih.gov/38587239/