

 <p>UniSR Università Vita-Salute San Raffaele</p>	<p>APPLICATION TO ACT AS SUPERVISOR AND RESEARCH PROJECT PROPOSAL</p>	<p>MO 20-5 ed. 01 del 21/02/2025 PO 20 Page 4 of 11</p>
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PROJECT

Supervisor:

Landoni Giovanni

Title:

Physiology and physiopathology of extracorporeal support for cardiac and respiratory failure: from molecular basis to clinical outcomes.

Curriculum:

Experimental and Clinical Medicine

Link to the personal page of the University or relevant hospital site website:

<https://research.hsr.it/en/clinical-research/cardiovascular-research-center/intensive-care-and-anesthesia.html>

Description of the Project (max 3,000 characters including spaces)

Background/gap of knowledge

Heart failure (HF) and respiratory failure (RF) are leading causes of mortality worldwide with a mortality rate reaching 50% in the most severe presentations, such as cardiogenic shock (CS) and severe acute respiratory distress syndrome (ARDS).^{1,2}

Mechanical circulatory support (MCS), on top of pharmacological therapy, has emerged as a potential lifesaving strategy in patients refractory to first line standard care therapies. The recently published DANGER shock trial demonstrated the efficacy of temporary MCS with microaxial flow pump in reducing the risk of death from any cause at 180 days from ST-segment elevation myocardial infarction complicated with cardiogenic shock.³ Following these results the latest guidelines on the management of patients with coronary syndromes suggested the use of temporary MCS in selected patients with severe refractory cardiogenic shock as a reasonable strategy to reduce death (class of recommendation 2a, level of evidence B-R).⁴ Similarly the latest ARDS guidelines suggest the use of veno-venous extracorporeal membrane oxygenation in selected patients with severe ARDS (conditional recommendation, low certainty of evidence).⁵ However, different phenotypes of HF and RF exist, with different etiologies and clinical trajectory, and several MCS devices are available, making the identification of the most appropriate treatment particularly complex.⁶ Furthermore, long-term implantable devices are currently the unique therapeutic option, together with heart transplantation, for end stage HF.⁷

Rationale and hypothesis



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The treatment with both short-term and long-term MCS is associated with numerous adverse events including acute kidney injury, thromboembolic events and bleeding mining the possible recovery of HF and RF patients.³

The basis of these complications can be primarily traced back to the biocompatibility of material composing the MCS devices affecting both inflammation and coagulation pathways: the comprehension of these phenomena is still limited but represents a critical knowledge gap to be addressed in order to improve the outcome of HF and RF patients. Recent studies have underscored the role of several potential concomitant mechanisms, from hemodynamic factors (e.g. type and degree of left ventricle unloading) to hemocompatibility, and platelets microRNA expression.⁸⁻¹² Furthermore, MCS cost-effectiveness need to be analyzed more deeply.¹³

Objectives and specific aims

In this project both clinical and translational expertise will be applied to go deep into the pathophysiology of HF, RF and MCS to study the rate and nature of extracorporeal support related mechanisms, and in particular to:

- characterize the phenotype of HF and RF populations with respect of the need of MCS, clinical pathways of care and clinical outcomes;
- investigate the molecular basis of patient-device interaction and MCS related adverse events.

Expected outcomes

The use of MCS in HF and RF is increasing, however, the rate of associated complications remains high. A phenotyping approach to the patients pathology and molecular analyses of the MCS devices biocompatibility will lead to a better understanding of the patient-device interplay and open the way to an improvement in clinical outcomes.

Skills that the student should acquire (max. 600 characters including spaces):

Skills in clinical and experimental research: design and conduction of studies, critical interpretation and analysis of results, and effective scientific communication.

In-depth knowledge of cardiac and pulmonary physiology, pathophysiology of acute and chronic heart failure, respiratory failure, and molecular interactions with mechanical circulatory support systems.

Interdisciplinary collaboration with specialists from various fields and researchers.



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Understanding of research ethics and a translational vision, from basic research into practical applications to improve patient care.

References (max. 15)

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2. Bellani G, Laffey JG, Pham T, et al. Epidemiology, Patterns of Care, and Mortality for Patients With Acute Respiratory Distress Syndrome in Intensive Care Units in 50 Countries. *JAMA* 2016;315(8):788–800.
3. Møller JE, Engstrøm T, Jensen LO, et al. Microaxial Flow Pump or Standard Care in Infarct-Related Cardiogenic Shock. *N Engl J Med* 2024;390(15):1382–93.
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7. Mehra MR, Goldstein DJ, Cleveland JC, et al. Five-Year Outcomes in Patients With Fully Magnetically Levitated vs Axial-Flow Left Ventricular Assist Devices in the MOMENTUM 3 Randomized Trial. *JAMA* 2022;328(12):1233–42.
8. Pappalardo F, Schulte C, Pieri M, et al. Concomitant implantation of Impella® on top of veno-arterial extracorporeal membrane oxygenation may improve survival of patients with cardiogenic shock. *Eur J Heart Fail* 2017;19(3):404–12.
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10. Selmi M, Chiu W-C, Chivukula VK, et al. Blood damage in Left Ventricular Assist Devices: Pump thrombosis or system thrombosis? *Int J Artif Organs* 2019;42(3):113–24.
11. Consolo F, Pozzi L, Pieri M, et al. Influence of Different Antithrombotic Regimens on Platelet-Mediated Thrombin Generation in Patients with Left Ventricular Assist Devices. *ASAIO J* 2020;66(4):415–22.
12. Lombardi M, Bonora M, Baldetti L, et al. Left ventricular assist devices promote changes in the expression levels of platelet microRNAs. *Front Cardiovasc Med* 2023;10:1178556.
13. Rognoni C, Ardito V, La Fauci D, Pieri M, Scandroglio AM, Tarricone R. Impella Versus VA-ECMO for Patients with Cardiogenic Shock: Preliminary Cost-Effectiveness Analysis in the Italian Context. *Cardiol Ther* 2025;