

 <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 12</p>
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PROJECT

Supervisor:

Prof. Pappone Carlo

Title:

Immuno-genetic factors involved in primary arrhythmias susceptibility in the acute phase of myocardial infarction (**FORTUNA** trial)

Curriculum:

Experimental and Clinical Medicine

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

<https://www.unisr.it/en/docenti/p/pappone-carlo>

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

Background/gap of knowledge

Sustained arrhythmias during the acute phase of myocardial infarction (AMI) critically impact survival. Ventricular arrhythmias (VA) are a major cause of sudden cardiac death (SCD), occurring in 3–10% of ST-segment elevation myocardial infarction (STEMI) cases, and are linked to increased in-hospital mortality, though not to worse long-term prognosis.^{1,2,3}

Supraventricular arrhythmias (SVA), especially atrial fibrillation, affect 5–20% of STEMI patients and are associated with prolonged hospitalization and increased mortality.^{4,5} Despite their clinical relevance, the mechanisms underlying the development of these arrhythmias in the acute setting of AMI, as well as their prognostic implications beyond the hospital stay, remain incompletely understood. Further investigation is needed to refine risk stratification strategies and optimize management approaches for patients experiencing these arrhythmias.

Rationale and hypothesis

Several factors have been proposed to explain susceptibility to arrhythmias during AMI, including polymorphisms in adrenergic receptors⁶, oxidative stress⁷, and ion channel gene variants. Among these, SCN5A—encoding the cardiac sodium channel NaV1.5—has been the most studied for its role in electrical disorders, but its contribution to VA in AMI is still debated.^{8,9,10,11}

Growing evidence suggests a potential role of autoimmunity in cardiac diseases, particularly through antibodies targeting ion channels.¹² Inflammation has also been implicated in the occurrence of SVA during STEMI, highlighting a possible link between immune activation and arrhythmogenesis.¹³



Recent findings have identified anti-Nav1.5 autoantibodies in arrhythmogenic conditions, alongside gene expression changes in immune pathways and elevated IFN- γ levels.¹⁴ However, no studies have systematically examined immune-mediated responses to coronary occlusion in relation to arrhythmias, representing a key gap in knowledge.

Objectives and specific aims

Overall Objective:

To investigate the mechanisms involved in the development of VA and SVA during AMI, with particular focus on immune-mediated processes, including inflammation and autoimmunity.

Specific Aims:

Genetic and Molecular Analysis

- Assess the role of ion channel gene variants (e.g., SCN5A) in VA during AMI.

Autoimmune and Inflammatory Mechanisms

- Investigate the presence and significance of anti-Nav1.5 autoantibodies.
- Analyze immune pathway activation, (e.g., cytokine and IFN signaling).

Clinical and Prognostic Implications

- Examine the impact of immune-driven arrhythmias on clinical outcomes.
- Develop a risk model integrating genetic, immunological, and clinical factors.

Expected outcomes

The study is expected to clarify the role of genetic and immune factors in arrhythmias during AMI, offering new insights into their pathogenesis. By investigating ion channel variants, inflammation, and autoantibodies, it aims to identify key molecular-clinical interactions. Results may support improved risk stratification and new therapeutic strategies, ultimately guiding personalized approaches to care in AMI patients.

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

- Expertise in clinical and experimental research, with strong analytical skills and critical interpretation of clinical and molecular data.
- Solid understanding of cardiac anatomy, physiology, and AMI management.



- Knowledge of molecular disease mechanisms and pathophysiology.
- Effective communication in academic and clinical settings.
- Experience in interdisciplinary collaboration, research ethics, and project management.
- Commitment to translational research aimed at improving patient care.

References (max. 15)

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[8] Wang F, Liu Y, Liao H, et al. Genetic Variants on SCN5A, KCNQ1, and KCNH2 in Patients with Ventricular Arrhythmias during Acute Myocardial Infarction in a Chinese Population. *Cardiology.* 2020;145(1):38-45. doi: 10.1159/000502833. Epub 2019 Nov 21. PMID: 31751991.

[9] Jabbari R, Glinge C, Jabbari J, et al. A Common Variant in SCN5A and the Risk of Ventricular Fibrillation Caused by First ST-Segment Elevation Myocardial Infarction. *PLoS One.* 2017 Jan 13;12(1):e0170193. doi: 10.1371/journal.pone.0170193. PMID: 28085969; PMCID: PMC5234807.

[10] Hu D, Viskin S, Oliva A, Carrier T, et al. Novel mutation in the SCN5A gene associated with arrhythmic storm development during acute myocardial infarction. *Heart Rhythm.* 2007 Aug;4(8):1072-80. doi: 10.1016/j.hrthm.2007.03.040. Epub 2007 Apr 10. PMID: 17675083; PMCID: PMC1978483.



[11] Boehringer T, Bugert P, Borggrefe M, Elmas E. SCN5A mutations and polymorphisms in patients with ventricular fibrillation during acute myocardial infarction. *Mol Med Rep.* 2014 Oct;10(4):2039-44. doi: 10.3892/mmr.2014.2401. Epub 2014 Jul 21. PMID: 25051102.

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