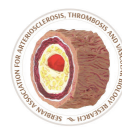
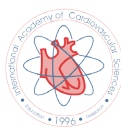




## ABSTRACTS of the

**7<sup>th</sup> Meeting of the European Section  
and  
8<sup>th</sup> Meeting of the North American Section  
of the  
International Academy of Cardiovascular  
Sciences (IACS)**

**Banja Luka, 20-23 September 2021**



**Organised by:**

International Academy of Cardiovascular Sciences (IACS) – European and North American Sections

University of Banja Luka, the Republic of Srpska, Bosnia & Herzegovina

Faculty of Medicine, University of Banja Luka, the Republic of Srpska, Bosnia & Herzegovina

Serbian Association of Arteriosclerosis, Trombosis and Vascular Biology Research, Belgrade, Serbia

Association for Atherosclerosis and Cardiovascular Research, Banja Luka,  
the Republic of Srpska, Bosnia and Herzegovina



# The Effects of a Meldonium Pre-Treatment on the Sepsis-Induced Rat Heart Injury

Iva Lakić,<sup>1</sup> Siniša Đurašević,<sup>1</sup> Aleksandra Ružičić,<sup>1</sup> Tomislav Tosti,<sup>2</sup> Saša Đurović,<sup>3</sup> Sofija Glumac,<sup>4</sup> Slađan Pavlović,<sup>5</sup> Slavica Borković-Mitić,<sup>5</sup> Ilijana Grigorov,<sup>5</sup> Sanja Stanković,<sup>6, 7</sup> Nebojša Jasnić,<sup>1</sup> Zoran Todorović,<sup>4, 8</sup> Jelena Dorđević<sup>1</sup>

## Abstract

**Background:** Sepsis is a life-threatening condition caused by the dysregulated and overwhelming response to infection, accompanied by exaggerated pro-inflammatory state and lipid metabolism disturbance leading to sequential organ failure.<sup>1,2</sup> Meldonium is an anti-ischemic and anti-inflammatory agent, clinically used to treat myocardial ischemia.<sup>3</sup> By shifting energy production from fatty acid oxidation to glycolysis, as an oxygen less consuming pathway, meldonium interferes negatively with lipid metabolism.

**Methods:** Thus, we investigated the effects of a 4-week meldonium pre-treatment in 300 mg/kg b.m./day dosage on the course of the sepsis induced by a single intraperitoneal injection of faeces (0.5 g faeces/1 mL saline/100 g b.m.) in Sprague-Dawley male rats. The degree of the heart injury was evaluated by measuring tissue pro-apoptotic Bax and anti-apoptotic Bcl-2 ratio, tissue level of the necrotic marker - high mobility group box 1 protein level (HMGB1), together with the heart histology analysis. Sepsis-associated heart inflammation was assessed by measuring level of an activated form of NF-κB p65 (phospho-NF-κB p65).

**Results:** In the heart whole homogenates of the septic group of animals (S) HMGB1 level increased 1.7-fold, in comparison to control rats, while meldonium reduced sepsis-induced increase by 18 % (M+S). The underlying mechanism of the proinflammatory action of HMGB1 includes activation of NF-κB signalling pathways tissue, so the increased HMGB1 level was followed by a 1.4-fold increase of p-NF-κB p65 in the heart of the S group of rats and a 19 % decrease in the heart of M+S group. The apoptotic marker Bax/Bcl-2 ratio changed in the same manner: 1.4-fold increase in the heart of animals from the S group and a 32 % decrease in the heart of the M+S group. On the other hand, heart histology analysis shows that meldonium worsened the heart histological score, causing the severe and diffuse interstitial mononuclear infiltration along with a greater loss of myocytes and myofibrillar contraction band necrosis. The heart lipidomic analysis suggests that meldonium exhibits potentially harmful effects under septic condition due to the lipid-mobilization impairment.

**Conclusion:** Meldonium exerted anti-inflammatory, anti-apoptotic, and anti-necrotic effects, while it worsened the septic rat heart histology.

**Key words:** Sepsis; Heart; Inflammation; Lipidomics; Rat.

**References:** 1. Kim MH, Choi JH. An update on sepsis biomarkers. *Infect Chemother* 2020 Mar;52(1):1-18. 2. Rossi MA, Celes MRN, Prado CM, Saggiaro FP. Myocardial structural changes in long-term human severe sepsis/septic shock may be responsible for cardiac dysfunction. *Shock* 2007 Jan;27(1):10-8. 3. Dambrova M, Makrečka-Kuka M, Vilskersts R, Makarova E, Kuka J, Liepinsh E. Pharmacological effects of meldonium: biochemical mechanisms and biomarkers of cardiometabolic activity. *Pharmacol Res* 2016 Nov;113(Pt B):771-780.

- (1) Faculty of Biology, University of Belgrade, Belgrade, Serbia.
- (2) Faculty of Chemistry, University of Belgrade, Belgrade, Serbia.
- (3) Institute of General and Physical Chemistry, University of Belgrade, Belgrade, Serbia.
- (4) School of Medicine, University of Belgrade, Belgrade, Serbia.
- (5) Institute for Biological Research "Siniša Stanković"- National Institute of Republic of Serbia, University of Belgrade, Belgrade, Serbia.
- (6) Centre for Medical Biochemistry, University Clinical Centre of Serbia, Belgrade, Serbia.
- (7) Faculty of Medical Sciences, University of Kragujevac, Kragujevac, Serbia.
- (8) University Medical Centre "Bežanijska kosa", University of Belgrade, Belgrade, Serbia.

Correspondence:  
IVA LAKIĆ  
E: djiva@bio.bg.ac.rs

## ABSTRACT INFO

Abstract ID: 67  
Submitted: 30 August 2021