



Scientific projects presented at the Serbian Conference on INTERventional cardioloGY and cardiovascular imaging – SINERGY 2017 (September 7–9, 2017, Belgrade, Serbia)

Members of the Scientific Committee of the SINERGY 2017

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On September 9, 2017, Serbian Conference on INTERventional cardioloGY and cardiovascular imaging (SINERGY 2017) hosted a half-day scientific meeting dedicated to ongoing research in the field of cardiovascular medicine in Serbia. Twenty-four presentations representing different institutions and research groups were delivered - the full list of presentations and authors is available on the conference website: <http://sinergy-belgrade.com/#Room3>. Starting from 2015, this was the third time that SINERGY organizers have assembled cardiovascular researchers from Serbia from basic to translational and clinical domains, to present and discuss their ongoing projects in an attempt to foster cross-institutional cooperation on the national level. The projects presented here were part of the original presentations during the SINERGY 2017 meeting. For the next SINERGY edition, on September 6-8, 2018, in Belgrade, leading cardiovascular researchers are planned to reconvene and to present the current status of their ongoing projects and discuss potential cooperation agreements.

On the behalf and with permission of the Scientific Committee of the Serbian Conference on INTERventional cardioloGY and cardiovascular imaging – SINERGY 2017 and its director and founder, academician Professor Goran Stankovic, the Vojnosanitetski pregled published some of the cardiovascular scientific projects presented at the Conference.

“CardioNS E1 – multifunctional ECG – application in different clinical scenarios”, Project of the Institute of Cardiovascular Diseases Vojvodina, Sremska Kamenica, Serbia

Srdan Sladojević^{†,□}, Miroslava Sladojević^{**}, Ilija Srdanović^{*,**}, Andraš Anderla^{†,□}, Marko Arsenović^{†,□}, Velicki Lazar^{*,**}

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AIM: “CardioNS E1 – multifunctional ECG – application in different clinical scenarios” is a project implemented by a multidisciplinary team comprised of Srdan Sladojević, Miroslava Sladojević, Ilija Srdanović, Andraš Anderla, Marko Arsenović, and Lazar Velicki. CardioNS E1 is simple, but fully featured, precise and reliable 3-channel mobile multifunctional ECG device designed and developed as a dongle to be used as an USB device by on-the-go (OTG) enabled mobile phones or tablets. The purpose of this project was to develop portable and efficient ECG device that could be used in a variety of different clinical scenarios and for the research purposes including resting and stress ECG recorder, Holter monitor, remote monitoring device and Mobile Cardiac Telemetry (MCT) device. We are looking for clinical and biomedical partners interested in CardioNS E1 testing and conceptualization of innovative clinical and research purposes. Detailed presentation of the project is available on the Web - <http://panonit.com/cardions>. **Corresponding author:** Lazar Velicki, MD, PhD; e-mail: lazar.velicki@mf.uns.ac.rs

Crossing boundaires: from anatomy to surgery and beyond. Cardiovascular anatomy in clinical practice

Prof. dr Milan Milisavljević, prof. dr Branislav Filipović, prof. dr Laslo Puškaš, prof. dr Aleksandar Maliković, prof. dr Zdravko Vitošević

Institute of Anatomy "Niko Miljanić", Faculty of Medicine, University of Belgrade, Belgrade, Serbia

AIMs of our studies are:

1. To examine arteries and veins of the heart, their positions, course, relationships and variations
2. To measure the number, calibers, lengths and branching angles of cardiac arterial vessels
3. To study the coronary branching pattern
4. To compare morphological data obtained from fetal and adult hearts
5. To provide rare learning opportunities where the participants dissect and use human cadavers for themselves and the benefit of the group. The process of doing so is pro-

found since the participants witness, are engaged in, and experience the whole human anatomy

Methods of our studies are:

1. Traditional anatomical injection of colored liquid latex, fixation in 10% formalin, dissection and measurements under the stereoscopic microscope

2. Histological method of taking parts of tissue, embedding in paraffin and sectioning serially in 5 µm thick slides staining with Masson trichrome method

3. Corrosion cast method using methylmetacrylate injection and immersion in a 30% solution of potassium hydroxide for corrosion. Following washing out and drying, the obtained vascular casts are examined and measured under the stereoscopic microscope in our Laboratory for vascular anatomy

4. *Integral Anatomy Dissection Workshops (unfixed and fixed)* designed primarily for specialists who are hands-on practitioners of some therapeutic modality as well as for surgeons professionals, cardiologists, radiologists, teachers and the like who have prior professional knowledge of anatomy of which they make regular use.

Experimental cardiovascular models for study of the effects of hyperhomocysteinemia (acute and subchronic), hypermethioninemia (acute and subchronic), heart failure and diabetes mellitus in rats

Dragan M. Djurić¹, Vladimir Lj. Jakovljević²

¹*Institute of Medical Physiology "Richard Burian", Faculty of Medicine, University of Belgrade, Belgrade, Serbia;* ²*Department of Physiology, Faculty of Medical Sciences, University of Kragujevac, Kragujevac, Serbia*

Aim: Study of the effects of homocysteine and homocysteine-related compounds on cardiovascular system: role of gaseous transmitters NO, H₂S and CO (Research grant no. OI 175043, Ministry of Education, Science and Technological Development, Republic of Serbia, 2011-, principal investigator Dragan M. Djurić)

Ongoing Subprojects/PhD Theses:

1. The effects of subchronic homocysteine overload on coronary hemodynamics and oxidative stress in a rat: the effects of sulfur aminoacids (methionine, L-cysteine and N-acetyl-L-cysteine) and inorganic sodium hydrogen sulfide administration

2. Functional, biochemical and morphohistological changes in a rat cardiovascular system following acutely induced hyperhomocysteinemia or subchronic methionine overload – the effects of sulfur aminoacids (L-cysteine and N-acetyl-L-cysteine) administration

3. Functional, biochemical and immunohistochemical changes in a rat cardiovascular system following monocrotaline-induced heart failure – subchronic effects of vitamin B6 and folic acid administration

4. Functional, biochemical and immunohistochemical changes in a rat cardiovascular system following streptozotocin-induced diabetes mellitus – subchronic effects of vitamin B6 and folic acid administration

5. Mechanisms of cardiodynamic and vasoactive effects of systemic anaesthetic propofol in a rat: the impact of oxidative stress, gasotransmitters and cardiovascular biomarkers

European Research Network

COST Action CA16225, Action Title: Realising the therapeutic potential of novel cardioprotective therapies (2017-2021)

COST Action BM1005, Action Title: Gasotransmitters: from basic science to therapeutic applications (ENOG: European Network on Gasotransmitters) (2011-2015)

Assessment of predictors of mortality, major bleeding and chronic thromboembolic pulmonary hypertension in patients with pulmonary embolism and individualization of therapy

Military Medical Academy, Faculty of Medicine, University of Defence, Belgrade, Serbia

Slobodan Obradović (sloba.d.obradovic@gmail.com), Boris Džudović, Siniša Rusović, Bojana Subotić, Nataša Novičić; *Institute for Pulmonary Diseases of Vojvodina, Sremska Kamenica, Serbia:* Jovan Matijašević (jovanmat99@yahoo.com), Milica Milić, Jadranka Trobok, Sandra Peković, Sovilj. *Zvezdara University Medical Center, Belgrade, Serbia:* Nataša Marković-Nikolić (nmarkovicnikolic@gmail.com). *Clinical Centre Niš, Niš, Serbia:* Dragana Stanojević, Sonja Šalinger (sonja.salinger@gmail.com). *Institute for Cardiovascular Diseases of Vojvodina, Sremska Kamenica, Serbia:* Ilija Sredanović, Aleksandra Vulin, Milana Jaraković (milana.jarakovic@ikvbnv.ns.ac.rs). *Clinical Centre Kragujevac, Kragujevac, Serbia:* Vladimir Miloradović (vanja.miloradovic@gmail.com), Nikola Jagić, Maja Nikolić.

AIM: The purpose of this project is to create multicenter registry of patients with pulmonary embolism and to study predictors of mortality, major bleeding and development of chronic pulmonary embolic disease. The second goal is to examine efficacy and safety of different thrombolytic protocols and the role of direct oral anticoagulant drugs in the treatment of pulmonary embolism. The participants in the project are from several university clinics, however we will include each hospital which takes part in the management of pulmonary embolism patients.

Effects of remote conditioning on reperfusion injury in patients with acute coronary syndrome

Clinical Centre Kragujevac, Kragujevac, Serbia: Vladimir Miloradović (vanja.miloradovic@gmail.com), Stefan Simovic (simovicst@gmail.com),

The purpose of this project is to evaluate effects of remote conditioning on reperfusion injury in patients with acute myocardial infarction with and without ST segment elevation and unstable angina as well as its effects on markers of oxidative stress and anti-oxidative parameters. One of the purposes will also be to investigate whether different protocols for remote conditioning have different effects. The participants in the project are from single university clinic, however we will include each hospital which take part in the trial, exploring effects of remote conditioning on reperfusion injury.

Ultrasound of extravascular lung water: detection and prognostic value of pulmonary congestion in heart failure patients

Prof. dr Marina Deljanin Ilić^{1,2} (corresponding author: Telephone: 018 502 045; e-mail: marinade@mts.rs), Dr Dejan Simonović². ¹*Faculty of Medicine, University of Niš, Niš, Serbia;* ²*Institute for Treatment and Rehabilitation, Cardiology Clinic, Niška Banja, Serbia*

AIM: Assessment of pulmonary congestion remain challenging without a gold standard, so there is a critical

need for quantitative markers of pulmonary congestion, its correlation with echocardiographic parameters with the aim to increase the speed and accuracy of diagnosis, facilitate early treatment, inform treatment titration and potentially improve risk stratification. Patient population: This is prospective, multi centre, observational study in adults, with the HF hospitalization irrespective of left ventricular ejection fraction. All patients will be divided into three groups according to ESC guidelines for the diagnosis and treatment of acute and chronic heart failure (patients with heart failure with preserved (HFpEF), mid-range (HFmrEF) and reduced ejection fraction (HFrEF). Lung ultrasound imaging protocol: Lung ultrasound examinations will be performed on admission to hospital as well as at discharge, evaluating 28 intercostal points on the anterior chest wall with the patient in the supine position (B model; scoring system, 6-15 B-lines mild degree pulmonary congestion, 16-30 moderate degree and > 30 B-lines severe degree pulmonary congestion). All patients will undergo detailed echocardiographic examination on admission and at discharge from hospital. Follow-up and definition of cardiovascular events and primary clinical end-point. Patients will be prospectively followed via phone call, every 3 months for at least 12 months. All hospitalizations and cause of hospitalization, death as well as causes of death should be documented. The primary clinical endpoint will be the time to first heart failure hospitalization or all-cause death.

Multidisciplinary study of diseases of aorta and its branches: pathogenesis, diagnosis and treatment

Prof. Lazar. Davidović, Principle Investigator; Investigators: Prof. Miroslav Marković, Prof. Dušan Kostić, Prof. Slobodan Cvetković, Prof. Dragan Marković, Doc. Marko Dragaš, Asist. Nikola Ilić, Asist. Igor Končar, Asist. Andreja Dimić. *Clinic for Vascular and Endovascular Surgery, Clinical Centre of Serbia, Belgrade, Faculty of Medicine, University of Belgrade, Belgrade, Serbia*. Contact: drmiroslav@gmail.com; davidovic.lazar@gmail.com

AIM: multidisciplinary and contemporary approach to diseases of aorta and its branches regarding pathogenesis and treatment.

1. Demographic characteristics and ultrasound screening for the patients with increased risk of aneurismatic and atherosclerotic disease of aorta

2. Analysis of biomechanical and biochemical parameters of aortic aneurism (Cooperation with *the Faculty of Mechanical and Civil Engineering, University of Kragujevac, Kragujevac, Serbia*)

3. Determination of genetic and clinical markers of the initial carotid atherosclerosis

4. Participation in BIOLEAK study (Multicenter prospective study of MMP9 in blood as marker of endo-leak after endovascular reconstruction of aortic aneurism). Clinicaltrials.gov, No NCT01965717 (Cooperation with *Universities in Genova, Plzen and Gdansk*)

5. Study of the association between genetic markers and aortic diseases with PCR microarray testing (Cooperation with the *Laboratory for Radiobiology and Molecular Genetics, Institute of Nuclear Sciences Vinca, Belgrade, Serbia*)

6. Study of the methods for the protection of spinal cord during the surgery on thoracic and abdominal aorta

7. Study of the certain circulating markers for the prediction of the progression of aortic aneurism diameter and rupture

8. Study of the correlation between MRI imaging and biomechanical characteristics of aortic aneurism and relation with the existence of intra-aortic atherosclerosis and thrombus

9. Participation in the Horizon study of the new aortic stent grafts

10. Participation in the multicenter European study "Hernia" for the methods of the closure of laparoscopic wounds and its relation to post-operative hernias after surgery of abdominal aorta * (No NCT02012270, international register of clinical studies – cooperation with *the Clinic for Abdominal Surgery in Gant Belgium*)

Impact of coronary microcirculation dysfunction on the extent of myocardial necrosis in patients with ST-elevation myocardial infarction treated with primary percutaneous coronary intervention

Prof. Goran Stanković (corresponding author), Dr. Dejan Milašinić

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Rationale: Although previous studies have indicated the potential of coronary microvascular resistance to predict outcomes in patients with ST-elevation myocardial infarction (STEMI), treated with primary percutaneous coronary intervention (PCI), several different microcirculatory indices were used, and showed inconsistent results, including thermolulution-derived index of microcirculatory resistance (IMR) and doppler-derived hyperemic microvascular resistance (HMR).

Aim: Our project aims to assess the ability of a novel, doppler-derived index of coronary microvascular resistance, pressure at zero flow (PzF), to predict infarct size in STEMI patients treated with timely primary PCI.

Organization: Coronary microcirculation will be prospectively interrogated using a Doppler wire in STEMI patients after a successful primary PCI. The obtained indices will be correlated with the CMR-assessed infarct size, biomarkers of cardiac injury and echo-derived parameters of left ventricular function.

Cooperation: The study will be primarily conducted in the Department of Cardiology of the Clinical Center of Serbia, with pending inter-institutional cooperation agreements on both the national level (standardized non-invasive imaging protocols and biomarker assessment) and internationally (microcirculatory indices computing).

PRETreatment with Ticagrelor versus clopidogrel in patients undergoing early invasive intervention for Non-ST segment Elevation Myocardial Infarction (PRETTY-NSTEMI)

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Rationale: Ticagrelor has recently been associated with favorable clinical outcomes, when compared with Clopidogrel, in patients with acute coronary syndrome (ACS), including non-ST segment elevation myocardial infarction (NSTEMI), treated with percutaneous coronary intervention (PCI). However, the exact mechanisms of the potentially

beneficial effects of Ticagrelor over Clopidogrel remain unknown.

Aim: Our study was designed to assess the impact of pretreatment with Ticagrelor vs. Clopidogrel on the extent of myocardial injury, expressed by the in-hospital peak and total release of high-sensitivity Troponin T (hsTnT), in patients with NSTEMI referred to early invasive management.

Organization: Patients are randomized to receive either Ticagrelor or Clopidogrel loading dose immediately upon diagnosis of NSTEMI and prior to referral to the catheterization laboratory and the primary endpoint is the extent of in-hospital hsTnT elevation. Afterwards, patients will receive the recommended maintenance doses of Ticagrelor and Clopidogrel and will be clinically followed-up for a year along with the assessment of secondary clinical endpoints including both ischemic and bleeding events.

Cooperation: The study has already commenced and the inclusion is underway in the Department of Cardiology of the Clinical Center of Serbia, with the planned transition to a multicenter randomized trial, pending the cooperation agreements with PCI-capable institutions on the local and national level.

Mechanical dispersion in patients with heart failure and severely depressed left ventricular function with bundle branch blocks*

Investigators: Ivan Stankovic (PI), Aleksandra Janicijevic, Aleksandra Dimic, Milica Stefanovic, Radosav Vidakovic, Biljana Putnikovic, Aleksandar N. Neskovic; *Clinical Hospital Center Zemun, Faculty of Medicine, University of Belgrade, Belgrade, Serbia*

Rationale: Evaluation of bundle branch blocks (BBB)-related mechanical dyssynchrony and dispersion may improve patient selection for device therapy in patients with heart failure and severely depressed left ventricular ejection fraction (LVEF). However, their effect on the natural history in

this patient population is unknown. **Methods:** We investigated a total of 155 patients with LVEF $\leq 35\%$ and BBB, not treated with device therapy. Mechanical dyssynchrony was defined as the presence of either septal flash or apical rocking on two dimensional echocardiogram. Contraction duration was assessed as a time interval from the electrocardiographic R-(Q-) wave to peak longitudinal strain in each of 17 left ventricular segments. Mechanical dispersion was defined as either the standard deviation of all time intervals (dispersion_{SD}) or as the difference between the longest and shortest time intervals (dispersion_{delta}). Patients were followed for cardiac mortality during a median period of 33 months. **Main findings:** While mechanical dyssynchrony was not associated with survival, more pronounced mechanical dispersion_{delta} was found in patients with dyssynchrony than in those without it. In the multivariate regression analysis, patients' functional class, diabetes mellitus and dispersion_{delta} were independently associated with mortality. **Conclusions:** Mechanical dispersion measured by deformation imaging (strain), but not dyssynchrony, was associated with poor outcome in patients with severely depressed left ventricular function and bundle branch blocks. Evaluation of mechanical dispersion may have potential to be used for the risk stratification of patients with heart failure and bundle branch blocks.

*presented in part at the ESC Congress in Barcelona 2017; currently *in press* in the Annals of Medicine (*Stankovic I, et al. Mechanical dispersion is associated with poor outcome in heart failure with a severely depressed left ventricular function and bundle branch block. Ann Med. 2017 Oct 13:1-11. doi:10.1080/07853890.2017.1387282.*)

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