

**3rd Meeting of the Baltic Physiological Societies**

# **ABSTRACTS**



**December 9–10, 2019**

**Kaunas**

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# **ABSTRACTS**

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Lithuanian, Latvian and Estonian Physiological Societies

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## The physiological adaptation to exercise following cardiac rehabilitation in patient after several cardiopulmonary resuscitations and severe hypoxia – case study

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**Background and objectives:** The inadequate supply of oxygen (e.g. severe hypoxia) to the tissues (also the brain tissue) could bring many health deteriorations resulting sometimes in death. Here we describe, for the first time, the case study of the patient with aortic valve stenosis threatened by aortic valve replacement (AVR), who survived many resuscitations, severe hypoxia and tetraplegic paralysis. *Materials and Methods:* A 59 year old female patient with aortic stenosis, hypertension and hypercholesterolemia suffered several resuscitations and hypoxia. The observation of patient lasted from November 2018 till now. The initial echocardiography revealed severe organic changes of aortic valve [non-rheumatic aortic valve stenosis (ICD-10: I35.0)] as well as concentric hypertrophy (interventricular septum = 13 mm; left ventricle end-diastolic posterior wall thickness= 12 mm; EF = 55%). After the AVR operation (5<sup>th</sup> March 2019) the hypertension incident (200 mmHg), chest haematoma as well as cardiac arrest (3 minutes) occurred. The computed tomographic revealed hypodense areas of the thalamus in the brain, which could be the reason why tetraplegia occurred. The multi-disciplinary rehabilitation consisted of bed-side and neurological rehabilitation during patient's stay in the Intensive Care Unit as well as cardiopulmonary rehabilitation using exercise till exhaustion. The heart rate and blood pressure was monitored before (initial), during all exercise and 4 minutes after the end of exercise (recovery phase) during 24 days of observation. **Results:** The patient progressed from NYHA II to NYHA I. After cardiopulmonary rehabilitation the

patient was able to maintain the exercise till 33 minutes (before only 10 minutes) with 25W load (before 10W). The resting as well vs. peak exercise heart rate decreased after rehabilitation [pre =67.5; post=65.0 vs. pre=83.7 (10W); post=72.5 (25W), respectively]. **Conclusions:** The holistic rehabilitation after severe incidence affecting cardiovascular and neurological system could boost the physiological recovery.

**Keywords:** rehabilitation, heart, tetraplegic, hypoxia, aortic valve, stenosis

## The correlation between lumbar low-grade scoliosis and the magnitude of physiological curvatures of the spine in standing and sitting positions in children

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**Background and objectives:** The physiological curvatures are important to the sagittal balance of the spine. The idiopathic scoliosis (IS) is a three-dimensional deformity, which could change the magnitude of physiological curvatures of the whole spine. The aim of this study was to assess the impact of body position on physiological curvatures (Th kyphosis and L lordosis) in patients treated because of left lumbar low-grade idiopathic scoliosis (LLIS). **Materials and Methods:** This study comprised of 60 girls: (A) 30 patients with LLIS (11 – 17 years old; Cobb angle: 10-21°), not treated with bracing; and (B) 30 healthy patients (10-17 years old). The study was performed in standardized standing (P1) and sitting (P2) positions using ZEBRIS CMS-10 (Zebris Medical GmbH, Germany). The mean angle of kyphosis and lordosis was compared in both studied groups. The changes in kyphosis and lordosis angle were analysed depending on changes in the body position. **Results:** The mean value of the angle of lumbar curvature in P1 was higher in group A in comparison with group B. However, there were no differences between groups in P2. The mean value of Th kyphosis angle was higher in group A compared to group B. However, these data weren't statistically significant. The statistically significant differences between mean angle of lumbar curvature in group A in P1 as well as in P2 compared to group B was observed ( $p=0.046$ ). **Conclusions:** The occurrence of lumbar low-grade scoliosis (LLS) is associated with hyperlordosis in standing position. LSS doesn't change the kyphosis curvature in standing as well as sitting positions.

**Keywords:** scoliosis, sagittal plane, lordosis, physiology, curvature, children

## Clinical complications after spinal cord injury in pediatric patients

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**Background and objectives:** Annual incidence of spinal cord injuries (SCI) in European countries is approximately 17 individuals per 1 million. A 5-9% of these cases are children and adolescents. SCI is a serious condition that requires long-lasting therapy and rehabilitation. The aim of this paper is to present clinical complications in patients after SCI, where the neurological component occurs. Thus, this makes the rehabilitation process more difficult. **Materials and Methods:** A seven pediatric patients with spinal cord injury were hospitalized in the Clinic of Rehabilitation over the period 2014 - 2019. As a multi-specialized center the Children's Hospital in Olsztyn provides such patients with comprehensive care and therapy. Early rehabilitation interventions are implemented immediately after surgery, already in the Orthopedic Ward. If the general condition of SCI survivor is stable, the patient is directed to the Clinic of Rehabilitation and follows the rehabilitation program. The intensive early stage rehabilitation can last from 6 weeks up to 3 months in a row. Both the patient approach and the implemented therapy are scheduled individually for every patient. Among medical conditions that significantly make the process of regaining function more difficult are: recurrent urinary tract infections, nephrolithiasis, pain, deep vein thrombosis, pressure ulcers, pneumonia, and bronchiectasis. These complications are non-specific and can occur also in patients hospitalized due to other health conditions than SCI. Problems characteristic for patients after spinal injury, especially above T6 level, require special medical attention. These include cardiovascular disorders resulting from autonomic dysfunction such as: hypotension and bradycardia, orthostatic hypotension and autonomic dysreflexia. Thermoregulation disorders and periarticular ossification should also be underlined.

**Conclusions:** Although SCI is classified as a rare pathology, its prevalence in younger population has a rising tendency. Our efforts should primarily concentrate on spinal

injury prevention. Current research focuses mainly on treatment promoting neuronal tissue regeneration. However, clinical experience in recognizing and treating the autonomic system dysfunctions in patients after SCI is still limited among health professionals. Therefore further promotion of knowledge on this topic seems vital.

**Key words:** spinal cord injury, autonomic dysfunction, neurological rehabilitation



## The role of stem cells in the myocardial regeneration and cardiac repair

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**Background and objectives:** The physiology of regeneration process is crucial for the future of medicine. The use of stem cells in the treatment of different diseases (e.g. spinal cord injury, cardiovascular disease, neurodegenerative diseases etc.) falls within the scope of interest of many researchers. Resident cardiac stem cells has been found in human heart. Thus, the use of stem cells in the regeneration after myocardial infarction has been proposed. **Materials and Methods:** The MEDLINE, EMBASE, Scopus/Elsevier, Science Direct as well as The Cochrane Central Register of Controlled Trials (CENTRAL), USA Clinical Trials registry, and The International Web of Science up to December 2019 has been searched. The key words such as “stem cells”, “cardiac repair”, “myocardial infarction”, “stem cells transplantation”, “progenitor cells” and “regeneration” has been used. **Results:** The cells which are used in cardiac repair are mainly: allogeneic: embryonic stem cells (ESCs) from inner cell mass of blastocyst, foetal cardiomyocytes, human umbilical cord-derived cells; as well as autologous (adult stem cells): resident cardiac SCs; adipose-derived SCs, skeletal muscle myoblasts (SMs), cells from other tissues such as bone marrow [bone marrow-derived stem cells (BMSCs) e.g. mononuclear/CD34+ fraction and mesenchymal stem cells – MSC] as well as induced pluripotent SCs (iPS). Finding the physiological way of improving the cardiogenic differentiation of stem cells is crucial for the transplant success. Then, the effective regeneration of injured myocardium could be achieved. **Conclusions:** Stem cell transplants are relatively safe. However, in some patients after myoblast of skeletal muscles transfer (SMs) the occurrence of arrhythmias and ventricular tachycardia has been reported. Still the mechanisms of stem cell action in donor body are not fully understood.

**Keywords:** rehabilitation, heart, tetraplegic, hypoxia, aortic valve, stenosis

## Pain is associated with changes of salivary cortisol and melatonin levels

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**Introduction.** The key to adequate pain management is assessing its presence and identifying exact severity of the pain. Current 'gold-standard' pain assessment tools rely on self-reporting, requiring an ability to communicate this personal experience [1]. Self-reporting varies from patient to patient and could be inaccurately understood by healthcare professionals. There is a dearth of knowledge about the link between following hormones cortisol and melatonin and pain sensitivity. Pain diagnosis and management would benefit from the development of objective markers of nociception and pain.

**Aim.** To investigate concentration of salivary cortisol and melatonin in children with acute pain and compare it with severity of pain and changes in vital signs.

**Methods.** The present study was performed at Lithuanian University of Health Sciences Hospital Pediatric emergency department (PED). The study involved twenty-six patients (16 boys and 10 girls) complained of acute pain. The age median was 10 (4-16) years. 14 cases were trauma patients, whereas in the other 12 cases the cause of the pain was not related to trauma. Patients with chronic conditions (cancer, immunodeficiency, diabetes, etc.), fever, dehydration, or chronic pain were excluded. The following vital signs (heart rate (HR), blood pressure (BP), respiratory rate (RR), temperature (t°), and oxygen saturation (SaO<sub>2</sub>)) were monitored and recorded. The pain scale was used to evaluate the pain localization, severity and duration. Saliva samples were collected from the patients in order to determine cortisol and melatonin levels using ELISA kits.

**Results.** We found that HR and BP increase with regard to pain. Other parameters (RR, t°, SaO<sub>2</sub>) were within the age range. The median of cortisol and melatonin levels were 287.5 (68-1330) pg/ml and 17.6 (8.6-46.8) pg/ml respectively. There were several findings related to saliva hormone level and intensity of pain, duration of pain and it's link to vital signs. There was a tendency to melatonin reduction with increased intensity of pain (p=0.136). The longer the pain lasted, the higher cortisol levels were identified (p=0.01). However, there was no association between abnormal vital signs and changes in salivary cortisol and melatonin levels.

**Conclusions.** Our primary results show a cortisol rise with regard to pain in time-dependent manner. Melatonin levels decreased in relation to increased pain intensity. These results show a potential of cortisol and melatonin as biomarkers in acute pain diagnostics. However, further investigations in this field are needed.

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## The impact of $\beta$ -hydroxybutyrate for permeability in Caco-2 cells monolayer

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**Background.** A chronic low-grade has been associated with obesity and is a probable underlying reason for the upcoming of type II diabetes mellitus linked with fat tissue inflammation. The source of the inflammation is unknown, but lipopolysaccharide (LPS) penetrating the intestinal epithelium has been suggested as a possible factor. HMG-CoA synthase activity increase in obesity, leading to increased production of ketone bodies (KB), specially  $\beta$ -hydroxybutyrate (BHB) [1]. We hypothesize that higher levels of ketone bodies may enhance intestinal paracellular permeability to large molecules like LPS.

**Aim.** To elucidate the impact of BHB associated permeability in Caco-2 cells monolayer in vitro. **Methods.** Caco-2 cells were cultured on membrane and snap-wells in 2 weeks before treatment with  $\beta$ -hydroxybutyrate. The cells on snap-wells were exposed luminal  $\gamma$  by  $\beta$ -hydroxybutyrate in different concentrations (3.1 mM; 6.25 mM; 12.5 mM, 25 mM; 50 mM) for 24h) also having the control. Molecular probe FD4, KB was estimated basolaterally after 3, 6, 24 h. The cells on the membrane were scraped off and saved for later Western blot analyses of Claudin 1, Claudin 2, and Claudin 3, proteins.

**Results.** BHB was present in all of the used concentration only at a 24 h time point, respectively, 0.2, 0.4, 2.3, 4.9, 6.6 mM. We did not detect BHB in the control group. Permeability of FD4 probe in Caco-2 cells cultured on membrane tends to be higher in 25 mM (n=6) and 50 mM (n=6) concentration groups. However, no significant difference was found between the groups. Tight junction protein Claudin 1 showed lower expression 0,7 in optical density (OD) units compared with control group 1,5 OD (p=0.068), Claudin 2 expression was higher in all of the concentration treated by

BHB in contrast with control ( $p=0.145$ ). Claudin 3 was found higher in cells treated with 12,5mM and 50mM of BHB (0.115).

**Conclusions.** BHB showed an effect increasing probe FD4 and BHB permeability throughout the Caco-2 cells, however only reduced expression of Claudin 1 displayed dependence on BHB treatment.

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## Ultrasonic modulation of drug action

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**Background.** The low frequency ultrasound (LUS) induces endothelium-independent vasodilation in vivo (Fischell et al. 1991), (STEFFEN et al. 1994). The LUS induces vascular relaxation in the canine coronary arteries (Miyamoto et al. 2003), human superficial femoral arteries (Robert J. Siegel et al. 1992) and brachial arteries (Iida et al. 2006). Contradictory findings show, that the LUS induced vasodilation is endothelium dependent, and is abolished by the nitric oxide synthase inhibition (Suchkova et al. 2002). Some authors propose that the LUS induced vascular relaxation is mediated via changes in the prostacyclin release (Maruo et al. 2004). Recently, it has been shown, that the insonation before contraction promotes the vascular contraction in human thoracic arteries and that calcium is involved in the contraction mechanism (Bubulis et al. 2017). Very recently, high intensity ultrasound (27.38 MHz) has been presented as a mean to modulate the voltage-gated potassium currents [in pyramidal neurons] (Lin et al. 2019), thus it is more likely than not that the potassium channels (K<sup>+</sup>) are involved in the vascular LUS effects.

**Aim.** To investigate if the LUS can alter the pharmacological effects of drugs on the isolated rat mesentery and human pulmonary vessels.

**Methods.** Third branch mesenteric arteries were dissected from the mesenteric vascular bed, and mounted on 40- $\mu$ m steel wires in microvascular myographs (Danish Myotechnology, Aarhus, Denmark) for isometric tension recording as previously described (Mulvany and Halpern, 1976). Data were presented as mean  $\pm$  S.E.M. with a significance level of  $p < 0.05$ . The two-way analysis of variance (ANOVA) was used to compare the different conditions. The graphs and statistical analyses were performed using SAS.

**Results.** The vessels were, either contracted with noradrenalin, or physiological saline solution with high potassium concentration (KPSS), then incubated with the capsaicin, dopamine or fenoldopam (with and without glibenclamide) and insonated. The insonation was also conducted on the vessels, incubated in the Ca<sup>2+</sup> free physiological

saline solution (PSS), contracted with the increasing extracellular  $\text{Ca}^{2+}$  concentrations and noradrenalin. The human pulmonary arteries were contracted with the KPSS and dopamine. Then the vessels were insonated. The LUS inhibited the influx of external  $\text{Ca}^{2+}$ , the dopamine induced vascular contraction in the KPSS (reversed with glibenclamide), reduced the vasorelaxant effects of the capsaicin and increased the gentamicin induced vascular relaxation. Insonation increased the dopamine induced contraction in the KPSS in human pulmonary arteries.

**Conclusion.** The low-frequency (20,71 kHz) insonation inhibits extracellular  $\text{Ca}^{2+}$  entry, modulates the action of drugs that have effect on the extracellular  $\text{Ca}^{2+}$  entry (amlodipine and capsaicin), or have adrenergic effects (dopamine, that causes vascular contraction via  $\alpha 1$  and  $\alpha 2$  adrenoreceptor activation). The insonation also modulates the action of dopamine in human pulmonary arteries and, thus has potential role to locally modulate the vasoactive drug action in the lungs, a beneficial property with potential clinical use in pulmonary hypertension.

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## Involvement of endothelial NO in GYY4137 relaxation of rat mesenteric small arteries

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**Background.** Hydrogen sulphide (H<sub>2</sub>S) is considered an important signaling molecule in the cardiovascular and nervous systems (Szabó, 2007),(Sun, Tang, DU, & Jin, 2011),(Wallace, Vaughan, Dickey, MacNaughton, & de Nucci, 2018) and a variety of pathophysiological changes including cancer, glycometabolic disorders, diabetes, and sepsis are associated with altered endogenous levels of H<sub>2</sub>S (Kang, Neill, & Xian, 2017), (Yang et al., 2017). In the cardiovascular system endogenous H<sub>2</sub>S can lead to both vasodilatation and vasoconstriction (Hedegaard, Gouliava, et al., 2016), (S. Li, Ping, Cao, Mi, & Cao, 2015), (Gheibi, Jeedi, Kashfi, & Ghasemi, 2018). Different types of K channels are involved in H<sub>2</sub>S vasodilatation including ATP-sensitive K channels (KATP), voltage-gated K channels (KV7, KCNQ) and large conductance calcium-dependent potassium channels (BKCa) (Cacanyiova, Berenyiova, & Kristek, 2016). It has also been postulated that H<sub>2</sub>S effects NO mediated vascular relaxation (Gheibi S. et al. 2018)

**Aim.** To investigate if the L-cysteine effect of H<sub>2</sub>S mediated vascular relaxation is related with the endothelial nitric oxide.

**Methods.** Third branch mesenteric arteries were dissected from the mesenteric vascular bed, and mounted on 40- $\mu$ m steel wires in microvascular myographs (Danish Myotechnology, Aarhus, Denmark) for isometric tension recording as previously described (Mulvany and Halpern, 1976). Data were presented as mean  $\pm$  SD with a significance level of  $p < 0.05$ . The graphs and statistical analyses were performed using SAS.

**Results.** Vessels were contracted with U46619. GYY4137 (1000 $\mu$ M) relaxed -85.78 % (35.46), GYY 4137 (1000 $\mu$ M) incubated with L-cysteine relaxed vessels -51.81 % (192.49), GYY4137 incubated with L-NAME relaxed vessels -89.74 (30.40) and GYY4137 incubated with L-cysteine and L-NAME -59.18 (42.16). Vessels incubated with L-NAME and GYY 4137 (observed relaxation (OR)-77.23 %) or Na<sub>2</sub>S (OR-87.61%)



relaxed to addition of SNP ( $10^{-4}$ M). L-NAME inhibited the vascular relaxation to acetylcholine, this effect was not observed with L-Cysteine. The experiments were repeated at least 5 times.

**Conclusion.** Endothelial nitric oxide synthesis, does not seem to have any effect on L-cysteine mediated inhibition of H<sub>2</sub>S (GY 4137) mediated vascular relaxation.

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## **Significance of antioxidant defense system status for renal cell carcinoma patient survival**

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**Objectives:** Kidney cancer is the third leading urological tumor after prostate and bladder cancers. It is known that oxidative stress is implicated in renal cell carcinoma pathogenesis, growth and progression. The aim of this study was to reveal whether the oxidative stress parameters are associated with overall survival of renal cell carcinoma patients.

**Methods:** A total of 49 patients were enrolled in the study. The blood samples of patients before and after the surgery were analyzed for oxidative stress parameter, malondialdehyde level and for the activity of antioxidative enzymes, superoxide dismutase and catalase, levels of glutathione S-transferase and of antioxidant glutathione.

**Results:** The preoperative or postoperative superoxide dismutase and catalase activities were not associated with patients' survival. Low preoperative malondialdehyde, high glutathione and low glutathione S-transferase levels showed a tendency for better survival of renal cell carcinoma patients. The increase of postoperative glutathione S-transferase level, when compared to preoperative, also indicated a better patients' survival.

**Conclusions:** Malondialdehyde, glutathione and glutathione S-transferase levels can be used for estimation of renal cell carcinoma patients' disease prognosis.

## Peculiarities in cardiac intercellular signaling

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Gap junction (GJ) channels formed from connexin (Cx) proteins provide a direct pathway for electrical and metabolic cell-cell communication. We have focused on several Cxs expressed in the heart, CNS, visual system and other tissues: Cx26, Cx30.2, Cx36, Cx40, Cx43, Cx45, Cx47 and Cx57. GJ channels are highly sensitive to intracellular pH ( $pH_i$ ), which can vary substantially among different tissues and changes under ischemia and other pathological conditions. We examined  $pH_i$ -dependent modulation of blocking capacity of several uncoupling agents: octanol and other long carbon chain *n*-alcohols (LCCAs), carbenoxolone (a derivative of glycyrrhetic acid), mefloquine (antimalarial drug), flufenamic acid (anti-inflammatory drug), isoflurane (volatile anesthetic) and arachidonic acid. Dual whole-cell patch-clamp and fluorescence microscopy were used to measure junctional conductance ( $g_j$ ) and  $pH_i$ . Acidification and all examined uncoupling agents blocked cell-cell coupling in cell lines but with Cx-type dependent  $pK_a$ s and  $IC_{50}$ s. Alkalinization to  $pH \approx 8$  increased  $g_j$  in cells expressing mCx30.2, Cx45 and Cx57, decreased  $g_j$  in cells expressing Cx36 and Cx43, and had negligible effect in cells expressing Cx26, Cx40 and Cx47. Unexpectedly, cells expressing Cx45, but not other Cxs, exhibited full coupling recovery when exposed to  $NH_4Cl$  (15 mM;  $pH_i$  increased from 7.3 to 8.1) under continuous presence of LCCAs, isoflurane or mefloquine which applied alone completely blocked  $g_j$ . Under similar experimental conditions there was no coupling recovery by alkalinization in the presence of flufenamic acid, carbenoxolone and arachidonic acid. The histidine brominating agent N-bromosuccinimide significantly reduced the stimulatory effect of  $NH_4Cl$  and inhibitory effect of octanol on Cx45 GJ channels suggesting that at least some GJ uncoupling agents act through hydrogen bonds with histidine residues. The obtained data allow us to discuss potential mechanisms that explain Cx-type dependent differences in  $g_j$  regulation by  $pH_i$  and uncoupling agents.

## **Short carbon chain *n*-alcohol-induced potentiation of Cx36 gap junction channel conductance is caused by disulfide bond re-shuffling**

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We have demonstrated earlier that short carbon chain *n*-alcohols (up to octanol) stimulated while long carbon chain *n*-alcohols inhibited the conductance of connexin 36 (Cx36) gap junction (GJ) channels. In contrast, GJ channels composed of other types of Cxs all were inhibited by *n*-alcohols independently on their carbon chain length. Structural modeling of Cx36 protein docking with hexanol and isoflurane that stimulated as well as nonanol and carbenoxolone that inhibited the conductance of Cx36 GJs revealed their multiple common docking sites and a single pocket accessible only to hexanol and isoflurane. The pocket is situated in the vicinity of three unique cysteine residues, namely C264 in the fourth, and C92 and C87 in the second transmembrane domain of the neighboring Cx36 subunits. To examine the hypothesis that disulfide bonding might be involved in the stimulatory effect of hexanol and isoflurane, we generated cysteine substitutions in Cx36 and demonstrated by a dual whole-cell patch-clamp method that in HeLa and N2A cells these mutations reversed the stimulatory effect of hexanol and isoflurane to inhibitory one, typical of other tested Cxs (Cx26, Cx30.2, Cx31, Cx43, Cx45 and Cx47) that lack respective cysteines and/or a specific docking pocket for these compounds.

Our findings suggest that the stimulatory effect of hexanol and isoflurane on Cx36 GJ conductance could be achieved by re-shuffling of the inter-subunit disulfide bond between C264 and C92 to the intra-subunit one between C264 and C87.

## **The effect of cranberry and chokeberry pomace extracts on cancer cell viability, clonogenic activity and cell-to-cell coupling**

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The extracts of various berries are rich of flavonoids, phenolic acids, tannins, vitamins, stilbenes and other compounds that are known to possess anticancer activities. The aim of this study was to evaluate the composition of cranberry and chokeberry pomace extracts (CRE and CHE), and to examine their effect on cancer cell viability, colony formation and cell-to-cell coupling. MTT and flow cytometry assays revealed that all tested cell lines (DLD-1, HCT116, HeLa expressing exogenous connexin 45 (HeLa-Cx45) and Novikoff) were more sensitive to CHE (40-1000  $\mu\text{g/ml}$ ) treatment compared to CRE (40-1000  $\mu\text{g/ml}$ ) in reducing cancer cell viability and proliferation. Clonogenic assay showed that CHE also was more effective in suppression of cancer cell colony formation. The strongest effect was achieved using 1000  $\mu\text{g/ml}$  of CHE. Impaired intercellular communication of cancer cells is related with their oncogenic properties. We measured gap junction (GJ) conductance ( $g_j$ ) between HeLa cells expressing exogenous connexin 45, and Novikoff cells expressing endogenous connexin 43 by dual whole-cell patch-clamp technique. CRE (100  $\mu\text{g/ml}$ ) stimulated  $g_j$  of Cx45 GJ channels but had no effect on Cx43 channel  $g_j$ . In contrast, CHE (200  $\mu\text{g/ml}$ ) had no effect on Cx45 GJ channels but decreased Cx43 channel  $g_j$ . Taken together our results suggest that CRE and CHE, both possess anticancer activity but differently regulate cell-to-cell coupling through Cx45 and Cx43 GJ channels.

## Effect of acute systemic intermittent and continuously hypoxia on vascular adaptive reactions in skin microcirculation

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Microcirculation have an important role when hypoxic stimulus induces a homeostatic disruption. Adaptation must happen continuously to maintain healthy tissues. The cutaneous microcirculation responses in different types of systemic hypoxia are unclear; even more cutaneous circulation has multiple vessel circuits which broad regulation including systemic hemodynamic, neuronal, myogenic and metabolic factors. The aim was to evaluate effect of acute systemic continuous and intermittent normobaric hypoxia on forearms cutaneous microcirculation and local regulatory factors.

Twenty-three healthy subjects (n=23, 25.0±3.3 years old) participated in this study. All participants were randomly tested three times by normoxic (FiO<sub>2</sub>=21%), intermittent (4x5min) and continuously (20min) hypoxic (FiO<sub>2</sub>=12%) protocols. Systemic cardiovascular parameters, regional blood flow and cutaneous blood flow were recorded. Wavelet analysis was used to evaluation of local regulatory factors; fluctuations in the frequency intervals represented endothelial (0.0095–0.021), sympathetic (0.021–0.052), and myogenic (0.052–0.145) activities.

Systemic hemodynamic was significantly elevated, however vascular conductance were not changed during both hypoxias. Cutaneous blood flow increased (N = 39.7 (34.0; 53.2) vs. CH = 51.6 ± 13.9, PU; P = 0.002 and vs. IH = 44.6 ± 10.9, PU; P = 0.03), but local regulatory factor activity was not changed in all conditions.

In conclusion the acute systemic continuous and intermittent hypoxia caused increase in systemic hemodynamic's, regional blood flow and forearms skin blood flow, however, didn't change skin vasomotor reactions.

**Keywords:** acute systemic hypoxia, intermittent hypoxia, continues hypoxia, cutaneous microcirculation, vasomotion

## **Myostatin inhibition in fighting muscle weakness; Effects on muscle mass after functional overloading and caloric restriction**

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Myostatin is a negative regulator of skeletal muscle growth [8]. It promotes muscle proteolysis [6], while myostatin inhibition increases muscle mass and improves muscle function in mice affected by muscle dystrophy [2]. The potential of myostatin inhibition in preservation of muscle mass has been discussed in relation to ageing-related muscle weakness [3], kidney disease [11], heart disease [10] and cancer cachexia [7]. However, there are also less favourable effects of myostatin dysfunction. Impaired myostatin function was associated with increased susceptibility of skeletal muscles to exercise-induced muscle damage and reduction in specific muscle force [1]. Myostatin dysfunction was also associated with less pronounced hypertrophy of soleus muscle after functional overloading [9]. Lack of functional myostatin did not protect mice from muscle atrophy after fasting or caloric restriction. In summary, usefulness of myostatin inhibition in preservation of muscle mass might be limited to diseases and conditions associated with severe muscle wasting. There are also grounds to believe that myostatin inhibition might have detrimental effects on adaptations of skeletal muscles to exercise training.

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## Renal function by developing population pharmacokinetics in Lithuania

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Immunosuppressive drugs exhibit high variability in metabolism and pharmacokinetics that may result in drug toxicity or lack of efficacy. Low immunosuppressant drug exposure increases the risk of transplant rejection in the acute post-transplant period, while supratherapeutic drug concentration entails higher risk of adverse drug reactions [1]. These issues may be resolved by population pharmacokinetic modeling.

Population pharmacokinetic modeling might be performed and researched by clinical pharmacologists, recently established clinical pharmacology residency in Lithuania may play a role in this area as well [2].

### Aims

To broaden the competence of Lithuanian clinical pharmacologists by developing one-compartment model with first-order absorption of tacrolimus.

### Methods

Anonymized medical records of kidney recipients receiving immunosuppressant tacrolimus and hospitalized at Limoges University Hospital (France) were included in the study. Tacrolimus analyses were performed using a liquid chromatography-tandem mass spectrometry method. A one-compartment model with first-order absorption was used as implemented in the NLMIXED procedure [3], which fits nonlinear mixed models.

Data analysis was performed by using SAS University Edition software. Model parameter estimated are provided with p-values and confidence limits computed by NLMIXED procedure. The p-values and confidence limits were computed from approximate standard errors (using the delta method) for the estimates.

### Results

Anonymized medical records of 189 patients receiving immunosuppressant tacrolimus (2–20 mg/d BID regimen) were analyzed and a one-compartment model with first-order absorption was constructed. The population estimates in the final population model of tacrolimus were: clearance 14.64 L/h (CI 9.66; 19.62),  $p < 0.0001$ , elimination rate  $0.001657 \text{ min}^{-1}$  (CI: 0.00098; 0.002336),  $p < 0.0001$  and absorption rate 2.7119 (CI: - 45.7083; 51.1321),  $p = 0.912$ . Mean value of concentration was 13.62



(SD: 7.5) µg/L, predicted concentration 10.83 (SD: 10.83) µg/L. Pearson correlation between measured and predicted concentrations was  $r=0.79$  ( $p<0.0001$ ).

### **Conclusions**

1. Population pharmacokinetic models should be developed in-house and clinical pharmacologists should participate in pharmacokinetic modeling process.
2. Kidney parameters still have a significant effect on the pharmacokinetics of medicines.

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## **Astroglial calcineurin - a novel regulator of CNS proteostasis: Implications for neurodegeneration and epilepsy**

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Astrocytes perform important housekeeping functions in the nervous system including maintenance of adequate neuronal excitability, although the regulatory mechanisms are currently poorly understood. The astrocytic  $\text{Ca}^{2+}$ /calmodulin-activated phosphatase calcineurin (CaN) is implicated in the development of reactive gliosis and neuroinflammation, but its roles in healthy brain is unknown. We have generated a mouse line with conditional knockout (KO) of CaN B1 (CaNB1) in glial fibrillary acidic protein (GFAP)-expressing astrocytes (astroglial calcineurin knock-out, ACN-KO). We found that postnatal and astrocyte-specific ablation of CaNB1 did not alter normal growth and development as well as adult neurogenesis. However, we found that at 1 mo of age specific deletion of astrocytic CaN selectively impairs intrinsic neuronal excitability in cerebellar granule cells (CGCs) and hippocampal CA1 pyramidal neurons. This impairment is due to functional inactivation of astroglial  $\text{Na}^+/\text{K}^+$  ATPase. Shotgun mass spectrometry proteomics analysis of hippocampal and cerebellar synaptosomes showed altered expression of astroglial as well as neuronal proteins. Gene ontology analysis revealed specific overrepresentation of terms linked synaptic functions and mitochondria. Pathway analysis revealed emergence of neurodegenerative diseases like Alzheimer's, Parkinson's and Huntington's diseases and Seizures. To check predictability of our model for a disease we followed ACN-KO mice for the presence of seizures and observed that, beginning from 6 months of age ACN-KO mice show increased risk to develop spontaneous epileptic seizures. In conclusion, astrocyte-specific CaN KO shows features of several neurological and neurodegenerative disease, indicating that alteration of its activity may be involved in the early stage pathogenesis of brain diseases. More generally, astroglial calcineurin may be a master-regulator of the CNS homeostasis.

## Radical radiotherapy and radiochemotherapy of non-small cell lung cancer patients – survival analysis

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Lung cancer is the most common type of cancer, the first cause of death from cancer. The aim of the study was to report the efficiency of radical radiotherapy and radiochemotherapy in non-small cell lung cancer (NSCLC) in the group of locally advanced non-operable disease (Clinical Stage III). 92 patients with diagnosed NSCLC who underwent curative radio- or radiochemotherapy between 2013-2016 in Nu-Med Center in Elblag were included to analysis. Overall survival (OS) was obtained from national state registry, estimated by Kaplan-Meier method and analyzed in relation to clinical and demographical factors. The most of patients were men (72, 78%). Median age was 64 years. The most patients were treated in clinical stage (CS) IIIA (53, 58%) and IIIB (31, 34%). 2-year OS for all patients was 36% (median 1.5 years). From all analyzed prognostic factors, performance status (PS) during first consultation was significant. Patients with PS 0-1 had better 2-year OS (39%, median 1.6 years) compared with PS 2 (median 0.7 years). However, radiochemotherapy as a method of treatment also was associated with better survival outcomes of NSCLC patients. 26 patients (28%) underwent concurrent radiochemotherapy and 38 patients (41%) treated with sequential radiochemotherapy had statistically significant better 2-year OS in comparison with 28 patients (31%) treated with alone radiotherapy (respectively 46% and 37% vs 25%,  $p \leq 0.05$ ). Total treatment time, age, sex, BMI, place of residence, lymph node metastasis, CS, tumor localization, type of histopathology, PET examination had no impact on OS.

Almost 50% of NSCLC patients treated with concurrent radiochemotherapy survived 2 years. Good PS (0-1 vs 2) was associated with better prognosis of patients.

**Keywords:** non-small cell lung cancer, concurrent radiochemotherapy, overall survival

## **Challenges for teaching of physiology in PBL environment in LSMU**

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Since the introduction of problem-based learning (PBL) in the Faculty of Medicine of the Lithuanian University of Health Sciences (LSMU) in 2007, teaching of physiology has changed significantly. The program of a single discipline was split among different preclinical modules on thematic basis throughout 2–3 study years. Traditional classes for physiology and other subjects (anatomy, histology, biochemistry, pharmacology, etc.) were combined with PBL tutorials into the integrated module curriculum.

Curriculum reorganization and introduction of PBL tutorials as integrated interdisciplinary classes have brought new challenges for teachers of physiology in academic, personal and organizational areas. This included change of the teacher's role from presenter of knowledges to facilitator for studies, change of focus from mostly theory-oriented teaching to more clinically applicable, need for deeper understanding of the material from other subjects and improvement of personal communication competences.

Despite some encouraging data about changes in the attitude toward learning among PBL students, there is a lack of information how successfully teachers of physiology (or other preclinical subjects) cope with these challenges, and how this affects students' ability to integrate knowledge from different preclinical subjects into a whole and use them to make diagnostic and treatment decisions during subsequent studies and residency training.

Such study could possibly help to improve the preparation of teachers for PBL and the integration of physiology discipline into the PBL curriculum.

## Author Index

Abramavičius S. ....	13, 15, 23	Mickevičiūtė G. C. ....	9
Akramenė A. ....	17	Mickus R. ....	19
Badzio A. ....	26	Minderis P. ....	22
Bajoriūnas V. ....	13	Nawrocki S. ....	26
Bałyda E. ....	3	Osowiecka K. ....	26
Bubulis A. ....	13	Paparde A. ....	21
Casselbrant A. ....	11	Petersen A. G. ....	15
Circenis K. ....	21	Plakane L. ....	21
Dabkevičienė D. ....	17	Protasiewicz-Fałdowska H. ....	5
Daktaras V. ....	11	Radzevičienė A. ....	23
Didžiapetrienė. ....	17	Raškevičius V. ....	19
Fokin A. ....	22	Ratkevičius A. ....	22
Ganzijeva K. ....	9	Renaltan N. S. ....	15
Gromadziński L. ....	3	Saint-Marcoux F. ....	23
Hedegaard E. R. ....	15	Sarapinienė I. ....	20
Jablonskienė V. ....	17	Simonsen U. ....	15
Jančiukė G. ....	20	Skeberdis V. A. ....	18
Jankauskaitė L. ....	9, 11	Stankevičius E. 3, 6, 8, 13, 15, 23, 24	
Jankevičius F. ....	17	Szostakiewicz B. ....	26
Kaduševičius E. ....	23	Šaulys K. G. ....	20
Kamelska-Sadowska A. M. ....	3, 5, 6, 8	Tretjakovs P. ....	21
Kazbarienė B. ....	17	Tunaitytė A. ....	13
Korotkich I. ....	27	Ulys A. ....	17
Kowalski I. M. ....	3, 5, 6, 8, 13, 18	Venslauskas M. ....	13
Kurowicki M. ....	26	Volkevičiūtė A. ....	13
Kvedaras M. ....	22	Warmowska-Dawid A. ....	5, 6
Laukevičienė A. ....	27	Whiteman M. ....	15
Lim D. ....	25	Zaborowska-Sapeta K. ....	5, 6, 8
Malinauskas M. ....	9, 11	Żechowicz T. ....	3

## Table of Contents

The physiological adaptation to exercise following cardiac rehabilitation in patient after several cardiopulmonary resuscitations and severe hypoxia – case study.....	3
The correlation between lumbar low-grade scoliosis and the magnitude of physiological curvatures of the spine in standing and sitting positions in children.....	5
Clinical complications after spinal cord injury in pediatric patients.....	6
The role of stem cells in the myocardial regeneration and cardiac repair .....	8
Pain is associated with changes of salivary cortisol and melatonin levels .....	9
The impact of $\beta$ -hydroxybutyrate for permeability in Caco-2 cells monolayer .....	11
Ultrasonic modulation of drug action.....	13
Involvement of endothelial NO in GYY4137 relaxation of rat mesenteric small arteries.....	15
Significance of antioxidant defense system status for renal cell carcinoma patient survival.....	17
Peculiarities in cardiac intercellular signaling .....	18
Short carbon chain n-alcohol-induced potentiation of Cx36 gap junction channel conductance is caused by disulfide bond re-shuffling .....	19
The effect of cranberry and chokeberry pomace extracts on cancer cell viability, clonogenic activity and cell-to-cell coupling .....	20
Effect of acute systemic intermittent and continuously hypoxia on vascular adaptive reactions in skin microcirculation .....	21
Myostatin inhibition in fighting muscle weakness; Effects on muscle mass after functional overloading and caloric restriction .....	22
Renal function by developing population pharmacokinetics in Lithuania.....	23
Astroglial calcineurin - a novel regulator of CNS proteostasis: Implications for neurodegeneration and epilepsy .....	25
Radical radiotherapy and radiochemotherapy of non-small cell lung cancer patients – survival analysis.....	26
Challenges for teaching of physiology in PBL environment in LSMU .....	27