# CROATIAN INTERNATIONAL PUBLICATIONS

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**Kutlesa M, Novokmet A, Josipovic Mraovic R, Filar B, Mardesic P, Barsic B. Extracorporeal membrane oxygenation treatment for H1N1-induced acute respiratory distress syndrome (ARDS): results of the Croatian Referral Center for Respiratory ECMO. Int J Artif Organs. 2014;37:748-52.**

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INTRODUCTION: Extracorporeal membrane oxygenation (ECMO) has been effective in the treatment of H1N1-induced ARDS across the globe. However, the evidence supporting the use of ECMO in ARDS is still being collected. The intention of this study was to add a piece of puzzle to the growing body of evidence on the use of ECMO in ARDS patients. METHODS: The study included adult patients with H1N1-induced ARDS treated with ECMO at the University Hospital for Infectious Diseases in Zagreb, Croatia between October 2009 and December 2013. RESULTS: 17 patients with H1N1-induced ARDS treated with ECMO were included in the study. The patient cohort of the study was young with a median age of 43 years (range 23-74). The hospital mortality was 35%. Possible variables associated with mortality were analyzed and only hemolysis was found to be significant. CONCLUSIONS: Our results confirm the usefulness of ECMO treatment in patients with H1N1-induced ARDS.

**Dzaja D, Hladnik A, Bicanic I, Bakovic M, Petanjek Z. Neocortical calretinin neurons in primates: increase in proportion and microcircuitry structure. Front Neuroanat. 2014;8:103.**

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In this article we first point at the expansion of associative cortical areas in primates, as well as at the intrinsic changes in the structure of the cortical column. There is a huge increase in proportion of glutamatergic cortical projecting neurons located in the upper cortical layers (II/III). Inside this group, a novel class of associative neurons becomes recognized for its growing necessity in both inter-areal and intra-areal columnar integration. Equally important to the changes in glutamatergic population, we found that literature data suggest a 50% increase in the proportion of neocortical GABAergic neurons between primates and rodents. This seems to be a result of increase in proportion of calretinin interneurons in layers II/III, population which in associative areas represents 15% of all neurons forming those layers. Evaluating data about functional properties of their connectivity we hypothesize that such an increase in proportion of calretinin interneurons might lead to supralinear growth in memory capacity of the associative neocortical network. An open question is whether there are some new calretinin interneuron subtypes, which might substantially change micro-circuitry structure of the primate cerebral cortex.

**Katunaric M, Jurisic D, Petkovic M, Grahovac M, Grahovac B, Zamolo G. EGFR and cyclin D1 in nodular melanoma: correlation with pathohistological parameters and overall survival. Melanoma Res. 2014;24:584-91.**

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Considering that nodular melanoma (NM) has the potential to show an early distant metastasis, there is

an urgent need for the discovery and evaluation of new diagnostic and prognostic biomarkers. We aimed to investigate the protein expression of membrane and nuclear epidermal growth factor receptor (EGFR), cyclin D1, and the corresponding gene status in NM samples and correlate the results obtained with clinicopathological parameters and overall survival of patients. Immunohistochemical and fluorescence in-situ hybridization analyses were carried out on tissue microarrays constructed from 110 NM samples, 30 compound nevi, and 38 dysplastic nevi. NM samples showed 24% strong cyclin D1 and 37% strong Ki67 protein expression compared with 3 and 0% strong cyclin D1 and Ki67 expression in the control group. Membrane EGFR expression was detected in 50% of NM cases, whereas EGFR gene amplification was detected in only 4% of NM cases. Multiple NM samples presented simultaneous membrane and nuclear EGFR expression. We found a negative correlation between tumor thickness and membrane EGFR expression. It was also observed that membrane EGFR 3+ NM samples presented ulceration significantly more often than membrane EGFR-negative (0) NM samples. In univariate analysis, carried out on 44 patients with follow-up data, both nuclear and membrane EGFR overexpression showed a correlation with a shorter overall survival. Nuclear EGFR (++, +++) showed 3.06 and membrane EGFR (2+, 3+) showed 2.76 higher risk of mortality compared with patients with low and negative nuclear and membrane EGFR expression (P<0.05).

**Mikolasevic I, Racki S, Zaputovic L, Lukenda V, Sladoje-Martinovic B, Orlic L. Nonalcoholic Fatty Liver Disease (NAFLD) And Cardiovascular Risk In Renal Transplant Recipients. Kidney Blood Press Res. 2014;39:308-314.**

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BACKGROUND/AIMS: Renal transplant recipients (RTRs) are at high risk for cardiovascular (CVD) mortality. Recently, nonalcoholic fatty liver disease (NAFLD) has been recognized as a new risk factor for adverse CVD events in the general population. We examined whether transient elastography (TE) defined NAFLD was associated with atherosclerosis in RTRs, as measured by ultrasound in the carotid arteries. METHODS: Carotid atherosclerosis was assesses in 71 RTRs with a TE proven NAFLD. With the help of TE liver stiffness was used to assess liver fibrosis and Controlled Attenuation Parameter (CAP) was used to detect and quantify liver steatosis. NAFLD was defined by the presence of steatosis with CAP values ≥238 dB.m-1. RESULTS: RTRs with NAFLD showed more carotid atherosclerosis than RTRs without NAFLD. RTRs-NAFLD patients had the mean intima-media measurements (ITM) of 1.1±0.1 mm and that was statistically significant higher than the mean ITM founded in RTRs without NAFLD (1.1±0.1 vs. 0.9±0.1 mm; p<0.0001). Furthermore, RTRs-NAFLD patients had statistically significant higher prevalence of plaques in comparison with RTRs without NAFLD (p=0.021). CONCLUSION: We showed for the first time that carotid atherosclerosis is advanced in RTRs with NAFLD. Detection of NAFLD by TE should alert to the existence of an increased cardiovascular risk in RTRs.

**Makarovic Z, Makarovic S, Bilic-Curcic I. Sex-dependent association between coronary vessel dominance and cardiac syndrome X: a case-control study. BMC Cardiovasc Disord. 2014;14:142.**

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BACKGROUND: Previous studies have demonstrated the relevance of left coronary artery dominance in the outcome and prognosis of obstructive coronary artery disease (CAD). However, no studies have investigated the influence of coronary vessel dominance on non obstructive CAD. The aim of this study was to establish the association of left and mixed dominance of the major epicardial arteries with the development of non obstructive CAD and evaluate potential sex-dependent differences in the coronary artery supply. METHODS: A total of 484 patients underwent the same diagnostic procedures. The patients were divided into two groups based on their coronary angiogram results: the control group (242 patients with obstructive CAD; coronary artery stenosis of ≥50%) and the experimental group (242 patients with non obstructive CAD; coronary artery stenosis of <50%). RESULTS: Significantly more women than men were affected by non obstructive CAD (P = 0.005). Left dominance was more frequent in the non obstructive CAD group than in the control group (P = 0.018) and was more pronounced in women than in men (P = 0.013). Among men with non obstructive CAD, a left supply was more frequent than a mixed supply (P = 0.012). Women with non obstructive CAD had a higher frequency of a left supply, whereas a mixed supply was less frequent

in men than in patients with obstructive CAD (P = 0.013 and 0.018, respectively). CONCLUSION: These results suggest that left dominance (particularly in women) and the absence of a mixed supply in men could cause regional ischemia, thus affecting the development of non obstructive CAD. Furthermore, sex may determine the incidence of specific coronary artery supply types, therefore influencing disease development and prognosis.

**Tomljenovic D, Pinter D, Kalogjera L. Perceived stress and severity of chronic rhinosinusitis in allergic and nonallergic patients. Allergy Asthma Proc. 2014;35:398-403.**

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Chronic stress exposure carries greater risk of onset of atopic respiratory disorders such as rhinitis and asthma. The interaction between depression, anxiety, and severity of chronic rhinosinusitis (CRS) has been suggested. We aimed to access the relationship between psychological stress, severity of CRS, and atopy. Sixty-three consecutive patients referred with CRS were asked to score the severity of rhinosinusitis symptoms on a visual analog scale and to fill in questionnaires on the disease-specific quality of life and perceived stress-22-item Sino-Nasal Outcome Test (SNOT-22) and measure of perceived stress (MPS) scale, respectively. Inclusion criteria for the study were a reliable allergy evaluation and a recent computerized tomography (CT) scan of the sinuses. Patients with nasal polyps (NPs), asthma, and previous surgery were excluded. The study group consisted of 14 allergic and 18 nonallergic patients with CRS without NPs (CRSsNPs). Correlation between MPS and SNOT-22 scores in the study group was highly significant (Pearson r = 0.61; p = 0.001). Patients with higher stress scores had significantly stronger postnasal discharge, thick discharge, cough, disturbed sleep, fatigue, and sadness. Postnasal drip was significantly stronger in patients with allergy. The correlation between SNOT-22 and CT scores was insignificant. The correlation between MPS and SNOT-22 scores suggests an interaction between severity of CRS and chronic stress, but not with the extent of the disease on CT in CRSsNPs. Chronic psychological stress might be one of the factors that modifies the disease severity and may lead to uncontrolled disease in CRS patients.

**Bajs Janovic M, Kalember P, Janović S, Hrabac P, Folnegovic Grosic P, Grosic V, Rados M, Henigsberg N. No change in N-acetyl aspartate in first episode of moderate depression after antidepressant treatment: (1)H magnetic spectroscopy study of left amygdala and left dorsolateral prefrontal cortex. Neuropsychiatr Dis Treat. 2014;10:1753-62.**

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BACKGROUND: The role of brain metabolites as biological correlates of the intensity, symptoms, and course of major depression has not been determined. It has also been inconclusive whether the change in brain metabolites, measured with proton magnetic spectroscopy, could be correlated with the treatment outcome. METHODS: Proton magnetic spectroscopy was performed in 29 participants with a first episode of moderate depression occurring in the left dorsolateral prefrontal cortex and left amygdala at baseline and after 8 weeks of antidepressant treatment with escitalopram. The Montgomery-Asberg Depression Rating Scale, the Hamilton Rating Scale for Depression, and the Beck Depression Inventory were used to assess the intensity of depression at baseline and at the endpoint of the study. At endpoint, the participants were identified as responders (n=17) or nonresponders (n=12) to the antidepressant therapy. RESULTS: There was no significant change in the N-acetyl aspartate/creatine ratio (NAA/Cr) after treatment with antidepressant medication. The baseline and endpoint NAA/Cr ratios were not significantly different between the responder and nonresponder groups. The correlation between NAA/Cr and changes in the scores of clinical scales were not significant in either group. CONCLUSION: This study could not confirm any significant changes in NAA after antidepressant treatment in the first episode of moderate depression, or in regard to therapy response in the left dorsolateral prefrontal cortex or left amygdala. Further research is necessary to conclude whether NAA alterations in the first episode of depression could possibly be different from chronic

or late-onset depression, and whether NAA alterations in stress-induced (reactive) depression are different from endogenous depression. The potential role of NAA as a biomarker of a treatment effect has yet to be established.

**Boric M, Jelicic Kadic A, Puljak L. Cutaneous expression of calcium/calmodulin-dependent protein kinase II in rats with type 1 and type 2 diabetes. J Chem Neuroanat. 2014;61-62C:140-146.**

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Changes in calcium-calmodulin protein kinase II (CaMKII) have been well demonstrated in nervous tissue of diabetic animal models. Skin shares the same ectodermal origin as nervous tissue and it is often affected in diabetic patients. The goal of this study was to analyze expression of CaMKII in rat foot pad 2 weeks and 2 months after induction of diabetes type 1 and 2. Forty-two Sprague-Dawley rats were used. Diabetes mellitus type 1 (DM1) was induced with intraperitoneally (i.p.) injected 55mg/kg of streptozotocin (STZ) and diabetes mellitus type 2 (DM2) with a combination of high-fat diet (HFD) and i.p. injection of low-dose STZ (35mg/kg). Two weeks and two months following diabetes induction rats were sacrificed and skin samples from plantar surface of the both hind paws were removed. Immunohistochemistry was performed for detection of total CaMKII (tCaMKII) and its alpha isoform (pCaMKIIα). For detection of intraepidermal nerve fibers polyclonal antiserum against protein gene product 9.5 (PGP 9.5) was used. The results showed that CaMKII was expressed in the skin of both diabetic models. Total CaMKII was uniformly distributed throughout the epidermis and pCaMKIIα was limited to stratum granulosum. The tCaMKII and pCaMKIIα were not expressed in intraepidermal nerve fibers. Two weeks after induction of diabetes in rats there were no significant differences in expression of tCaMKII and pCaMKIIα between DM1 and DM2 compared to respective controls. In the 2-month experiments, significant increase in epidermal expression of tCaMKII and pCaMKIIα was observed in DM1 animals compared to controls, but not in DM2 animals. This study is the first description of cutaneous CaMKII expression pattern in a diabetic model. CaMKII could play a role in transformation of skin layers and contribute to cutaneous diabetic changes. Further research on physiological role of CaMKII in skin and its role in cutaneous diabetic complications should be undertaken in order to elucidate its function in epidermis.