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# When Tradition Meets Innovation
# Five Decades of Research at the Department of Physiology in Martin

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## Summary

The Department of Physiology at Jessenius Faculty of Medicine, Comenius University in Martin celebrates its 50$^{th}$ anniversary in academic year 2016/2017. The reader is invited to the exciting journey through the history since Department´s establishment till present, through five decades of development, new methods, domestic and international cooperation, interdisciplinarity and original achievements in the experimental and clinical-physiological research areas. The article focuses on early results as well as main current findings especially in the field of respiratory reflexes, pulmonary surfactant, autonomic nervous system involvement in heart rate and blood pressure control in physiological and pathological conditions, psychophysiology, and clinical and experimental perinatal physiology.

***Early history of the Department of Physiology***

The teaching and research in Physiology as a basic medical subject started in Martin in the academic year 1966/67. At the beginning, prof. Juraj Antal, MD, DSc. from Institute of Physiology, Faculty of Medicine in Bratislava and his co-workers regularly commuted to Martin and arranged Physiology lectures and practicals. The first head of the Department of Physiology (Jessenius) Faculty of Medicine in Martin, Comenius University in Bratislava (JFM CU) became assoc. prof. Vladimír Kirilčuk, MD, CSc. After his emigration to USA in 1968, prof. Zoltán Tomori, MD, DSc. from the Institute of Pathological Physiology, Faculty of Medicine, P. J. Šafárik University Košice has led and shaped Department for following 17 years. Prof. Tomori continued in his research previously done in Košice with focus on respiratory reflexes, especially mechanisms of cough and aspiration reflex, laryngeal and lung receptor activities (with prof. Stránsky), the central activity of respiratory center neurons (with prof. Jakuš) and cardiorespiratory relations during respiratory reflexes (with prof. Kamil Javorka). The electrophysiological respiratory research was transferred to the Department of Biophysics JFM CU in Martin after prof. Albert Stránsky and prof. Ján Jakuš moved there. Prof. Tomori published a number of full-text scientific papers and monographs, of which the most significant is Korpas J, Tomori Z. Cough and Other Respiratory Reflexes. Karger, 1979, awarded in 1983 by State Price of the Czechoslovak Federal Republic.

The most important achievements in the 1970s and middle 1980s at the Department of Physiology in Martin are the detailed description of the mechanisms of coughing with concomitant effects as well as cardiovascular effects of respiratory reflexes in animals; detailed description of the function and importance of larynx in coughing and sneezing (in co-operation with prof. Widdicombe, Oxford, London) the discovery of nasopharyngeal aspiration (Tomori´s) reflex, which activates the inspiratory brain stem generator and may resume regular breathing even in the terminal stages and restart cardiovascular function, and which is patented in several countries; the explanation of the role of pulmonary slowly adapting receptors and bulbar neuronal respiratory activity in defensive airway reflexes; the explanation of several airway and lung reflexes and accompanying cardiovascular effects; the preparation and verification of an experimental model of acute reversible cardiorespiratory failure which was adopted also by other laboratories to study resuscitation techniques.

In late 1980s and in early 1990s the high frequency jet ventilation (HFJV) and its special inpulsion and expulsion effects have been studied in collaboration with the Konštrukta Trenčín, Chirana Stará Turá and Faculty Hospital in Motol, Prague (ing. Brychta, ing. Jurček, dr. Zábrodský).

Over the past decades, two main research branches have been developed: experimental and clinical – physiological.

***Experimental research*** is performed in two main areas, in the field of pulmonary surfactant and related models of respiratory diseases, especially of neonatal age, and in the area of respiratory and cardiovascular regulation in hyperthermia and fever.

Pulmonary surfactant is a lipid-protein complex which reduces surface tension at the air/liquid interphase, thereby preventing lung collapse. The research in the area of pulmonary surfactant started to intensively develop in early 1990s in line with perinatology and ontogenetic aspects of the respiratory system. This period was characterized by search for suitable model, isolation of rabbit natural surfactant and evaluation of the effects of mechanical ventilation, particularly high-frequency modes, on the function of surfactant. The cooperation with surfactant pioneers, prof. Robertson and prof. Curstedt from Karolinska Institutet in Stockholm, has opened new research possibilities. At present, the topics that are addressed at the Department, became attractive to young researchers who are interested in the post-graduate study and post-doc positions.

Experimental model of acute respiratory distress syndrome (ARDS) is elicited by repetitive saline lung lavage and model of meconium aspiration syndrome (MAS) is induced by intratracheal instillation of human meconium, both in young rabbits (for review see Mokra and Calkovska 2017). These models are used for evaluation of efficacy of various ventilatory modes including non-conventional approaches, such as high-frequency oscillatory ventilation and high-frequency jet ventilation (HFJV). At present, APVV project is implemented in co-operation with Chirana a.s., Stará Turá, the producer of medicinal technique and patient ventilators, on preclinical testing of newly developed neonatal ventilator. In addition to ventilation treatment, effects of various potentially beneficial drugs are evaluated in these models. The activity focuses on studying the therapeutic potential of various anti-inflammatory drugs in these models of surfactant-deficiency, in cooperation with Department of Pharmacology. Synthetic glucocorticoids, antioxidants and inhibitors of phosphodiesterases have been successfully used in experimental MAS. In the model of ARDS, the effect of intravenous dexamethasone, intratracheal budesonide (Mokra *et al*. 2016), nitric oxide donor SNAP as well as intravenous non-selective PDE inhibitor aminophylline and selective PDE3, 4 and 5 inhibitors have been recently evaluated (Kosutova *et al.* 2017). Actually, the effect of nitrosylated steroids and selective agonists of glucocorticoid receptors has been compared to classical synthetic glucocorticoids to reveal whether this treatment can be as or even more effective than the classical glucocorticoids. In experimental MAS, exogenous surfactant was delivered even intratracheally through the jet of HFJ ventilator by means of inpulsion regimen or by lung lavage with diluted surfactant (Sevecova-Mokra *et al.* 2004). Positive effects of exogenous surfactant on the lung functions were further improved by concurrent delivery of synthetic glucocorticoid budesonide, antioxidants N-acetylcysteine or superoxide dismutase, inhibitor of NF-kappa B (Kopincova *et al.* 2017), nitric oxide donor SNAP or anti-interleukin-8 antibody. These studies have indicated the potential of combined therapy by exogenous surfactant and appropriate anti-inflammatory drugs.

Although the administration of the above-mentioned substances improves the lung function and alleviates inflammation and lung tissue injury, the favorable effects can be limited by adverse effects to the other organs. For this reason, the changes of cardiovascular parameters are also evaluated (Mokra *et al.* 2008). Possible biochemical, morphological and functional changes in the lungs, heart and liver have been determined and correlated with plasma levels of markers of tissue injury and treatment (with Departments of Histology and Embryology, and Medical Biochemistry). Recently, the research was extended (with Clinic of Children and Adolescents and Clinic of Pulmonology and Phthisiology) to the role of nitric oxide and possibilities of its detection in experimental models, and healthy volunteers or selected groups of patients (Antosova *et al.* 2017a, b).

The above-mentioned models have been recently extended by lipopolysaccharide (LPS)-induced acute lung injury in rats to study LPS vs. surfactant interactions (Kolomaznik *et al.* 2017) and by measurement of surfactant surface activity with pulsating bubble surfactometer.

The further main achievements in the field of pulmonary surfactant physiology are: the finding of the positive influence of some additives on the biophysical and physiological properties of the surfactant; herein we found out that the enrichment of exogenous surfactant Curosurf with dextran improves meconium clearance and lung functions in surfactant-lavaged rabbits with meconium aspiration (Calkovska *et al.* 2008); the finding of direct relaxing effect of animal-derived exogenous surfactants on airway smooth muscle (Calkovska *et al.* 2015); the detection of the role of surfactant proteins in the animals with endotoxemia (Kolomaznik *et al.* 2014) and in clinical study in patients with chronic rhinosinusitis with or without nasal polyps (Uhliarova *et al.* 2016); the finding that at least one common haplotype GATGACA of the *SFTPB* gene can be protective in RDS of preterm newborns – in close cooperation with Clinic of

Neonatology (prof. Zibolen) and Department of Molecular Medicine (assoc. prof. Lasabova); in the area of the regulation of the respiratory and cardiovascular system during change of body temperature it was found out that hyperthermia is accompanied by reduced functional cardiorespiratory reserve and a higher risk of respiratory and circulatory failure in haemodilution/anemia (Brozmanova *et al.* 2004); the finding of altered neural control of breathing in LPS-induced fever demonstrated by decreased power of Hering-Breuer inflation reflex which may facilitate thermal tachypnoe and/or play a role in the origin of respiratory instability accompanying febrile response (Zila *et al.* 2012). The review of Zila *et al.* (2017) in this issue makes a bridge between autonomic nervous system (ANS) and inflammation pointing out our future research perspectives.

***Clinical-physiological research*** focused on cardiorespiratory regulation started in the first half of 1970s in co-operation with the Department for Premature Newborns in Martin. The main results achieved at that time were the identification of the peculiarities in respiratory control through the airway reflexes as well as Hering-Breuer inflation reflex in healthy premature newborns (Javorka *et al.* 1980) and specifics in the respiratory reflexes in neonates with respiratory distress syndrome (RDS) (Javorka *et al.* 1985); the evidence that certain autonomic reflexes are present also in healthy premature newborns and that heart rate variability and chronotropic reactions are reduced in premature newborns with RDS (Javorka and Zavarska 1978); specification of the values of systemic blood pressure in relations to gestational age and birth weight and the discovery of the diurnal rhythm of blood pressure (PB) and heart rate (HR) in premature newborns using a prototype of an ultrasound tonometer (with dr. Kellerova) (Javorka and Zavarska 1983, Javorka *et al.* 1992); the finding of the tachycardic and hypotensive reactions in premature infants with phototherapy (Javorka and Zavarska 1990); the involvement of ANS dysbalance in the pathophysiology of primary juvenile hypertension (Javorka *et al.* 1988); the involvement of renal ptosis and compromised venous outflow in orthostatic proteinuria in pediatric patients (with Clinic for Children and Adolescents JFM CU, prof. Buchanec); the detection of ANS changes in regulation of peripheral vessels and also in chronotropic regulation of heart activity in patients with occupational angiopathy (with Clinic of Occupational Medicine and Toxicology in Martin, prof. Buchancova).

Nowadays, the research on regulation/dysregulation of the cardiovascular system continues on the basis laid in the past. Heart rate variability (HRV) is spontaneous oscillations of heart rate around its mean value. In analogy, blood pressure variability (BPV) is short term spontaneous oscillation of blood pressure at rest. Both parameters represent a unique window into regulatory mechanisms of cardiovascular system mainly *via* ANS. Thus, HRV and BPV analysis may contribute to the diagnosis of autonomic dysregulation. First, it was necessary to establish standards of the HRV parameters and reference values of cardiovascular tests (orthostatic test, deep breathing, Valsalva maneuver) in healthy children and adolescents (Tonhajzerova *et al.* 2002). The analysis of the developmental changes in HRV and cardiovascular reflexes indicating maturation of cardiac autonomic regulation was done. Later the examination of HRV and cardiovascular reflexes was performed in children and adolescents, mainly with diabetes mellitus (DM) and obesity, in the cooperation with Clinic of Children and Adolescents in Martin.

Even in young diabetics shortly after the diagnosis of DM1, HRV evaluation can reveal the onset of heart dysregulation – the presence of relative sympathicotony, which was also manifested by shorter RR intervals. The HRV reduction and abnormalities in deep breathing test are not only dependent on compensation of DM1 but also on other factors (e.g. physical activity) that affect the ANS (Javorka *et al.* 1997, Javorka *et al.* 1999). Thus, the chronotropic dysregulation in children and adolescents with DM1 may be, at least partially, caused by functional abnormality resulting from a lack of physical activity (Javorka *et al.* 2001). Methodological approaches and some results of research in this area were summarized in the monographs (Javorka K. *et al.* 2008, Javorka M. *et al.* 2010).

***Application of nonlinear dynamics methods***

The analysis is focused on the nonlinear characteristics of heart rate oscillations which is methodologically more appropriate. The researchers from the Department belong to the first who applied the novel nonlinear methods to characterize the heart rate oscillations focusing on system complexity, a description of the dynamical states recurrences and time irreversibility quantification (Javorka M. *et al.* 2002, Trunkvalterova *et al.* 2008, Chladekova *et al.* 2012). In cooperation with biomedical engineers and physiologists, including scientists from cooperating teams from

Adelaide, Australia (dr. Baumert), Witten, Germany (dr. Cysarz) and Brno, Czech Republic (prof. Honzikova, dr. Svacinova), and have been a part of the groups publishing methodological scientific papers focused on the adaptation of nonlinear time series analysis tools taking into consideration the specific features of real heart rate oscillations. In addition, important papers introducing the application of nonlinear methods in the heart rate variability analysis in young diabetics (Javorka M. *et al.* 2008), obese adolescents (Javorka M. *et al.* 2016) and in newborns (Uhrikova *et al.* 2015) demonstrating the advantages of newly developed methods were published.

As the next step, the analysis was focused on the mutual interaction between cardiovascular (Krohova *et al.* 2017) and respiratory signals by recently developed tools from nonlinear dynamics (Baumert *et al.* 2015) and by methods taking into consideration the causal interactions between oscillations. Several pioneering papers in this rapidly developing field have been published recently in cooperation with partners from Trento, Italy (e.g. Javorka M. *et al.* 2017).

***Psychophysiological research***

In 2005, Department of Physiology started the cooperation with Psychiatric clinic of JFM CU and UHM (assoc. prof. Ondrejka) resulting in intense psychophysiological research which is focused on two basic aims: first, to study the autonomic regulatory outputs to distinct effector systems (HRV, BPV), measurements of electrodermal activity, pupillometry in complex stress response to various stressors in healthy young subjects (reviewed in Tonhajzerova and Mestanik 2017) and second, to study of complex autonomic characteristics in stress-related and mental disorders as ADHD, autism, depressive disorder (Mestanikova *et al.* 2017), hypertension in the aspect of stress-response in adolescent age characterized by specific maturational mental and physiological patterns. The specific attention is given to detection of genetically determined temperament traits and character dimensions. This analysis will enable further assessment of potential biomarkers of high-risk groups in terms of personal predisposition to stress-related or mental disorders associated with higher cardiovascular risk (Visnovcova *et al.* 2014, Visnovcova *et al.* 2016). In the context of cardiovascular risk, the psychophysiological research has expanded to the study of arterial stiffness in stress-related and mental disorders, especially for determination of early subclinical atherosclerotic changes using an unique set of devices for evaluation of endothelial dysfunction with RH-PAT method (Reactive Hyperaemia Peripheral Arterial Tonometry) and quantification of arterial stiffness by novel markers CAVI (Cardio-Ankle Vascular Index) and $CAVI_0$ (Mestanik *et al*. 2016).

The main goal of the psychophysiological research is to identify objective transdiagnostic biomarkers enabling to characterize complex individual personality and "stress-profile" characteristics important for successful treatment in various disorders associated with stress.

***Studies in neonates***

The intensive co-operation with the Clinic of Neonatology JFM CU and UHM (prof. Zibolen and coworkers) as well as common topics for PhD study has open the possibility to continue in the research in neonatal physiology (as evidenced also by Lenhartova *et al.* 2017).

*Heart rate variability*

In premature infants, there is reduced HRV and very low or absent spectral activity in the HF (parasympathetic) band in comparison to the term neonates. HR and HRV were compared between hypotrophic (small for gestational age, SGA) and eutrophic (appropriate for gestational age, AGA) newborns. The intrauterine growth restriction have been linked to the immaturity of the autonomic cardiac control with typically higher sympathetic component seen in the HRV measures in SGA infants compared with AGA infants. A higher contribution of sympathetic activity to HRV was demonstrated by sequence plot (Lehotska *et al.* 2007).

No significant differences in HR and in HRV time domain parameters have been detected in *various modes of delivery* (vaginal with/without epidural anesthesia vs. caesarean section). However, the children after physiological vaginal delivery and in standard maternal care had lower relative power of low-frequency band (LF%) and higher relative power of high frequency band (HF%) in chronotropic cardiac regulation as revealed by frequency domain analysis (Kozar *et al.* unpublished observation).

Using nonlinear dynamics a subtle shift in cardiovascular control towards increased parasympathetic activity and/or reduced sympathetic activity in jaundiced newborns were found (Uhrikova *et al.* 2015). Linear analysis (time and frequency domains) of the HRV did not reveal any significant changes during and after phototherapy. The application of nonlinear dynamics has shown significant changes in symbolic dynamics and time irreversibility indices. The response of the ANS during and after phototherapy was characterized by a shift in sympatho-vagal balance towards sympathetic dominance (Uhrikova *et al.* 2015).

Many other neonatal conditions (hydrocephalus, therapeutic drainage in hydrocephalus, rewarming from therapeutic hypothermia etc.) may be associated with HRV reduction. The changes in HRV in recovery phase are potential prognostic marker (reviewed in Javorka K. *et al*. 2017).

*Blood pressure variability and baroreflex sensitivity*

On the basis of volume-clamp method by Peňáz we have measured noninvasively and continuously BP from the wrist of premature newborns according to Drouin *et al.* (1997) and Andriessen *et al.* (2004) and evaluated blood pressure variability (BPV) and baroreflex sensitivity (BRS) in premature newborns by this method. Spectral analysis of systolic and diastolic blood pressure showed a decrease in HF power in $BP_{diast.}$ and positive correlation of the ratio LF/HF (a sympathetic index) with gestational and postconceptional age and birth weight. It indicates increasing influence of sympathetic activity on the regulation of blood vessels during early postnatal development.

Results on BRS in premature infants are discussed in Haskova *et al.* (2017) in this issue. It is shown that baroreflex is active also in premature newborns even in the first postnatal day and points a close correlation of BRS, HR and respiratory rate with gestational age, postconceptional age, birth weight and body weight at the time of measurement. An increase in the age and weight corresponds to increased BRS and diastolic arterial pressure, and to decreased heart and respiratory rates.

Simultaneous recording and analysis of HRV (parasympathetic regulation) and BPV (dominant sympathetic regulation), and evaluation of baroreflex sensitivity provides an important tool in assessment of cardiovascular control even in the early postnatal period, in children and adolescents and broadens the possibilities of early diagnosis.

The Department of Physiology cooperates closely with other Departments and Clinics as a part of the Center for Experimental and Clinical Respirology and Center of Excellence of Perinatological Research established with support of European Union funds. An important milestone in the Department´s history was the movement to the new facilities of the Martin Biomedical Center (BioMed) in the summer 2015. A new place offers unique infrastructure and opportunity for multidisciplinary basic and applied research. In line with four major research areas at the Jessenius Faculty of Medicine in Martin and the philosophy of BioMed, all research described above is now conducted in frame of Division Neurosciences and Division Respirology in four laboratories (Laboratory of autonomous nerve system, Laboratory of psychophysiology, Laboratory of experimental physiology and Laboratory for surfactant research).

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