REVIEW ARTICLE

Variability and reactive changes of the peripheral blood flow, blood pressure and of the electrical behavior of the heart

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Abstract

Shortly after legalization of the Slovak Academy of Sciences, (SAS) at the turn of 1953, Prof. Ladislav Dérer established at the 1st Clinic of Internal Medicine of the Faculty of Medicine Comenius University, the Laboratory of Clinical Physiology of the Higher Nervous Activity in Man SAS. It was one among other laboratories, representing the historical base of the present Institute of Normal and Pathological Physiology SAS. The Laboratory was set up to promote the research in the field of psychophysiology and of human cardiovascular physiology, aimed namely at the peripheral vasomotor activity in man, at the physiological variability, reactivity and developmental aspects of blood pressure, with respect to hypertension and at the physiological, clinical and model studies of the cardiac electric field. Shortly an experimental team studying the peripheral vasomotor regulatory mechanisms in dogs joined temporarily the Laboratory. The aim of this review is to summarize at least partly, the contribution of the results to the normal and pathological physiology of the cardiovascular system.

INTRODUCTION

In the everyday life, animals and humans are engaged in various activities, requiring rapid, specific and integrated adjustments of different physiological functions, to face a particular situation as a whole and in an appropriate manner. Here we review a piece of our experience with cardiovascular adjustments, which often form an important link in reactions to different stimuli, to the environment and to the more or less emotionally charged situations. Our studies were oriented namely on i) peripheral vascular reactivity, ii) developmental aspects of blood pressure and on iii) electrophysiological characteristics of the heart.

REACTIVITY OF THE RESISTANCE AND CAPACITANCE VESSELS OF THE EXTREMITIES

Differential nervous vasomotor control is the most important factor in systemic cardiovascular homeostasis. On one hand it permits the maintenance of an adequate central arterial pressure, on the other it is the prerequisite – with contribution of the local regulatory factors – for a flexible distribution of blood to different organs. Circulation in the vascular bed of extremities is not only a sensitive marker of the peripheral hemodynamics with regard to the responses of the organism to the physiological impulses and situations, but also an indicator of possible structural changes due

to physiological or pathological processes acting for a longer time.

Clinical-physiological and experimental research attacked this field in fifties, with respect to the vasomotor regulatory mechanisms (Barcroft *et al* 1960; Brod *et al* 1959). Most of the basic human studies on peripheral vasomotor reactivity in muscle and skin reported in this paper, were performed in the past by various plethysmographic techniques. Plethysmography is a composite measurement of volume of different segments of the extremities, or of blood flow (BF) through all the tissues enclosed in the investigated segment, by venous occlusion plethysmography. Forearm and calf segments are representative of muscle blood flow, measurements in the acral parts – hands and feet, with minimal volume of muscles, quantify the skin BF. Nevertheless, the computerized high-tech measuring techniques of today did not really change these principles of BF evaluation in representative limb segments. Venous tone (VT) is used as a parameter to quantify the active constriction of the capacitance vessels, by pressure changes measured in occluded superficial veins of the distal forearm or hand.

In the presented studies mainly two types of vasomotor reflexes were used. One of the most constant vasoconstrictor reactions in the acral skin regions, elicited by a single deep breath (DB) (Bolton 1936), which does not undergo extinction when repeated, its size is characterized by periodic oscillations and it can be readily conditioned (Ruttkay-Nedecký 1963). The reaction consists of a short-lived 10–15 s. decrease of BF and a longer lasting constriction of the capacitance vessels – up to 60 s., paralleled by a decreased volume of the investigated segment (Kellerová & Delius 1970; Delius & Kellerová 1971). It may be used to characterize the spontaneous or provoked oscillations in the peripheral vasomotor excitability (Kellerová 1971; 1975) and to test the pharmacodynamic effect of some drugs on vasomotor activity. In fifties Reserpine was widely used in psychiatry by normotensive subjects. In a comparative study with other central depressant drugs (bromide, phenobarbital, chlorpromazine), only Reserpine – evidently by the depletion of catecholamines in nerve endings, inhibited the vasoconstrictor response to DB, already after 0.5 mg p.o., with an after-effect of several days, but no effect on BP (Ruttkay-Nedecký & Kellerová 1962).

A large amount of studies was published using mental arithmetic (MA) as a probably most consistent test, which involves increased alertness with intellectual and emotional strain, provoking the so called defense reaction – with mobilization of the organism to "flight or fight". Active muscle vasodilatation is the most constant characteristic response to the sustained stressful mental arithmetic test. On the other hand the skin vessels usually respond by a significant constriction, i.e. by decreased BF (Delius & Kellerová 1971).

As cardiac output is dependent upon venous return, changes in venous capacity, due to the sympathetic vasoconstrictor activity can profoundly influence the efficiency of the cardiac pump. An increase of efferent sympathetic discharge – which in general is a part of the defense reaction – elicits also in the MA test a significant venoconstriction, documented by an increased venous tone in the forearm, in the average up to 218% of its resting value. It is extended beyond the arteriolar constriction in skin – with an after-effect lasting about 1 min. longer than the MA – but closely correlated in amplitude and duration with the increased forearm BF (Delius & Kellerová 1971). Seemingly the active venoconstriction represents a neurogenic compensatory mechanism preventing the pooling of blood in regions with an increased muscular BF.

Preceding detailed studies on peripheral arterial and venous reactions to several maneuvers causing circulatory adjustment in man (Delius & Kellerová 1971; Kellerová & Delius 1969) were followed by well-documented studies of Delius *et al* (1972a, 1972b) on sympathetic vasomotor outflow in human muscle and skin nerves at rest and during vasomotor responses to DB, MA, cold, body position and smoking.

Practically in all human studies starting with Barcroft *et al* (1960) and Brod *et al* (1959), the measurements of the peripheral skin and muscle blood flow were performed in the segments of the upper extremity (hand and forearm). In spite of this, the results became generalized. In one of our studies based on the simultaneous segmental BF measurements on the upper and lower extremities (Kellerová & Delius 1969), we revealed, that there are significant regional differences in the BF at rest as well as in the response of the skin and muscle vessels to the psycho emotional stress. The reactive vasodilatation was less pronounced in the calf muscles, in the average 130% of the resting BF compared to 210% in the forearms. Inconsistently with the significant cutaneous vasoconstriction in hands, to 30% of the resting BF, there was no reaction of the skin vessels to MA in feet. Reflex vasoconstrictory response in skin to a DB was as well significantly less in amplitude in the feet (decrease only to 46% of the BF at rest, but down to 17% in hands). It was concluded, that there are differences in vasomotor reactivity comparing the upper and lower part of the body (observed for instance also in thermoregulatory reactions or in hemiplegics), more precisely, with higher reactivity and specific sensitivity to emotional stimuli in the upper extremity (Kellerová & Delius 1969).

By measuring the tissue clearance of $Na^{131}J$ in acral skin regions and in forearm and calf muscle, we documented, that the reactive BF changes due to MA, involve all consecutive vascular sections including the nutritional capillary part. During the MA test, the capillary BF in the forearm muscle increases, whereas in the subcutaneous tissue it decreases. The significant difference between the vasomotor activity of upper and lower extremities observed at rest and during reactions to MA in the total segmental BF, was confirmed in the capillary BF as well (Ondrejička *et al* 1974).

Vasomotor reactivity and essential hypertension

The cardiovascular components of the defense reaction do not need an extreme distress, to be fully displayed. They are evident in daily life already with trivial stimuli producing an alerting response. Studies on stress in animals have demonstrated that prolonged or repeated situations producing the autonomic-hormonal-metabolic mobilization for the defense reaction can interfere seriously with the normal functioning of the body. Repeated situations with defense reactions aroused, but dissociated from willingly suppressed somatomotor components of "fight or flight", may lead to pathophysiological states (Charvát *et al* 1964). Multifactorial analysis identified suppressed aggression to be associated with the greatest blood pressure increments, particularly in hypertension prone subjects, i.e. those in the upper normal and borderline pressure range (Perini *et al* 1991). Psychological factors play a permissive role in high blood pressure development, rather than being its consequence.

Supposition that an increased sympathetic drive of central origin contributes to the onset of human primary hypertension, was for the first time supported by pioneering human physiological studies showing in borderline hypertensive at rest, cardiovascular pattern similar to that displayed in emotional defense reactions (Brod *et al* 1959, 1962). The results from a large number of studies performed then after, are not uniform in describing the pattern of peripheral vasomotor tone redistribution. Many of them generalize the vasodilatation in forearm muscles in defense reaction and in hypertension as characteristic for the entire vascular bed of skeletal musculature. Our measurement of capillary BF confirmed in Hypertension I. an increased vascular resistance – i.e. lower BF – in skin of hand and lower leg at rest, as well as more pronounced vasoconstrictory reactions due to MA and cold, compared to controls. As expected, the increased capillary BF in the forearm muscle in hypertensive, in the average to 136% of that in normotensive controls, indicated vasodilatation at rest, just as during MA or exercise. Surprisingly the reverse – a vasoconstriction was discovered in the calf muscle – by a decreased BF to 60% of the control (Ondrejička *et al* 1972, 1974). Guanethidine causing a highly selective sympathetic blockade, simultaneously with the significant blood pressure decrease normalized in hypertensive the pattern of vascular resistance, i.e. returned it to levels measured in normotensive controls. The previously low capillary BF in skin of hand and lower leg as well as in the calf muscle increased, whereas the high resting flow in forearm muscle decreased under the influence of the drug (Pecháň *et al* 1974).

*Vasomotor reactivity in patients with
chronic myocardial infarction*

Peripheral circulation in patients with coronary heart disease is of considerable clinical significance since, on the one hand, it plays a role in maintaining arterial BP and venous return but, on the other, the reflex vasoconstrictor episodes by increasing BP augment the mechanical load on the heart and thereby also the demand-energy imbalance.

In patients in a chronic phase of myocardial infarction (MI) compared to controls, in a situation involving increased alertness with intellectual and emotional strain (MA test), the reactive BP and HR increments were slightly but significantly smaller, nevertheless lasting longer after the test. The vasomotor response to MA showed more pronounced and prolonged vasoconstrictor reactions in skin, involving the resistance as well as capacitance vessels. The muscle blood flow at rest was significantly lower and its reactive emotional increase was significantly less pronounced and of shorter duration (Kellerová *et al* 1980). None of the patients had an evident heart failure, but we have to consider the impaired function of the heart as a possible reason for the observed changes in peripheral hemodynamics and for neuro-humoral sympathergic activation (Nestel *et al* 1967). Last, but not least, the factor of endothelial dysfunction limiting the production of vasodilating substances in these patients is probable as well.

BLOOD PRESSURE DEVELOPMENT FROM NEONATES TO ADOLESCENTS, PHYSIOLOGICAL VARIABILITY AND REACTIVITY

Evidence-based medicine and population studies repetitively confirmed the increased blood pressure as a significant risk factor of the cardiovascular diseases (CVD) morbidity and mortality, namely because of its etiologic role in the ischemic heart disease, myocardial infarction, heart failure, cerebrovascular disease and stroke. The statistical data show that the CVD are with 52.8% still the leading contributor to the death rate in the Slovak republic.

In contrast to the amount of data published on physiological aspects of BP regulation, on its reactivity, hereditary predispositions, environmental influences and factors altering its control in the adults, studies devoted to these problems during ontogeny in healthy individuals, including neonates, are relatively rare. The present article surveys our results from an ongoing program of research that has focused on physiological BP variability in different periods of postnatal development, in relation to the somatic growth, reactivity to different stimuli, environmental and risk factor influences, in different age groups from neonates to adolescents.

The first convincing evidence about the contribution of regionally differentiated sympathetic vascular activation to the onset of human primary hypertension, comes from human physiological studies by Brod *et al* (1962) in the late 50's. It was supported by a finding of hyperkinetic circulation with an increased stroke volume and cardiac output at rest, in 70% of young hypertensive from a field study (Widimský *et al* 1957).

Described cardiovascular pattern is similar to that displayed in defense reactions, suggesting an increased sympathetic drive of central origin. Since then there was a long way to persuade cardiologists as well as pediatricians that – mild elevations of BP during childhood are more common than previously recognized – roots of essential hypertension extend back to the childhood – a child with elevated BP shows a higher probability of developing hypertension in adulthood – that there is a familial aggregation of hypertension, and that the cardiovascular risk factors are effective in children as well, namely in the critical developmental periods.

The developmental curves of BP related to sex, age, height, weight or to body surface, represent a statistical construction based on transversal data collected from different groups of subjects, declared as "National reference BP data". There is a significant dispersion between them, caused methodologically and by different impact of many other factors (geographic, ethnic, socio-economic, environmental, nutritional, familiar, etc.), directly or indirectly influencing the BP and its development, and by a possible admixture of unrecognized prehypertensive or increasing proportion of obese subjects, namely boys. Obesity (BMI >30) was found in 37% of children and adolescents with elevated BP (Kellerová 1992, 1996; Kellerová & Regecová 2011; Regecová *et al* 1998, 2009, 2011b, 2012a).

Therefore it is inevitable in the future, to define the distribution of BP in the normal population of children in Slovakia, related to the age and to selected somatic parameters. For this purpose is at the Institute of Normal and Pathological Physiology SAS, an open electronic database of the casual BP, heart rate , basic anthropometric parameters and contingent risk factors from approximately 45 000 subjects, aged 3–18 years, from different regions of Slovakia, at disposal for cooperative studies. The data were collected in the frame of research program of the Institute and in collaboration with pediatricians, cardiologists and coworkers of the National Health Information Center and Public Health Authority of the Slovak Republic.

As only little was known on association of obesity and hypertension before maturation, we focused our study first on the evaluation of different methods for assessment of body fat distribution, with respect to the relationship between obesity and blood pressure in children and adolescents. Subscapular-triceps ratio as well as the abdominal circumference (waist) related to the height (relative abdominal circumference) resulted as sensitive, discriminative indexes characterizing the hypertensive subjects, independently of their BMI, or of total fat percentage, i.e. also in the normal or lean groups. Both are more suitable for assessment of the cardiovascular risk factors in children and juveniles, than BMI or body fat percent. Relative abdominal circumference is easy to measure and calculate, and so it is considered for application in practice (Regecová 2003; Regecová *et al* 2007)).

In a cohort of 15 448 children and adolescents aged 11 and 17 y, 52% of B and 30% of G exceeded the ESH limit of optimal systolic blood pressure for the adults. Significantly higher BP values in obese children shifted the percentile distribution to the right. The incidence of BP over 90 P. was 14.6% in a group with normal weight, 39.7% in the obese and in those with abdominal obesity over 50%. Among somatic parameters the abdominal obesity seems to be a very relevant risk factor in development of hypertension (Regecová *et al* 2007, 2009a,b, 2011c, 2012b).

Comparison of representative data on BP and somatometric parameters in children and adolescents in the age range 11–17 years, from SR, CZ, PL, HU, IT, EN and USA(2004) documented the highest values in body height – for-age in SK and CZ boys. Irrespective to age and sex, BP values in EU teenagers were significantly higher as compared to USA, with highest BP in SR and CZ (Regecová *et al* 2011a).

From a transversal study comparing after a decade 2001 and 2010 the incidence of BP values ≥120/80 mmHg in 10 y. old children, in relation to obesity and residence in Slovakia followed, that the mean BMI, as well as the prevalence of overweight and obesity increased significantly, mainly in girls from the rural communities. The systolic BP-for-height values were in the average significantly higher, not only in the obese, but also in those with normal body weight. The greatest increments of systolic BP were observed in rural regions of Middle Slovakia. The diastolic BP did not change. The incidence of prehypertension and hypertension increased in the total by 9%, but surprisingly more in children from rural regions (from 15.5% to 28%) (Regecová *et al* 2011b).

Trends in the time span 2001–2011 show in adolescents aged 16–18 y. a significant increase of body height, BMI and of systolic BP and HR in boys and of body height and systolic BP in girls. Good news – in both sexes the level of total cholesterol slightly, but significantly decreased. The proportion of obese boys rose significantly from 24 to 31.6%, in G remained at the same level around 23%. The incidence of 1–3 cardiovascular risk factors increased in the urban population by approx. 7% (Regecová *et al* 2012a, 2012b).

The dynamics of the BP evolution in children is nonlinear. Noninvasive systolic and diastolic BP measurement in 150 physiologic neonates, by a Doppler-ultrasonic instrument LUD-802 TESLA – invented by Kellerová *et al* (1978a,b) – show that the most steep rise of BP ever, takes place in the first postnatal days (systolic by 22% and diastolic by 19% – from their respective, first-day average of 57±8/33±7 mmHg, up to 69±10/39±6 mm Hg on the 4th day) (Kellerová & Andrásyová 1990). At the same time, the heart rate decreases by 6%. Thereafter a relatively intense BP increment, in the average by 2 mm Hg per week, lasts up to the age of about 6 weeks, when the total BP accretion is close to 20 mm Hg. Subsequently the developmental

increase of BP, lasting to the adulthood, slows down to 1–2 mmHg per year for systolic, and l mm Hg for diastolic BP. There are no gender differences in the slow development of BP, until the age of 13–14 years. The proportion of systolic BP values >120 mmHg increased continually with age from about 2% at 3 yrs. reaching a plateau of 30–40% in girls at the age of 12 yrs., but continuing up to 60–65% in boys from the age of 15 yrs.

Already in the early postnatal life BP begins to follow a pattern. The so called "tracking phenomenon", most probably starting already in the early childhood at the age 1–4 years, plays a significant role in the individual's BP development. Children with the BP level in the upper percentiles of the BP distribution according to their age, are presumed to have also higher BP readings as adults (Bao *et al* 1995). Substantial are the results of the longitudinal re-screening, showing, that up to 37% of juvenile hypertension correlates with hypertension in the adulthood, with all clinical consequences (Jandová & Widimský 1983).

In a semi longitudinal study (Regecová & Kellerová 1987), reexamination of a group of 1–6 year old children, after an interval of 3.5 years, revealed 51% of subjects with a significant increase of BP – systolic in the average by 9 and diastolic by 6 mm Hg, but still in the normal limits of BP. These children were characterized with respect to age and gender, by a more pronounced increase of body weight (in the average by 2.5 kg), of relative body weight, and of skin-fold thickness. Interestingly, the familiar factor came to light as well. The average BP values of parents of children, whose BP rose during the observation period, were significantly higher, even if in normal limits, as compared to those with unchanged BP. The maternal factor seemed to be more important. Ševčíková *et al* (1999) observed, that also an isolated obesity in mothers, represents a considerable risk factor of hypertension in their children.

ACTOPHYSIOLOGICAL ASPECTS OF BLOOD PRESSURE VARIABILITY IN CHILDREN

Blood pressure is a very variable hemodynamic function that is influenced by many factors of the internal and external environment of the organism. Although the BP control in man has been extensively investigated, studies on physiological factors inducing its reactive changes, character of the BP reactions, and their postnatal development in the early infancy, and especially in neonates are scarce, with some doubts about their functional effectiveness. Here we review a piece of our experience from over 500 physiological neonates, aged 1–4 days, studied in different subgroups.

Sleeping and waking
At the age of 12–24 h, there were no differences of BP and heart rate levels related to the state of vigilance. They developed gradually and became significant at the age of 72–96 h (BP awake 72/40 vs. asleep 63/35 mmHg,

HR 127 vs.115 beats/min), independently on the time of the day (Kellerová & Andrásyová 1990). However, at the same time, we documented lower BP values at night, independent on vigilance – approximately 90% of the daily mean. indicating in about a half of the babies, already in the first postnatal days possibility of the circadian periodicity (Kellerová 1981; Kellerová & Regecová 2006).

Crying and waking up
Crying provoked a reactive increment of BP by 22/11 mmHg, HR by 19 beats/min on the average, with a marked intra – and interindividual variability, dependent mainly on the intensity and duration of crying, length of the expiratory phase, etc. (Kellerová & Andrásyová 1990) Interestingly, waking up from the sleep, or crying at night, provoked a more pronounced increase of BP, in comparison with the day-time reactions (Kellerová & Regecová 2006).

Feeding response
Feeding and locomotion are at the top of the class of activities identified as essential to life. Feeding is a complex activity, which has to be divided into two disparate periods: food intake (ingestion, eating, drinking and sucking), and the postprandial period (digestion). There is a substantial difference in the prandial and postprandial cardiovascular component of the reaction. The hemodynamic changes that occur during food intake are not restricted only to the gastrointestinal tract. Changes in the regional hemodynamics – markedly increased blood flow in the carotid region and on the other hand a significant increase of the peripheral resistance in the kidneys and in the large regions of the hind limbs, described in dogs (Antal 1993), enable a better understanding of the intense pressure response during the act of food intake. Due to the cortico-hypothalamic activation, they can be characterized to a certain degree as a part of a generalized sympathomimetic response (Fronek & Stahlgren 1968), resulting in a considerable blood pressure and heart rate increase. It was shown in newborn lambs (Jones *et al* 1993), that the hypertensive response during feeding was significantly reduced by combined alpha- and beta- adrenergic blockade and completely eliminated by ganglionic blockade in rats (Scalzo & Myers 1991). The hypertensive BP response to feeding is universal, more significant in carnivores and omnivores than in herbivores, and much more pronounced in the young ones, in comparison to the adults of the same species (for details see Antal 1968, 1993; Kellerová 1993; Kellerová & Regecová 2003; Myers *et al* 2005).

Among BP and HR changes coincident with different physiological situations and activities in human neonates and infants, the increments during feeding are the most prominent. Feeding caused from the first postnatal days a significant rise of BP systolic by 12–33%, diastolic by 13–38% and of HR by 14–20% of

their respective mean values at rest (65/36 mmHg and 123 b.m.). The response is greater during bottle feeding, compared to breast feeding and dependent on the body position – higher in babies held slightly elevated in arms vs. supine (Kellerová 1981, 1993; Kellerová & Andrásyová 1993; Kellerová & Regecová 2003). These findings were later confirmed by Cohen *et al* (1992).

The reaction is abrupt, immediate, elicited practically by the start of sucking and the first gulp of milk in mouth, outlasting all the feeding time, present in every subject, however inter-individually variable in magnitude, and with return of BP an HR to baseline within several seconds after the end of feeding. It is present also during non-nutritional sucking at a comforter. From this follows, that to quiet a baby for BP measurement by a comforter, causes falsely high BP readings. The BP increment is significantly more pronounced on the first postnatal days, present also in the older neonates and infants, however than no more significantly age-dependent (Kellerová & Regecová 2003). The increase of BP to bottle feeding in infants of M. Rhesus, and baboons (investigated by us in collaboration with the Institute of experimental pathology and therapy of USSR AMS, Sukhumi), was comparable to the human reaction (Kellerová *et al* 1984).

From the ABPM records follows, that food ingestion has an important influence on BP and HR also in the adults. In spite of the fact, that the results of ABPM evaluation were statistically significant, we consider them preliminary, as they are based on coincidence of accidental BP measurements with situations marked by the subjects as "meal time". However we would like to point out that unrecognized coincidence of BP readings with eating or drinking may have a significant effect on "spontaneous" fluctuation of BP during the day and has to be taken into account when applying ABPM to the BP evaluation.

Changing body position

To estimate the cardiovascular regulatory functions in man, body-tilting maneuvers are commonly used. The BP responses to changes in body position from supine to upright were extensively studied in healthy adults, teenagers as well as in children. Some data on newborns were obtained under variable conditions, only casually in small samples, and with partially contradictory results.

In neonates the head-up tilt to 45° provoked a significant increase in systolic and in diastolic BP, with moderately increased HR (Kellerová1985b). This response was even more pronounced, when the babies were instead tilting, lifted-up on arms. This "hypertensive type" of reaction was present in more than 80% of full-term newborns, and still present in about 70% of 3-year old children. In contrast to the decreased venous return and stroke volume due to standing up in the adult, the different proportionality of the blood volume distribution, which is localized in neonates and children predominantly in the large head and in the upper part of the body, results immediately after assuming the upright posture, in an increased venous return, filling of the heart, and higher cardiac output. This is one of the components of the hypertensive type of the reaction.

According to our results character of the orthostatic reaction develops age-dependently, stage by stage from the relatively stabilized orthostatic cardiovascular reaction, seen in the younger children, with balanced, slight increments of BP and HR. At the pubertal age, a disbalanced orthostatic response occurs, where in spite of the significant tachycardic response, the systolic BP decreases, and the diastolic BP is not sufficiently supported by the vasoconstrictor mechanisms. In this age group orthostatic hypotension and fainting are more frequent. In the adolescents a sympathergic adult-type of this postural reaction takes over, with significantly increased HR and diastolic BP, while systolic BP scarcely changes (Kittová 1977; Kellerová & Regecová 1983; Regecová 1992).

Highly probably the same mechanism, i.e. an increased venous return from the abdominal region and visceral organs, plays a role in the neonate in the significant BP increment by more than 20% of the respective supine values, following the change of body position from lying supine to lying prone (Kellerová & Andrásyová 1993). To put a neonate to sleep lying prone (abdominal position) is, based on our results, not recommended. The pronounced, sustained increase of BP, may eventually produce compensatory bradycardic response, and endanger babies prone to SIDS.

Nonauditory effect of urban noise

Urban noise – the unwanted mixture of sounds – is an inescapable, permanently increasing, ubiquitous and persistent stressing factor of the civilized environment. About 20% (80 million) of the population in the European Union experience daily noise levels that are believed to have detrimental effects on human health. A further 42% reside in areas, where noise pollution is severe enough to cause occasional serious nuisance. Studies in adults documented, that living in streets with high traffic density may increase the occurrence of hypertension beyond the magnitude explained by other factors (Eiff & Neus 1980).

We performed a cross-sectional study of causal blood pressure and heart rate in more than 1 500 preschool children aged 3–6 y. attending the kindergartens in all districts of the Bratislava city, grouped according to their outdoor traffic noise emission levels. Prescriptive limit for living and school areas was 60 dBA. Localities under this limit were considered quiet, up to 69 dBA as noisy, 70 and more dBA as very noisy. Only 18% of all children lived and visited kindergartens in quiet places. Others were exposed to permanent noise load over 60 dBA, either at their homes, either at kindergartens, or 28% of them at both places.

Children, attending nursery schools situated in areas with high traffic noise (>60 dBA), had higher

mean systolic and diastolic blood pressures and lower mean heart rate than children in quiet areas. Incidence of children with BP values surpassing the respective 95th percentile according to NHBPEP (1987), was significantly higher. Limits of the 90th percentile of BP for respective age were significantly higher by 5 to 10 mmHg, in comparison with children from quiet places. Moreover, children living in Bratislava more than 3 years had significantly higher mean sBP. The effect of the noise in kindergarten areas was more pronounced in comparison with home areas. This may be explained by the time of day spent in the nurseries, when traffic noise is louder (Regecová & Kellerová 1995).

The mapping of urban noise levels with awareness of its health-risk effects, should be undertaken, to serve local authorities to generate action plans for intended corrective measures, for legislation on noise control, and for future urbanity planning of the city development. In this respect our results were cited and served as arguments for several experts' reports published in the frame of EU.

Circadian and ultradian rhythms of blood pressure and heart rate in neonates.

Since the study of Hellbrugge (1960), the belief persisted, that the circadian rhythms in cardiovascular functions in man, develop gradually several weeks after the birth, and consecutively, with maturation of the respective control systems. Construction of an ultrasound instrument for noninvasive BP measurement (Kellerová *et al* 1978a; 1978b, Kellerová 1981) enabled us to perform noninvasive and repeated measurements of systolic, as well as of diastolic BP even in neonates, several hours after birth.

We gained priority by the evidence of the circadian oscillation of BP and HR in neonates, already in the first postnatal days (Kellerová & Kittová 1980, Kellerová 1981, Kellerová *et al* 1985). Later, submitting the data to the population-mean cosinor evaluation (Bingham *et al* 1982), we confirmed their significant ($p<0.01$) circadian periodicity characterized by an amplitude of 9–10% of the respective BP mesor values (one half of the difference between the highest and lowest value in the cycle defined by the cosinor curve). The acrophase in term newborns was close to 11 AM (Kellerová 1985). It was not related to the condition of sleeping or waking. This finding was confirmed by us in individual series of data by a chronobiometrical processing, combining cosinor and periodogram analysis, taking into account three most prominent rhythms (Kellerová *et al* 1989). The result revealed in 9 from 19 newborn babies a circadian BP and HR oscillation, with amplitude significantly differing from zero, in combination with slow (6–12 h) and fast (2–6 h) ultradian periodicities, which were less frequent in the adults (Kellerová *et al* 1989). Surprisingly it was possible to detect the circadian BP oscillation also in the group of prematures (gestational age 33.7 weeks, birth weight 2136±104 g, postnatal age

44±4 h), but of smaller amplitude 5–6% of the mesor and only marginally significant ($p<0.05$) (Kellerová *et al* 1985).

The discovery of the existence of the circadian rhythm in neonatal BP and HR was later confirmed by others (Halberg *et al* 1986; Sjutkina *et al* 1990; Sitka *et al* 1994).

PHYSIOLOGICAL VARIABILITY AND REACTIVE CHANGES OF THE ELECTROPHYSIOLOGICAL CHARACTERISTICS OF THE HEART

This field of research was the main domain of Ivan Ruttkay-Nedecký. As a protagonist of physiological and computer model analysis of the sources and mechanisms of the variability and reactivity in electrical behavior of the heart, in norm and pathology, he looked for the quantitative assessment of investigated parameters and their changes. He initiated a broad collaboration in theoretical research as well as in clinical diagnostic. Results were published in many papers, here are some of the representative (Ruttkay-Nedecký 1978, 1983, 2001; Ruttkay-Nedecký & Cherkovich 1977; Ruttkay-Nedecký & Regecová 2000, 2002; Ruttkay-Nedecký *et al* 1982; Szathmáry & Ruttkay-Nedecký 2002, 2006). The computer model of ventricular depolarization and repolarization (Szathmáry & Osvald 1994) is still used for analysis and diagnostic interpretation of different ECG patterns (Bachárová *et al* 2011, 2012).

From the first beginning in 1959 Ruttkay-Nedecký participated for many years in organizing the international meetings on electrical behavior of the heart – Colloquia Vectorcardiographica later continuing as International Symposia on Vectorcardiography, and in 1974 transformed into International Congresses on Electrocardiology held every year. So that the 40th International Congress on Electrocardiology held 2013 in the University of Glasgow, Scotland was the occasion to celebrate the 55th anniversary of these meetings.

The first study (Ruttkay-Nedecký & Kellerová, 1960), with a quantitative evaluation of the ventricular gradient (G) in the course of an active orthostatic reaction, documented significant changes of (G) – related to the ventricular repolarization, in subjects having high normal BP, but not in those with normal BP. Possible effect of an increased influence of sympathetic on the working myocardium was presumed.

Since then electrophysiological parameters characterizing ventricular repolarization have repeatedly been shown in normal subjects to be influenced by a variety of physiological situations involving autonomic cardiovascular control. Namely – magnitude of the spatial maximal repolarization vector (sTmax), – magnitude of the ventricular gradient (G), – spatial angle between integral depolarization and repolarization vectors and amplitudes of the integral body surface potential maps in repolarization. These parameters were suggested as quantitative measures of the direct sympathetic influ-

ence on the ventricular myocardium, complementary to the heart rate, which reflects complex vagal and sympathetic effects on the pacemaker (Ruttkay-Nedecký 1978). The effects of sympathetic over-activity were documented by our results in – head-up body tilting (Kellerová *et al* 2002, 2010; Andrásyová *et al* 2002), – psychoemotional load (MA) (Ruttkay-Nedecký 1978; Andrásyová *et al* 2002; Kellerova *et al* 2000, 2006) – hand grip test (Andrásyová *et al* 2002), and observed in subjects with high normal BP and Hypertension I. (Andrásyová *et al* 2001, 2002; Kellerová *et al* 2000; Regecová *et al* 2000). Infusion of Dopamine – the immediate precursor of norepinephrine, caused in spite of a mild chronotropic effect – a significant decrease of the magnitude of the repolarization vector due to its synchronizing influence on ventricular repolarization (Kellerová *et al* 1984).

Over the dividing value of optimal BP $\leq 120/80$ mmHg, the repolarization parameters point to an increased ventricular adrenergic tone or reactivity at rest, already in the class defined by ESH (2003), as normal and high normal, but by JNC-VII as prehypertensive. These changes are similar to those, observed under mental or physical strain.

The discriminative power of the repolarization integral body surface potential maps was strong enough to distinguish the by MA induced changes in the superficial cardiac electric field, in spite of its large variability at rest. These transient adrenergic alterations in ventricular recovery may be of importance in subjects at risk for ventricular arrhythmias (Kellerová *et al* 2006).

To improve the reliability of criteria for normal values of VCG characteristics namely magnitude of spatial vectors of atrial and ventricular activation and ventricular repolarization, their relation to age and to several anthropometrical parameters was quantified. The average magnitudes of maximal spatial vectors increase during maturation and early adulthood. To the end of the 2nd decade, they start to decrease. With increasing endomorphy magnitude of the vectors decreased but increased with higher linearity and index of fitness (Regecová 2002; Regecová & Andrásyová 2002 ; Regecová & Ruttkay-Nedecký 1996)

Beat-to-beat analysis of a train of ECG BSPMs, provided the first evidence of spontaneous non-random, respiratory (15–20 c/min) and low frequency (3–10 c/min) oscillations of the ventricular repolarization pattern and allowed the first insight into the dynamics of body posture associated changes in ventricular recovery (Kellerová *et al* 2010).

The previously unexplored dynamic beat-to-beat pattern of the reactive changes in the ventricular depolarization and repolarization parameters of the integral BSPMs, documented, that the response to a mental stress test started in all subjects with a short latency, after initiation of the mental task, usually peaked significantly at 30–60 seconds, returning to the control values to the end of the test, or some heart beats after. The main parameter of the integral repolarization BSPM – the QRSTampl fell from 154 to 126 µVs, whereby the ventricular depolarization remained practically unchanged. The pattern of the responses was inter-individually conformable, however variable in magnitude. It is concluded, that these findings are explained by pattering of the sympathetic response, which involves selective activation of the ventricular myocardium in the response to mental challenge.

Beneficial effect of physical activity turning down the cardiovascular sympathergic responses to stress was evidenced by a minimal increase of BF in the forearm muscle, and by a significantly less decrease of the repolarization T-wave space vector magnitude due to the psychoemotional load (MA test), in trained athletes in the average by 17% in comparison to 40% in non-sporting university students (Kellerová & Štulrajter 1989). Stimulation of the positive emotiogenic area of the lateral hypothalamus in chronic experiments in rabbits , abolished – or even prevented what may be considered emotionally induced cardiovascular disturbances. The by immobilization and hypothalamic defense area stimulation provoked BP and HR increases and dysrhythmias returned to control values (Uljaninskij *et al* 1987).

Based on these results, it is not necessary to point out the role of positive emotions and importance and protective effect of systematic physical training at adequate load, used today not only in rehabilitation, but also in prevention of cardiovascular diseases in risk groups.

At the end let me quote a 165 year old reflection, applicable also these days to the epidemic character of hypertension, obesity, perilous life style etc., jeopardizing already our youth.

… Don't crowd diseases point everywhere to deficiences of society? One may adduce atmospheric or cosmic conditions or similar factors. But never do they alone make epidemics. They produce them only where due to bad social conditions people have lived for some time in abnormal situation.

The history of artificial epidemics is therefore the history of disturbances in human culture. They announce to us in gigantic signs the turning points of culture into new directions.

Epidemics resemble great warning signs on which a true statesman is able to read that the evolution of his nation has been disturbed to a point which even a careless policy is no longer allowed to overlook …

Rudolf Wirchow
1821–1902
"Father of pathology" founded also the field of "Social medicine"

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