

From the First Spectral Analysis of Blood Pressure Variability in the World to the Present Time: Contribution of the Department of Physiology of the Faculty of Medicine, Masaryk University, Brno

Dedicated to Professor MUDr. Nataša Honzíkuvá, CSc., on the occasion of her 65th birthday

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Short title: Spectral analysis of blood pressure variability

Summary:

The review shows the significance of blood pressure regulation studies conducted during several decades at the Department of Physiology, Faculty of Medicine, Masaryk University, Brno. Continuous non-invasive blood pressure measurement was first introduced and patented here and, with the obtained data, the first spectral analysis of blood pressure was performed. This method was used in many different physiological studies on the relationship of blood pressure regulation to circulatory parameters, breathing, and baroreflex sensitivity. The article deals with studies on risk stratification of sudden cardiac death according to decreased baroreflex sensitivity, 24-hour heart rate variability, the amount of extrasystoles and late potentials. Importance of the new method of determination of one summation risk index is described here. A summary of the new conception of the relationship between low baroreflex sensitivity and hypertension is presented. Here, not only pathological changes of the vessel

wall but also increased sympathetic activity and genetic predisposition play a role. Importance of studies conducted in young adults is highlighted, as inherited BRS decrease contributes to earlier blood pressure increase in the young. This research is highly topical, since prevention of hypertension in childhood is possible. Recent studies are dedicated to blood pressure regulation in young diabetics.

Key words: Finger arterial blood pressure – Blood pressure variability – Baroreflex sensitivity – Sudden cardiac death – Hypertension – Area under receiving operating curve

Introduction

It is a great honour for me to review, on the occasion of the 65th birthday of Professor MUDr. Nataša Honzíková, CSc., the significance of studies in blood pressure regulation conducted during several decades at the Department of Physiology of the Faculty of Medicine, Masaryk University. Born in Brno on 11 August 1948, Professor Nataša Honzíková has belonged to distinguished Czech physiologists and her life has been entirely devoted to studies of cardiovascular regulation. She started to work in the laboratory of Professor MUDr. Jan Peňáz, CSc., in co-operation with Professor MUDr. Bohumil Fišer, CSc., in the seventies of the last century and she conducted this research during the last decades.

This research team laid the foundations of later internationally used methods of evaluation of short-term blood pressure variability using spectral analysis, and of additional methods derived from spectral analysis of short-term variations of circulatory parameters involved in blood pressure regulation.

History of the introduction of spectral analysis of blood pressure variability recorded continually and non-invasively from finger arteries

We have to return to the year 1969, when Jan Peňáz patented the non-invasive continuous method of blood pressure measurement from finger arteries and constructed a reliable device called plethysmomanometer (Peňáz 1969). Shortly afterwards, during his stay in the Netherlands, he applied spectral analysis to the quantifications of short-term variability of heart rate and blood flow measured beat-to-beat by plethysmography (Peňáz *et al.* 1968). Such an approach had not been used in the physiology of circulation. At that time Nataša Honzíková started to work at the Department of Physiology as a student and, in 1973, as an assistant. Under the guidance of Peňáz, she started to work on the implementation of spectral analysis in blood pressure variability recorded continuously by Peňáz's plethysmomanometer. To understand the significance of the introduction of spectral analysis of waves in blood pressure in Brno, it is useful to describe more closely the conditions under which these first studies in the world on spectral analysis of blood pressure were created. It was before four decades in Czechoslovakia, where computer technology was not commonly available. The present generation of young novices of science can hardly imagine work under such conditions. The methodical approach, programming and computation were at that time realised by Professor Ing. Jan Honzík, CSc., who was a young assistant at the Department of

Computers of the Faculty of Electrical Engineering of the Brno University of Technology. Already the first analysis was conceived with the idea to get information about controlling linkage between rhythmical variations in blood pressure, heart rate, finger blood flow, and respiration. It was necessary to manually read tens of thousands of values and to transfer them onto punched cards. The results of this exacting study were presented in 1975 (Honzíková *et al.* 1975), full-extent papers were published in 1978 (Peňáz *et al.* 1978; Fišer *et al.* 1978). It is noteworthy how much information valid till now is contained in these pioneering studies – starting from the relationships between variability in more parameters (systolic, diastolic, and pulse pressures, cardiac intervals, finger blood flow and respiration), to coherence and phase shift between these signals, and individual differences and repeatability after 20 minutes as well. These key studies remained for a longer time without any response, because no laboratory had at its disposal a device for a non-invasive continuous blood pressure recording. It was Professor Karel Wesseling in the Netherlands who recognised the significance of this methodology. He contributed to a further technical development of this method; Let me mention just some examples from a whole group of publications from this period (Wesseling *et al.* 1982; Molhoek *et al.* 1984). This development led to the commerce device Finapres (Ohmeda, USA) which, after introduction to the market, opened a boom in studies based on spectral analysis of blood pressure variability.

In the 1980s, Nataša Honzíková pursued the analysis of the relationship between variability in circulation on the one hand and variation of depth and rate of respiration on the other. She was the first to draw attention to the fact that the influence of respiration on circulation is manifested not only in the typical respiratory frequency, in the so-called high-frequency spectral range (HF), but also in the so-called low-frequency range (LF). Although she, for political reasons, did not find doors opened for publication in Czechoslovakia in the 1980s, she was repeatedly invited abroad as an invited speaker, and she was successful in presenting there studies on the interpretation of differences in the power spectra of blood pressure, heart rate and respiration in man (Honzíková *et al.* 1987), and on the role of changes in depth and rate of respiration played in changes of respiratory rhythms during mental load (Honzíková *et al.* 1988). The study on individual characteristics of circulatory and respiratory spectra at one year's distance was also of high priority at that time (Honzíková *et al.* 1990).

During this period studies were published in Brno on the thermoregulatory effects on circulatory and respiratory variability (Honzíková *et al.* 1984), on the effect of regular and random respiration on circulatory spectra (Honzíková and Peňáz 1985), a study was published on the circulatory spectra during static workload (Honzíková *et al.* 1986), and the most

important of them was a monograph which was written in the eighties, but published later after political changes in our country (Honzíková 1990). This monograph summarised her own previous studies on circulatory spectra in the context of the current state of knowledge, but it also contained a fully new procedure of evaluation of the fluctuation of peripheral resistance based on changes of the rate of blood pressure decrease during the diastole. This monograph was one of very rare books issued at that time in the world. They were mostly published in the Netherlands, where Finapres was developed (de Boer 1985).

The conference “Volume-clamp recording of blood pressure in man”, which was organised as part of the Regional Meeting of the International Union of Physiological Societies in honour of Peňáz in 1991, was a considerable contribution to international access to methods based on continual blood pressure recording in finger arteries. It was followed by the publication of a set of 30 papers by authors all over the world in several issues of the journal *Homeostasis* edited by N. Honzíková, T. H. Schmidt from Hannover, and K. H. Wesseling from Amsterdam, where Nataša Honzíková also contributed by some studies (Honzíková *et al.* 1995a, b; Weise *et al.* 1995; Honzíková *et al.* 1996).

Determination of baroreflex sensitivity by spectral method

Blood pressure is controlled by many nervous and humoral mechanisms - systemic and local. As regards nervous regulation of blood pressure, baroreflex is the most important mechanism. It has several branches, but heart rate response to blood pressure variations is studied mostly quantitatively. Changes of cardiac intervals caused by variations in blood pressure via stimulation of baroreceptors are usually quantified as index baroreflex sensitivity (BRS) that corresponds to a change of the cardiac interval due to a change of blood pressure (ms/mmHg). This mechanism operates beat by beat and is evaluated from continuous recordings of blood pressure and cardiac intervals. There is a variety of methods of baroreflex sensitivity determination, as for instance evaluation of beat-to-beat changes of blood pressure and cardiac intervals after the administration of a vasoactive drug, which opened such studies (Smyth *et al.* 1969), and a whole array of further methods which were introduced during the following decades: evaluation of upward- and downward-sloping groups of pulses in spontaneous recordings, various indices based on cross-spectral analysis, alpha index, wavelet approach, and LP analysis. A number of studies have compared BRS results as obtained by different methods (Krticka *et al.* 2000; Persson *et al.* 2001; Krticka and Honzikova 2001; Lipman *et al.* 2003; Laude *et al.* 2004).

The introduction of determination of baroreflex sensitivity by the spectral method in the 1980s (Robe *et al.* 1987) represented a methodological step forward in the exploitation of spectral analysis of the blood-pressure and heart-rate variabilities. Nataša Honzíková in co-operation with Bohumil Fišer and Jan Honzík were among the first to apply the cross-spectral method for BRS determination at a frequency of 0.1 Hz during orthostasis, static and emotional load, and to compare it with other methods of BRS determination (Honzíková and Fišer 1991; Honzíková *et al.* 1992a, b). Nataša Honzíková's participation in one of the first comparative studies of methods of BRS determination was a natural consequence of her international appreciation (Persson *et al.* 2001).

In a variety of methodological studies conducted by our group extended by younger co-workers and in co-operation with Professor Swenne and his colleagues in the Netherlands we have shown that there is a difference between BRS values determined at a respiratory frequency and a frequency of 0.1 Hz (Fredericks *et al.* 1997; Bothova *et al.* 2010; Fredericks *et al.* 2000; Swenne 2013). These studies have also shown that the value of BRS determined at a breathing frequency overestimates on average the real BRS in comparison with that determined at a frequency of 0.1 Hz, even though an opposite relationship between both values may be present in some subjects. This effect is dependent on a different mechanism of the development of variation in blood pressure and cardiac intervals, which is not only a result of baroreflex. With respect to the fact that respiratory sinus arrhythmia is also affected by additive reflexes, for instance from pulmonary mechanoreceptors (Hainsworth 1974), or by a central irradiation of activity from the respiratory centre (Eckberg 2003; Eckberg and Karemaker 2009), we examine BRS at a frequency of 0.1 Hz using metronome-controlled breathing at a frequency which is substantially higher than 0.1 Hz and is not a multiple of 0.1 Hz to eliminate the respiratory baroreflex-non-related influence and a resonance effect on heart rate fluctuations. It is important that BRS represents an individually characteristic feature, even though it is spontaneously fluctuating to some extent (Jíra *et al.* 2006; Dietrich *et al.* 2010). From the point of view of diagnostic application of this method it is important that spontaneous fluctuation of BRS is low in persons with its low value, which is associated with essential hypertension and is a risk factor in many cardiovascular diseases (Jíra *et al.* 2006). It is also necessary, during a diagnostic evaluation of the BRS changes, to take into account the fact that the value of the BRS index in ms/mmHg is influenced by mean duration of the cardiac interval, which may mask some fine changes of baroreflex sensitivity, for instance its decrease at the age between 10 and 19 years when vagal tone and mean heart rate develop. In such cases a baroreflex sensitivity decrease is proved by the BRSf index in

mHz/mmHg, which is less dependent on the mean cardiac interval (Závodná *et al.* 2006). On the other hand, a change of the mean cardiac interval may cause a change of the BRS index which need not be found in the BRSf index (not yet published results of a study of early changes of baroreflex sensitivity in adolescents with type 1 diabetes mellitus). Naturally, both indices, BRS and BRSf, provide the same information at high pathological decrease of baroreflex sensitivity (Honzíková *et al.* 2006a).

Prediction of the risk of sudden cardiac death

As early as some 20 years ago, Professor Honzíková posed herself a question on the possible significance of spectral analysis of blood pressure variability for practical medicine. In the 1990s she started, in co-operation with Professor Bohumil Fišer and with the First Department of Cardiology headed by Professor Bořivoj Semrád, to test the significance of the BRS decrease determined by spectral analysis of resting recordings of blood pressure in finger arteries in patients after myocardial infarction (Honzíková *et al.* 1993; 1994; 1995c). A decreased BRS as a marker of the risk of sudden cardiac death was evaluated at that time using intravenous application of the vasoconstrictor phenylephrine first in animals (Schwartz *et al.* 1988) and later in patients (Bigger *et al.* 1989; La Rovere *et al.* 1998). An explanation of the mechanism by which high BRS prevents sudden cardiac death is as follows: Quick prolongation of the cardiac interval following a sudden blood pressure elevation decreases cardiac workload. This is important in an ischaemic myocardium, especially after myocardial infarction, and therefore high BRS decreases the risk of sudden cardiac death. The importance of the approach to BRS determination based on spectral analysis of a non-invasive resting recording of blood pressure is in a reduced load of the patients after myocardial infarction by such an examination. It was shown that a critical risk value of BRS determined by the spectral method is comparable with that obtained by the phenylephrine method (Honzíková *et al.* 2000a) and represents an important risk factor (Honzíková *et al.* 2000b). The above-mentioned study (Honzíková *et al.* 2000b) was broadly conceived and showed that the simultaneous evaluation of indices characterising changes in autonomic control of heart rate (BRS and SDANN index derived from 24 hour ECG monitoring), of a lowered pumping function of the heart (ejection fraction), of an increased excitability of the myocardium (the number of extrasystoles per 24 hours determined during ECG monitoring), and of changes in activation of the myocardium (presence of late potentials) disclosed a different and mutually amplifying effect of individual factors on the risk of sudden cardiac death. These studies were

quickly accepted and included in an American study on the decision to implant a cardioverter defibrillator after myocardial infarction (Bailey *et al.* 2007). Nevertheless, tens of further studies on prediction of the risk of sudden cardiac death have shown that no single index exhibits a satisfactory sensitivity and specificity in a therapeutic decision in risky patients. On the other hand, a multiple regression analysis comprising more risk indices brought evidence of the increased risk when more risky factors were present. However, such statistical analysis cannot give a clear answer whether a particular patient should be included in a highly risky group. Nowadays, the process of decision is resolved in several steps. Several years ago, Professor Honzíkóv started to co-operate with Petr Honzík on the development of a mathematical method of the determination of one summation risk index of risky patients which included a group of risk factors. This index includes: (1) significance (weight) of the individual risk factors; (2) fuzzification of the critical value, that means blurring of the critical risky value of individual indices, because the critical values were determined statistically and did not take into account that the risk rate of a patient is also influenced by values of indices near to critical values (Honzik 2005; Honzík *et al.* 2002; 2003; 2009). Thus, they created a general instrument which we applied also in other areas of research, in a study of early states of hypertension in adolescents or in cardiomyopathy (Krontorádov *et al.* 2008; Honzík *et al.* 2010). We suppose that this concept will also be profitable in other areas of clinical research.

Low baroreflex sensitivity as a symptom of essential hypertension and as a factor conditioning its development

Myocardial infarction is a frequent complication of essential hypertension. This is one of the reasons why studies of BRS in hypertensive patients are important with respect to prediction of a potential risk of these patients in case of myocardial infarction.

Low BRS (under 5 ms/mmHg) was repeatedly observed in patients with hypertension several years ago. Naturally, a question arose what is the cause of a BRS decrease in hypertensive patients. It was proved that low BRS in hypertensive patients was associated with a thickening of the carotid intima-media in the carotid bulb, a region with a high baroreceptor density and with the presence of atherosclerosis (Zanchetti *et al.* 1998; Gianaros *et al.* 2002). In our studies we have also confirmed a linkage of remodelling and thickening of the carotid intima-media of the carotid wall with high blood pressure and low baroreflex sensitivity (Labrova *et al.* 2005; Honzíkóv *et al.* 2006b).

There are also several additive factors, such as sympathetic activation in obesity due to the release of leptin, which also secondarily suppresses BRS. It has been shown that obesity is associated with a higher risk of high blood pressure in both adults and children (Lurbe *et al.* 1998; Rahmouni *et al.* 2005; Honzíková *et al.* 2006a; Lazarová *et al.* 2009; Honzíková and Fišer 2009). All these studies lead to the interpretation that the decrease of BRS in hypertonic patients should be understood as a symptom dependent on several factors (increased arterial stiffness, increased sympathetic activity and obesity). There are some epidemiological proofs that the growing obesity in young population increases the prevalence of hypertension in adolescents and young adults (Freedman *et al.* 1999; Sorof 2002).

Professor Honzíková with Dr. Z. Nováková initiated several studies in children and adolescents (Nováková *et al.* 1997, 1998; Honzíková *et al.* 2000c) with the aim to evaluate whether an inborn disposition to a low BRS could also influence, as one of the primary factors, the risk of early blood pressure elevation. It was in a period when there was hardly any interest in studying baroreflex in children in the world, because hypertension and its complications are diseases of adult population. That is to say that we made an interesting observation in our physiological study showing that about 5 % of a group of 400 healthy children and adolescents (aged 10-19 years) had their BRS as low (3.9 ms/mmHg) as could well be supposed to be a symptom of hypertension and to suggest a disposition of the patient to complications such as myocardial infarction (Závodná *et al.* 2006).

This analysis evoked an interest in studying inborn dispositions to low BRS. Previously, basic information had been obtained from studies on twins. Significant correlations were found for BRS in monozygotic, but not in dizygotic twin pairs (Tank *et al.* 2001). It is not surprising that nowadays genetic studies are performed; we also started such an analysis (Jira *et al.* 2010). Nevertheless, a serious understanding of the genetic conditioning of BRS will be very complicated, because the genetic contribution to a BRS value could involve different components of the baroreceptor reflex arc, including baroreceptors, reflex afferent and efferent pathways, central neuronal transmission, and the sinoatrial node. In all of these parts there act numerous ligands, receptors, channels, etc. Summarisations of the current knowledge of the genetics of BRS were published last year (Honzíková and Závodná 2012; Jordan and Biaggioni 2012).

It seemed therefore useful to examine BRS in a broader young population and to find some indirect proof of the influence of a primarily low BRS on blood pressure. We have found a decreased BRS and BRSf in children, adolescents and young adults (11-21 years) with white-coat hypertension and early hypertension (Honzíková *et al.* 2006a). The stepwise blood

pressure elevation in these groups was associated, besides a stepwise decrease of BRS/BRSf, also with a stepwise increase of the body mass index. Such a finding in hypertonics may correspond with a possible starting atherosclerotic process and remodelling of the arteries. A quite different situation is in those with white-coat hypertension. These young subjects have a mostly physiological blood pressure all over the day and there is no reason for a remodelling of the arterial wall. However, their hyperreactivity of blood pressure changes may be influenced by primarily low BRS.

A direct evidence that low baroreflex sensitivity is a partially independent risk factor for the development of essential hypertension was provided by our study Krontoradova *et al.* (2008). Although young hypertonic subjects of this study had a significantly lower BRS and a significantly higher BMI than the controls, there was no correlation between BMI and BRS either in the group of hypertonics or in the controls. We applied our original method (Honzik *et al.* 2002, 2010) in a detailed evaluation of the effect of both factors, BMI and BRS, on blood pressure elevation. The predicting power of BMI, BRS, and an index determined on the basis of combination of values of BMI and BRS was further evaluated. The optimal critical values for the diagnostics of hypertension were determined by the receiver-operating curves (ROC) for all three indices. The sensitivity, specificity, and the area under the ROC were increased in predicting hypertension for a summation index based on a combination of both factors, BRS and BMI. This documented that low BRS could be a partially independent risk factor for the development of essential hypertension

Professor Honzíkóvá summarised, in a chapter in a monograph (Honzíkóvá and Závodná 2012), this new insight into the role of low baroreflex sensitivity in essential hypertension – as a generally accepted symptom linked with arterial stiffness, sympathetic activation and obesity on the one hand and as a possible additive factor conditioning its development on the other.

Application of spectral analysis of blood pressure variability in diagnostics in children and adolescents

Last but not least, Professor Honzíkuvá, in co-operation with Professor Hrstková and co-workers, also took part in clinical studies of blood pressure regulation in childhood. The aim of these studies was to find some markers of early changes of control in circulation in special groups of patients with increased risk of cardiovascular complications in future. This was especially a prospective study in children and adolescents after antitumour therapy by drugs with possible negative side effects on the cardiovascular system. Even though these young people are fully healthy, we have found in some of them decreased BRS and a tendency to a slowed development of blood pressure compared with its physiological increase during adolescence, and also a large drop of blood pressure in the night hours (Nováková *et al.* 2007; Nováková *et al.* 2010).

Another risk group from the point of view of functioning of the cardiovascular system in later decades of life is represented by children with type 1 diabetes mellitus. A study performed in co-operation with the team of Assoc. Prof. M. Javorka (Martin, Slovakia) disclosed their tendency to an early BRS decrease (Javorka *et al.* 2011) and a shift of the spectral peak frequency (cross-spectrum of variations in blood pressure and cardiac intervals) in the range around 0.1 Hz to lower frequencies (Honzíkuvá *et al.* 2012).

Conclusion

In conclusion I would like to summarise the value of the lifelong studies of Professor Honzíkuvá for the understanding of the physiology of circulation control. In the 1970s, Professor Honzíkuvá participated in the introduction of spectral analysis of blood pressure variability recorded by the non-invasive continuous method from finger arteries into quantification of the control mechanisms of blood pressure, which has nowadays been generally used in thousands of studies all over the world, and also in the development of a method for the determination of dynamic compliance of finger arteries (Peňáz *et al.* 1997), which awaits its further applications. Her indubitable contribution to the evaluation and understanding of the physiology of beat-by-beat blood pressure variability, its ontogenetic development and individual characteristics should be acknowledged. From the point of view of clinical medicine the studies of the risk of sudden cardiac death after myocardial infarction are of the utmost importance. The complex of studies of baroreflex sensitivity in children and adolescents, which brought evidence that inborn low baroreflex sensitivity may be linked with the early blood pressure elevation in youth, may be of importance in future. This area of research is highly topical with respect to preventative medicine.

It is only natural that the majority of the studies was conducted in co-operation with clinicians. Professor Honzíkuvá encouraged such co-operation, also with a substantial share of doctoral students. Some of her previous students continue doing research at our Department of Physiology, others continue in medical practice and research in the Faculty Hospital in Brno. It is an honour for me that I could grow under the leadership of Professor Honzíkuvá and take part in many of these studies.

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