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PROCEEDINGS

SYMPOSIUM

CARDIOVASCULAR COORDINATION IN HEALTH AND BLOOD PRESSURE DISORDERS

Dedicated to the Seventieth Anniversary of Professor Jan Peňáz.

Edited by: F. HALBERG, T. KENNER, B. FIŠER, J. SIEGELOVÁ

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Cardiovascular coordination in health and blood pressure disorders

Dedicated to the Seventieth Anniversary of Professor Jan Peňáz.

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INTRODUCTION

P. BRAVENÝ

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This meeting is to commemorate the outstanding achievements in physiology of the septuagenarian Jan Peňáz. The other aniversary which deserves to be reminded is 50 years since Jan Peňáz appeared in this Department of physiology. Remarkably, he has never changed the place.

The whole scientific career of Jan Peňáz has been hall-marked by his extraordinary technical and mathematical talents combined with excellent medical education. In his early days, Jan substantially improved then available plethysmograph and constructed an orthochronograph for continuos recording of RR intervals. These techniques made it possible to study quantitively the relations between respiration and blood circulation. Later, Jan developed a stimulator with frequency modulated output in order to study the nervous regulation of cardiovascular functions. In the mid sixties, Jan focused his attention to spontaneous oscillations of cardiovascular parameters. For this purpose he developed the first version of his photoplethysmograph based on volume-clamp technique which made it possible to record continuously and non-invasively the blood pressure and to apply the spectral analysis to physiological research, one of Jan's priorities. In the course of the last thirty years, Jan has gradually and painstakingly brought his most significant invention, the servotonometer, to perfection. Though internationally recognized, at home Jan's merits could be openly appreciated only recently. He was promoted Full Professor, was awarded by Golden Medal of the Faculty of Medicine and by the City of Brno Prize 1995. An international symposium was held in Prague to highlight Jan Peňáz'merits. Today, we would like to contribute to all those appraisals and thanks once again.

Prof. PAVEL BRAVENÝ, M.D., PhD.
Vice-rector Masaryk University

VIBRATION PLETHYSMOGRAPHY: A METHOD TO ESTIMATE VISCOELASTIC PROPERTIES OF ACRAL BLOOD VESSELS

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The principle of photoelectric vibration plethysmography has been described in previous communications (3,4): relatively fast vibrations (e.g. 50 Hz) are superimposed to a steady or slowly changing pressure in a finger cuff; the amplitude of vascular volume oscillations are measured by a photoelectric sensor and recorded as a continuous waveform. The principle was used for indirect measurement of diastolic pressure in the finger (6) and for continuous set point correction in an automatic noninvasive blood pressure monitor (2). It was suggested that the vibration plethysmogram reflects dynamic changes of vascular compliance (DVC) (2,3,4). The present study was aimed to test this hypothesis and to analyse the relation of this peculiar signal to other acral vascular functions.

METHODS

46 records of blood pressure (BP) using a new noninvasive blood pressure monitor (2) or the Finapres 2300 (Ohmeda), of normal photoelectric plethysmogram (PG) and of vibration plethysmogram (VP) under linearly rising and decreasing cuff pressure (CP) were taken in two adjacent fingers (3rd and 4th) in 23 healthy subjects (19 – 69 years, both sexes). Two successive records were made in each subject; after the first one the finger cuffs were swapped to avoid a possible influence of pressure differences between fingers. The VP signal was transformed to the DVC waveform by analog circuits (selective amplification at 50 Hz, rectification and smoothing) to obtain the DVC pulse wave (4). The four signals passed a 12 bit A/D converter to be processed on a PC using the graphic module ScopeWin (5) working under MS-Windows 3.1. Having been originally designed for technical problems, the module had to be slightly adapted for analysis of cardiovascular signals.

The capabilities of this program module were used, a.o., to draw XY plots to illustrate mutual relations between the DVC, transmural pressure (TMP) and PG both in a slow time scale (mean values) and within each pulse interval (instantaneous values); in the latter case, only diastolic parts of the curves and a limited TMP range were used for the analysis. Relationship between the shape of the

PG and DVC pulse wave was quantitatively assessed by computing the correlation coefficient of the two waves (R).

RESULTS

Our previous finding (3,4) that the shape and polarity of DVC waves dramatically change in dependance on transmural pressure (TMP = BP – CP) was fully contested (Fig.1). At positive TMP (CP below mean BP) the DVC waveform resembled an inverted volume pulse (PG): correlation coefficient (R) was near –1. At negative TMP (CP above mean BP) the two waves ran more or less in parallel: R approached +1. The inversion point i.e. the point where R was zero layd near, but not exactly at zero transmural mean pressure (TMPm = BPm – CP), usually a few mmHg above zero. The same was true about the maximal amplitude of the PG pulse waves – a parameter commonly used in instruments for indirect measurement of (mean) blood pressure: the maxima were found near but not exactly at zero TMPm. The two critical points, i.e. R equaling zero and maximal PG amplitude, were quite close to each other but in some records there was also a difference of a few mmHg.

XY plots of fast changes of DVC, PG and TMP occurring during individual pulses (diastolic parts of them) revealed the following relations (Fig.2): In the chosen range of CP (between diastolic and systolic BP i.e. for TMP mean between cca –30 and +20 mmHg) the DVC wave showed a diastolic maximum or peak lying very near to zero value of instantaneous TMP. Dispersion of these TMP values was as low as that found for mean values (a few mmHg). On the other hand, the relationship of the DVC diastolic peak to the instantaneous vascular volume (PG) was less distinct: with increasing CP the DVC peak shifted to a smaller vascular volume and vice versa. In both cases, however, the diastolic DVC peak closely corresponded to the area of the highest slope in the PG/TMP plot, or inversely, of the plateau in the TMP/PG plot.

These and other relationships could be observed also at a closer inspection of the expanded time plots: in the above mentioned limited CP range the DVC diastolic peaks occurred very near to the intersection points of CP and BP i.e. at moments where instantaneous TMP equaled zero. The instantaneous values of PG waves corresponding to the DVC peaks, however, were less constant and shifted down with increasing CP and up with decreasing CP.

The time position of the diastolic DVC peaks also depended on the CP (or TMP): when CP was at or below the diastolic BP, the DVC peak was reached only at the very end of the pulse wave, just before the upstroke of the next PG wave. At the moment where CP just crossed the diastolic BP this "end-diastolic" DVC peak reached its highest value. Measuring the cuff pressure and viewing the DVC waveform one could easily estimate the diastolic pressure in indirect

way; this approach is simpler and faster than that originally proposed by Shimazu et al.(6).

A similar situation occurred when the CP was in the vicinity of systolic pressure: the DVC peak has shifted towards the onset of the pulse wave, and the moment where this systolic maximum started to decrease the momentary cuff pressure could be taken as a measure of systolic pressure.

DISCUSSION

The present study clearly confirms our earlier observations on the DVC waveform beeing strikingly dependent upon the cuff (i.e. transmural) pressure (2,3,4). That time, the described transformations have been explained on the basis of the S-shaped P/V (pressure-volume) characteristics (1,2): in its lower part which is convex towards the X axis, i.e. at negative transmural pressure, the amplitude of volume oscillations produced by fast pressure vibrations increases with rising transmural pressure during the pulse – and so does the DVC signal.In the upper part of the P/V curve which is concave to the X-axis, the amplitude of volume oscillations decreases with each pressure pulse – hence the negative deflection of DVC wave. In the middle part of the P/V curve, where its slope attains its maximum but diminishes to both sides, the fast volume oscillations and the DVC waveform – the envelope curve of these oscillations – instantaneously reflect any change in position on the P/V relation due to pulsatile changes of transmural pressure – hence the complicated DVC waveform and zero correlation to the PG wave.

This explanation is clearly oversimplified: the above mentioned S-shaped P/V characteristics is valid for static conditions, which are difficult to fulfill even in experiments on isolated arteries. Even when transmural pressure is changed very slowly (only a few mmHg per s), dynamic phenomena like hysteresis are very marked (1); the term quasi-static should be therefore preferred. In a faster time scale such as a single pulse interval the time-dependent phenomena become predominant. (By the way, this was the reason why only diastolic portions of the pulse waves were used to construct the XY plots.) In this respect, it is interesting that our fast PG/TMP plots showed very similar qualitative features as the quasi-static plots. Above all, the S-shaped form with a maximum slope at zero TMP was quite apparent.

Time-dependent factors may be supposed to play a major role in fast (50 Hz) pressure vibrations the frequency of which was much higher than the most important frequencies constituting a normal pressure wave. Strange enough, the DVC wave behaved like if it was conditioned mainly by elastic forces – with the important exception of its amplitude which was only a very small fraction of the value that could be forecast on the basis of quasi-static P/V relationship or the ratio PG amplitude/pulse pressure. The shape of the DVC waveform and the

relationship of its diastolic peak to transmural pressure and to the maximum slope in the P/V plot is an obvious indication that it reflects – without excluding other factors such as frictional or inertional ones – instantaneous changes of vascular compliance. Our original designation of a waveform obtained by vibration plethysmography as DVC wave (an abbreviation of Dynamic Vascular Compliance) seems thus justified; the adjective "dynamic" is used here as delimitation against the term (static or quasi-static) "vascular compliance" in the usual sense.

CONCLUSION

The vibration plethysmography has already proved its practical usefulness e.g. for measurement of diastolic pressure (6) and for continuous correction of the setpoint in a blood pressure monitor (2,4). The method can yield a fast information about viscoelastic state of small arteries in the examined area. While the present study has been performed on healthy subjects and in normal physiological conditions, interesting findings can be expected in fuctional or pathological changes of the acral circulation.

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Fig. 1:

Expanded section of a recording. Original traces of blood pressure (BP), cuff pressure (CP), plethysmogram (PG) and dynamic vascular compliance (DVC) were completed by computed variables: mean blood pressure (MBP), amplitude of plethysmographic pulses (AMP), and correlation coefficient (R) between DVC and PG pulses. Vertical scale (a.u.) for pressure curves is in mmHg, for PG in % of total absorbtion, for AMP the same times 3, R is multiplied by 10 and shifted down by 10 (in fact it moves between -1 and +1).

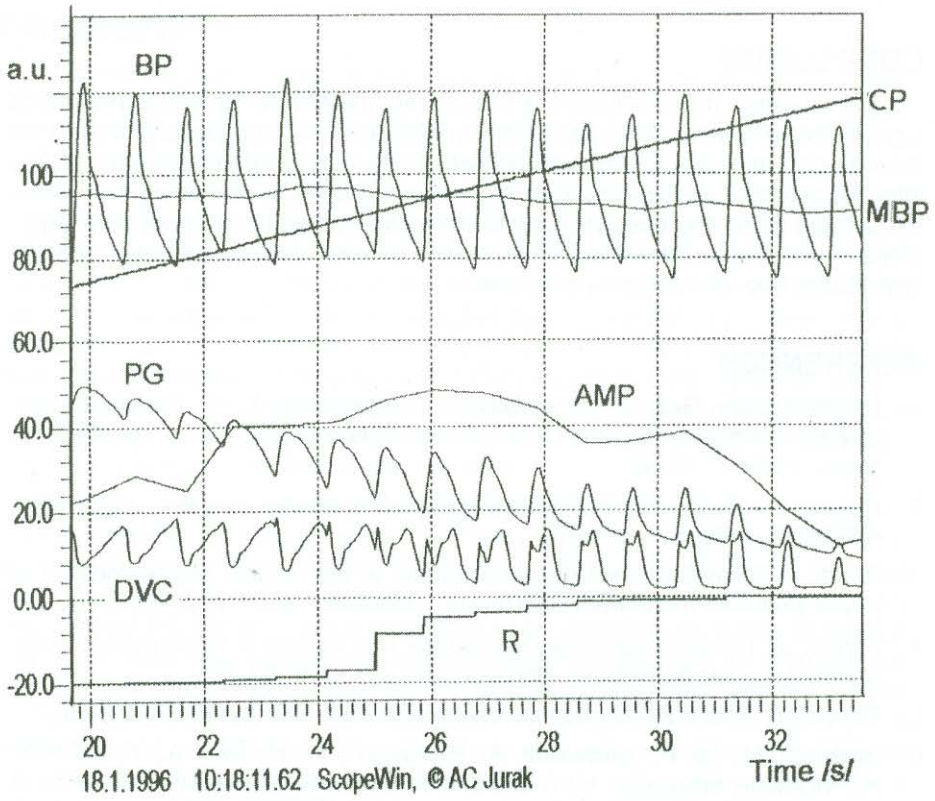
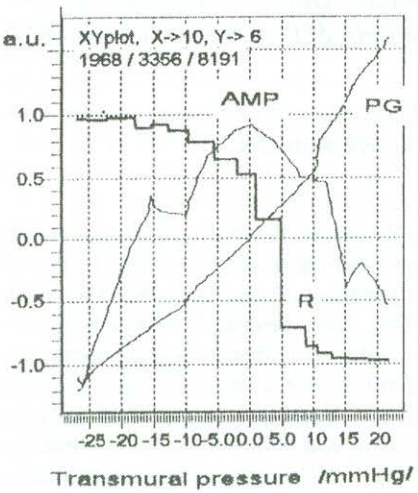
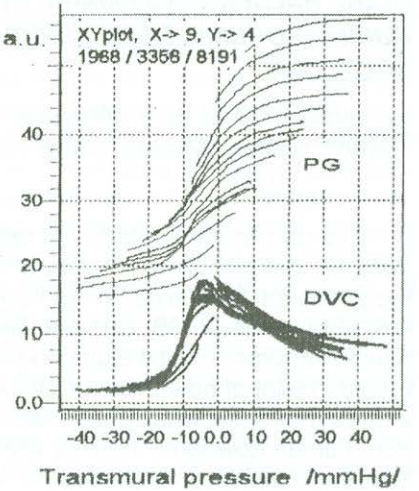


Fig. 2:

Left: Quasi-static relationship of mean PG, AMP and R upon mean transmural pressure. - Right: XY plot of DVC and PG against instantaneous transmural pressure during the diastolic phase of 12 successive pulses of record in Fig.1.





CIRCADIANI, CIRCASEPTANI, CIRCASEMISEPTANIQUE IN CHRONOMIS SECLUSORUM, PRAEMATURORUM, SENIUMQUE: IN HONOREM JOHANNIS PENAZENSIS MODO MENDELIANO, GOEDELIANO, KEPLERIANOQUE

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This part of the world is not only a seat of genetics, mathematics and astronomy, but it is home to pioneering in physiological monitoring: the home of the school of Jan Penaz. In his honor, it is a pleasure to present data that deal with about- half-weekly (circasemiseptan; CSS) components in the time structure (chronome) of vital signs. In the human baby, chronome components are buried in a lot of noise. If computability is a contribution of Kurt Goedel, it takes a lot of it to show what Goedel also insisted upon, consistency of CSS in data from human newborns in Brno, where monitoring was initiated by Academician Miloslav Uhlir. Also, in Minnesota, Moscow and La Coruna, a look at the data leads to despair.

It takes time series analyses before about-weekly (circaseptan; CS) and about-daily (circadian; CD) components in the time structure of human blood pressure (BP) and heart rate (HR) can be documented, as in earlier publications from the international womb-to-tomb chronome endeavor (1–3). New data document, for the CSS as well as for the CS and CD components, and the circadian, CD, the phase wobble or drift, if not free-run, notably of CSS during 267 days of isolation from society. This is an indirect line of evidence for the built-in nature of this component. The CSS of BP is found not only very early in life, but it is particularly prominent very late in life as well (5). In the newborn's BP and HR, the computability of complex yet consistent intermodulations between a CD that drifts in acrophase, notably during the first week of life, and a CS can be demonstrated by the use of parametric and nonparametric approaches. The intermodulating components of the BP and HR chronomes can be displayed also by plexograms of data before and after isolation from society and for monthly data sections during isolation. The half-weekly pattern can then be seen with the naked eye. Chronobiologic serial sections reveal dissociations in BP of the CS from the CSS and of the CSS in BP from that in HR. When multiple components are fitted nonlinearly to approximate the time structure of data, there are explicit inferences, as Kurt Goedel would have liked to have it.

In the homeland of Kepler, associations of the physiology of HR and BP and of vascular pathology, such as myocardial infarctions, with physical events in the cosmos, notably changes in the vertical component, Bz, of the interplanetary magnetic field's induction vector are pertinent (2, 6, 7). Relations among the physiology of chronomes and the cycles in cosmophysics, from Pc pulsations to circaundecennian solar cycles and beyond, can be rigorously examined for coherences cross-spectrally. A remove-and-replace approach reminiscent of the endocrinologists' study of hormonal effects in the presence or absence of a gland comes to mind when nature plays the role of the surgeon, removing or replacing cycles, the effects of which chronobiotechnology in the footsteps of Jan Penaz can assess. Someday, a weather report of storms in space can serve for the prevention of various kinds of nascent cosmochronopathology. The legacy of Jan Penaz, the pioneer of physiological monitoring, is the challenge of concomitant physiological and physical monitoring, preferably ambulatorily, on earth and in satellites. Thus, with all precautions that would satisfy Goedel, we could eventually explore not only the genetic heritage in BP and HR, a legacy of Gregor Mendel, but also new, now confirmed dimensions of our dependence upon the environment far and near as we may resonate with CS frequencies in the velocity changes of the solar wind (8). Complementing the archeologist's stratigraphy, perhaps, we learn from the physiology of chronomo-ontogeny, in combination with the phylogeny of chronomes, about the physical cycles in the environment at the time when life evolved. The concomitant monitoring of vital signs for much of a lifespan, now feasible, can gain from the co-monitoring of physical variables, the challenge to environmental physiology.

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CURRENT LIMITATIONS AND PROMISE OF AMBULATORY BLOOD PRESSURE MONITORING

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AIM

To compare circadian rhythm characteristics of systolic (S) and diastolic (D) blood pressure (BP) and heart rate (HR) measured by oscillometry (osc) or auscultation (aus) by the same instrument (TM–2421 from A&D) or measured oscillometrically by two different ambulatory monitors (TM–2421 from A&D and ABPM–630 from Colin Medical Instruments; CMI).

BACKGROUND

With the CMI monitor which also provides osc and aus BP measurements, the osc-SBP was found to be on the average higher than the aus-SBP, while the osc-DBP was on the average lower than the aus-DBP. The checking of ambulatory BP monitors for accuracy usually entails no more than a linear regression of single measurements taken under standardized controlled conditions from a group of subjects with widely differing BP values, an approach favoring large correlation coefficients that are highly statistically significant. This study aimed at assessing the extent of agreement not only in terms of a rhythm-adjusted 24-hour BP mean (MESOR) or of a single BP value, but also in terms of some of the measures of the dynamic characteristics of change in BP and HR, namely the circadian amplitude and acrophase.

SUBJECTS AND METHODS

From January 13 to 20, 1995, 4 clinically healthy adults (2 men and 2 women) measured their BP and HR around the clock with a monitor from A&D (TM-2421) at 15-min (GC) or 30-min intervals (JS, JD, BF). The latter three subjects also measured their BP and HR concomitantly at 30-min intervals with a monitor from CMI (ABPM-630), the two instruments being carried each on a different arm. Both instruments measure BP by osc and aus. Each data set was analyzed by single component (for parsimony) single cosinor to obtain estimates of the MESOR (rhythm-adjusted mean) and of the double circadian amplitude and acrophase (measures of the extent and timing of predictable change within a day, respec-

tively). These circadian parameters are compared by parameter tests between the osc and aus readings of the A&D monitor and between the osc readings from the A&D vs. CMI instruments. Linear regressions were also carried out between paired osc and aus readings obtained with the A&D monitor.

RESULTS

Linear regression analyses indicate a highly statistically significant correlation between the osc and aus readings obtained with the A&D instrument ($P<0.001$). The linear equation relating one kind of measurement to the other, however, shows an intercept that almost invariably differs from zero with statistical significance and a slope that also invariably differs from unity. Except for one series for which rhythm detection was not achieved, all A&D osc and aus acrophases were in good agreement ($P>0.10$), the difference not exceeding 1 h 15 min and averaging only 24 $\pm$7 min. The double circadian amplitudes also tended to be in good agreement, showing a statistically significant difference only for the SBP of one subject (GC), the aus in this case being larger than the osc estimate. A consistently higher MESOR of the osc vs. aus SBP was found, which is statistically significant for 3 of the 4 subjects. A higher MESOR of the osc vs. aus DBP was also found for 2 of the subjects. No statistically significant difference was found in any of the HR characteristics. No statistically significant differences in HR characteristics were found between the two instruments either. Differences are, however, found for both the MESOR and the circadian double amplitude of osc BP between the two instruments. These differences are not consistent among the 4 subjects. Such differences may stem not only from differences in instrumentation, but also from other reasons, notably the fact that the two instruments were carried on different arms. While the differences were not consistent from one subject to another, they were not small and could exceed 5 mm Hg (MESOR) and 10 mm Hg (double amplitude). No statistically significant differences in acrophase were found.

DISCUSSION AND CONCLUSION

Whereas overall there is good agreement for the timing of the circadian rhythm of BP and HR with two different instruments and between the two different ways of measuring BP, differences in the estimates of the BP MESOR and circadian double amplitude should be kept in mind when evaluating the BP status of a patient. This is the more noteworthy that the monitoring profiles considered herein spanned 7 days while a 24-h profile is usually, albeit inappropriately (1, 2) considered to be a gold standard. Our results point to the need for automatic monitors that are unobtrusive enough to be used on a long-term basis for the purpose of continuous surveillance when need be. The pioneering con-

tributions of Dr. Jan Penaz including his development of a BP measurement technique that does not require an arm cuff are a major step forward toward a chronobiologic assessment of the risk of catastrophic, notably vascular disease prevention.

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ONE HUNDRED YEARS SINCE RIVA-ROCCI'S INVENTION OF THE CUFF-TECHNIQUE

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One hundred years ago, in 1896, Dr. Scipione Riva-Rocci published the description of the cuff-technique for the measurement of the arterial blood pressure in a local Italian clinical journal. He was a pediatrician and Professor at the University of Pavia. In clinical jargon, probably all over the world, the initials of his surname, RR, are used to indicate the result of the non-invasive measurement by the use of the cuff-technique, of the arterial blood pressure.

The development of the Riva-Rocci technique was a most significant event in an evolution which obviously must have started with the discovery of the observation of arterial pulsations – most probably in ancient time of mankind.

Therefore, in this short essay I will discuss the physical and biological meaning and also the effects of pressure as well as the historical development of the non-invasive recording techniques. The development of the cuff-technique more recently had another peak event, when Professor J.Penaz invented the special controlled-arterial unloading procedure which permits not only to measure the calibrated blood pressure values but, at the same time, to record the time course of the arterial pressure pulsations.

The measurement of blood pressure is still one of the medical procedures which are most often performed on human imdividuals. On one hand this fact is due to the diagnostic and prognostic importance of blood pressure. On the other hand, the usual non-invasive techniques are so simple and safe that nearly no limitation to the frequency of application is necessary. Several earlier (Kenner and Gauer 1962) and more recent studies and reviews on the theory and application of direct and indirect blood pressure measurement (Kenner, 1988), have summarized historical viewpoints and new developments.

The discussion of the problem of measuring the arterial pressure can be related to some observations concerning the palpation of the pulse with the finger:

Touching the artery softly permits to feel the pulsatile distension of the artery.

A stronger touch lets the finger percieve pressure like an indenting tonometer. Still stronger touch makes it possible the force which is necessary to completely suppress flow. Touching the artery with two or three fingers in a row – the Chinese way to palpate – permits to sense the propagation velocity of the pulse.

Finally, lifting or lowering the arm during palpation permits to sense the influence of gravity on the pulse.

Well before the first attempt for a guantitative measurement or recording of blood pressure, physicians have observed the pulse with palpating fingers. Using this technique, quite complex sensations can be felt by the physician. These sensations are described in terms of so called "pulse qualities". These qualities are related to heart rate, to rhythm, to the velocity of pressure rise during systole, to the pressure amplitude and to the amount of force necessary to suppress pulsations. Thus, an experienced physician may even be able to give a rough estimation of the blood pressure by using this technique. The technique of palpation is particularly well established, trained and performed in the traditional Chinese medicine. It may be mentioned that the complex sensation of this palpation has been described by musical notation (Kummel 1977).

Many attempts have been made to measure blood pressure noninvasively by application of a technique, which uses the indentation or applanation of an artery by a local device for the estimation of arterial pressure. Actually, this approach is older than the cuff method. One technique of this type was constructed by S. von Basch in Vienna, 1876 (cited by Lesky 1965). It is, of course, possible to apply the principle of the arterial unloading technique locally with a tonometric device. Further developments may be able to apply modern methods of ultrasound echo, X-ray or NMR-imaging techniques in order to localize the artery and to estimate the degree of unloading or expansion.

Pressure is a so-called intensive property. As a consequence, this means that pressure can only be measured by the effect of spatial or temporal gradients.

From a historical point of view the first principle which has been used for indirect blood pressure measurement was-as mentioned above – tonometry (Basch 1876). This was before the invention of the cuff technique by Riva Rocci (1896). One basic problem with all techniques of indirect blood pressure measurement without a cuff is the necessity of a proper calibration of the recording. This can be discussed with the example of the tonometric measurement.

A marked improvement of tonometric recording led to a technique which was first applied and described by Wagner in1942. His technique in a certain sense converged towards a cuff technique and, actually is a predecessorof the technique invented by Penaz in 1969.

My first personal experience with indirect blood pressure measurement in 1959 was the attemp to calculate the value of the peripheral resistance and thus the pressure in the pulmonary artery from X-ray recordings with the then available technique EKY (Electrokymography). The example of this attempt demonstrates the necessity to apply mathematical models for the interpretation of results. I would like to mention here so-called transmission line models which can be

applied to determine the frequency dependence of the inputimpedance and of the transmission function of arteries (Wetterer and Kenner 1968).

One further important group of techniques for the indirect measurement of blood pressure is based on the relation between arterial pressure and pulse wave velocity. From a statistical viewpoint the pulse wave velocity is a function of age and blood pressure, as was nicely shown by Schimmler in 1965. Unfortunately in each individual a special calibration has to be made and, furthermore, the result depends on the physiological state of the person. A third important influence on the result of the measurement depends on the localisation of the pulse sensors and on the question whether the time period of the pulse propagation has been measured between two locations on the artery or between a signal like the R-wave of the EKG and a peripheral pulse. Furthermore, phenomena like hysteresis have to be taken into account. This means that the result of the measurement depends on the current trend of the blood pressure. In this group of methods for the indirect measurement of blood pressure, again, the use of mathematical models and also of certain mathematical algorithms has to be mentioned.

An interesting procedure to calibrate a pressure measurement is based on the influence of gravity on the static pressure in all arteries. The first observations concerning the effect of gravity on the pulse contour have been published by V. Kries in 1891. Raising and lowering of the arm leads to a variation of the local pressure in the radial artery which amounts to about 50 to 70 mmHg, depending on the length of the arm. Moser and co-workers (1994) in the department of Physiology in Graz had the opportunity to compare the effects of variations of the arm position on the pulse wave velocity in weightlessness and under condition of 1 G on ground in several cosmonauts of the Russian spaceship MIR.

Interestingly enough, nearly all of the problems concerning the relation between pulse propagation and arterial blood pressure have already been studied many years ago, then have been forgotten, and new have a renaissance with improved technological support.

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BAROREFLEX HEART RATE SENSITIVITY IN HYPERTENSIVES: THE ROLE OF ANTIHYPERTENSIVE THERAPY

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INTRODUCTION

It is now clear that hypertension (essential or secondary – renal, hormonal) have a neurogenic component. More recent evidence suggests that neural mechanisms, particularly impairment of arterial baroreflexes, play an important part (1).

One of the hypotheses that is proposed to explain the effect of antihypertensive drugs is that these agents enhance the sensitivity of the arterial baroreflex (2). However, studies in humans using ACE-inhibitors (3), ß-adrenergic blocking agents (4–11) and calcium antagonists (12) have produced diverging results. A possible explanation for these discrepancies is that evaluating baroreflex sensitivity (BRS) by the neck chamber or the vasoactive drug method has important limitations (13).

Robbe et al. (14) proposed a method of determining BRS that is based on spectral analysis of systolic pressure (SBP) values and pulse intervals (PI) times, namely the modulus (or gain) in the mid frequency band (0.07 – 0.14 Hz) between these two signals. Modulus in the mid frequency band between SBP and PI gives equivalent results to those obtained using phenylephrine method. It thus appeared to be a useful index of BRS.

The aim of the present study was to examine the effect of Ca antagonist antihypertensive therapy and enalapril therapy on BRS in essential hypertesive patients, using the method of spectral analysis of spontaneous fluctuation of SBP and of PI. Blood pressure (BP) was continuously recorded by means of noninvasive volume-clamp method (5).

SUBJECTS AND METHODS

Fifty two subjects were included in the present study. Experimental group consisted of 20 patients with essential hypertension randomly allocated to verapamil or nitrendipine treatment. Ten patients were examined before (EH PV)

and after treatment (EH V) with verapamil (Isoptin SR 240, Knoll), 10 patients before (EH PN) and after treatment with nitrendipine (EH N), Baypress, Bayer. The third group, composed of 11 patients with essential hypertension was examined before (EH PEN) and after treatment with enalapril (EH EN). Enalapril Lachema.

First control group (C) consisted of 11 healthy subjects, second control group (EH E) consisted of 10 patients with essential hypertension treated by ACE-inhibitor enalapril (12.4 ±4.1 mg in single daily dosis). The diagnosis of essential hypertension was based on WHO criteria, patients were defined as hypertensive if they had sitting diastolic blood pressure (DBP) of >90 mmHg and SBP of >140 mmHg on three different occasions at least 1 weak apart.

The usual clinical, x-ray and laboratory tests ruled out any form of secondary hypertension. Characteristics of the subjects are seen in Table 1.

Twenty four hours blood pressure monitoring

For 24-h ambulatory blood pressure record, Accutracker II monitor (Suntech Medical Instruments, Ltd, 8604 Jersey Court, Raleight, USA), auscultatory, with mandatory electrographic gating was used. Approximatively three measurements in one hour during daytime and one in every hour at night (from 10 p.m. to 6 a.m.) were performed in each subject, in the first three groups before and after therapy. The data were analyzed according to single cosinor analysis for every individual and in groups using population mean cosinor analysis.

Determination of BRS

Subjects were examined in sitting possition. Noninvasive beat-to-beat SBP, DBP and PI measurements from the third finger (by photoplethysmographic transducer, Finapres 2300, Ohmeda Monitoring System, Engelwood, Connecticut, USA) were recorded (15,16). Signals were acquired and stored on a personal computer-based system. The patients were instructed to inhale-exhale in synchrony with a metronome indicator for 7 min. The last 5 min records were analysed. The frequency of respiration was 0.28 Hz. The tidal volume was not controlled, and subjects were allowed to breath comfortably to allow for adjustments to the acid-base balance.

As the interpolated time series of SBP, DBP and PI were required for spectral estimations, these values were linearly interpolated at 2 Hz to ensure equidistant sampling in each time series. The baseline linear trend was removed from all the signals. The power spectral densities and cross-spectral densities were calculated from the auto- and cross-correlation functions using the Hanning spectral window. The value of cross-spectral power density of PI and SBP fluctuation [ms*mmHg] was divided by the value of spectral power density of SBP fluctua-

tion [mmHg*mmHg] at 0.1 Hz. The obtained value called modulus [ms/mmHg], corresponded to that of BRS (14,17). The amount of linear coupling between SBP and PI fluctuations in the frequency domain can be expressed by means of the coherence function. The coherence at 0.1 Hz was calculated as a square root of a ratio between the square of cross-spectral density of PI and SBP fluctuations and a product of power spectral density of PI fluctuation and power spectral density of SBP fluctuation.

Coherence higher than 0.5 indicated the reliability of the modulus determination (17).

Study protocol

The protocol of the study was approved by the ethical committee of the Medical Faculty, Masaryk University, Brno and informed consens was obtained from each subject.

Twenty hypertensives were divided at random in two groups. The third group was examined separately later. The first group was examined after 2 weeks of placebo therapy (EH PV) and after 3 months with verapamil (Isoptin SR 240, 240 mg, one day dosis) therapy (EH V), the second after 2 weeks placebo therapy (EH PN) and after 3 months with nitrendipine (Baypress, 20 mg daily in two dosis) therapy (EH N). The third group was examined after 2 weeks of placebo therapy (EH PEN) and after 1 month with enalapril therapy (Enalapril Lachema, 16.5 ±5.3 mg/day).

The examination started at 8 a.m. with 24-hours ambulatory monitoring which was finished at 8 a.m. next morning. Immediately the measurement of BRS was performed. The patients in three groups were examined at the end of placebo therapy and after the three months of Ca-antagonist therapy or one month of enalapril therapy. The same protocol was applied for investigation of both control groups C and EH E, they were investigated only once.

Statistical analysis

Data for the different groups were compared using Wilcoxon tests for paired and unpaired observations. Values are expressed as means ±SD, and $p<0.05$ was considered statistically significant.

RESULTS

Mean 24-h blood pressure profile is shown in Fig. 1, Fig. 2, Fig. 3, Fig. 4, Fig. 5.

The results of population cosinor analyzis of 24-h ambulatory BP monitoring in five groups are shown in Table 2. After three months of verapamil therapy,

SBP and DBP in EH V was significantly lower in comparison to placebo therapy in EH PV ($p<0.01$, Wilcoxon). The nitrendipine therapy decreased SBP and DBP, the differences between EH PN and EH N were significant ($p<0.01$). The enalapril therapy significantly decreased SBP and DPB after one month ($p<0.01$).

The results of SBP, DBP and PI obtained by noninvasive blood pressure record during BRS determination are together with BRS values seen in Table 3. BRS in C group is significantly higher than in EH E, EH PN, EH N, EH PV, PH V, EH PEN, EH EN ($p<0.05$). Also the difference in BRS between EH PV and EH V and between EH PEN and EH EN is significant ($p<0.05$).

Despite BRS was increased after verapamil therapy and after enalapril therapy, the mean value of BRS remained significantly lower than in healthy subjects.

Controlled respiratory frequency enabled us to calculate averaged spectra (in relative units) of both groups before and after treatment by calcium antagonists (standard deviations are indicated). Power spectral densities of pulse interval (PI), systolic (SBP) and diastolic (DBP) blood pressure are shown in Fig. 6 before and after verapamil therapy, in Fig. 7 before and after nitrendipine therapy and in Fig. 8 before and after enalapril therapy. The analysis revealed that calcium antagonists did not change the shape of spectra. Only the value of modulus at 0.1 Hz, which corresponds to BRS is in a group EH PV lower than in EH V and in the EH PEN than in EH EN.

DISCUSSION

Two approaches have been mainly used to study baroreflex functions in humans. These are collars that permit application of pressure or suction at the neck to alter the transmural pressure at the carotid sinus and infusions of vasoactive drugs. When the neck collar is used, it is possible to make measurement of BP, heart rate, cardiac output, and organ blood flow during the initial seconds after a change in collar pressure. This time limitation is due to the fact that, as the carotid reflexes are engaged and alter systemic pressure, the aortic baroreceptors are exposed to the opposite change in transmural pressure and evoke opposing reflex adjustmens. The disadvantages of using vasoactive drugs to study baroreflexes include the possibility of direct effect of the drug on the response of the mechanoreceptor, and the inability to measure the reflex changes in arterial pressure, cardiac output, and organ blood flow in response to a change in transmural pressure at the receptors (18).

Application of spectral analysis techniques has several benefits as compared with the phenylephrin method. The injection of phenylephrine and the subsequent rise of BP may not be desirable for some patients, short-term BP regulation are not affected by the measuring method itself and spectral analysis of spontaneous fluctuations can be applied repetitively (14).

One implication of these advantages of the spectral analysis technique is that this method could be applied to noninvasive BP monitoring data (15,16).

The noninvasive method makes possible the repeated BRS estimations in healthy subjects and in patients during various experimental situation. Studying normotensive subjects during bicycling we found prominent decrease of BRS during exercise (19). We found BRS 16.2±4.8 ms/mmHg at rest, 5.8±3.3 ms/mmHg during cycling 0.5 W/kg of body weight and 2.1±1.1 ms/mmHg during cycling 1 W/kg. We confirmed the results of Pagani et al. using intraarterial blood pressure measurement and both, spectral and epinephrine methods in subjects with mild hypertension (17). It is self-evident that the decrease of BRS during exercise in both studies was accompanied with the decrease of PI.

In our laboratory we evaluated BRS in 33 healthy students 30 minutes before and 30 minutes after the oral examination (20). We used noninvasive record of BP during metronome-controlled breathing lasting 3 minutes. We found significant decrease of BRS during mental stress before examination (7.11±3.03 ms/mmHg versus 8.74±4.69 ms/mmHg after examination). These changes of BRS were accompanied by the changes of PI. Mean PI before examination was 609±97 ms, after examination 677±101 ms.

Twenty four hours continuous intraarterial blood pressure measurement and spectral method was used by Parati et al. to study the effect of ß-blockade on BRS (11). Both drugs acebutolol and labetalol increased BRS, however, even after ß-blockade, the 24-hours BRS remained far below normal and that was the case during either the day or the night. The increase of BRS was also here accompanied by the increase of mean PI.

Studying the effect of ACE-inhibitor enalapril we examined BRS in healthy control, nontreated patients with essential hypertension and hypertensives treated at least one year with enalapril (3). BP of treated patients was significantly lower than in nontreated patients (129/80 mmHg versus 146/88 mmHg), but BRS was not different (4.9±2.7 ms/mmHg versus 4.7±1.8 ms/mmHg). On the other hand BRS in healthy controls was 7.8±3.8 ms/mmHg, significantly higher than in all groups of hypertensives. The difference in heart rate between treated and nontreated hypertensives was not found. Also heart rate in controls was not different. Our group before and after enalapril therapy showed also an increase in BRS, but the value does not reached the value observed in normotensives. The increase of BRS was also here accompanied by the increase of mean PI. The above mentioned results indicate that the changes of BRS elicited by treatment or exercise or mental stress were accompanied by changes of heart rate, but taking PI into account BRS in either treated or nontreated hypertensive subjects is always lower than in normotensives.

It is possible that changes of BRS evoked by treatment can contribute to the hypotensive effect of a drug but because the normalization of BRS during treat-

ment was never achieved this contribution is probably small. Our methods allow us to assess only the baroreflex heart rate reflex and this reflex function may not always reflect the baroreflex control of peripheral circulation and blood pressure. This is a limitation of our study.

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Table 1: *Clinical characteristics of our groups.*

	C	EH E	EH PV, EH V	EH PN, EH N	EH PEN, EH EN
n	11	10	10	10	11
Age years	48 ±7	46 ±7	46 ±6	44 ±7	49 ±9
Weight kg	84 ±6	85 ±7	87 ±3	88 ±6	90 ±9
Height cm	179 ±6	177 ±7	178 ±6	176 ±4	178 ±6

Table 2: *Population cosinor of 24-h blood pressure monitoring.*

	SBP			
	mesor mmHg	amplitude mmHg	acrophase degree	p - value
C	122.5	11.2	–221	0.001
EH E	129.6	7.8	–189	0.113
EH PI	136.9	11.3	–191	0.005
EH I	132.9	13.4	–187	0.006
EH PB	142.6	10.8	–193	0.013
EH B	137.8	11.1	–208	0.00023
EH PEN	146.6	9.9	–204	0.009
EH EN	135.4	9.9	–195	0.011
	DBP			
	mesor mmHg	amplituda mmHg	acrophase degree	p - value
C	76.9	9.1	–212	0.001
EH E	81.6	6.4	–193	0.005
EH PI	83.6	10.1	–195	0.002
EH I	80.5	9.4	–197	0.002
EH PB	85.3	9.3	–191	0.001
EH B	77.2	7.8	–204	0.001
EH PEN	81.7	8.6	–190	0.001
EH EN	75.3	7.3	–199	0.013
	HR			
	mesor ms	amplitude ms	acrophase degree	p - value
C	77.4	13.7	–201	0.001
EH E	84.6	10.9	–192	0.001
EH PI	86.2	10.5	–199	0.008
EH I	81.4	13.4	–201	0.001
EH PB	76.5	12.1	–200	0.001
EH B	76.8	10.2	–204	0.001
EH PEN	77.1	9.3	–201	0.010
EH EN	79.4	11.0	–206	0.001

p = p-value from zero-amplitude test.
Probability for hypothesis: Amplitude = 0

Table 3: *Cardiac interval (I), SBP, DBP and baroreflex heart rate sensitivity (BRS) in controls (C), in patients with EH after 1 year enalapril therapy (EH E), in patients with EH before (EH PV) and after verapamil therapy (EH V), in patients with EH before (EH PN) and after nitrendipine (EH N) therapy, in patients with EH before (EH PEN) and after enalapril therapy (EH EN).*

	I ms	SBP (mmHg)	DBP (mmHg)	BRS (ms/mmHg)
C	924 ±112	119 ±13	69 ±12	7.8 ±3.8
EH E	732 ±114	128 ±14	78 ±6	4.9 ±1.1
EH PV	653 ±74	143 ±7	92 ±4	2.9 ±4.7
EH V	732 ±71	132 ±4	80 ±4	4.2 ±3.6
EH PN	710 ±94	146 ±14	91 ±5	4.8 ±2.7
EH N	722 ±92	126 ±10	76 ±7	4.9 ±2.3
EH PEN	734 ±118	134 ±12	83 ±12	5.1 ±2.9
EH EN	717 ±106	117 ±12	69 ±9	5.5 ±2.9

Fig. 1: *Blood pressure profile in normotensives (C, mean±SD).*

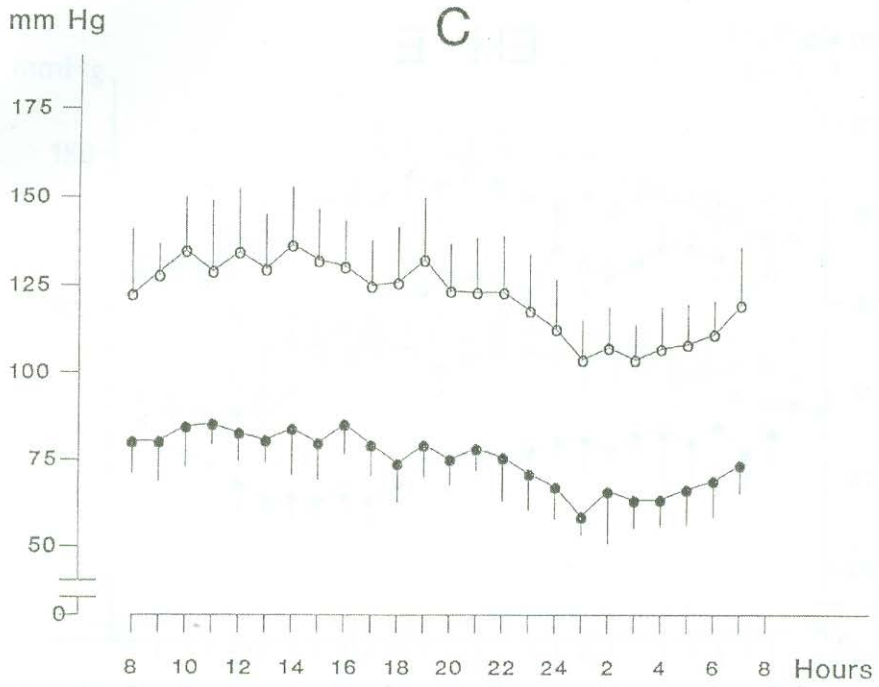


Fig. 2: *Blood pressure profile in patients with essential hypertension after one year enalapril therapy (EH E, mean±SD).*

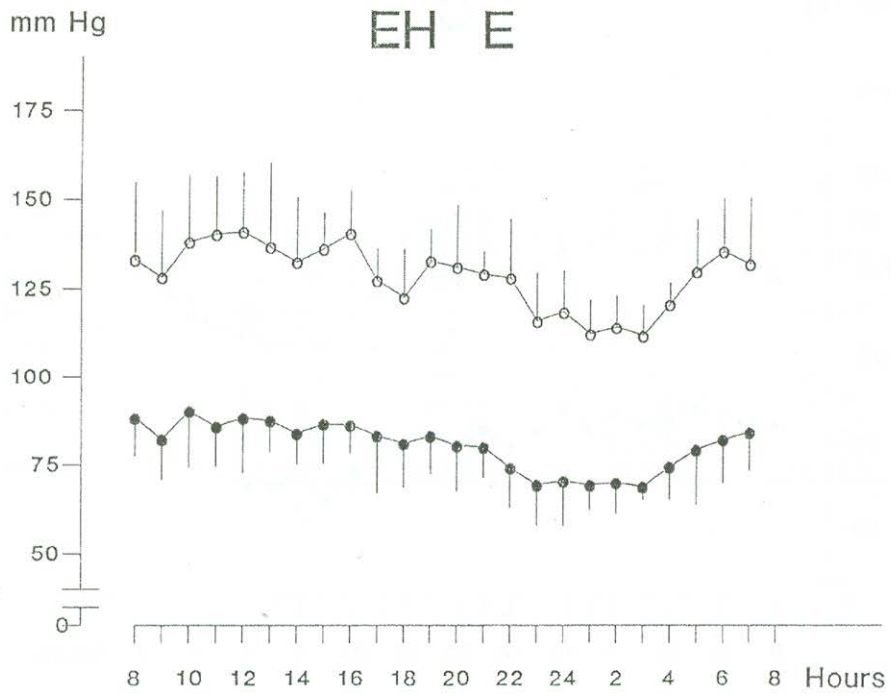


Fig. 3: *Blood pressure profile in patients with essential hypertension before (EH PV) and after verapamil therapy (EH V, mean±SD).*

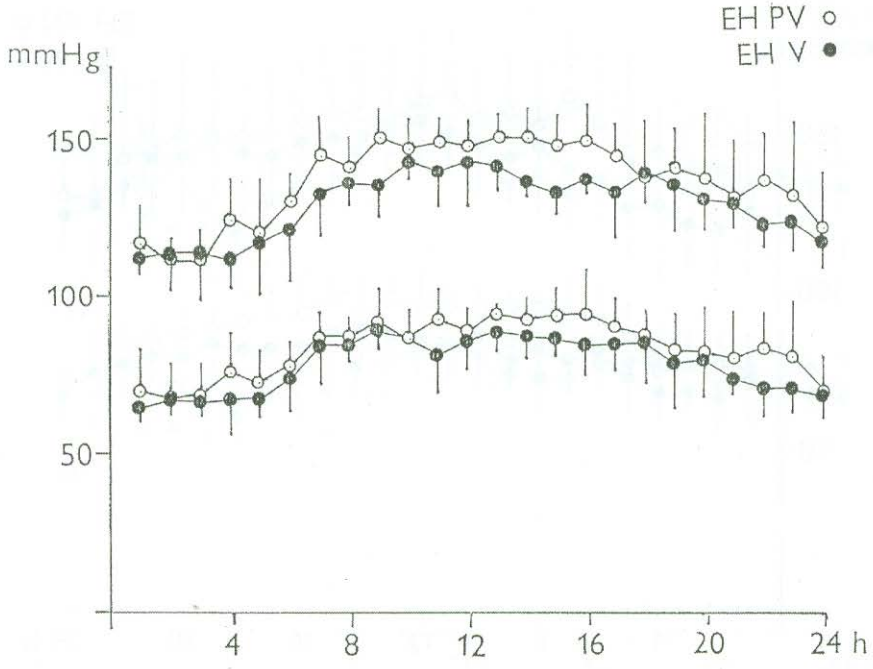


Fig. 4: *Blood pressure profile in patients with essential hypertension before (EH PN) and after nitrendipine therapy (EH N, mean±SD).*

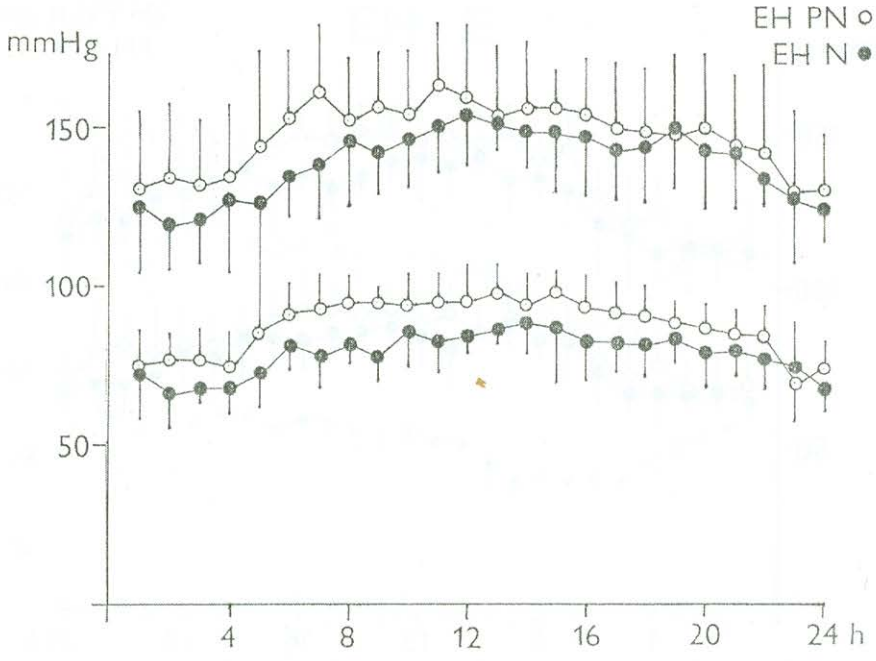


Fig. 5: *Blood pressure profile in patients with essential hypertension before (EH PEN) and after enalapril therapy (EH EN, mean±SD).*

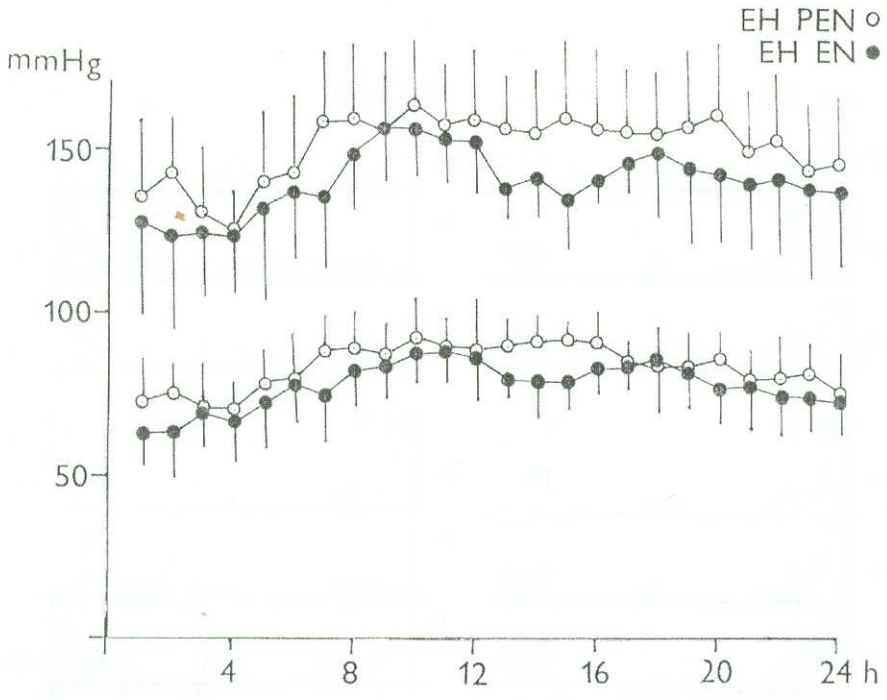


Fig. 6: *The power spectral densities of fluctuations of pulse interval (PI), systolic blood pressure (SBP), diastolic blood pressure (DBP) after placebo administration (EH PV) in the upper part left of the Fig. and after verapamil therapy (EH V) in the bottom of the Fig. left, in the right part the power spectral density of PI, modulus (M), the value of modulus at 0.1 Hz determines BRS, coherence (C) in EH PV and EH V. Mean curves ±SD are indicated.*

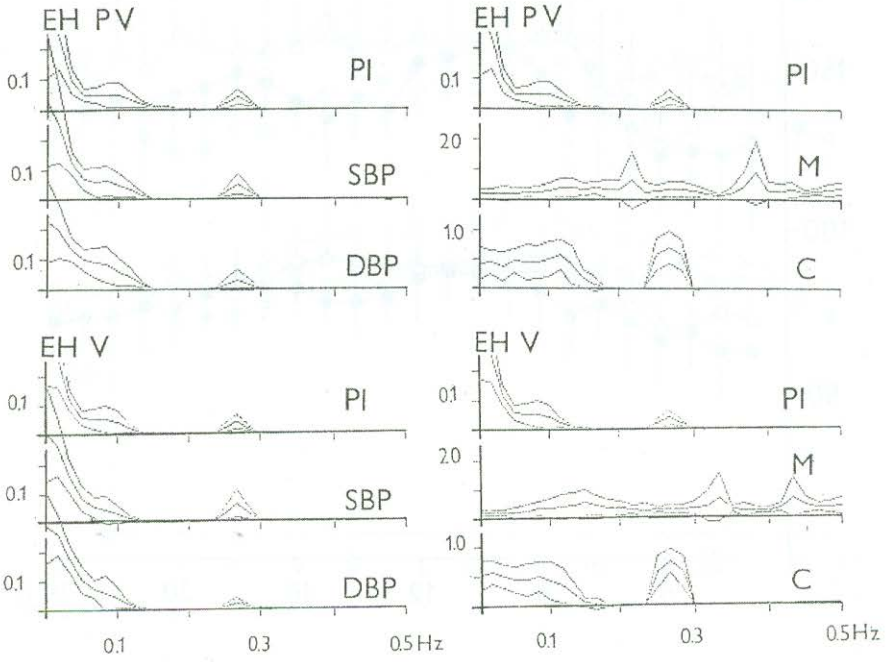


Fig. 7: *The power spectral densities of fluctuations of pulse interval (PI), systolic blood pressure (SBP), diastolic blood pressure (DBP) after placebo administration (EH PN) in the upper part left of the Fig. and after nitrendipine therapy (EH N) in the bottom of the Fig. left, in the right part the power spectral density of PI, modulus (M), the value of modulus at 0.1 Hz determines BRS, coherence (C) in EH PN and EH N. Mean curves ±SD are indicated.*

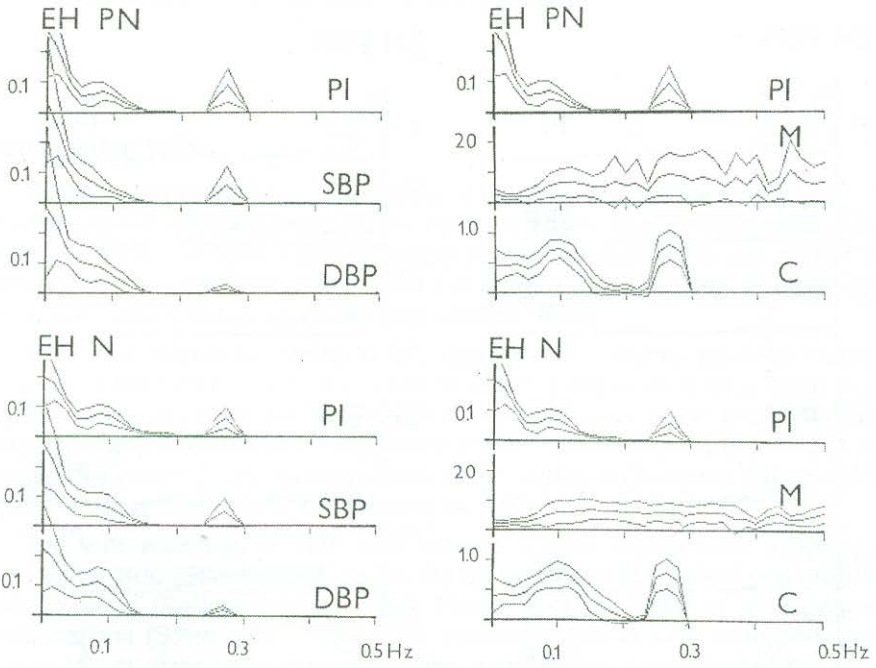
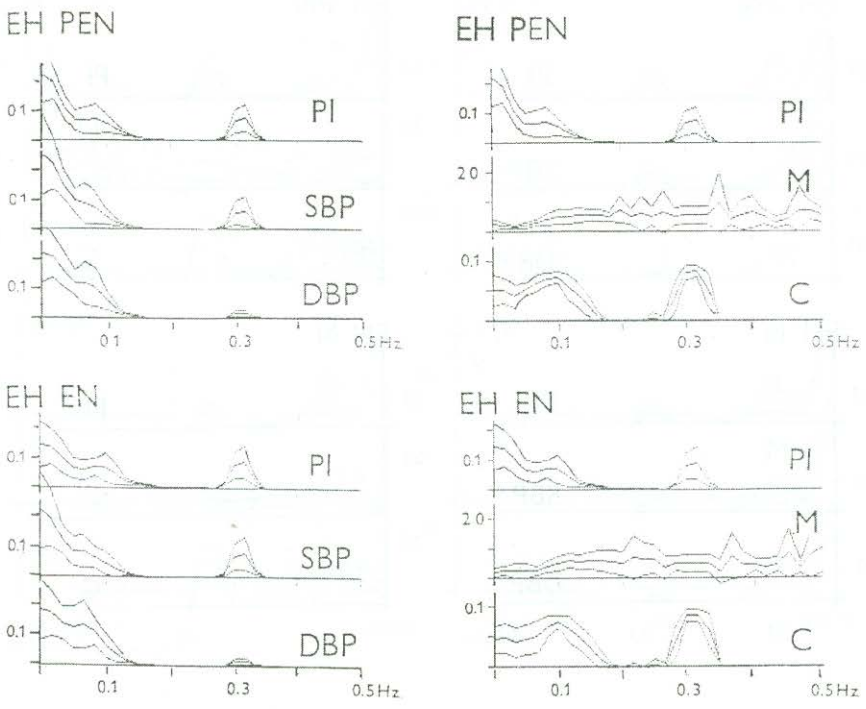


Fig. 8: *The power spectral densities of fluctuations of pulse interval (PI), systolic blood pressure (SBP), diastolic blood pressure (DBP) after placebo administration (EH PEN) in the upper part left of the Fig. and after enalapril therapy (EH EN) in the bottom of the Fig. left, in the right part the power spectral density of PI, modulus (M), the value of modulus at 0.1 Hz determines BRS, coherence (C) in EH PEN and EH EN. Mean curves ±SD are indicated.*



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NONINVASIVE MEASUREMENT OF BLOOD VELOCITY IN MIDDLE CEREBRAL ARTERY AT REST AND DURING ABRUPT DECREASE OF BLOOD PRESSURE IN MAN

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INTRODUCTION

The brain more than any other organ is extremely dependant on a multitude of delicately balanced homeostatic mechanisms to ensure a constant extracellular environment for its cells. Cerebral blood flow autoregulation is just one of the homeostatic mechanisms at work, but it is better developed than in most other organs for example kidney (Barry and Lassen, 1984).

In face of normal variations in BP, such as occur during postural change, defecation and coitus, cerebral blood flow (CBF) is maintained fairly close to the resting level dictated by the metabolic demands of the brain through autoregulatory adjustment of resistance vessel calibre. During a pressure decrease, the cerebral resistance vessels dilate, during an increase they constrict (Mac Kenzie and el., 1979, Kontos and al., 1978).

The autoregulation of CBF was studied in man during slow injection of vasoactive drug (Strandgaard, 1976), during breathing of different gas mixtures concentration (Bailliart and al., 1993; Maeda and al., 1994) or after postural modifications (Savin et al., 1995). The measurements of CBF were perforemd only at steady state levels in these studies. Instantaneous modifications of blood flow have been studied only on animals.

The aim of present paper was to study the time course of the autoregulatory reaction of cerebral circulation. For this purpose, blood velocities in middle cerebral artery (MCA) and in superficial temporal artery (TSA) after abrupt change in blood pressure (BP) were measured and compared to common carotid artery (CCA) blood velocities. The rapid decrease of blood pressure was achieved by a manoeuvre used several years ago for the non invasive measurement of baroreflex sensitivity (Fišer and Honzíková, 1991; Fišer et al., 1994). Results may allowed to verify if territories of CCA are regulated in the same way when they vascularise extra or intracranial territories.

MATERIAL AND METHODS

The experimental protocol was approved by the local Ethics Committee and complied with the Declaration of Helsinki. The protocol was explained to ten healthy men who gave their written informed consent. Their mean age was 38.9±7.0 yr, height 180.3±6.6 cm, and body mass 73.2±7.2 kg.

Subjects were studied in supine position. Two inflatable cuffs (width 12 cm) were placed on both thighs of subject. After 20 minutes rest, the cuff pressure was increased abruptly to 180 mmHg (in 0.5 s) and kept for 5 min. The suprasystolic pressure in occluding cuffs caused a complete arrest of circulation in both lower extremities. The rapid decrease in occluding pressure after 5 minutes of occlusion elicited decrease of peripheral resistance in both extremities and thus decrease in systolic and diastolic pressure of about 10 mmHg.

BP, MCA and TSA blood velocities and CCA diameter and velocity were measured at rest, during occlusion and during cuffs release. Simultaneous and continuous records of velocities, flow and pressure were made 2 s before and 15 s after the release of cuffs. All the values were calculated beat to beat. Heart rate was evaluated from pressure recordings.

BP was measured non-invasively, MCA velocities and TSA velocities were determined by using treanscranial Doppler velocimeter, CCA blood flow by using a range gated Doppler velocimeter.

BP in digital arteries was recorded by means of non-invasive continuous volume clamp method of Peňáz, 1973; Molhoek et al., 1984). We used a Finapress BP Monitor 2300 (Ohmeda – USA). Mean pressure was calculated as a sum of diastolic and one third of pulse pressure.

CCA blood flow was measured with a range gated Doppler flowmeter (8 MHz; Echovar Doppler, Alvar Electronic, Montreuil–Paris–France) which allows determination of vessel diameter and of instantaneous and mean blood velocities (Chauveau et al., 1985; Anderson and Mark, 1989; Laurent et al., 1990; Bailliart et al., 1990). Then mean blood flow was calculated for CCA.

Blood flow velocities in MCA were determined with a low frequency transducer (2 MHz, D.M.S. Angiodop, Montpellier – France) working at a high-power directed via the squamous portion of the "window" in the temporal bone (Aaslid et al., 1982; Bishop et al., 1986).

Blood velocities in the TSA were recorded using an 8 MHz continuous Doppler apparatus (GammaDop, Technimed, St Leu la Foret – France) (Patrick et al., 1980).

Doppler measurements were performed on the right common carotid artery (CCA), right middle cerebral (MCA) and right superficial temporal (TSA) arteries and recorded continuously.

Mean blood flow in CCA was calculated as a mean of instantaneous velocities during each cardiac cycle.

Statistical analysis

The data of systolic, diastolic and mean pressure, of systolic, diastolic and mean velocities and flow were evaluated all 0.5 s intervals by means of linear interpolation starting at the moment of the pressure release in the occluding cuffs.

These data were used for calculation of average curves. Results are expressed as mean ± standard deviations. The statistical sifnificances of differencies were determined by Wilcoxon test or Wilcoxon test for paired data. Only a P value less than 0.05 for both tests was considered as significant.

RESULTS

Original records of changes of mean blood velocity in MCA and blood pressure are seen in Figure 1.

Blood pressure

Some objects reacts in a different way to the inflation of occluding cuffs. Immediately after the abrupt inflation to 180 mmHg, BP increased up to 15 mmHg but decreased rapidly and after one minute returned to original level. The occlusion elicited vasodilatation of leg vessels. A quick adjustment of cuff pressure to 60 mmHg (0.5s) lasting for 1 minute caused a decrease in BP followed by an increase in heart rate.

No significant differences in blood pressure were observed between rest and occluding cuffs. After cuff release, systolic and diastolic blood pressure decreased by 8.7±3.5% ($P<0.05$) at the 1st s, 12.2±3.2% ($P<0.05$) at the 5th s and remained decreased at the 10th s (8.0±4.0%, $P<0.05$) after the release of occlusion. After half a minute, blood pressure returned to the resting value.

MCA blood velocities

Blood velocities at rest and in the 4th min of occlusion were not different. After release of occluding pressure, velocity in MCA decreased by 16.7±4.6% ($P<0.05$) at the 1st s and increased rapidly after, so that the original level was reached between 5 and 10 s (in 5th s, decrease was 1.6±9.7%, NS, and in the 10th s increase was 2.9±12.0%, NS) after the decrease in cuff pressure.

TSA blood velocities

Temporal blood velocities were not different between rest and in the 4th min. of occlusion. The blood velocity in the superficial temporal artery after release of occluding cuffs was modified. One second after the change of occluding pressure, the velocity decreased by 30.4±9.0% ($P<0.05$). After 5 s the decrease in velocity was observed but was 22.6±10.9% ($P<0.05$) under the original level and remained after 10 s (22.4±11.0%, $P<0.05$). After half a minute the original level was reached.

CCA blood velocities

All along the experiment, no change occured in common carotid artery diameter. We have not observed differences between rest and occlusion (4th min) blood velocities. Blood velocity in CCA was modified after occlusion release. After 1 s, the velocity decreased by 22.2±12.4% ($P<0.05$); in the 5th s by 5.9±15.5% (NS) and in the 10th s by 2.2±11.6% (NS). Then 5 seconds after occlusion release, common carotid blood velocities were not different of rest value.

Mean data and statistical differences are presented in Table 1.

The Fig. 2 shows the mean values of MCA and TSA blood velocities ±SD and CCA mean blood flow and BP during occlusion and after occlusion release (0 to 15 s).

Differences of relative values of velocities in MCA and in TSA at 1.5 and 10 s were observed ($P<0.05$). The relative values of flow in CCA were between values of NCA and TSA. The difference between CCA and MCA was lower than the difference between CCA and TSA. The statistically significant differences between CCA and TSA were not observed.

DISCUSSION

The disadvantage of the non invasive blood pressure measurement according to Peňáz is the possibility of a difference between the peripheral and the central blood pressure (Peňáz, 1973). This is not important for our measurements because we evaluated a time course of blood pressure reaction after the cuff pressure release. In our experiment, we decrease the cuff pressure to 60 mmHg and not to 0 to block the increase in venous return and thus to prevent the rapid return of blood pressure to the initial level via the increase of cardiac output.

For non invasive studies of vascular reactivity, Doppler velocity measurements is of importance especially for evaluating instantaneous changes in the

circulation of the brain (Aaslid et al., 1982). Currently, this method has been used to measure MCA velocities but in other circumstances (Muller et al., 1991; Savin et al., 1994). Transcranial Doppler recordings allows to detect cerebral flow modifications (Madsen et al., 1993).

The finding of prominent autoregulary reaction in middle cerebral artery is no surprising because to the autoregulatory reaction observed in animal experiments (Peňáz and Buriánek, 1963). The autoregulatory reaction of temporal superficial artery is significantly lower than cerebral artery but is also important. From the point of view of the theory of regulation, the autoregulatory reaction is a positive feed back because vasodilatation caused by the decrease in blood pressure elicits further decrease in blood pressure. This reaction is compensated by the baroreflex.

Although autoregulation is effective over a wide range of systemic pressure, there is a lower blood pressure limit of autoregulation, below which a lower blood flow fails as pressure falls (Strandgaard, 1976; Strandgaard, 1978; Kontos et al., 1978). The lower limit of autoregulation is shifted to the lower pressure in chronic hypertension. Whereas the structural changes in the resistance vessels improve the tolerance to high pressures, they impair the tolerance to hypotension, presumably because autoregulatory vasodilatation is compromised by the wall thickening and luminal narrowing. The shift of the lower limit of autoregulation to higher pressure is proportional to the severity of hypertension (Strandgaard et al., 1973; Fišer et al., 1994). The clinical consequence of the shift in the lower limit of autoregulation is that if the blood pressure of a hypertensive patient is rapidly lowered to normotensive levels, cerebral blood flow will fall, possibly causing ischaemia brain damage. Thus, rapid and severe pharmacological reduction of blood pressure, as in emergency treatment of malignant hypertension can be dangerous. The method used in this paper for recording of autoregulation reaction can serve as a clinical test in such situation. The test enables to modify the intensity of treatment according to the needs of individual patients.

Transcranial Doppler velocimetry does not permit the calculation of blood flow since arterial diameter is not measured. For this reason, we compared the autoregulation reaction of middle cerebral artery with that of common carotid artery. The changes of flow in common carotid artery reflected the changes of flow velocity in the cerebral artery. This finding is not surprise because cerebral arteries blood flow represents approximatively two thirds of common carotid blood flow. We suppose that the measurement of flow in common carotid artery during release of occlusion of lower extremities can be also used as a clinical test of the cerebral blood flow autoregulation.

The more prominent autoregulatory reaction of middle cerebral artery is also demonstrated by greater area surrounded by the flow pressure curve in comparison to superficial temporal artery and common carotid seen in Fig. 3. The

flow pressure curve of common carotid artery is more similar to the curve of middle cerebral artery than to the curve of superficial temporal artery. The value of resistance index calculated at 1st s after the change is lower than the value immediately before release of occlusion pressure. During so short time, the resistance could not change. On the other hand, the differences betwen values at 1st s and 5th s after release of occlusion was not observed despite the fact that prominent vasodilatation occured during that time. It is concluded that resistance index is not good indicator of rapid changes of vascular resistance.

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Fig. 1: *Original record of middle cerebral artery velocity systolic and diastolic, cm.s^{-1}) and blood pressure (systolic and diastolic, mmHg) during occlusion release in a representative case).*

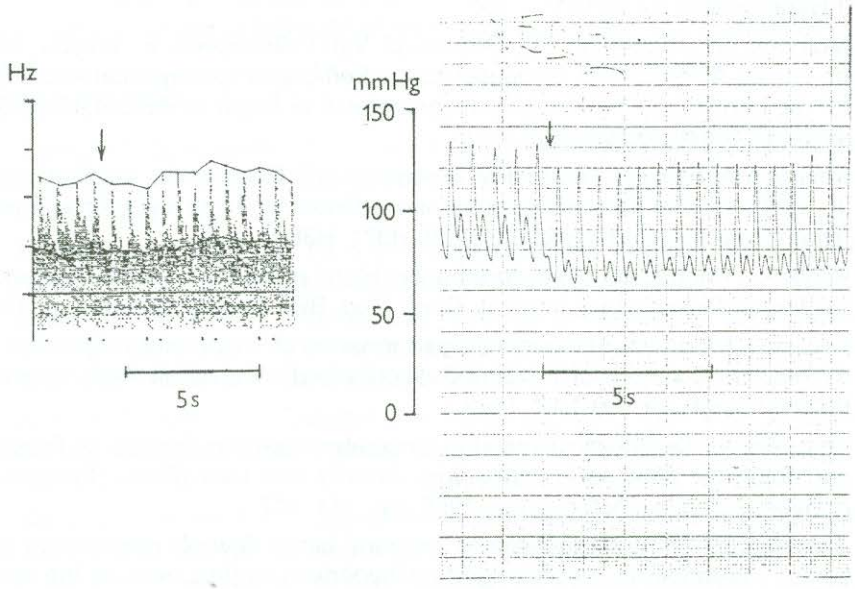
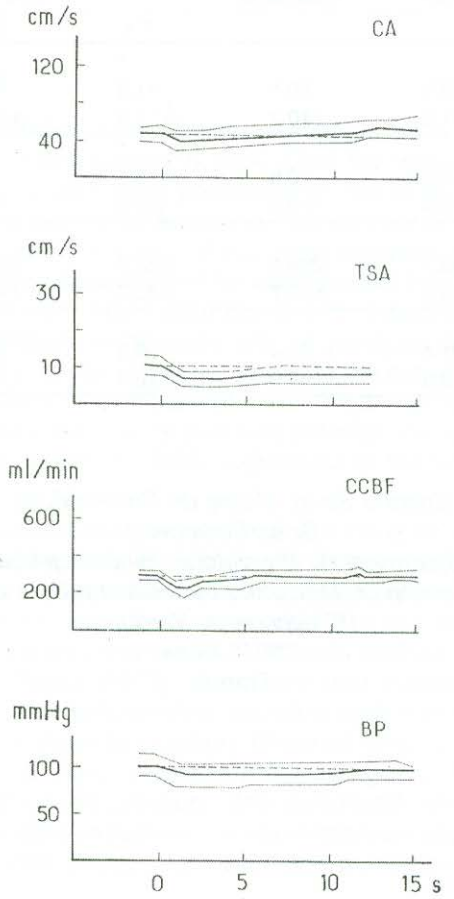


Fig. 2: *Average curves (mean ±SD) of middle cerebral artery (CA), temporal superficial artery (TSA) velocities (cm.s^{-1}), common carotid blood flow (CCBF, ml.min^{-1}), and blood pressure (BP, mmHg), during and after occlusion release which starts at 0.*



Tab. 1: *Middle cerebral artery (MCA), superficial artery (TSA) velocities (cm . s^{-1}) and common carotid artery blood flow (CCA) ml.min^{-1} and blood pressure (mmHg) at rest, during occlusure and after cuff release (1,5 and 10 s) for 10 subjects (values are means ±SD, * = $p < 0.05$; comparison with rest value).*

	Rest	Occluding	Cuff release		
			1 s	5 s	10 s
			*		
MCA	50.3	50.1	41.8	49.3	51.6
cm . s^{-1}	±11.6	±10.2	±11.6	±10.9	±10.5
			*	*	*
TSA	10.9	10.6	7.4	8.2	8.2
cm . s^{-1}	±2.5	±2.6	±2.5	±2.2	±2.4
			*	*	*
CCA	305.1	299.1	232.7	281.5	292.5
ml . min^{-1}	±23.4	±23.7	±33.2	±43.3	±29.6
			*	*	*
Blood pressure	101.4	98.4	89.8	86.4	90.5
mm . Hg	±9.9	±9.9	±10.3	±10.0	±10.0

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THE NONINVASIVE ESTIMATION OF THE GAIN OF THE ARTERIAL BARORECEPTOR REFLEXES IN MAN

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INTRODUCTION

The baroreceptor reflexes have been investigated since the discovary of the aortic nerves by Cyon and Ludvig in 1866. Over the intervening years, nearly every imaginable study have been performed (Scher et al., 1991). Despite this the gain of the arterial baroreflex system in man has not been determined. The gain of a control system is the ratio of a change in output to a change in input when both are the same physical variables expressed in the same units (Sagawa, 1983). The open-loop gain of the baroreflex system is most easily determined as the slope of the relationship between arterial pressure and pressure at the baroreceptor when the two are isolated. Because the surgical experimental isolation is impossible the contemporary methods enable us to evaluate only one branch of the baroreflex, the arterial pressure induced changes of heart rate, i.e. baroreflex heart rate sensitivity (BRS) expressed in ms/mmHg (Smyth et al., 1969).

The aim of the present study was to evaluate the gain of both components of the baroreceptor reflex, the sympathetic and parasympathetic nerves controlled cardiac output and sympathetic nerves controlled systemic peripheral resistance (PR). The product of cardiac output and PR is the arterial pressure. The calculations are based on noninvasive continous method of arterial pressure record according to Penaz (1973). Blood pressure changes were elicited by means of the decrease of peripheral resistance in both lower extremities caused by the ischemia of five minutes duration. Changes of stroke volume were estimated from changes of pulse pressure (PP), changes of PR from the rate of diastolic decrease of arterial pressure. The calculated gain was compared in three groups, in hypertensive patients, in normotensive subjects of the approximately same age, and in young adults with high baroreflex sensitivity.

METHODS

The investigations were performed in three groups of subjects: Ten healthy subjects, 21 – 58 years old, mean ±S.D.: 34.6 ±14.4 (N).

Ten patients with essential hypertension, 38 – 58 years old, mean ±S.D.: 46.5±6.4 (H).

Ten healthy subjects 21 – 24 years old. Baroreflex sensitivity in this group was investigated four times during one day and the responses with the highest value of BRS in each subject were included into the further analysis. This group was analysed as a group of subjects with high BRS (HBRS)

The subjects were in supine position 30 minutes, blood pressure was continuously measured by volume clamp method (Finapres, Ohmeda, USA), the occluding cuffs were placed on both thighs and the pressure in the cuffs was abruptly raised to 180 mmHg to cease the circulation in both lower extremities for 5 minutes. After the release of occlusion increased blood flow into ischaemia dilatated vessels of lower extremities caused a decrease in systolic and diastolic blood pressure of approximately 10–20 mmHg. This blood pressure decrease elicited an increase of heart rate by means the baroreflex mechanism. The release of occluding pressure in the cuffs was to 60 mmHg only. The cuff pressure of 60 mmHg blocked the rapid venous return from low extremities to the heart and so preserved the stimulation of low pressure receptors. The cuff pressure was decreased to zero after one minute.

Calculation of BRS.

Mean systolic blood pressure was measured during 5 s before the release of occlusion and during the interval 3 – 8 sec after the occlusion release. During this interval blood pressure is relatively constant and 10 – 20 mmHg lower than before occlusion. The difference of both presure values was calculated. Similarly mean cardiac interval was calculated during 5 sec interval before and 5 – 10 sec after the release of occlusion. Also cardiac interval remained relatively constant during this period. The difference between this two values of mean interbeat cardiac was calculated. BRS corresponded to the ratio calculated dividing the difference in cardiac intervals by difference in systolic blood pressure. BRS was expressed in ms/mmHg.

Estimation of relative changes of stroke volume (SV).

Principaly the applied method corresponds to the normalization of PP according to the arterial pressure. The calculation is based on an assumption of the relationship SV=C*PP where C is compliance. Because C is pressure-dependent (Liu et al., 1986) PP depends on mean arterial pressure (MAP) at constant SV (PP=a+b*MAP). Assuming that SV is pressure-independent during the whole maneuvre (fifty beats, starting point five beats before the release of occlusion) we can replace MAP by diastolic blood pressure (DBP) and calculate a and

b by regression analysis. Then we can calculate PP(normalized)=a+b*DBP. Relative SV of every beat then corresponds to a ratio PP(measured)/PP(normalized). Thus we could calculate relative changes of SV beat-to-beat.

Estimation of relative changes of PR.

The rate of the decay of arterial pressure during diastole depends on the systolic pressure (SBP) where the decay starts. Assuming constant compliance the relationship is exponential. Because the compliance is pressure dependent, the pressure – rate of pressure decay relationship is more complicated but for relative small changes in blood pressure of about 15% we can use a linear approximation. The value of diastolic decay (DD), which is the difference between SBP and DBP of the following beat, depends also on the duration of the cardiac interval (I). For this reason we used the multiple regression analysis for normalisation. Thus DD(normalized)=c+d*SBP+e*I. After calculation of c,d and e we calculated DD(normalized) beat-to-beat and relative changes of TPR we expressed as a ratio DD(normalized)/DD(measured). It is an analogous approach with the calculation of the relative stroke volume.

RESULTS

Evaluation of 10 healthy subjects.

The results of healthy people (N) and hypertensives (H) are seen in Fig.1. The decay of blood pressure after cuff pressure release is followed by the decrease of cardiac interval. BRS corespons to the ratio difI/difSBP where difI is a difference between I before deflation of cuffs and minimum value of I during interval 5 s which starts 5 s after deflation. Similarly difSBP was calculated (the 5 s period started 3 s after the occlusion release). We found mean (±S.D.) value of BRS of N: 7.3±4.9 ms/mmHg.

Relation between BRS and age was also studied. The correlation was negative and significant ($r=-0.740$, $p<0.05$).

Time course of relative changes of stroke volume is similar to changes in I.

The increase of relative values of stroke volume was 0.43±0.48 % of SV/mmHg (measured 10 s after the decrease of pressure in occluding cuffs), the increase of relative values of cardiac output was 0.56±0.55 % of CO/mmHg (measured et the same time as SV) was significant.

The abrupt decrease of PR during deflation of occludings cuffs corresponds to the decrease in resistence of vessels of both lower extremities. Despite the vasodilatation is more prolonged (In an other serie of experiments we measured flow in femoral artery by Doppler pulsed velocimetr and found maximal flow 5

beats after deflation and then slow decrease of flow (Fiser et al., 1993)) relatively rapid baroreflex mediated increase of resistence was observed. The value of the change in PR at 10 s was determined and the difference between this value and the value of change in PR at time of occlusion was divided by the change in SBP. This ratio corresponds to the baroreflex systemic resistence sensitivity. We found 0.34±0.38% of PR/mmHg. Response of hypertensives.

The decrease in SBP and DBP caused by deflation was similar as in normotensives but BRS was non-significantly lower in hypertensives (4.5±5.1 ms/mmHg). This corresponds to the smaller decrease of I in H than in N. Also the relative increase of SV calculated at 10 s after occlusion release was non-significantly lower in hypertensives (0.24±0.36 %/mmHg) than in N. On the other hand lower increase in relative CO at the same interval (H: 11.2±3.4% of CO/ mmHg) is in comparison to N significant ($p<0.05$). Relative change of PR at 10 s after occclusion (0.96±0.36% of TPR/mmHg) is higher than in normotensives but non-significant.

It is concluded that in hypertensives baroreflex elicited changes of PR are similar as in normotensives but the response of cardiac efferent branche of the baroreflex is decreased.

Response in young adults.

The results of young adults (HBRS) and subjects with low BRS (LBRS) are seen in Fig. 2. The baroreflex was studied in every subject 4 times during day and the response with highest BRS in every subject was selected for further analysis. Following values of baroreflex response were obtained, HBRS: 11.3±3.1 ms/mmHg, 0.42±0.47 % of SV/mmHg, 1.73±0.57% of CO/mmHg, 1.92±0.67% of PR/mmHg

The differencis in BRS, CO and PR responses are in HBRS significantly higher than in N ($p<0.05$).

Response in subjects with low BRS.

Five subjects with smallest BRS were selected from the normotensive group N to study the response of relative SV, relative CO and relative PR in subjects with lower BRS separately. Mean age was 44.6±12.5 years (range 21 – 58).

Following values were obtained: 3.9±2.7 ms/mmHg, 0.39±0.28% of SV/mmHg, 0.48±0.76% of CO/mmHg and 0.19±0.15% of PR/mmHg.

The differences between LBRS and HBRS groups were significant in all followed parameters except SV ($p<0.05$). It is concluded, that in subjects with lower BRS also the response of cardiac output and of resistance vessels is decreased.

The comparison between measured changes of mean blood pressure and calculated changes of PR elicited by the release of occlusion.

The mean blood pressure (MBP) was calculated as MBP=(SBP–DBP)/3+DBP and decrease of MBP was expressed in percents of MBP befor the occlusion release. Because this value corresponds to change in PR the comparison of changes in MBP and in PR is a test of a reliability of our mathematical model. We calculated both values from mean curves of all groups and found: N: 17.3% in MBP, 17.1% in PR; H: 8.7% in MBP, 9.1% in PR; HBRS: 14.0% in MBP, 15.4% in PR; LBRS: 11.3% in MBP, 8.0% in PR. Only in LBRS group which consits of 5 subjects the discrepancy is seen.

The estimation of the gain of different branches of the baroreflex and of the half-time of blood pressure return after release of occluding pressure.

We calculated the gain of cardiac branch of baroreflex as a ratio between the decrease in MBP in % and the increase in CO in %. Following values were found: N: 1.01, H: 0.43, HBRS: 1.38, LBRS: 0.43.

Similarly the gain of PR branch was calculated as a ratio between the decrease of MBP in % and the increase in PR in %. N: 0.87, H: 0.85, HBRS: 1.46 and LBRS: 0.29.

These results are in accord with data of baroreflex sensitivity of individual baroreflex branches. Interesting is relatively high gain in PR branch and low gain in cardiac branch in hypertensive subjects.

The total gain of baroreflex we calculated by multiplication of the increased CO and PR. We found: N: 1.91, H: 1.33, HBRS: 2.84, LBRS: 0.99.

Our data indicates that relatively large variability can be observed as the difference between healthy people with high and low BRS demonstrates. The ratio of total gains of this two groups is 1:2.87.

Regulation of blood presure in hypertensives is different than in healthy subjects. The gain of cardiac branch is relatively lower, the gain of vascular branche relatively higher in comparison to healthy people. The results are seen in Fig. 3.

The half-time of the return of blood pressure to the original level.

The method we used enabled us to estimate the relative power of baroreflex independently on mathematical model. We measured the time between occlusion release and the moment when blood presure returning to the original level

reached the half of the value between the minimum value of pressure and original level.

Following data were found: N: SBP – 9.2s, DBP – 16.4s; H: SBP – >20s, DBP – >20s; HBRS: SBP – 9.2s, DBP – 10.7s; LBRS: SBP – >20s, DBP – >20s.

Most rapid blood presure return in HBRS confirmed our results of baroreflex gain calculation. Also the small gain and slow return of blood pressure in LBRS group confirmed our results. The results in hypertensives is difficult to interpret. Probably the results of the calculation of the gain of both branches separately is more reliable than the total gain calculation.

DISCUSSION

Methods based on noninvasive measurements are limited by the precision of obtained values. Noninvasive blood measurement gives different values in comparison to direct intraarterial measurements but the differencies are within several mmHg, it is within 10%. Because the interindividual variation of BRS is much higher, the noninvasive blood pressure measurements is suitable for BRS determination. On the other hand there is more difficult to prove the reliability of the estimation of relative values of cardiac output because neither invasive nor noninvasive method which can be taken as golden standart exists. Method estimating relative changes of cardiac output based on pulse contour analysis (Remington et al., 1948) of finapres recorded waveform was described. Because in our experience the pulse waveform is often different not only in different subjects but also on different fingers of the same subject, we decided to use more simple calculation based on the assumption that pulse pressure is a function of stroke volume. The fact that compliance of large arteries is dependent on mean arterial pressure (Liu et al., 1986) was taken into account despite the fact that our measurement is performerd in a narrow range of pressure of about 15 to 20 mmHg. Also the fact that the pulse pressure in peripheral arteriesis can be increased because of an overshot caused by reflection of the pulse wave on periphery (London, 1995) need not modify our results if the magnitude of overshoot corresponds to the magnitude of aortic pulse pressure and so to the stroke volume. This is probable. The error of estimate of peripheral resistance is probably high because the changes of systolic and diastolic pressures between beats are sometimes lower than 1 mmHg what is a maximal precission of blood presure measurement in our experiments. Because the fluctuation of blood pressure caused by respiration and natural variation is sometimes several mmHg during short time the estimate of peripheral resistence on individual basis is not very reliable. On the other hand baroreflex gain was calculated as a ratio between changes of peripheral resistence during the first and tenth second after the change of pressure and this value need not be influenced if a systematic

underestimation or overestimation of peripheral resistence occured. The finding of correllation between BRS and gain of the peripheral resistence response which indicate that in subjects with low BRS baroreflex as a whole is attenuated should be probably higher if the the estimate of peripheral resistence changes will be more precise. On the other hand the correlation beween the decrease in blood pressure during the cuff release expressed in percents and the value of peripheral resistence decrease in individuals groups supports the reliability of the estimate of peripheral resistence baroreflex gain on the group basis.

The findings of people with a low baroreflex makes necessary to reevaluate the physiological role of baroreflex as a whole. Sometimes the baroreflex is mentioned together with othostatic changes but our subjects with low baroreflex had not experience with orthostatic hypotension. Because the difference between people with normal and abnormal baroreflex is mainly seen during active standing and not during passive tilting up we can speculate that baroreflex is more connected with circulatory response on exercise. This support also fact, that baroreflex gain in small animals as rabits and cats where the postural changes elicit changes of blood pressure of maximal several mmHg is similar or higher than in man. Baroreflex can rapidly increase blood pressure after the decrease caused by the decrease of peripheral resistence in working muscles. Alternative should be increased blood pressure in rest with a increased tension-time index of the left ventricle and increased myocardial oxygen consumption. This should be probably overcome by heart adaptation as we seen in the giraffe. More important is probably to defence the cerebral arteries against high blood pressure induced hypertrophy of media which is in some hypertensives connected with the lower cerebral blood flow during rapid decrease of blood pressure. This idea is supported by the fact, that receptors of baroreflex are in the arteries supllying brain circulation.

Not only BRS but also cardiac output response is lower in hypertensives. This finding support Sleight (1991) idea that ineffected baroreflex play a role during the development of hypertension. The increase of blood pressure then elicits the structural changes in resistance arteries and this hypertrophy of smooth muscle then make arteries more sensitive to changes of sympathetic nervous system activity. This normalize the baroreflex gain and can contribute to the baroreflex reseting. The fact that people with low baroreflex exist without hypertension indicates that baroreflex as a defence mechanism against high blood presssure can be replaced by others, for example renal physiological mechanisms.

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Fig.1. The calculated changes (mean±SD) of peripheral resistance (PR), cardiac output (CO), stroke volume (SV) and measured changes of pulse interval, systolic and diastolic blood pressure in normotensive (N) and hypertensive (H) subjects. Time of occlusion release – 0 s.

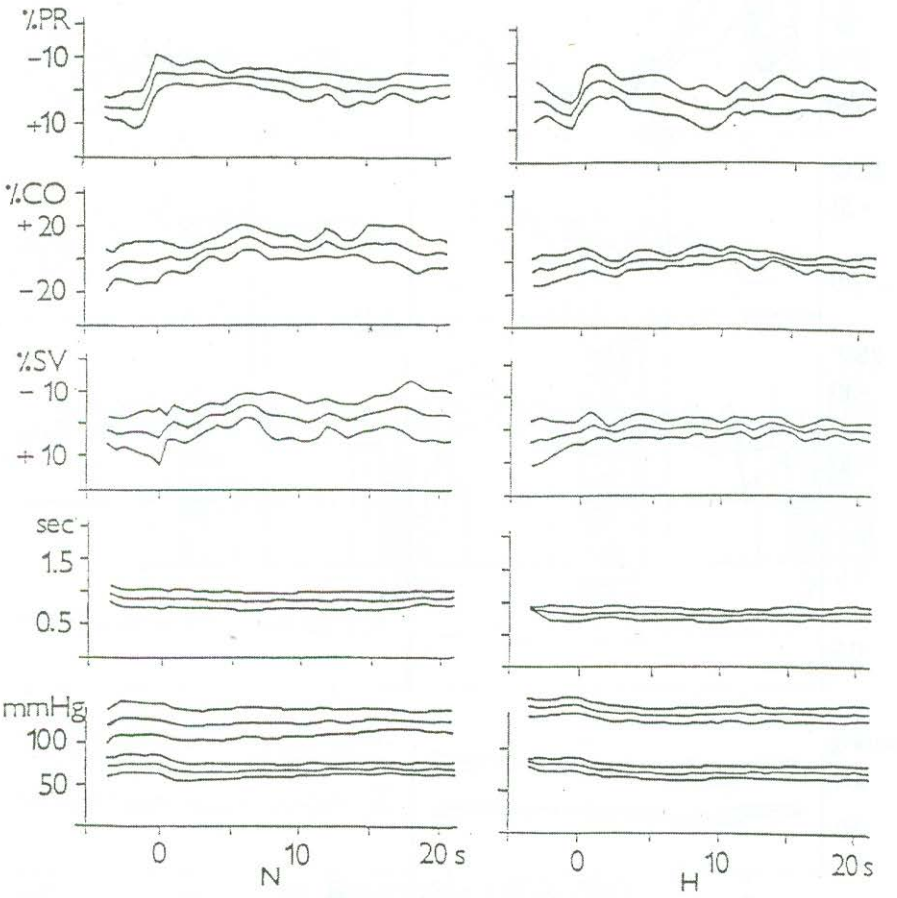


Fig.2. *The changes of calculated circulatory variables in people with high (HBRS) and low (LBRS) baroreflex sensitivity. Description as in Fig. 1.*

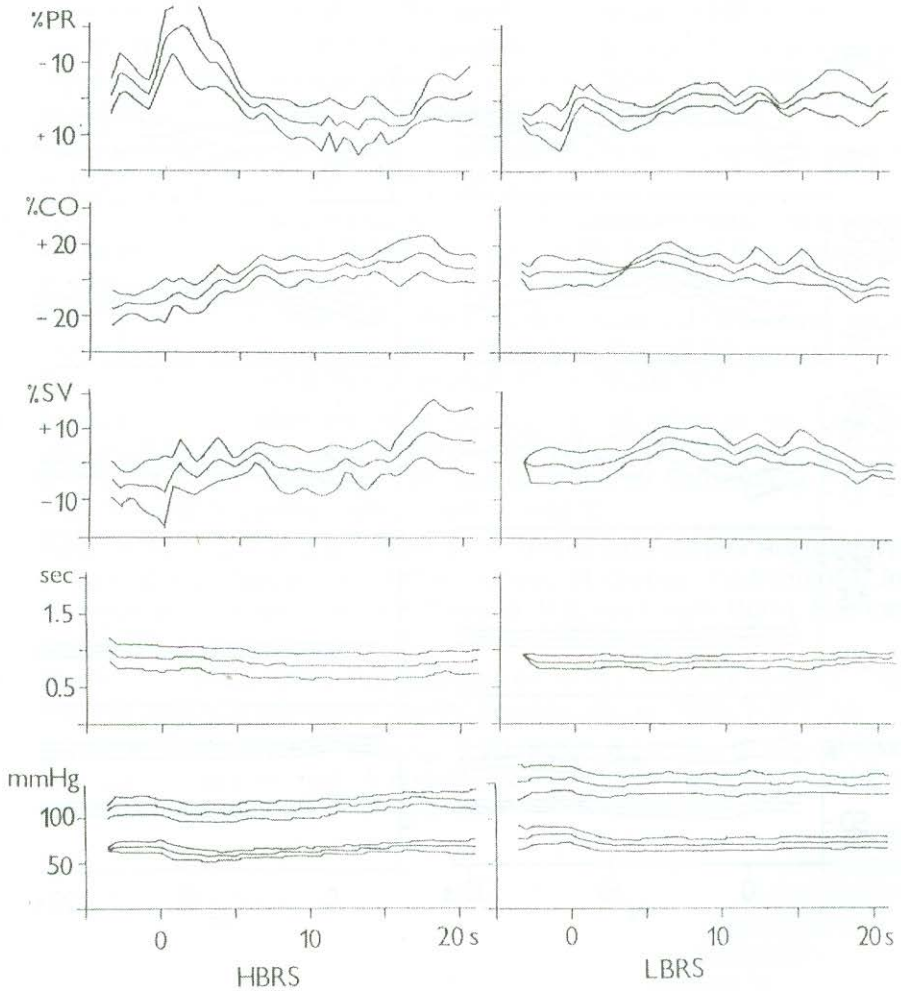
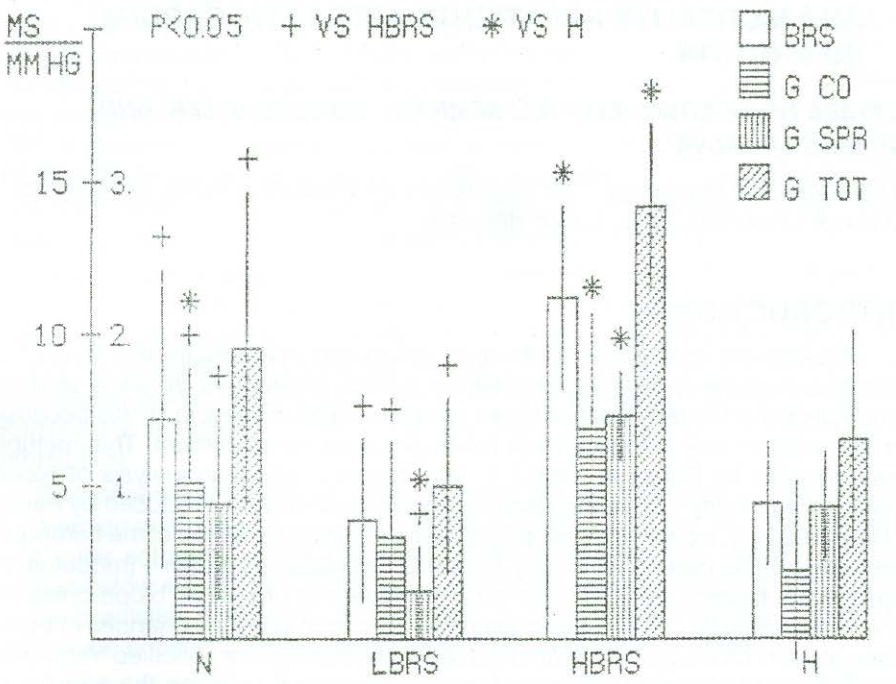


Fig.3. Estimated BRS and gain of baroreflex. Description in text.



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CORRELATION BETWEEN NON-INVASIVELY DETERMINED BAROREFLEX SENSITIVITY, HEART RATE VARIABILITY AND MORTALITY IN PATIENTS AFTER MYOCARDIAL INFARCTION

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INTRODUCTION

The present availability of the fully automated instruments that allow the continuous noninvasive measurement of arterial pressure is the long awaited step forward in the technique of blood pressure measurement in clinics because of the inherent risk of intra-arterial blood pressure measurement. This method was invented by Peňáz in 1969 [1]. Application of spectral analysis of blood pressure variability into cardiovascular research which was introduced by Peňáz et al. in 1968 [2], led to the development of the nonivasive method of the baroreflex sensitivity (BRS) determination [3]. BRS was calculated as the gain (modulus) of the transfer function between spontaneous variations of systolic blood pressure and pulse intervals. The modulus expressed the ratio between changes in pulse intervals and changes in systolic pressure in ms/mmHg in a specified frequency band. It could be calculated only if a high coherence between the spectra of pulse intervals and blood pressure were present. The fluctuation of the 10s rhythm primarily originates in blood pressure and influences the pulse intervals by the baroreflex. The origin of fluctuation at other frequencies is more complex[4] and that is why the BRS at the 10s rhythm is the most suitable frequency range for the assessment of BRS by spectral analysis [5].

In the present study, we correlated the changes of BRS, which was determined noninvasively, using spectral analysis of spontaneous blood pressure fluctuations, with other noninvasively recorded indexes of cardiac function and of autonomic control of the heart with respect to their prognostic value in patients after myocardial infarction.

Patients surviving acute myocardial infarction (MI) are at risk of sudden death which is associated with abnormalities of the autonomic control of the heart. Several studies have used the analysis of heart rate variability (HRV) and baroreflex sensitivity (BRS) to identify at-risk patients[6].

Spectral (7) and nonspectral (8) parameters are commonly used as measures of HRV. HRV, determined by spectral analysis, is assessed especially for the frequency ranges of respiratory sinus arrhythmia (RSA) and the 10second rhythm. Nonspectral parameters of HRV are derived from ECG Holter monitoring. They are calculated, for example, as the standard deviation of all normal RR intervals during 24-hours[8], SDANN (standard deviation of 5-minute mean RRs in 24 hours) and SD (mean of 5-minute standard deviations of RRs in 24 hours)[9]. HRV is generally depressed in patients at high risk of sudden cardiac death (SCD)[7,8]. Although the decrease of HRV is usually due to decreased vagal tone, RSA, which is also closely related to vagal tone[10], seemed to be of less prognostic value than the lower frequency ranges of HRV [7].

BRS, in post-infarction patients, has mainly been assessed by calculating the regression line, relating the phenylephrine- induced increase of systolic blood pressure, to the prolongation of RR intervals. A reduced BRS after myocardial infarction, associated with increased mortality, was initially found in dogs[11]. A decrease of BRS in patients after myocardial infarction [12] was later described. Significantly increased mortality was associated with a BRS lower than 3ms/mmHg [13].

Extensive research has also been focused on the association between sudden cardiac death after myocardial infarction and clinical tests of heart function: ventricular ectopy [14], the presence of late potentials [15] and an ejection fraction below 40%[14] have been shown to have independent prognostic value for the prediction of sudden cardiac death or total cardiac mortality. The noted papers are chosen as examples from several prospective studies.

The aim of our study was to find criteria for selecting patients who are at risk of sudden death, requiring special therapeutical intervention.

METHODS

Subjects

We studied all consecutive patients (90) discharged from the coronary care unit in a 12 month period. There were 63 men, 27 women, mean age 59.8±8.2 years, range 38–70 years. The diagnosis of acute myocardial infarction was based on conventional clinical, electrographic and enzymatic criteria. Fifty-three patients had an inferior MI, 31 an anterior MI, 3 a posterior MI and 3 an inferior and posterior MI. Seventy patients had Q-wave and 20 patients a non-Q-wave MI. During the initial seven month, 7 patients died (5 sudden cardiac death, 1 after aorto-coronal bypass, 1 heart and hepatorenal failure), 1 survived an episode of ventricular fibrillation and resuscitation being included in statistics among total cardiac mortality. Mean age of PD was 65.3±3.2 years, range 60–69 years.

82 patients survived the period of seven month after MI. Mean age of PS was 57.8±8.1 years, range 38–70 years.

Since the aim of our study was to evaluate the feasibility of noninvasively assessed BRS for the assessment of risk of sudden cardiac death as a standard clinical regimen, the patients were examined under appropriate treatment.

The study was approved by the ethics committee, and each patient gave informed consent.

The majority of Holter monitoring, BRS determination, echocardiogaphic investigation and signal averaged ECG recording was done between the 8th and 14th days, before discharge from hospital. A longer duration for some investigations was due to a longer period of hospitalization because of some complication of the desease. We did not exclude these measurements because the aim of our study was to evaluete the feasibility of non-invasively assessed BRS as a standard clinical regimen.

Holter Monitoring

A two-channel, 24-hour ECG recording (Oxford Excell) was performed between days 10 and 19 after MI. The recordings were manually edited, artefacts were removed.

Arrhythmias were evaluated and classified (ventricular ectopic beats – simple, bigeminal, multiform, repetitive or R on T), the count of ventricular ectopic beats was determined.

Two non-spectral indexes of heart rate variability involving conventional statistical methods were computed: The SDANN index – the standard deviation of mean RR intervals determined in 5-minute periods in 24 hours. SDANN is sensitive to frequencies below 0.0017 Hz (10-minute cycle). The SD index – the mean of standard deviations of RR intervals determined in 5-minute periods in 24 hours – is sensitive mostly to frequencies above 0.003 Hz.

Baroreflex Sensitivity Assessment

Indirect continuous blood pressure recordings from finger arteries (Finapres, Ohmeda) lasting for 3 min, were performed in sitting, resting patients, 8–22 days after the first signs of acute myocardial infarction, between 9 a.m. and 12 a.m. Recordings were taken during spontaneous and synchronized breathing. During the latter, only the rhythm of breathing was controlled at 20 per min, (0.33 Hz); the subjects were allowed to adjust the tidal volume according to their own comfort.

Beat-to-beat values of systolic and diastolic pressures and of pulse intervals were measured for further analysis.

We calculated the mean and standard deviation of pulse intervals (PI), systolic pressure (SP) and diastolic pressure. For the spectral analysis, all parameters were linearly interpolated and equidistantly sampled at 2 Hz. The linear trend was removed. The auto-correlation and cross-correlation functions, relative power spectra (the relative division of the power into frequency ranges in arbitrary units) and absolute power spectra (the relative power multiplied by the squared standard deviation) and cross-spectra, coherence and modulus between pulse intervals and systolic pressure, were calculated[16]. The gain factor, e.g. modulus H[f] of the transfer function between variations in systolic blood pressure and pulse intervals is an index of BRS in the frequency range [f].

$$Gxy(f) = H(f).Gx(f)$$

where Gxy(f)

corresponds to the cross-spectral density between SP and PI

Gx(f)

corresponds to the spectral density of SP.

The value of modulus at the frequency of the 10-second rhythm was taken as the measure of BRS. The 10-s spectral peak in patients after MI is often shifted to the lower frequencies. Therefore, the value of modulus was assessed in the frequency range of 0.07 to 0.12 Hz at the highest coherence.

Respiratory sinus arrhythmia (spectral power at 0.33 Hz during synchronized breathing) was taken as a measure of the parasympathetic control of the heart.

Ejection Fraction

A 2-dimensional echocardiogram using an Acuson 128 XP/10 unit was obtained. Evaluation of left ventricular ejection fraction by Simpson's formula was performed.

Late Potentials

Late potentials were evaluated using the HIPEC – analyser ECG Averaging System. Filtering at 40 Hz was used and 200 beats were averaged to achieve a final noise less than 0.3 μV. The presence of late potentials was defined as positive if two of the three Simson's criteria were met: filtered QRS complex greater than 120 ms, root mean square voltage less than 25 microvolts during the last 40 msec of the filtered QRS complex and duration of the QRS complex

greater than 40 msec after voltage decreased below 40 microvolts. A prolonged QRS was not considered a positive criterion if the QRS duration measured from the standard ECG was greater than 120 msec.

Statistics

The patients were divided into two groups: survivors and patients deceased during the initial year after myocardial infarction.

All values of parameters which were measured were expressed as mean and standard deviation in each group. Differences were compared by means of the Wilcoxon test, or chi-squared test. The relationship between continuous variables were examined by means of the non-parametric Spearman's correlation coefficient. A p value<0.05 was considered significant.

BRS lower than 3 ms/mmHg[13], SDANN lower than 50 ms[17], SD lower than 30 ms[17], ejection fraction lower than 40%[14], presence of late potentials[15] and 10 or more ventricular ectopic complexes per hour[18] were taken as criteria of high-risk patients. The standard definitions for specificity, sensitivity and predictive values were used.

RESULTS

The differences between the mean values of each parameter in survivors and patients deceased later was determined. A significant difference was present between survivors (PS) and deceased patients (PD) at $p<0.01$ in BRS (mean$\pm$s.d. of PS; mean$\pm$s.d. of PD: 5.9$\pm$4.1ms/mmHg; 2.6$\pm$0.6ms/mmHg), SD (45.6$\pm$16.9ms; 20.5$\pm$1.6ms), SDANN(78.6$\pm$46.3ms; 60.3$\pm$53.2ms) and mean RR(869$\pm$132ms; 671$\pm$125ms), at $p<0.05$ in the presence of ventricular premature complexes (7.86$\pm$27.1; 33.5$\pm$36.0), in ejection fraction (46.3$\pm$10.7%; 35.4$\pm$11.7%) and in RSA in absolute value (23.2$\pm$10.7ms*ms$\pm$8.81.6.57ms*ms), insignificant in late potentials (19 from 74 positive; 3 from 6 positive).

The correlation of BRS and each factor studied (mean pulse interval, SD, SDANN, ejection fraction, late potentials, mean number of extrasystols per hour, RSA in relative and in absolute values and age) was calculated. The only significant correlation was found between BRS and mean pulse interval ($r=-0.331$, $p<0.01$). Therefore, the combination of the assessment of BRS and other indexes might enhance the risk stratification of patients.

Table I lists the specificity, sensitivity and positive predictive value of the differences between survivors and deceased patients for a critical value of BRS of 3 ms/mmHg, of SDANN 50 ms, of SD 30 ms, of VPSc 10 per hour, of ejection

fraction 40% and of positive late potentials. The highest sensitivity was observed with BRS, the highest specificity with SDANN. These results confirmed that indexes of autonomous nervous activity are the best predictors of cardiac death in post-infarction patients.

DISCUSSION

Ischemic injury of the myocardium is frequently complicated by ventricular arrhythmias, the obvious cause of sudden cardiac death. Parasympathetic activity, which is often altered in patients after myocardial infarction, exerts a protective effect against the appearance of ventricular tachyarrhythmias. It is, therefore, of particular interest to assess tonic and reflex vagal activity – e.g. by HRV and BRS[19] respectively – and to assess the risk of sudden cardiac death.

Our method for the determination of BRS differs from commonly used methods (administration of vasoactive drugs and/or neck suction). We compute BRS by the spectral analysis (modulus) of blood pressure, recorded noninvasively for three minutes. We thus avoid further risk from vasoactive drug administration for the patient. The evaluation of data is a computer automated process. Naturally, our method had to be compared with classical methods. The correlation between BRS determined by the phenylephrine method and by modulus was found to be very high in some studies ($r=0.94$)[3]. The comparison of BRS determination by neck suction, stimulation and deactivation of baroreceptors through phenylephrine or nitroglycerin in post-infarction patients, has shown that the method does not influence the quality of information about the value of BRS[20]. Earlier, we showed that the value of BRS determined by spectral analysis at the 10s rhythm is independent of the respiratory rate[5] and BRS can also be calculated from recordings taken during spontaneous breathing.

Respiratory sinus arrhythmia depends on the frequency of respiration. We therefore used regular, controlled breathing for the respiratory sinus arrhythmia determination. The mild mental load during controlled breathing does not substantially influence the amplitude of respiratory sinus arrhythmia if the frequency of respiration is not changed[21]. Regular controlled breathing made it possible to compare the amplitude of respiratory sinus arrhythmia. Surprisingly, the determination of respiratory sinus arrhythmia seemed to be of low prognostic value. The explanation could be in the physiology of the complex peripheral and central origin of respiratory sinus arrhythmia[4]. Because RSA is almost exclusively vagally mediated, we expected that RSA would be of some important prognostic value. It now seems, that fluctuation of vagal activity is not so important a preserving factor for the heart, as is generally accepted.

The noninvasive determination of BRS used, and the analysis of heart rate variability based on nonspectral analysis of 24-hour ECG recordings, defined

the patients at risk of cardiac death very well. Each method explores different aspects of the autonomic control of the heart - HRV analysis reflects the vagal tone, whereas BRS reflects the readiness of vagal reflexes. Our results are in agreement with data obtained by the phenylephrine method and HRV analysis[8,13,19,20].

The SDANN and SD methods seem to have a very high predictive value. However, the evaluation of data by these methods is time consuming because the recording has to be made free of extrasystoles. The triangular method[22], which has been recently introduced, avoids this disadvantage. It might be expected that the triangular method assessing 24-hr HRV, would give similar results to SDANN and SD.

Our results indicate that ejection fraction has a low prognostic value and late potentials do not have significant prognostic value.

As to the decision which criterion or combination of indexes give the best predictive information, it is useful to take into account the value of sensitivity at the positive predictive value higher than 0.5. From this point of view, the best criterion seems to be the combination of BRS with SDANN and/or SD.

It may be argued that the patients should have been studied after pharmacological washout. However, the association of decreased BRS, HRV and other indexes with sudden cardiac death after myocardial infarction is well known [6–8, 11–13, 14–15, 19–20, 22] and we attempted to discover if these methods are of practical usage. Therefore, we preferred to examine all consecutive patients.

Our study presents a modified approach of the non-invasive identification of patients with an increased risk of death after MI. The method of BRS determination by spectral analysis is easily usable in clinical practice. Its use in routine risk stratification would aid in the decision whether to use additional therapeutic intervention or to expedite the patient's discharge from the hospital[23]. It would thus improve patients care.

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Table 1: *Sensitivity, Specificity and Predictive Values of Risk Predictors*

Predictors defining high-risk group	Sensitivity	Specificity	Positive predictive value
BRS	1.00	0.73	0.25
SD	0.88	0.86	0.38
SDANN	0.63	0.95	0.55
VPSc	0.50	0.82	0.25
EF	0.86	0.78	0.25
LP	0.50	0.70	0.11
BRS, SDANN	0.57	0.97	0.60
BRS, SD	0.86	0.91	0.46
BRS, SDANN, SD	0.57	0.97	0.66
BRS, SDANN, SD, VPSc	0.28	0.98	0.66
BRS, SDANN, SD, EF	0.33	0.98	0.66
BRS, SDANN, SD, LP	0.28	1.0	1.0

BRS, baroreflex sensitivity; SD, mean of 5-minute standard deviations of RRs in 24 hours; SDANN, standard deviation of 5-minute mean RRs in 24 hours; VPSc, ventricular premature complexes; EF, ejection fraction; LP, late potentials.

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