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NONINVASIVE METHODS IN CARDIOLOGY 2016

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Under the auspices of

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Prof. MUDr. Jarmila Siegelová, DrSc.

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Cooperation with University of Minnesota

Cooperation with Professor Franz Halberg and with professor Germaine Cornélissen, Dr. Othild Schwartzkopff Halberg Chronobiology Center of the University of Minnesota, USA started in 1988 and with Brno team - professor Bohumil Fišer, Jiří Dušek, M.D. and professor Jarmila Siegelová. The common studies of circadian variability of cardiovascular variables and baroreflex sensitivity were published in many papers as the result of this common work and our Brno team participated on international projects Womb to Tomb, later BIOCOS, under the direction from Halberg Chronobiology Center from Minnesota.

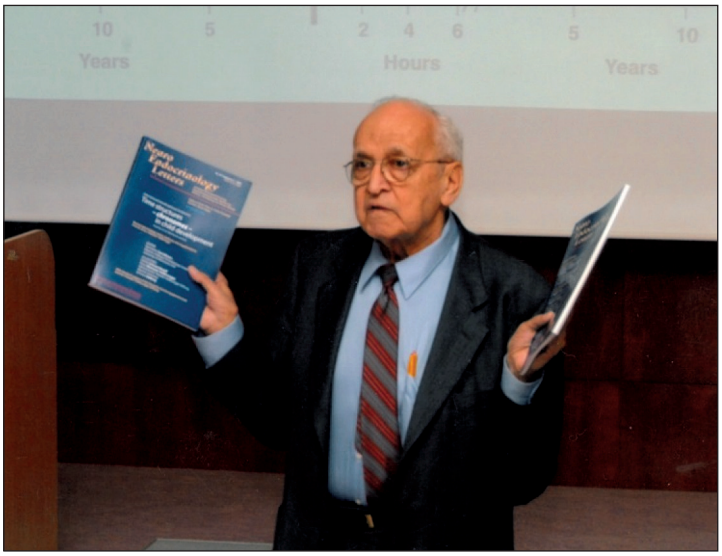

Figure 1: *Franz Halberg, M.D., Dr. h.c. (Montpellier), Dr. h.c. (Ferrara), Dr. h.c. (Tyumen), Dr. h.c. (Brno), Dr. h.c. (L'Aquila), Dr. h.c. (People's Friendship University of Russia, Moscow), Professor of Laboratory Medicine and Pathology, Physiology, Biology, Bioengineering and Oral medicine (* 5. 6. 1919 – † 9. 6. 2013)*

Cooperation with University Graz

The international cooperation continued with Professor Thomas Kenner, from the Department of Physiology in University in Graz (Austria), where the original studies of heart rate variability, baroreflex sensitivity and chronobiology have been realized and included in the common international project of analysis of cardiovascular control in physiology and pathophysiology.

Figure 2: *Prof. Dr. Thomas Kenner, M.D., Dr. h.c. mult. Dr. h. c. Universität Jena, 1990 Dr. h. c., Semmelweis University Budapest, 1998 Dr. h. c., Masaryk University Brno, 2000*

Cooperation with University of Paris

The international cooperation continued with Professor Jean-Paul Martineaud and Professor Dr. Etienne Savin, Medical Faculty, Lariboisiere Hospital, University of Paris (France) and was very intensively developed. There are the common original studies of aortic compliance and blood flow regulation in cerebral arteries, baroreflex sensitivity in healthy subjects and patients with essential hypertension.

Figure 3: *Prof. Jean Paul Martineaud, M.D. (*27.3.1931 - †29.11.2010)*

Prof. MUDr. Jan Peňáz, CSc., Department of Physilogy, Faculty of Medicine, Masaryk University Brno

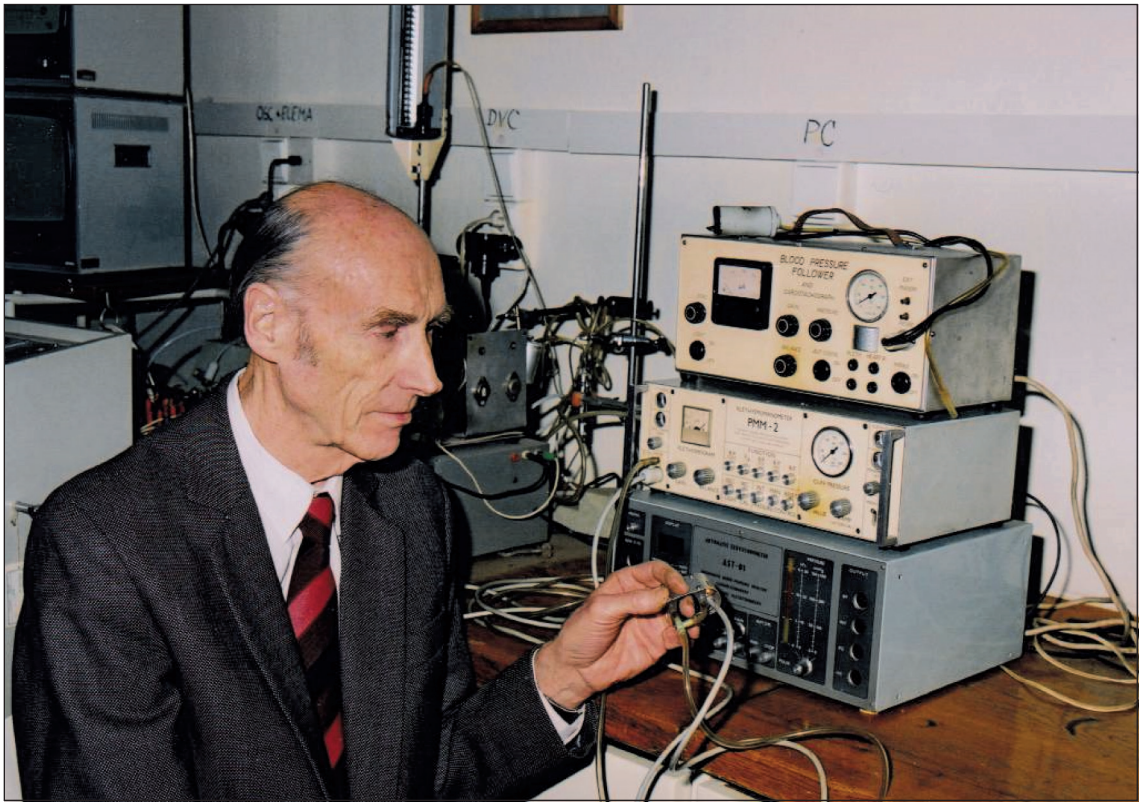

Figure 4: *Prof. MUDr. Jan Peňáz, CSc. (*20.6. 1926 - †24.4.2015)*

Prof. MUDr. Jan Peňáz, CSc. from Masaryk University, Faculty of Medicine, Department of Physiology will be remembered foremost as an exceptional physiologists who focused primarily on cardiovascular physiology. He studied cardiovascular reflexes and control of blood pressure in animal studies and in men. One of the main discovery of Prof. Peňáz was volume-clamp method of non-invasive blood pressure measurement beat by beat.

One of the common meetings was organized in 1996 at the occasion of Professor Peňáz birthday.

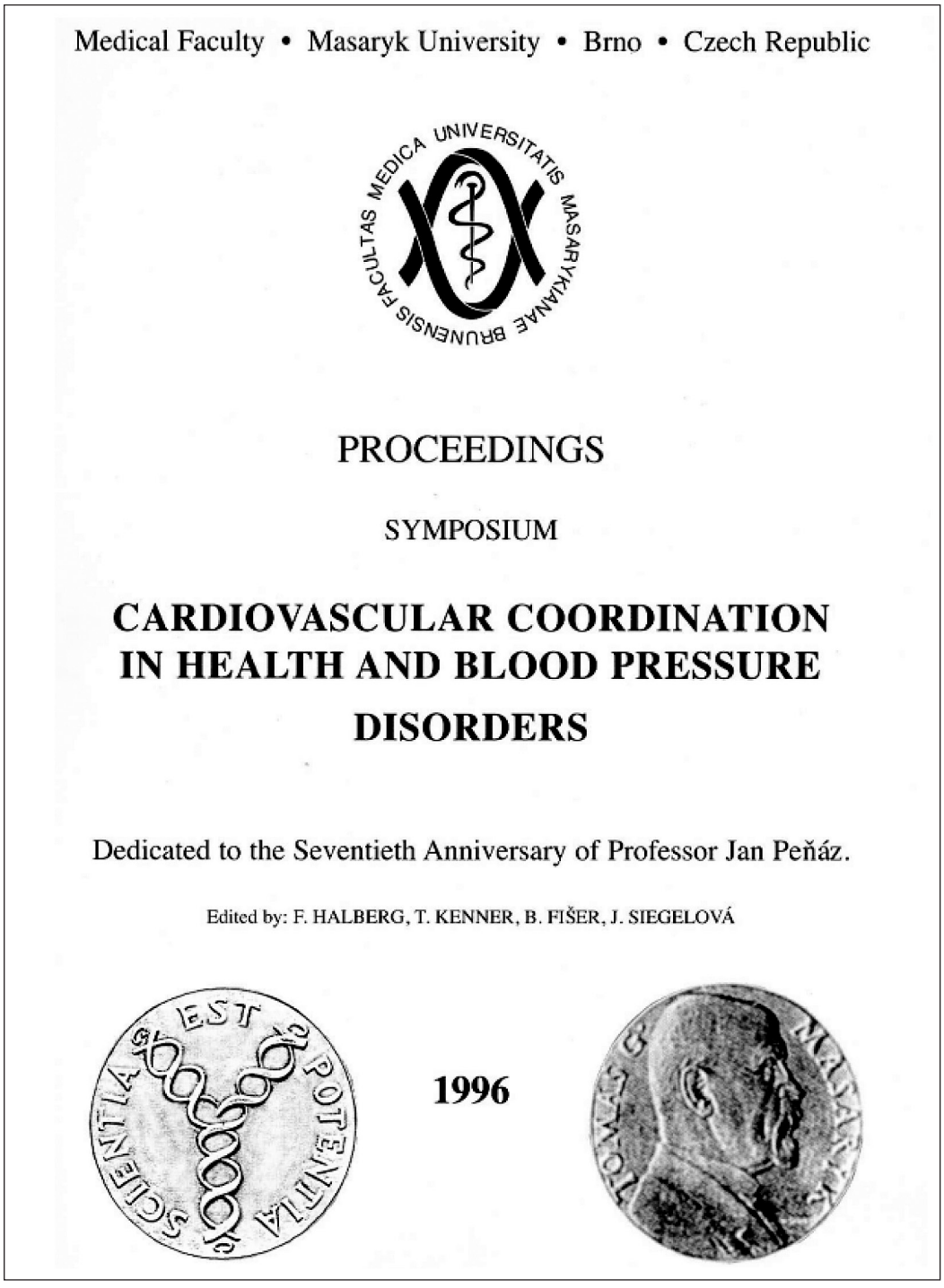

Figure 5: ***Proceedings from Symphosium 1996 in Masaryk University***

One Symposium of international scientific cooperation among Masaryk University and University of Minnesota, University of Graz and University of Paris was dedicated to the Seventieth Anniversary or Professor Jan Peňáz.

Professor Pavel Bravený, M.D., Ph.D., Vice-rector Masaryk University in 1996, described the whole scientific career of Jan Peňáz and his international recognition.

Professor Franz Halberg, M.D., d. h. c. mult., gave the lecture Circadiani, circaseptani, circasemiseptanique in chonomis seclusorum, praematurorum, seniumque: in honorem Johannis Penazenis modo Mendeliano, Goedeliano, Keplerianoque.

This part of the world (Brno) is not only a seat of genetics, mathematics and astronomy, but it is home to pioneering in physiological monitoring: the home of school of Jan Penaz.

Professor Germaine Cornélissen and others presented Current limitations and promise of ambulatory blood pressure monitoring. She concluded that the pioneering contributions of Dr. Jan Penaz including his development of a BP measurement technique are a major step forward towards a chonobiologic assessment of the risk of vascular disease.

Professor Thomas Kenner, M.D., d. h. c. mult., remembered in presentation One hundred years since Riva-Rocci´s invention of the cuff-technique. He also mentioned his first personal experience with indirect blood pressure measurement in 1959.

Professor Jarmila Siegelová, Professor Bohumil Fišer, Dr. Mohamed Al-Kubati, Dr. Jiří Dušek together with team from Minnesota presented Barorefelex heart rate sensitivity in hypertensives: the role of antihypertensive therapy.

Professor Etienne Savin, Professor Jean Paul Martineaud and Dr. Philipe Bonnin together with Prof. Siegelová and Prof. Fišer presented common results Noninvasive measurement of blood velocity in middle cerebral artery at rest and during abrupt decrease of blood pressure in man.

Professor Bohumil Fišer and other presented The noninvasive estimation of the gain of the arterial baroreceptor reflexes in man.

Professor Nataša Honzíková, Professor Bořivoj Semrád, Professor Bohumil Fišer and Dr. Růžena Lábrová presented Correlation between non-invasively determined barorefelex sensitivity, heart rate variability and mortality in patients after myocardial infarction.

All presented lectures were connected with the blood pressure measurement, also beat by beat measurement of blood pressure based on volume clamp method of Professor Peňáz.

Figure 6: *Professor Franz Halberg, Professor Nataša Honzíková, Professor Pavel Bravený, Brigitter Kenner, Professor Thomas Kenner, Professor Jan Peňáz in 1996*

Figure 7: *Professor Franz Halberg, Professor Pavel Bravený, Brigitte Kenner, Professor Thomas Kenner, Professor Jarmila Siegelová, Professor Jan Peňáz, Professor Bohumil Fišer in 1996*

Figure 8: *Professor Jarmila Siegelová, Professor Jan Peňáz, Professor Bohumil Fišer in 1996*

There are further examples of other scientific activities of the cooperation between University of Minnesota, USA, University of Graz, Austria, University of Paris and Masaryk University.

Figure 8: *Professor Franz Halberg, Brno International Congress MEFA 2005*

Figure 10: *Dr. Jiří Dušek, Professor Franz Halberg, Dr. Othild Schwartzkopff, Professor Thomas Kenner, Brno International Congress MEFA 2005*

Figure 11: *Professor Germaine Cornélissen, Brno Congress Noninvasive Methods in Cardiology 2003*

Figure 12: *Professor Thomas Kenner, Professor Jarmila Siegelová, Brno International Congress MEFA 2003*

Figure 13: *Professor Jean-Paul Martienaud, Professor Bohumil Fišer, Brno International Congress MEFA 2003*

Figure 14: *Professor Thomas Kenner, Brigitte Kenner, Professor Jarmila Siegelová, Professor Jean-Paul Martienaud, Brno International Congress MEFA 2003*

Figure 15: *Professor Bohumil Fišer, As. Professor Michal Pohanka, Professor Thomas Kenner, Brigitte Kenner, Dr. Othild Schwartzkopff , Professor Franz Halberg, Dr. Jiří Dušek, Professor Jarmila Siegelová, Brno Congress Noninvasive Methods in Cardiology 2008 (Brno Consensus)*

Chronobiology, studied by Franz Halberg, showed broad spectrum of rhythms in us and around us; they are being marched up by the dozens but have not yet been recognized in terms of their pertinence to everyday life.

We feel honored to have had the possibility of cooperation with Prof. Halberg since 1980s.

Chronobiologically interpreted blood pressure and heart rate monitoring detects prehypertension, prediabetes and a premetabolic syndrome in vascular variability disorders, that interact with a reliably diagnosed MESOR hypertension that can carry a risk greater than a high blood pressure and that can

coexist to form vascular variability syndromes, unrecognized in a conventional health care, but some of them already treatable.

Figure 16: *Professor Franz Halberg, Dr. Othild Schwartzkopff, Professor Germaine Cornélissen in Halberg Chronobiolgy Center University Minnesota on May 3-4, 2013 during Symposium (videoconference) in Masaryk University Brno*

In 2008 during Congress of Noninvasive methods in cardiology this Brno Consensus on vascular variability disorders and vascular variability syndromes was presented. It was published as Halberg et al. Extended consensus on means and need to detect vascular variability disorders and vascular variability syndrome. In World Heart J 2010;2,4:297-305 and World Heart J 2011;3,1:63-77.

Prof Halberg suffered by the fact, that his ideas overrun the development of science for tens of years. A lot of lectures from Prof. Halberg, Prof. Kenner, former president of University of Graz, Austria, Prof. Cornelissen, Prof. Fišer, Dr. Dušek, prof. Siegelová were presented at international scientific conferences, hold every year in Brno and published.

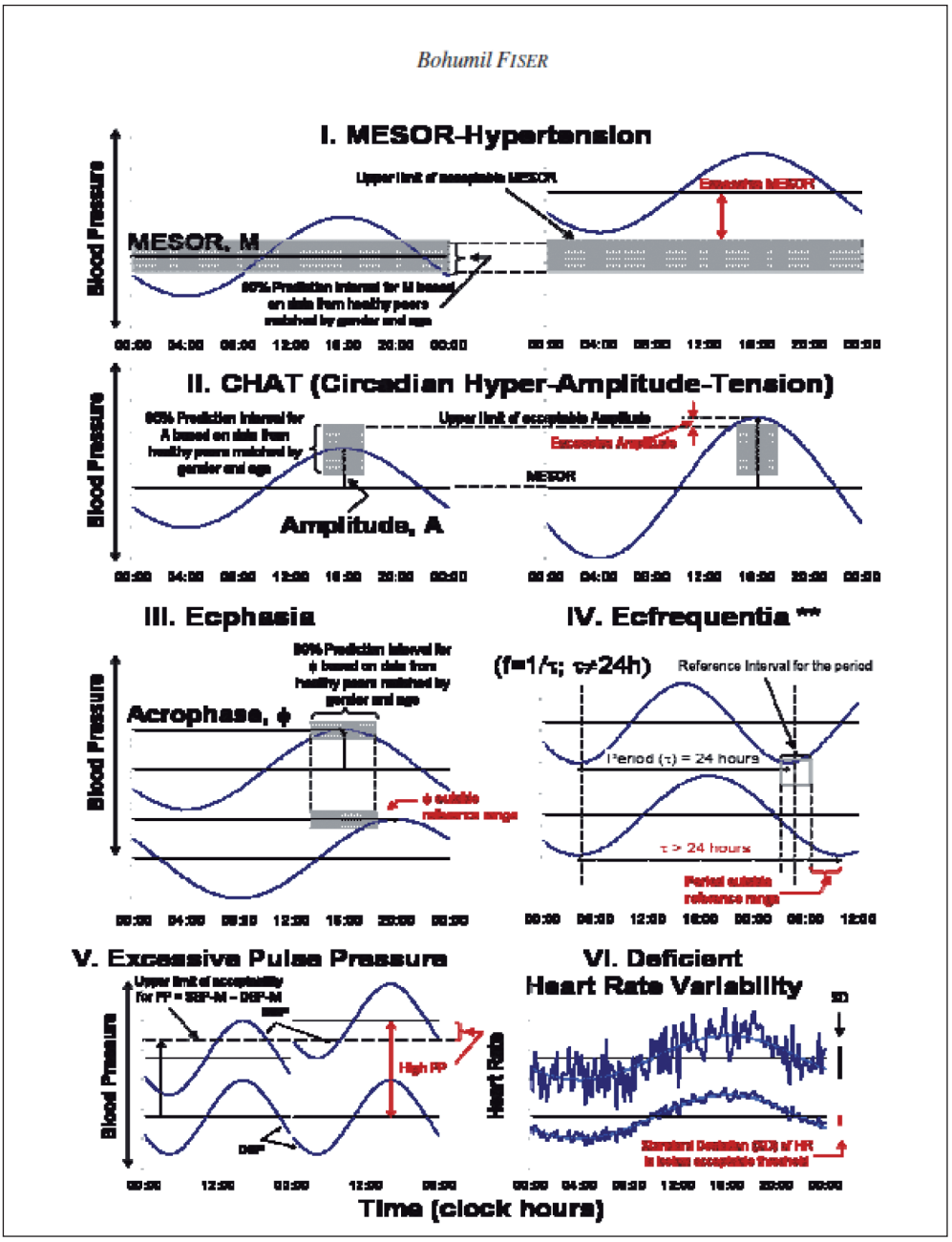

Figure 17: *Brno Consensus on vascular variability disorders and vascular variability syndromes*

Prof. Petr Dobšák add the cooperation with Bourgond University, Dijon, France with Prof. Jean Eric Wolf and Dr. Jean Chritoph Eicher and Tohoku University, Sendai, Japan, Prof. Masario Kohzuki and Prof. Tomoyuki Yambe.

30 years until now the chronobiological data measured in Czech population in Brno were immediately analyzed by Prof. Germaine Cornelissen and the results of these analyses served not only for scientific work, but also for therapy. Between the years 2000 and 2008 the Brno team consisting of Prof. Fišer, Dr. Dušek and me collected 73 888 sets of blood pressure and heart rate measurements and all data were in the following day analyzed by Prof. G. Cornélissen. The daily data exchange and analysis continues until now.

Prof. Germaine Cornelissen presented and still presents with her team from Halberg Chronobiology center Minnesota lot of publications for congresses and symposia in Brno as is documented in every year publications of Noninvasive methods of cardiology.

We hope that we will continue the cooperation between Halberg Chronobiology Center and Professor Germaine Cornélissen to finish the international scientific projects as BIOCOS and with Professor Thomas Kenner from University of Graz, Austria and his team and other foreign centers from France and Japan. We will also implement ideas of science in the foot steps of the great scientists, who left us Professor Halberg, Professor Peňáz, Professor Martineaud, Professor Semrád and Professor Fišer.

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Time Structure of Blood Pressure and Aging: the Brno Database

Germaine Cornelissen[1], Jarmila Siegelova[2], Alena Havelkova[2], Leona Dunklerova[2], Jiri Dusek[2], Larry Beaty[1], Kuniaki Otsuka[3]

[1]Halberg Chronobiology Center, University of Minnesota, Minneapolis, MN, USA,
[2]Masaryk University, Brno, Czech Republic
[3]Tokyo Women's Medical University, Daini Hospital, Tokyo, Japan

Dedicated to the memory of Franz Halberg.

Abstract

The circadian system tends to weaken with advancing age. The circadian amplitude of many physiological variables is reduced and the circadian acrophase becomes more labile, often occurring earlier in older people. The Brno database consists of 297 7-day/24-hour records from men (N=219) and women (N=78), 20-84 years of age, obtained by ambulatory blood pressure monitoring between January 2000 and June 2011. Subjects resided in Brno, Czech Republic, and were mostly clinically healthy at the time of monitoring. All but 23 records covered a week. Data from the 274 complete records were analyzed by the extended cosinor. Least squares spectra were computed in the frequency range from 1 cycle per week to 7 cycles per day. Population-mean cosinor spectra were obtained to assess the infradian-to-circadian (frequencies of 1 to 7 cycles per week) and circadian-to-ultradian (frequencies between 1 and 7 cycles per day) spectral domains. The circadian period was estimated by the nonlinear fit of a cosine curve with a trial period of 24 hours. With increasing age, the circadian amplitude of blood pressure was reduced and the circadian acrophase of blood pressure was advanced. In men, but not in women, the circadian period of blood pressure shortened with age. It deviated from 24 hours in over 10% of the population. There was also a transposition of the variance from the circadian to both the infradian and ultradian domains. The weakening of the circadian system was also apparent from a widening of the 95% confidence intervals of the relative amplitude, acrophase, and period. These results provide further evidence for the need to refine reference standards by accounting for changes with age in circadian (and other) rhythm characteristics.

Keywords: Aging, Blood pressure, Circadian, Heart rate, Infradian, Ultradian, Variance transposition**.**

Introduction

As many other variables [1], blood pressure and heart rate have a decreased circadian amplitude in older individuals [2]. With increasing age, disease risk and incidence of morbid events also increase. In order to differentiate between an increased disease risk and natural aging, it is necessary to derive reference values as refined as possible by accounting for predictable variability in health.

One source of predictable variation consists of the usually very prominent circadian variation. Other components, such as the week and half-week observed in physiology [3] and pathology [4] are also periodic. The circadian waveform also undergoes predictable changes as a function of age, which can be assessed by the harmonic content. Changes with age in the circadian waveform of blood pressure involve an increase in nightly values and a deepening of the postprandial dip in the early afternoon, accentuating the contribution of a 12-hour component to the circadian waveform [2, 5].

Changes with age in the time structure of blood pressure and heart rate are examined herein in the Brno database, consisting of 7-day/24-hour records obtained by ambulatory monitoring from mostly clinically healthy men and women [6-8]. It represents a homogeneous population, which lends itself well to assess changes in blood pressure and heart rate in a relatively wide frequency range spanning from one cycle per week to 7 cycles per day. Information can thus be obtained regarding variability from one day to another as well as variability accounting for changes in the circadian waveform.

Subjects and Methods

Blood pressure and heart rate from mostly clinically healthy men and women, 20-84 years of age, were measured around the clock, mostly at 30-minute intervals for 7 days in Brno, Czech Republic, using the TM-2421 device from A&D (Tokyo, Japan), as outlined previously [8]. Between January 2000 and June 2011, 297 records (78 from women and 219 from men) were obtained. Of those, 23 were incomplete and were not used in this investigation. Oscillometric measurements from the remaining 274 records are analyzed. The study was approved by the Ethics committee of Masaryk University. The study was explained to the subjects before they gave written, informed consent.

Each data series was analyzed by the extended cosinor [9-11]. Specifically, least squares spectra were computed in the range of 1 to 7 cycles per week to assess the infradian-to-circadian time structure, and in the range of 1 to 7 cycles per day to assess the circadian-to-ultradian time structure. In addition to the MESOR (Midline Estimating Statistic Of Rhythm, a rhythm-adjusted mean value, usually more precise and more accurate than the arithmetic mean), estimates of the amplitude (half the predictable extent of change within a cycle) and of the acrophase (measure of the timing of overall high values recurring in each cycle) were obtained at each trial period. The circadian period was estimated by the nonlinear fit of a cosine curve with a trial period of 24 hours, using Marquardt's algorithm [12].

Circadian rhythm characteristics and their 95% confidence intervals were linearly regressed as a function of age, separately for men and women. Linear regression analyses also considered a quadratic model as a function of age, as well as the combined effects of age and body mass index (BMI), Population-mean cosinor spectra were computed for subjects classified in 7 age groups: younger than 25 years (Group A; 19 records), 25-34 years (Group B; 25 records), 35-44 years (Group C; 33 records), 45-54 years (Group D; 80 records), 55-64 years (Group E; 78 records), 65-74 years (Group F; 32 records), and 75 years or older (Group G; 7 records). Groups A and B and Groups F and G were pooled for some analyses in view of their smaller sample sizes. Phase-unweighted amplitude spectra were also obtained, and amplitude ratios were computed to compare the circaseptan (about-weekly) and circasemiseptan (about-half-weekly) amplitudes with the corresponding circadian amplitude. Log_{10}-transformed amplitude ratios were compared among the different age groups by one-way analysis of variance (ANOVA). P-values below 0.05 are considered to indicate statistical significance.

Results

A circadian rhythm was detected with statistical significance in the large majority of individual records. On a population basis, it was invariably statistically significant (P<0.001) in each age group, Table 1. It can be seen that the MESOR of systolic blood pressure increases with advancing age from 123.4 ± 1.3 mmHg in subjects younger than 35 years of age to 129.5 ± 1.5 mmHg in subjects 65 years of age and older (P<0.05). The MESOR of diastolic blood pressure also changes as a function of age but does not show a steady increase with age. Instead, it increases until mid-adulthood from 73.8 ± 1.0 to 81.2 ± 0.8, when it reaches a maximum to drop to 77.2 ± 1.5 mmHg in the oldest age group (P<0.001). These trends with age are also documented by linear regression, as illustrated in Figures 1 and 2. The circadian amplitude of blood pressure of subjects 55 years and older is also much smaller than that of younger subjects (P<0.001), and their circadian acrophase occurs about 1 hour earlier, Table 1 and Figures 3 and 4. In the case of heart rate, the MESOR increases slightly until mid-adulthood from 69.1 ± 1.2 to 72.6 ± 0.9 beats/min, then decreases sharply to 64.8 ± 1.6 beats/min in the oldest age group (P<0.001) and the circadian amplitude decreases with advancing age (P<0.001), Table 1 and Figures 5 and 6.

The weekly and half-weekly components are also detected with statistical significance. Their amplitude is larger in mid-adulthood than at younger or older ages (P<0.05). The circaseptan-to-circadian amplitude ratio of systolic blood pressure increases with age from 25.2% in subjects younger than 35 years to 49.1% in subjects 65 years and older (1-way ANOVA: F=5.281, P<0.001). Similar results are found for the circasemiseptan-to-circadian amplitude ratio of systolic blood pressure, which increases from 20.4% to 41.8% (F=4.501, P=0.002).

With advancing age, there is transposition of the variance from the circadian domain to both the infradian and ultradian domains, as illustrated for systolic blood pressure in Figures 7 and 8, respectively. This is particularly the case for blood pressure. Whereas the circadian component remains the most prominent one in all age groups, its amplitude progressively decreases with advancing age.

With advancing age, as the circadian amplitude decreases, the circadian period is more likely to deviate from 24 hours, and the width of its 95% confidence interval increases, Figure 9. The increased uncertainty in the estimation of the period is statistically significant, except for women's heart rate (Men: SBP, r=0.242, P<0.001; DBP, r=0.209, P=0.002; HR, r=0.186, P=0.006; Women: SBP, r=0.389, P<0.001; DBP, r=0.452, P<0.001; HR, r=0.134, NS). The width of the 95% confidence interval of the circadian acrophase also increases with age (Men: SBP, r=0.268, P<0.001; DBP, r=0.242, P<0.001; HR, r=0.200, P=0.003; Women: SBP, r=0.408, P<0.001; DBP, r=0.456, P<0.001; HR, r=0.147, NS), Figure 10. So does that of the circadian amplitude when it is expressed relative to the amplitude (in order to compensate for the marked decrease in circadian amplitude as a function of age), Figure 10 (Men: SBP, r=0.288, P<0.001; DBP, r=0.266, P<0.001; HR, r=0.201, P=0.003; Women: SBP, r=0.425, P<0.001; DBP, r=0.477, P<0.001; HR, r=0.141, NS).

Discussion and Conclusion

A variance transposition from circadians to neighboring extra-circadians has been reported earlier, both in terms of infradians [17] and ultradians [17, 18]. In an earlier investigation [17], 72 participants 12-106 years of age provided a 7-day record of blood pressure measured indirectly with an ambulatory monitor, mostly at 15-60-minute intervals. Amplitudes in least squares spectra at frequencies of 1 to 7 cycles per week and 1 to 8 cycles per day were analyzed by a two-way analysis of variance for subjects

classified in four age groups (12-39, 40-59, 60-74, and ≥75 years of age). The decreasing circadian blood pressure amplitude with age was accompanied by an increase in the amplitude of infradian and ultradian components. The day-to-day variability in circadian characteristics was also found to increase with age [17].

In another study [18], 180 clinically healthy adults monitored their blood pressure automatically, mostly at 15-minute intervals, for 24 hours. They were assigned to three age groups (20-49, 40-60, and >60 years of age). Amplitudes in least squares spectra at frequencies of 1 to 14 cycles per day were analyzed by 2-way analysis of variance after being expressed as a percentage of the 24-hour amplitude and $\log_{10}$-transformed. The harmonic content was found to increase with advancing age in both men and women [18]. The circadian-to-ultradian variance transposition is readily seen in a comparison of blood pressure records from centenarians (N=11) and medical students (N=64), Figures 6A-C, where the different behavior of blood pressure and heart rate can also be observed [19].

Older populations are more likely to take medications, including anti-hypertensive drugs, and to be less active. As noted above, circadian rhythms have been shown to persist in the absence of physical activity [3, 4]. Depending on the kind, dose and timing of daily administration of anti-hypertensive treatment, the circadian amplitude of blood pressure may be increased or decreased [20]. The effect of salt intake on the circadian rhythm of blood pressure, reviewed elsewhere [21], also depends on its relative distribution among the three daily meals [22]. Admittedly, physical activity, medications, diet, as well as emotions all affect blood pressure [23]. These confounding factors make it difficult to distinguish between healthy aging and the presence of overt disease or elevated disease risk. It is the more critical to derive time-specified reference values in health to make that distinction. The reduced amplitude and earlier acrophase of the circadian blood pressure rhythm reported herein are, however, general features of senescence, also seen in other variables [2], in clinical studies as well as in the experimental laboratory [24]. The similarity of circadian rhythm alterations observed with increasing age and after bilateral lesioning of the suprachiasmatic nuclei was noted by Franz Halberg, who suggested their involvement as a mechanism underlying changes with age [25].

In view of the prominent circadian variation in blood pressure and heart rate observed at all ages, it is recommended to take measurements around the clock for an assessment of the circadian rhythm characteristics. This is the more important that several outcome studies have shown that alterations in circadian rhythm characteristics of blood pressure and/or heart rate are associated with cardiovascular disease risk beyond the risk contributed by an elevated blood pressure [26]. For a more reliable estimation of circadian rhythm characteristics, it is recommended to monitor blood pressure around the clock for more than a single 24-hour span, preferably for at least one week at the outset [27], to examine the extent of day-to-day variability in circadian parameters [28, 29] and to obtain an estimate of the circaseptan and circasemiseptan rhythm characteristics. These components may indeed provide valuable information in their own right [30].

In view of the marked changes in the time structure of blood pressure and heart rate as a function of age, as illustrated herein, it is also mandatory to further qualify the time-specified reference values by age (as well as by gender and ethnicity). Doing so led to the definition of vascular variability disorders [20, 21] which have been shown to correlate with an increased cardiovascular disease risk [20]. With the availability of ambulatory monitors to automatically measure blood pressure around the clock for a week or longer, the availability of chronobiologic methods for the analysis of the data thus collected, and the availability of time-specified reference values qualified by gender and age in clinical health for a chronobiologic interpretation of the results, the time is ripe to bring this technology to the clinic for routine patient care.

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Table 1. *Circadian rhythm characteristics in subjects of different age groups*

Age Group	k	PR (%)	P-value	M ± SE	A (95%CI)	ϕ (95%CI)
Systolic Blood Pressure (mmHg)						
A,B: <35y	44	21	<0.001	123.4 ± 1.3	9.5 (8.2, 10.7)	−232° (−224, −238)
C: 35−44y	33	23	<0.001	125.0 ± 1.5	10.4 (8.3, 12.5)	−225° (−217, −233)
D: 45−54y	80	25	<0.001	125.9 ± 1.0	11.2 (9.6, 12.7)	−219° (−215, −224)
E: 55−64y	78	15	<0.001	126.1 ± 1.2	8.3 (6.8, 9.9)	−214° (−207, −222)
F,G: ≥65y	39	11	<0.001	129.5 ± 1.5	6.4 (2.0, 9.2)	−215° (−202, −229)
Diastolic Blood Pressure (mmHg)						
A,B: <35y	44	21	<0.001	73.8 ± 1.0	7.4 (6.3, 8.5)	−229° (−222, −235)
C: 35−44y	33	22	<0.001	79.7 ± 1.3	8.0 (6.4, 9.6)	−223° (−215, −233)
D: 45−54y	80	25	<0.001	81.2 ± 0.8	8.2 (7.2, 9.2)	−213° (−208, −218)
E: 55−64y	78	15	<0.001	78.6 ± 0.8	5.6 (4.7, 6.5)	−208° (−202, −216)
F,G: ≥65y	39	12	<0.001	77.2 ± 1.5	4.9 (3.3, 6.5)	−211° (−198, −223)
Heart Rate (beats/min)						
A,B: <35y	44	18	<0.001	69.2 ± 1.2	8.4 (7.2, 9.6)	−215° (−207, −223)
C: 35−44y	33	16	<0.001	71.7 ± 1.4	6.7 (5.3, 8.1)	−224° (−214, −236)
D: 45−54y	80	19	<0.001	72.6 ± 0.9	7.0 (5.8, 8.1)	−214° (−207, −221)
E: 55−64y	78	13	<0.001	68.1 ± 0.9	5.1 (3.9, 6.2)	−219° (−210, −228)
F,G: ≥65y	39	14	<0.001	64.8 ± 1.6	5.1 (3.4, 6.8)	−217° (−209, −226)

PR: Percentage Rhythm, proportion of overall variance accounted for by the fit of a 24-hour cosine curve to individual records; M: MESOR (Midline Estimating Statistic Of Rhythm), a rhythm-adjusted mean; SE: Standard Error; A: 24-hour amplitude; ϕ: 24-hour acrophase; CI: Confidence Interval.

Acrophase expressed in (negative) degrees, with 360° equated to 24 hours and 0° set to local midnight.

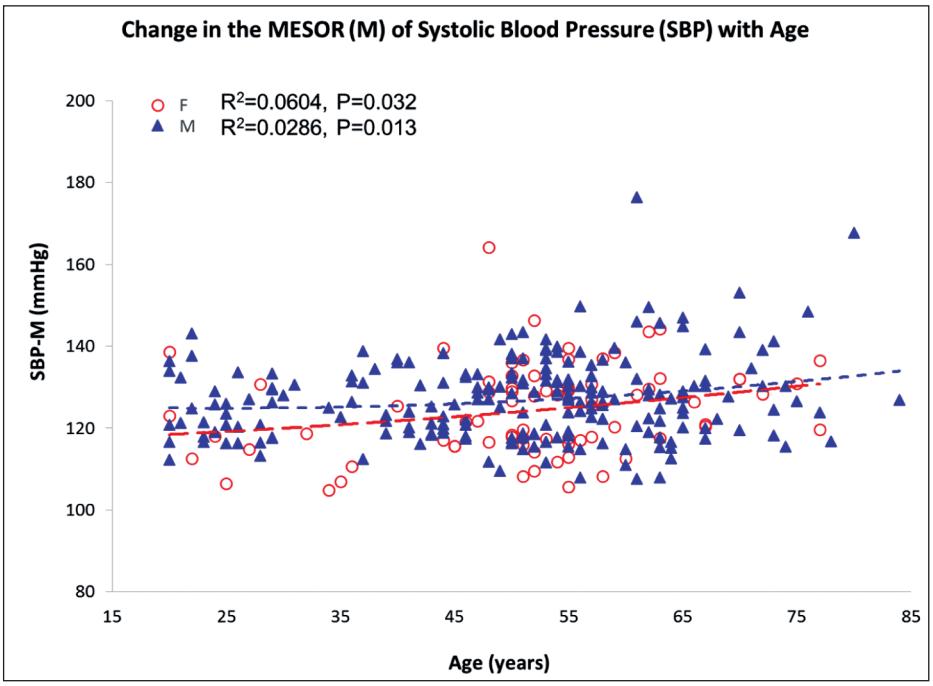

Figure 1: *The MESOR of systolic blood pressure steadily increases with age, shown by quadratic regression.* © Halberg Chronobiology Center.

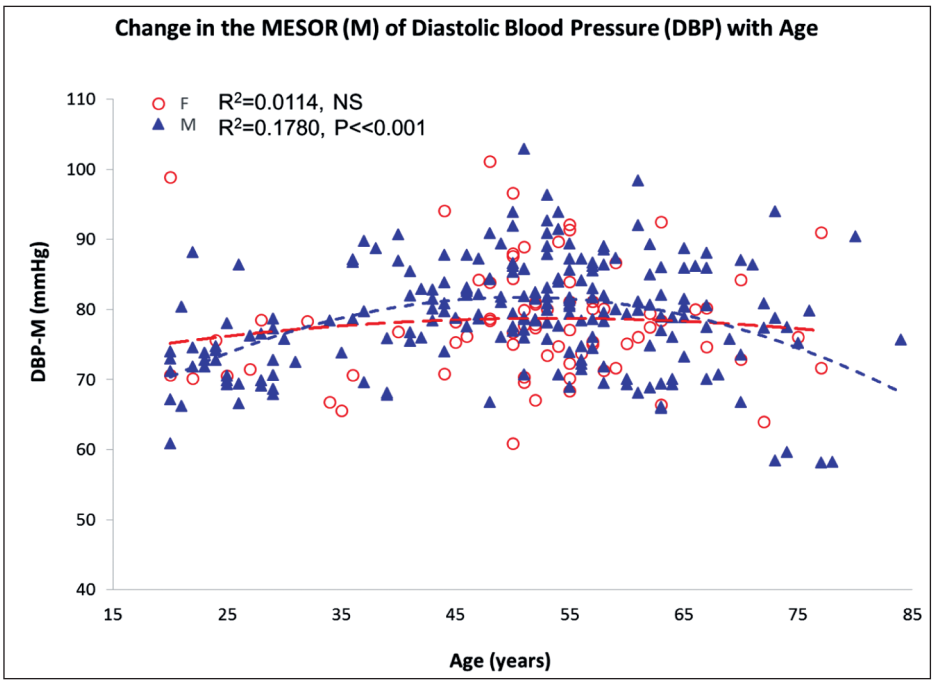

Figure 2: *The MESOR of diastolic blood pressure reaches a maximum around 53.4 years of age in women and around 50.6 years in men, as shown by quadratic regression.* © Halberg Chronobiology Center.

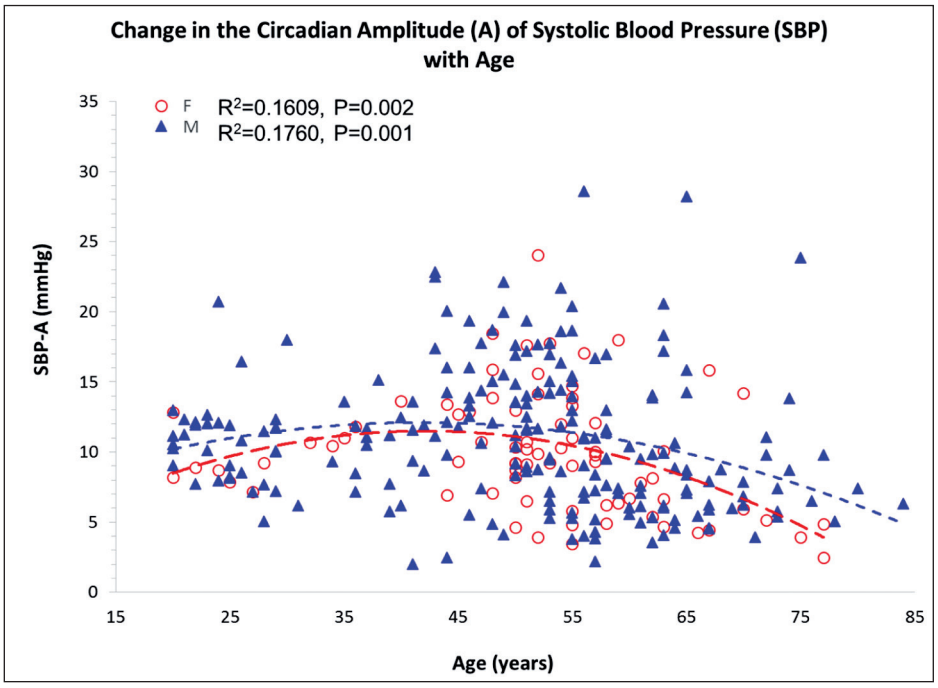

Figure 3: *The circadian amplitude of systolic blood pressure reaches a maximum around 42.0 years of age in women and around 41.7 years in men, as shown by quadratic regression.* © Halberg Chronobiology Center.

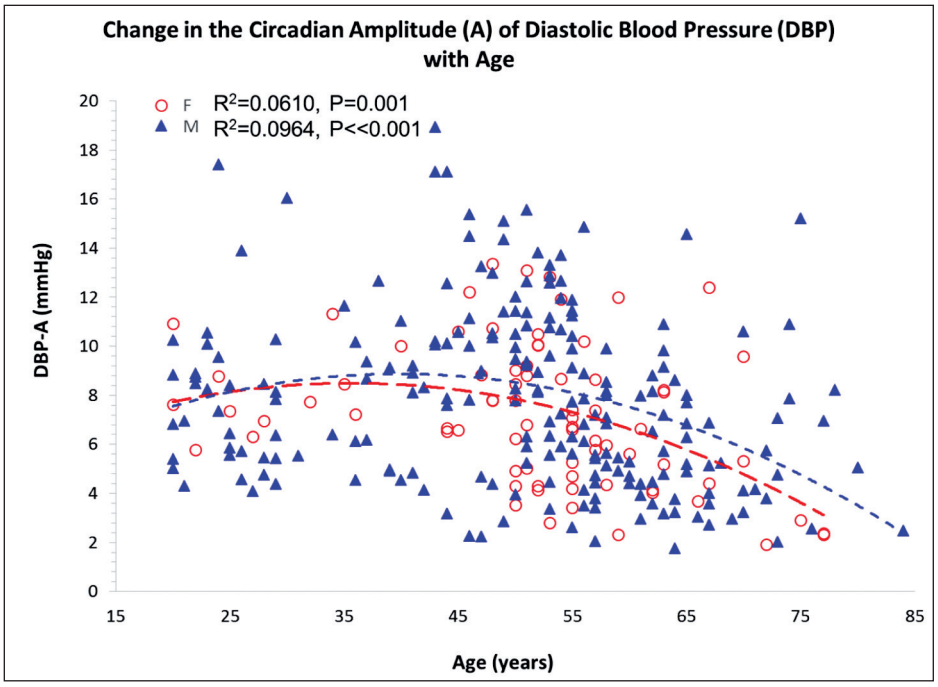

Figure 4: *The circadian amplitude of diastolic blood pressure reaches a maximum around 35.6 years of age in women and around 39.9 years in men, as shown by quadratic regression.* © Halberg Chronobiology Center.

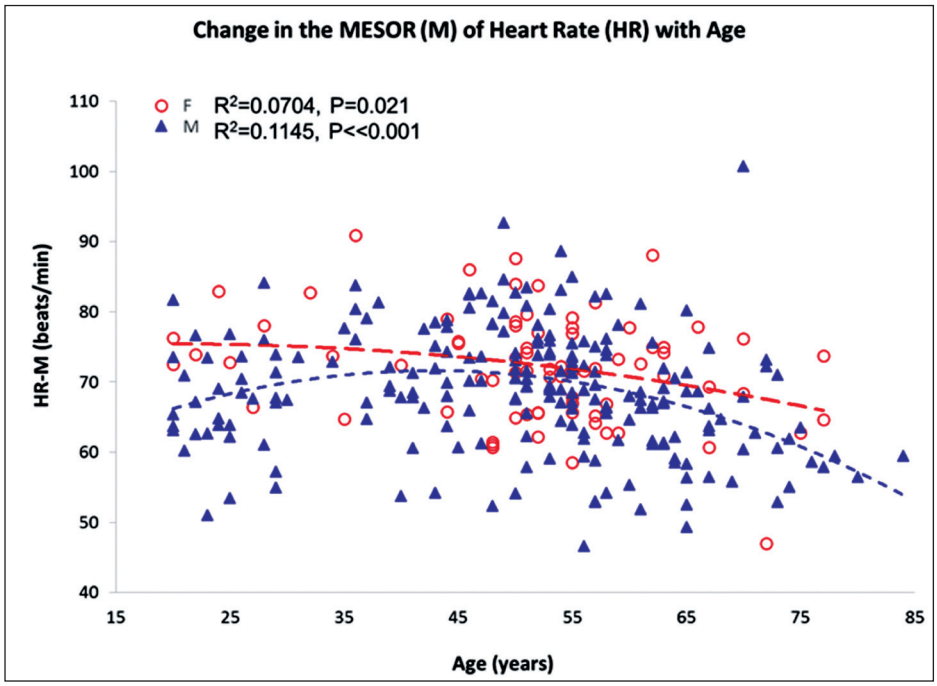

Figure 5: *The MESOR of heart rate steadily decreases with age in women and reaches a maximum around 42.8 years of age in men, as shown by quadratic regression.* © Halberg Chronobiology Center.

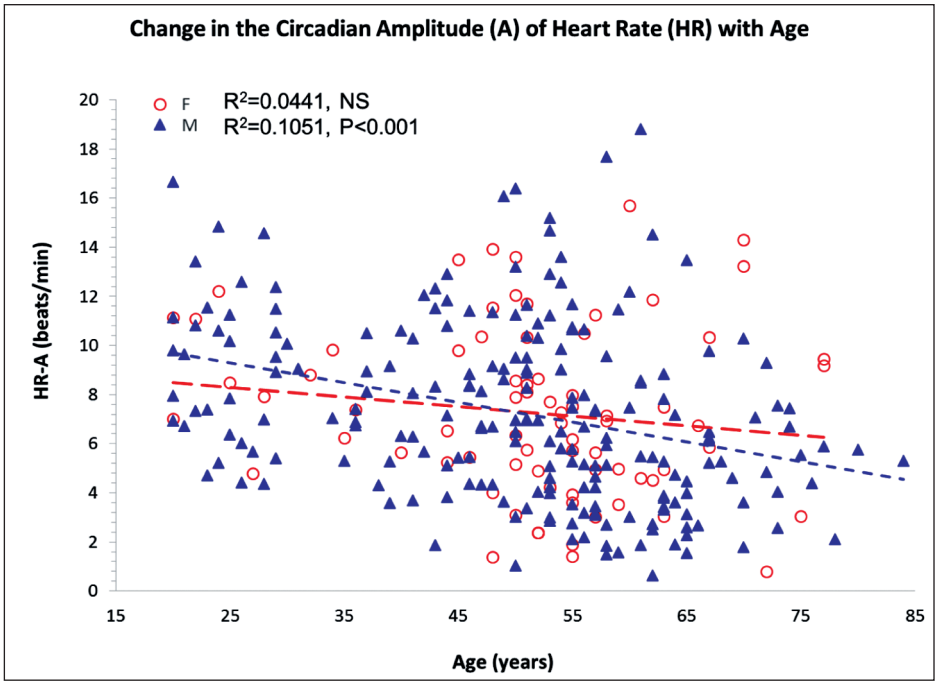

Figure 6: *The circadian amplitude of heart rate steadily decreases with age, as shown by quadratic regression.* © Halberg Chronobiology Center.

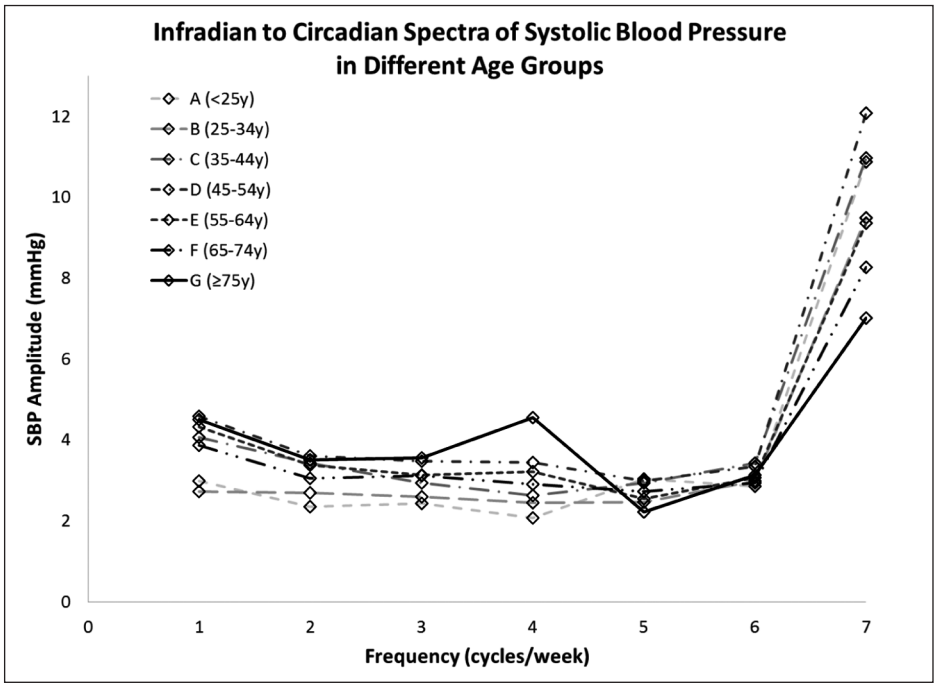

Figure 7: *Phase-unweighted population-mean least squares spectra of systolic blood pressure in the infradian-to-circadian frequency domain. A decrease in circadian amplitude as a function of age is accompanied by increased amplitudes of components with periods longer than one day.* © Halberg Chronobiology Center.

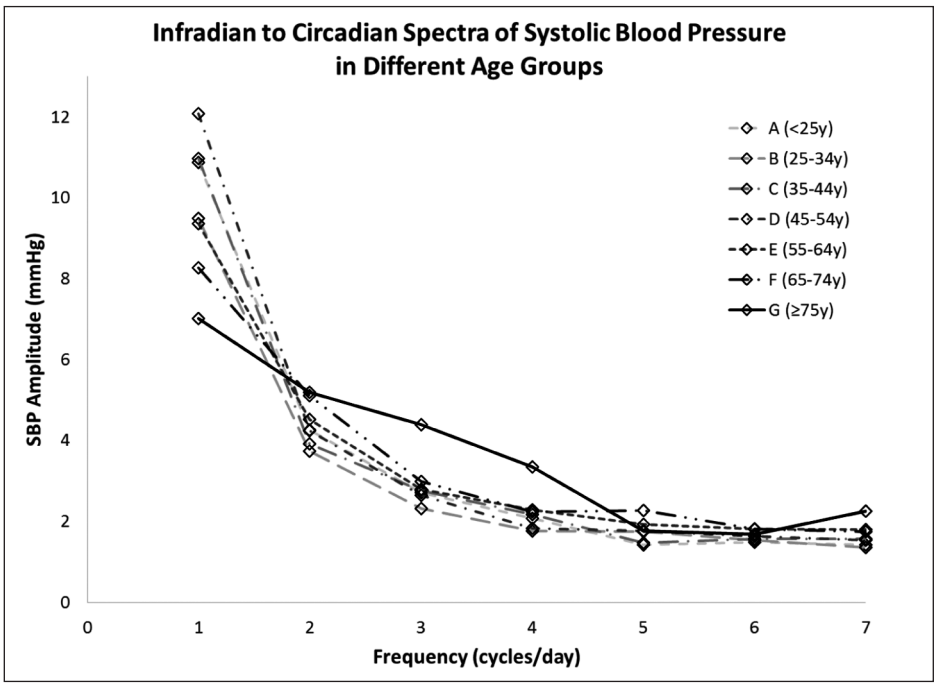

Figure 8*: Phase-unweighted population-mean least squares spectra of systolic blood pressure in the circadian-to-ultradian frequency domain. A decrease in circadian amplitude as a function of age is accompanied by increased amplitudes of components with periods shorter than one day.* © Halberg Chronobiology Center.

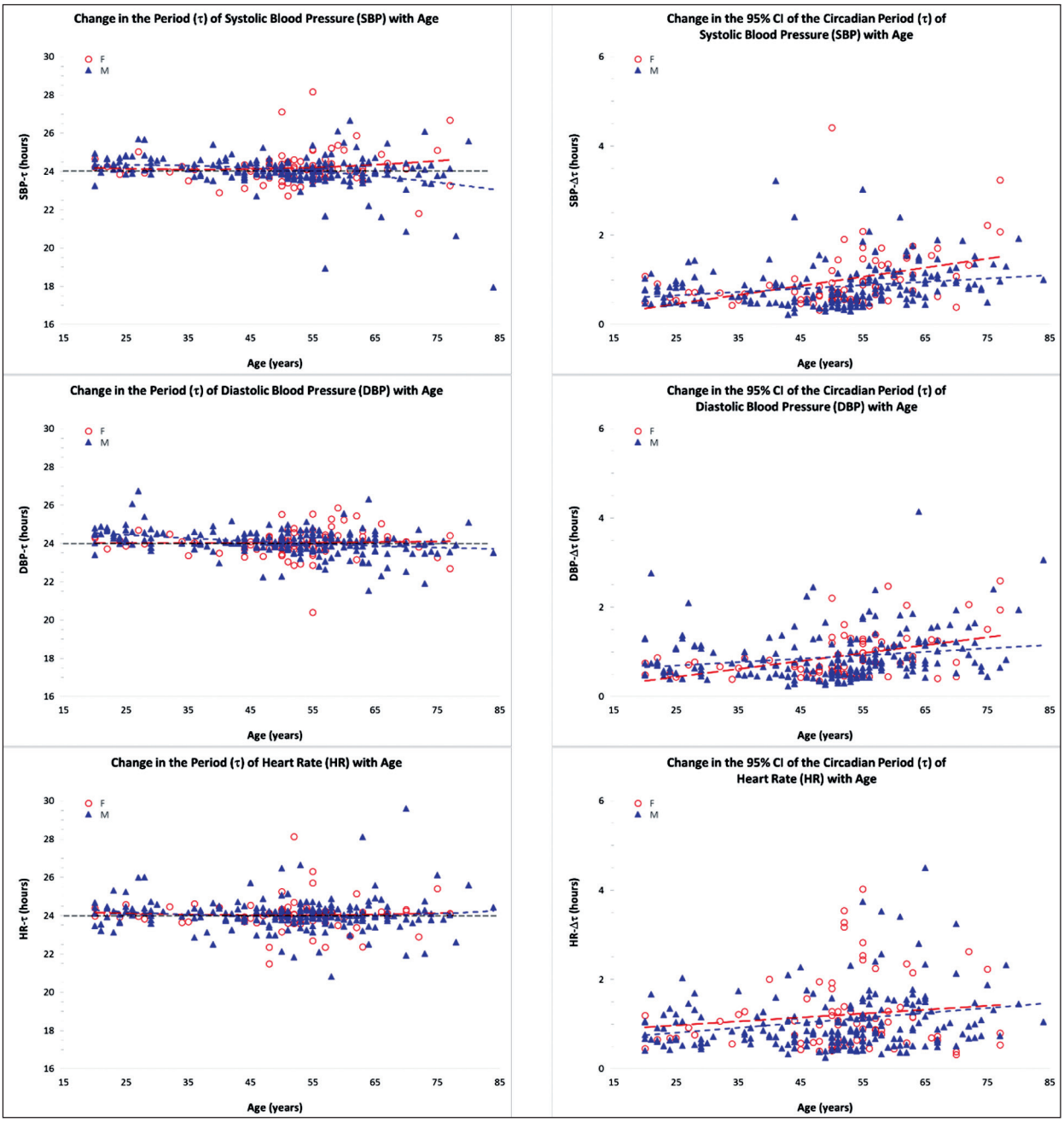

Figure 9: *With increasing age, the circadian period is more likely to deviate from 24 hours (left) and the width of its 95% confidence interval increases (right). The latter is statistically significant, except for women's heart rate.* © Halberg Chronobiology Center.

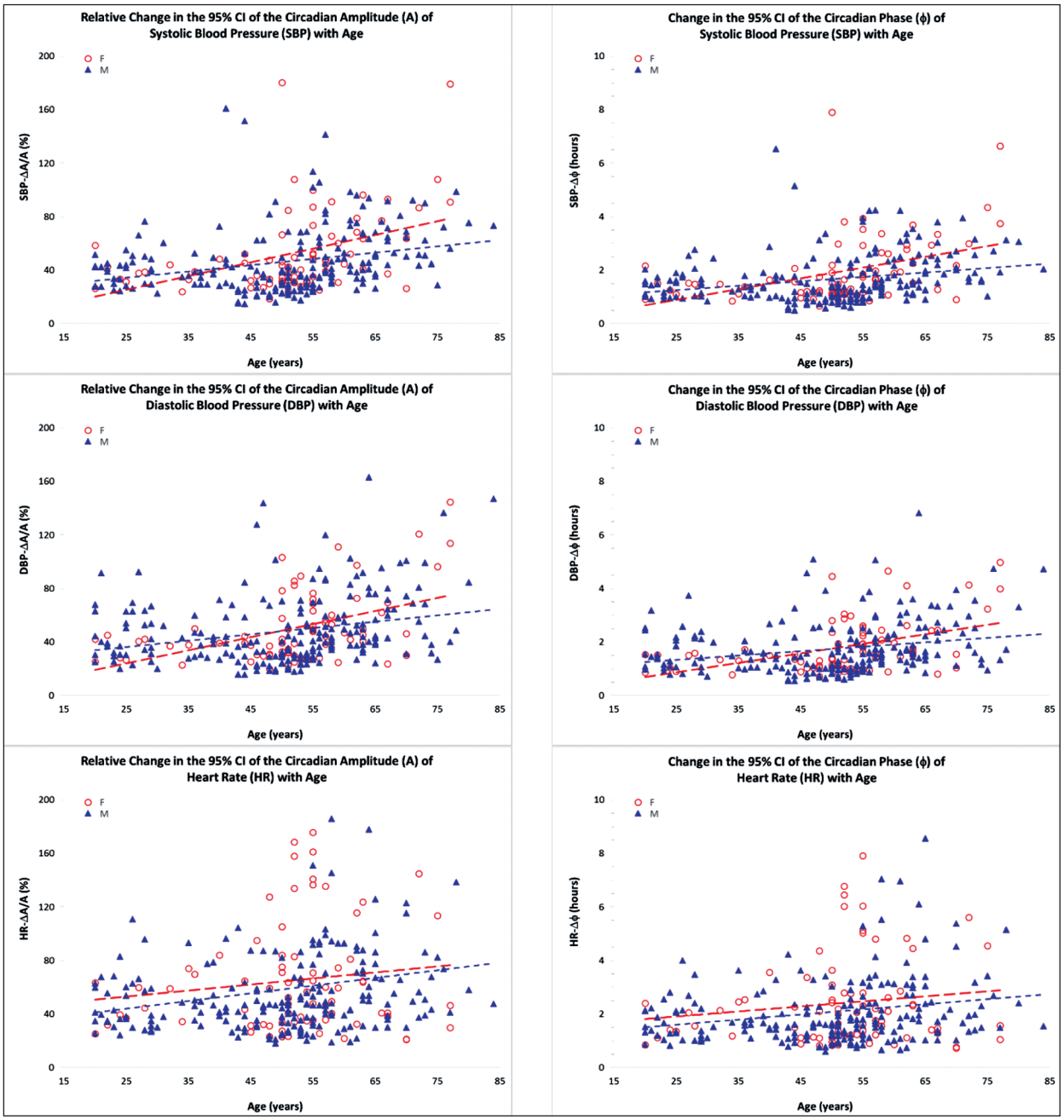

Figure 10: *The width of the 95% confidence interval of the circadian amplitude (normalized by the amplitude) (left) and acrophase (right) increases with age. Results are statistically significant, except for women's heart rate.* © Halberg Chronobiology Center.

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Lessons Learned from Worldwide Chronobiologically-Interpreted Blood Pressure Monitoring

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Dedicated to the memory of Franz Halberg who led the way on this journey.

Introduction

Only recently do guidelines [1] start considering the circadian variation in blood pressure (BP). For a long time, fixed limits of 140/90 mmHg (systolic/diastolic BP) were used to diagnose hypertension in all adults 18 years and older. The circadian rhythm in BP was thought to primarily reflect the rest-activity schedule rather than being in part endogenous [2]. While this is no longer the case, ambulatory BP monitoring is still restricted to "special cases", often limited to 24 hours. Evidence is presented herein for the need to routinely screen for BP and heart rate (HR) variability, and for continued monitoring in patients in need of treatment.

Self-measurements

Before the availability of devices for the automatic measurement of BP, chronobiologists relied on self-measurements taken a few times a day for two or more days to assess the circadian variation. Sampling requirements were specified [3] that include the need for at least one nightly measurement, preferably taken by another person in order not to disturb the subject's sleep, Figure 1. Despite the obvious shortcomings of self-measurements, usually taken with a mercury sphygmomanometer, important findings were made that laid the foundation for recognizing the importance of BP variability. Children with a positive family history of high BP and/or related cardiovascular diseases were found to have a larger circadian amplitude of BP than children with a negative such family history in several studies in schools in Italy, Portugal, and several states in the USA (Arkansas, Connecticut, and Minnesota) [4-13]. This result was later extended to neonates [14] once devices for the automatic around-the-clock monitoring of BP became available, in studies conducted in Minnesota, Italy, Japan, Russia, the Czech Republic, and Spain.

The Arteriosonde: an analog blood pressure monitor

In adults, the first automatic around-the-clock measurements of BP were obtained with the Arteriosonde, within the scope of the Minnesota-Kyushu study of breast cancer risk [15]. This analog device necessitated the manual taking off of data from graphic recordings. Despite this limitation, cardiovascular disease risk was related to the circannual amplitude of both BP and circulating aldosterone, Figure 2 [15, 16].

Portable Nippon-Colin BP monitor

With a portable – albeit not ambulatory – monitor from Masayuki Shinoda (Nippon Colin, Komaki, Japan), our first truly automatic BP measurements were collected. It was instrumental in demonstrating that BP increases toward mid-sleep, well before awakening, the latter associated with a larger and faster increase in BP [17], thus providing indirect evidence for the partly built-in nature of the circadian BP rhythm. Indirect evidence for the endogenous nature of the circadian variation in BP had been obtained much earlier by free-running: the circadian period of systolic BP of an afebrile boy with intermittent fever deviated statistically significantly from 24 hours, whereas it remained 24-hour synchronized for core temperature measured concomitantly around the clock [18].

The portable Nippon-Colin BP monitor also served to demonstrate the novelty effect and to assess the extent of day-to-day variability in circadian rhythm characteristics [19-21]. We showed that by extending the monitoring span from 24 to 48 hours, the uncertainty on the estimation of circadian parameters was reduced by 30%, with another 10% gain by prolonging the record to 7 days [7, 19].

Ambulatory BP monitoring

The next model from Nippon Colin was the ABPM-630, which operated on gas cartridges. It allowed us to collect around-the-clock data in several populations of clinically healthy individuals on 3 continents from neonates to centenarians, and during pregnancy [22-26]. These data were essential to derive time-specified reference values qualified by gender and age, on which our sphygmochron analysis is based [27-29]. They were critical for the assessment of outcomes from prospective as well as retrospective clinical trials [30].

The latter corroborated the risk associated with an excessive circadian amplitude of BP (CHAT, brief for Circadian Hyper-Amplitude-Tension). Outcome studies in Japan, Taiwan, Minnesota, the Czech Republic, and Germany further identified other abnormalities in the variability of BP and heart rate, which we named Vascular Variability Disorders (VVDs). Ongoing monitoring around the world by BIOCOS investigators and others, first with the ABPM-630, then with the TM-2421 and TM-2430 from A&D (Tokyo, Japan), continues to accumulate evidence for the need to routinely screen for VVDs and for the continued monitoring of patients in need of anti-hypertensive treatment [31].

Treatment is best optimized by timing (chronotherapy) on an individualized basis [32]. VVDs were found to occur in each cooperating center, Figure 3 [33]. Some VVDs were shown to be treatable. Indirect evidence documents that the elimination or reduction of CHAT reduces by more than a factor 2 the incidence of adverse cardiovascular events [34].

Discussion and Conclusion

As illustrated above, important lessons were learned from BP monitoring, which now await introduction into routine clinical care with focus on both primary and secondary prevention. Many more applications can benefit from a chronobiologic approach to BP monitoring, such as the determination of healthy lifestyle choices, in terms of tobacco use [35], alcohol consumption [36], salt intake [37], and prayer [38].

Longitudinal monitoring of BP also contributes invaluable information for health surveillance, for monitoring of the environment (e.g., pollution), and even for gaining a better understanding environmental and cosmic influences on physio-pathology [39, 40].

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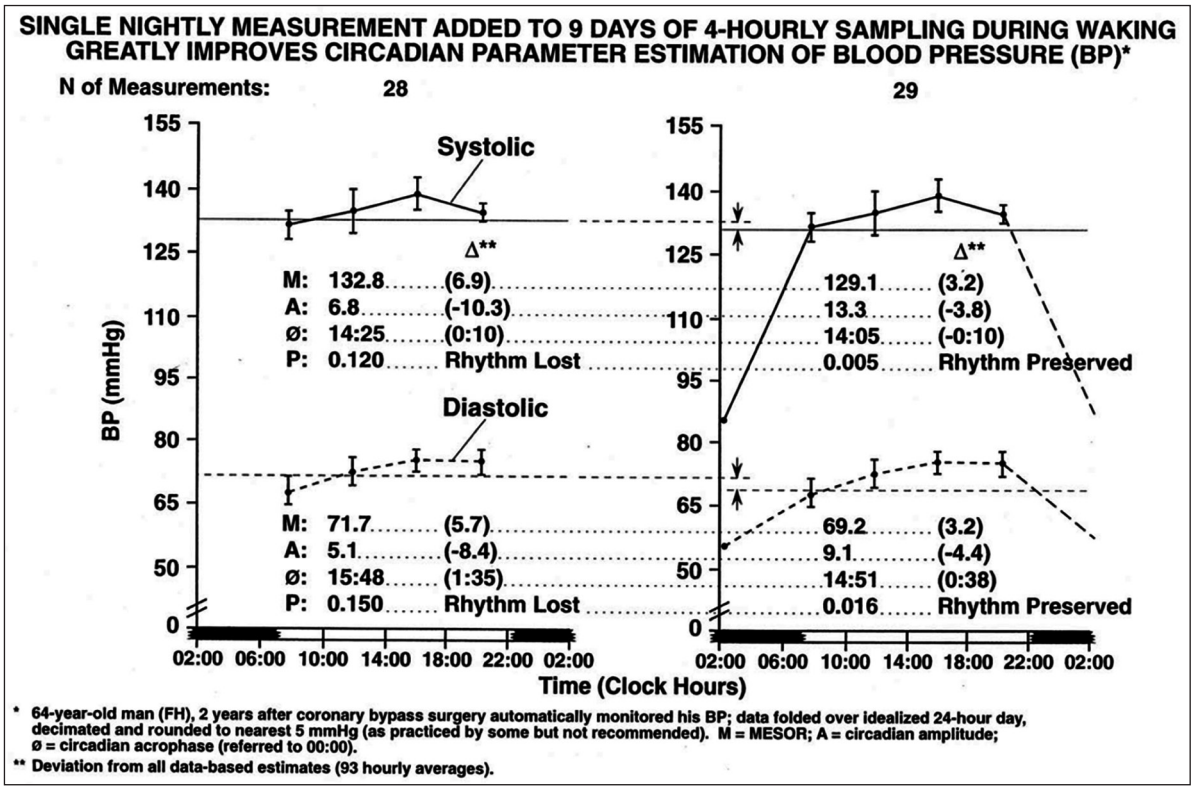

Figure 1: *Illustration of the need for nightly measurements of blood pressure to obtain a more reliable estimation of its circadian variation.* © Halberg Chronobiology Center.

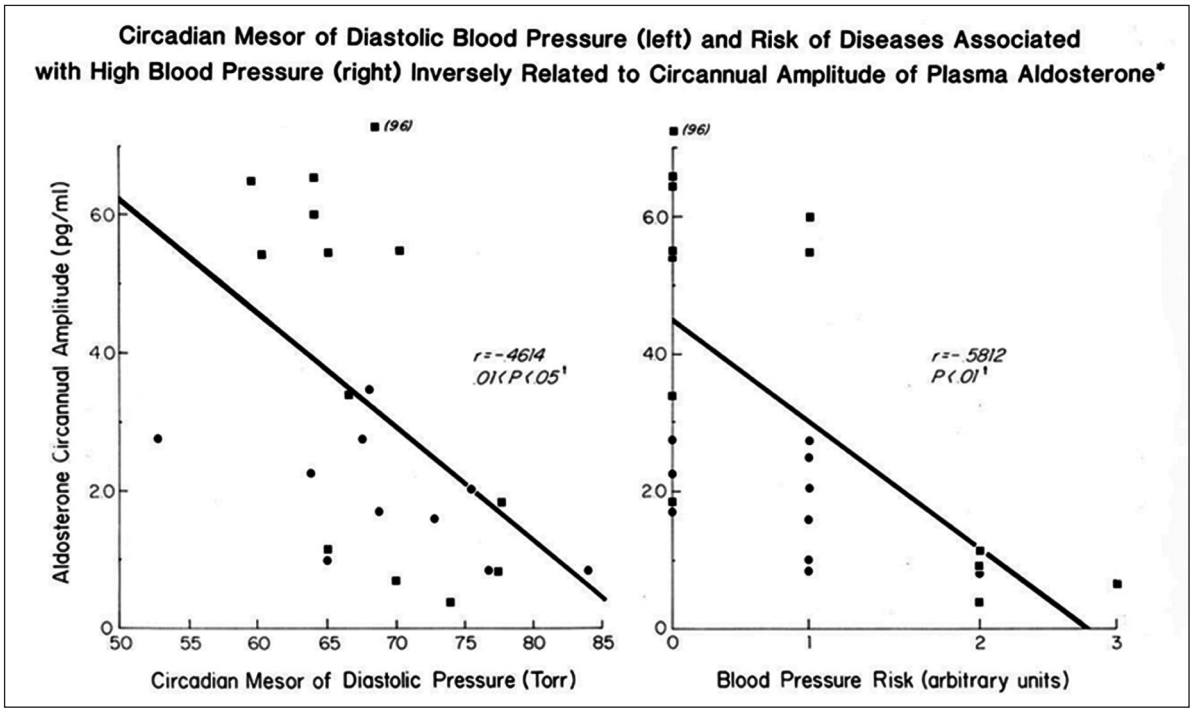

Figure 2: *Cardiovascular disease risk and diastolic BP are both related to the circannual amplitude of aldosterone [15].* © Halberg Chronobiology Center.

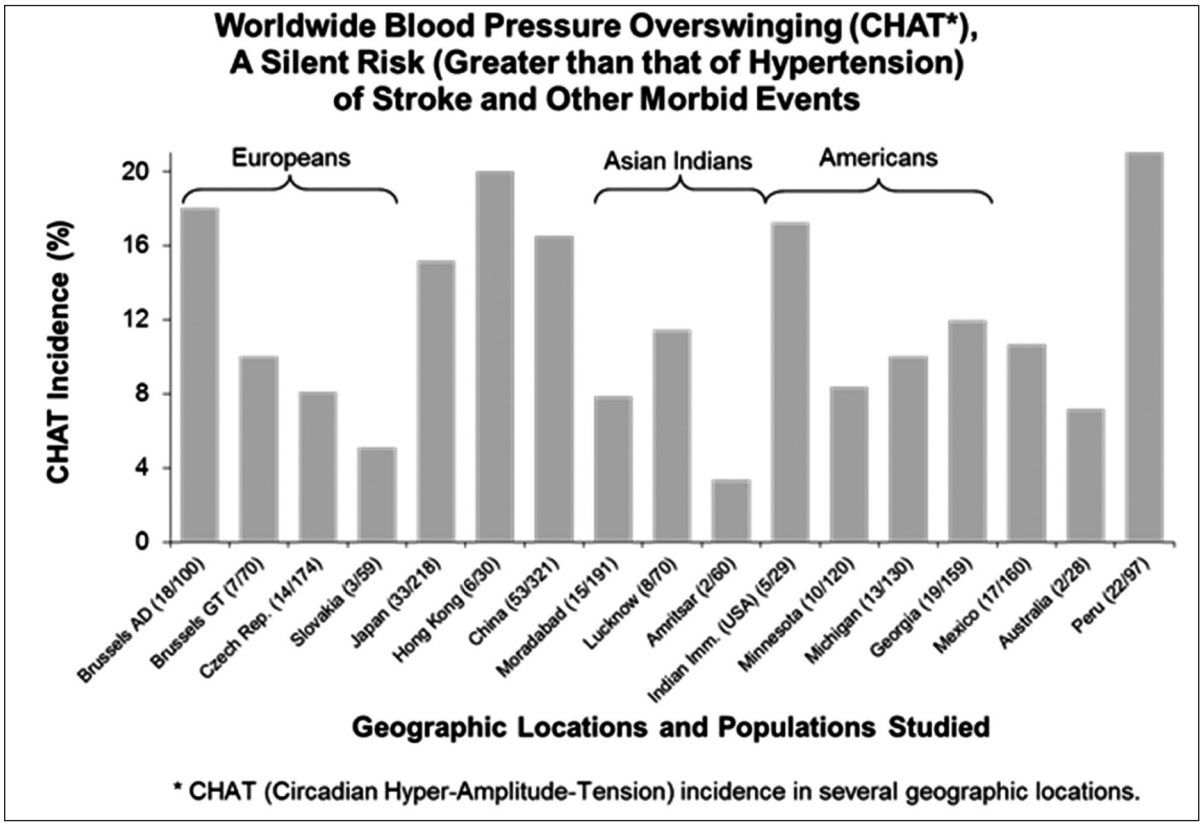

Figure 3: *Vascular Variability Disorders (VVDs) such as CHAT (Circadian Hyper-Amplitude-Tension) are detected in different geographic locations.* © Halberg Chronobiology Center.

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Three Hypertensive Patients' Ambulatory Blood Pressure Reduced by Acupressure

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Aim

This study aimed at determining the effectiveness of acupressure at the HE GU (LI-4), GOKOKU point in lowering blood pressure in a small sample of three patients. Any effect on blood pressure variability was also examined.

Introduction

Ancient traditional Chinese medicine texts include a wide range of indications for Chinese HE GU (LI-4) (in Japanese, GOKORU) point -- from headaches and constipation to general pain (1). Today, it is clinically used for "stress", facial pain, headaches, toothaches and neck pain (2, 3). This point has been extensively studied through randomized, controlled trials and clinical research. Recent studies from the Journal of Orofacial Pain showed that the stimulation of HE GU (LI-4) (GOKORU) point significantly reduced myofascial pain of the jaw muscles (2). A recent systematic Cochrane review on acupuncture in migraine and tension-type headaches suggests stimulation of acupoints is an effective and valuable option for alleviating migraines and tension-type headaches (3).

HE GU translates in English as "union valley". HE GU (LI-4) (GOKORU) is located at the highest point of the muscle when thumb and index fingers are held close together, a dime-sized spot on the top of the hand, located between the thumb and the forefinger. An effect of acupressure at HE GU (LI-4) (GOKORU) on blood pressure (BP), however, is not well-known. The possibility of lowering BP by non-pharmacologic means was demonstrated earlier by us, using interventions such as autogenic training (4-7).

Subjects and methods

Three female hypertensive patients, aged 38–68 years (mean ± SD: 53.7 ± 15.0), participated in the study between March and September 2016. All 3 patients were seen at the outpatient clinic of Tokyo Women's Medical University, Medical Center East, or at the Nippori Clinic, in Japan. Despite treatment by non-pharmacologic interventions, such as sodium restriction, for one month or longer, they had not reached the goal for systolic (S)/diastolic (D) BP values below 140/90 mmHg, as recommended by the Japanese Society of Hypertension (JSH) (8).

Patients were taught how to self-administer acupressure at the HE GU (LI-4) (GOKORU) point, Figures 1-4. They performed acupressure for 5 minutes on each hand two or three times a day. Instructions were provided as follows: "The HE GU (LI-4) (meaning "union valley" in English) point

is a dime-sized spot on the top of the hand, located between the thumb and the forefinger. This point is located at the highest point of the muscle when thumb and index finger are held together. Locate the point between the web of the first and second finger. When applying acupressure, try to relax and breathe deeply as you massage this area. To use acupressure at this point, locate the point, then use deep, firm pressure to massage and stimulate the area for 4-5 seconds. The massage and the acupressure can be done by yourself, or by someone else who is there to assist you."

Before starting acupressure and at monthly intervals thereafter, each patient automatically measured SBP, DBP, and heart rate (HR) around-the-clock at 30-minute intervals for 7 days, using the TM-2430 ambulatory monitor from A&D (Tokyo, Japan).

Each ABPM record was analyzed by sphygmochron (9, 10). This method involves the least squares fit of a two-component model consisting of cosine curves with periods of 24 and 12 hours to the data, complemented by a non-parametric comparison of the subject's profile to time-specified 90% prediction limits derived from data obtained by clinically healthy peers matched by gender and age. Estimates of the MESOR (Midline Estimating Statistic Of Rhythm, a rhythm-adjusted mean) and of the 24-hour amplitude (half the extent of predictable change within a day based on the 24-hour cosine fit) on treatment were compared to those before start of treatment by Student t-test. Estimates of the standard deviation (SD) of HR and of pulse pressure (PP = SBP-M – DBP-M) were similarly compared.

Results

Table 1 lists estimates of the MESOR and 24-hour amplitude of SBP, DBP and HR of each subject after 1, 2, and 3 months of treatment, compared to before treatment. Results for PP and HR-SD are also displayed. Since not all subjects provided a 7-day ABPM record at each monthly follow-up, responses from all 3 subjects at all 3 follow-up times were pooled.

As seen from Table 1, SBP-M was invariably decreased on treatment as compared to before treatment. On the average, SBP-M was reduced by 5.0 ± 2.1 (SE) mmHg in association with acupressure (Student t = 2.308, P=0.041; one-tailed test). On the average, the circadian amplitude of SBP was also reduced by 6.8 ± 3.1 mmHg on treatment (Student t = 2.183, P=0.047; one-tailed test). The MESOR and circadian amplitude of DBP were also reduced, albeit to a lesser extent: DBP-M was lowered by 2.1 ± 1.4 mmHg and DBP-2A by 1.9 ± 1.1 mmHg. A statistically significant decrease of 3.6 ± 1.2 mmHg in PP was demonstrated (Student t = 2.998, P=0.020; two-tailed test).

Discussion and conclusion

Results on these very few subjects suggest that acupressure at the HE GU (LI-4) (GOKORU) point may also be effective in relation to blood pressure in addition to its effects on pain and headaches. Not only was the MESOR of blood pressure reduced, but the procedure was also associated with a reduction in pulse pressure and in the circadian amplitude of blood pressure. If confirmed on a larger sample size, this finding may be important since an excessive pulse pressure and an excessive circadian amplitude of blood pressure are vascular variability disorders documented to increase cardiovascular disease risk beyond that associated with an elevated BP MESOR (11, 12).

Both conditions were diagnosed in one of the three subjects before treatment and were no longer present during treatment. Too large a pulse pressure was also diagnosed in another subject for whom treatment reduced it, but not sufficiently to bring it within acceptable limits.

After the several acupressure sessions, participants feel the warmth in their upper body. This feeling may be caused by dilation of the peripheral blood. The reduction of SBP can be accounted for by the vasodilation effect of acupressure.

This non-pharmacologic approach to reducing the average blood pressure as well as other abnormalities in blood pressure variability is relatively easy to implement. It can be done without help by another person and it is not overly time-consuming. Further studies should examine whether these results can be extended to larger sample sizes and whether the effect can be sustained on a longer than 3-month basis.

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Table 1. *Individual responses to acupressure*

Subject ID	SBP-M	DBP-M	HR-M	SBP-2A	DBP-2A	HR-2A	HR-SD	PP
Before treatment								
01NM	153.70	88.50	78.70	38.47	17.07	20.15	11.87	65.20
02AM	139.80	70.90	63.10	25.70	12.01	9.63	6.40	68.90
03FN	139.80	88.30	63.00	7.72	8.61	19.57	10.94	51.50
After 1 month of treatment								
01NM	140.60	81.50	74.00	24.19	13.94	19.66	13.44	59.10
02AM	139.00	71.30	63.60	23.04	10.18	12.96	8.03	67.70
03FN								
After 2 months of treatment								
01NM								
02AM	135.30	69.50	64.20	16.24	8.39	12.64	7.24	65.80
03FN	135.50	85.40	62.50	10.86	11.01	18.46	12.03	50.10
After 3 months of treatment								
01NM								
02AM	137.70	71.20	61.00	14.81	8.62	10.53	5.69	66.50
03FN								

SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; HR: Heart Rate; PP: Pulse Pressure

M: MESOR (rhythm-adjusted mean); 2A: double 24-hour amplitude (extend of predictable change within a day); SD: standard deviation.

SBP, DBP, PP expressed in mmHg; HR expressed in beats/min.

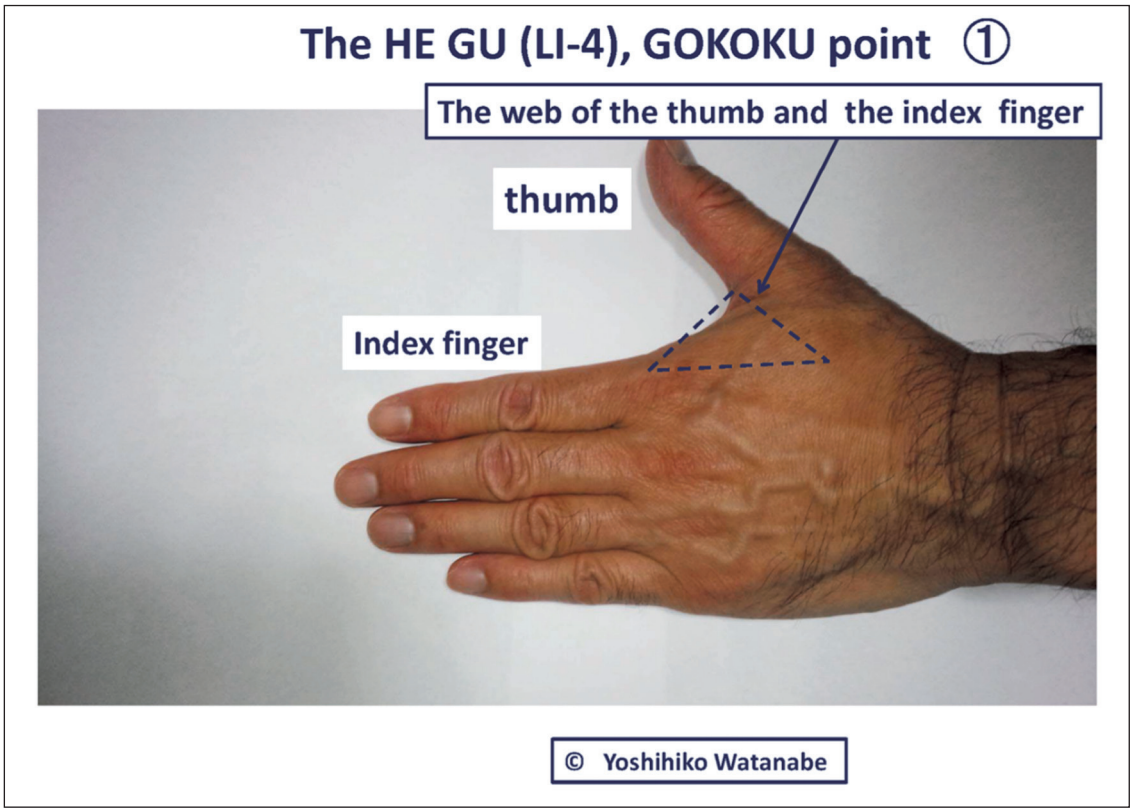

Figure 1: *Locating the HE GU (LI-4), GOKORU point.*

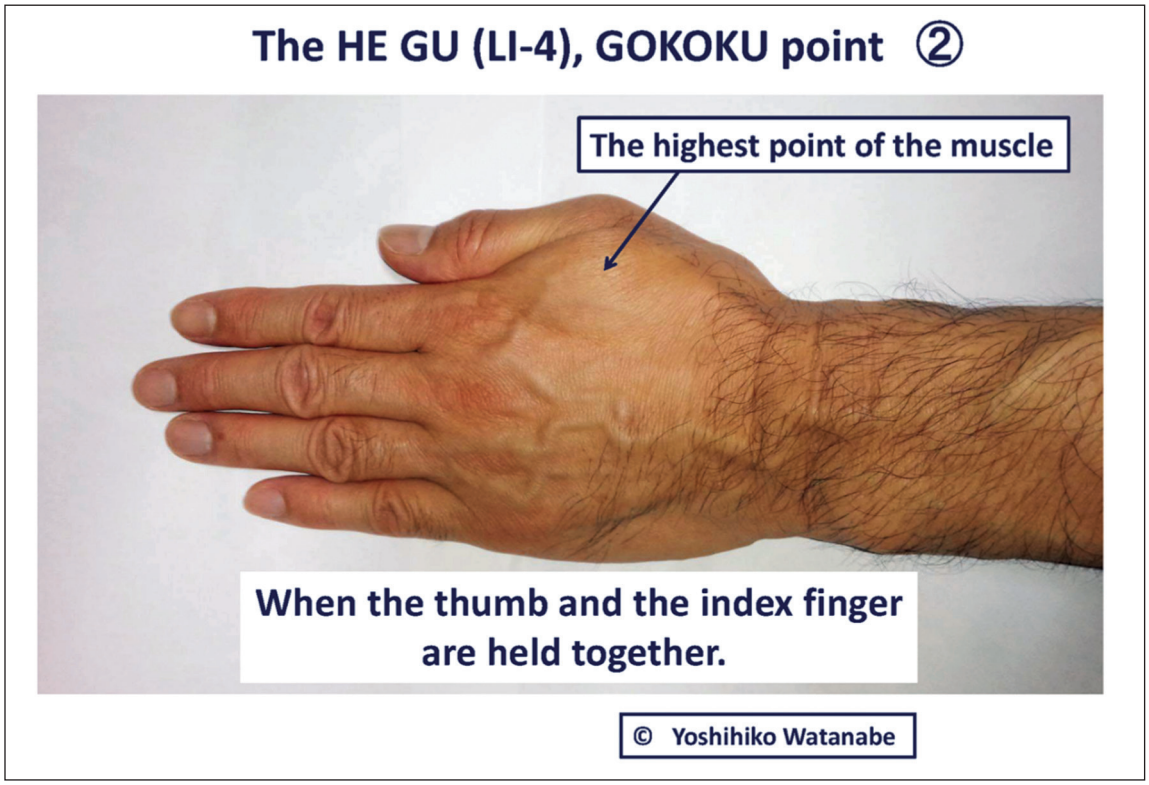

Figure 2: *Locating the area of the HE GU (LI-4), GOKORU point to be massaged and stimulated. First, find the highest point of the muscle when the thumb and index finger are held together.*

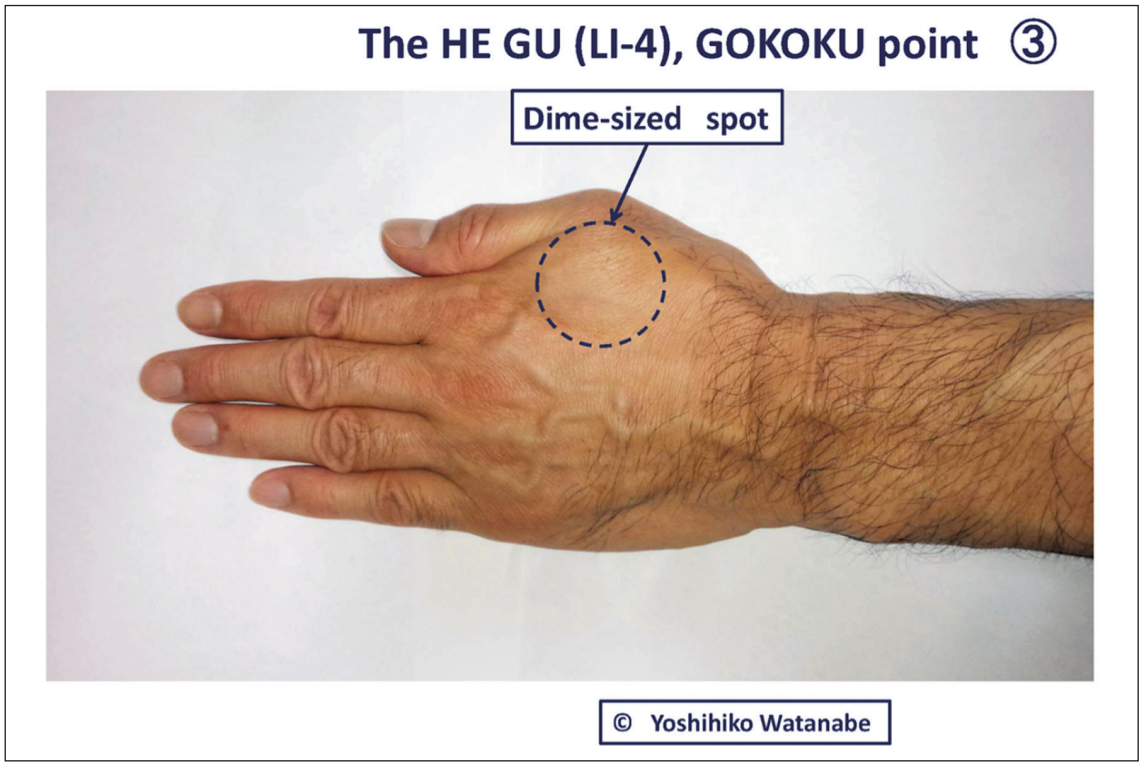

Figure 3: *Locating the area of the HE GU (LI-4), GOKORU point to be massaged and stimulated: dime-sized spot at the highest point of the muscle when thumb and index finger are held together.*

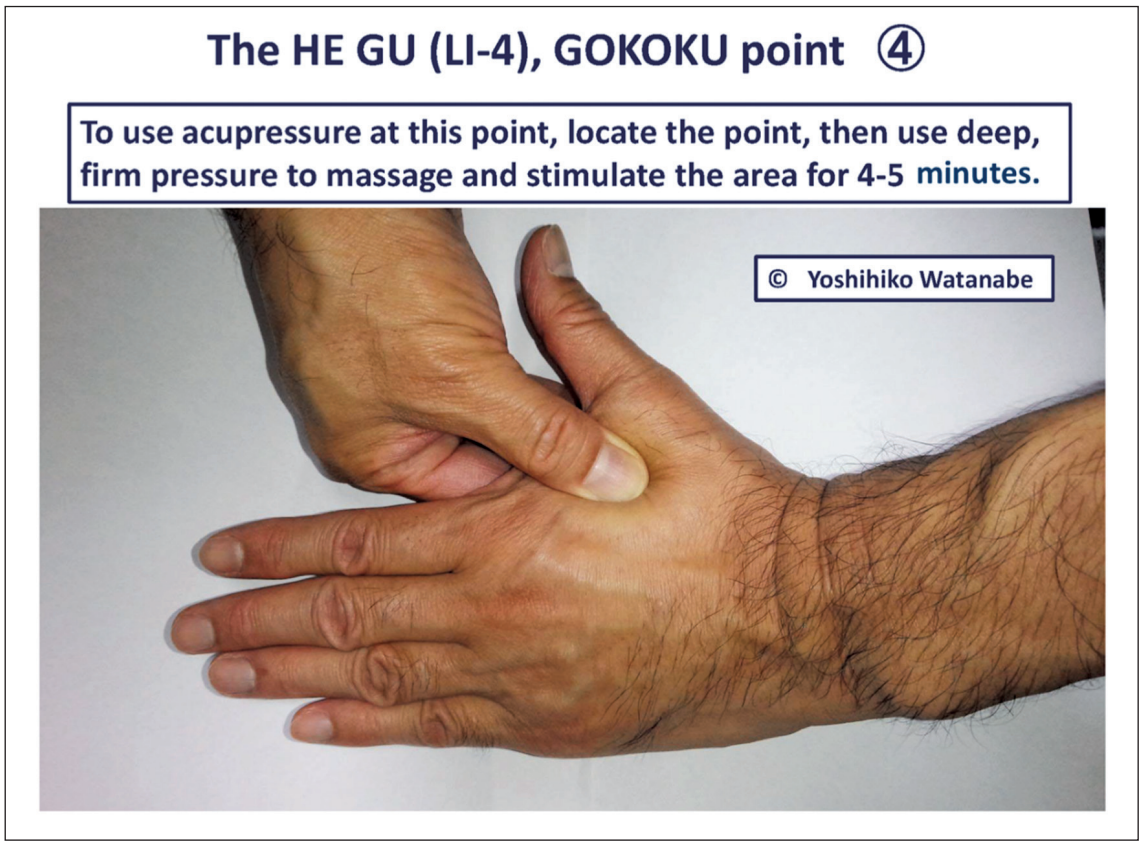

Figure 4: *How to massage and stimulate the HE GU (LI-4), GOROKU point for 4-5 minutes on each hand.*

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Changes with Age in the Circadian Rhythm of Circulating Melatonin

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Abstract

A number of variables are known to decrease in circadian amplitude as we age, and advance in circadian phase: prolactin, estrogens (E1 and E2), 17-OH-progesterone, aldosterone, DHEA-S. The same has been found in blood pressure and heart rate. Various coronary artery disease (CAD) factors are known to be lowered by melatonin treatment. Here we look at the effect of age and gender on the circadian rhythm (MESOR, amplitude and acrophase) of melatonin. Circulating melatonin was measured every 4 hours for 24 hours in 345 mostly healthy subjects from Florence, Italy. A circadian rhythm was clearly identified using 24-hour cosinor of $\log_{10}$-transformed data. Linear and quadratic regressions clearly show a decreasing circadian amplitude of melatonin with age. A plateau or uptick in melatonin amplitude is seen for the oldest age group, in quadratic regressions, possibly reflecting a healthier melatonin amplitude and better overall health in those who live longer. Parameter tests on the results from population-mean cosinor analyses show the MESOR is higher in women than men, and the amplitude is larger in men than in women. And the acrophase shifts earlier by about one hour in men.

Introduction

Melatonin is a primary factor in the modulation of circadian rhythms, acting as a synchronizer of hormones and systems throughout the body, including the sleep/wake cycle. Circulating melatonin peaks as you become drowsy, and drops when you awaken. Blue light, a component of daylight (sunlight) on earth, is believed to be a synchronizer for melatonin. Melatonin is reduced upon exposure to blue light. Electronics and some types of LED lighting give off blue light, and can interfere with normal circadian rhythms, especially after evening exposure (Stevens et al., 2013). Circadian disruptions are associated with negative health effects, and are thus important to predict and understand.

Melatonin has been observed to lower blood pressure, and when given before bed, it amplifies the night-time dip, increasing circadian amplitude (Grossman et al., 2006; Zaslavskaya et al., 2003; Zeman et al., 2005). Such an increase in amplitude is associated with increased health. Caution must be used, however, to be sure the amplitude does not become too large, as a blood pressure amplitude that is too large can also be unhealthy (Halberg et al., 2003).

Oxidative stress has been proposed as one of the major mechanisms leading to the development of pulmonary hypertension (Qiao et al., 2015). Melatonin is a very powerful free-radical scavenger and anti-oxidant, which may be how it reduces blood pressure. It also acts to enhance the effect of other

anti-oxidants. And unlike other radical scavengers, its metabolites are anti-oxidants (Anisimov et al., 2006). Vitamin E is the next most effective radical scavenger we know of, after melatonin, and it is only half as effective. Melatonin interacts with the immune system, creating an anti-inflammatory effect (Anisimov et al., 2006).

In addition to reducing blood pressure, melatonin treatment has been shown to reduce the pulsatility index in the internal carotid artery, decrease platelet aggregation, and reduce serum catecholamine and norepinephrine (but not epinephrine) concentrations (Arangino et al., 1999; Pandi-Perumal et al., 2016). Low circulating melatonin values are reported in individuals with CAD, arterial hypertension, and congestive heart failure (Pandi-Perumal et al., 2016). The morning reduction in melatonin may constitute one of the mechanisms of the morning peak in frequency of cardiovascular events.

Impacts and pathways of interaction are numerous. It will be beneficial to gain further insight into melatonin's impact on cardiovascular health.

Herein we further analyze melatonin data from a previously published study (Tarquini et al., 1997) to look at changes with age. A number of variables, including melatonin (Cornélissen et al., 2000), are known to decrease in circadian amplitude as we age. Prolactin, estrogens (E1 and E2), 17-OH-progesterone, aldosterone, DHEA-S all exhibit a circadian amplitude that is statistically significantly reduced in post-menopausal women as compared to adult menstruating women (Halberg et al., 1981). In addition, a number of variables also advance in circadian phase. We demonstrated in several populations that the circadian amplitude of blood pressure and heart rate decreased in older people, and the acrophase advanced (Zaslavskaya et al., 2003).

Table 1: *Decreased circadian amplitude with age of several hormones*

Hormone (units)	N	Group I	Group II	Group III
Prolactin (ng/ml)	29	12.4	16.5	11
E1 (pg/ml)	27	17.6	15.9	11.4
E2 (pg/ml)	26	28	28.4	8.1
17-OH Progesterone (pg/ml)	29	181	196	128
Aldosterone (ng/dl)	25	4.1	2.5	1.8
DHEA-S (ng/ml)	28	580	370	230

Note: Groups I and II: adult menstruating women; Group III: post-menopausal women. (Halberg et al., 1981)

Materials and Methods

Circulating melatonin was measured by radioimmunoassay from 345 (244 women, 101 men) mostly healthy subjects in two separate studies in Florence, Italy. Ages varied from 20 to 90 years (mean ± SD: 48.5 ± 17.1). Intra- and inter-assay coefficients of variation were 6.6% and 5.9%, respectively; sensitivity was 3 pg/ml. Measurements were taken every 4 hours over 24 hours (at 08:00, 12:00, 16:00, 20:00, 00:00 and 04:00).

The data were $\log_{10}$-transformed to normalize their distribution. One-way ANOVA was performed on the transformed data from a subset of 133 women and 61 men (study A), separately by gender,

across five age categories (20-25, 26-40, 41-60, 61-75, >75 years) to test the equality of the means at each of the 6 timepoints.

Each subject's data had previously been analyzed (Tarquini et al., 1997) by cosinor (Halberg, 1980; Cornelissen, 2014) to obtain estimates of the rhythm-adjusted mean (MESOR, Midline Estimating Statistic Of Rhythm), the amplitude and the acrophase (phase of maximum by reference to local midnight) of a 24-hour cosine. The procedure is illustrated for one subject in Figures 1 & 2, using the freely-available software CATkit (z.umn.edu/CATkit).

Regression with age was performed on the MESOR and amplitude for each gender. Both linear and quadratic regressions were done in each case. Each analysis was performed on the two study groups (A & B), separately, and together.

A population-mean cosinor was performed, by gender and age group, on individual MESORs, amplitudes and acrophases from the 24-hour cosinor fit, resulting in a population MESOR and a vectorial average of the circadian amplitude-acrophase pair. Tests comparing these resulting parameters (Bingham et al., 1982) were done to test the equality of circadian parameters between age groups and gender.

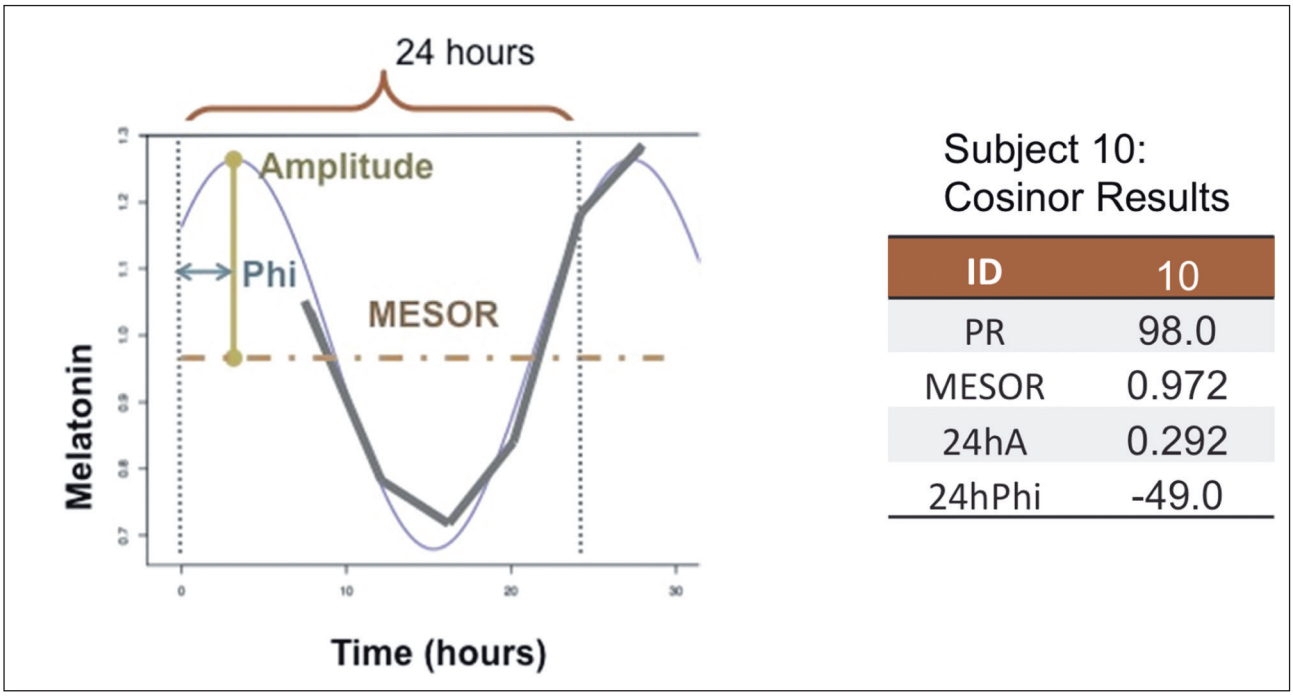

Figure 1: *Subject 10. Grey line is the time course of melatonin over 24 hours. The light blue line is the cosinor model used to estimate MESOR, amplitude and acrophse (phi).*

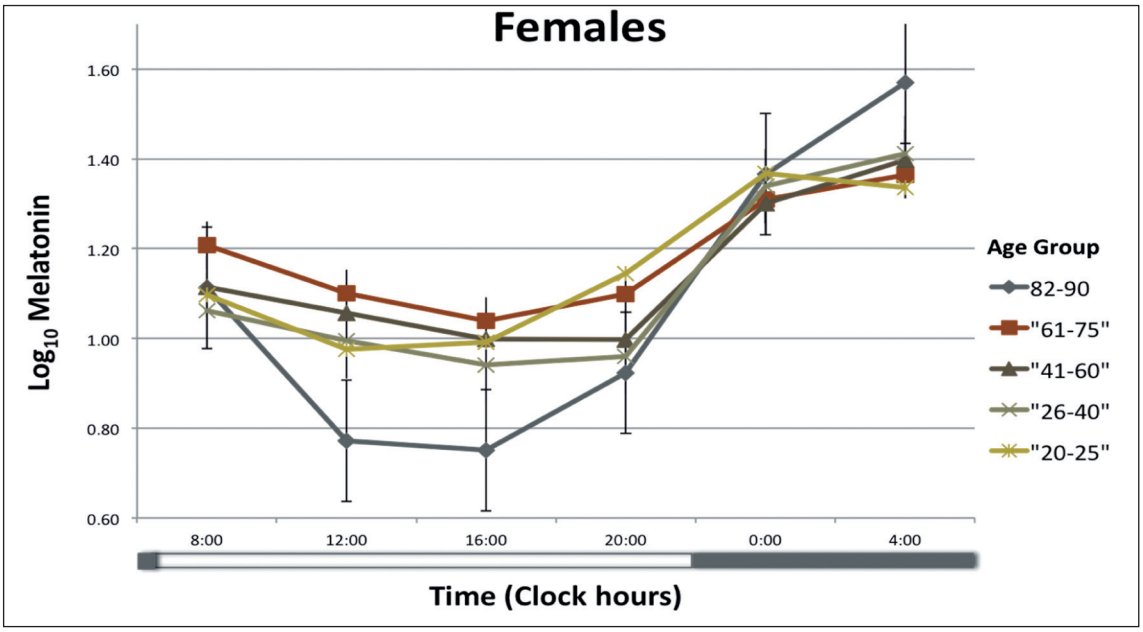

Figure 3: *Mean and SE melatonin at each sampling time, for 5 age groups in women of Study A. Notice the oldest age group has the largest swing, going lower in the day and higher at night.*

Results

Averages for each age group of the $\log_{10}$-transformed data from Study A are plotted in Figures 3 & 4. One-way ANOVA shows that differences in melatonin between the 6 time points are statistically significantly different from zero for both genders and all age groups, supporting the presence of a circadian rhythm (invariably $P<0.05$).

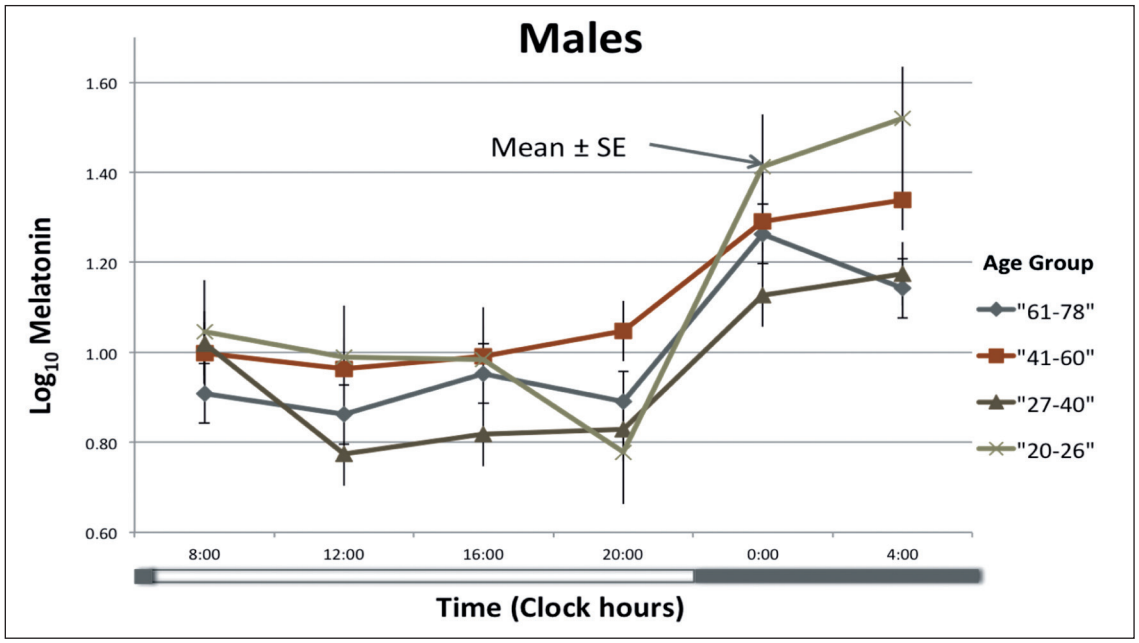

Figure 4: *Melatonin at each sampling time, for 4 age groups in men of Study A. Notice the youngest age group has the largest concentration at night. (One 78 year-old was included in the 61-75 group.)*

There are less than half as many men as women (244 vs 101) in the study. Also, there are only 5 men over the age of 75, in the combined studies, and only 1 in study A. With these qualifications, regression analyses of the cosinor-obtained MESOR with age (Figure 5) for the combined studies showed no statistically significant change across age groups.

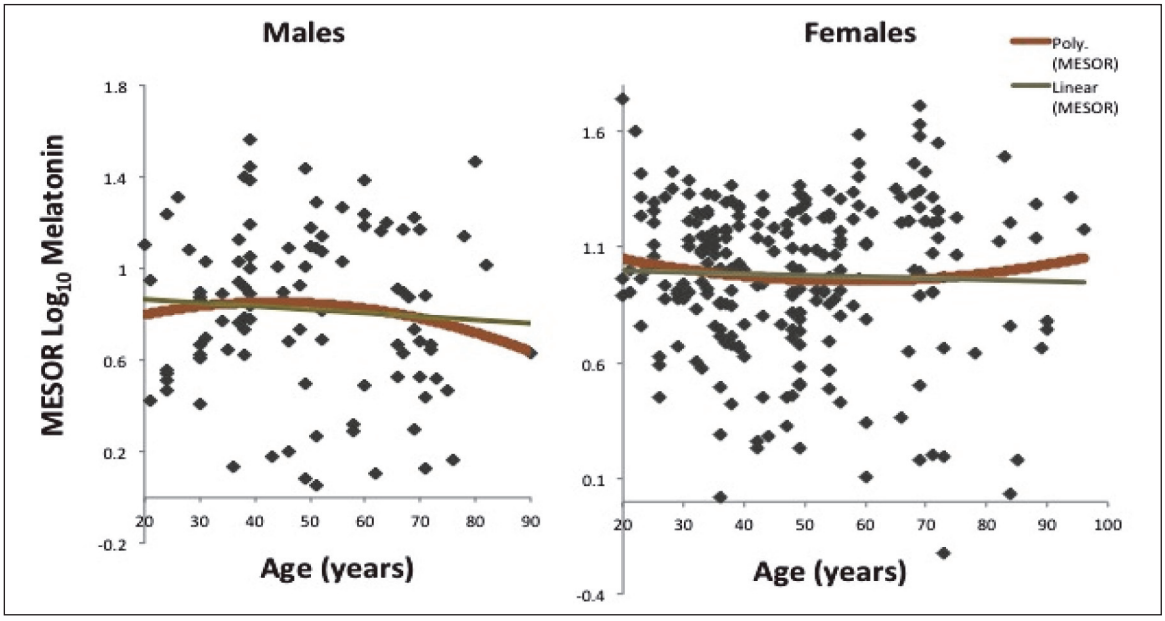

Figure 5: *MESOR of melatonin regressed over age*

The regression does show, however, a decrease in circadian amplitude with age in both men and women (Figure 6). But we are also seeing a possible uptick, or at least a leveling off of the decrease in amplitude. In men (Figure 6), there is a large uptick in amplitude in the oldest age group, albeit it may stem in part from the small number of men over 75 years.

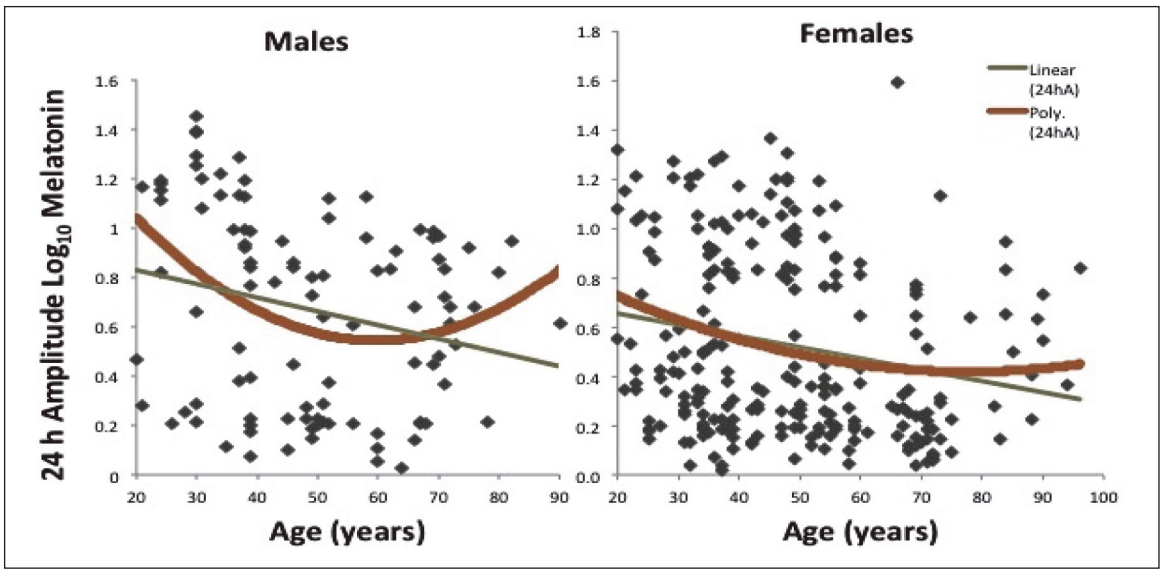

Figure 6: *24-hour amplitude of melatonin regressed over age*

Looking at the two studies separately, the uptick in amplitude was not consistently apparent in every grouping. Figure 7 shows results of regressions for Study B, where a decrease in amplitude with

age is again significantly present. The decrease in MESOR is also significant for females in Study B, where it was not in the combined studies, but it is not significant for males.

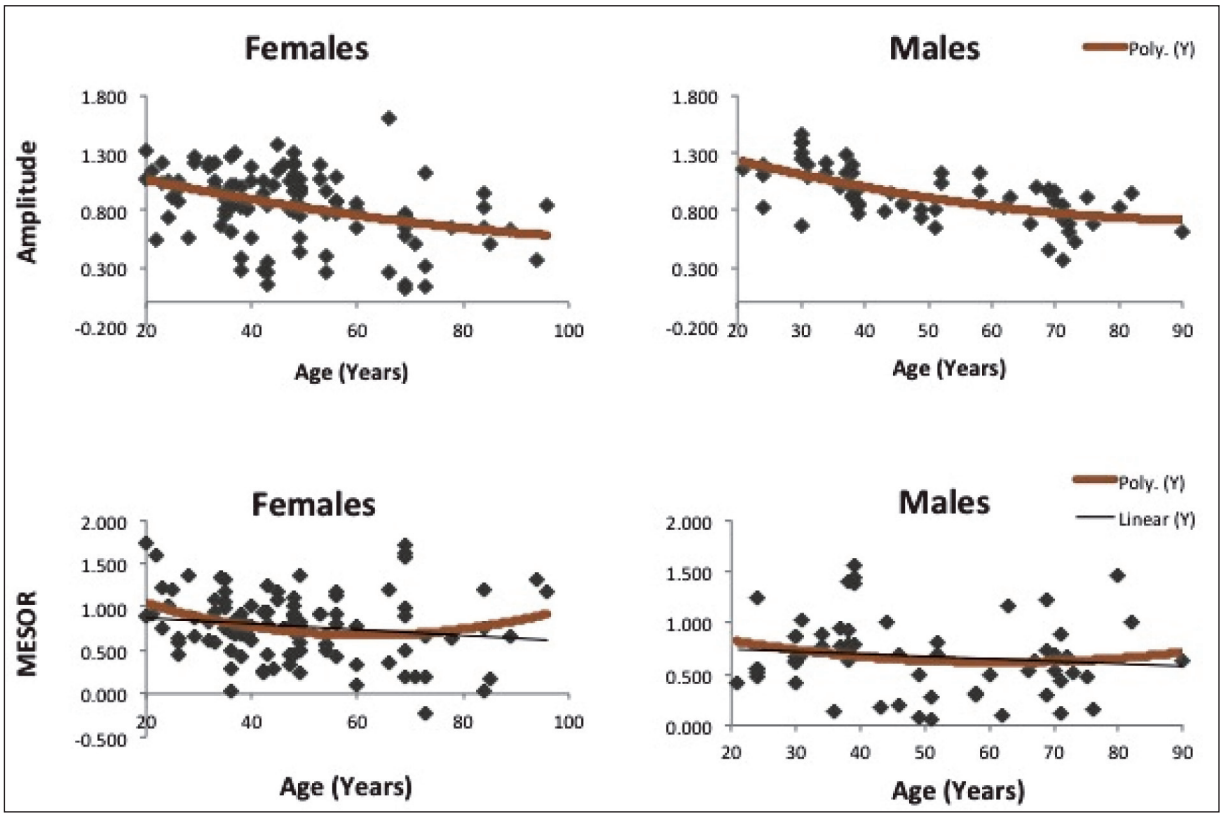

Figure 7: *The uptick in amplitude seen in the full population is not consistently present in Study B.*

The population-mean cosinor assesses the presence of a rhythm on a population basis, provided subjects represent a random sample of the population, as can be assumed in this study. It calculates a population MESOR and a vectorial average of the circadian amplitude-acrophase pair for the population from rhythm characteristics of individual subjects. This method is used to validate a circadian rhythm in the population; in this study, a circadian rhythm is validated for all age groups of both genders, except for the oldest age group in men, which is very small. Full results are shown in Table 2. Results from a comparison of circadian rhythm characteristics between men and women are shown in Table 3.

Table 2A: *Females: Population-mean cosinor results*

Age	Count	Mesor	Amplitude	Acro-phase	P-value
<26	22	1.058	0.666	-46	<0.001
27-40	77	0.988	0.504	-43	<0.001
41-60	89	0.933	0.484	-48	<0.001
61-75	40	1.048	0.287	-53	<0.001
>75	14	0.894	0.458	-48	<0.001

Table 3: *Parameter tests of Population-Mean Cosinor results*

Parameter(s)	F	P
Mesor	14.9131	0.0001
Amplitude	10.9342	0.0010
Acrophase	0.6308	0.4276
(A, phi)	5.4838	0.0043

Table 2B: *Males: Population-mean cosinor results*

Age	Count	Mesor	Amplitude	Acro-phase	P-value
<26	9	0.789	0.824	-52	0.003
27-40	33	0.893	0.78	-54	<0.001
41-60	31	0.822	0.473	-39	<0.001
61-75	23	0.719	0.563	-48	<0.001
>75	5	0.882	0.555	-37	0.106

Plots (Figures 8, 9, and 10) of the MESOR, amplitude and acrophase (obtained by population-mean cosinor) as they change across age groups, for each gender give a visual representation of these changes by age.

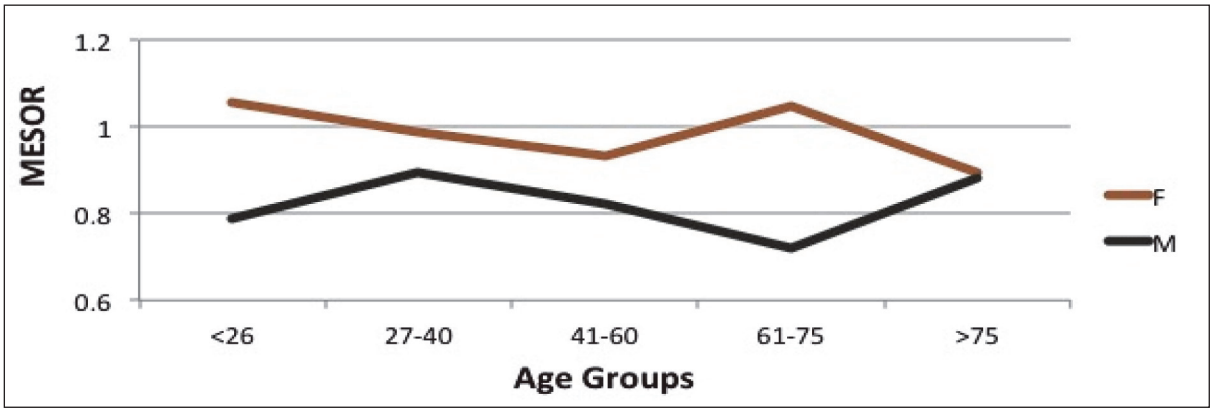

Figure 8: *Population-mean cosinor MESOR estimates in 5 different age groups: Parameter test comparing MESOR for men or women across age groups shows no significant difference across ages, for either gender (Men: F=0.86; P=0.49; Women: F=1.38; P=0.24) Women have a significantly higher MESOR than men (F=14.913; P=0.0001).*

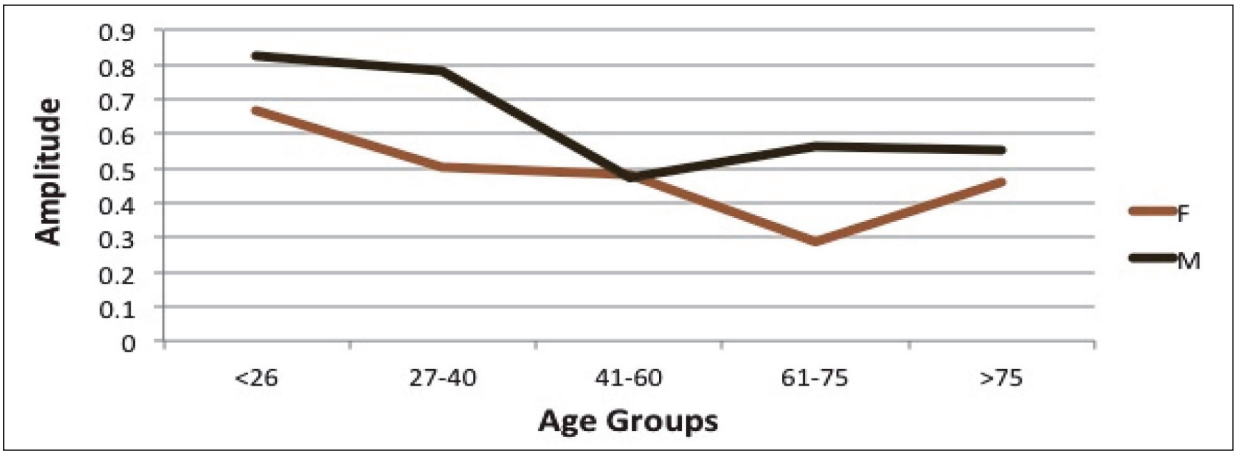

Figure 9: *Population-mean cosinor 24-hour amplitude estimates in 5 different age groups. Parameter test comparing amplitude for men or women across age groups shows there is a significant drop across ages, for both genders (Men F=3.26; P=.015; Women F=4.07; P=.0033). Men have a significantly higher amplitude than women (F=10.934; P=.001).*

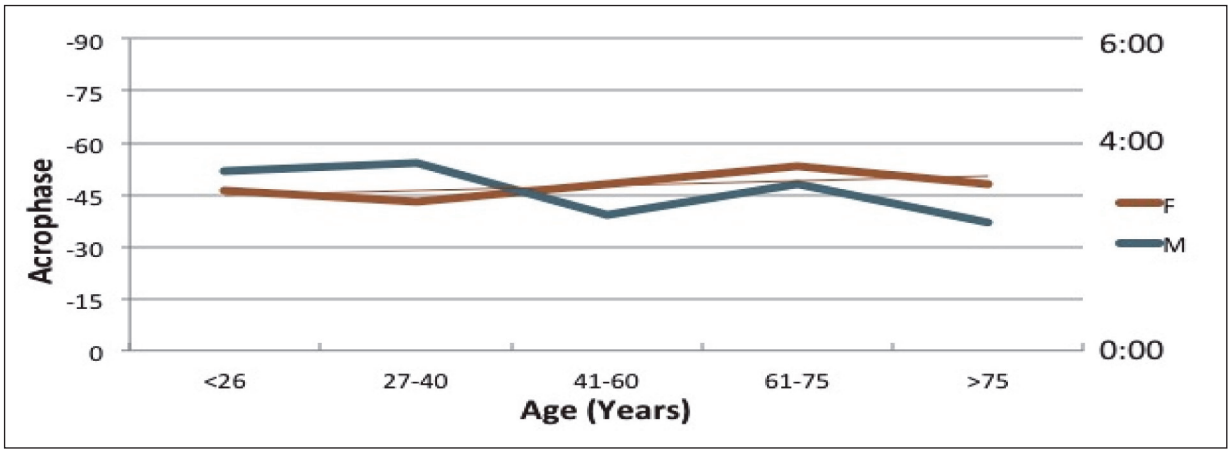

Figure 10: *Acrophase plot. Parameter test comparing acrophase for men or women shows there is a significant advance of log(Melatonin) acrophase across ages for men, but no significant change for women (Men: F=2.63, P=0.039; Women: F=0.698, P=0.594). Men (-52˚ → -39˚) ~52 min earlier; Women (-46˚ → 48˚). There is no significant difference between men and women acrophases.*

From Figures 8-10 it can be seen that

1. Circadian amplitudes of log(melatonin) fall with age in both women and men;
2. There is a plateau, or slight uptick in amplitude in the oldest women and men;
3. The circadian amplitude of log(melatonin) is higher in men than in women;
4. The MESOR of log(melatonin) is higher in women than in men;
5. The circadian acrophase shifts earlier by approximately 1 hour in men. No shift seen in women.

Conclusions

Numerous studies have found a decreasing amplitude and a phase advance with increasing age, in diverse variables, just as we have found with melatonin. Low circulating concentrations of melatonin are also reported in individuals with CAD, and congestive heart failure. Less well known is the possible plateauing or even rebound seen in the very old, although it has been observed in several endpoints of heart rate variability, including RR50, SDmean, and HF power (Otsuka, 1998).

The uptick or plateau may be a product of the oldest group being the healthier individuals, in view of the old age they have reached. Further study is needed. The uptick in amplitude of melatonin in the oldest age group further motivates the question of whether studies should carefully adjudicate the state of health or disease in elderly subjects and whether to include those who are not clinically healthy. Given that lower amplitudes are associated with both aging and the presence of disease in many variables, is the trend toward lower amplitudes in melatonin with aging, found herein, a reflection of disease status, or is it a reflection of aging?

One avenue toward unraveling the confounding of disease status and aging is through the use of longitudinal studies, where those who develop disease can be removed from the population, improving the ability to distinguish between “healthy” aging, and those who develop disease (or show pre-disease states) with aging. The trend toward increasing amplitudes in the oldest age groups supports a need for age- and gender-appropriate reference data, from longitudinal studies, which can provide a more refined understanding of what constitutes “healthy” patterns in circulating melatonin.

The Halberg Chronobiology Center has built this type of reference database for blood pressure and heart rate, based on gender- and age-appropriate metrics from healthy individuals, allowing a more accurate gauge of an individual's blood pressure health. We use this age-appropriate indicator to identify potential health risks, where the AMA uses single blood pressure measurements for individuals 18 years and older, of either gender.

A reference database of age- and gender-appropriate values for melatonin, or any molecule or variable, would be a step toward a more refined understanding of health, and more proactive diagnostics for practitioners.

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Seven Day /24 h Ambulatory Blood Pressure Monitoring: Circadian Variability of Pulse Pressure

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Introduction

Excessive pulse pressure is defined by a difference between systolic and diastolic blood pressure record more than 60 mmHg. Acceptable pulse pressure is below 60 mmHg. According vascular variability disorders excessive pulse pressure increase risk of increased cardiovascular morbidity and mortality (1-4). Excessive pulse pressure is evaluated from casual measurement of blood pressure. Casual blood pressure has great variability during 24-h and there are not enough information about the variability of the pulse pressure during seven day/ 24 hour blood pressure monitoring in man. From seven day /24 hour blood pressure monitoring it is possible by means of diagnosis of vascular variability disorders (VVD) evaluate also pulse pressure and other factors. Beside of increased mean 24-hours values of BP evaluated using Halberg cosinor analysis (we call it MESOR for rigorous mathematical approach and increased MESOR is an attribute of MESOR hypertension), there are excessive differences between day and night BP values (CHAT), the excessive pulse pressure and the decreased heart rate variability. Our results using the determination of pulse pressure by means of seven day/24h ambulatory BP monitoring showed increased variability of pulse pressure in every subject day by day and the seven day mean value of pulse pressure could show us the real risk of this parameter (5-16).

On October 6, 2008, consensus meeting held at Masaryk University, Brno, Czech Republic, St.Anna Teaching Hospital, proposed current guidelines for diagnosing high blood pressure, so-called MESOR hypertension, connected with other "Vascular Variability Disorders", Excessive pulse pressure, Circadian-Hyperaplitude-Tension, Deficient Heart Rate Variability, diagnosed on seven day/24 hour ambulatory blood pressure measurement. The leading scientist was Prof.Dr.Franz Halberg, d.h.mult. with other participants Prof. Dr. Germaine Cornelissen, Dr. Othild Schwarzkopff, University of Minnesota, USA, Halberg Chronobiology Center, Prof.Dr.Thomas Kenner, D.H.c.mult., University Graz, Austria, Prof. MUDr. Jarmila Siegelová, DrSc., Prof. MUDr.Bohumil Fišer,CSc, Prof. MUDr. Petr Dobšák,CSc., MUDr.Jiří Dušek, CSc, Prof. MUDr. Zdeněk Placheta, DrSc, MUDr. Pavel Homolka, PhD., Dr. Mohamned Al-Kubati, PhD. Masaryk University Brno, St.Anna Teaching Hospital, CZ participated on this consensus and signed the consensus (Fig. 1). Other important data and results were brought by the members of the international BIOCOS project (Japan, Russia, India, USA, Mexico, Europa).

Excessive pulse pressure is important risk factor for cardiovascular morbidity and mortality, but there is not enough information about the variability during seven day/ 24 hour blood pressure monitoring in man. From seven day /24 hour blood pressure monitoring it is possible by means of diagnosis of vascular variability disorders (VVD) evaluate also pulse pressure and other factors (1-4).

Evaluation of hypertension is determined by two factors. If we start from the calculation of lost years of healthy life, hypertension is the most important disease globally. Treatment of hypertension can avoid negative impact of the disease on mortality and morbidity. Side effects of drug therapy of hypertension are relatively mild, so it pays to treat everybody and to avert such adverse event - stroke, myocardial infarction or cardiac death.

We prefer therapy of high blood pressure which is still based on more than century - old method of measuring blood pressure in the doctor‘s office. The shortcomings of this approach are already known. Australian study from 1980 showed that 40% of patients were wrongly diagnosed as in hypertensive placebo - treated branches were normotensive at the next examination, and originally normotensive were at follow-up examination hypertensives (17). The fact is explained by the high variability of blood pressure measurement in the doctor‘s office and the statistical phenomenon of regression to the mean, no effect of treatment with placebo.

Modern approach was proposed already 60 years ago by founder of chronobiology Prof. Franz Halberg Minnesota from Minnesota, USA and it is ambulatory blood pressure measurements. We published the first Czech study using ambulatory blood pressure monitoring 23 years ago together with Prof. Bohumil Fiser, dr. Jiří Dušek, Prof. Bořivoj Semrád, Prof. Germaine Cornelissen and Prof. Franz Halberg (18). Notwithstanding modern guidelines for the diagnosis and treatment of hypertension (6) do not give priority of ambulatory monitoring in the diagnosis of hypertension as a method of the first choice, although the financial costs ambulatory blood pressure monitoring significantly decreased in the last time. The ambulatory blood pressure monitoring can be replace by home blood pressure measurements carried out by the patient using low-cost automatic device several times day. The fact that the therapy proceed according to the principle, initiate treatment in case of doubt, it is advantageous for both pharmaceutical companies and patients carefully taking care of your health. On the other hand, the fact that we treat more patients unnecessarily, it leads medical team to inconsistencies in the medical therapy control and there is not inconsistent pressure on the patient to comply with treatment regimens, including prescribed drug.

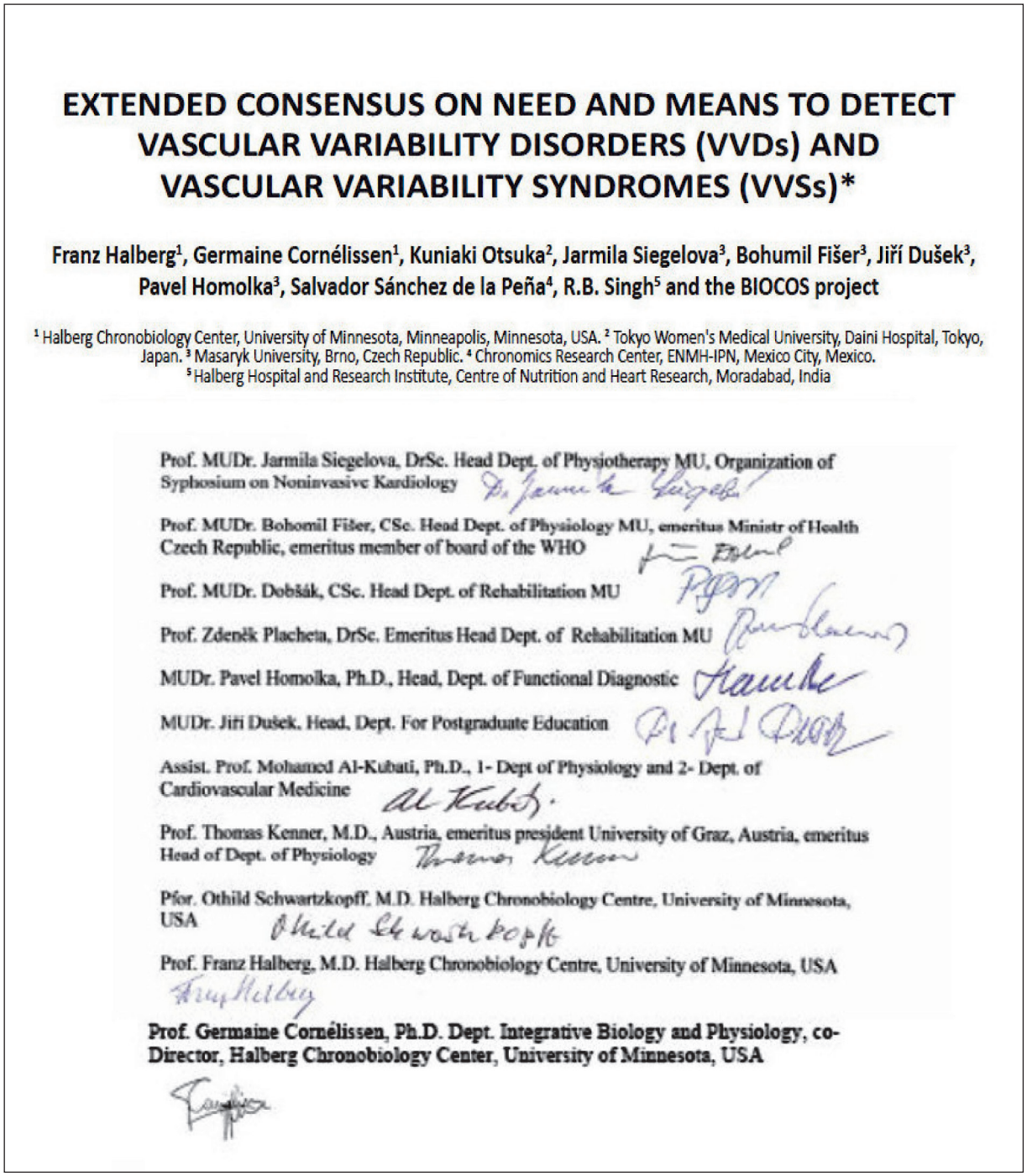
It is therefore desirable for both the doctor and the patient in the group of hypertensive patients greatly diversify approach and focus on patients with a higher risk of organ damage, adverse events and premature death.

This allows us to diagnosis of vascular variability disorders on the basis of long-term ambulatory blood pressure monitoring or home measurement of blood pressure patients (1-4).

Vascular Variability Abnormalities (VVAs) or Disorders (VVDs) include with an elevated blood pressure (BP) (MESOR-hypertension), an excessive pulse pressure (EPP), too large a circadian amplitude of BP (CHAT, short for Circadian-Hyper-Amplitude-Tension), an odd timing of the circadian variation in BP but not of heart rate (HR) (ecphasia), too small a standard deviation of HR (DHRV, short for deficient HR Variability), to high pulse pressure and a circadian period of BP and HR deviating with statistical significance from 24 hours when measured under ordinary conditions in a 24-hour synchronized environment (ecfrequentia). Vascular variability disorders are based on mathematical methods for the assessment of dynamics of long lasting, also seven days /24 hour ambulatory blood pressure monitoring originally prepared by Prof. Dr. Germaine Cornelissen, revised in Brno, by those undersigned (Fig. 1) (1).

The aim of the present study was to assess excessive pulse pressure from long lasting blood pressure monitoring. Our study is aimed to determinate of pulse pressure by means of seven day/24h ambulatory BP monitoring showed increased variability of pulse pressure in every subject day by day and the seven day mean value of pulse pressure could show us the real risk of this parameter.

Excessive pulse pressure (PP) can be calculated as the difference between SBP and DBP mean value of hourly measured blood pressure around the 24 hours; is in terms of increased brachial pulse pressure more than 60 mmHg. Increased brachial pulse pressure is associated with another increased risk of cardiovascular morbidity and mortality. It is another factor of vascular variability disorder. In this study we evaluated circadian variability of pulse pressure from seven day /24 hours ambulatory blood pressure monitoring.



EXTENDED CONSENSUS ON NEED AND MEANS TO DETECT VASCULAR VARIABILITY DISORDERS (VVDs) AND VASCULAR VARIABILITY SYNDROMES (VVSs)*

Franz Halberg[1], Germaine Cornélissen[1], Kuniaki Otsuka[2], Jarmila Siegelova[3], Bohumil Fišer[3], Jiří Dušek[3], Pavel Homolka[3], Salvador Sánchez de la Peña[4], R.B. Singh[5] and the BIOCOS project

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Figure 1: *Brno Consensus in: Intl. J. of Geronto-Geriatrics, 11 (14) 119-146, December 2008*

Methods

Subjects

From our Brno database of 496 patients with ambulatory monitoring of blood pressure for seven day/24 hours, thirty patients were recruited for seven-day blood pressure monitoring. One-hour means of systolic and diastolic blood pressure were evaluated, when night-time was considered from midnight to 0600 h and day time from 1000 to 2200 h, avoiding the transitional periods. Mean day-time and mean night-time systolic and diastolic pressures were evaluated every day, and from this data we calculated pulse pressure.

7-day monitoring of blood pressure was made by means of the instrument TM – 2421 of Japanese firm AD operating on the principle of oscillometric analysis. The instrument measured blood pressure for 7 days repeatedly every 30 min from 5 to 22 o'clock and once an hour from 22 to 5 o'clock. We calculated the 7-day mean for pulse pressure and every day mean for pulse pressure.

The study was approved by local ethics committee and the patients signed the informed consent.

Results

The patients were ordered according mean 7-day SBP (patient No 1: 107 mmHg, patient No 30: 131 mmHg; median value: 123 mmHg).

The variability of one-daytime SBP values during 7-day monitoring is seen in Fig. 2.

Taking 135 mmHg of day-time systolic pressure as a threshold for indication to treatment, then 13 patients (43 %) were under this value every day and nobody was over this value every day. 17 patients (57 %) were one day indicated for treatment and the other day not.

The night-time SBP values are seen in Fig. 3. Similarly, if 120 mmHg of night-time systolic pressure is the threshold, then 10 subjects (33 %) were indicated one day for treatment and the other day not.

Corresponding value of threshold for diastolic day-time pressure is 85 mmHg, thus 22 patients (73 %) were one day indicated for treatment and the other day not (Fig. 4) and for night diastolic pressure of 70 mmHg 24 patients (80 %) were indicated one day for treatment and the other day not. Only one patient (3%) was indicated for treatment every day on the DBP night basis (Fig. 5).

Those data demonstrate large day-to-day SBP and DBP mean day-time and mean night-time variability.

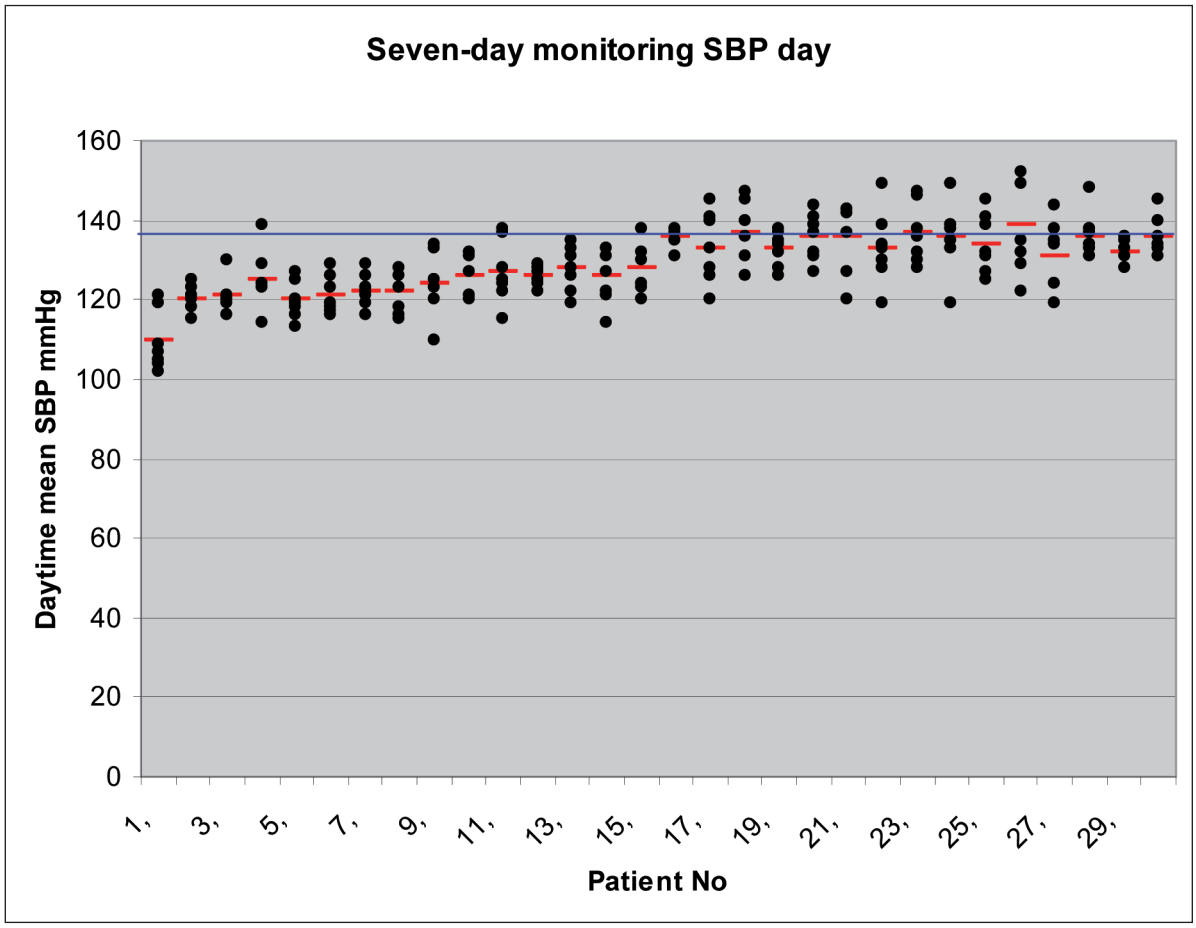

Figure 2: *The variability of one-daytime SBP values during 7-day monitoring. The patients were ordered according mean 7-day SBP (patient No 1: 107 mmHg, patient No 30: 131 mmHg; median value: 123 mmHg). One-day mean values (point) and 7-day mean values (dash) are indicated.*

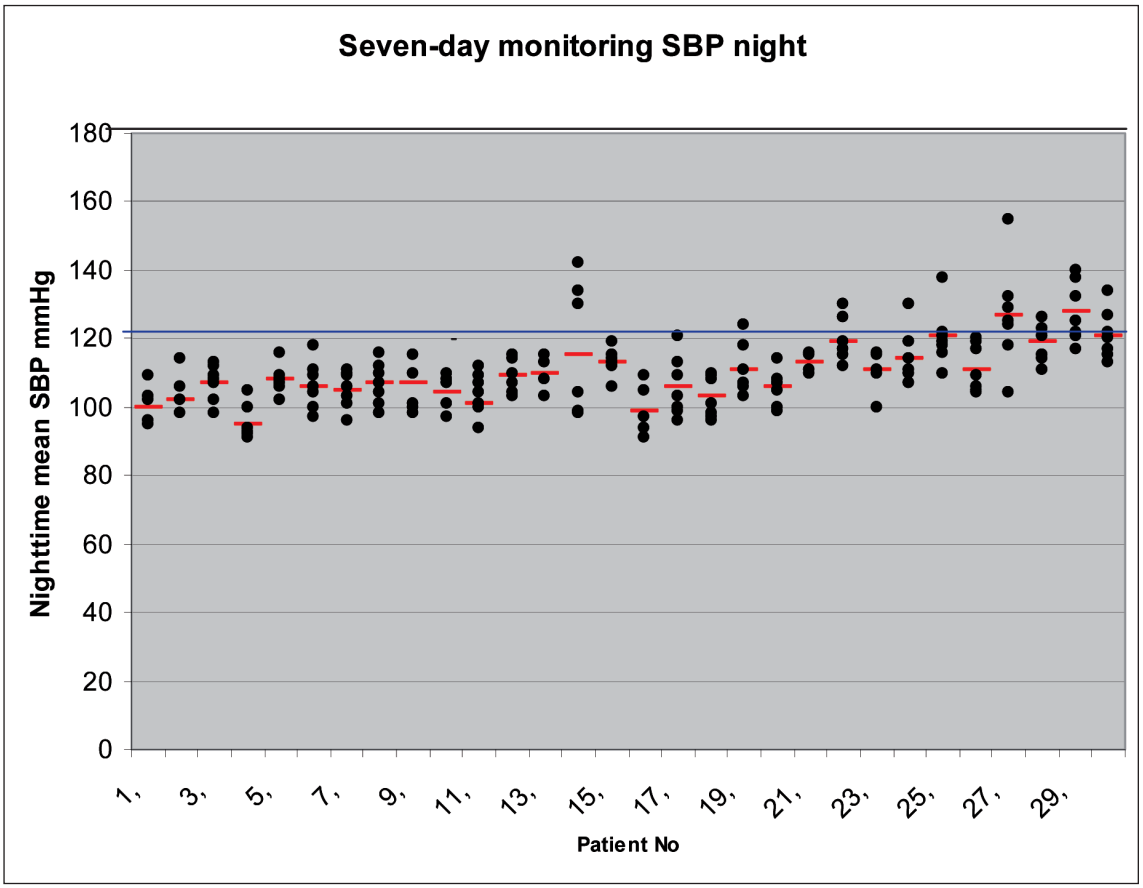

Figure 3: *The variability of one-nighttime SBP values during 7-day monitoring. The patients were ordered according mean 7-day SBP (patient No 1: 107 mmHg, patient No 30: 131 mmHg; median value: 123 mmHg). One-day mean values (point) and 7-day mean values (dash) are indicated.*

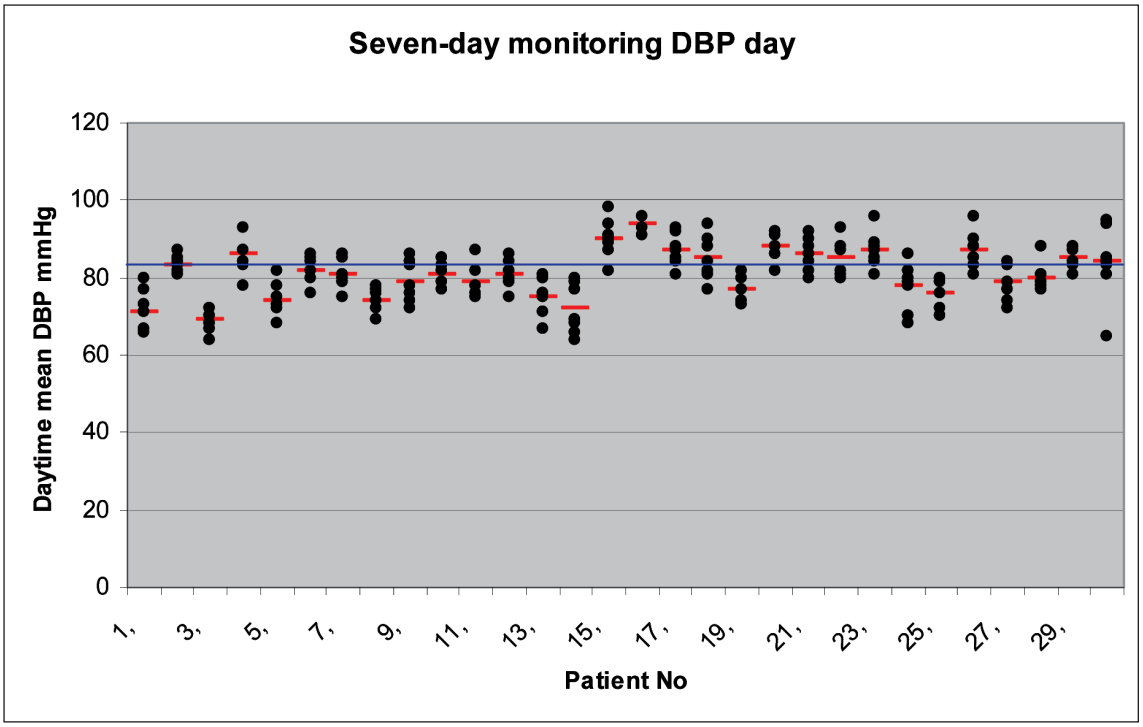

Figure 4: *The variability of one-daytime DBP values during 7-day monitoring. The patients were ordered according mean 7-day SBP (patient No 1: 107 mmHg, patient No 30: 131 mmHg; median value: 123 mmHg). One-day mean values (point) and 7-day mean values (dash) are indicated.*

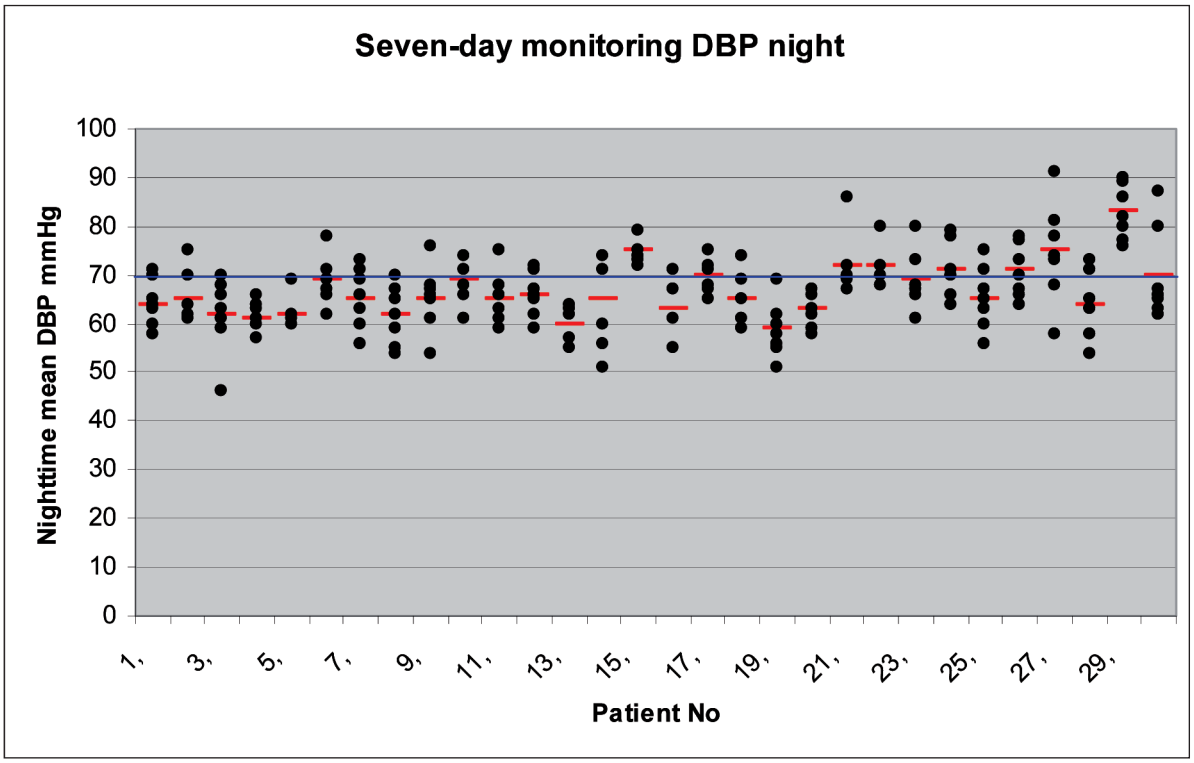

Figure 5: *The variability of one-nighttime DBP values during 7-day monitoring. The patients were ordered according mean 7-day SBP (patient No 1: 107 mmHg, patient No 30: 131 mmHg; median value: 123 mmHg). One-day mean values (point) and 7-day mean values (dash) are indicated.*

Pulse pressure is taken as a risk value for appearance of cardiovascular diseases, if the value is 60 mmHg and more. In our patients the mean values of pulse pressure in the different days varied in the daily times, as is shown in Table 1.

The variability of pulse pressure in different days in the daytime and at night in every individual was present. In the daytime in 20 subjects were the values of pulse pressure in all measurements of seven day blood pressure monitoring under the value of 60 mm Hg. In 10 individuals in daily hours the mean values of pulse pressure in different days were under 60 mmHg in 50 measurements and more than 60 mmHg in 17 measurements. In contrary to these results, the seven day mean values of pulse pressure in the daytime, evaluated from seven day/ 24 hour ambulatory blood pressure monitoring, in all 30 individuals in the daily times were lower than 60 mmHg.

Table 1: *Pulse Pressure (mmHg) during daily times (hour)*

SUBJECTS	1.	2.	3.	4.	5.	6.	7.	MEAN	SD
1.	38	36	39	35	36	42	41	38	2
2.	38	36	36	40	38	34	36	37	2
3.	54	60	51	48	52	53	49	52	4
4.	42	40	40	46	37	36	37	40	3
5.	40	43	42	44	55	48	46	45	5
6.	43	36	42	41	38	39	36	39	3
7.	44	44	40	40	41	42	40	42	2
8.	48	42	49	44	49	56	46	48	4
9.	47	46	58	39	38	47	42	45	6
10.	42	46	44	38	42	49	50	44	4
11.	51	43	46	55	50	49	39	48	5
12.	43	44	45	48	47	45	45	45	2
13.	54	51	55	53	57	39	59	53	6
14.	42	50	48	52	63	64	57	54	7
15.	34	36	38	44	39	41	34	38	3
16.	42	41	45	40	42	41	41	42	1
17.	48	41	49	40	48	58	39	46	6
18.	57	41	42	54	58	42	66	51	9
19.	55	52	51	52	58	61	61	56	4
20.	45	46	45	50	51	46	52	48	3
21.	49	59	38	53	57	47	50	50	6
22.	50	51	56	47	31	52	52	48	8
23.	45	51	46	51	47	49	58	50	4
24.	60	59	56	51	63	55	65	58	4
25.	61	63	66	61	49	55	53	58	6
26.	56	39	61	44	62	49	54	52	8
27.	55	55	36	60	52	50	58	52	7
28.	46	56	55	59	55	67	54	56	6
29.	44	43	50	47	48	48	53	48	3
30.	45	66	51	51	55	50	50	53	6

Table 2: *Pulse Pressure (mmHg) during night time (hour)*

SUBJECTS	1.	2.	3.	4.	5.	6.	7.	MEAN	SD
1.	33	37	38	38	33	35	38	36	2
2.	39	37	36	37	38	34	36	37	1
3.	44	52	48	45	46	38	43	45	4
4.	37	35	27	39	36	32	34	34	4
5.	48	47	47	47	41	44	47	46	2
6.	40	40	30	38	40	38	35	37	3
7.	38	40	39	40	38	46	37	40	3
8.	39	42	51	40	45	55	44	45	5
9.	50	44	48	37	34	32	47	42	7
10.	33	36	36	42	36	35	33	36	3
11.	39	37	35	39	38	43	38	38	2
12.	41	45	42	44	45	44	37	43	3
13.	51	56	48	45	45	45	51	49	4
14.	39	42	33	63	68	59	47	50	12
15.	40	41	41	38	39	33	37	38	3
16.	36	33	38	38	36	38	38	37	2
17.	32	29	41	34	34	46	32	35	5
18.	40	38	39	36	35	39	36	38	2
19.	51	47	56	45	51	55	60	52	5
20.	38	41	41	46	44	41	47	43	3
21.	29	44	40	44	44	42	44	41	5
22.	45	42	54	51	47	45	50	48	4
23.	49	44	42	39	43	43	35	42	4
24.	46	48	41	41	51	36	39	43	5
25.	63	54	53	56	54	51	56	55	4
26.	39	39	39	39	40	46	43	41	3
27.	55	43	64	50	51	74	30	52	13
28.	48	60	52	50	53	63	60	55	5
29.	45	40	45	40	50	49	46	45	4
30.	47	52	55	51	56	50	47	51	3

The mean values of pulse pressure of different subjects varied in the hours at night and it is shown in Table 2. The variability of pulse pressure in every individual was present at night too.

At night in 25 subjects were the values of pulse pressure in all measurements of seven day blood pressure monitoring under the value of 60 mm Hg. In 5 individuals at night the mean values of pulse pressure in different days under 60 mmHg in 27 measurements and more than 60 mmHg in 8 measurements. In contrary to these results, the seven day mean values of pulse pressure at night evaluated from seven day/ 24 hour ambulatory blood pressure monitoring in all 30 individuals at night were lower than 60 mmHg.

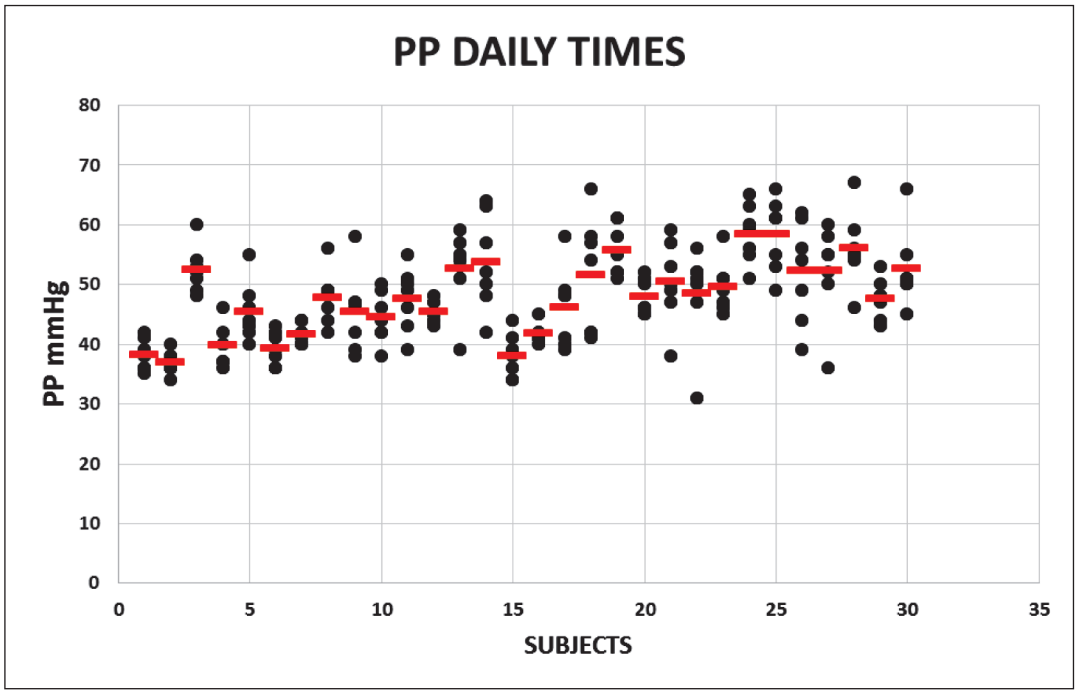

Figure 6: *The variability of pulse pressure daily times during 7-day monitoring. The subjects were ordered according mean 7-day SBP. One-day mean values of pulse pressure (point) and 7-day mean values (red dash) are indicated.*

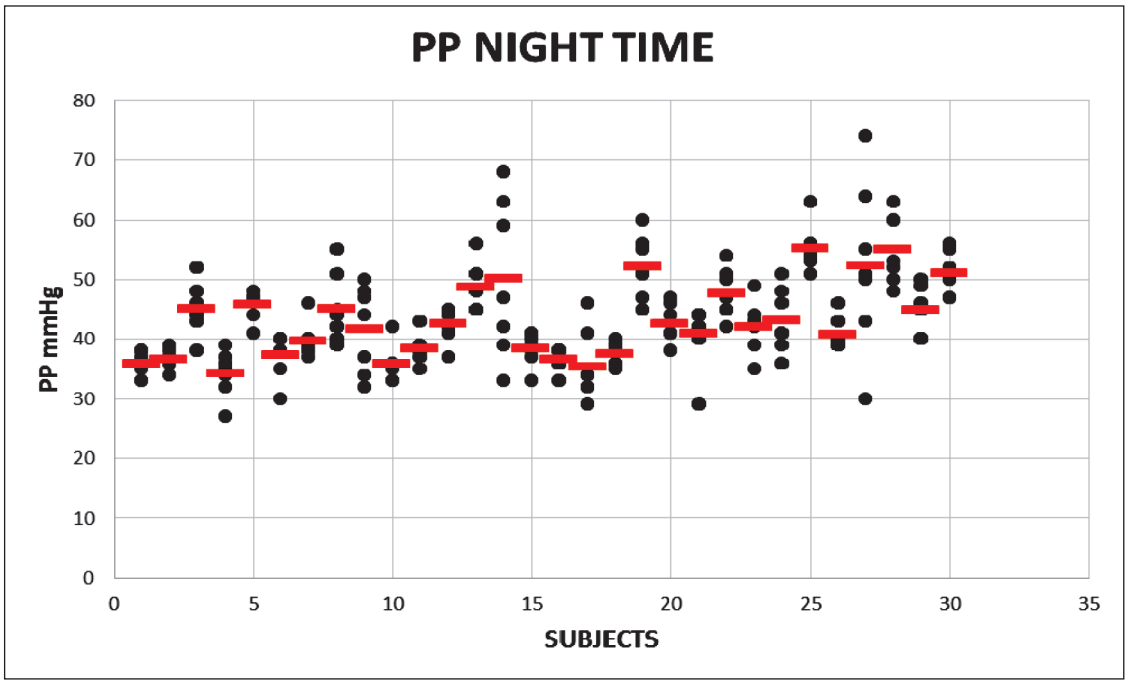

Fig. 7: *The variability of pulse pressure night time during 7-day monitoring. The subjects were ordered according mean 7-day SBP. One-day mean values of pulse pressure (point) and 7-day mean values (red dash) are indicated.*

The variability of the mean values of pulse pressure during the daily times in different days evaluated from seven day/ 24 h blood pressure monitoring is presented in the Fig 6. The seven day means of pulse pressure during the daily times in every individual are different from mean values in the daily times in different days.

The variability of the mean values of pulse pressure at night in different days of seven day/ 24 h blood pressure monitoring is presented in the Fig 7. The seven day means of pulse pressure in every individual are different from mean values of pulse pressure at night in different days too.

Discussion

Ambulatory blood pressure monitoring has an important place in defining abnormal pattern of blood pressure. Also clinical measurement of blood pressure will continue to be useful for screening and management of suspected and true hypertension, ambulatory blood pressure monitoring provides considerable added value toward accurate diagnosis and the provision of the optimal care in uncompleted hypertension as well as for patients with moderate or severe cardiovascular risk. The cardiovascular risk is based on an assessment of all major risk factors, age, sex, waist circumferences, BMI, family history, blood lipids, glucose metabolism, style of life (6).

In previous studies Halberg et al. (1-4) and Siegelova et al. (5, 15) have shown the differences in repeated ambulatory blood pressure monitoring, therefor we started with the ambulatory blood pressure monitoring lasting seven consecutive days.

In our earlier studies we have described on the basis of Brno database of seven day/ 24 hour ambulatory blood pressure monitoring large variability in systolic blood pressure and diastolic blood pressure between different days from seven days, the variability was present in the day time hourly means and at night time hourly means (5, 7). Prof. Cornelissen with us 2016 analyzed in the 297 data of blood pressure profiles from Brno database and showed also novelty effect from seven day 24 hour records.

Our finding also showed large night-day ratio variability in individual subjects, what corresponds to the results of other studies. The night-to-day blood pressure ratio is subject to regression-to-the mean (14).

Dipping status has also a low reproducibility, with up to 40 % of individuals from Europe (19) and Asia (20) changing status between repeat recordings.

In our former study we demonstrated that the relation between night-to-day ratio and risk of cardiovascular events is not linear as it is in the case of mean 24-hour systolic and diastolic pressure (21,22). We observed at low circadian double amplitude which roughly corresponds to the difference between night and day blood pressure (5 mmHg of systolic and 4 mmHg of diastolic pressure) about 30 % higher incidence of cardiovascular events than at circadian double amplitude of 15 to 35 mmHg systolic and of 12 to 20 mmHg diastolic pressure but at double amplitude higher than 35 mmHg in systolic and 28 mmHg in diastolic pressure the incidence was double. This indicates the existence of over-swinging or Circadian Hyper-Amplitude-Tension (CHAT) syndrome which is associated with a large increase in cardiovascular disease risk. The incidence of ultra-dipping is more frequent that the incidence of CHAT but existence of CHAT alone can lead to misdiagnosis of risk based on night-to-day blood pressure ratio (1-4).

Pulse pressure variability in the present study showed the appearance of the excessive pulse pressure in subjects who monitored seven day/24 hour ambulatory blood pressure under usual conditions of daily life. The excessive pulse pressure appeared more often in the daily times hours then at night. The seven day lasting blood pressure monitoring in our studied group of subjects have not found in any time excessive pulse pressure if calculated as seven day mean values for daytime hours or at night.

In conclusion, the determination of excessive pulse pressure value is useless for management risk of individual subjects is important to use long lasting, preferably seven day, ambulatory blood pressure monitoring.

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Cardio-Ankle Vascular Index (CAVI) for Arterial Stiffness – Theory and Significance –

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Introduction

Arterial stiffness is a very important factor in the pathophysiology of blood circulation, but also a good marker for the diagnosis and prognosis of cardiovascular and cerebrovascular diseases. Therefore, its assessment is prerequisite for clinical medicine (1). For example, the increase of arterial stiffness is commonly observed in patients having atherosclerosis, hypertension, diabetes, and hyperlipidemia.

Several methods have been utilized for clinically evaluating arterial stiffness (2). For example, to determine arterial pressure-diameter relations and wall stiffness, arterial diameter and blood pressure are measured with ultrasonic echo-tracking techniques and cuff-type sphygmomanometry, respectively, in such conduit arteries as the common carotid artery and the abdominal aorta (3). Pulse wave velocity (PWV) has been more commonly used in clinical medicine (4). This method is based on the principle that the propagation of pressure wave is faster in a stiffer tube than in a softer one (5, 6); clinically, we measure blood pressure waves at two different sites along the arterial tree, and calculate the velocity of pressure propagation which is related with arterial stiffness.

On the other hand, many parameters have been proposed to quantitatively express arterial stiffness and distensibility using simple parameters for practical medicine, which include pressure-strain elastic modulus (Ep), stiffness parameter (β), and vascular compliance (Cv) (7, 8). As is widely known, however, these parameters except for stiffness parameter β change depending on blood pressure at the time of measurement. Because our blood pressure changes in a short period of time, say within one day, one week, and even during measurement, we cannot use these as patient-specific parameters. To overcome this problem, Shirai et al. (9) have proposed a method for linking β with PWV and proposed a novel blood pressure-independent parameter named Cardio-Ankle Vascular Index (CAVI). With this method, pressure-dependent PWV is measured between the heart and the ankle, and then it is transformed into pressure independent β, which is used as CAVI. CAVI has been applied to the diagnosis and prognosis of many cardiovascular and cerebrovascular diseases, and also their risks; now, a great number of data and results on CAVI are being accumulated (8).

In the present article, first, non-linear pressure-diameter relations of arteries and several parameters used to represent arterial stiffness are explained. Then, the basic theory of β and its advantages are introduced. After a brief explanation of PWV, the relation between β and PWV is demonstrated together with the method for obtaining CAVI from β using heart-ankle PWV.

Nonlinear Pressure-Diameter Relationship and Arterial Stiffness

If blood pressure is increased from the range of low pressure, arterial diameter start increasing largely with increase in pressure; however, the rate of diameter increase gradually decreases with increase in pressure (Figure 1) (2). Like this, arterial wall deforms greatly and nonlinearly with increase in pressure, which is one of the characteristics common to biological soft tissues. Therefore, arterial stiffness, which corresponds to the slope of the tangent to a pressure-diameter curve (ΔP/ΔD) (see Figure 1), increases with increase in blood pressure.

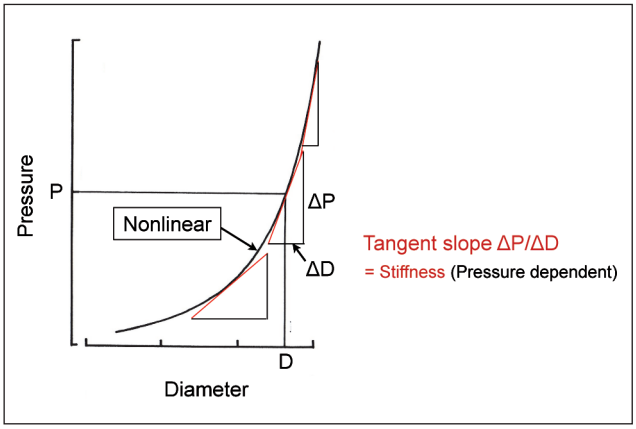

Figure 1: *Arterial pressure-diameter relation and stiffness represented by its tangent slope.*

For practical applications, it is convenient to represent such arterial pressure-diameter relation and wall stiffness with a simple parameter. In particular, for noninvasive diagnoses in clinical medicine, the expression of arterial stiffness or compliance should be simple, yet quantitative. For this purpose, several parameters have so far been proposed, including "pressure-strain elastic modulus, Ep" (10) and "vascular compliance, Cv" (11).

These parameters are respectively described by:

$$Ep = \Delta P/(\Delta D/D) = D(\Delta P/\Delta D) \quad \text{and} \quad Cv = (\Delta V/V)/\Delta P = 2(\Delta D/D)/\Delta P = 2(\Delta D/\Delta P)/D, \quad [1]$$

where D and V are the diameter of a blood vessel and its volume per unit length, respectively, both at pressure P, and ΔD and ΔV are their increments for pressure increment ΔP at P. Parameters Ep and Cv are obtained from the slopes of tangent, ΔP/ΔD and ΔD/ΔP, to pressure-diameter and diameter-pressure curves at pressure P, respectively.

It should be noted, however, that these parameters are defined at specific pressures, and have different values at different pressures, because arterial pressure-diameter relations are nonlinear and their slope ΔP/ΔD changes depending on pressure as stated above (see Figure 1). Our blood pressure easily and always changes in a short period of time even in a healthy person, which eventually affects these parameter values. Therefore, such parameters as Ep and Cv may not be useful for the representation of definite, patient-specific arterial stiffness and compliance, respectively.

Stiffness Parameter β

To overcome the shortcoming in the above-mentioned parameters for arterial stiffness, we proposed "stiffness parameter, β" which does not depend on blood pressures at the time of measurement (12).

This parameter is obtained as follows. First, we select an arbitrary standard pressure Ps, for example 100 mmHg or diastolic blood pressure, and determine arterial diameter Ds at this pressure (Figure 2, left), and then calculate pressure ratio P/Ps and distension ratio D/Ds. If we calculate the logarithm of P/Ps, ln(P/Ps), and plot it against D/Ds, a linear relation is obtained between them in a wide pressure range (between 60 and 200 mmHg in Figure 2, right). This semi-logarithmic relationship is simply described by:

$$\ln(P/Ps) = \beta(D/Ds - 1). \quad [2]$$

It should be noted, however, that Equation [2] does not always fit to all pressure-diameter relations, for example, to relations below and above the physiological pressure range (see Figure 2, right) and also to relations of muscular arteries strongly contracted by the excessive activation of smooth muscle (13).

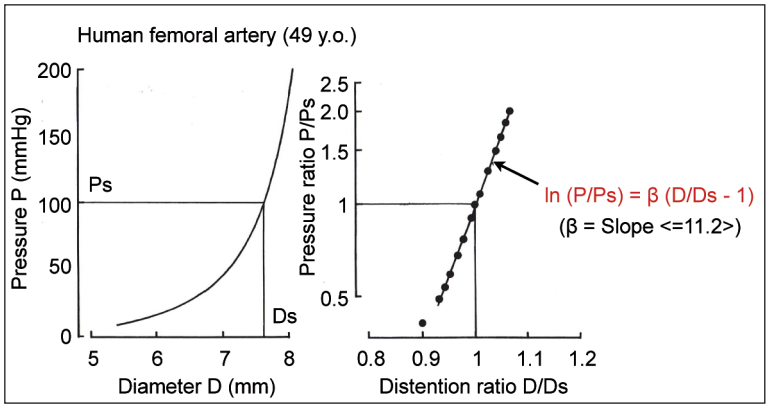

Figure 2: *Pressure-diameter curve of an artery and definition of stiffness parameter* β *(12).*

The slope of the semi-logarithmic relation gives stiffness parameter β, which represents the stiffness of arterial wall. As can be understood from the above explanation or from Figure 2, stiffness parameter β does not depend on pressure. This is one of the most important advantages of this parameter in comparison with the other parameters.

If we take Ps and P as diastolic blood pressure Pdia and systolic blood pressure Psys, respectively, we can rewrite Equation [2] into a clinically useful expression:

$$\ln(Psys/Pdia) \ \beta \ \Delta D/Ddia) \quad \text{or} \quad \beta = (Ddia/\Delta D) \ln(Psys/Pdia), \quad [3]$$

where ΔD is the diameter change produced by pulse pressure ΔP (8).

This parameter has been applied to many studies not only in vascular mechanics and pathophysiology but also in clinical medicine, including aging, hypertension, atherosclerosis, and cerebrovascular diseases (2,7,14,15).

Pulse Wave Velocity (PWV)

Pulse wave velocity PWV has been more frequently used in clinical medicine than Ep, Cv, and β, because it can be easily and non-invasively determined for the evaluation of arterial stiffness in practical medicine.

On the basis of Newton's second law of motion, Bramwell & Hill (16) derived the following equation for pulsatile blood flow (see 8 for the deduction):

$$PWV = [(D/2\rho)(\Delta P/\Delta D)]1/2, \quad [4]$$

where ρ is the density of blood. This form is clinically very useful, because it indicates that PWV can be calculated from pulse pressure ΔP and arterial dilation ΔD, both of which can be measured in vivo. This equation indicates that PWV is proportional to $(\Delta P/\Delta V)^{1/2}$ and, therefore, this represents arterial stiffness.

Equation [4] can be modified to:

$$Ddia/\Delta D = (2\rho/\Delta P)\ PWV2. \quad [5]$$

Relation between Stiffness Parameter and Pulse Wave Velocity

To determine stiffness parameter β, we need to measure arterial diameter and blood pressure. Clinically, blood pressure is often obtained with cuff-type sphygmomanometry, while diameter is measured, for example, with ultrasonic echo-tracking techniques. However, ultrasonic systems are generally quite expensive. Moreover, it is not so easy to precisely measure arterial diameter and stiffness with this technique in daily, routine clinical medicine. On the other hand, PWV can be easily and non-invasively determined for the evaluation of arterial stiffness, and therefore this has been widely used in practical medicine with a long history. However, as stated above, PWV depends on blood pressure at the time of measurement. To solve this problem, we linked pressure dependent PWV with pressure independent β in the following way.

The substitution of Equation [5] to Equation [3] gives:

$$\beta = (Ddia/\Delta D)\ ln(Psys/Pdia) = (2\rho/\Delta P)\ PWV^2\ ln(Psys/Pdia)$$
$$= PWV2\ [2\rho/Psys\text{-}Pdia]]\ ln(Psys/Pdia). \quad [6]$$

This equation indicates that pressure-independent stiffness parameter β is obtained from pulse wave velocity PWV, and systolic and diastolic blood pressures Psys and Pdia, all of which can be measured clinically (9,17). In other words, pressure dependent PWV is transformed into pressure independent β.

Cardio-Ankle Vascular Index - CAVI

Several methods have been utilized for the clinical measurement of PWV, which include carotid-femoral PWV (cfPWV) (18) and heart-femoral PWV (hfPWV) (19). The measurement of cfPWV is easy and has been most widely used in clinical medicine (4).

Although any PWVs can be used for Equation [6], Shirai et al. have recommended the use of the velocity between the heart and the ankle, haPWV (Figure 3), considering the accuracy, reproducibility, and accessibility (9). In this case, this equation, and therefore stiffness parameter β, is described by:

$$\beta = [2\rho/Psys\text{-}Pdia]]\ ln(Psys/Pdia)\ haPWV2. \quad [7]$$

This parameter obtained from haPWV was named Cardio-Ankle Vascular Index, CAVI (9). Because CAVI is equivalent to blood pressure independent parameter β, it does not depend on blood pressure.

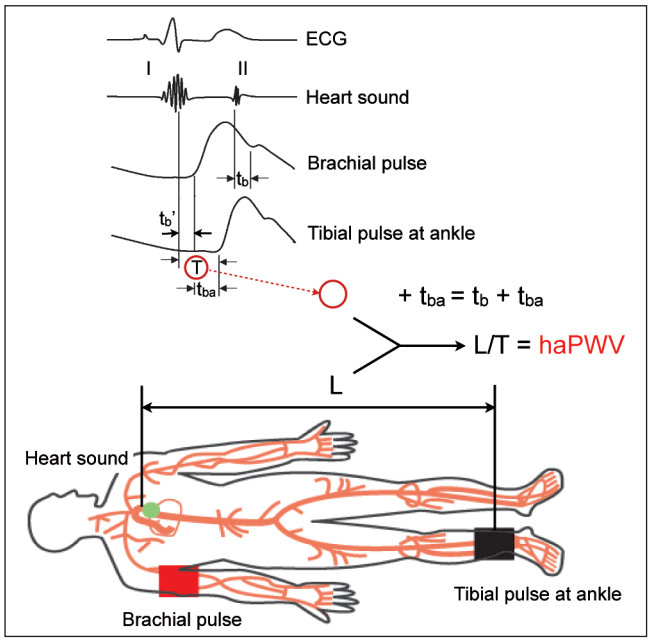

Figure 3: *Measurement of heart-ankle pulse wave velocity haPWV (9).*

There may be several questions we have to consider: for example, 1) is CAVI really independent of blood pressure? and 2) is it acceptable to link β originally determined from a local arterial segment with PWV reflecting the stiffness of a long arterial tree?

With regard to the first question, Shirai et al. (20) experimentally showed that CAVI values were not affected by blood pressure when blood pressure was reduced with the administration of β1 blocker, metoprolol. As is well known, β1 blocker decreases blood pressure by the reduction of heart muscle contraction, and therefore their result clearly indicates that arterial stiffness represented by CAVI is not changed even though blood pressure changes. Furthermore, we measured blood pressure, haPWV, and CAVI in human subjects for 2 days 6 times per day, and studied the influence of blood pressure on haPWV and CAVI. The results demonstrated that there were significant correlations of systolic and diastolic blood pressures with haPWV, but not with CAVI (unpublished data). These results support the independency of CAVI from blood pressure variations at the time of measurement. Of course, arterial stiffness is influenced by the chronic exposure of arterial wall to increased blood pressure; in fact, CAVI showed high values in patients with hypertension (21).

For the second question, Takaki et al. (22) obtained the results showing that CAVI values have good correlations with β-values ultrasonically measured from local segments both in the descending thoracic aorta and the common carotid artery; their correlation coefficients were 0.67 and 0.39, respectively, and confidence coefficients were less than 0.01 for both. Similar results were also obtained by Horinaka et al. (23) from the ascending and descending aortas. We can confirm from these results that stiffness parameter β determined from a local arterial segment is linked with PWV representing the stiffness of a long arterial tree.

For the past several years, a lot of reports have been published on the clinical applications of CAVI (8, 15, 24, 25). And, CAVI is now recognized as one of the most useful markers for the diagnosis and prognosis of cardiovascular and cerebrovascular diseases and also for the pathophysiology of the systemic circulation.

Conclusion

Stiffness parameter β represents pressure-diameter relations of arteries and, therefore, their stiffness. This is not affected by blood pressure changes. Clinically it is measured, for example, with ultrasonic systems, as local arterial stiffness. On the other hand, pulse wave velocity PWV is commonly measured in clinical medicine, but it changes depending on blood pressure changes at the time of measurement. It represents the overall stiffness of a long arterial tree. Cardio-Ankle Vascular Index CAVI is obtained from linking these two parameters. PWV is theoretically linked with β, by which pressure dependent PWV is transformed into pressure independent β. Stiffness parameter β determined using heart-ankle PWV, haPWV, was named Cardio-Ankle Vascular Index, CAVI. As CAVI is equivalent to β, CAVI is independent of blood pressure changes. The theoretical background and recently accumulated many clinical results clearly indicate that CAVI is a very reliable and useful marker for the diagnosis and prognosis of cardiovascular and cerebrovascular diseases.

Acknowledgement

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Effects of Exercise Training on Arterial Stiffness in Patients with Ischemic Coronary Artery Disease

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Abstract

Aim Increased arterial stiffness is an important factor limiting physical performance and a signal of higher cardiovascular risk. The purpose of this clinical study was to examine the effects of exercise rehabilitation program on arterial stiffness (AS) in patients with coronary artery disease (CAD). Patients and methods Patients with stable CAD [n = 116; M/W 88/28; mean age 62 (11) years; mean EF 48(12) %; mean BMI 28.6 (3.7)] underwent 12 weeks of supervised exercise training program. Arterial stiffness (measured using cardio-ankle vascular index) and selected functional parameters (VO_{2peak}, W_{peak} and HR_{peak}) were assessed before and after 12-weeks of training. Results Overall CAVI value significantly decreased between admission and 6th week and 12th week of RHB program respectively; the mean decrease of CAVI was -0.28 at 6th week and -0.29 at 12th week. Also the mean value of VO_{2peak} (+8.1%) improved significantly. Conclusion The present study demonstrated that the majority of the AS and important functional parameters improved after the supervised aerobic exercise training program. However, these results need to be confirmed in future randomized clinical studies controlling potential confounders.

Key Words: arterial stiffness – aerobic exercise – cardio-ankle vascular index – peak oxygen uptake – cardiovascular rehabilitation

Introduction

The central arterial system serves as a conduit delivering blood to the organs and tissues, and acts as a "buffer" by distending during cardiac ejection to provide an optimal and continuous peripheral blood flow. Since the buffering fiction of large arteries is determined by the arterial wall mechanical properties, deteriorations in the arterial structure lead to reduced diastolic blood pressure and impairment of coronary perfusion (1). Epidemiological studies provide evidentiary support of a significant association between central arterial stiffness and coronary artery diseases (CAD), including myocardial infarction (2). Structural and functional changes in the vascular system (e.g. fibrosis, elastin fragmentation and degeneration, release of vasoactive substances by the endothelium and vascular smooth muscle, etc.), accompanying some chronic diseases, such as hypertension and diabetes, are responsible for an increase in the AS, especially in the large central arteries (3, 4). Arterial stiffening associated with CAD may have greater implications for exercise capacity than in other disease states because it may determine the ischemic threshold independent of stenosis severity and other covariates

(5). Arterial stiffness rises also with age and is associated with age-related increase in the morbidity of cardiovascular disease (6, 7). Taking into account the risk associated with an increased AS, it seems to be of particular relevance to patients with CAD the development and implementation of effective interventions to attenuate or even reverse AS. Exercise training alone or incorporated in a cardiac rehabilitation program has shown to be safe and to promote positive effects on several factors that are associated with elevated AS, such as endothelial dysfunction and inflammation (8). In the past decade, a new parameter of arterial stiffness, called cardio-ankle vascular index (CAVI) has been introduced into clinical practice (9). In brief, CAVI reflects stiffness of aorta, femoral and tibial arteries as a whole in the direction heart muscle – ankles. In comparison with the widely used PWV, the parameter CAVI is blood pressure independent. It has been conclusively proved that CAVI value increases with age and in subjects with increased cardiovascular risk, such as coronary artery disease (CAD), hypertension, diabetes mellitus, chronic renal insufficiency or metabolic syndrome (9, 10, 11). The main purpose of this clinical study was to examine the effects of exercise rehabilitation program on arterial stiffness (AS) in patients with coronary artery disease (CAD).

Patients and Methods

One hundred and sixteen patients (88 men and 28 women) with CAD and stable pharmacological treatment (not changed during rehabilitation program) completed 12 weeks of supervised exercise training program Initial characteristics of the patients are outlined in Table 1.

Table 1: *Initial patient´s characteristics.*

Parameter	
age (years)	62 (11)
M/W	88 / 28
EF (%)	48 (12)
BMI (kg/m2)	28.6 (3.7)
coronary artery disease	116
dyslipidemia	77
hypertension	44
diabetes mellitus	41
valvular heart disease	8

All study participants were volunteers recruited from the Ist Department of Cardioangiology, St. Anne´s University Hospital in Brno, a regional medical center in the Region of South Moravia (Czech Republic). Prior to study participation, patients were screened for inclusion and exclusion criteria. The study inclusion criteria were hospital admission due to a CAD-related diagnosis and willing to undergo CV-RHB program. Exclusion criteria included cardiac transplantation or ventricular assist device placement, cardiac arrhythmia or heart failure without concurrent diagnosis of CHD.

Functional capacity evaluation. Physical capacity was determined by cardiopulmonary exercise test (spiroergometry) on bicycle ergometer (Ergoselect, Ergoline®, Bitz, Germany) according to standardized protocol (12).

Heart rate was monitored continuously using 12-lead electrocardiograph (AT-104 PC, Schiller®, Baar, Switzerland). The VO_{2peak} (and other functional variables) was measured using a blood gas analyzer (Power Cube, Ganshorn® Medizin Electronic, Niederlauer, Germany), and was collected by the method of breath by breath. The highest VO_2 obtained during the last 30s of the test was considered the VO_{2peak}.

Protocol of exercise training. All the patients underwent supervised combined exercise training in state hospital rehabilitation center (Fig 1).

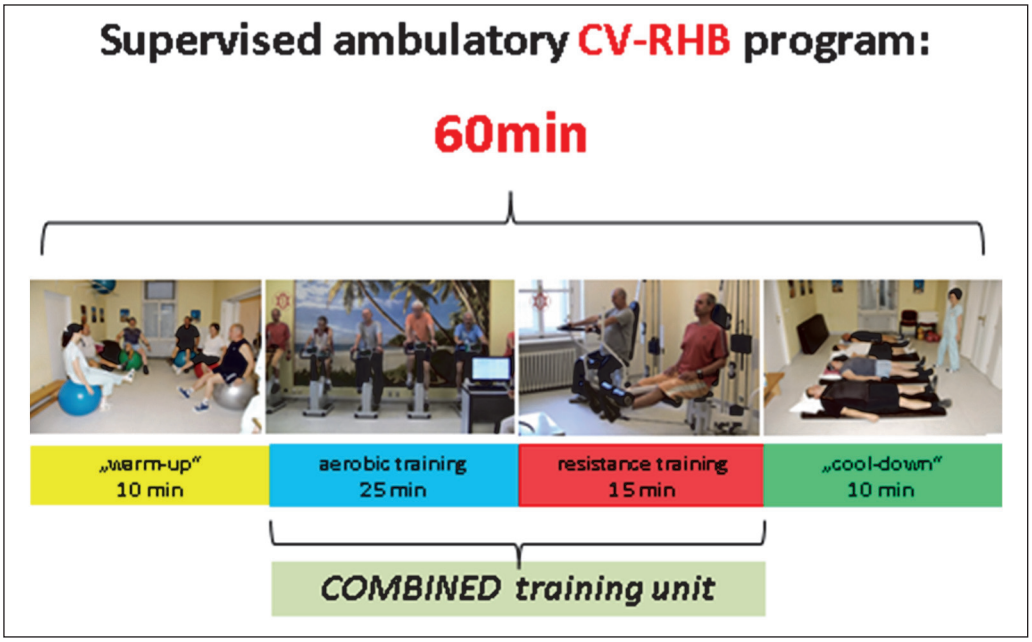


Figure 1: *Scheme of the exercise training unit*

Combined training consisted of two phases – aerobic endurance training (25min) and resistance training (15min). Aerobic training of interval type (30s of work – 60s of relaxation) was performed for 40 minutes on electromagnetically braked bicycle ergometers (REHA E900, Ergoline®, Bitz, Germany) with the intensity at the level of the first ventilatory threshold (VT-1) obtained in the spiroergometric test. The VT-1 is characterized by the highest intensity of physical exertion fully maintained by aerobic energy pathways, and is considered a marker of exercise consistent with mild to moderate intensity and is usually found to be between 40 and 60% of VO_{2peak}. The intensity control was done by means of the heart rate value obtained at VT-1. The resistance training contained three standard exercises: pulley lifting, kicking-off and bench-press. The load for resistance training was always assessed individually using entrance test 1-RM (one repetition maximum). Each training session lasted 60min (warming phase 10min, combined training 40min and 10min phase of relaxation). The realization of the exercise training was done under supervision of medical staff (doctor, physiotherapist and nurse). The training sessions were performed 3 times a week for the total period of 12 weeks. The training program was conducted in accordance with the recommendations of the Guidelines of the Czech Society for Cardiology (13).

CAVI assessment. CAVI was measured by VaSera® 1500 device (Fukuda Denshi Co, Tokyo, Japan) using standard protocol (9). Examination was performed in supine position. Four pressure cuffs were placed on limbs, 1 microphone (phonocardiogram) above upper margin of sternum and 2 ECG leads on both upper limbs. CAVI was automatically calculated according to following formula:

$$CAVI = a\ [\{2\rho \times 1/(SBP - DBP)\} \times \ln \{(SBP/DBP) \times PWV2]\} + b$$

(ρ = blood density; a and b = constants)

Patients with ankle-brachial index (ABI) lower than 0.9 were excluded from this study.

Ethics. Volunteers meeting study criteria signed informed consent to participate in the study. The study was approved by the local Ethics Committee and conforms to the principles outlined in the Declaration of Helsinki (revised 2013 in Fortaleza, Brasil) and to the GCP guidelines of the European Community.

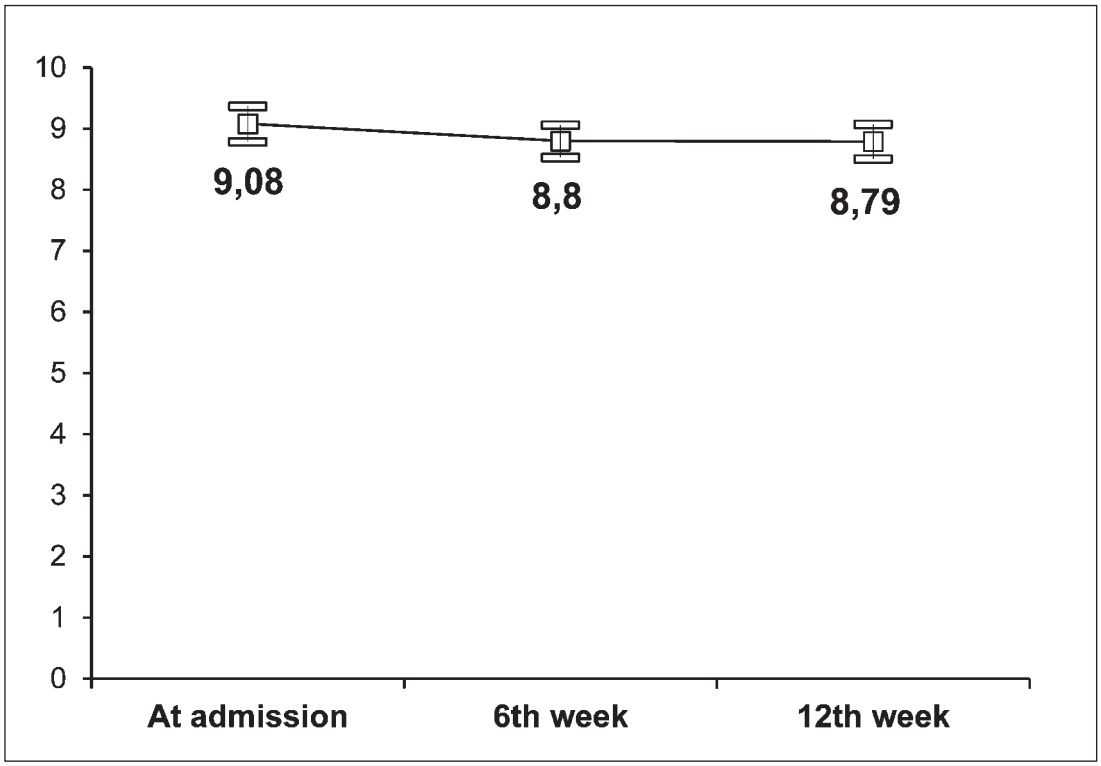
Statistics. Standard descriptive statistics was applied in the analysis: a) continuous variables: mean with 95% confidence interval (CI) or standard deviation (SD) and median with 5th and 95th percentile; and, b) categorical variables: absolute and relative frequencies. Statistical significance of CAVI changes in time between admission and 6th week or 12^{th} week was tested using paired t – test. All statistical analyses were computed using SPSS 19.0.1 (IBM Corporation, 2010). A value $p < 0.05$ was accepted as boundary of statistical significance in all applied tests.

Results

All patients included in the study completed the entire cardiovascular rehabilitation program and tolerated the training protocol very well. There were no episodes of arrhythmias, sudden changes in HR, blood pressure or reports of muscle pains, apnea, nausea, etc.

A statistically significant improvement of parameter CAVI was observed after 6 and 12 weeks of RHB exercise program (P = 0.01 and P = 0.006, respectively). This finding may be interpreted as improvement (decrease) of arterial wall stiffness due to long-term regular physical exertion (Graph 1).

Regarding time-related effects due to examined training program, the statistical analysis revealed significant improvement of the initial values in most important patient's characteristics, such as VO_{2peak} and Wpeak (Table 2).



Graph 1: *CAVI changes in time.*

Table 2: *Summary of evaluation of CAVI and main functional parameters*

Parameter:	At baseline:	After 12 weeks of RHB program:	p*
peak oxygen uptake *(ml . kg^{-1})*	19.7 ± 5.4	21.3 ± 6.3	0.01
peak workload *(W . kg^{-1})*	1.5 ± 0.5	1.7 ± 0.6	0.05
RER	1.10 ± 0.09	1.12 ± 0.09	NS
heart rate (HR_{peak}) *(bpm)*	127 ± 21.4	131 ± 21.3	NS

Discussion

In the present study, we investigated the long-term effects of regular aerobic exercise on arterial stiffness in subjects with CAD. The AS reduction after 12 weeks of training observed in the present study was similar to the previously published clinical reports (14, 15). Several studies have reported the favorable effects of long-term aerobic exercise and physical activity on arterial stiffness. Exercise training significantly improved systemic arterial compliance in healthy young subjects (16). Regular physical activity helps to stabilize arterial stiffness in post-menopausal women (17). Also endurance-

trained elderly men had lower arterial stiffness than sedentary ones, suggesting that regular aerobic exercise can mitigate the age-associated rise of AS (18). Finally, it was demonstrated that endurance exercise training improves systemic arterial stiffness in patients with coronary artery disease (19). The relaxation of vascular smooth muscle induced by the endothelial production of nitric oxide in response to the shear stress caused by increased blood flow (20) is likely to account for the acute elevation in arterial compliance and by exercise (21). Repetitive aerobic exercise for a long period of time induces anti-atherogenic effects through numerous mechanisms, including improvement of lipid metabolism, insulin sensitivity, and blood pressure reduction (22). Carotid-femoral pulse wave velocity (PWV) is traditionally considered the 'gold standard' non-invasive measurement of aortic wall stiffness (23) and there is evidence that PWV has a strong and independent predictive value for cardiovascular and all-cause mortality, including CAD (23). Therefore, measurement of the PWV is very useful in early diagnosis of arteriosclerosis. However, aortic PWV is pressure dependent, and must be corrected for diastolic blood pressure using the Hasegawa method (24). Moreover, carotid and femoral pulse waves are often difficult to detect, thus limiting use in daily clinical practice. Hayashi et al. proposed the concept of an arterial stiffness β index which became the basis for the recently developed parameter CAVI (25). I brief, CAVI is a simple non-invasive diagnostic test, which is similar to PWV in measurement technique but CAVI is not affected by blood pressure at the time of measurement (9). The coefficient of variation for CAVI is reported to be 3.8%, and the reproducibility seems to be sufficient for clinical application (9). Evaluation of exercise effects on the arterial stiffness using CAVI in CAD patients is still absent in current literature. Decreased elasticity resulting from structural changes precedes formation of atherosclerosis, but the crucial fact is that CAVI reflects the condition not only of elastic, but also of muscular arteries (26). Thus CAVI is affected by smooth muscle cells activity in arterial wall, where both vasoconstriction (angiotensin II, endothelin, etc.) and vasorelaxation factors (nitric oxide, prostacyclin, etc.) act. The overproduction of inflammatory and vasoactive substances triggers vessel wall remodelation. Therefore, it is probable that these biosignals generated by endothelium may increase CAVI also in CAD patients. Recent studies showed that CAVI may reflect global inflammatory reaction of vessels in whole organism. Wakabayashi et al. reported that CAVI rises with increased plasmatic level of CRP, amyloid A, fibrinogen, etc. in diabetes mellitus type 2 (27). The significant decrease of the parameter CAVI in the present study could reflect the positive impact of regular muscle exercise and may indicate a resulting beneficial effect on overall neuro-humoral stability and endothelial functions, as well as a decrease of vasoconstrictive activity. Purposeful exercise and increased habitual physical activity are important lifestyle components for patients with coronary heart disease (CHD). These behaviors have many benefits for patients with CHD including increased aerobic capacity, quality of life, anginal threshold, and ability to carry out daily activities and live independently. Exercise is also important in the secondary prevention of CHD. Current recommendations suggest that a comprehensive exercise program, including aerobic, flexibility, and strength training components, is most beneficial for patients with CHD (28). Numerous factors influence patients' ability to engage in exercise such as lack of time, fear of injury, and considering it unimportant (29). Participation in outpatient cardiac rehabilitation is a viable option for patients with CAD to facilitate adoption of exercise, but disappointingly, is not universally embraced by all eligible patients or referring physicians (30). Some authors reported that fewer than half of all patients who are eligible for outpatient RHB programs actually enroll after being discharged from acute care hospitals (31). Many patients do not attend CV-RHB because they have negative perceptions of their control over health. Still others do not attend due to financial constraints imposed by inadequate health insurance and inability to pay for such services (32). Limited accessibility (transportation, distance, winter weather) to outpatient CR services may also restrict many patients from participating in organized exercise sessions after hospital discharge (33). Other important factors that prevent enrollment in an

outpatient CV-RHB program are return to work and lack of physician referral (8). Despite the benefits, many patients with CHD do not adhere to regular participation in CV-RHB or unsupervised exercise programs because they have low self-efficacy for participation in and adherence to a program of regular exercise (34). Recently, Oliveira et al. in a detailed review article reported that the information about the effects of training programs on AS in patients with CAD is still very rare (35). Thus, the generally observed reduction of AS after attendance of an exercise training is based only on a small number of studies, none of them a randomized controlled trial. Especially for that reason it is strongly recommended that future studies dealing with this topic should be randomized and controlled.

Conclusion

The presented results showed that long-term supervised aerobic exercise decreased AS and important functional parameters. This conclusion is in concordance with previous trials based on of PWV measurements. We demonstrated that the recently introduced parameter CAVI accurately reflects the positive exercise-induced vascular changes leading to decrease of peripheral resistance. There were several limitations in this study. First, there is no other study focusing on the effects of exercise training on AS assessed by CAVI in patients with CAD. Moreover, we did not give careful consideration to exercise habituation at home of the subjects included. For these reasons, further investigations with CAVI measurement of AS will be needed. However, according to the analyzed data it is possible to conclude that CAVI parameter could be very useful diagnostic tool for clinical assessment of arterial stiffness in patients with CAD.

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Basic Concepts and Importance of Renal Rehabilitation

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Chronic kidney disease (CKD) is a worldwide public health problem. In patients with CKD, exercise endurance, measured as maximal oxygen uptake (VO2 max), etc. is lowered and this phenomenon becomes more distinct as the renal dysfunction advances. Poor physical condition and skeletal muscle wasting are associated with CKD. This is due to the combined effects of uremic acidosis, protein-energy malnutrition and inflammatory cachexia, which lead to and are further aggravated by a sedentary lifestyle. Hemodialyzed patients with chronic renal failure are for long-term exposed to the negative impact of this chronic disease that is systemic, progressive and incurable. Paradoxically, other side effects are related to the chronic treatment by hemodialysis 2-3 times weekly. During the hemodialytic procedure most of patients are in supine postition for up to 5 hours, which brings further decondition. High level of fatigue and long-term tiredness are very frequent and unpleasant problems of these patients. Together, these factors result in a progressive downward spiral of deconditioning. Renal rehabilitation (RR) is coordinated, multifaceted interventions designed to optimize a renal patient's physical, psychological, and social functioning, in addition to stabilizing, slowing, or even reversing the progression of renal deterioration, thereby reducing morbidity and mortality. RR includes five major components: such as exercise training, diet & fluid management, medication & medical surveillance, education, psychological & vocational counseling.

Therefore, the main goal of our team of doctors, physiotherapists, nurses and students was to influence this present unsatisfactory status by creating an intradialytic rehabilitation (ID-RHB) program. This type of rehabilitation is very useful also from the point of view of the time spent in bed during hemodialysis.

We used specific equipment that can be easily used in supine position – portable stimulators REHA X2 (Cefar, Sweden) for neuromuscular electrostimulation of large muscle groups in legs, or ergometer MOTOmed letto2 (MotoMed®, Germany) which is designed for aerobic training (Fig.1).

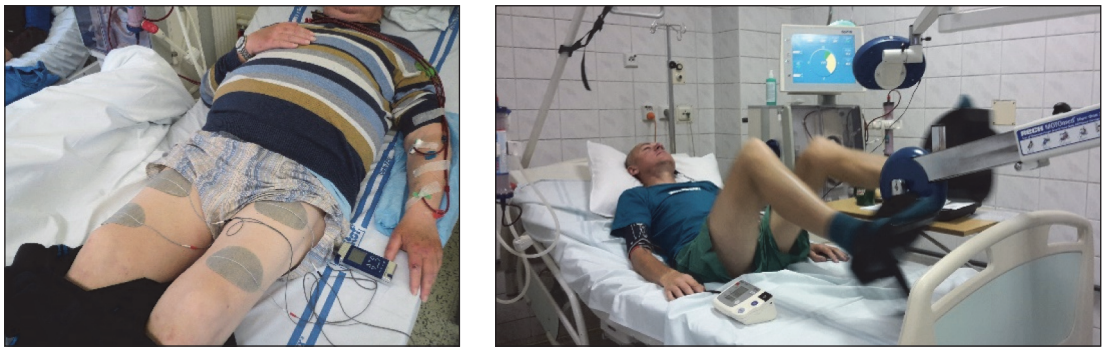

Figure 1: *ID-RHB session in hemodialysis center in St. Anne´s Faculty Hospital in Brno (electrostimulation of legs and aerobic Exercise on bed-side ergometer).*

Furthermore, we also introduced our own battery of kinesiotherapy exercises, such as stretching, relaxation and fitness exercises, activation of deep stabilizating system of spine, elements of respiratory

rehabilitation, sensomotorics, etc., according to mobility and current status of the patient. All these exercises are always performed with fixed non-dominant upper limb, in order to prevent damage of shunt or interference with hemodialysis process.

Intradialytic rehabilitation is still not very widespread form of rehabilitation in the Czech Republic. In fact, ID-RHB is up to the present a unique form of treatment available only in large medical centers in Prague and Brno. The situation is quite different, for example in Germany or Japan, where the intradialytic rehabilitation is a standard prerequisite for admission to the hemodialysis program in the dialysis units (Fig.2).

Figure 2: *ID-RHB session in hemodialysis center in Germany and Japan*

Physical inactivity is well recognised as a major health issue in today's society. Regular exercise is important in maintaining health and preventing chronic disease, it is increasingly accepted as a valuable therapeutic intervention in many long-term conditions. Patients with end-stage renal disease (ESRD) on maintenance haemodialysis have very high mortality, and yet higher mortality risk has been reported for sedentary hemodialysis patients [1]. As well as being a strong cardiovascular risk factor, physical inactivity is associated with increased risk of rapid kidney function decline in CKD [2].

Unfortunately, the role of physical activity in renal disease has been largely overlooked and provision of exercise advice and rehabilitation programs for kidney patients lags well behind that of cardiology and pulmonary services. Levels of physical exercise among CKD patients with hemodialysis are low. Regular exercise frequency varied widely across countries and across dialysis facilities within a country.

The positive effects of physical exercise reported in the general population may be highly relevant for ESRD patients. Increased physical activity has been associated with improved ability and capacity to perform activities in everyday life, occupational tasks, health-related quality of life and survival. Therefore regular exercise is recommended to this population. Results from an international study of haemodialysis patients indicate that regular exercise is associated with better outcomes in this population and that patients at facilities offering exercise programs have higher odds of exercising. A systematic literature search was completed in August 2010 to identify randomized, controlled trials of exercise training studies in hemodialysis patients. A subsequent meta-analysis was conducted and the search repeated in December 2010 [3]. Fifteen studies, yielding 565 patients were included. Baseline, peak VO_2 values were 70% of age-predicted values, exercise intervention patients improved post-training peak VO_2 to 88% predicted. Exercise training produced 26% improvements in eight studies that reported peak VO_2. Equivocal results for change in short-form 36 health questionnaire scores were reported post-training. Significant improvements in lean body mass, quadriceps muscle area, knee extension, hip abduction and flexion strength were also reported [3]. They did not find any deaths directly associated with exercise in 28.400 patient-hours and no differences in withdrawal rates between exercise and control participants. Exercise training for 6 months or more conveyed larger

improvements in peak VO_2 than shorter programs. Therefore, Exercise training is safe and imparts large improvements in peak VO_2, and heart rate variability in hemodialysis patients [3]. Moreover, a growing evidence base suggests that exercise training in patients with hemodialysis improves in VO_{2peak}, left ventricular function, cardiac sympathetic and parasympathetic disharmony, malnutrition-inflammation-atherosclerosis syndrome, anemia, sleep quality, anxiety, health-related quality of life, activities of daily living, shunt size, Kt/V and mortality [4]. Further research is necessary to both understand the observed lack of obvious benefits and strategies to improve the exercise regimens in patients with hemodialysis.

Therefore, regular exercise is recommended to hemodialysis patients. The problem of exercise therapy or rehabilitation for patients with visceral impairment such as renal or cardiac impairment is a low implementation. Because the beneficial effects of rehabilitation on exercise capacity, quality of life, and prognosis (mortality) in patients with visceral impairment have been established, the low implementation rate of rehabilitation implies that patients are kept away from the established benefits of rehabilitation by reasons unrelated to the patient conditions. Thus, efforts should be made urgently to increase the implementation rate of rehabilitation. Major reasons for not implementing cardiac rehabilitation (CR) were lack of staff, equipment and space, and the absence of the approval for the CR facility standards [5].

The recently published Kidney Disease Outcomes Quality Initiative (K/DOQI) clinical practice guidelines on management of cardiovascular disease state that, “all dialysis patients should be counseled and regularly encouraged by nephrology and dialysis staff to increase their level of physical activity” [6]. Despite the guidelines, counseling behavior has not increased. Published guidelines are insufficient to reach younger nephrologists [7]. They also reported that dialysis patients were interested in physical activity [8]. They reported that the majority of participants strongly agreed that a sedentary lifestyle was a health risk (98%) and that increasing exercise was a benefit (98%). However, 92% of participants reported at least one barrier to physical activity. The most commonly reported barriers were fatigue on dialysis days and non-dialysis days and shortness of breath. In multivariate analysis, a greater number of reported barriers was associated with lower levels of physical activity. Lack of motivation was associated with less physical activity. Endorsement of too many medical problems and not having enough time on dialysis days were also associated with less activity in adjusted analysis [8]. Perhaps a larger barrier to implementation of exercise programs in the dialysis population is the lack of a clearly defined “best” program. The location of the exercise training is also an important factor influencing adherence. In HD patients, intradialytic programs have been found to achieve higher adherence rates compared to home exercise programs or supervised programs on nondialysis days [9]. Dialysis facility efforts to increase patient physical activity may be beneficial. Studies of the barriers to patient participation in exercise and to provider assessment and recommendations are needed so that more widely generalisable interventions can be developed.

There is increasing evidence of the benefit of regular physical exercise in a number of longterm conditions including chronic kidney disease (CKD). However, this evidence has mostly come from studies in end stage patients receiving regular dialysis. It should be noted that the majority of published studies were small and enrolled patients were undergoing hemodialysis. Relatively few studies have included patients with stage 1 to 4 CKD, which limits the generalization of findings to predialisis CKD patients.

It is also necessary to consider the influence of exercise on renal functions because acute exercise causes proteinuria and subsequent reductions in both the renal blood flow and glomerular filtration rate. It has also been demonstrated clinically that sudden exercise decreases renal function. There are few reports on the influence of chronic exercise on renal function and there is little information about

the effect of exercise on predialysis CKD patients. The optimal intensity and duration of exercise for patients with chronic renal failure has not yet been formulated. Recently, it is reported that exercise therapy for 12 weeks significantly improved the anaerobic metabolic threshold and high-density lipoprotein cholesterol (HDL-C) levels, and estimated glomerular filtration rate (eGFR) in patients with cardiovascular disease (CVD) and CKD [10]. Change in eGFR correlated significantly and positively with change in anaerobic metabolic threshold and HDL-C. Exercise therapy correlates with improving renal function in CVD patients with CKD through modifying lipid metabolism. Therefore, exercise therapy could be an effective clinical strategy to improve renal function.

Renal rehabilitation (RR) is defined as: "… coordinated, multifaceted interventions designed to optimize a renal patient's physical, psychological, and social functioning, in addition to stabilizing, slowing, or even reversing the progression of renal deterioration, thereby reducing morbidity and mortality. RR includes five major components: such as exercise training, diet & fluid management, medication & medical surveillance, education, psychological & vocational counseling" [11]. The first step to successful RR is ensuring that the clinical prerequisites of anemia control, adequate dialysis, exercise, a well-functioning vascular access, and proper nutrition are in place. The Life Options Rehabilitation Advisory Council (LORAC) developed a comprehensive approach to RR, based on the principle of „5 E's": Encouragement, Education, Exercise, Employment, and Evaluation [12].

Medical science basically aims to „Adding Years to Life" by increasing life expectancy. Rehabilitation generally aims to „Adding Life to Years" by helping patients with impairment achieve, and use, their full physical, mental and social potential. However, recent growing evidence suggests that rehabilitation for patients with visceral impairment such as cardiac, renal and pulmonary impairment can not only improve exercise performance and quality of life, but also increases survival [13]. Therefore, modern comprehensive rehabilitation for patients with visceral impairment does not simply aim to „Adding Life to Years" but "Adding Life to Years and Years to Life", which is a new rehabilitation concept [13].

In RR, we should improve not only quality of life but also biological lifespan in patients with CKD. RR is a feasible, effective and safe secondary prevention strategy following CKD, and offers a promising model for new field of rehabilitation. Future RCTs should focus more on the effects of exercise training and rehabilitation programs as these subjects and exercise types have not been studied as much as cardiovascular exercise. Moreover, efforts should be made urgently to increase the implementation rate of the RR.

Conclusion

In the Czech Republic, when patients are diagnosed with end-stage renal failure, most are never given information on exercise and physical activity. If they ask, typically they are told to take it easy or not to overdo it. This „advice" poses questions and plants doubt in the minds of patients and their families, who will be extremely protective. Moreover, patients usually don´t feel well and are fatigued, so they opt for no activity. The dialysis staff who see the patients regularly for their treatment, often reinforce their inactive lifestyle. Not surprisingly, then, many patinetns are skeptical about becoming physically active because they don´t see any benefit. Patients interact primarily with their dialysis providers and thus receive little or no information from other health care specialists. And here it is necessary to highlight the crucial role of exercise professionals who should reach out to dialysis staff about how exercise can benefit their patients and assure them that the programs initiated will be safe and will not interfere with the treatment. This education should also include ideas about how the dialysis staff can encourage patients to be physically active. Permanent encouragement and reinforcement can greatly facilitate patient efforts in rehabilitation and physical activity. Although the nephrology community is

becoming more interested in improving physical functioning of CKD patients, most of nephrologists and dialysis staff are still not familiar with how many benefit their patients or how to evaluate physical functioning or prescribe exercise. A trained health care professional who knows about the problems associated with dialysis may be an important addition to patient care team.

Acknowledgement

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The Use of MOTOmed in Subacute Phase of Rehabilitation after Total Knee Arthroplasty

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Summary

The main goal of the study was to evaluate quadriceps femoris muscle (QFM) power in patients after total knee arthroplasty (TKA) after completing a week of rehabilitation (RHB). Two groups of patients were included in the study: a) group with rehabilitation combined with MOTOmed; and, b) group with standard rehabilitation (without RHB on MOTOmed). The aim of the study was to find out and evaluate the effects of adding a MOTOmed to the standard rehabilitation program on quadriceps muscle power witch was measured using an isometric dynamometer.

Key words: total knee arthroplasty, quadriceps femoris muscle, MOTOmed, rehabilitation

Background

Lower extremity osteoarthritis (OA) and quadriceps muscle impairments are associated with functional limitations and worse mobility performance in older adults. The primary aims of TKA are to decrease pain, improve functional mobility, such as walking and stairs climbing, and to promote return to physical activity. TKA has been shown to be very effective in reducing knee pain associated with OA.

Functional outcome scores reported via questionnaires indicate an improvement in quality of life following surgery, but actual physical performance measures and the individual's perception of functional ability remain worse than the age-matched healthy population. Individuals 1 year after a TKA surgery perceived their functional ability to be approximately 80% of a group of similar age.

In another self-report study only 50% of the TKA recipients considered their knee function normal compared to the healthy same-age persons. While quadriceps weakness may have a limited association with perceived functional ability, it tends to have a strong relationship with performance. Quadriceps weakness in older adults has been associated with an increased fall risk, decreased gait speed and impaired stair-climbing ability.

Rehabilitation following a TKA should still be directed towards pain control and improving knee ROM, but a focus on exercises to address quadriceps muscle impairments appears necessary to achieve the best functional abilities.

Objective

The purpose of this study was to evaluate an effect of adding a MOTOmed (MotoMed®, Germany) to standard rehabilitation following TKA on quadriceps muscle strength. We supposed the use of MOTOmed to be an effective method to address quadriceps muscle weakness and finally result in better functional performance outcomes compared to standard rehabilitation protocol.

The goal of our study was to assess isometric power of QFM in early phase of rehabilitation in patients after TKA. The measurement was held in the beginning and in the end of one-week rehabilitation program.

Methods

In total, thirty-five patients (19men and 16women), mean age 67.2 years, undergoing a primary unilateral tri-compartmental TKA, were included in this study. They were randomly assigned to receive either standard (non-MOTOmed group) rehabilitation or rehabilitation accompanied with MOTOmed (MOTOmed group).

The patients underwent surgery at The Orthopedic Clinic at St. Anne´s University Hospital or The SurGal Clinic Brno and then the rehabilitation program took place at The Inpatient Rehabilitation Department at St. Anne´s University Hospital.

Both rehabilitation programs (Table 1) lasted one week, with two physiotherapy sessions a day. The patients were divided into two groups: a) non-MOTOmed group underwent a standard rehabilitation protocol; b) the physiotherapy of MOTOmed group was accompanied with MOTOmed training, two times a day for 5-10minutes (Fig.1). Informed consent was obtained from all participants.

Table 1: *Rehabilitation program in patients after TKA*

Range of motion (ROM)
● Active–assistive ROM for knee flexion
● Passive knee extension stretch
Strength
● Quad sets, straight leg raises, hip abduction, hamstring curls, isometric strengthening
Fuctional activities
● Gait training, stairs climbing, self–care activities
Modalities
● Ice, positioning (flexed–extend)
Manual techniques
● Soft tissue techniques for scarf, patellar mobilization, muscle re lease techniques

We measured QFM strength on isometric dynamometer PS-2SDT (EXAMO® Recens, Brno, Czech Republic). The starting testing was done before rehabilitation program (13 ± 3 days after surgery), the final testing at the end of rehabilitation (21 ± 2 day after surgery). The parameter of maximal voluntary isometric contraction (MVIC) was used for the evaluation of maximal muscle power.

Participants were positioned in an isometric dynamometer (Fig.2) stabilized with 90 degrees of knee and hip joint flexion. An isometric contraction lasted 3 seconds and was repeated up to 3 times, with 4 seconds of rest between each trial. Then, the best attempt with the largest MVIC value was used for data analysis.

Figure 1: *MOTOmed*

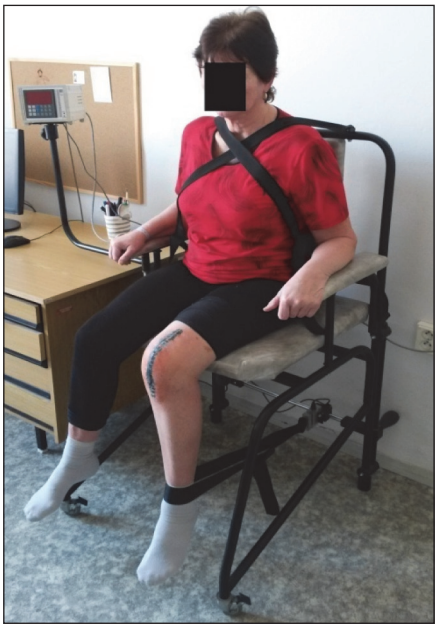


Figure 2: *Isometric dynamometer*

Results

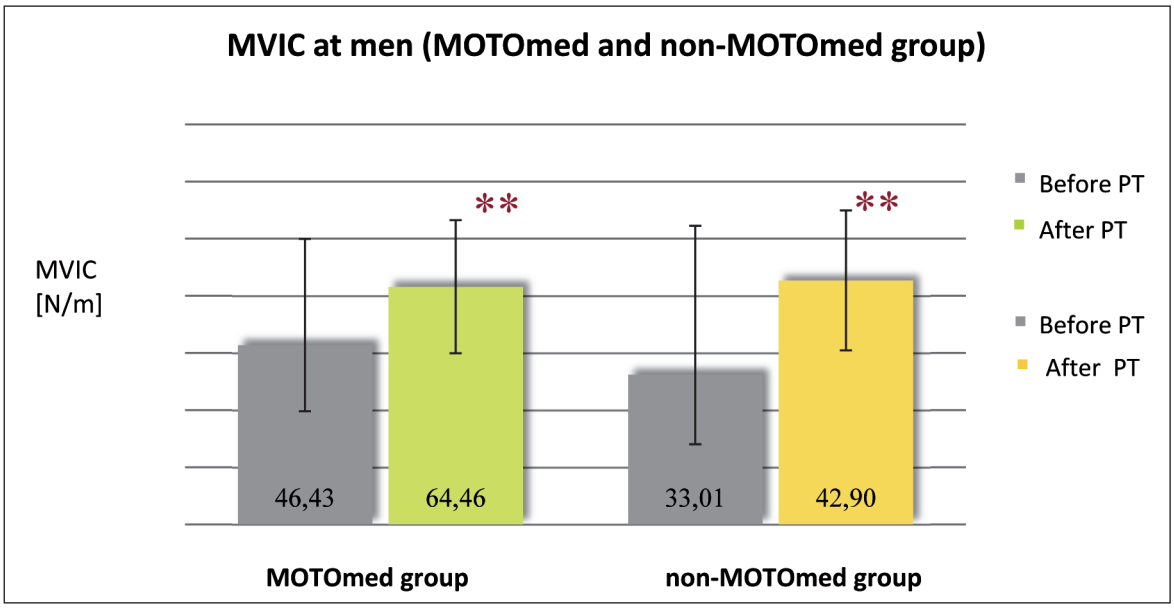
Beneficial outcomes were observed in both types of rehabilitation programs in patients after TKA. QFM power improved significantly in both groups (+25% in average). In MOTOmed group the values of MVIC of QFM increased from initial 31.44 N/m to final 41.60 N/m (+27% in average). In the non-MOTOmed group the improvement (+23%) was from 26,28 N/m to 42,70 N/m.

The improvement of QFM power in group of men using a MOTOmed was significantly better (+45% in average) than in the group of men without MOTOmed use. The improvement in the group of women using a MOTOmed compared to non-MOTOmed women group was not significant (+34% in average). The individual values of each group of patients are presented in Table 2, and Graphs 1 and 2.

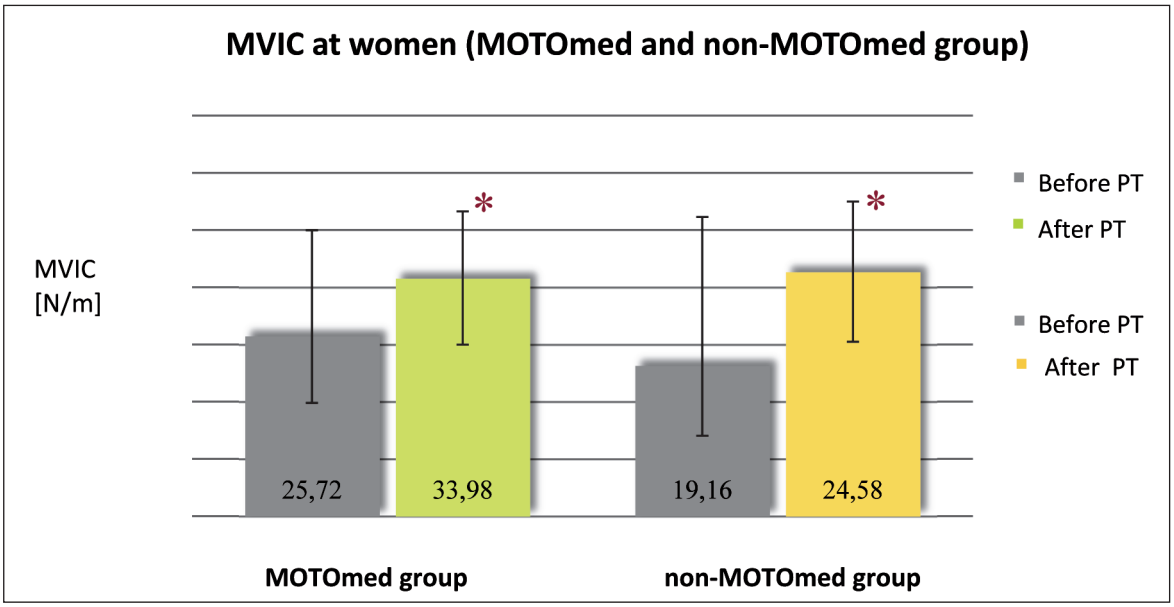
Table 2: *MVIC values of QFM in patients after TKA*

Group of patients	MVIC values [N/m]		Test result (p ≤ 0,01)
	Starting	Final	
Women MOTOmed	25,72±11,02	33,98±9,79	*
Women non–MOTOmed	19,16±12,63	24,58±14,77	*
Men MOTOmed	46,43±20,99	64,46±27,29	**
Men non–MOTOmed	33,01±12,48	42,90±15,80	**

Explanation: MVIC – maximal voluntary isometric contraction, N/m – Newtonmeter, p – test result



Graph 1: *Comparison of the baseline and final values of MVIC of QFM in men (MOTOmed vs. non-MOTOmed group of patients following TKA rehabilitation)*



Graph 2: *Comparison of the baseline and final values of MVIC of QFM in women (MOTOmed vs. non-MOTOmed group of patients following TKA rehabilitation)*

Conclusion

The improvement of QFM power was achieved in both groups of patients after TKA (with or without addition of MOTOmed). Rehabilitation intervention based on MOTOmed seems to be an effective method additional to standard physiotherapy.

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Department of Physiology, Faculty of Medicine, Masaryk University Brno: History and Contemporary Scientific Projects

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Physiology department was founded in 1919 by Prof. Edward Babák, renowned physiologist and scientist. Since then, it has become one of leading institutes among theoretical and pre-clinical departments of Faculty of Medicine. During its almost century-lasting history, numerous scientists as well as clinicians participated in the research and teaching activities of the department. Among all, there are names which have to be mentioned: Prof. Edward Babák, Prof. Vladislav Kruta, Prof. Jan Peňáz, Prof. Pavel Bravený, Prof. Bohumil Fišer, Prof. Jarmila Siegelová, Prof. Bořivoj Semrád, Prof. Miroslav Kukleta, Doc. Josef Šumbera.

Research activities of Physiology department were and – with short interruptions and excursions – still are focused mainly on cardiovascular system. In this area, world recognized findings were published, such as restitution of contractility (Kruta and Bravený) or non-invasive recording of blood pressure by photopletysmography (Peňáz).

At present, three research groups are working at the department:

Laboratory of Cellular Electrophysiology

Laboratory of Cellular Electrophysiology (headed by Markéta Bébarová), was founded in 1992 by Jiří Šimurda and Milena Šimurdová, former co-workers of Pavel Bravený and Josef Šumbera. The main interest of this group lays in pharmacological studies performed on isolated rat cardiomyocytes, using whole-cell patch clamp technique (both voltage-clamp and current-clamp modification). Recently, researchers from this group studied the effect of ethanol, nicotine and various antipsychotics on ionic currents in atrial as well ventricular cardiomyocytes. Also the technique of human specific ionic channels transfection into cell lines is available. Important part of the work in this group represents mathematical modelling of electrical events on cardiomyocyte, outstandingly done by Michal Pásek and his co-workers.

Laboratory of Experimental Cardiology

Laboratory of Experimental Cardiology, founded in 1998 by its head Marie Nováková, represents continuation of research done by Vladislav Kruta, Pavel Bravený and Josef Šumbera. This working group represents a link among other groups at the department and also some co-operating institutions (e.g. Institute of Biomedical Engineering, Brno University of Technology, Department of Biochemistry and Department of Pharmacology, Faculty of Medicine, Brno, Faculty of Pharmacy, University of Veterinary and Pharmaceutical Sciences Brno). Numerous techniques and specific approaches are available in this laboratory, from cellular to whole-animal level: isolation and cultivation of

cardiomyocytes from various species, isolated heart – both Langendorff and Neely models, recording of monophasic action potentials using optical methods (voltage sensitive dyes, e.g. di-4-ANEPPS), multicellular heart preparations (atria and ventricular papillary muscle), metabolic cages, non-invasive recording of blood pressure and ECG in small laboratory animals (without need of anaesthesia), telemetric recording of numerous parameters in small laboratory animals, etc. In cooperation with biomedical engineering specialists, not only recordings of high quality have been developed, but also very sophisticated analyses of acquired biosignals are available. Recently the laboratory is working on several projects - cardiac sigma, IP3 and dopaminergic receptors, relationship between electrical activity and blood flow in ventricles, cardiovascular effects of various drugs (cytostatics, newly synthetized b-blockers, etc.) and many others.

Laboratory of Non-invasive Methods in Cardiology

Laboratory of Non-invasive Methods in Cardiology (headed by Zuzana Nováková), is the only laboratory which worked without interruption during past several decades. It was founded by Jan Peňáz around 1965. Many highly recognized scientists spent important part of their professional life in this group: Bohumil Fišer, Jarmila Sieglová, Bořivoj Semrád, and Nataša Honzíková. At present, the main projects of this laboratory are focused on cardiovascular regulation, with special emphasis on dysbalance of autonomic nervous system. In detail, cardiovascular regulation in healthy and diseased subjects (hypertension, diabetes mellitus, and metabolic syndrome), cardiovascular regulation in children and adolescents, effects of cardiotoxic therapy in oncological patients on autonomic nervous system, and many other aspects are studied. The available methods are continuous blood pressure measurement – Peňáz method, measurement of pulse wave velocity, analysis of pulse wave, echocardiography, ultrasound estimation of intima-media thickness, CAVI index, ABI index (Vasera, Denshi, Japan). Acquired data are off-line processed by advanced methods of biomedical engineering. The flagship of these approaches is estimation of baroreflex sensitivity by cross-spectral analysis. Other analyses are done in the area of HR and blood pressure variability, etc.

Core Facilities

Core Facilities represent the youngest working group of the department. It was founded by head of the department Petr Babula in 2014. This laboratory provides certain services, mainly in area of molecular physiology, for other working groups of the department. Available techniques are various microscopy techniques, methods of molecular biology, methods of spectro- and fluorimetry, and cell lines cultivation. The main project at present is studying of small molecules and their cardiotoxic effects.

All working groups of the department are open to any scientific and teaching co-operation, accepting students (both pregraduate and postgraduate) and grant proposals co-operation.

Left Atrial Strain Is Highly Predictive of Pulmonary Artery Pressures in Patients with Severe Aortic Stenosis

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Introduction

In patients with severe aortic stenosis (AS), pulmonary hypertension (PH) portends poor prognosis and is one the most powerful predictors of outcome, beyond aortic valve area or left ventricular (LV) function.

Usually PH is considered as the result of passive upstream transmission of the increased left ventricular pressure due to LV hypertrophy and LV diastolic dysfunction: this is ordinary post-capillary pulmonary hypertension.

Sometimes patients present with severe, out of proportion PH, thought to be due to a pre-capillary component: this is called reactive pulmonary hypertension, or pre and post capillary PH.

However, the exact mechanisms of severe PH occurring in the setting of aortic stenosis are not fully understood, but according to some recent reports the left atrial reservoir function may play a key role.

The aim of our study was to try to determine the best predictor of severe PH in aortic stenosis patients: Is it the severity of aortic stenosis, the importance of LV hypertrophy, the degree of LV systolic or diastolic dysfunction, or the left atrial function?

Patients and Methods

80 consecutive aortic stenosis patients referred to our center for pre-operative assessment were enrolled. Severe AS was defined by an aortic valve area less than 1 cm^2 or less than 0.6 cm^2/m^2.

All the patients underwent right heart catheterization with the recording of right atrial, pulmonary arterial, capillary wedge pressure, and cardiac output.

All the echocardiographic examinations were performed using a GE Vivid E9 ultrasound system. Echocardiographic assessment comprised LV measurements, left ventricular ejection fraction (LVEF) using the biplane Simpson's method, LV mass, LV diastolic function including the E/A and E/e' ratios, as well as the E wave deceleration time. Aortic stenosis severity was assessed with the mean aortic gradient and the aortic valve area using the continuity equation.

Right ventricular function was assessed using the TAPSE and the tissue Doppler systolic velocity at the tricuspid annulus. Systolic pulmonary artery pressure was estimated from the tricuspid regurgitant flow velocity. Left atrial measurements comprised the left atrial volume using the biplane Simpson's method, and the left atrial systolic longitudinal strain using speckle tracking analysis in the 4 and 2 chamber views was assessed as an estimation of the left atrial reservoir function.

Results

Table 1: *Demographic and haemodynamic data*

	Overall population (n = 80)	sPAP ≤55 mmHg (n = 51)	sPAP > 55 mmHg (n = 29)	p
Age (years)	80.3 ± 8.4	78,8 ± 7,6	83,5 ± 9,4	0.11
Sex ratio (M/F)	0.48	0.5	0.45	0.86
Mean aortic gradient (mmHg)	45.5 ± 18	48 ± 18	40.1 ± 1.3	0.16
Aortic valve area (cm^2)	0.74 ± 0.18	0.72 ± 0.14	0.75 ± 0.23	0.61
Mean pulmonary artery pressure (mmHg)	29.3 ± 9.7	24.2 ± 7.2	41.4 ± 6.5	< 0.001
Mean capillary wedge pressure (mmHg)	18.4 ± 8.3	14.3 ± 5	28.3 ± 5.5	< 0.001
Diastolic ulmonary gradient (dPAP – PCWP)	–0.07 ± 4	0.48 ± 3.9	–1.5 ± 4.6	0.17

Table 2: *Left ventricular measurements*

	Overall population (n = 80)	sPAP ≤ 55 mmHg (n = 51)	sPAP > 55 mmHg (n = 29)	p
LV ejection fraction (%)	61.7 ± 14.3	63.9 ± 12.3	55.6 ± 17.6	0.07
LV mass, indexed (g/m^2)	147.6 ± 41.2	146.9 ± 35.8	155.8 ± 49.3	0.5
LV longitudinal strain (%)	– 16.4 ± 4.3	– 16.8 ± 4.2	– 13.6 ± 3.4	0.07
LV end diastolic diameter (mm)	**51.6 ± 6.7**	**50.5 ± 5.3**	**55.4 ± 7.7**	**0.02**
E/A ratio	**0.96 ± 0.5**	**0.76 ± 0.21**	**1.52 ± 0.64**	**< 0.001**
E/e' ratio	**17.7 ± 7.02**	**15.7 ± 5.9**	**22.5 ± 7.4**	**0.001**
E deceleration time (ms)	**209.3 ± 81.2**	**230 ± 83.4**	**169.5 ± 64.8**	**0.02**

Table 3: *Left atrial measurements*

	Overall population (n = 80)	sPAP ≤ 55 mmHg (n = 51)	sPAP > 55 mmHg (n = 29)	p
LA volume (ml/m²)	49.9 ± 29	47.4 ± 31.5	59.8 ± 21.9	0.13
LA strain (4 c view)	**17.4 ± 7.6**	**20.4 ± 6.65**	**10.7 ± 5.3**	**< 0.001**
LA strain (2 c view)	**18.5 ± 8.05**	**21.1 ± 8.2**	**9.9 ± 5.5**	**< 0.001**

Table 4: *Predictors of severe PH > 55 mmHg (univariate analysis)*

Factors	(95% IC)	r	p
Age	0.32 (−0.19 to 0.85)	0.17	0.21
Aortic valve area	−5.1 (−33.9 to 23.6)	−0.05	0.72
Mean aortic gradient	−0.24 (−0.05 to 0.01)	−0.27	0.06
LV end diastolic diameter	**1.09 (0.4 to 1.8)**	**-0.27**	**0.002**
LV ejection fraction	−0.29 (−0.6 to 0.07)	−0.25	0.11
Indexed LV mass	0.08 (−0.003 to 0.17)	0.22	0.06
Indexed LA volume	0.14 (−0.04 to 0.3)	0.26	0.14
LV strain	**1,44 (0.16 to 2.7)**	**0.42**	**0.028**
E deceleration time	**-0.07 (-0.12 to -0.02)**	**-0.36**	**0.006**
E/A ratio	**16 (12.3 to 19.9)**	**0.50**	**< 0.001**
E/e' ratio	**0.77 (0.26 to 1.27)**	**0.33**	**0.004**
TAPSE	**-1.14 (-2.02 to -0.25)**	**-0.41**	**0.012**
S Tricuspid annulus	−0.002 (−0.04 to 0.04)	−0.002	0.90
sPAP/TR	**0.78 (0.58 to 0.99)**	**0.76**	**< 0.001**
LA strain 4 c view	**-1.43 (-1.95 to -0.91)**	**-0.68**	**< 0.001**
LA strain 2 c view	**-1.13 (-1.59 to -0.67)**	**-0.67**	**< 0.001**

Patients were 80 year-old in average. Regarding left ventricular measurements, ejection fraction, mass and longitudinal strain were not significantly different between the 2 groups but end-diastolic diameter was higher (Tab. 1).

Patients with severe pulmonary hypertension had more severe diastolic function parameters than other patients, with higher E/A and E/e' ratios and shorter E wave deceleration times.

Regarding left atrial measurements, the left atrial volume was higher in patients with severe pulmonary hypertension, but the difference was not statistically significant. However, the left atrial systolic longitudinal strain, which is a parameter of left atrial reservoir function, was more severely decreased in patients with severe pulmonary hypertension, with a highly significant difference compared to patients with lower pulmonary artery pressures (Tab. 2, 3).

In univariate analysis, the predictors of severe pulmonary hypertension were the left ventricular end diastolic diameter, the left ventricular systolic longitudinal strain, the diastolic function parameters, the TAPSE, the tricuspid regurgitant velocity, and the left atrial strain (Tab. 4).

However, in multivariate analysis, the only independent echocardiographic parameter associated with severe pulmonary hypertension was the left atrial strain, with a good negative correlation: the more the left atrial strain decreases, the more the systolic pulmonary artery pressure increases (figure 1).

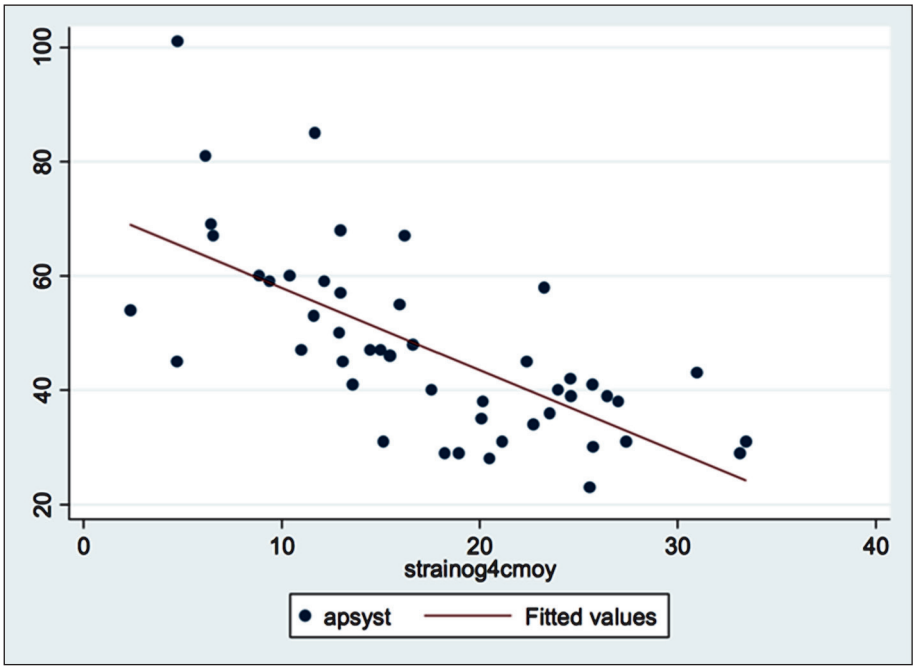

Figure 1: *Relationship between left atrial strain and systolic pulmonary artery pressure*

ROC analysis showed that with a cut off value of 13%, left atrial strain was predictive of a systolic pulmonary artery pressure above 55 mmHg with a sensitivity of 85% and a specificity of 78% (figure 2).

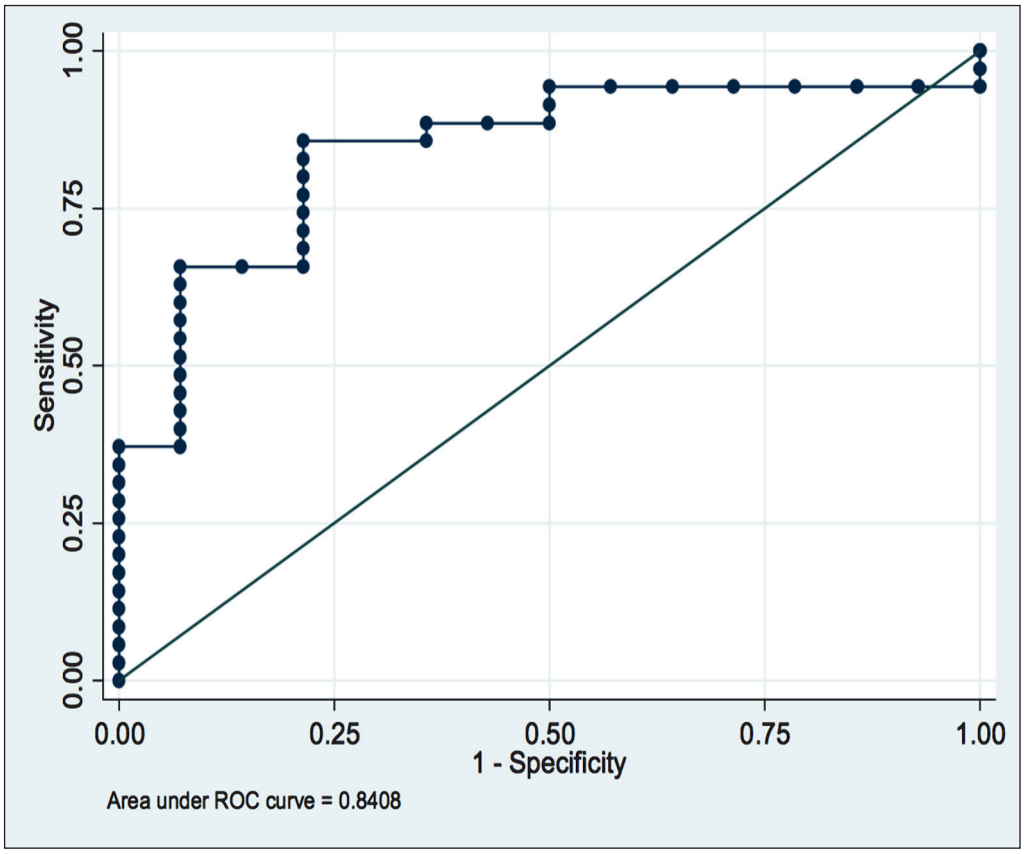

Figure 2: *ROC analysis for left atrial strain predicting systolic pulmonary artery pressure above 55 mmHg*

Discussion

In a normal heart, left heart chambers are compliant and the pressures are low.

In heart failure with preserved ejection fraction, pathophysiology of increased pulmonary pressure is usually considered to be due to a stiff left ventricle, but this can only explain increased diastolic pressures.

In systole, the mitral valve is closed, so the final chamber is the left atrium which has consequently an important reservoir function; if the left atrium in non-compliant, there is an increased V wave and an increased systolic artery pressure.

Therefore, in aortic stenosis, we could propose the following paradigm: aortic stenosis is a model of heart failure with preserved systolic function; as the left ventricle becomes stiffer, the diastolic pressure increases, the left atrial is submitted to an increased afterload and becomes stiffer itself, and as it loses its reservoir function the systolic pulmonary arterial pressure increases.

Conclusion

Thirty six % of patients with AS had severe PH > 55 mmHg. PH is not predicted by AS severity, LV mass or ejection fraction. Patients with PH have worse LV diastolic function and LV longitudinal

strain. In multivariate analysis LA strain measured by speckle tracking analysis is the only independent predictor of pulmonary artery pressure in patients with severe AS

These results suggest that the increase in systolic PAP is tightly linked to the decrease in left atrial reservoir function.

The prognostic value of LA strain should be further assessed.

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Vascular Function in Health and Disease: A Gender Comparative Study

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Objectives

Orthostasis or drop in blood pressure during upright posture, is a product of the activity of the gravitational force on the cardiovascular system, which if the cardiovascular system is not able to compensate will cause loss of consciousness, or syncope In some people by which, because of different pathological condition, the cardiovascular system is not able to maintain a normal blood pressure during upright posture, and leads to syncope. Postural hypotension in the elderly age group, reduces cerebral blood flow and carries considerable morbidity from dizziness, falls and injury. In acute stroke, cerebral perfusion is dependent on systemic blood pressure because cerebrovascular autoregulation is impaired. Thus, postural hypotension in acute stroke patients may further impair cerebral blood flow, increase stroke risk, or hinder recovery.

Methods

This study consist of three cohorts: (A), (B), and (C).

Subjects: In the cohort (A) we will examine (60) Healthy volunteers (males, n=30; females, n=30) with no histories of vasovagal syncope. Subjects should be non-obese, not on any medications and non-smokers. Any pathological (neurological, cardiovascular, endocrine) condition will be considered an exclusion criterion. Exercise and engaging in stressful activity 2 days before the tests will not be allowed. Furthermore, 24 hours before commencement of the tests abstinence from coffee and other stimulants will also be required. To compensate for random and unavoidable climatic effects on the cardiovascular system, every day one protocol (at 9-11am) will be performed. All subjects will be tested during the same time of the day for all the trials. In the cohort (B) we will examine elderly patients with Parkinson' disease, PD (n=20), Alzheimer's disorder, AD (n=20), or Stroke (n=20) will do a sit-to-stand test for 6 min every three months and vascular responses monitored. Each subject will do a sit to stand test between 9-1 1 am, every 3 monthly. While in the seated position, subjects will be fitted with a non-invasive blood pressure monitor and a three-lead ECG (see below) as well as a Transcranial Doppler device. In cohort (C) is a control group, and will be examined age matched healthy subjects (n=60).

Experimental equipment: Endothelial dysfunction will be assessed by non-invasive flow-mediated dilatation (MyLab Five Ultrasound Colour Doppler, and Cardiovascular Suite). Hemodynamic monitoring will include blood pressure (upper arm oscillometry and finger plethysmography), heart rate (3-lead ECG) and thoracic impedance measurements using a Task Force Monitor® (TFM, CNSystems, Graz, Austria). Power spectrum analysis of heart rate (HR) variability assesses sympathovagal balance. Low (LF: 0.04 - 0.15 Hz) and high frequency (HF: 0.15 - 0.40 Hz) power components of RR-

intervals (RRI)`, diastolic blood pressure (DBP) and systolic blood pressure (SBP) will be evaluated. Baroreceptor sensitivity will be calculated from continuous monitoring of HR and SBP. As vascular changes over time may affect blood flow to the brain, cerebral blood flow velocity will be measured using transcranial Doppler ultrasonography (Doppler-Box, DWL, Sipplingen, Germany). At the end of 30 min supine rest period and post pre-syncope and 15 and 30 min following pre-syncope, 20 ml blood will be collected. We will measure:

Plasma volume changes; Plasma hormones: aldosterone, PRA, arginine vasopressin (AVP), adrenomedullin and galanin will be measured.

Expected results

1. We expect that the result will show differences in the orthostatic responses between males and females. Some studies suggest that the stroke volume and stroke index paramters were lower in women compared with men and that women have higher HR during progressive LBNP and at pre-syncope compare to men. (Fu Q. at all, 2004). In another study the results indicate that elderly men have poorer orthostatic tolerance under enduring postural stress then women of the same age (Mellingsaeter R. M, 2013).
2. Also we expect that differences in orthostatic responses between old healthy and stroke subjects. The results of a prospective study reveal the abolition of the circadian rhythm of heart rate variability and a loss of the relative vagal nocturnal dominance in patients with acute ischemic stroke (Korpelainen T. J at al, 1997). In another study it was observed that during passive head up tilting, patients with histories of stroke show drops in blood pressure (Enishi et al., 2004).
3. Also Differences in hemodynamic parameters over seasons. Based on the data from our pilot studies- in which we observed seasonal variations in some volume regulating hormones-, we expect that orthostatic tolerance will vary across seasons

Expected impact

With this project we will achieve significant information on the effects of orthostatic load and circannual rhythms on vascular and endothelial function in patients with PD/ AD/ Stroke. In a future scenario our results can be used for power/sample size calculations.

Expected is also a contribution on prevention and treatment of falls to save in lives and cost of the public health system. Syncope is dangerous due to injury sustained when subjects fall, resulting in fractures. Knowledge from this project will lead to lives saved, by reducing number/ severity of syncopal events and falls. Falls are common among elderly, and elderly women fall nearly twice as often as men, albeit differences seem to disappear after the age of 90. Reasons for fall are multiple: gait and balance disturbances, use of sedatives, polypharmacy, reduced muscle strength, frailty, acute and chronic diseases, dementia, poor vision and syncope. However, among elderly people, gender differences in orthostatic tolerance and potential mechanisms are even less studied, possibly because it is difficult to separate changes due to disease and medication from aging of the cardiovascular system.

At last we expect the improving of treatments of cardiovascular disorders. With increasing age, the frequency of cardio-vascular events and syncope increases. We wish to establish whether orthostatic load, circadian rhythms and seasonality affect endothelial function in healthy young subjects and the elderly, with/without PD/ AD/ Stroke and across gender.

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Variabilität in der Blutdruckmessung

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Einladung

zu einem Gastvortrag von

Prof. MUDr. Jarmila Siegelová

Dept. of Sports Medicine and Rehabilitation

Faculty of Medicine, Masaryk University, Brno

„Variabilität in der Blutdruckmessung“

Freitag, 8. Juli 2016; 10:00 Uhr

Seminarraum 07.51, Institut für Physiologie

Vorklinik, Harrachgasse 21/V

Kontinuierliche Blutdruckmessung „Beat by Beat“ Tierstudien

akceleraci tepové vlny trvající asi 0,04 sec. Zaoblený hrot tepové vlny se zapisuje přibližně exponenciálním poklesem derivační křivky k nulové linii s naznačeným anakrotickým hrotem B. Decelerace tepové vlny se vyznačuje dikrotickým minimem D pod nulovou linií a trvá asi 0,04 sec. Hrot maxima A a minima D ostře ohraničují trvání ejekční fáze levé srdeční komory (obr.).

Ejekční fáze u zdravých ležících lidí trvá 0,239 ± 0,011 sec a činí 27 % srdečního cyklu. Její absolutní hodnota se nemění v rozmezí systolických tlaků od 105 do 180 mm Hg, lehce se prodlužuje při bradykardii a zkracuje při tachykardii. U 60% hypertoniků bez klinických známek insuficience levé srdeční komory se ejekční fáze prodlužuje více než odpovídá srdeční frekvenci a to nejvíce po 60 letech života.

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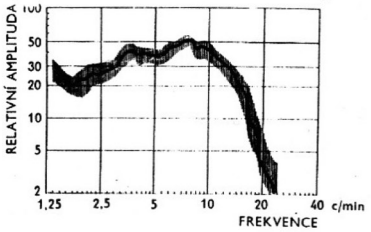
FREKVENČNÍ SPEKTRUM SPONTÁNNÍCH VLN KREVNÍHO TLAKU U NENARKOTISOVANÝCH KRÁLÍKŮ. *J. Siegelová, B. Fišer, J. Peňáz,* Fysiologický ústav lékařské fakulty university J. E. Purkyně, Brno. Předneseno na 18. fysiologických dnech v Hradci Králové dne 20. 9. 1966.

U králíků bez narkosy, připoutaných v poloze na zádech, jsme zaznamenávali krevní tlak v a. femoralis vždy po dobu 20 minut. Preparační oblast jsme anestesovali lokálním nástřikem novokainem. Celkem jsme získali k analyse 16 záznamů na 8 pokusných zvířatech.

Záznamy byly provedeny jednak běžnou optickou metodou na fotografický papír, jednak v podobě šířkových záznamů na kontrastní film; tyto záznamy jsme pak analysovali stejným způsobem jako v předchozí práci (1), tj. určili amplitudu pro každou frekvenci v pásmu od 1,25 do 40 c/min. Tak jsme získali frekvenční spektra jednotlivých záznamů, jež vykazovala většinou několik maxim. Pro malou statistickou spolehlivost spekter, získaných u jednotlivých, pro tuto analysu poměrně krátkých záznamů, jsme výsledky z celé pokusné série shrnuli do jednoho souhrnného grafu, v němž již nebyla uvedená dílčí maxima zřetelná. Toto frekvenční spektrum má tvar křivky s jedním plochým vrcholem ve frekvenčním pásmu 3–12 c/min. a s prudkým poklesem nad tímto pásmem (viz obr.). Spontánní, tzv. Traube–Hering–Mayerovy vlny představují tedy do značné míry náhodný, v podstatě neperiodický proces, v němž mají převahu určité frekvence, pravděpodobně díky resonančním vlastnostem některých regulačních mechanismů.



Průměrná amplituda spontánních vln krevního tlaku připadající na jednotlivé frekvence. (Šrafování znázorňuje střední chybu průměru.)

1. Peňáz J., Fišer B.: Čs. fysiol. – 15:517, 1966.

VPLYV CHIRURGICKEJ DENERVÁCIE SRDCA NA ENERGETICKÝ METABOLIZMUS SRDCA. PRÍSPEVOK K TROFICKÉMU VPLYVU NERVOVÉHO SYSTÉMU. *E. Barta, E. Breuer, E. Pappová, L. Zlatoš,* Katedra experimentálnej patológie Lek. fak. UK, Bratislava. Prednesené na 18. Fyziologických dňoch v Hradci Králové dňa 20. 9. 1966.

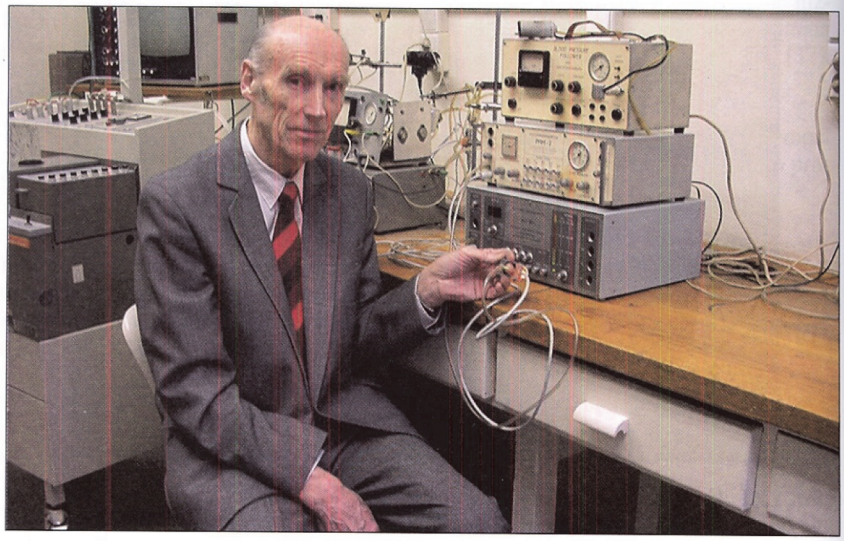
U 12 psov sa sledovali metabolické zmeny a práca srdca 14–18 dní po kompletnej chirurgickej selektívnej denervácii srdca, uskutočnenej metódou podľa Černého a Oláha (2), a porovnali sa s nálezmi získanými pred denerváciou, ako aj s nálezmi získanými u 37 zdravých psov. Zistilo sa, že denervácia srdca má za následok pokles arteriálneho tlaku, spomalenie frekvencie srdca, pokles minútového objemu, koronárneho prietoku, ako aj zníženie práce ľavej komory a účinnosti ľavej komory. Celkový periferný odpor a koronárna vaskulárna rezistencia sa zvýšili. Spotreba jednotlivých energetických látok (glukózy, kyseliny mliečnej, kyseliny pyrohroznovej a neesterifikovaných mastných kyselín) a kyslíka/100 g svaloviny ľavej komory/min. sa po denervácii významne znížila. Značne poklesla aj účasť kyseliny mliečnej a pyrohroznovej na tvorbe oxydatívnej energie v denervovanom srdci. Zmeny pomeru laktát/pyruvát pri prietoku krvi cez myokard odhalili, že denervovaný myokard pracuje v podmienkach hypoxie. Intenzita dýchania tkaninových rezov z denervovaného srdca bola nižšia ako u kontrol.

Predpokladá sa, že ide o primárny pokles intenzity metabolických procesov v denervovanom

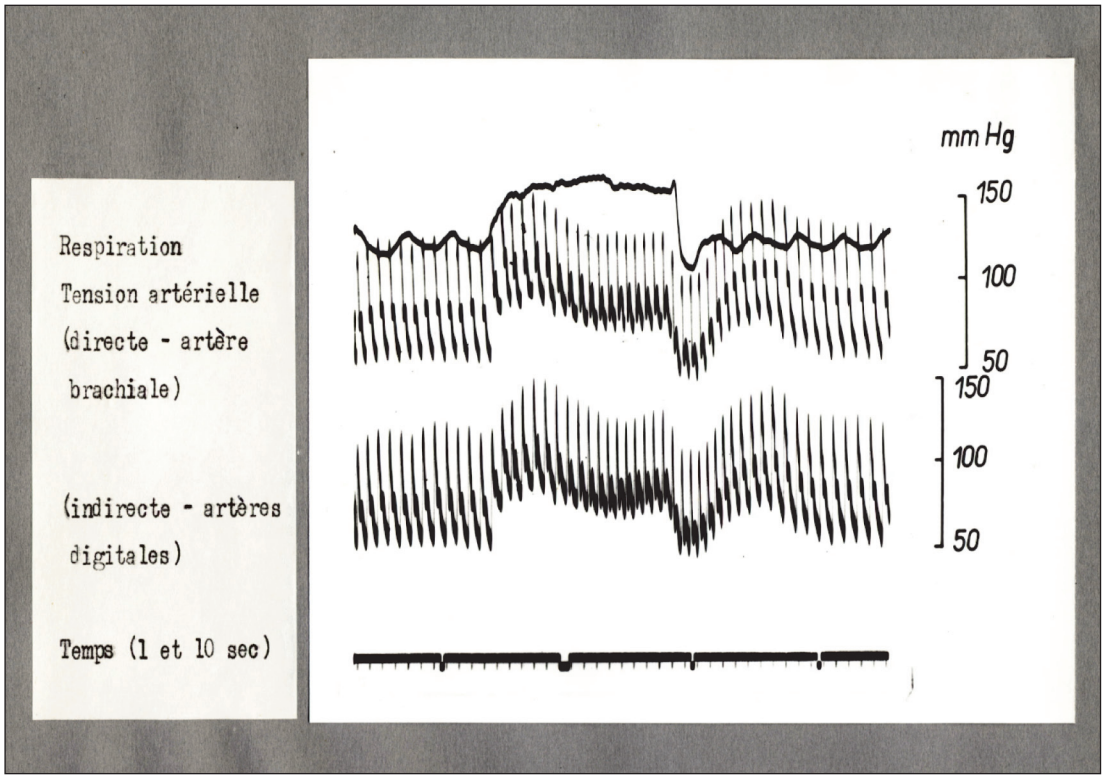
36 Čs. fysiol. 16 (1967)

Peňáz J. Fišer B. Siegelová J. Frequenz Spektrum von spontan Blutdruckschwankungen in nicht narkotisierten Kaninchen. Čs. fyziol. 1967, n. 16, p.16.

Studien am Menschen



Obr. 1.61 *Prof. MUDr. Jan Peňáz, CSc., s prvním prototypem přístroje na kontinuální měření systémového krevního tlaku pomocí metody digitální fotopletysmografie, který zkonstruoval a vyrobil v roce 1966.*



Invasive und nicht-invasive Blutdruckmessung an der Person von Professor Fišer, 1966

POWER SPECTRA OF SPONTANEOUS VARIATIONS OF INDIRECTLY RECORDED BLOOD PRESSURE, HEART RATE AND ACRAL BLOOD FLOW

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Department of Physiology, Faculty of Medicine, J. E. Purkyně University, Brno, Czechoslovakia

(*Received March 28, 1977*)

Heart rate (HR), diastolic pressure (DP), systolic pressure (SP), pulse pressure (PP) and finger blood flow (FF) were recorded by means of indirect photoelectric methods in 15 subjects. The autocorrelation functions, power spectral densities, crosscorrelation functions, cross-spectral densities, phase angles and coherences of these circulatory variables and respiration were calculated.

Despite the differences of power spectral densities in different subjects, characteristic frequency maxima were observed in all curves.

The respiratory rhythm (8–18 c/min) is most apparent in HR, less in SP, PP and DP, and absent in FF. A distinct peak in the frequency band 5–8 c/min (10-s rhythm) was detected in all records of HR, in some records of SP, DP and PP, and only exceptionally in FF. In the frequency band of 3–5 c/min, one or two peaks were regularly found in DP, sometimes in SP and PP, occasionally in HR. Very slow rhythms (0–3 c/min) were present in all circulatory events with maximal amplitude in FF.

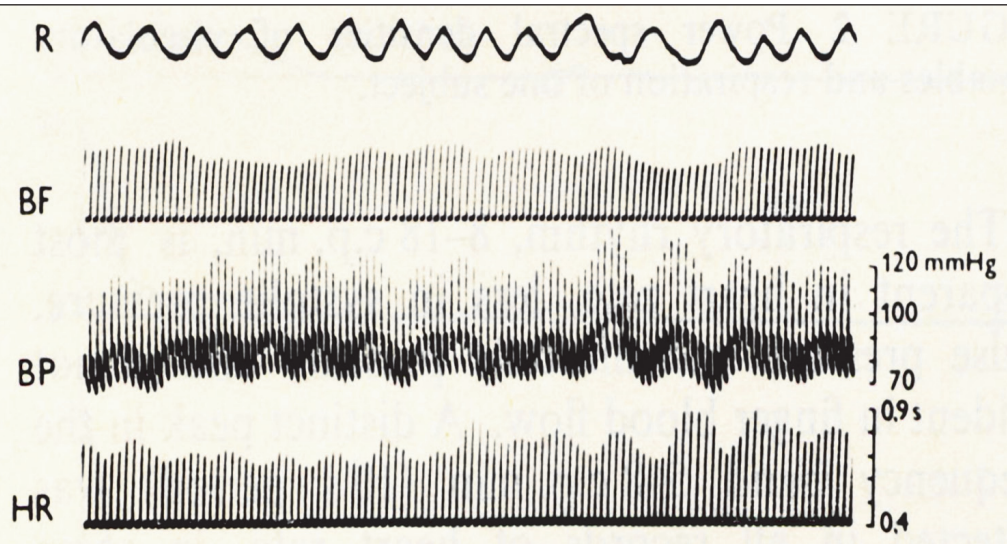
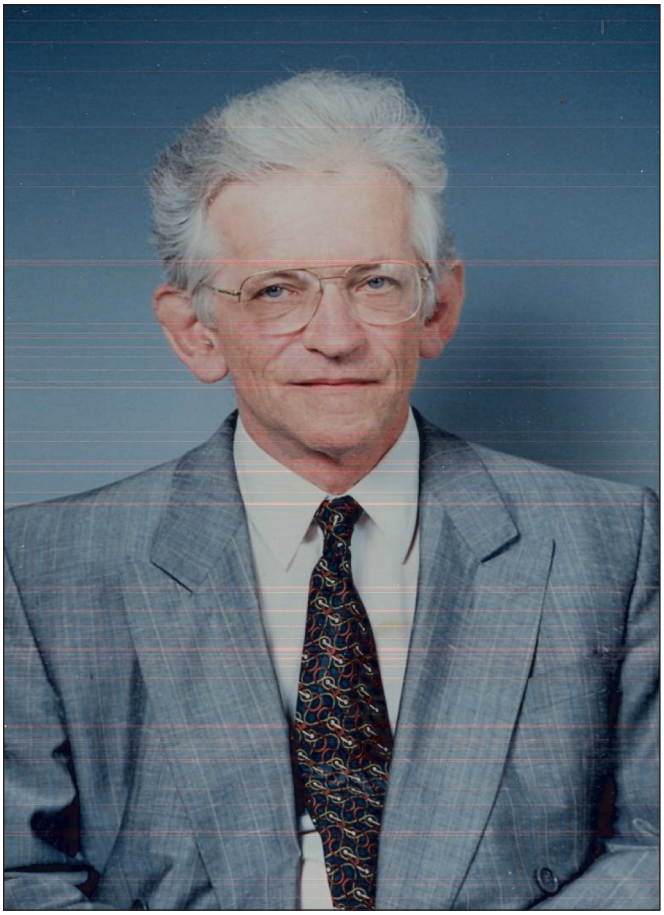


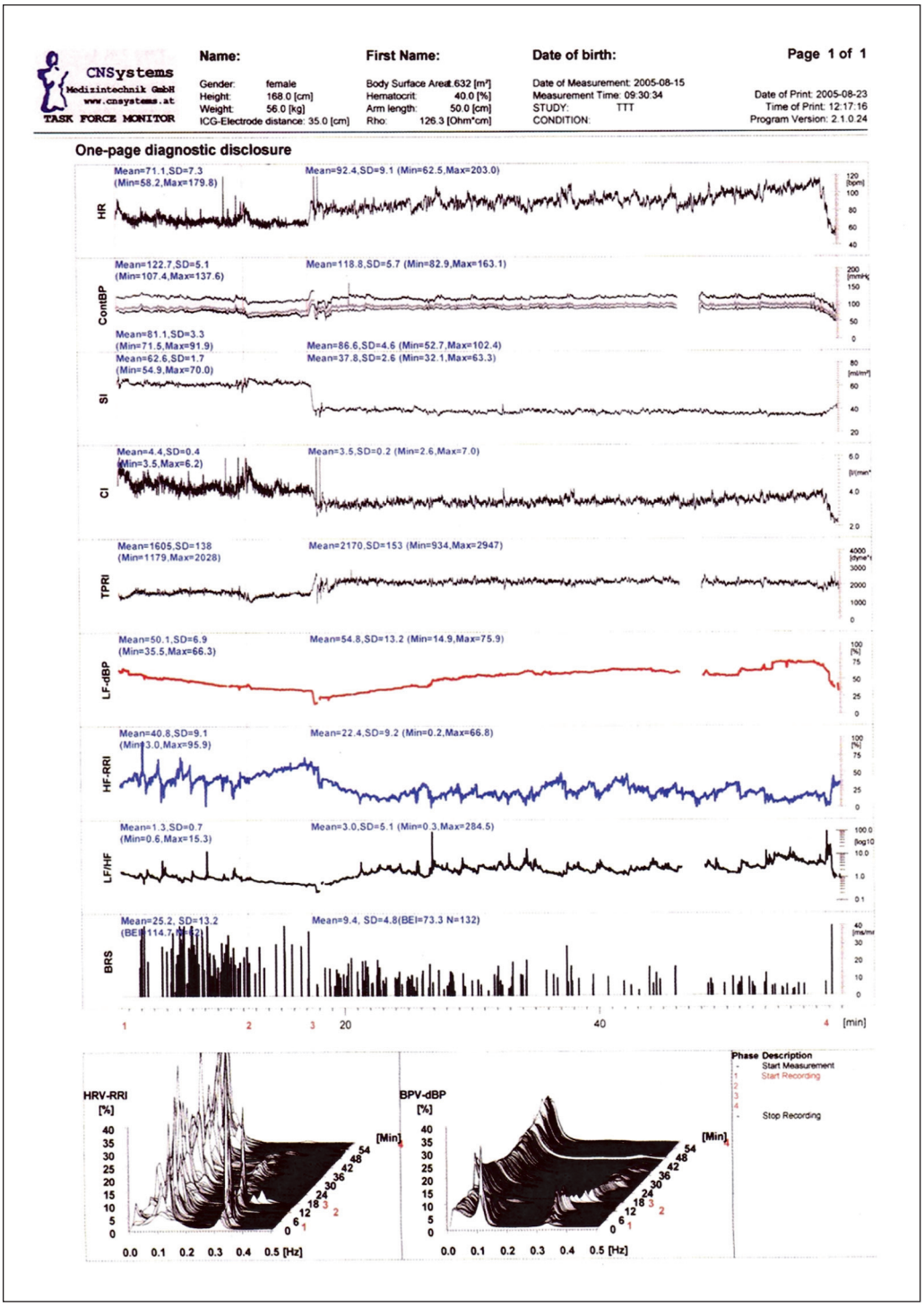
FIGURE 1 An example of a record of circulatory variables and respiration. R: respiration; BF: acral blood flow; BP: blood pressure; HR: heart rate.

Zusammenarbeit mit der Universität Graz



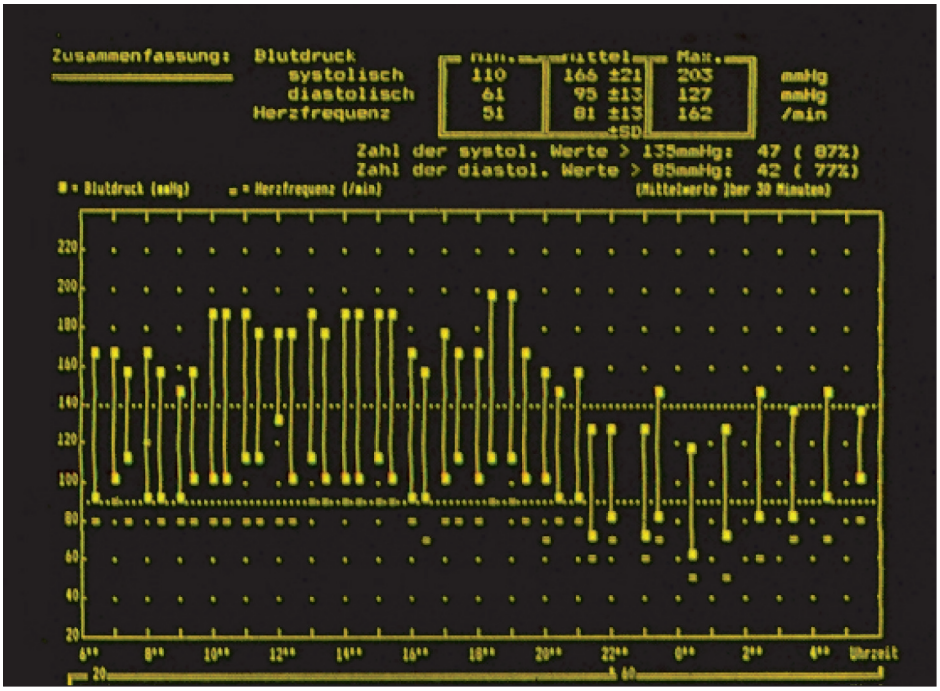
Prof. Dr. Thomas Kenner, M.D., Dr. h.c. mult.
Dr. h. c. Universität Jena, 1990
Dr. h. c., Semmelweis University Budapest, 1998
Dr. h. c., Masaryk University Brno, 2000

Auf der Grundlage der Zusammenarbeit mit der Universität Graz, kauften wir das Gerät Task Force-Monitor von Graz, auch von Wissenschaftlern und Kollegen vom Institut für Physiologie unter der Leitung von Professor Kenner geschaffen.

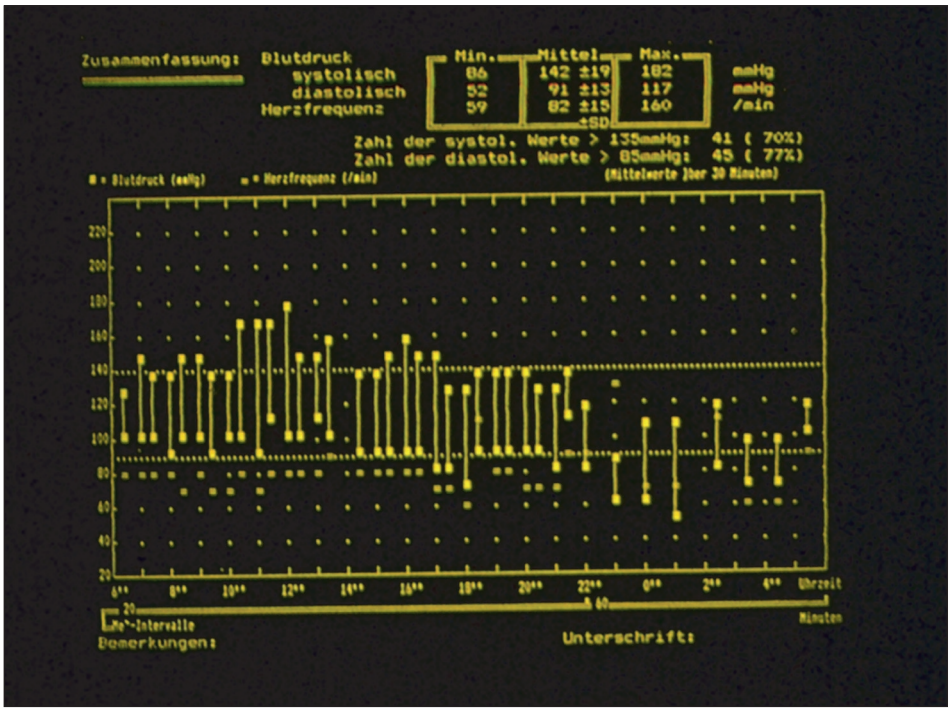


Task Force Monitor Report, Brno 23.8.2005

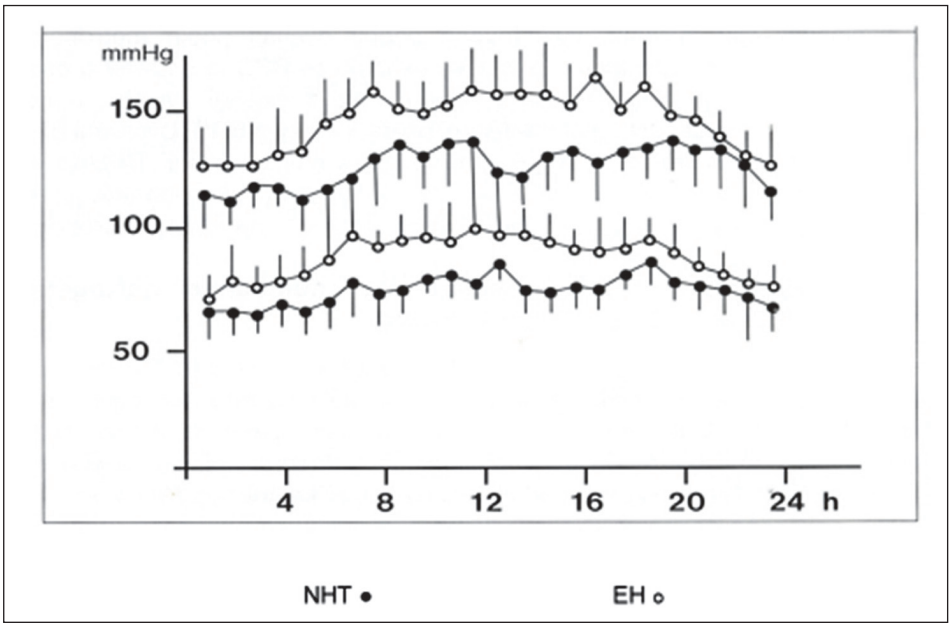
24-Stunden Ambulatorische Blutdruckmessung



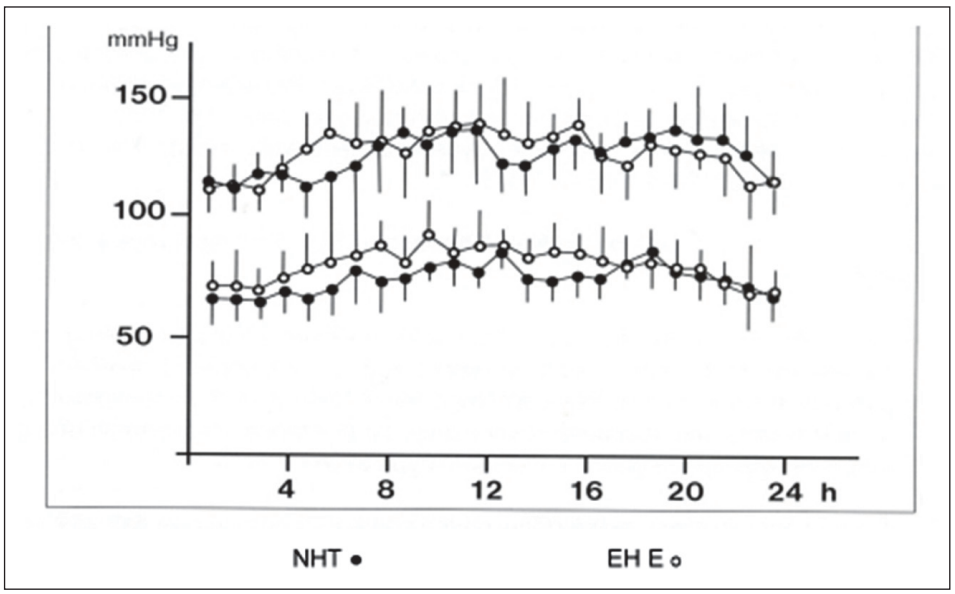
Accutracker II Report



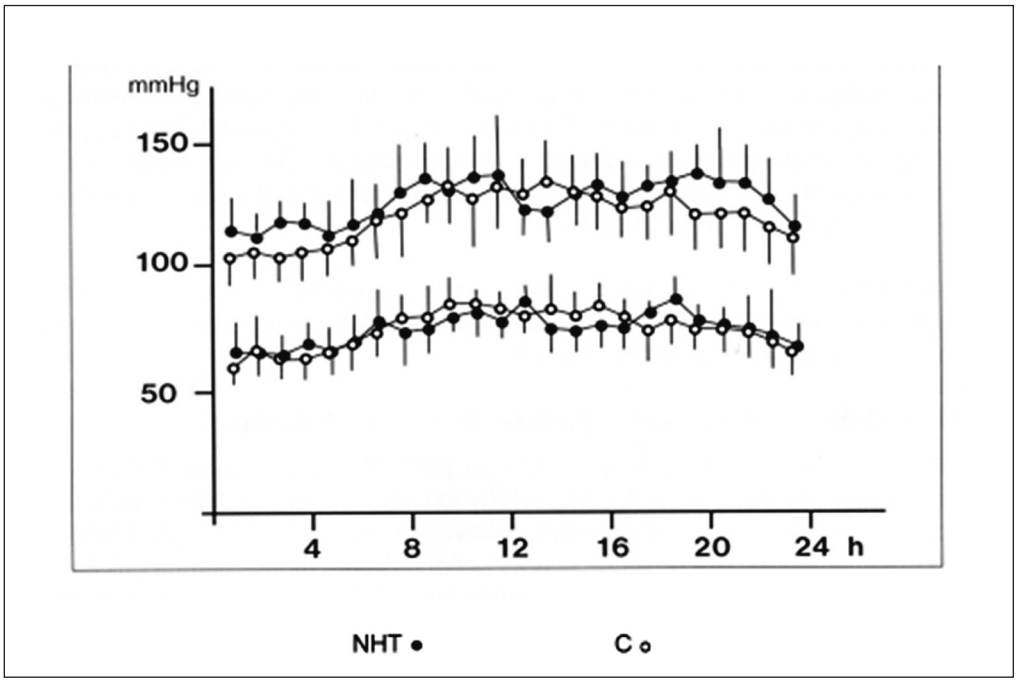
Accutracker II Report



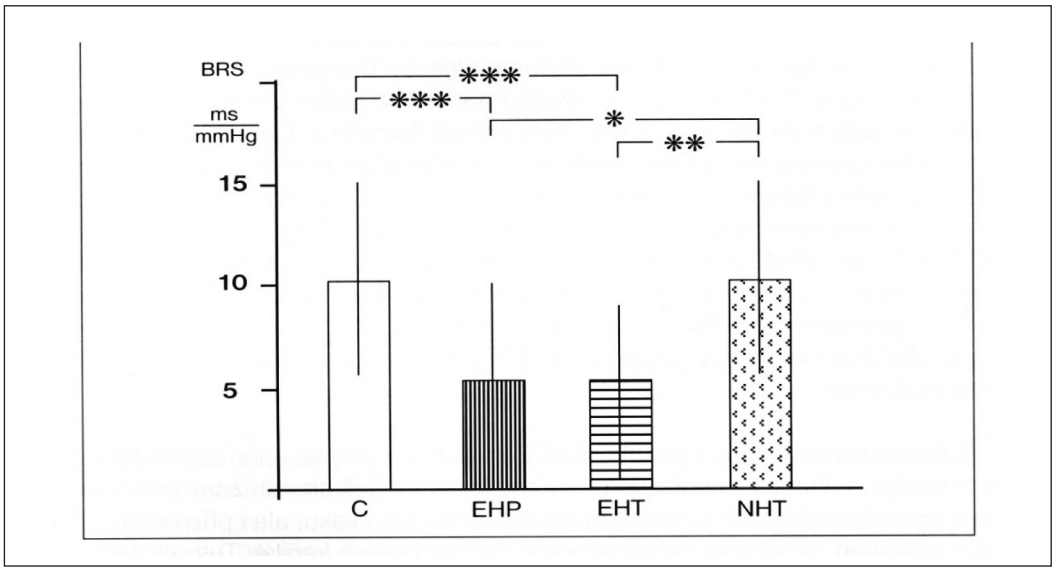
Mittelwerte in Stunden von systolischem und diastolischem Blutdruck (±SD) während 24-Stunden ambulanter Blutdruckmessung in einer Gruppe von Patienten mit behandelter nephrogener Hypertonie (gefüllte Symbole) und einer Gruppe von Patienten mit unbehandelter essentieller Hypertonie (offene Symbole).



Mittelwerte in Stunden von systolischem und diastolischem Blutdruck (±SD) während 24-Stunden ambulanter Blutdruckmessung in einer Gruppe von Patienten mit behandelter nephrogener Hypertonie (gefüllte Symbole) und einer Gruppe von Patienten mit behandelter essentieller Hypertonie mit Enalapril (offene Symbole).

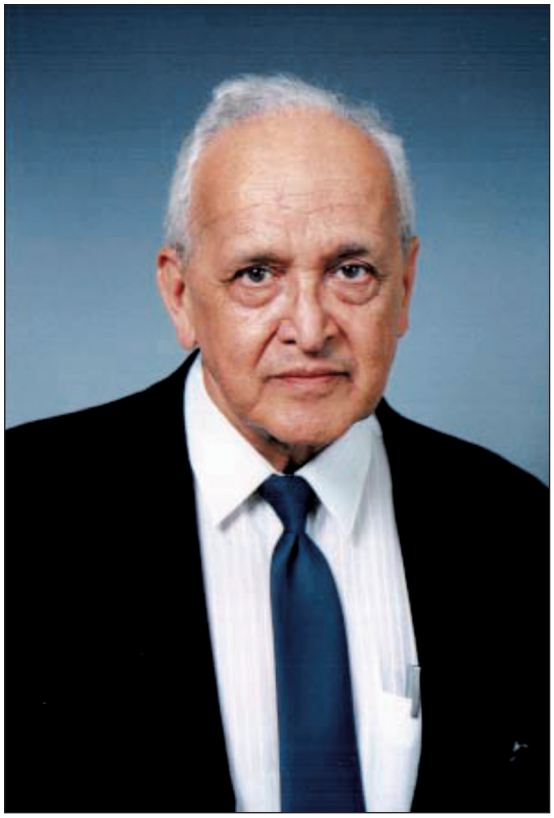


Mittelwerte in Stunden von systolischem und diastolischem Blutdruck (±SD) während 24-Stunden ambulanter Blutdruckmessung in einer Gruppe von Patienten mit behandelter nephrogener Hypertonie (gefüllte Symbole) und einer Gruppe von Normotonikern (offene Symbole).

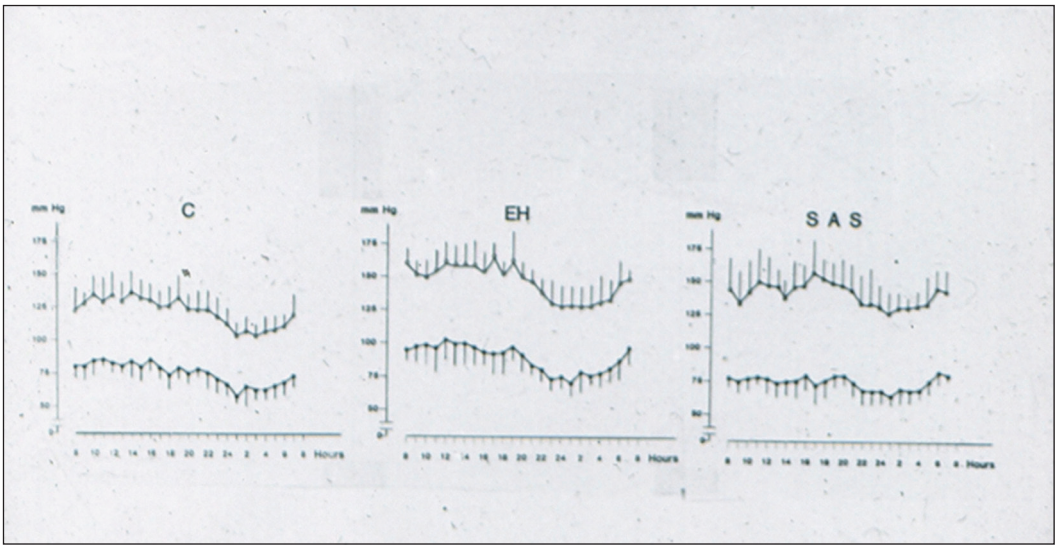


Baroreflexsensitivität (±SD) in Normotonikern (C), bei Patienten mit essentieller Hypertonie behandelt mit Placebo (EH P), bei Patienten mit essentieller Hypertonie behandelt mit Enalapril (EH T), und bei Patienten mit nephrogener Hypertonie behandelt mit Enalapril (NHT).

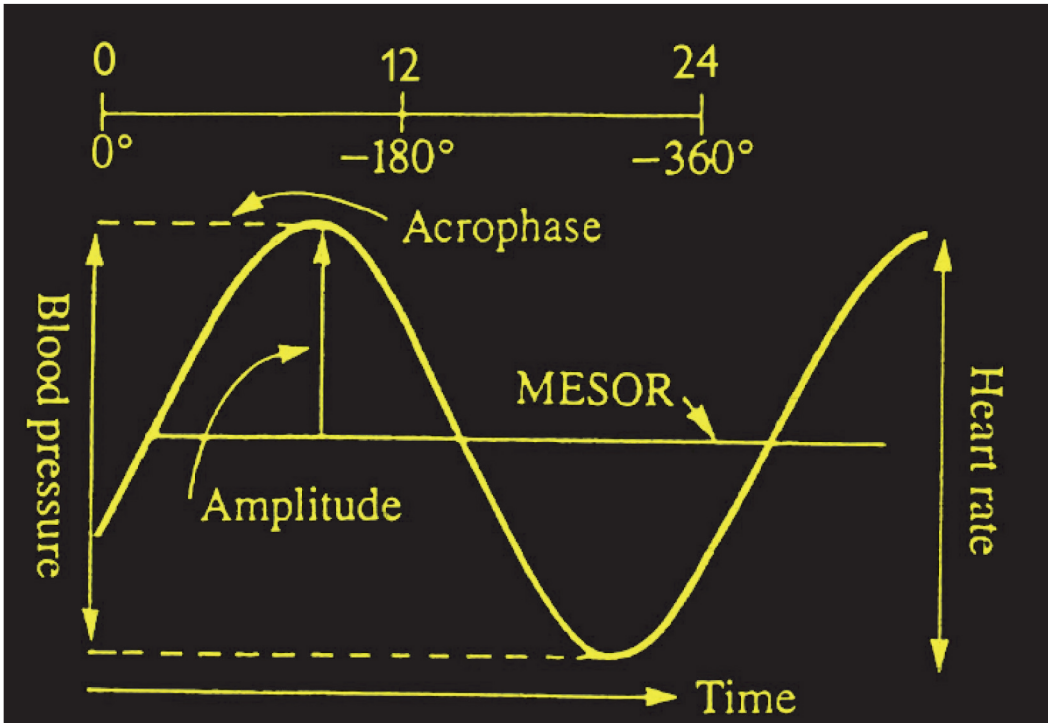
Zusammenarbeit mit der Universität Minnesota



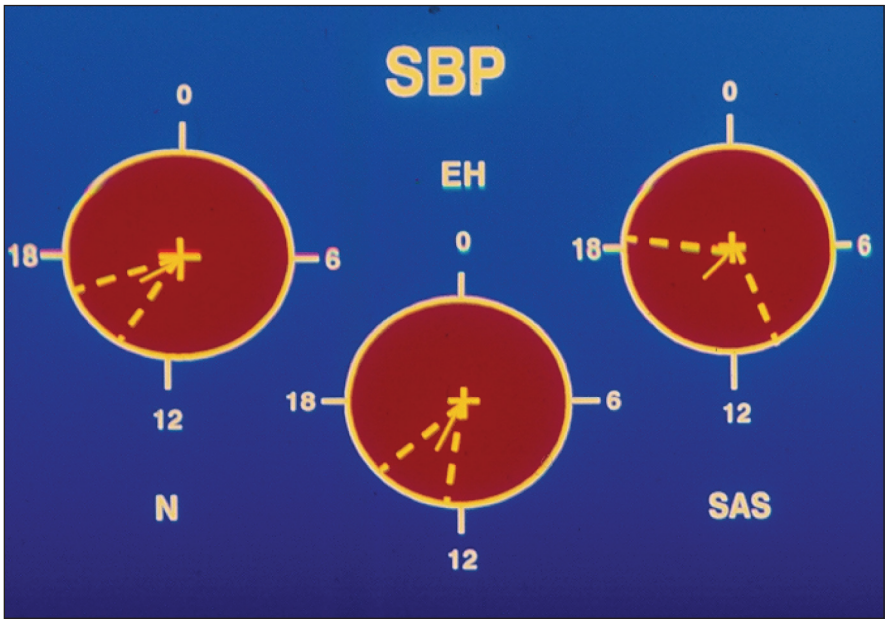
Franz Halberg, M.D., Dr. h.c. (Montpellier),
Dr. h.c. (Ferrara), Dr. h.c. (Tyumen),
Dr. h.c. (Brno), Dr. h.c. (L'Aquila), Dr. h.c.
(People's Friendship University of Russia, Moscow),
Professor of Laboratory Medicine and Pathology, Physiology, Biology, Bioengineering and Oral medicine,
Director, Halberg Chronobiology Center, University of Minnesota, USA
(1919 – 2013)



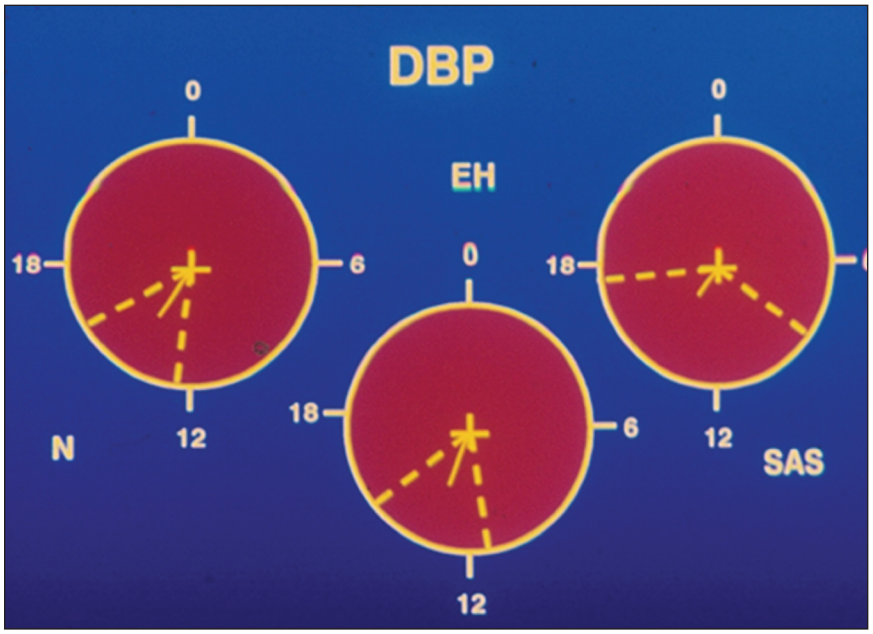
C – controls, EH – essential hypertension, SAS – sleep apnea syndrom



Halberg Cosinor Analyse

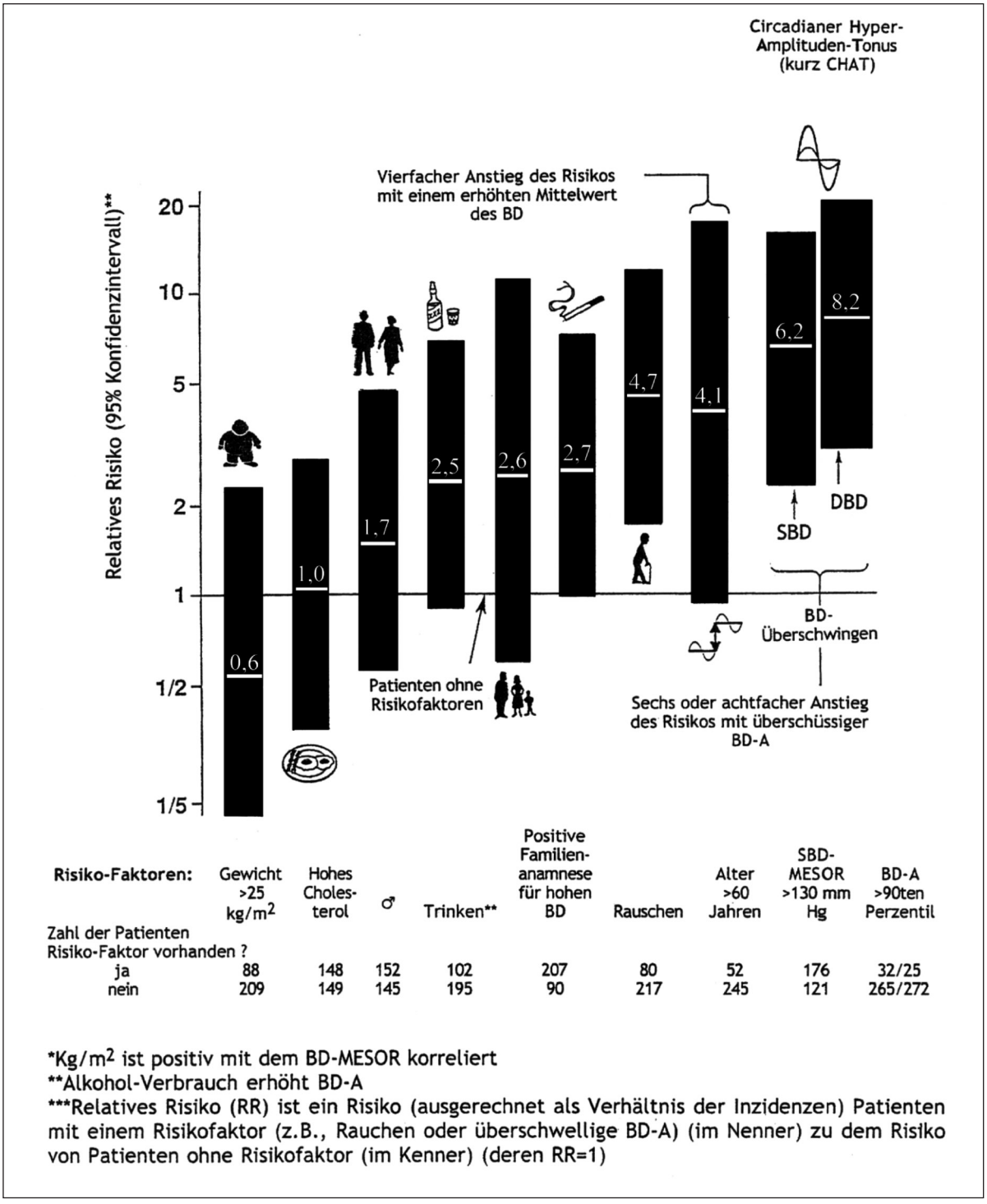


Acrophases
N – controls, EH – essential hypertension, SAS – sleep apnea syndrom



Acrophases
N – controls, EH – essential hypertension, SAS – sleep apnea syndrom

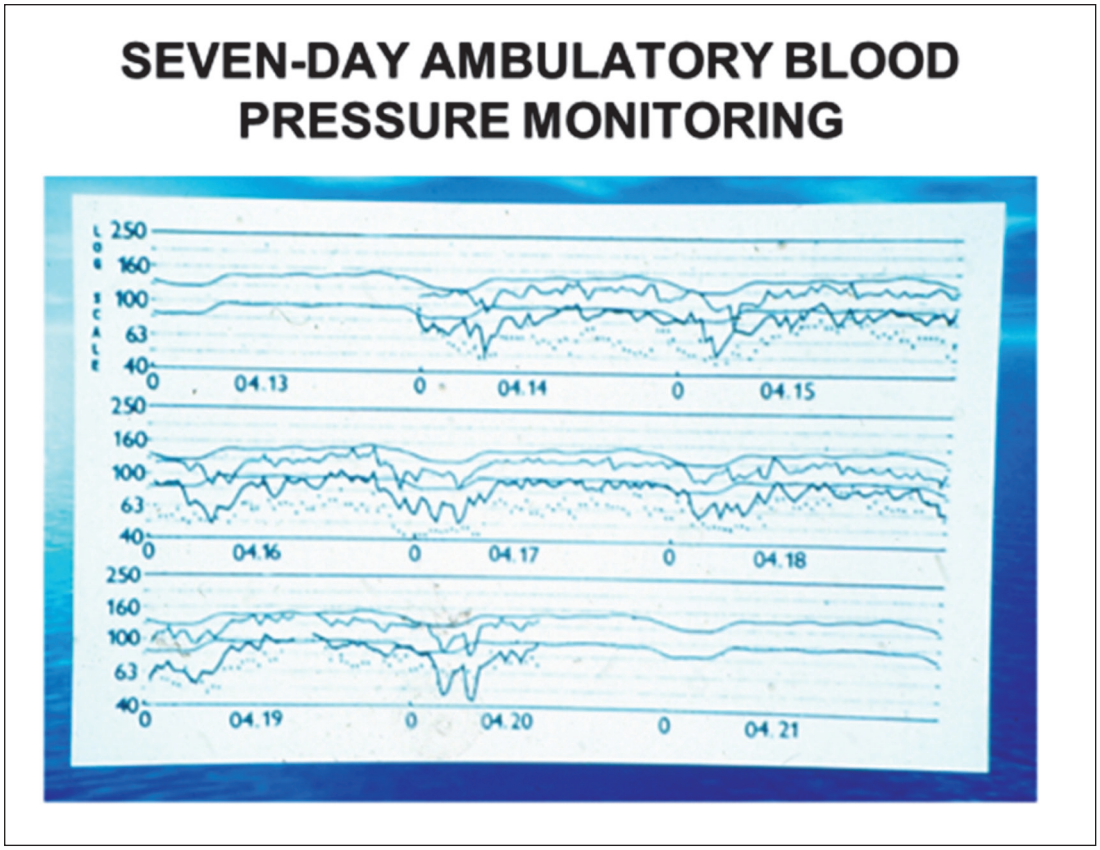
Risikofaktoren für Ischämischen Schlaganfall



Risiko-Faktoren:	Gewicht >25 kg/m²	Hohes Cholesterol	♂	Trinken**	Positive Familienanamnese für hohen BD	Rauschen	Alter >60 Jahren	SBD-MESOR >130 mm Hg	BD-A >90ten Perzentil
Zahl der Patienten Risiko-Faktor vorhanden ?									
ja	88	148	152	102	207	80	52	176	32/25
nein	209	149	145	195	90	217	245	121	265/272

*Kg/m² ist positiv mit dem BD-MESOR korreliert
**Alkohol-Verbrauch erhöht BD-A
***Relatives Risiko (RR) ist ein Risiko (ausgerechnet als Verhältnis der Inzidenzen) Patienten mit einem Risikofaktor (z.B., Rauchen oder überschwellige BD-A) (im Nenner) zu dem Risiko von Patienten ohne Risikofaktor (im Kenner) (deren RR=1)

Sieben Tage/ 24-stunden Ambulante Blutdruckmessung



14.4. – 20.4.1996 sieben Tage nicht-invasive Blutdruckmessung an der Person von Professor Fišer

In den Jahren 1996 - 2008 wurden 307 Tests von siebentägiger, 24 Stunden ambulanter Blutdruckmessung aufgezeichnet und diese Resultate bilden die „Datenbank Brno“. Diese Daten haben wir in Brno als Mittelwerte analysiert und auch an das Halberg-Chronobiology Center (Minnesota) geschickt. Prof. Cornélissen hat diese Daten mittels Halberg‘scher Cosinor-Analyse ausgewertet.

Erhöhter Blutdruck: Diagnose und Behandlung

Für die Diagnose der Hypertonie gilt bis zum heutigen Tag die dreimalige

Sprechstundenmessungen des Blutdrucks in Abständen von 7 Tagen, wie es schon seit 1904 und auch in der Zwischenzeit vorgeschlagen wurde.

Die ambulante 24-Stunden Blutdruckmessung, zur Zeit die entscheidende Instanz, ist für eine Diagnose wichtig. Am Halberg Chronobiology Center wurden über viele Jahre die Daten von 24-Stunden ambulanten Blutdruckmessungen von mehreren Staaten gesammelt.

Die Europäische Gesellschaft für Hypertonie („European Society of Hypertension“) analysierte die 24 Stunden ambulante Blutdruckmessung mit Grenzwerten für Hypertonie.

2007 hat die ESH eine Auswertung für Diagnose von Hypertonie publiziert und darin die Grenze für Hypertonie in mmHg festgelegt und zwar für Sprechstundenmessung, ambulante 24- Stundenmessung und Selbstmessung des Blutdruckes zu Hause.

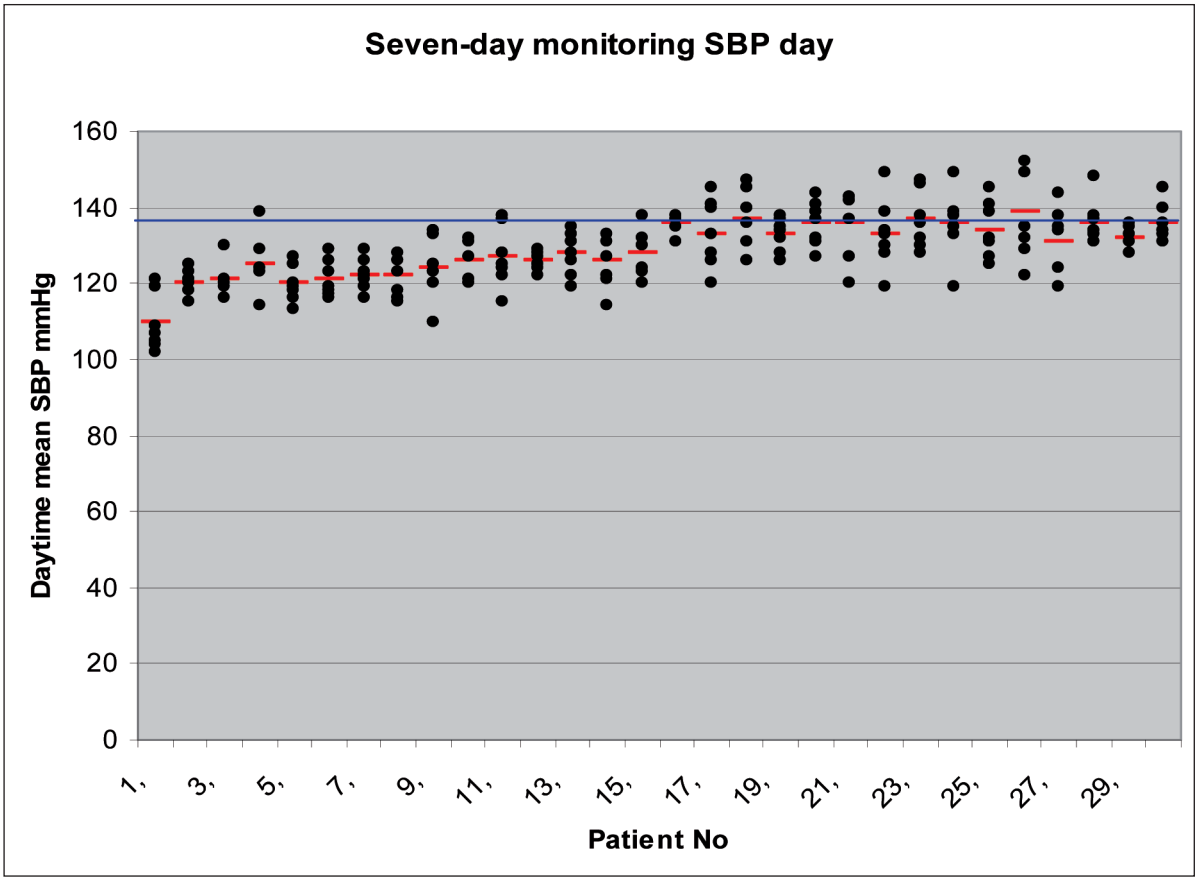
Table 5 Blood pressure thresholds (mmHg) for definition of hypertension with different types of measurement

	SBP	DBP
Office or clinic	140	90
24-hour	125–130	80
Day	130–135	85
Night	120	70
Home	130–135	85

J Hypertension, 2007

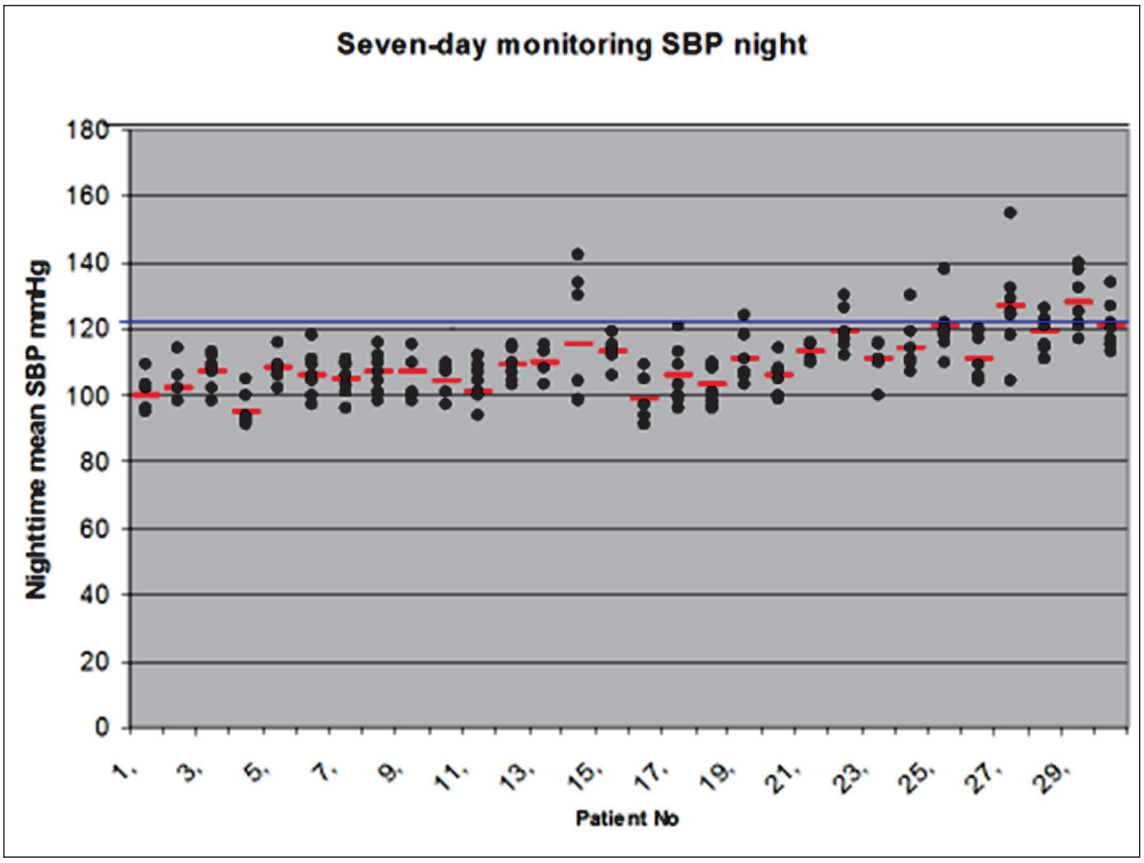
Brno Database

Unsere Resultate von 7 Tage/24 Stunden ambulanter Blutdruckmessung zeigen eine grosse intraindividuale Variabilität im Blutdruck zwischen verschiedenen Wochentagen.



Die Variabilität des täglichen systolischen Blutdruckes während 7 Tagen ist dargestellt in der Abbildung zusammen mit der Grenzwert 135 mmHg von Hypertonie. 13 Patienten (43 %) waren jeden Tag der 7 Tage der ambulanten Blutdruckmessung unter diesem Wert.

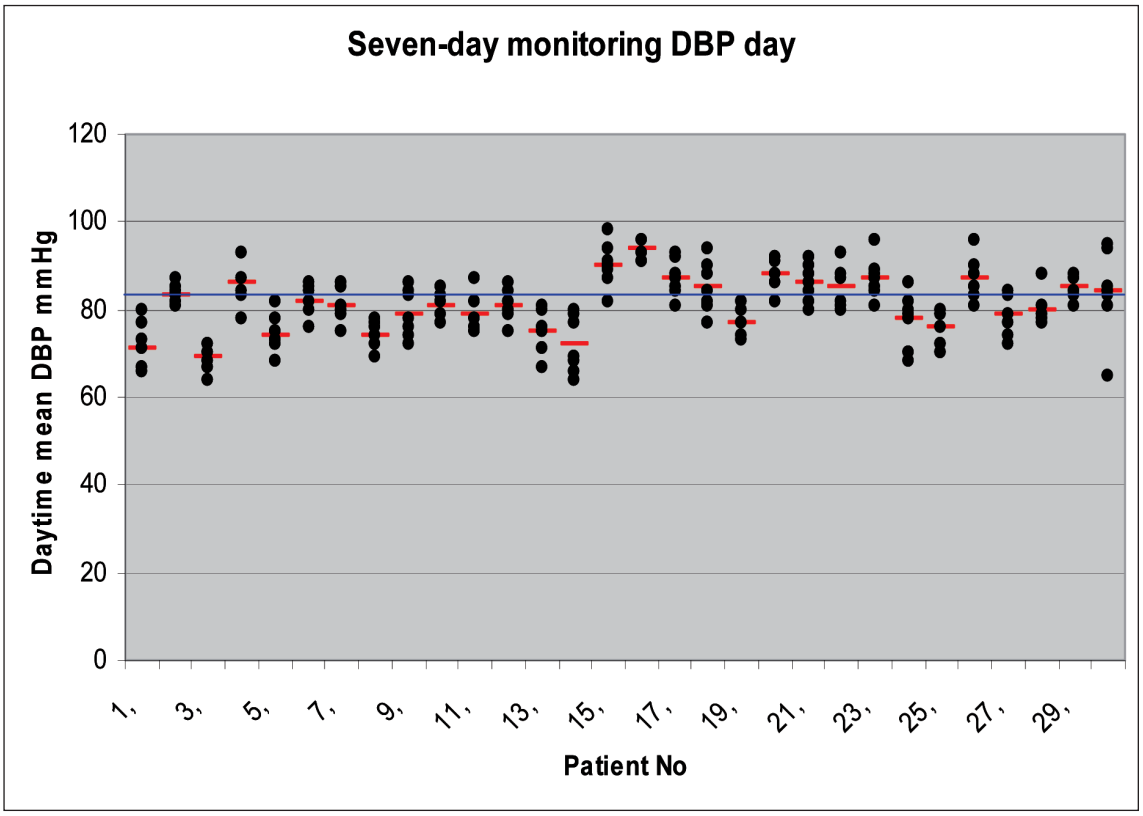
17 Patienten (57%) waren sowohl an Tagen über dem Grenzwert von 135 mmHg, als auch an Tagen unter diesem Wert und damit laut obiger Definition sowohl Hypertoniker als auch Normotoniker.



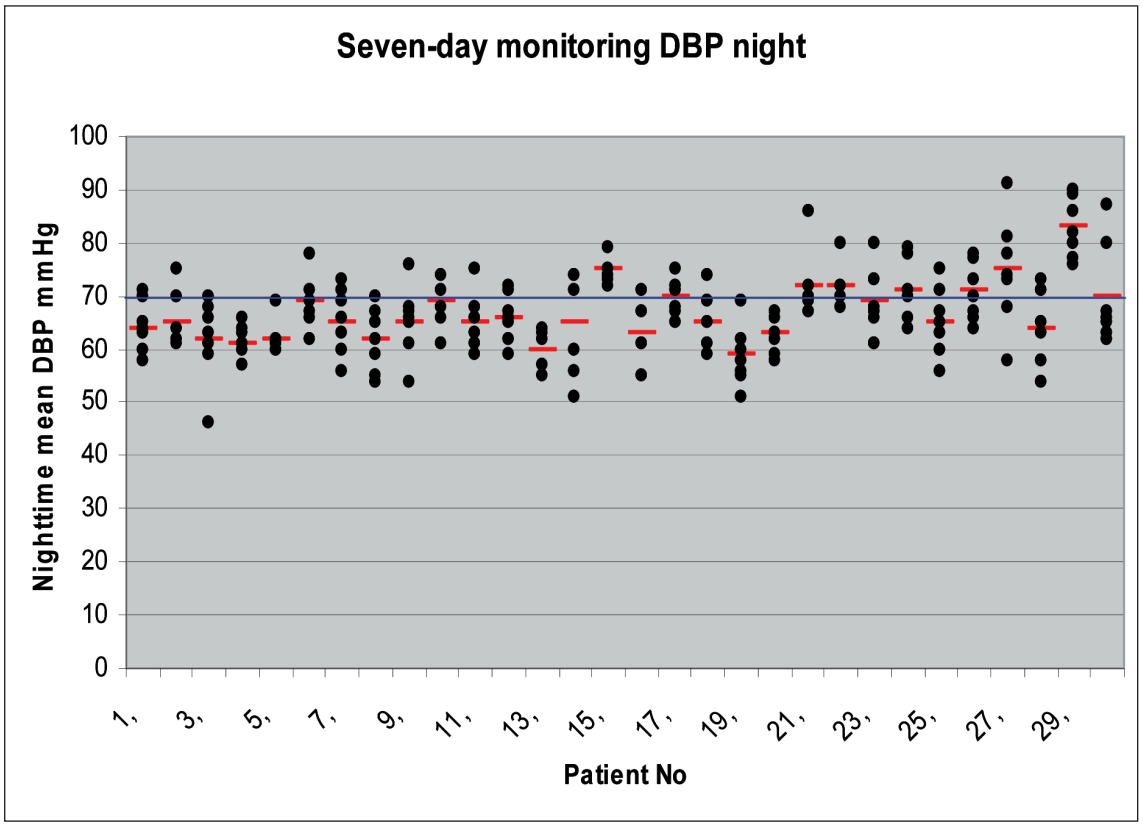
Die Variabilität des nächtlichen systolischen Blutdruckes während 7 Tagen ist dargestellt in der Abbildung zusammen mit dem Grenzwert 120 mmHg von Hypertonie.

10 Patienten (33 %) waren 1 Tag über dem Wert von 120 mmHg, diese Werten des systolischen Blutdruckes erfüllen der Diagnose des hohen Blutdruckes - Hypertonie und den zweiten Tag unten dem Wert von 120 mmHg und damit Normotoniker.

Die Variabilität des täglichen diastolischen Blutdruckes während 7 Tagen ist dargestellt in der Abbildung zusammen mit der Grenzwert 85 mmHg für Hypertonie.



22 Patienten (73 %) waren 1 Tag über dem Wert von 85 mmHg, diese Werte des diastolischen Blutdruckes entsprechen der Diagnose für hohen Blutdruck - Hypertonie und den zweiten Tag unten dem Wert von 85 mmHg.



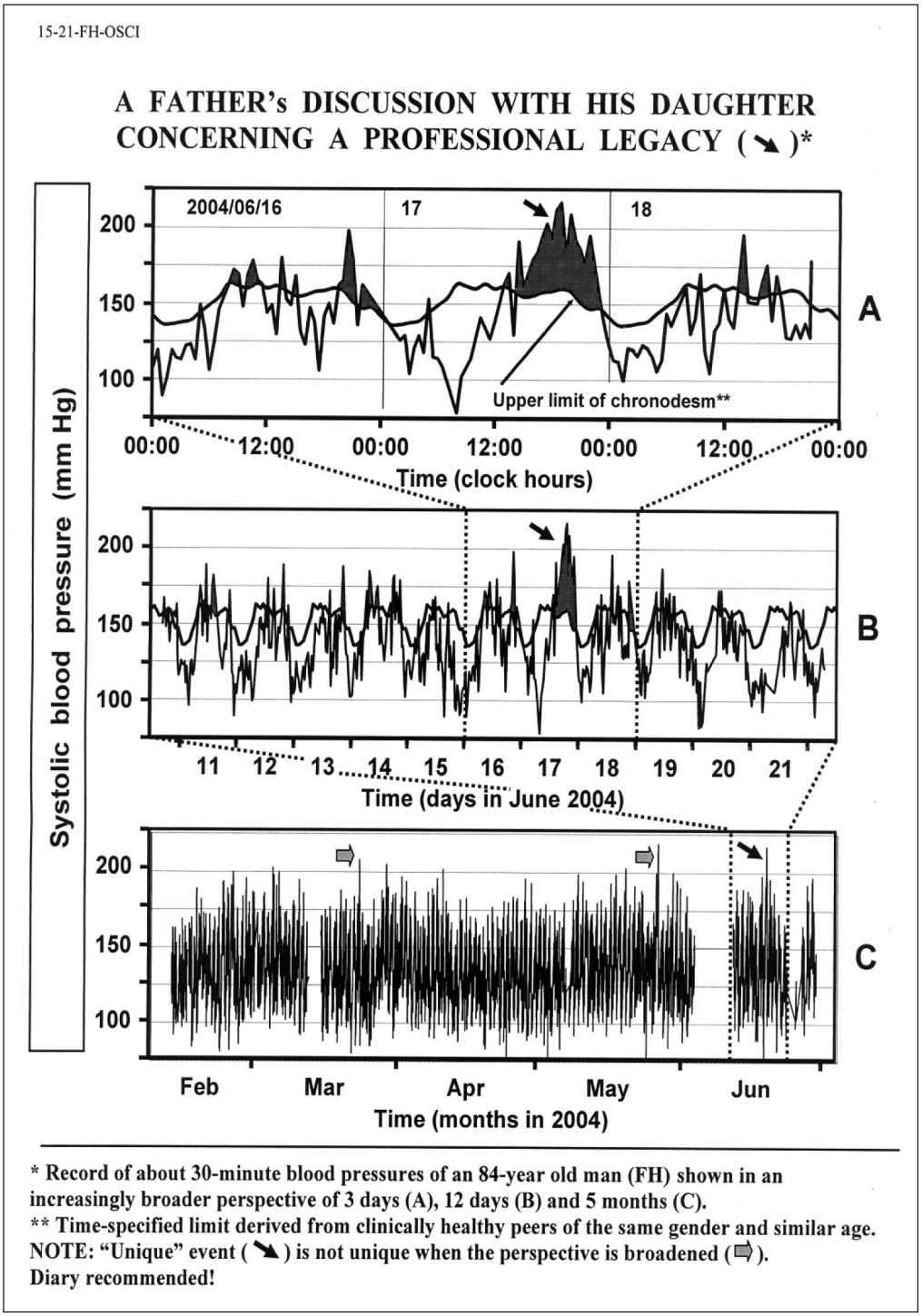
Die Variabilität des nächtlichen diastolischen Blutdruckes während 7 Tagen ist dargestellt in der Abbildung zusammen mit der Grenzwert 70 mmHg von Hypertonie.

24 Patienten (80 %) waren 1 Tag über dem Wert von 70 mmHg, diese Werten des diastolischen Blutdruckes entsprechen der Diagnose des hohen Blutdruckes - Hypertonie und den zweiten Tag unten dem Wert von 70 mmHg. Nur 1 Patient (3 %) war jeden Tag in dem Bereich von Hypertonie.

Unsere Daten aus der Brno Datenbank (tägliche Mittelwerte) zeigen eine große Variabilität von systolischem und diastolischem Blutdruck, verglichen mit den 7-Tage-Mittelwerten am Tag als auch in der Nacht.

Der Systolische Blutdruck

Professor Franz Halberg hat sich mehrere Jahre Blutdruck selber 24 Stunden gemessen.

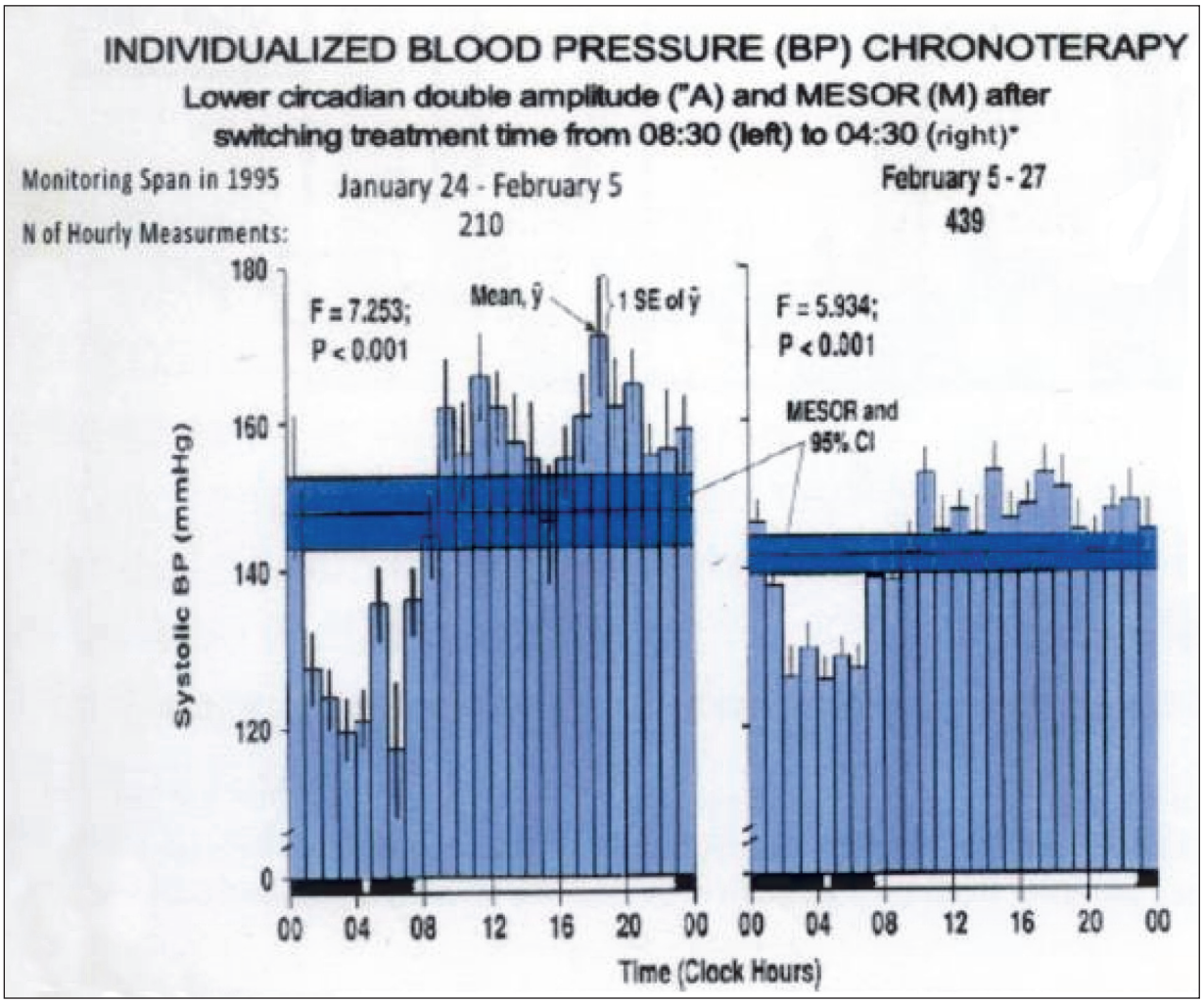


*** Record of about 30-minute blood pressures of an 84-year old man (FH) shown in an increasingly broader perspective of 3 days (A), 12 days (B) and 5 months (C).**
**** Time-specified limit derived from clinically healthy peers of the same gender and similar age.**
NOTE: "Unique" event (↘) is not unique when the perspective is broadened (⇨).
Diary recommended!

Chronotherapy

Professor Franz Halberg hat Blutdruckmessung allein 24 Stunden mehrere Jahre durchgefuhrt und er hatte Hypertonie.

Er benutzte antihypertensive Therapie (Blokalcin), und er nahm diese Therapie vom 24. Januar bis 5. Februar um 8.30 Uhr morgens, von 5. Februar bis 27. Februar morgens, um 04.30 Uhr. Einnahme des Arzneimittels Blokalcin um 04.30 reduzierte den systolischen Blutdruck deutlich im Vergleich mit der Einnahme des Medikaments um 8.30. Die Medikamentendosis von Blokalcin war in den beiden Fallen die gleiche.



Brno Concensus

Professor Franz Halberg, Professor Germaine Cornélissen, Dr. Othild Schwarzkopff, University of Minnesota, Professor Thomas Kenner, Brigitte Kenner, University Graz, Professor Jean-Paul Martineaud, University Paris, Professor Jarmila Siegelova, Professor Bohumil Fišer, As. Professor Michal Pohanka, Dr. Jiří Dušek, Professor Petr Dobšák, Masaryk University nahmen 2 mal im Jahr in Brno seit 1990 an den wissenschaftlichen Konferenzen in Brno teil und präsentierten die neuesten Befunde in der Erforschung der nicht-invasiven kardiovaskulären Regulation und Chronobiologie.

Im Jahr 2008, im Herbst Symposium wurde der Brno Consensus proklamiert: Unter der Leitung von Professor Halberg wurden die Überlegungen über Riskofaktoren der Hypertonie auf der Grundlage der Halberg'schen Chronobiologischen Analyse von sieben Tagen/24-Stunden Blutdruckmessungen aus mehreren Ländern von Asien(Japan), Europa und Amerika zusammengefasst.

Professor Bohumil Fišer, As. Professor Michal Pohanka, Professor Thomas Kenner, Brigitte Kenner, Dr. Othild Schwartzkopff , Professor Franz Halberg, Dr. Jiří Dušek, Professor Jarmila Siegelová, Brno Congress Noninvasive Methods in Cardiology 2008

World Heart Journal
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Bohumil FISER (*22.10.1943-†21.03.2011): Chronobiologist, Emeritus Head of the Physiology Department at Masaryk University (Brno, Czech Republic), Czech Minister of Health, and Executive Board Member of the World Health Organization: His Legacies for Public and Personalized Health Care

Franz Halberg[1], Germaine Cornélissen[1], Thomas Kenner[2], Jiri Dusek[3], Brigitte Kenner[2], Othild Schwartzkopff[1], and Jarmila Siegelova[4]

[1]Halberg Chronobiology Center, University of Minnesota, Minneapolis, MN, USA
[2]Department of Physiology, Medical University, Graz, Austria
[3]Health Medical Center, South Moravia Region, Brno, Czech Republic
[4]Department of Functional Diagnostics and Rehabilitation, St. Anna Teaching Hospital, Brno, Czech Republic

In 2003, one of us (JS) dedicated a special volume of papers dealing with non-invasive cardiology [1] to Bohumil Fiser, MD, our dear friend, Figure 1, and, his relatively young age notwithstanding, our mentor and supporter. In that volume, GC and JS laid the basis for a chrononeonatology. Another of us (OS) emphasized the need for long-term, preferably lifetime monitoring of blood pressure and heart rate as a concern for everybody and hence for government and ethics committees.

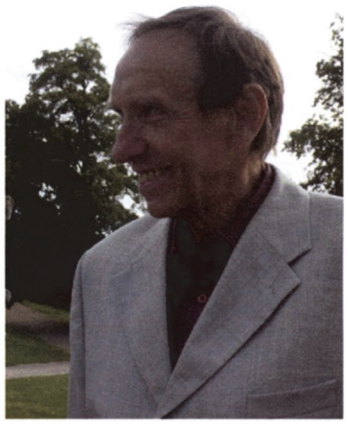

Figure 1. Bohumil Fiser (1943-2011).

Publiziert 2011

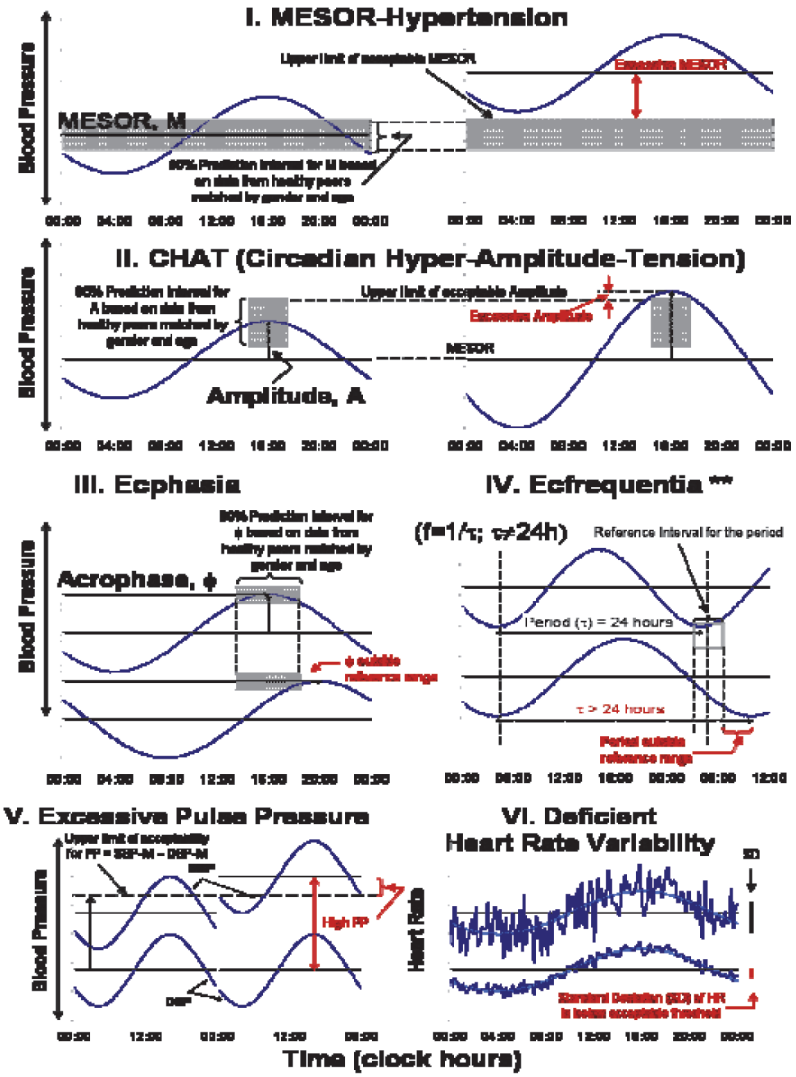

Figure 4. Vascular Variability Anomalies (VVAs) picked up by chronobiologically interpreted 7-day around-the-clock records of blood pressure and heart rate monitoring become Vascular Variability Disorders (VVDs) when they are replicated in successive 24-hour/7-day records. If several VVDs coexist, the risk of an ischemic stroke within 6 years increases from about 5% to near 100%. To the five VVDs in the consensus, we can add a sixth, a circadian desynchronization of the endocrines and the circulation more recently documented as ecfrequentia in association with adynamia and depression recurring mostly twice-yearly in an extensively studied 62-year-old woman [10]. © Halberg.

Zusammenfassung

Unsere Resultate der sieben Tage / 24 Stunden ambulanten Blutdruckmessung haben grosse Variabilität im Blutdruck gezeigt. Für die Diagnose und Behandlung der Hypertonie ist eine mehrere Tage dauernde ambulante 24-Stunden-Messung vorzuziehen.

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Prof. Dr. J. Siegelova, DrSc.
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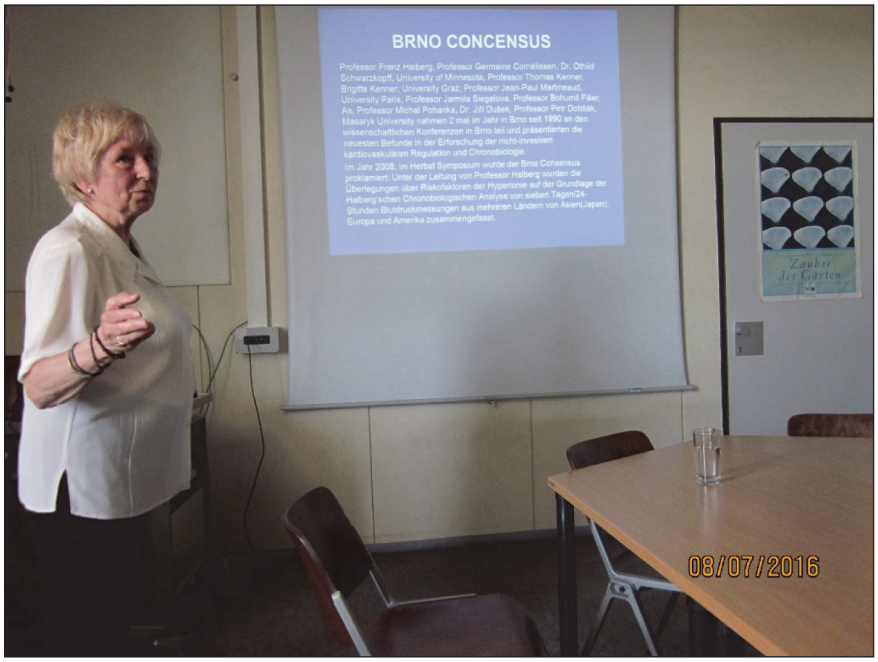
Univ. Prof. Dr. Thomas Kenner und Univ. Prof. Dr. Andrea Olschewski



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