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Under the auspices of
doc. PhDr. Mikuláš Bek, Ph.D., Rector of Masaryk University Brno
prof. MUDr. Jiří Mayer, CSc., Dean of Faculty of Medicine Masaryk University Brno

Reviewed by: doc. MUDr. Dušan Salát, CSc.

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THE HEART – ABLE TO PUMP WITHOUT VALVES – THE "LIEBAU EFFECT"

THOMAS KENNER
Medical University Graz, Department of Physiology, Graz

The "IMPEDANCE DEFINED FLOW"

The word "impedance" is used for describing the relation between pressure and flow if both of these magnitudes are complex and variable. In an artery the impedance describes the relation between blood-pressure and blood-flow, and both of them are variable, pulsatile – rhythmic – or arrhythmic. Since the impedance characterizes typical properties – like wall elasticity, fluid-properties and their interaction, one usually speaks of "characteristic impedance". In very small vessels or capillaries, the impedance becomes simply identical with the Poiseuille-resistance.

In the arterial system, the characteristic impedance increases from the aortic root towards the periphery. In order to examine the basic properties of such an inhomogeneous system, T. Kenner and E. Wetterer (1) performed experiments on a tapered rubber tube the inner diameter of which decreases linearly from 4 cm to 2 cm over a length of 200 cm. The tube is filled with water and perfused by means of a piston pump which is able to deliver either sinusoidal flow or triangular flow pulses. At the tube end, there is a variable hydraulic resistance. The pressure within the tube is measured by two miniature manometers located at the tube entrance and tube end; a third manometer mounted at a catheter tip can be shifted along the tube. If the reflection coefficient at the tube end is about +0.5, the pressure pulses generated by rhythmical triangular flow pulses show the main features of normal arterial pulses. The most typical feature of the tapered tube is the fact that the pressure amplitudes at the distal end of the tube are always higher than those at the tube entrance. The fact is –so to say – the first step to understand the mechanism of a valveless pump.

Dr. LIEBAU AND HIS PUMP

In April of the year 1969, I received the invitation by Professor Erik Wetterer, to join him to visit in Hannover the 1st Symposium with the title "The phenomenon of the pulsatile flow in the circulation of blood as seen from technological as well as from physiological and clinical viewpoints". The manuscripts of the presentations were published in a paperback booklet by E. Pestel and G. Liebau, 1970 (10)

At that time the ideas of Dr. Liebau (4, 5) concerning valveless pumps was recognized by many colleagues as some not quite realistic ideas. However, the problem of the pumping of fluid by pumps without valves both in models as well as in the biologic reality found more interest and research . Interestingly enough, Dr. Liebau already had received a patent for the structure of such a pump which certainly was able to pump fluid. Still, the use of such pumps was assumed to be rather useless. In the meantime many studies have been performed which could proof that the "Liebau effect" can really be used for pumping fluid and – especially for pumping blood.

Liebau described several examples where he interpreted a possible natural biological example of valveless pumping. One example is the valveless pumping in the early embryonic heart. He also wrote an article about the pumping function of the heart under the pathological condition of complete valvular failure.

About 20 years after the Mannheim-Meeting my assistant and coworker in the Department of Physiology in Graz, Max Moser initiated experiments to study the Liebau effect in Graz. We were assisted and supported by my Japanese friends Koichi Ono and I. Tanev.

Furthermore we were lucky that Prof. Abraham Noordergraaf joined our experiments and the interpretation of the results. (7,8))

A more detailed description of the effects within the asymmetric circular tube system can be found in the textbook "Blood in Motion" by Abraham Noordergraaf (8) which was published in 2011.

In the following section, which summarizes the interpretation of one of the most experienced cardiovascular specialists, I present a citation from Noordergraaf's textbook (2011, page 28):

"Commencing in 1954, and perpetuating his work for decades, the physician Liebau constructed hydraulic models, free of valves, to demonstrate the occurrence of steady flow in response to periodic compression at a particular site. Restructuring of one of his models confirmed Liebau's observations (Moser et al. 1998). His motivation was to show that similar compression of veins, free of valves, can aid blood flow around the cardiovascular circuit, even in the absence of cardiac valves (Liebau 1956). Despite support by contemporary fluid-dynamicists, he was unable to offer an interpretation why, and under what conditions, steady flow could be generated in such fluid-dynamic models. The issue continues to fascinate fluid dynamicists, e.g., Manopoulos et al. (6) (2006)." Further studies by Pahlevan and Gharib (9) and Lee V.C.-C. et al. (3) were published recently (2013).

In the following, a simple model – published in Moser and our group (7) in 1998 - is shown, which can be easily used to demonstrate the principle of valveless pumping.

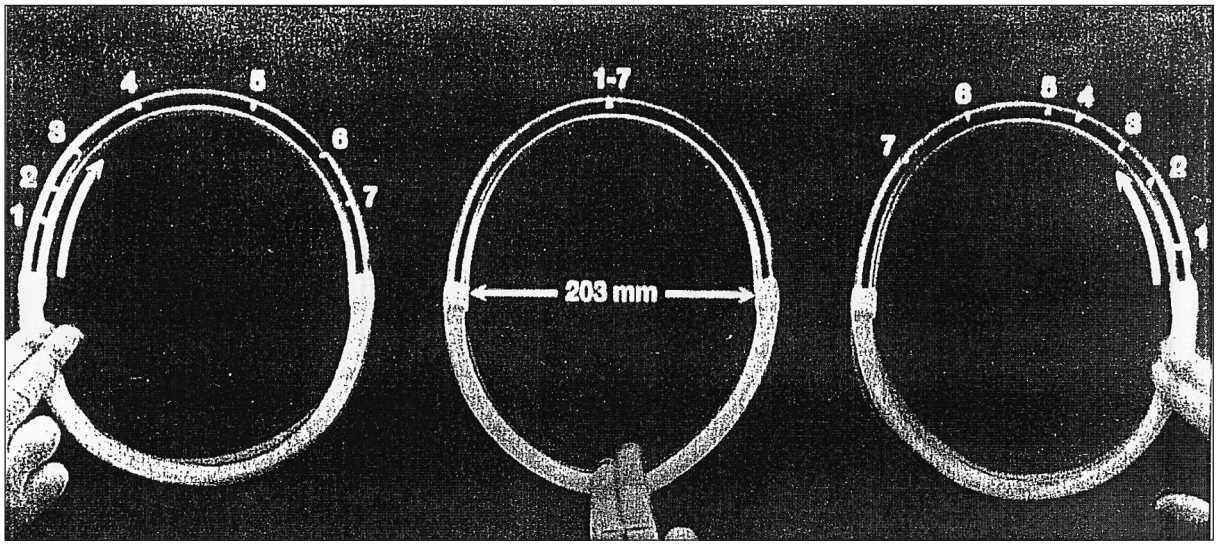

Figure 1

This figure shows a fluid filled valveless closed loop. It consists of a semicircular glass tube and a rubber tube. In the fluid a styrofoam marker permits to show the fluid movement. Shown are three modes of compression, each photographed by repeated exposure at the same frequency of the compressions by 2 fingers. The left panel demonstrates periodic compressions by 2 fingers on the left side of the rubber tube. The numbers indicate the position of the Styrofoam ball during a sequence of 7 compressions. The panels in the middle and right show the same sequence of compressions for different compression sites. The left Panel shows clockwise average flow. In the middle panel no average flow can be seen. In the right panel counterclockwise movement can be seen.

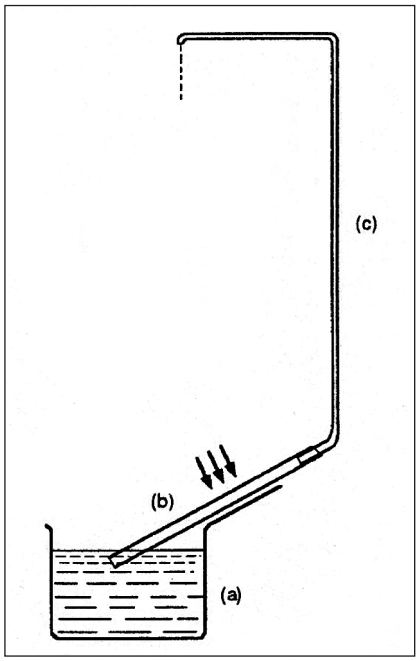

Figure 2

This straight construction by Liebau is published in Pestel and Liebau (10) in 1970 . It functions according the same principle as the closed loop system. The arrows show to the location, where the lower elastic tubing can be compressed. A rapid sequence of compressions has the effect, that fluid is moved from the lower cup through the elastic tube into the upper glass tube and outflow on top, as indicated in the figure.

The examples shown in the two figures can easily been built and one can experimentally observe the fact that these pumps can move fluid without valve.

What is important, is the fact that there must be a difference between the "soft" portion of the tube (low impedance) and the transmitting stiff (high impedance) fluid line. In our paper: Moser et al. (1998) the name "IMPEDANCE DEFINED FLOW" was used in the title. Impedance describes the pressure-flow relation in tubes – like arteries. In arteries the pressure pulse as well as the flow pulse can be measured. Here we can now more easily explain:

Impedance = pressure amplitude / flow amplitude

It is interesting, that in the case of the Liebau effect the fluid is moving from a tube with low impedance towards a tube with high impedance.

In the meantime, besides our own publications a series of work – including especially mathematical work - was published.

Asymmetry of time course

As far as functions in the circulation are concerned, the time course of the ejection of blood from the left ventricle into the aorta is an interesting example of asymmetry. The normal ejection function starts from zero with a steep increase of the flow to reach a peak; then the flow decreases with a slow declining down-slope which, in a typical normal example has a small bump. Wetterer and Kenner (2) have shown in their textbook (1968) and have discussed the contour of the ventricular ejection using a windkessel model

and/or an elastic tube model. It can be concluded, that the optimal and most economic ejection flow is markedly asymmetric in terms of time course.

In fact, there is another additional asymmetry of the time periods of the cardiac cycle. The normal cardiac cycle can be divided into a shorter systole and a longer diastole. It can be shown, that this asymmetry is essential for the optimal coronary perfusion (Kenner 1979).

Variability of asymmetric properties of pumps

Wetterer and Kenner (1968) have, in addition analyzed and explained the difference between a pressure pump which has a low internal resistance, and a flow pump which has a high internal resistance.

Furthermore, we have analyzed a pump which changes its property during the pumping action. The model consists of a reservoir with a fixed pressure level which is, through a valve, connected with an elastic fluid filled tube. When the valve is open the reservoir acts as a low resistance pressure pump. When the valve is closed the resistance at the location of the valve becomes infinite. Therefore, there is no more active pumping. However, in terms of its influence as a location of wave reflection, the closed valve acts as a high resistance. Of course, the described process appears as a rather simplistic model of systole and diastole from the viewpoint of the aorta. However, as we will see, the model is necessary to understand the Liebau effect.

LITERATUR

1. Kenner T., Wetterer E.: Experimentelle Untersuchungen zu einem Schlauchmodell, dessen Wellenwiderstand peripherwärts kontinuierlich zunimmt. Pflügers Archiv 295, 99 – 118 (1967)
2. Wetterer E., Kenner T.: Grundlagen der Dynamik des Arterienpulses. Springer-Verlag 1968
3. Lee V.C.-C., Abakr Y. A., Woo K.-C. : Valveless pumping using a two-stage impedance pump. Frontiers of Mech. Eng., Issue 3, pp. 311 – 318, September 2013
4. Liebau G.: Über ein ventilloses Pumpprinzip. Naturwiss. 41, pp. 327. 1954
5. Liebau G.: Aus welchem Grund bleibt die Blutförderung durch das Herz bei valvulärem Versagen erhalten? Z. Kreislaufforschung 45, pp. 481. 1956
6. Manopoulos C.G., Mathioulakis D.S., Tsangharios S.G.:_ One-dimensional model of valveless pumping in a closed loop and a numerical solution. Physics of Fluids 18: 017106, 2006
7. Moser M., Huang J.W., Schwarz G.S., Kenner T., Noordergraaf A.: Impedance defined flow, Generalization of William Hervey's concept of the circulation - 370 Years later. Int. J. Cardiovasc. Med. and Science 1: 205 – 211, 1998
8. Noordergraaf A.: Blood in Motion. Springer Science+Business Media, LLC 2011
9. Pahlevan NM., Gharib M.: In-vitro investigation of a potential wave pumping effect in human aorta. J. Biomech. 46 (13) 2122-9. 2013
10. Pestel E., Liebau G.: Phänomen der pulsierenden Srömung im Blutkreislauf aus technologischer, physiologischer und klinischer Sicht. Bibliographisches Institut. Mannheim/ Wien/ Zürich, 1970

ALCOHOL CONSUMPTION AND VASCULAR VARIABILITY DISORDERS

GERMAINE CORNÉLISSEN[1], KUNIAKI OTSUKA[2], YOSHIHIKO WATANABE[2], JARMILA SIEGELOVA[3]

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

Abstract

Drinking wine in moderation is widely considered to be beneficial in relation to cardiovascular health. This view has recently been reconsidered and the question raised whether any beneficial effect observed in previous studies may have resulted from biases in subject selection. Most studies examining an effect of alcohol consumption on the cardiovascular system, however, did not consider a chronobiological approach. Some earlier results are revisited herein in an attempt to reconcile discrepant views on the relative merits of moderate alcohol consumption.

Introduction

As noted earlier [1], the relationship between alcohol consumption and cardiovascular disease is complex and not fully elucidated. The idea that drinking moderately protects against coronary heart disease prevails and has been considered part of the benefit derived from a Mediterranean diet, sometimes referred to as the French paradox [2]. The epidemiological finding is supported by the apparent beneficial effects of wine on some mediators of cardiovascular disease (blood lipoproteins, clotting and fibrinolytic factors, insulin sensitivity, endothelin, NO, and LDL susceptibility to oxidation) [1].

Not all studies corroborate this view, however. For instance, in blacks, moderate alcohol consumption was associated with an increased risk of coronary heart disease [3]. It has been argued that moderate drinkers may follow a healthier lifestyle, which would account for the apparent beneficial effects of alcohol consumption reported in the literature [1]. The observational design of these studies may be flawed in that they cannot account for all possible confounding factors. For instance, the group of non-drinkers may contain people who have quit drinking in response to ill health, including cardiovascular disease, while light-to-moderate drinkers may display a range of healthy behaviors, such as better diet and more physical activity [5].

One harmful effect of alcohol consumption is that it increases blood pressure (BP) and the risk of developing hypertension [4]. The relationship between BP and the amount of alcohol consumed follows a J curve [6, 7], so that drinking more than 2 to 3 drinks per day is no longer considered to have beneficial effects. Beneficial vs. harmful effects of alcohol consumption are also subject to geographical variation, as noted in the INTERHEART study [8].

Even in studies relying on ABPM to assess effects of alcohol intake on BP, data are often analyzed only in terms of mean values, without a complete chronobiologic interpretation of the results. Any effect on BP variability such as on the circadian amplitude of BP would thus be missed. Herein, we reexamine effects of alcohol intake on BP from a chronobiologic perspective.

Blood pressure, alcohol, and cardiovascular disease risk

Several outcome studies have shown that abnormal patterns of BP and/or heart rate (HR) are also associated with increased cardiovascular disease risk, beyond an elevation of the BP mean value [9-11]. In particular, too large a circadian amplitude of BP (CHAT, brief for Circadian Hyper-Amplitude-Tension), an excessive pulse pressure, and decreased HR variability (gauged by the standard deviation, SD) are Vascular Variability Disorders (VVDs) that have been associated, singly or in combination, with an increased cardiovascular disease risk. CHAT has been found to be more prevalent among patients with borderline hypertension [12, 13] and may reflect in part the transition from MESOR-normotension to MESOR-hypertension (where MESOR stands for Midline Estimating Statistic Of Rhythm, a rhythm-adjusted mean).

In a 6-year prospective study of 297 patients [14, 15], the risk associated with different VVDs could be compared with other known risk factors, including alcohol consumption [16]. As seen in Figure 1, MESOR-hypertension and an excessive pulse pressure are associated with the largest cardiovascular risk. An excessive pulse pressure and CHAT, together with age, are also associated with a statistically significant increase in cardiovascular disease risk, and may be more specific than MESOR-hypertension since their relative risk has a narrower 95% confidence interval (height of bars in Figure 1). By comparison, alcohol consumption is associated with a smaller, albeit statistically significantly increased risk.

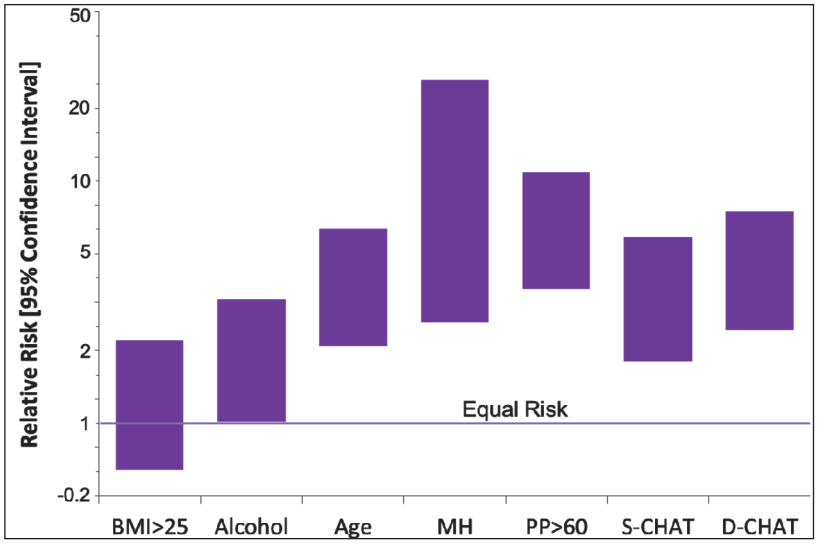

Figure 1 *Alcohol consumption is associated with a statistically significant increase in the incidence of adverse cardiovascular events within the 6-year follow-up of 297 patients. It is, however, smaller than the risk associated with age, or excessive pulse pressure (PP), CHAT, or MESOR-hypertension (MH). © Halberg Chronobiology Center.*

In this study, patients who consumed alcohol also had a larger circadian double amplitude of BP, on the average, Figure 2. Since the intake of alcohol could thus constitute a confounder in assessing the risk associated with CHAT, the relative risk of cerebral ischemic events and nephropathy was computed for the subpopulation of non-drinkers, as CHAT was more strongly associated with these outcomes than with the incidence of coronary artery disease or retinopathy [14, 15]. In each case, CHAT was still found to increase risk statistically significantly and had a relative risk higher than the risk of consuming alcohol [17].

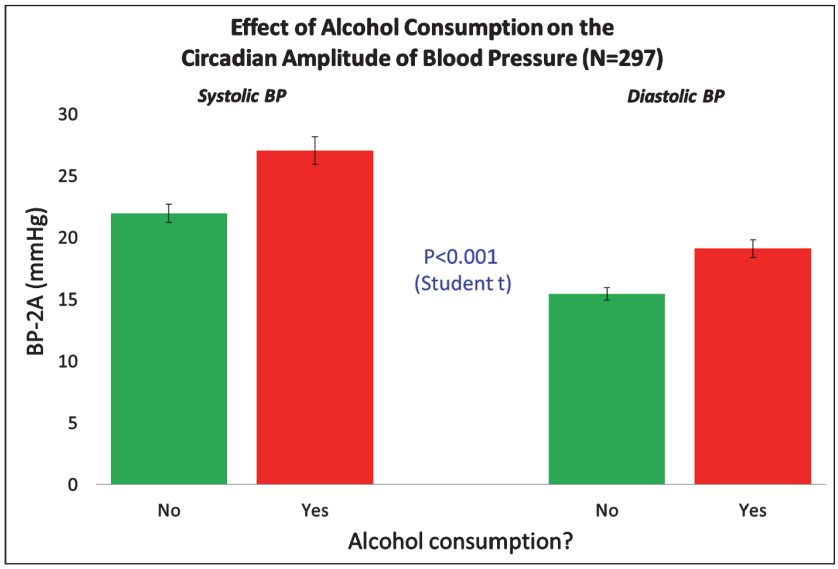

Figure 2 *On the average, patients who consumed alcohol had a statistically significantly larger circadian double amplitude (2A) of systolic and diastolic blood pressure. © Halberg Chronobiology Center.*

Effect of alcohol on circadian rhythm characteristics of blood pressure

In the study underlying results illustrated in Figures 1 and 2 [14-17], the amount of alcohol consumed was not specified. In order to better assess the effect of alcohol on BP, we turn to several small studies and case reports that investigated the effect of specific amounts of alcohol intake on BP and BP variability. One study on 7 healthy students compared the circadian BP pattern after 5 days of evening intake of 40 g alcohol versus orange juice [18]. As seen in Figure 3, opposite results were found when BP was compared between the two stages at 11:00 or at 01:00. The discrepancy is readily resolved by assessing the circadian variation in BP, which reveals that by comparison to orange juice, 40 g of alcohol in the evening was associated with a larger circadian amplitude of BP, but no change in the BP MESOR.

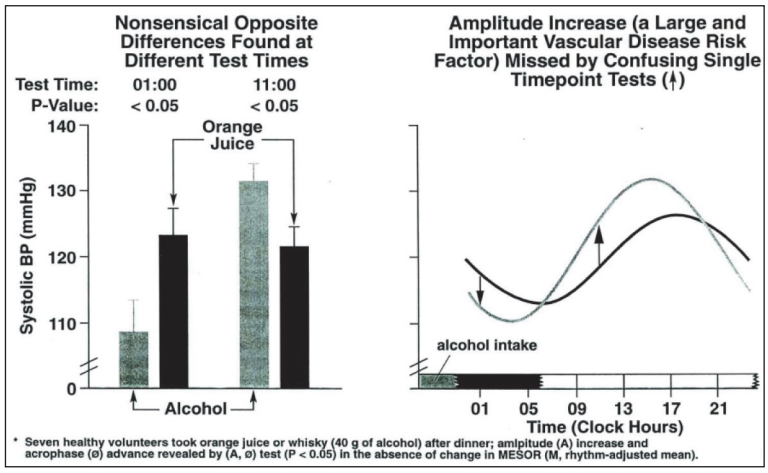

Figure 3 *The circadian amplitude of systolic BP is larger when 7 subjects received 40 g of alcohol per day or orange juice for 5 days in the evening. Testing at single times (11:00 or 01:00) yields opposite results, the discrepancy being resolved by assessing the circadian rhythm in BP. © Halberg Chronobiology Center.*

Two case studies corroborate the observation that the larger the amount of alcohol consumed, the larger is the circadian amplitude of BP. In one study [19], a 70-year old man diagnosed with MESOR-hypertension drank 7 to 8 180 mL-bottles of sake per day. In order to avoid problems often associated with alcohol withdrawal, he was advised to cut his alcohol intake gradually, first to half, then to one third of his

usual consumption, before quitting altogether. As seen in Figures 4 and 5, progressively reducing alcohol intake was associated with a decrease in the circadian amplitude of both systolic (S) and diastolic (D) BP.

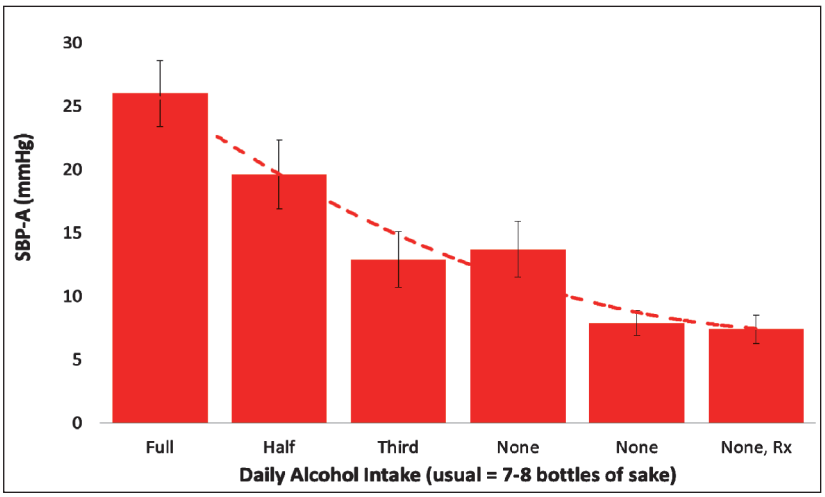

Figure 4 *Progressively decreasing daily alcohol intake by a 70-year old man is associated with a gradual decrease in the circadian amplitude of SBP. © Halberg Chronobiology Center.*

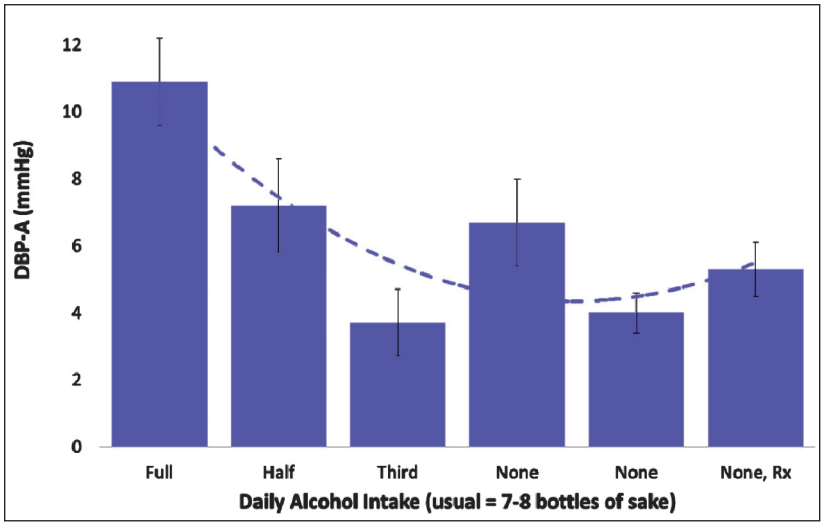

Figure 5 *Progressively decreasing daily alcohol intake by a 70-year old man is associated with a gradual decrease in the circadian amplitude of DBP. © Halberg Chronobiology Center.*

In the other study [20], a 68-year old man systematically decreased his daily intake of alcohol on two different occasions. This study was prompted when a routine 7-day/24-hour ABPM revealed the presence of CHAT. During the study span from September to November 1999, the subject changed his daily alcohol intake and the timing of his treatment for benign prostatic hypertrophy. As seen from Figures 6 and 7, alcohol consumption was related to a larger circadian amplitude of both SBP and DBP, irrespective of treatment time. In this case, alcohol consumption was also associated with a lower HR variability, gauged by the double circadian amplitude, Figure 8.

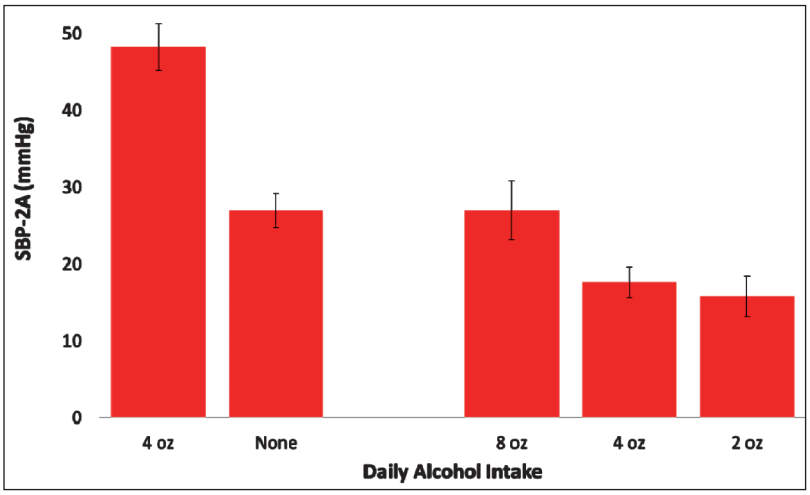

Figure 6 *Decreasing daily alcohol intake was associated with a decrease in the circadian double amplitude of SBP in a 68-year old man. Treatment for benign prostatic hypertrophy was switched from the evening (left) to the morning (right). © Halberg Chronobiology Center.*

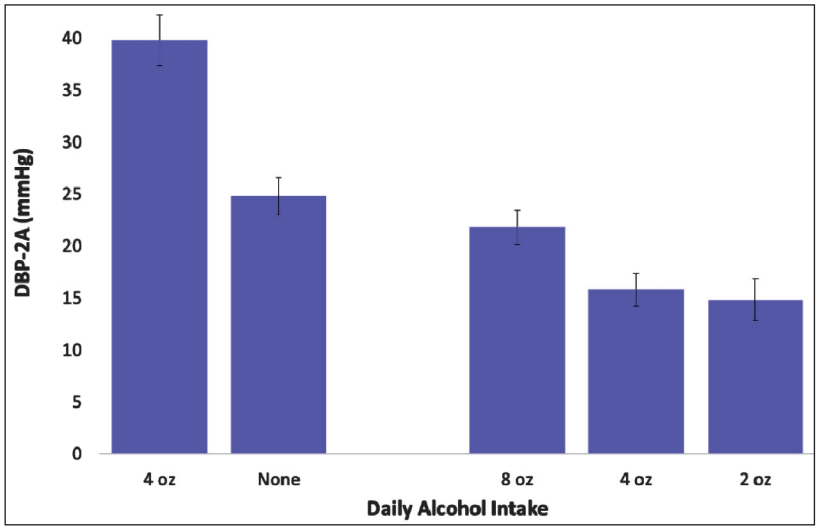

Figure 7 *Decreasing daily alcohol intake was associated with a decrease in the circadian double amplitude of DBP in a 68-year old man. Treatment for benign prostatic hypertrophy was switched from the evening (left) to the morning (right). © Halberg Chronobiology Center.*

Discussion

In order to contrast effects of alcohol with some components of alcoholic beverages (such as antioxidant polyphenols), Zilkens et al. [21] examined 28 healthy men who were assigned to four 4-week stages in a crossover study. The 4 stages consisted of abstention, red wine (375 mL/day or 39 g of alcohol), the same amount of dealcoholized red wine, and beer (1125 mL/day or 41 g of alcohol). At the end of each stage, each subject underwent a 24-hour ABPM session. The authors reported (1) no difference between abstinence and dealcoholized red wine, (2) 2.9 or 1.9 mmHg increases in awake SBP, and (3) 5.0 or 3.4 beats/min increases in asleep HR in association with red wine or beer compared to abstinence [21]. They conclude that red wine polyphenols do not have a significant role in mitigating the BP-raising effect of alcohol in men [21].

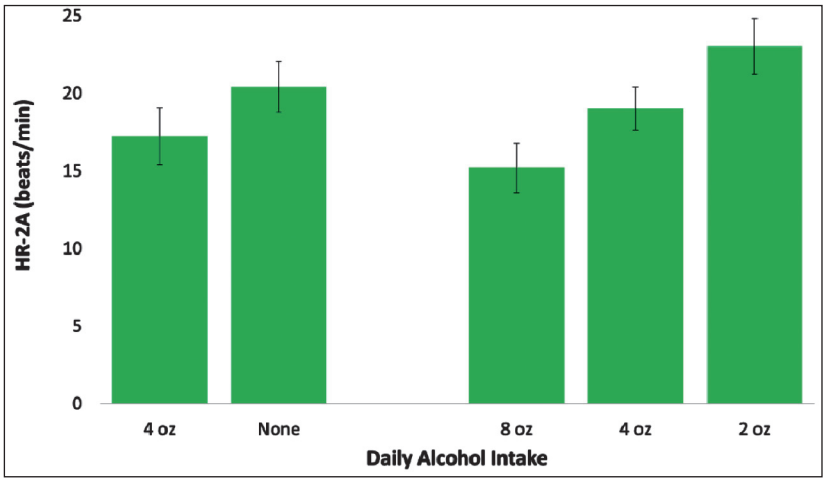

Figure 8 *Increasing daily alcohol intake was associated with a decrease in the circadian double amplitude of HR in a 68-year old man. Treatment for benign prostatic hypertrophy was switched from the evening (left) to the morning (right).*
© Halberg Chronobiology Center.

A reexamination of their study from a chronobiologic perspective confirms an increase in the MESOR of SBP but not of DBP and an increase in the MESOR of HR. In addition, as anticipated from results presented above, red wine was associated with a statistically significant increase in the circadian double amplitude of both SBP and DBP and with a decrease in the circadian double amplitude of HR, Figure 9.

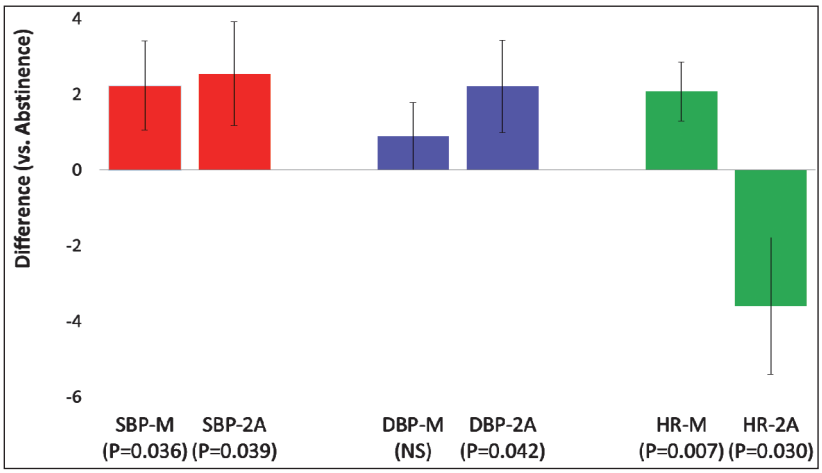

Figure 9 *As compared to abstinence, daily intake of red wine (39 g alcohol) for 4 weeks was associated not only with a small increase in the MESOR of SBP and HR, but also with an even larger effect on the double amplitude of SBP, DBP, and HR.*
© Halberg Chronobiology Center.

Supporting the conclusion of Zilkens et al. [21], a recent study [22] used the rs1229984 variant in the alcohol dehydrogenase 1B gene (ADH1B) as an instrument to investigate the causal role of alcohol in cardiovascular disease. In this Mendelian randomization meta-analysis of 56 epidemiological studies, ADH1B carriers consumed 17.2% less alcohol and had higher abstention odds ratio than non-carriers. Carriers also had lower SBP, interleukin-6 concentrations, waist circumference, and body mass index. They had lower odds of coronary heart disease, independently of the amount of alcohol consumption, and lower odds of ischemic stroke. The authors conclude that reducing alcohol consumption, even among moderate drinkers, is beneficial for cardiovascular health. Interestingly, an alcohol-induced increase in the circadian amplitude of BP may bring about CHAT among individuals who have a large circadian amplitude of BP at

the outset. As discussed above, CHAT has been associated with a large increase in cardiovascular disease risk in several outcome studies, notably in terms of cerebral ischemic events [9-11, 14-17].

The debate about a potential protective effect of moderate alcohol consumption on cardiovascular health may not be over. Changes in BP are only some of several effects of alcohol intake. Two studies report a beneficial effect of moderate alcohol consumption on cardiovascular status from the perspective of its effect on plasma dehydroepiandrosterone sulfate (DHEA-S). In one randomized, diet-controlled, crossover study of 19 healthy moderate alcohol drinkers, moderate alcohol consumption increased plasma DHEA-S concentrations by 16.5% (95%CI: 8.0 – 24.9) and serum HDL by 11.7% (95%CI: 7.3 – 16.0) [23].

Another study [24] investigated relationships between alcohol consumption and serum DHEA-S concentration and cardiovascular disease risk gauged by carotid ultrasonography in 404 consecutive men with non-insulin-dependent diabetes mellitus, subdivided into 3 subgroups (non-drinkers, moderate drinkers, and heavy drinkers). Plasma HDL was positively associated with the degree of alcohol consumption. Intima-media thickness and plaque score were lower in moderate than in non-drinkers. Serum DHEA-S concentrations were higher in moderate and heavy drinkers than in non-drinkers [24].

These results are in keeping with our own observations. In our international breast cancer study [25], we also found a large difference in plasma DHEA-S concentration in clinically healthy women tested in summer, in relation to the aspects of personality gauged by Scale 9 of an abbreviated Minnesota Multiphasic Personality Inventory [26], which in turn has been correlated with the risk of developing alcohol and drug abuse, Figure 10 [27].

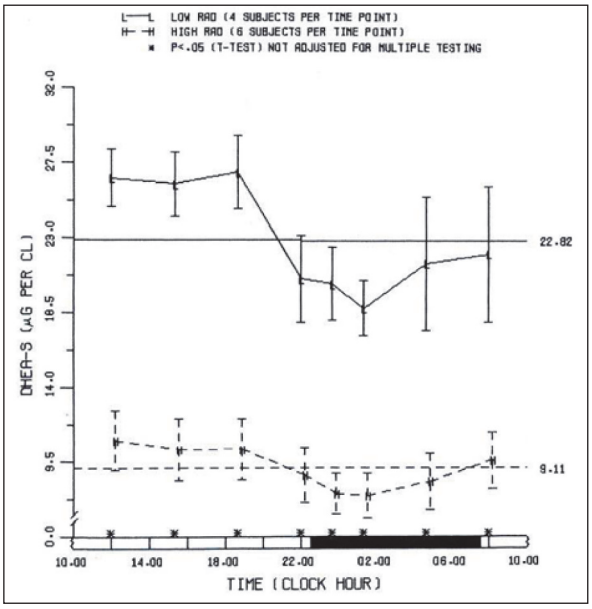

Figure 10 *Large difference in plasma DHEA-S concentration in clinically healthy women at high vs. low risk of developing alcohol and drug abuse assessed from questionnaire. DHEA-S concentrations are higher in low-risk than in high-risk women. © Halberg Chronobiology Center.*

Conclusions

As noted above, many confounders complicate the assessment of effects specifically related to alcohol consumption [1, 5, 8, 21, 22]. Crossover designs, such as that used in the study by Zilkens et al. [21], where subjects can serve as their own longitudinal control, have the advantage of greatly reducing effects of confounding factors. Since day-to-day variability in BP and even in their circadian rhythm characteristics can be very large [9, 17], however, monitoring for longer than 24 hours has been advocated [10].

An effect of alcohol intake on BP or some other mediators of cardiovascular disease may not necessarily translate into actual benefit or harm. Only actual outcomes can answer this question, but epidemiological studies have their own limitations, as discussed above, alcohol consumption being only one among many other features that are part of a person's diet and lifestyle.

A chronobiologic approach can be very useful in taking into consideration the usually prominent circadian variation in BP, HR, and many other physiological variables. It also estimates the effect of any given intervention (such as alcohol intake) on the circadian amplitude and/or acrophase beyond any effect on the MESOR. As illustrated herein, alcohol consumption affected the circadian amplitude of BP and HR more than these variables' MESOR. This observation has important implications when interpreted in the light of VVDs as they relate to cardiovascular disease risk. Indeed, alcohol intake may be more harmful to an individual who has a large circadian amplitude of BP or a small circadian amplitude of HR at the outset since it may bring about CHAT or deficient HRV, two VVDs associated with increased cardiovascular disease risk. Individuals with circadian amplitudes of BP and HR well within the acceptable range may not be exposed to the same potential harm from alcohol consumption, since the circadian amplitudes of BP and HR have a nonlinear relationship to cardiovascular disease risk [28]: the latter is increased only once the circadian amplitude of BP or HR exceeds a threshold. The results presented herein remind us of the importance of individualization, whether for dietary purposes or for anti-hypertensive treatment [29, 30].

References

1. Fuchs FD. Vascular effects of alcoholic beverages. Is it only alcohol that matters? Hypertemsion 2005; 45: 851-852.
2. Renaud S, de Lorgeril M. Wine, alcohol, platelets, and the French paradox for coronary heart disease. The Lancet 1992; 339(8808): 1523-1526.
3. Fuchs FD, Chambless LE, Folsom AR, Eigenbrodt ML, Duncan BB, Gilbert A, Szklo M. Association between alcoholic beverage consumption and incidence of coronary heart disease in whites and blacks: the Atherosclerosis Risk in Communities Study. Am J Epidemiol 2004; 160: 466-474.
4. Fuchs FD, Chambless LE, Whelton PK, Nieto FJ, Heiss G. Alcohol consumption and the incidence of hypertension: the Atherosclerosis Risk in Communities Study. Hypertension 2001; 37: 1242-1250.
5. Huynh K. Reducing alcohol intake improves heart health. Nature Reviews Cardiology 2014; 11: 495.
6. Kaplan NM. Primary hypertension: pathogenesis. In: Kaplan NM (Ed.) Kapan's Clinical Hypertension. Philadelphia, PA: Lippincott Williams & Wilkins; 2002: 56-135.
7. Fiser B. Prevention of harmful effects of alcohol intake. Czech Technological Food Platform, 2009 - 17 pages.
8. Leong DP, Smyth A, Teo KK, McKee M, Rangarajan S, Pais P, Liu L, Anand S, Ysuf S, on behalf of the INTERHEART investigators. Patterns of alcohol consumption and myocardial infarction risk: observations from 52 countries in the INTERHEART case-control study. Circulation. doi:10.1161/CIRCULATIONAHA.113.007627.
9. Halberg F, Cornélissen G, Otsuka K, Siegelova J, Fiser B, Dusek J, Homolka P, Sanchez de la Pena S, Singh RB, BIOCOS project. Extended consensus on means and need to detect vascular variability disorders (VVDs) and vascular variability syndromes (VVSs). World Heart J 2010; 2 (4): 279-305.
10. Halberg F, Powell D, Otsuka K, Watanabe Y, Beaty LA, Rosch P, Czaplicki J, Hillman D, Schwartzkopff O, Cornélissen G. Diagnosing vascular variability anomalies, not only MESOR-hypertension. Am J Physiol Heart Circ Physiol 2013; 305: H279-H294. doi: 10.1152/ajpheart.00212.2013.

11. Cornélissen G, Siegelova J, Watanabe Y, Otsuka K, Halberg F. Chronobiologically-interpreted ABPM reveals another vascular variability anomaly (VVA): excessive pulse pressure product (PPP) updated conference report. World Heart J 2012; 4 (4): 237-245.

12. Kumagai Y, Shiga T, Sunaga K, Cornélissen G, Ebihara A, Halberg F. Usefulness of circadian amplitude of blood pressure in predicting hypertensive cardiac involvement. Chronobiologia 1992; 19: 43-58.

13. Watanabe Y, Cornélissen G, Halberg F, Bingham C, Siegelova J, Otsuka K, Kikuchi T. Incidence pattern and treatment of a clinical entity, overswinging or circadian hyperamplitudetension (CHAT). Scripta medica (Brno) 1997; 70: 245-261.

14. Otsuka K, Cornélissen G, Halberg F. Predictive value of blood pressure dipping and swinging with regard to vascular disease risk. Clinical Drug Investigation 1996; 11: 20-31.

15. Otsuka K, Cornélissen G, Halberg F, Oehlert G. Excessive circadian amplitude of blood pressure increases risk of ischemic stroke and nephropathy. J Medical Engineering & Technology 1997; 21: 23-30.

16. Halberg F, Cornélissen G, Schwartzkopff O, Khasigawala P, Hillman D, Sothern RB, Katinas G, Hong S, Siegelova J. Decadal and multidecadal cycles in the cardiovascular system relating to diagnosis and treatment? In: Kenner T, Cornélissen G, Siegelova J, Dobsak P. (Eds.) Noninvasive Methods in Cardiology 2013. Masaryk University, Brno, Czech Republic 2013; 69-78.

17. Halberg F, Cornélissen G, International Womb-to-Tomb Chronome Initiative Group: Resolution from a meeting of the International Society for Research on Civilization Diseases and the Environment (New SIRMCE Confederation), Brussels, Belgium, March 17-18, 1995: Fairy tale or reality? Medtronic Chronobiology Seminar #8, April 1995, 12 pp. text, 18 figures. http://www.msi.umn.edu/~halberg/

18. Kumagai Y, Cornélissen G, Halberg F. Lessons learned from human circadian amplitude-hypertension associated with alcohol consumption in the evening. In: Otsuka K, Cornélissen G, Halberg F. (Eds.) Chronocardiology and Chronomedicine: Humans in Time and Cosmos. Tokyo: Life Science Publishing 1993; 79-89.

19. Watanabe Y, Cornélissen G, Otsuka K. Ohkawa S, Siegelova J, Halberg F. Effect of alcohol intake and treatment with calcium antagonist on blood pressure and heart rate assessed by ambulatory monitoring. Scripta medica (Brno) 2001; 74: 103-106.

20. Sonkowsky R, Cornélissen G, Fink H, Homolka P, Siegelova J, Halberg F. Day-to-day variability prompts seven-day and 24-hour blood pressure profiles. Scripta medica (Brno) 2002; 75: 267-274.

21. Zilkens RR, Burke V, Hodgson JM, Barden A, Beilin LJ, Puddey IB. Red wine and beer elevate blood pressure in normotensive men. Hypertension 2005; 45: 874-879.

22. Holmes MV et al. on behalf of The InterAct Consortium. Association between alcohol and cardiovascular disease: Mendelian randomization analysis based on individual participant data. BMJ 2014; 349: g4164

23. Sierksma A, Sarkola T, Eriksson CJ, van der Gaag MS, Grobbee DE, Hendriks HF. Effect of moderate alcohol consumption on plasma dehydroepiandrosterone sulfate, testosterone, and estradiol levels in middle-aged men and postmenopausal women: a diet-controlled intervention study. Alcohol Clin Exp Res 2004; 28 (5): 780-785.

24. Fukui M, Kitagawa Y, Nakamura N, Kadono M, Hasegawa G, Yoshikawa T. Association between alcohol consumption and serum dehydroepiandrosterone sulphate concentration in men with Type 2 diabetes: a link to decreased cardiovascular risk. Diabetic Medicine 2005; 22: 1446-1450.

25. Halberg F, Cornélissen G, Sothern RB, Wallach LA, Halberg E, Ahlgren A, Kuzel M, Radke A, Barbosa J, Goetz F, Buckley J, Mandel J, Schuman L, Haus E, Lakatua D, Sackett L, Berg H, Wendt HW, Kawasaki T, Ueno M, Uezono K, Matsuoka M, Omae T, Tarquini B, Cagnoni M, Garcia Sainz

M, Perez Vega E, Wilson D, Griffiths K, Donati L, Tatti P, Vasta M, Locatelli I, Camagna A, Lauro R, Tritsch G, Wetterberg L. International geographic studies of oncological interest on chronobiological variables. In: Kaiser H. (Ed.) Neoplasms—Comparative Pathology of Growth in Animals, Plants and Man. Baltimore: Williams and Wilkins; 1981. pp. 553-596.

26. Kincannon JC. Prediction of the standard MMPI scale scores from 71 items: The Mini-Mult. Journal of Consulting and Clinical Psychology 1968; 32: 319-325.

27. Halberg F. Quo vadis basic and clinical chronobiology: promise for health maintenance. Am J Anat 1983; 168: 543-594.

28. Cornélissen G, Halberg F, Otsuka K, Singh RB. Separate cardiovascular disease risks: circadian hyper-amplitude-tension (CHAT) and an elevated pulse pressure. World Heart J 2008; 1 (3): 223-232.

29. Cornélissen G, Halberg F, Bakken EE, Singh RB, Otsuka K, Tomlinson B, Delcourt A, Toussaint G, Bathina S, Schwartzkopff O, Wang ZR, Tarquini R, Perfetto F, Pantaleoni GC, Jozsa R, Delmore PA, Nolley E. 100 or 30 years after Janeway or Bartter, Healthwatch helps avoid "flying blind". Biomed & Pharmacother 2004; 58 (Suppl 1): S69-S86.

30. Watanabe Y, Halberg F, Otsuka K, Cornélissen G. Toward a personalized chronotherapy of high blood pressure and a circadian overswing. Clin Exp Hypertens 2013; 35 (4): 257-266.

Correspondence:
Germaine Cornélissen
Halberg Chronobiology Center
University of Minnesota, Mayo Mail Code 8609
420 Delaware St. S.E. Minneapolis, MN 55455, USA
TEL +1 612 624 6976 FAX +1 612 624 9989
E-MAIL corne001@umn.edu
Website: http://www.msi.umn.edu/~halberg/

Dedicated to the memory of Franz Halberg and Bohumil Fiser

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THE ROLE OF OSCILLATIONS OF BIOLOGICAL VARIABLES: "HILLCLIMBER" AND U-SHAPED CONTROL- FUNCTIONS

THOMAS KENNER

Medical University Graz, Department of Physiology, Graz

The field of chronobiology mainly is concerned with rhythms of different frequency, like circadian, circaseptan, circannual etc. (1). Although most periodic events are composed of periods of activity and periods of rest, or of periods of higher and lower activity, it appears that the term delay was so far, until recently, not yet of particular interest. There are two reasons why a short introduction to the chronobiological and chronopathological aspects of delay appear to be of interest.

Symmorphosis

Ewald E. Weibel has summarized important interactions between morphology and Physiological function with the word SYMMORPHOSIS.

The original definition of symmorphosis, as expressed by Taylor and Weibel 1981, is: "state of structural design commensurate to functional needs resulting from regulated morphogenesis whereby the formation of structural elements is regulated to satisfy but not exceed the requirements of the functional system."

He continues in his book: "It is immediately obvious that the principles of adaptation, integration, and economy are satisfied if structural design is commensurate to functional needs throughout the organism."

Oscillations

Random oscillations of our body are extremely important for the adjustment and the control of biological systems. The best known example of this control mechanism is the presence of minimal movemets of a upright standing person. The small movements permit our sensors for position and movemet, to record our position and movements. Without these movements we would be in danger to fall.

If somebody is walking, our movements are continuously recorded to adjust our upright position. Everybody has certainly observed: if somebody would balance on top of a small platform he automatically generates well visible movements of arms and hands in order not to fall down. This phenomenon is also called „to balance". There are quite a lot every-day observable phenomena of this type, even if somebody walks along a slippery way.

The same basic phenomenon of the adjustment of an equilibrium can be observed in many (if not all) of the autonomic control systems in our body. A detailed description and interpretation of examples can be found e.g. in the works of I. Priban and E. Monos.

As a fundamental rule one can summarize, that for each variable in the body (like blood pressure, temperature, blood-pH and oxygen tension, etc.) there is an certain operating point. Priban uses the name „hill-climber" because the top of the hill represents the ideal operating position of the variable (or several variables!), which should be adjusted uder normal condition. Of course this value may, to some extent – in addition - depend on the condition (like work, rest, sleep etc.). In order to shift the variables to the necessary operating point, slight oscillations of the variable help the correct modifications and adjustments. Fig. 1 (from Ian Priban,) represents the picture of the „top of the hill" which indicates the achieved normal combined values in the blood of pH, pCO_2 and pO_2 depending on respiration and on the adjusted respiratory gas exchange.

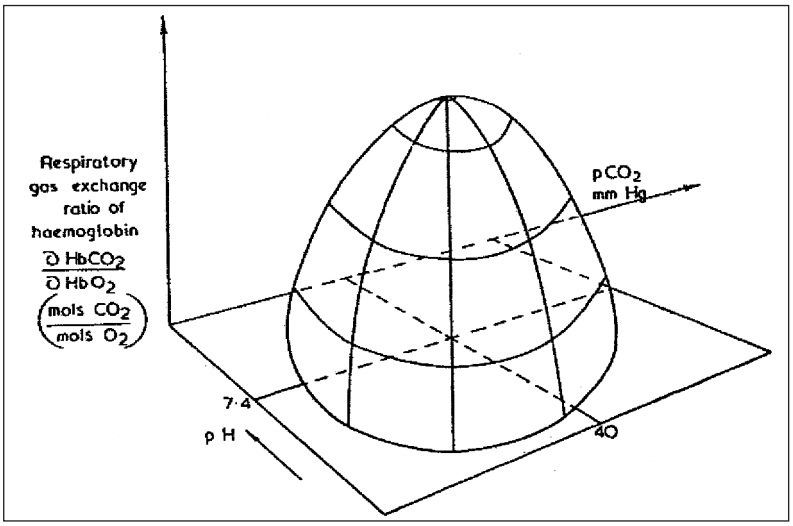

Figure 1 *Relation between the respiratory variables of blood*

It is clear that – according to this drawing - the way up to the hill top is not always straight. It can be observed that many variables in a living system can be found to oscillate and to set the trend of the „normal value“ in the direction of a upward or downward „hilltop“ as in fig. 1.

Furthermore: it has been observed that the central neural contol centers themselves generate small oscillations of each variable, in order to enable the hill-climbing-procedure.

An interesting U-shaped relation - Fig.2 from Weibel‘s book Symmorphosis (page 58) describes the optimum of the hematocrit in the vasular system, influencing viscosity of blood and influencing blood flow in such a way

To minimize the work for blood-transport.

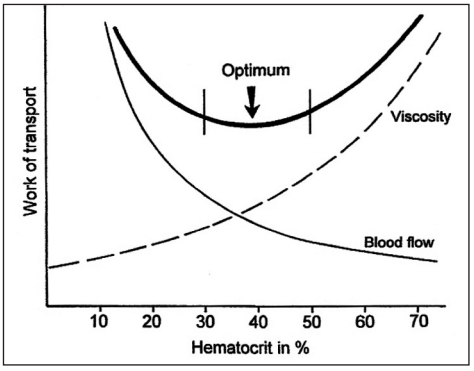

Figure 2

With respect to the general clinical value of the hematocrit it can be seen that the normal value is optimal for oxygen transport and for the flow-resistance of whole blood due to blood viscosity. The corresponding diagram again shows the optimal situation as the minimum peak of a U-shaped characteristic function.

A very interesting example of a „downward hill“ has been described by Monos et al. (1995), the authors who have measured and drawn the Fig. 3. The pressure dependent variations of the characteristic impedance of central arteries tend to a minimum in the „normal“ blood pressure values. This is again minimizing the work for blood transport.

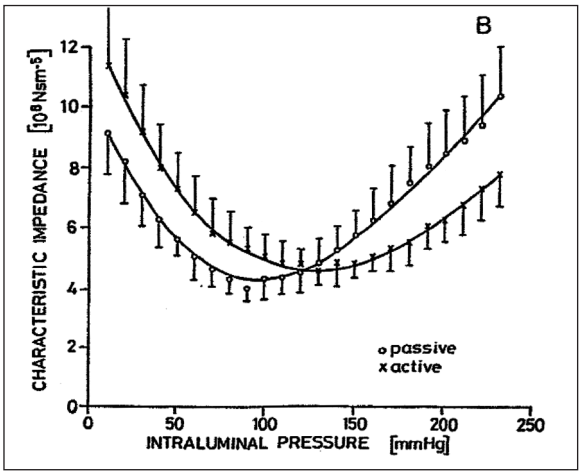

Figure 3

OSCILLATIONS OF THE WHOLE BODY

Whole-body oscillations generated by the working the heart beat (contraction and blood pumping) are well known by observing the ballistocardiogram. (A somewhat different name in Russian literature (Parin et al. 1997) from which the Fig 4 is taken, is: Seismo-kardiogram. Fig. 4) -The picture shows in the first line the Seismo-kardiogram of a Person. The amplitudes change with breath (lowest signal). In the middle: EKG , the amplitude of the R-wave varies also with breath due to movement of the axis of the heart.

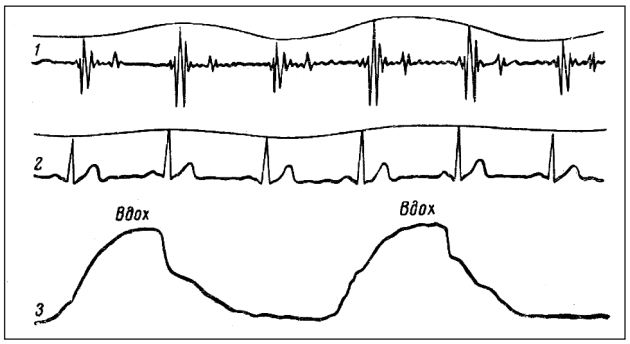

Figure 4

It is well known, that heart beat and respiration is synchronized. In the examle of Fig. 4 the synchronisation is 1: 3 (one breath – 3 heart beats).

Another example of oscillations in the body was described by the Viennese Professor of Psychology Hubert Rohracher and published in 1949 in Vienna: the socalled „microvibrations“ which are generated by and in different, and especially small muscles.

My Assistents E. Gallasch and M. Moser have designed equipment, which was used to record these microvibrations in the Russian space-ship MIR. Fig 6. shows a summary of

Microvibrations in one cosmonaut through some time of weightlessness.

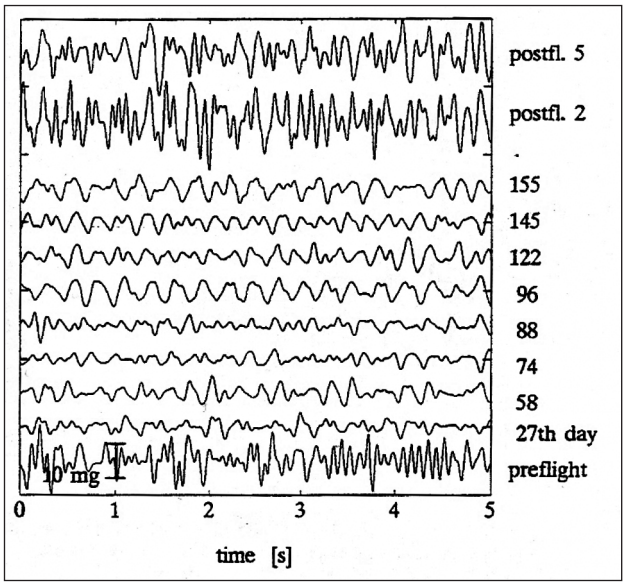

Figure 5 *Original accelerometric records of arm tremor from a 165-day orbital space flight (one preflight eight inflight and two postflight recordings). Text and the numbers oh the right-hand side indicate the day when the record was taken.*

The examples of recordings were taken preflight, then several times until day 155 of spaceflight (weightlessness). Finally 2 records of postflight situation were taken.

One can see a marked reduction of frequency and amplitude of the microvibrations in the condition of weightlessness in space.

A completely different application of the same technique is recording of microvibration in a baby (hand) during sleep, Gallasch et al. 1997: N1 to N4 – Non-REM –sleep / and R1 to R4 – REM - Sleep. (Fig. 7).

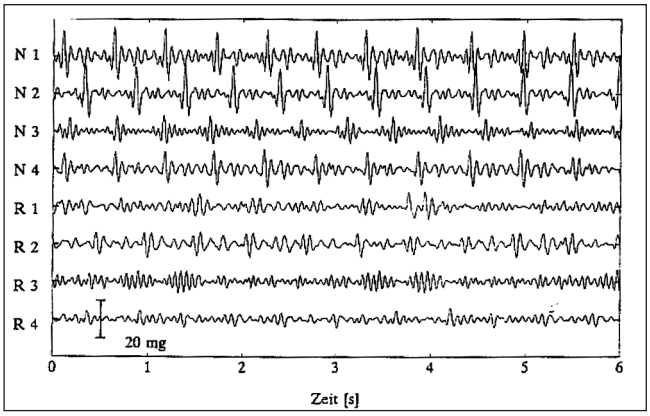

Figure 6

One can see, that in our bodies exist continuously normal oscillations of different frequencies, Some of these oscillations are synchronized. They might be synchronized with internal oscillations like heart beat. They might also be synchronized with external oscillations; e.g. in a autocar or in a railway-car.

Finally, I want to add, that many more details about not-normal or pathological oscillations could be reported.

A frequent example is the oscillating Cheyne-Stokes respiration which can be seen in high altitude – oxygen lack, or in persons with insufficiency of heart beat. The consequence is a failure in the proper control of the normal sequence of breath to breath. In Cheyne-Stokes respiration some breaths are deeper, then get smaller and smaller and then deeper again – and thus continuing.

Furthermore and finally there are normal oscillations in blood pressure and blood flow. These oscillations can change if the blood pressure is lowered by blood loss. The following picture shows oscillations in the femoral blood flow in an anesthetized dog during intravenous infusion of Acetylcholine. The picture shows from top down: Venous oxygen saturation, then: blood flow through femoral artery, then: blood flow through the femoral vein, and through the carotid artery. The last line finally shows the arterial blood pressure. This picture demonstrates , how the circulation can be destabilized – in this example of an experiment.

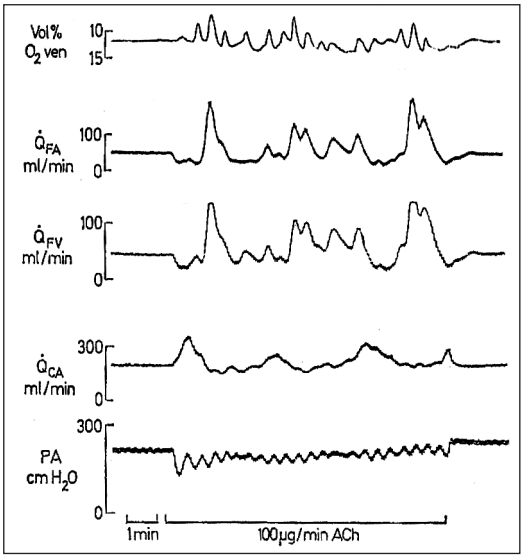

Figure 7

Literature

1. Rohracher H.: Mechanische Mikroschwingungen des menschlichen Körpers. Verlag Urban & Schwarzenberg/ Wien. 1949
2. Gallasch E., Rafolt D., Moser M., Hindinger J., Eder H., Wießpeiner G., Kenner T. : Instumentation for Assessment of Tremor, Skin Vibrations and Cardiovascular Variables in MIR Spacemissions. IEEE Transactions on Biomedical Engineering. Vol. 43. NO. 3. 1996
3. Gallasch E., Kenner T., Haidmayer R., Litscher G., Pfurtscheller G.: Mikrovibration und Muskeltonus des Säuglings in Abhängigkeit vom Schlafstadium. Z. EEG-EMG 28. (1997)
4. Kenner T., Ono K.: Analysis of slow autooscillations of arterial flow. Pflügers Archiv 331. 347 – 356 (1972)
5. Weibel E.R.: Symmorphosis. On Form and Function in Shaping Life. Harvard University Press, Cambridge, Massachisetts, London, England (2000)
6. Parin W.W., Baewsky R.M., Wolkow R.M., Gasenko O.G.: Kosmitscheskaia Kardiologia, Verlag „MEDIZIN“ 1997
7. Monos E., Szücs B.: Optimization of hemodynamic energy expenditure in the arterial system. Obes. Res. 1995 Dec 3 Suppl 5: 811 S – 818 S
8. Priban I.P., Fincham W.F.: Self-adaptive control and the respiratory system. Nature Vol. 208. 339 – 343 (1965)
9. Kenner T.: Biological asmmetry and cardiovascular blood transport. Cardiovascular engineering Vol. 4. No 2. June 2004

DAY-TO-DAY VARIABILITY IN CIRCADIAN CHARACTERISTICS OF SYSTOLIC BLOOD PRESSURE AND EFFECT OF EXERCISE

GERMAINE CORNÉLISSEN[1], CATHY LEE GIERKE[1], ALENA HAVELKOVA[2], JIRI DUSEK[2], JARMILA SIEGELOVA[2]

[1] Halberg Chronobiology Center, University of Minnesota, [2] Masaryk University, Brno, Czech Republic

Abstract

The extent of day-to-day variability in estimates of the MESOR (rhythm-adjusted mean) and 24-hour amplitude of systolic blood pressure (SBP) of 42 clinically healthy men and women, 20-41 years of age, who exercised twice a week, is assessed by means of the Bland-Altman plot. The method is adapted to estimate the bias, precision and limits of agreement for a comparison of daily estimates of SBP-M and SBP-A on days without or with exercise versus estimates from the 7-day record, and between days with and without exercise. The bias on SBP-M was small, whereas the precision was consistently around 4 mmHg. The precision on SBP-A was about 4.5 mmHg for men and 3.5 mmHg for women, with a positive bias stemming from larger estimates derived from 1-day than from 7-day records. A difference in SBP-A between days with versus without exercise is statistically significant for women but not for men. For the diagnosis of hypertension and other abnormalities in BP patterns, BP should be monitored around the clock for longer than 24-hour spans to obtain a reliable estimate of BP and BP variability, preferably accompanied by a diary reporting on daily activities such as exercise.

Introduction

Proper diagnosis and effective treatment of high BP require an accurate assessment of BP and BP variability, including circadian as well as day-to-day variation. Indeed, several outcome studies [1-6] have shown that abnormal circadian patterns of BP and HR are associated with an increased cardiovascular disease risk. Moreover, as compared to uncomplicated MESOR-hypertension, the presence of additional Vascular Variability Disorders (VVDs) (as these abnormal BP and HR patterns are called) greatly increases the risk of adverse vascular events [7]. These results led to guidelines agreed upon at a consensus meeting held at St. Anna Hospital, Masaryk University, Brno, Czech Republic, on October 6, 2008 [8].

There is also often considerable day-to-day variability in BP and HR, and in the circadian characteristics of these variables. Differences can be so large as to make the difference between MESOR-hypertensive diagnosed on one day and MESOR-normotension on another day [9]. This is due, in part, to the many factors that influence BP, from activity [10, 11], to diet and lifestyle [12, 13], and emotions [14, 15]. For these reasons, at the 2008 consensus meeting in Brno, it was advocated to measure BP and HR around the clock for at least 7 days at the outset [8].

End-organ damage associated with hypertension has been reported to correlate more with the 24-hour average BP derived from ABPM than with clinic BP [16]. It is also being recognized that the accuracy of clinic BP measurements is limited due to the presence of 24-hour BP variability, while 24-hour ABPM is viewed as having evolved into an accurate and reproducible tool for the assessment and management of hypertension [17]. The impression of reproducibility conveyed by correlation analysis may just be a sign that the comparison is made over a wide range of BP values. A high correlation does not automatically imply that there is good agreement between the two sets of data. This was illustrated for the case of

24-hour ABPM records obtained on two occasions, about one month apart, from 40 clinically healthy men, 20 to 60 years of age [18]. Whereas the MESORs and 24-hour amplitudes of SBP were highly correlated between the two profiles (M: r=0.586, P<0.001; 24h-A: r=0.739, P<0.001), there was an average difference of 7.1 mmHg in the MESOR and of 3.2 mmHg in the 24-hour amplitude of SBP between the two sessions. Differences in MESOR ranged between 0.2 and 31.1 mmHg for the MESOR and between 0.1 and 11.2 mmHg for the 24-hour amplitude, clearly documenting that different conclusions and interpretations can be reached whether results are summarized for the population or for the individual.

The Bland–Altman plot, or rather the Tukey mean-difference plot, is a method of data plotting used in analyzing the agreement between two sets of data based on individual differences [19, 20]. Bland–Altman plots serve to investigate the existence of any systematic difference between the measurements (bias) and to identify possible outliers. The mean difference is the estimated bias, and the standard deviation (SD) of the differences measures the random fluctuations around this mean. Computation of 95% limits of agreement (average difference ± 1.96.SD) indicates how far apart the two sets of measurements are more likely to be for most individuals. Originally designed to assess the agreement between two different assays, it is here adapted to analyze the agreement between the MESOR and 24-hour amplitude of SBP estimated from 24-hour or from 7-day ABPM records, on the one hand, and from 24-hour ABPM records on days with exercise versus days without exercise, on the other hand.

Subjects and Methods

As described elsewhere [21], 42 subjects (22 men and 20 women), 20-41 years of age, participated in the study. Each provided data at 30-min (05:00 – 22:00) or 60-min (22:00 – 05:00) intervals for 7 days (with occasional interruptions), using the TM-2421 ambulatory monitor from A&D (Tokyo, Japan). Oscillometric measurements were used for analysis. On 2 of the 7 days, they exercised on a bicycle ergometer (Kettler, type X7, Germany) for 1 hour at a fixed load (M: 120 W; F: 80 W). Every exercise session consisted of a 3-min warm-up, a 54-min cycling at a fixed load, and a 3-min cool-down [21]. The study was approved by the local ethics committee and all subjects signed an informed consent.

SBP data from each subject were analyzed by cosinor [22-24]. A 2-component model consisting of cosine curves with periods of 24 and 12 hours was fitted by least squares to the data, yielding estimates of the MESOR and of the amplitude and acrophase of each component. This model was fitted to the 7-day record and to consecutive days considered separately.

The Bland-Altman plot was adapted to estimate the bias, precision and limits of agreement for a comparison of daily estimates of SBP-M and SBP-A on days without or with exercise versus estimates from the 7-day record, and between days with and without exercise. Analyses were carried out separately for men and women.

Results

There is large variability in SBP-M, both among individual men and women and from one day to another, Figures 1 and 2. Dots represent daily estimates of SBP-M and dashes are SBP-M estimates from the entire record. Variability in SBP-A is also very large, Figures 3 and 4.

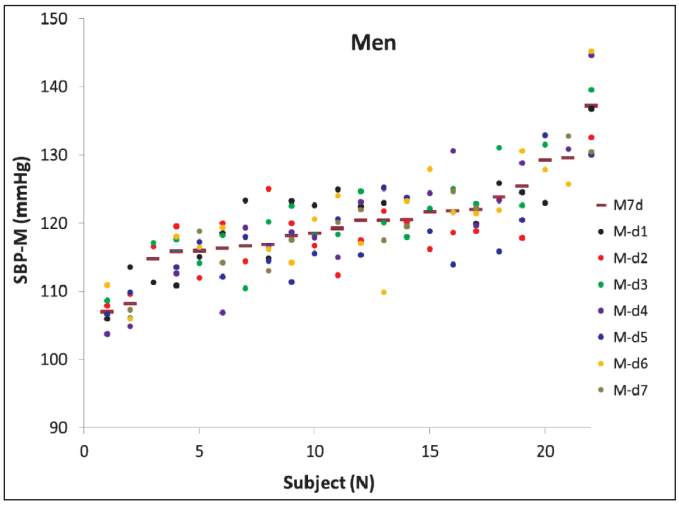

Figure 1. *SBP-M estimates from the entire record (dashes) and for separate daily spans (dots) show a large scatter in men. © Halberg Chronobiology Center.*

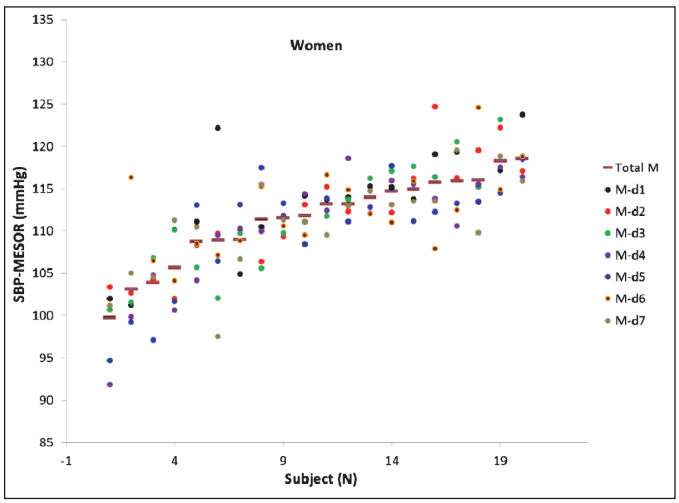

Figure 2. *SBP-M estimates from the entire record (dashes) and for separate daily spans (dots) show a large scatter in women. © Halberg Chronobiology Center.*

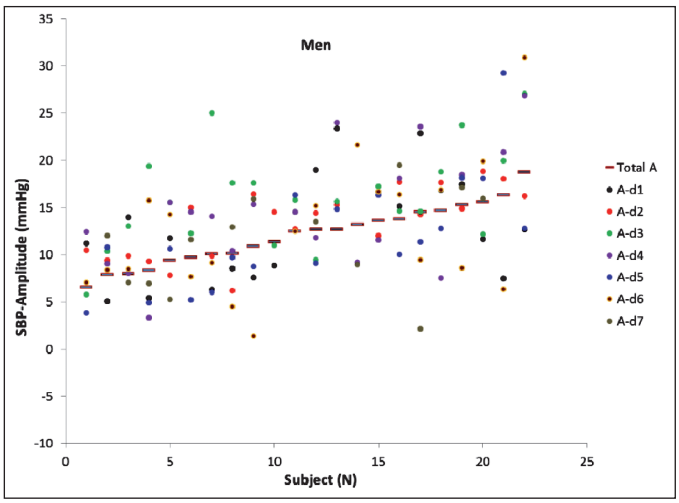

Figure 3. *Estimates of SBP-A from the entire record (dashes) and for separate daily spans (dots) also show a large scatter in men. © Halberg Chronobiology Center.*

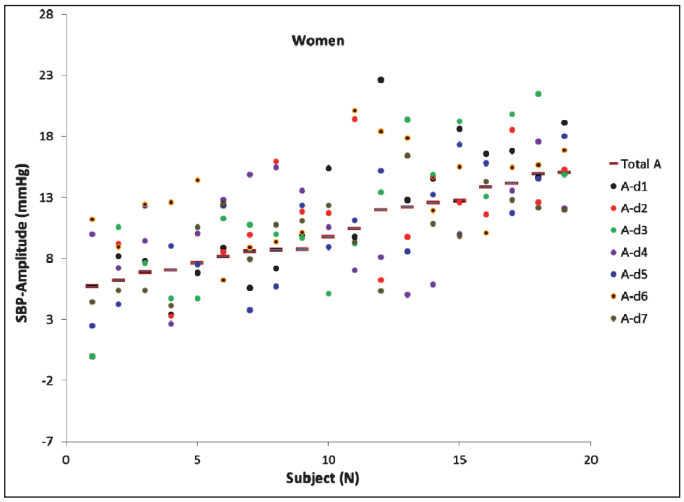

Figure 4. *Estimates of SBP-A from the entire record (dashes) and for separate daily spans (dots) also show a large scatter in women. © Halberg Chronobiology Center.*

Figures 5 and 6 are Bland-Altman plots comparing daily estimates of SBP-M on days without exercise with the 7-day SBP-M estimate for men and women, respectively. A comparison of daily estimates of SBP-M on days with exercise with the 7-day SBP-M estimate is provided in Figures 7 and 8 for men and women, respectively. It can be seen that the bias in SBP-M is small, ranging from -0.2 to 0.5 mmHg (P>0.50). The precision, however, is consistently around 4 mmHg. Hence, limits of agreement are approximately ± 8 mmHg.

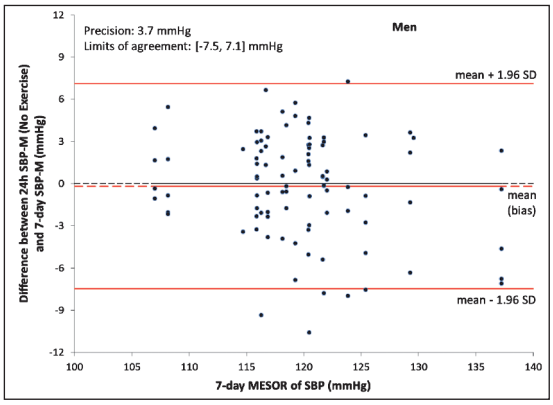

Figure 5. *Bland-Altman plot comparing daily estimates of SBP-M on days without exercise with the 7-day SBP-M estimate for men. © Halberg Chronobiology Center.*

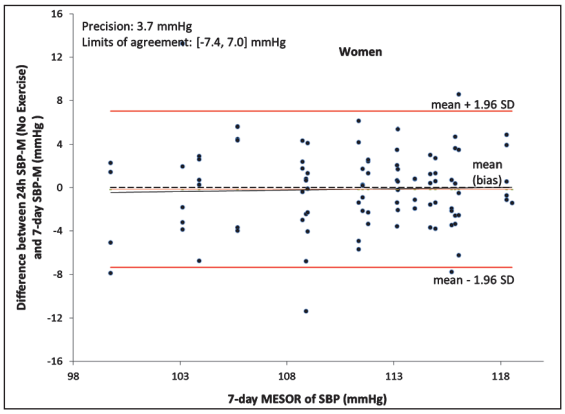

Figure 6. *Bland-Altman plot comparing daily estimates of SBP-M on days without exercise with the 7-day SBP-M estimate for women. © Halberg Chronobiology Center.*

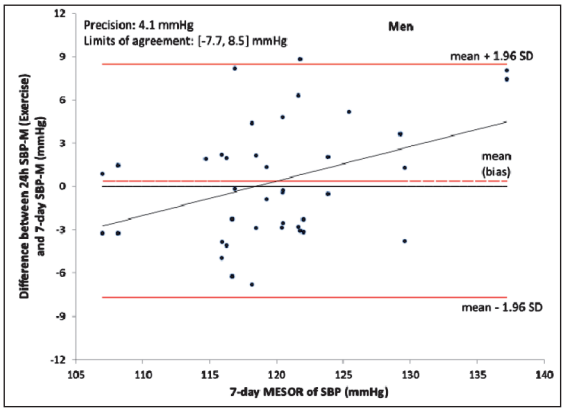

Figure 7.: *Bland-Altman plot comparing daily estimates of SBP-M on days with exercise with the 7-day SBP-M estimate for men. © Halberg Chronobiology Center.*

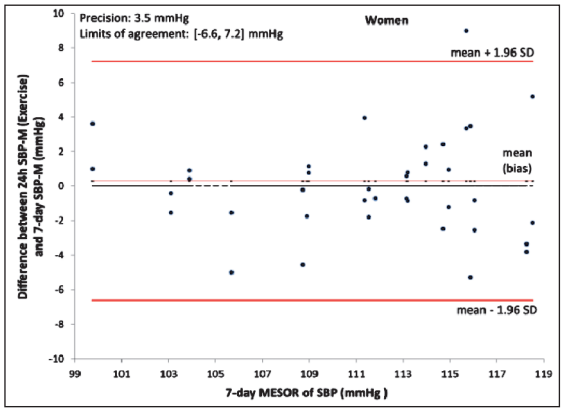

Figure 8.: *Bland-Altman plot comparing daily estimates of SBP-M on days with exercise with the 7-day SBP-M estimate for women. © Halberg Chronobiology Center.*

Figures 9 and 10 are Bland-Altman plots comparing daily estimates of SBP-A on days without exercise with the 7-day SBP-A estimate for men and women, respectively. A comparison of daily estimates of SBP-A on days with exercise with the 7-day SBP-A estimate is provided in Figures 11 and 12 for men and women, respectively.

The bias in SBP-A is invariably positive ($P<0.05$), the SBP-A estimate being larger from 1-day than from 7-day records. The precision is about 4.5 mmHg for men and 3.5 mmHg for women. The positive bias in SBP-A is in part related to the large day-to-day variability in SBP-M.

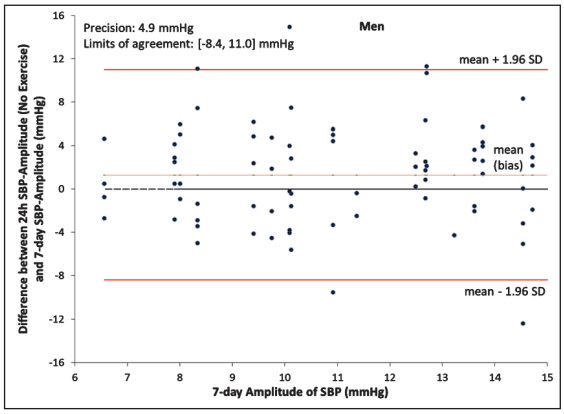

Figure 9. *Bland-Altman plot comparing daily estimates of SBP-A on days without exercise with the 7-day SBP-A estimate for men. © Halberg Chronobiology Center.*

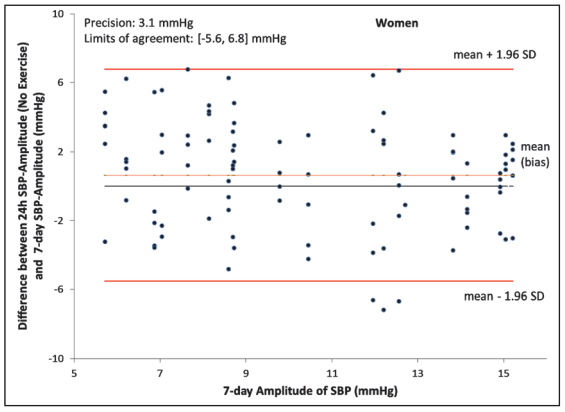

Figure 10.: *Bland-Altman plot comparing daily estimates of SBP-A on days without exercise with the 7-day SBP-A estimate for women. © Halberg Chronobiology Center.*

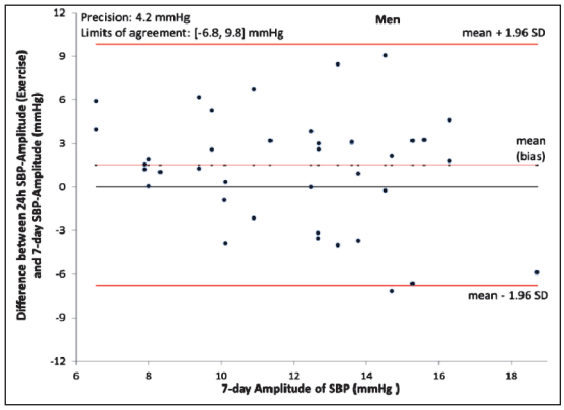

Figure 11. *Bland-Altman plot comparing daily estimates of SBP-A on days with exercise with the 7-day SBP-A estimate for men. © Halberg Chronobiology Center.*

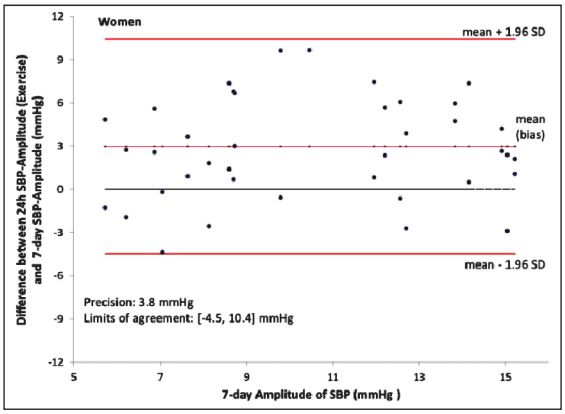

Figure 12. *Bland-Altman plot comparing daily estimates of SBP-A on days with exercise with the 7-day SBP-A estimate for women. © Halberg Chronobiology Center.*

Figures 13 and 14 are Bland-Altman plots comparing differences in daily estimates of SBP-M on days with versus without exercise with daily estimates of SBP-M on days without exercise for men and women, respectively. The precision is 4.5 mmHg for men and 5.2 mmHg for women, slightly larger than the precision associated with a comparison of SBP-M days with or without exercise versus the SBP-M estimate from the entire record. The bias, however, remains small, suggesting that SBP-M was not overly affected by the 1-hour exercise performed twice during the week of monitoring.

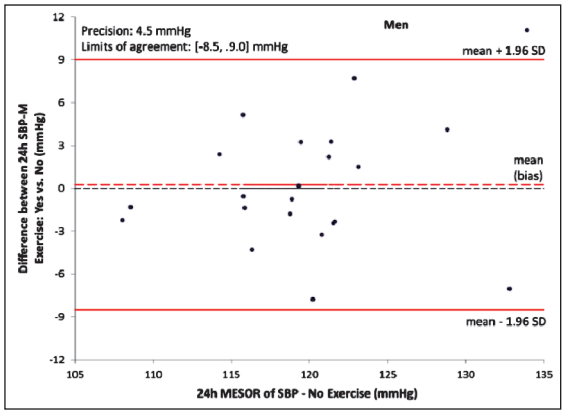

Figure 13. *Bland-Altman plot comparing differences in daily estimates of SBP-M on days with versus without exercise with daily estimates of SBP-M on days without exercise for men. © Halberg Chronobiology Center.*

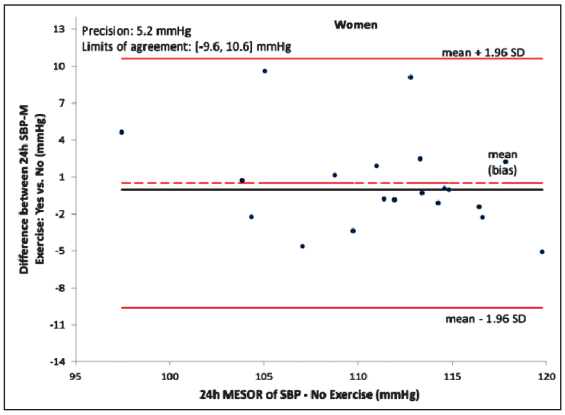

Figure 14. *Bland-Altman plot comparing differences in daily estimates of SBP-M on days with versus without exercise with daily estimates of SBP-M on days without exercise for women. © Halberg Chronobiology Center.*

Figures 15 and 16 are Bland-Altman plots comparing differences in daily estimates of SBP-A on days with versus without exercise with daily estimates of SBP-A on days without exercise for men and women, respectively. For men, but not for women, exercise is associated with an increase in SBP-A when the SBP-A on days with no exercise is small, and with a decrease in SBP-A when the SBP-A on days with no exercise is large. Whether this relationship is the result of a regression towards the mean [25] remains to be determined.

The precision is 3.9 mmHg for men and 3.6 mmHg for women, similar to the precision associated with a comparison of SBP-A days with or without exercise versus the SBP-A estimate from the entire record. The bias is positive for both men and women. It is statistically significant for women (2.3 mmHg, $P<0.01$), but not for men (0.4 mmHg, $P>0.50$). A summary of results is given in Table 1.

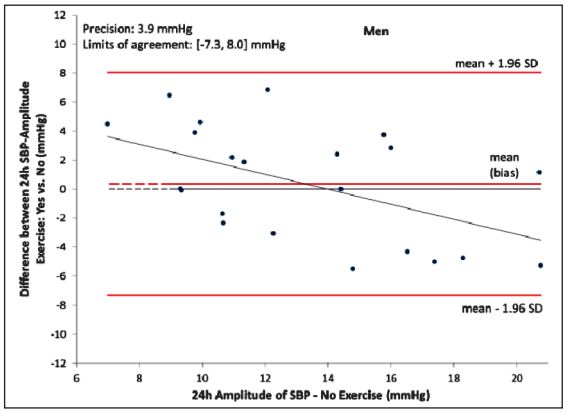

Figure 15.: *Bland-Altman plot comparing differences in daily estimates of SBP-A on days with versus without exercise with daily estimates of SBP-A on days without exercise for men. © Halberg Chronobiology Center.*

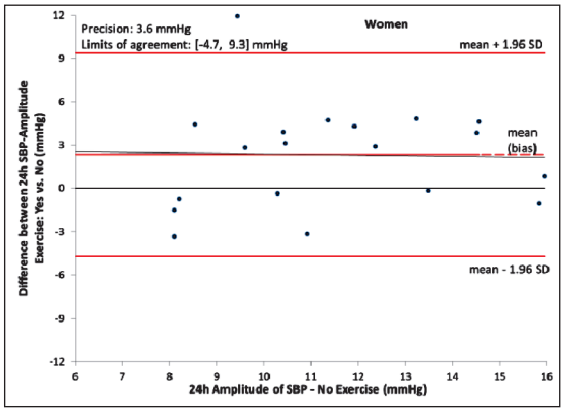

Figure 16.: *Bland-Altman plot comparing differences in daily estimates of SBP-A on days with versus without exercise with daily estimates of SBP-A on days without exercise for women. © Halberg Chronobiology Center.*

Table 1.: *Summary of results from Bland-Altman plots*

Comparison	Sex	N	SD	Limits of Agreement		Bias	Paired t	P-value
MESOR								
NoEx vs. 7d	M	95	3.7	-7.5	7.1	-0.2	0.490	0.625
Ex vs. 7d	M	40	4.1	-7.7	8.5	0.4	0.593	0.557
Diff vs. NoEx	M	22	4.5	-8.5	9.0	0.2	0.249	0.805
NoEx vs. 7d	F	99	3.7	-7.4	7.0	-0.2	0.436	0.664
Ex vs. 7d	F	40	3.5	-6.6	7.2	0.3	0.537	0.594
Diff vs. NoEx	F	20	3.9	-7.1	8.0	0.5	0.560	0.583
24-hour Amplitude								
NoEx vs. 7d	M	95	4.9	-8.4	11.0	1.3	2.554	0.012
Ex vs. 7d	M	40	4.2	-6.8	9.8	1.5	2.251	0.030
Diff vs. NoEx	M	22	3.9	-7.3	8.0	0.4	0.453	0.655
NoEx vs. 7d	F	99	3.1	-5.5	6.8	0.6	2.008	0.048
Ex vs. 7d	F	40	3.8	-4.5	10.4	3.0	4.965	<0.001
Diff vs. NoEx	F	20	3.6	-4.7	9.4	2.3	2.920	0.009

N: number of comparisons (days) – for comparison of days with vs. without exercise, results were pooled across all days either with or without exercise, resulting in a single comparison per subject; SD: Standard Deviation. SD, limits of agreement and bias expressed in mmHg.

NoEx: Days without exercise; Ex: days with exercise; Diff: days with – without exercise.

Discussion and Conclusion

Many factors contribute to the large day-to-day variability in BP, including exercise [10, 26, 27]. In this study, an effect of exercise was observed for the SBP-A of women but not men. Exercise in the evening was reported earlier to be associated with a larger circadian BP amplitude [28]. Whereas previous studies found a circadian stage-dependent effect of exercise on BP [26, 29], no such differences were found in the present study. It is possible that the inter-individual variability in circadian characteristics of SBP were too large to pool data from all subjects to test for a circadian stage-dependent effect of exercise. Studies documenting a circadian stage-dependent effect of exercise were indeed designed so that each subject would exercise in a standardized fashion at different times covering most of the 24-hour scale.

Results from this investigation indicate that BP variability within a day is quite large. In this study, SBP values in any given individual record varied in a range averaging about 100 mmHg. The standard deviation was about 15 mmHg. The 7-day SBP-2A, which estimates the amount of variation that can be expected to occur predictably within a day, averaged 23 mmHg, ranging from 11 to 37 mmHg among the 42 study participants.

The SBP-M, which represents an average of about 40 to 50 measurements per day taken around the clock, was found to vary greatly from one day to another, as evident from the 4 mmHg precision derived by the Bland-Altman plots. Individual SDs of daily SBP-Ms averaged 3.7 mmHg (range: 1.3 – 7.7 mmHg).

The resulting uncertainty from a single 24-hour record can make a large difference in terms of the diagnosis and the decision to treat [9]. For the diagnosis of hypertension and other abnormalities in BP patterns, BP should be monitored around the clock for longer than 24-hour spans to obtain a reliable estimate of BP and BP variability [7, 8, 30].

References

1. Otsuka K, Cornélissen G, Halberg F. Predictive value of blood pressure dipping and swinging with regard to vascular disease risk. Clinical Drug Investigation 1996; 11: 20-31.
2. Otsuka K, Cornélissen G, Halberg F, Oehlert G. Excessive circadian amplitude of blood pressure increases risk of ischemic stroke and nephropathy. J Medical Engineering & Technology 1997; 21: 23-30.
3. Schaffer E, Cornélissen G, Rhodus N, Halhuber M, Watanabe Y, Halberg F. Blood pressure outcomes of dental patients screened chronobiologically: a seven-year follow-up. JADA 2001; 132: 891-899.
4. Müller-Bohn T, Cornélissen G, Halhuber M, Schwartzkopff O, Halberg F. CHAT und Schlaganfall. Deutsche Apotheker Zeitung 2002; 142: 366-370 (January 24).
5. Cornélissen G, Halberg F, Otsuka K, Singh RB, Chen CH. Chronobiology predicts actual and proxy outcomes when dipping fails. Hypertension 2007; 49: 237-239.
6. Cornélissen G, Halberg F, Otsuka K, Singh RB. Separate cardiovascular disease risks: circadian hyper-amplitude-tension (CHAT) and an elevated pulse pressure. World Heart J 2008; 1 (3): 223-232.
7. Halberg F, Powell D, Otsuka K, Watanabe Y, Beaty LA, Rosch P, Czaplicki J, Hillman D, Schwartzkopff O, Cornélissen G. Diagnosing vascular variability anomalies, not only MESOR-hypertension. Am J Physiol Heart Circ Physiol 2013; 305: H279-H294.
8. Halberg F, Cornélissen G, Otsuka K, Siegelova J, Fiser B, Dusek J, Homolka P, Sanchez de la Pena S, Singh RB, BIOCOS project. Extended consensus on means and need to detect vascular variability disorders (VVDs) and vascular variability syndromes (VVSs). World Heart J 2010; 2 (4): 279-305.

9. Halberg F, Cornélissen G, International Womb-to-Tomb Chronome Initiative Group. Resolution from a meeting of the International Society for Research on Civilization Diseases and the Environment (New SIRMCE Confederation), Brussels, Belgium, March 17-18, 1995: Fairy tale or reality? Medtronic Chronobiology Seminar #8, April 1995, 12 pp. text, 18 figures.
10. Reinberg A, Ghata J, Halberg F, Gervais P, Abulker C, Dupont J, Gaudeau C. Rythmes circadiens du pouls, de la pression artérielle, des excrétions urinaires en 17-hydroxycorticostéroïdes, catécholamines et potassium chez l'homme adulte sain, actif et au repos. Ann Endocrinol (Paris) 1970; 31: 277-287.
11. Stadick A, Bryans R, Halberg E, Halberg F. Circadian cardiovascular rhythms during recumbency. In: Tarquini B. (Ed.) Social Diseases and Chronobiology: Proc. III Int. Symp. Social Diseases and Chronobiology, Florence, Nov. 29, 1986. Bologna: Società Editrice Esculapio 1987; 191-200.
12. Singh RB, Cornélissen G, Otsuka K, Juneja L, Halberg F. Coronary risk factors and ambulatory blood pressure and heart rate in Asian Indians. The Open Nutraceuticals J 2012; 5 (Suppl. 1-M5): 79-80.
13. Singh RB, Cornélissen G, Kumar A, Bathina S, Halberg F. Larger circadian amplitude of heart rate associated with active prayer in Hindu Indians in Asia. World Heart J 2008; 1 (3): 219-221.
14. Halberg F, Cornélissen G, Halberg E, Halberg J, Delmore P, Shinoda M, Bakken E. Chronobiology of human blood pressure. Medtronic Continuing Medical Education Seminars, 4th ed. Minneapolis: Medtronic Inc. 1988; 1-242.
15. Halberg F, Cornélissen G, Halberg Francine, Kessler T, Otsuka K. Measuring mental strain by duration of blood pressure overswing (CHAT): case report. World Heart J 2010; 2 (2): 141-167.
16. Mancia G, Santucciu C, Ulian L, Gelosa M, Rivolta MR, Sega R. Clinical value of ambulatory blood pressure monitoring. Journal of Cardiovascular Pharmacology 1994; 23 (Suppl 5): S1-S4.
17. Redon J. The importance of 24-hour ambulatory blood pressure monitoring in patients at risk of cardiovascular events. High Blood Pressure & Cardiovascular Prevention 2013; 20(1): 13-18.
18. Cornélissen G. Instrumentation and data analysis methods needed for blood pressure monitoring in chronobiology. In: Scheving LE, Halberg F, Ehret CF. (Eds.) Chronobiotechnology and Chronobiological Engineering. Dordrecht, The Netherlands: Martinus Nijhoff 1987; 241-261.
19. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. Lancet, 1986; i: 307-310.
20. Sedgwick P. Limits of agreement (Bland-Altman method). BMJ 2013; 346:f1630.
21. Siegelova J, Havelkova A, Dusek J, Pohanska M, Dunklerova L, Dobsak P, Singh RB, Cornélissen G. Seven-day ambulatory blood pressure monitoring: blood pressure variability at rest and during exercise. In: Kenner T, Cornélissen G, Siegelova J, Dobsak P. (Eds.) Noninvasive Methods in Cardiology 2013. Masaryk University, Brno, Czech Republic 2013; 87-95.
22. Halberg F. Chronobiology: methodological problems. Acta med rom 1980; 18: 399-440.
23. Cornélissen G, Halberg F. Chronomedicine. In: Armitage P, Colton T. (Eds.) Encyclopedia of Biostatistics, 2nd ed. Chichester, UK: John Wiley & Sons Ltd 2005; 796-812.
24. Refinetti R, Cornélissen G, Halberg F. Procedures for numerical analysis of circadian rhythms. Biological Rhythm Research 2007; 38 (4): 275-325.
25. Kruskal WH, Tanur JM. (Eds.) International Encyclopedia of Statistics. The Free Press, New York, 1978.
26. Levine H, Saltzman W, Yankaskas J, Halberg F. Circadian state-dependent effect of exercise upon blood pressure in clinically healthy men. Chronobiologia 1977; 4: 129-130.

27. Huynh W, Cornélissen G, Huynh Richie, Huynh Ryan, Halberg F. Feasible ambulatory blood pressure and heart rate monitoring in American secondary schools to assess chronomes in clinically healthy adolescents. In: Halberg F, Kenner T, Fiser B, Siegelova J. (Eds.) Noninvasive Methods in Cardiology. Faculty of Medicine, Masaryk University, Brno, Czech Republic 2010; 64-68.

28. Homolka P, Cornélissen G, Homolka A, Siegelova J, Halberg F. Exercise-associated transient circadian hypertension (CHAT)? III International Conference, Civilization diseases in the spirit of V.I. Vernadsky, People's Friendship University of Russia, Moscow, Oct. 10-12, 2005; 419-421.

29. Singh RB, Halberg F, Siegelova J, Cornélissen G. What is the best time to exercise? In: Halberg F, Kenner T, Fiser B, Siegelova J. (Eds.) Noninvasive Methods in Cardiology. Faculty of Medicine, Masaryk University, Brno, Czech Republic 2012; 163-164.

30. Halberg F, Cornélissen G, Schwartzkopff O. Self-surveillance assesses strain, vascular variability anomalies, VVAs, or disorders, VVDs, optimizes treatment and societal health. Sovremennaya medicinskaya nauka 2012: 123-156.

Correspondence:
Germaine Cornélissen
Halberg Chronobiology Center
University of Minnesota, Mayo Mail Code 8609
420 Delaware St. S.E. Minneapolis, MN 55455, USA
TEL +1 612 624 6976 FAX +1 612 624 9989
E-MAIL corne001@umn.edu
Website: http://www.msi.umn.edu/~halberg/

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University of Minnesota Supercomputing Institute

DEVELOPMENT OF CIRASEPTAN AND CIRCADIAN RHYTHM IN MAN

JARMILA SIEGELOVA, GERMAINE CORNELISSEN*

*Dept. of Physiotherapy and Rehabilitation, Dept. of Sports Medicine and Rehabilitation, St. Anna Teaching Hospital, Faculty of Medicine, Masaryk University, Brno; *Halberg Chronobiology Center, University of Minnesota, USA*

From the 80th in the last century cooperation between prof. Franz Halberg, Halberg chronobiology center and Masaryk University started. In Masaryk University, Brno chronobiology team, composed of Prof. B. Fiser (1943-2011), Dr. Dusek and Prof. Siegelova, organized every year together with Prof. Franz Halberg, Dr. med., Dr.h.c. mult. (1919-2013) and Prof. G. Cornelissen, Dr. Othild Schwarrtzkopff, Halberg Chronobiology Center, Minnesota, USA, Prof. Thomas Kenner, Dr. med., Dr.h.c. mult., University Graz, Austria and Prof. J.P. Martineaud (1931- 2010), Paris, France, Symposia and Congresses, held in Masaryk University, Brno and the presentations were published as scientific papers in Noninvasive Methods in Cardiology in 1999, 2002, 2003, 2004, 2006, 2007, 2008, 2009, 2010, 2011, 20012 and 2013, http://www.med.muni.cz/index.php?id=1376 (1-16). The publications were every year sent also to Prof. Theodor Friedrich Hellbrügge, Dr. med., Dr.h.c. mult., University Munich, Germany (1919-2014). Figure 7 shows the letter of Prof. Theodor Friedrich Hellbrügge who thanked us for it. Prof. Theodor Friedrich Hellbrügge described circadian and ultradian rhythm in premature babies and newborns (17, 18).

In the year 2000, the Rector of Masaryk University honored Prof. Franz Halberg, Dr. med., Dr.h.c. mult. and Prof. Thomas Kenner, Dr. med., Dr.h.c. mult. with the title Doctor honoris causa of Masaryk University Brno. Figures 1-4 show the ceremony in Masaryk University Brno, and Professor Theodor Friedrich Hellbrügge was also in Brno present.

Figure 1 *Prof. Franz Halberg, Prof. Thomas Kenner, Prof. Jiri Zlatuska (Rector of Masaryk University), Prof. Jarmila Siegelova, Prof. Libor Pac, Prof. Dr. med. Dr. h. c. mult. Theodor Friedrich Hellbrügge and others in Masaryk University Brno in 2000*

Figure 2 *Prof. Franz Halberg (1919-2013), University of Minnesota, USA, Prof. Thomas Kenner, University of Graz, Austria in Masaryk University Brno in 2000*

Figure 3 *Prof. Helena Illnerova, president of Czech Academy of Sciences, Dr. Othild Schwartzkopff-Halberg, Prof. Bohumil Fiser, Ministry of Health of the Czech Republic (1943-2011), Brigitte Kenner in Masaryk University Brno in 2000*

Figure 4 *Prof. Dr. med. Dr. h. c. mult. Theodor Friedrich Hellbrügge, University of Munich, Germany, in Masaryk University Brno in 2000*

Chronobiological studies in Masaryk University were aimed for long lasting blood pressure monitoring in premature babies and newborns, lasting 14 to 45 days and in adult people seven day lasting ambulatory blood pressure monitoring. We tested the hypothesis that neonatal blood pressure has an about 7-day circaseptan rhythm as prominent or even larger in amplitude than 24-h component, described and quantified as the major component in human adults. Blood pressure and heart rate were monitored automatically for 14 to 45 days, mostly at 30 minutes intervals from a total of 86 babies (18). Our results are summarized in figure 5. We have found large prominence of circaseptan component vs. circadian variation.

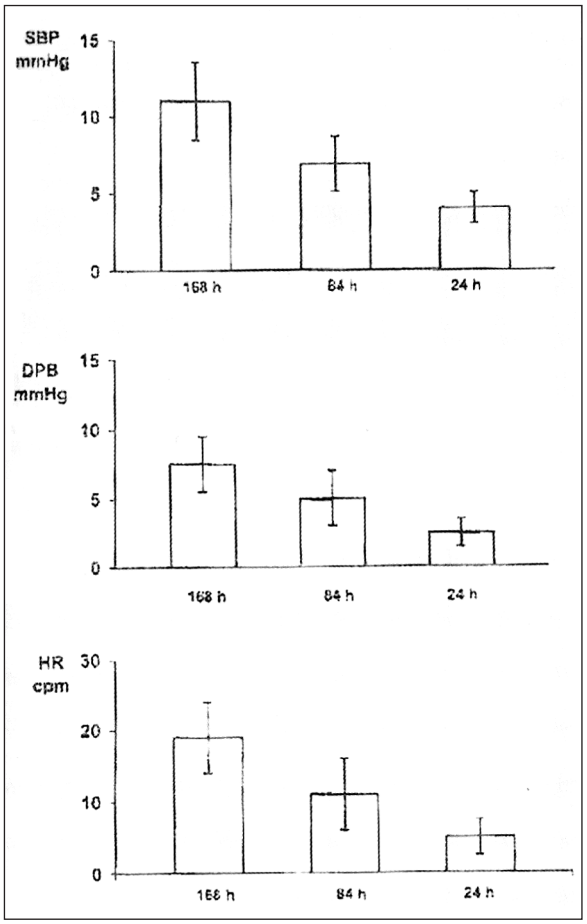


Figure 5 *Comparison of double amplitude of circadian (24 hours), semicircaseptan (84 hours) and ciraseptan of the circaseptan component (168 hours) of systolic blood pressure, diastolic blood pressure and heart rate in newborns in relation to the date of birth derived by cosinor analysis. Note large prominence of circaseptan component vs. circadian variation. Bars represent the double amplitude (means plus/minus 95% confidence limit) of cicaseptan and circadian components. Amplitudes of the two components differ with statistical significance ($p<0.01$, Kruskal-Wallis test).*

We examined healthy subjects using seven-day ambulatory blood pressure monitoring. From 7-day ambulatory blood pressure monitoring we assessed the chronome of 7-day/24-hour blood pressure (BP) and heart rate (HR) using Halberg cosinor analysis (1, 2, 3). Blood pressure and heart rate profiles at 30-min intervals from 145 subjects were analyzed by sphygmochron. Our data showed, using comparison of double amplitude of circadian (24 hours), semicircaseptan (84 hours) and ciraseptan and of the circaseptan component (168 hours) of systolic blood pressure and heart rate, large prominence of circadian component vs. circaseptan variation in adult healthy subjects. That is documented in figure 6.

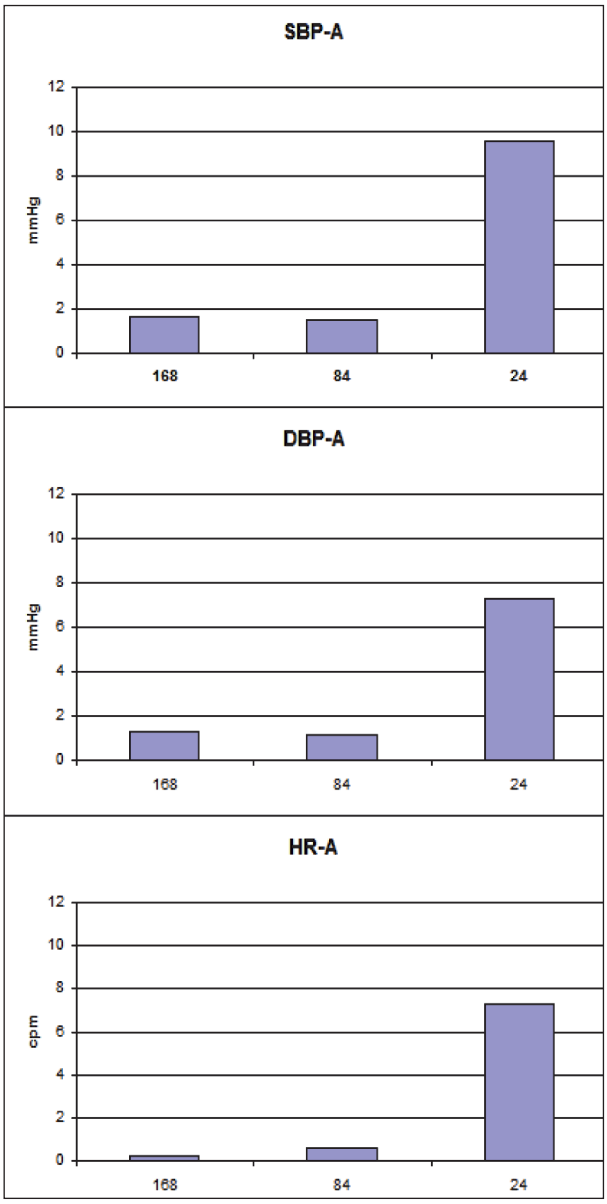


Figure 6 *Comparison of double amplitude of circadian (24 hours), semicircaseptan (84 hours) and ciraseptan and of the circaseptan component (168 hours) of systolic blood pressure and heart rate in adult man derived by cosinor analysis. Note large prominence of circadian component vs. circaseptan variation. Bars represent the double amplitude (means) of cicaseptan and circadian components. Circaseptan component is statistically significant for blood pressure but not for heart rate. The half-week is significant for all 3 variables, as is the circadian rhythm. The acrophases are around mid-week and mid-afternoon for the week and day, respectively.*

Conclusion

Long lasting monitoring in newborns showed slow oscillations with a different period between 5 to 10 days were found either in HR or in BP in all newborns. An identical period in HR, SBP and DBP was found in 31%. The peak of 24-hour periodicity in HR was found in 50% of newborns, in SBP and DBP only in 43%. The peak of 24-hour periodicity was always smaller than those found with circaseptan rhythm. Mean power spectra revealed a significant peak ($p<0.05$, Student t-test) at 0.16 cycles per day in HR, SBP and DBP. The results of this study brought the evidence: 1. the expression of a circadian rhythm during the first week of extra-uterine life, with an acrophase peaking in the early morning hours; 2. the larger prominences of the circaseptan vs. the circadian component of blood pressure and heart rate, with amplitude ratios larger

than 1.5 and 95% confidence intervals not overlapping; 3. the endogenicity of the circaseptan component, suggested by a synchronization among babies in relation to the time of birth, which carries no 7-day information, rather than relation to a calendar date, to which societal factors are related.

Seven day ambulatory blood pressure monitoring in adult subjects brought the evidence (from 145 subjects) of circaseptan component, statistically significant for blood pressure but not for heart rate. The half-week is significant for all 3 variables systolic blood pressure, diastolic blood pressure and heart rate. The circadian rhythm is much more prominent in all cardiovascular variables in adult subjects.

Prof. Dr. Dr. h.c. mult. Th. Hellbrügge
em. o. Professor für Sozialpädiatrie der Universität München
Kinderarzt

Kinderzentrum München

Heiglhofstraße 63
81377 München
Telefon (089) 710 09 - 312
Telefax (089) 719 36 10
www.theodor-hellbruegge-stiftung.de

Frau
Prof. MUDr. Jarmila Siegelova, DrSc
Katedra fyzioterapie a rehabilitace LF MU
Masarykova Univerzita
Pekarska 53
65691 Brno - Ceská Republika

09. Januar 2014 /w

Sehr verehrte Frau Kollegin Siegelova,

sehr herzlich möchte ich mich bei Ihnen bedanken für die Übersendung der Schrift über „Noninvasive Methoden in der Kardiologie 2013". Besonders hat mich der Artikel über meinen langjährigen Freund Franz Halberg bewegt. Mit Franz Halberg verbond mich über Jahrzehnte hinweg nicht nur eine wissenschaftliche Freundschaft.

Es würde mich sehr freuen, wenn in Zukunft zwischen der Medizinischen Fakultät, der Masaryk University in Brünn und dem Lehrstuhl für Sozialpädiatrie an der Technischen Universität München, Lehrstuhlinhaber Prof. Dr. med. Volker Mall, E-Mail: volker.mall@tum.de wieder eine Verbindung aufgebaut werden könnte.

Ein gutes Neues Jahr wünscht Ihnen

mit herzlichen Grüßen

Professor Dr. Dr. h. c. mult. Theodor Hellbrügge

Translation:

Dear Colleague Siegelova,

Thank you very much for sending us the brochure "Noninvasive Methods in Cardiology". I was especially affected by the article of my longtime friend Franz Halberg. It was not only a scientific friendship with Franz Halberg that connected us for decades.
I would be very happy if there could be established a connection in the future between the Medical Faculty, Masaryk University, Brno, and the Chair of Social Paediatrics at the Technical University Munich, chairholder: Prof. Dr. med. Volker Mall, E-Mail: volker.mall@tum.de.
All the best for the year 2014!
Best regards,
Professor Dr. Dr. h.c. mult. Theodor Hellbrügge

Figure 7 *The letter of Professor Theodor Friedrich Hellbrügge, Dr. med., Dr.h.c. mult., University Munich, Germany (1919-2014)*

References

1. Halberg F, Cornélissen G, Siegelova J, Fiser B, Dobsak P, Kenner T, Placheta Z, Dusek J, Homolka P, Al-Kubati M, Schwartzkopff O, Blagonravov MB, Chibisov SM, Agarwal RK. Blood pressure or, rather, blood pressure variability disorders, VVDs, discussed in Brno on October 6, 2008. Bulletin of People's Friendship University of Russia: Series Medicine 2008; (7): 26-30.
2. Halberg F, Cornélissen G, Otsuka K, Sanchez de la Peña S, Schwartzkopff O, Watanabe Y, Pati AK, Wall DG, Delmore P, Borer K, Beaty LA, Nolley ES, Adams C, Siegelova J, Homolka P, Dusek J, Fiser B, Prikryl P. Why and how to implement 7-day/24-hour blood pressure monitoring? Int J Geronto-Geriatrics 2005; 8 (1): 1-31. [Dated 2005 but published in June 2008.]
3. Halberg F, Cornélissen G, Otsuka K, Watanabe Y, Singh RB, Revilla M, Sanchez de la Pena S, Gonzalez C, Siegelova J, Homolka P, Dusek J, Zeman M, Singh RK, Johnson D, Fiser B. Home C-ABPM for preventive and curative health care and transdisciplinary science. World Heart J 2008; 1 (3): 233-261.
4. Halberg F, Kenner T, Fiser B, Siegelova J(eds): Cardiovascular coordination in health and blood pressure disorders. Faculty of Medicine, Masaryk University, Brno (1996).
5. Halberg F, Kenner T, Fiser B, Siegelova J(eds): Chronobiology and non-invasive methods in cardiology. Brno : IDV PZ, MU, 1999. ISBN 80-7013-279-5.Faculty of Medicine, Masaryk University, Brno (1999).
6. Halberg F, Kenner T, Fiser B (eds): The importance of chronobiology in diagnosis and therapy of internal diseases. Faculty of Medicine, Masaryk University, Brno (2002)
7. Halberg F, Kenner T, Siegelova J (eds): The importance of chronobiology in diagnosis and therapy of internal diseases. Faculty of Medicine, Masaryk University, Brno (2003)
8. Cornelissen G, Kenner T, Fiser B, Siegelova J (eds): Chronobiology in medicine. Faculty of Medicine, Masaryk University, Brno (2004).
9. Halberg F, Kenner T, Fiser B, Siegelova J (eds): Nonivasive methods in cardiology 2006. Faculty of Medicine, Masaryk University, Brno (2006).
10. Halberg F, Kenner T, Fiser B, Siegelova J(eds): Nonivasive methods in cardiology 2007. Faculty of Medicine, Masaryk University, Brno (2007).
11. Halberg F, Kenner T, Fiser B, Siegelova J (eds): Nonivasive methods in cardiology 2008 Faculty of Medicine, Masaryk University, Brno (2008).
12. Halberg F, Kenner T, Fiser B, Siegelova J (eds): Nonivasive methods in cardiology 2009 Faculty of Medicine, Masaryk University, Brno (2009).
13. Halberg F, Kenner T, Fiser B, Siegelova J(eds): Nonivasive methods in cardiology 2010; Faculty of Medicine, Masaryk University, Brno (2010).
14. Halberg F, Kenner T, Siegelova J (eds): Nonivasive methods in cardiology 2011; Faculty of Medicine, Masaryk University, Brno (2011).
15. Halberg F, Kenner T, Siegelova J, Dobsak P. (eds): Nonivasive methods in cardiology 2012; Faculty of Medicine, Masaryk University, Brno (2012). http://www.med.muni.cz/index.php?id=1376.
16. Kenner T, Cornelissen G, Siegelova J, Dobsak P. (eds): Nonivasive methods in cardiology 2013; Faculty of Medicine, Masaryk University, Brno (2013) http://www.med.muni.cz/index.php?id=1376.
17. Halberg F, Cornélissen G, Katinas G, Schwartzkopff O, Johnson D. Theodor Hellbrügge: 85 years of age – Ad multos transannos, sanos, fortunatos et beatos. J Circadian Rhythmus. ISSN: 1740-3391.
18. Siegelova J, Cornélissen G, Schwarzkopff O, Halberg F. Time structures in the development of children. Neuroendocrinology Let, 2003, Vol.24, Suppl. 1, p. 126-131. ISSN 0172-780X.

SOME REMARKS CONCERNING VASCULAR AND MUSCULAR PULSATIONS: MEASUREMENTS OF THE GRAZ-PHYSIOLOGY IN THE AUSTROMIR PROJECT

THOMAS KENNER

Department of Physiology, University of Graz, AUSTRIA

With this lecture I want to commemorate 4 persons who did remarkable work on the interpretation and analysis of vascular flow and pulsations. They were most important and helpful for my education in the field of hemodynamics:

Otto Gauer, Roland Ronniger, Erik Wetterer, Ernst O. Attinger.

Pulsations of arteries

Pulsations of arteries, in particuar pulsations of the radial artery and of the temporal artery were already well known to Hippokrates. It seems especially interesting, that on one hand, tempus has the meaning of time, and that that the feeling of the temporal artery has something to do with rhythmic music and dancing in historic times.

My personal interest in recording and interpretation started soon after my promotion as Medical Doctor and consequently to my activity as a young physician in a Department of Internal Medicine in a Viennese Hospital. I had the possibility to record arterial pulses with available equipment. In particular I also had the opportunity to use X-ray equipment to record pulses of the pulmonary artery and of the heart – using a special recording system with the name “Elektrokymograph”. With this system all pulsations of central arteries and of the heart could be recorded (1).

In the following time R. Ronniger taught me how to apply the methods to analyze and describe arterial pulsations and we published several papers on this topic (36). Further on my way led to the Professors Gauer, Wetterer and Attinger. With respect to hemodynamics I mention a book by Wetterer and Kenner (2).

The basic phenomenon in arterial pulsating blood flow is the fact that there is always a pressure pulse and a simultaneous flow pulse. During the propagation of both, they are influenced and modified by the socalled “characteristic impedance” of the elastic tube.

The characteristic impedance is described by

$$Z = c.g/Q$$

Where c is the pulse wave velocity, g is the density of blood and Q is the square area of the tube (RR,KW). We use the symbol for pressure amplitude = dp , and the flow amplitude = di . The influence of the characteristic impedance Z on the relation of pressure amplitude dp to flow amplitude di is described by:

$$dp = Z.di$$

An example of a tube with increasing characteristic impedance and corresponding pressure- and flow-amplitude can be seen in Fig. 1.

In the case, that at a certain location of a tube exists a sudden local narrowing of the artery, the effect on pressure- and flow- will be similar as just described, except, that in addition reflection of the wave has to be considered.

R. Ronniger was one of the first to apply a mathematical (or geometric) method to describe the behavior elastic tubes – filled with fluid; a method, which was already used for the phenomena of electricity in long-distance transmitting wires. In such wires electric impulses are propagated in a characteristic speed. If, similar as in arteries, of the distance between two locations on the waves is described as phase-angle. E.G.: if a tube without any reflection at the outflow-end is described, the result is a circle. If – like the aorta – the tube is inhomogeneous, the constructed figure looks like an ellipse. We will later come back to this method of description.

ANALYSIS and DESCRIPTION of PULSES

If one looks at recorded pressure pulses, there are following characteristic values:

Duration of one period, duration of systole and diastole, shape of the pulse, steepness of upstroke, shape of systolic period, diastolic pressure, pressure amplitude, if possible: pulse wave velocity.

If simultaneous pulses are recorded, then the difference between both pulses are of interest. The method of analysis which shall be explained in the following report has – in analogy to electric waves of alternating current which are propagated in long-distance wires - can be applied in the same mathematical way to arterial pulses.

In order to demonstrate the development of characteristic shapes of arterial pulses, Wetterer and Kenner (1, 2) used a 2 m long bicycle wheel rubber tube to observe and demonstrate the generation and reflection of waves. The "heart-pump" generated a central aortic flow pulse – similar to a normal left ventricle outflow. The result can be seen in Fig.1

AN IMPORTANT NOTE: My coworkers, in particular Dozent Max Moser and I agreed, that the design of new Instrumentation must have properties, which are necessary for an application in medicine - and particularly in the clinic.

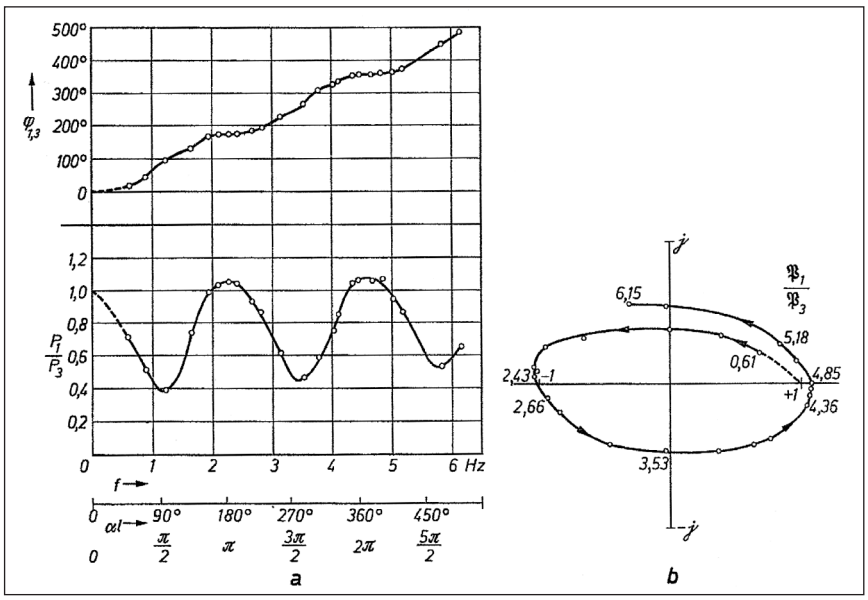


Figure 1 *An example of a tube with increasing characteristic impedance and corresponding pressure- and flow-amplitude Left: Recording of rhythmic pressure pulses and phase. Right: "locus-plot of pressure transmission"*

The method used – as mentioned above - in analogy to electric long distance wires, describes the distance of the running wave and is plotted in grades (Fig. 1 – upper part). In the lower part, the distance between the maxima of the pressure wave corresponds to 180 grades.

Fig. 2 shows – on the left side phase (upper part) and Quotient of pressure at the entrance of the tube p1 and at the end of the tube p3.

The elliptic shape is characteristic for a tube with a low resistance outflow at the end. The figures which were calculated – as indicated above – are called "LOCUS-PLOTS or mor specifically: PRESSURE TRANSMISSION FUNCTION.

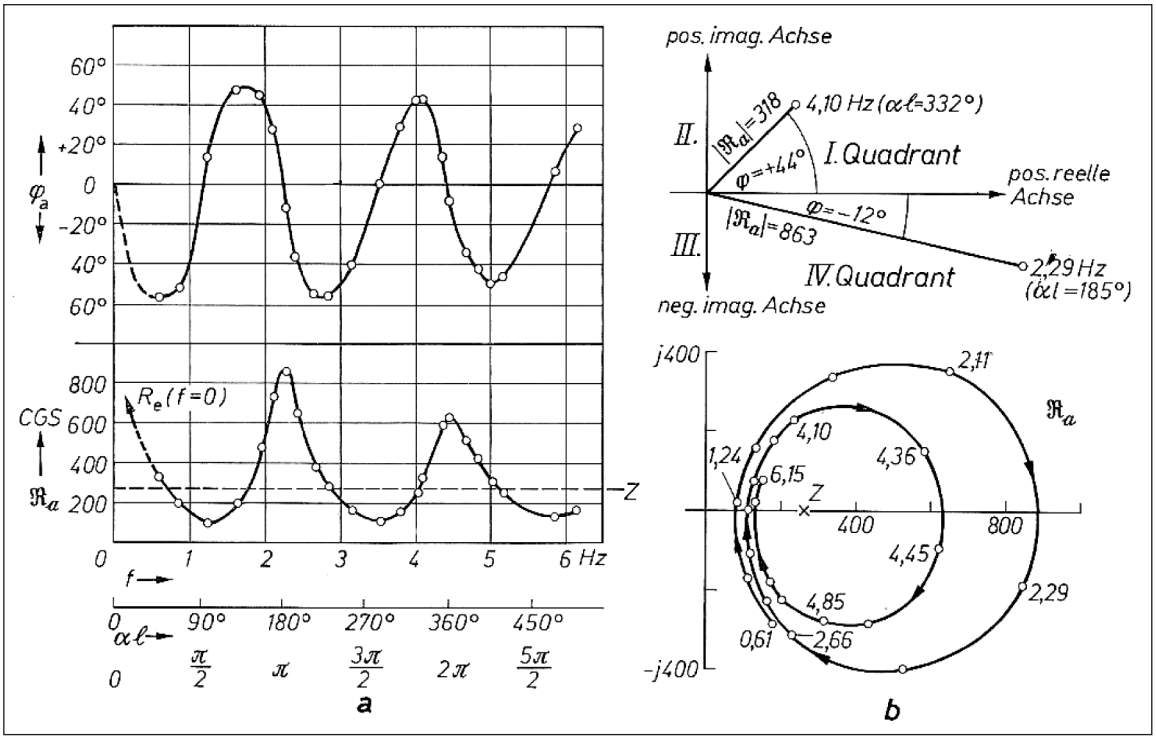


Figure 2 *Pressure transmission function.*
Left: Recording of pressure-flow relation (phase difference pressure versus flow).
Right: locus plot of the input impedance of the tube

Fig. 2 shows on the left side the characteristics of the pressure transmission and (right) the corresponding locus plot from an experiment in which sinusoidal input flow of varying frequency was used. The transmission function P0/PL (entrance and end) and P0/P2 (emtrance and two thirds) and P0/P1 (entrance and one-third are shown as locus plots. The basic features correspond to those calculated by Ronniger (1954) and those by Wetterer and Kenner (1968).

It can be shown, that in animal experiments, the injection of Noradrenalin and consequently vasoconstriction leads to a more flat shape of the transmission function (Fig. 3). The injection of Acetylcholine leads to more circular shapes, indicating peripheral vasodilatation.

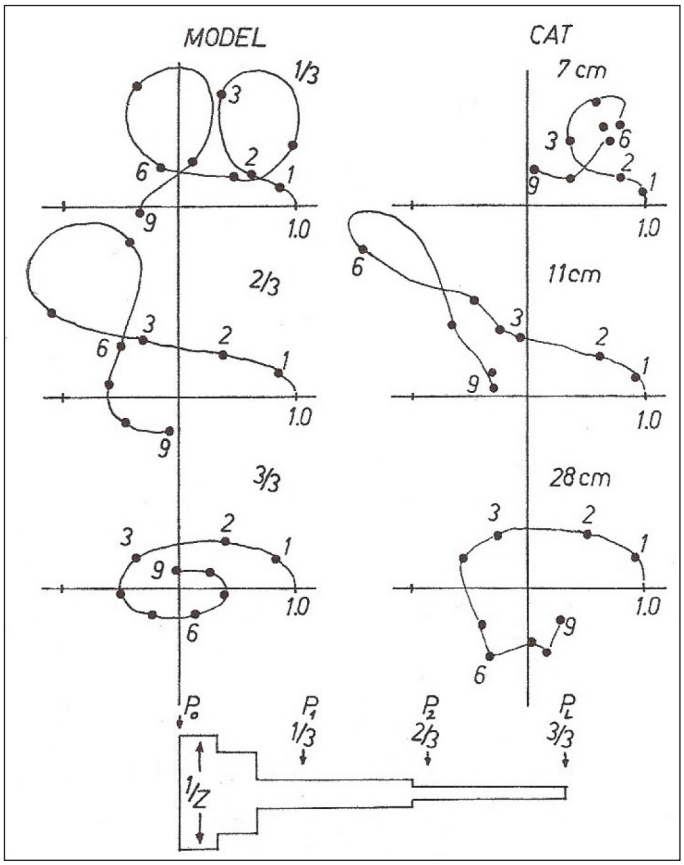


Figure 3 *Locus plots demonstrating pressure transmission:*
Left: calculated from the locations in the model with narrowing tubes.
Right: the locus plot was calculated from recordings in an anesthetized cat with different locations in aorta and femorl artery

The examples (below from an AUSTROMIR COSMONAUT) are shown, in order to enable the impression of the result of the transformation of two pulses by a mathematical analysis, which leads to the figure of locus plots. Such locus plots are helpful for interpretation and diagnosis. They are in agreement with model-calculation (Fig. 4).

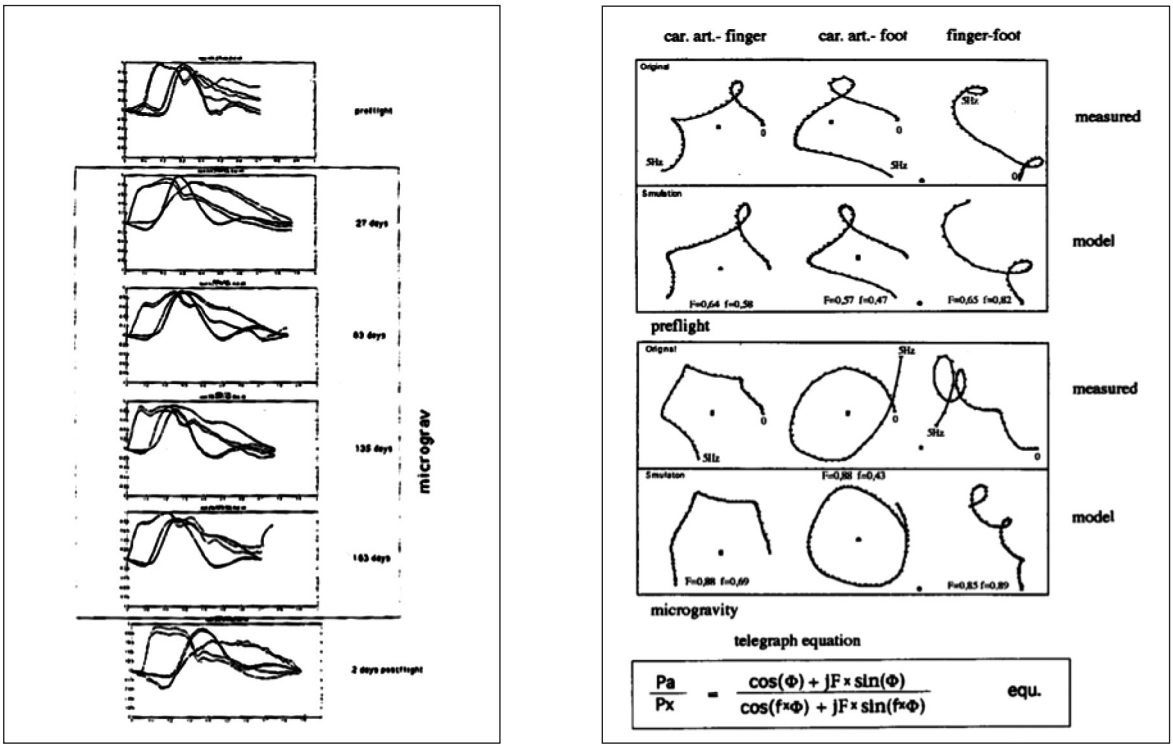


Figure 4 *The examples of ASTROMIR COSMONAUT*
Left: recordings in a cosmonaut with pulse sensors: carotis and foot (see also the next diagram). Right the calculated pressure-transmission locus plots. And corresponding model calculations.

The times with measurement during flight (= microgravity) is indicated in the figure.

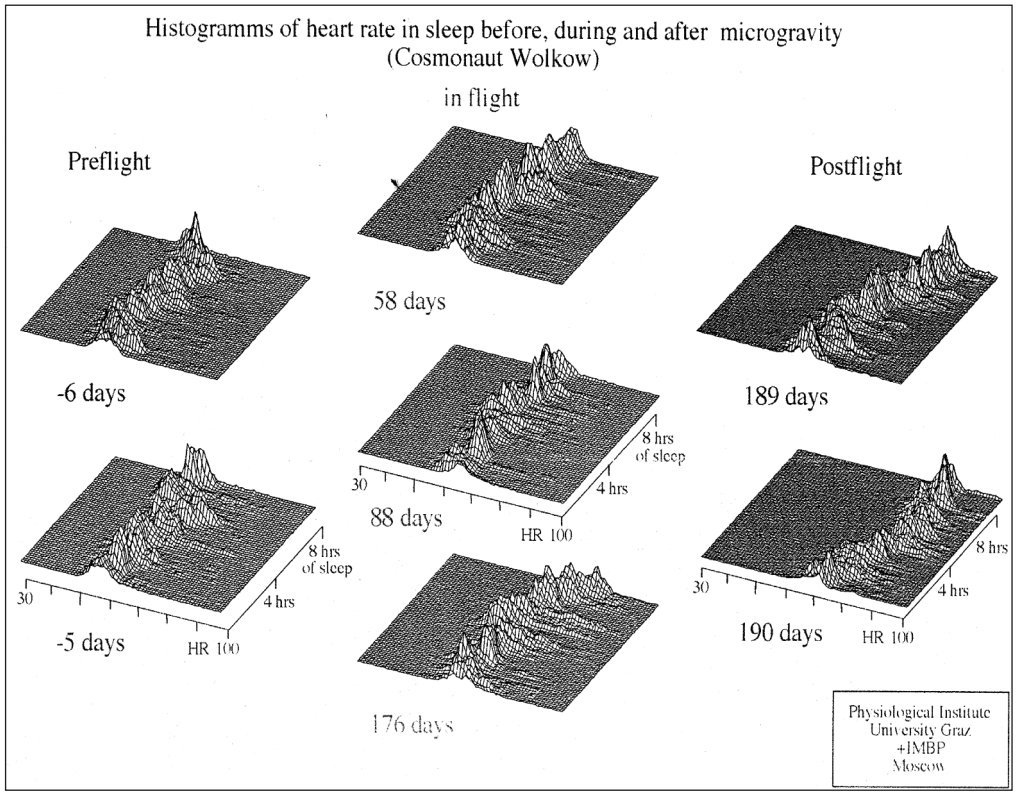


Figure 5 *Heart rate variability in sleep before, after microgravity*

In Fig. 5 we can see heart rate variability in sleep before, after microgravity of ASTROMIR COSMONAUT.

HISTORY OF BLOOD PRESSURE MEASUREMENT

First measurement of blood pressure was done by S. Hales (1677 – 1761) in horse (Fig. 6).

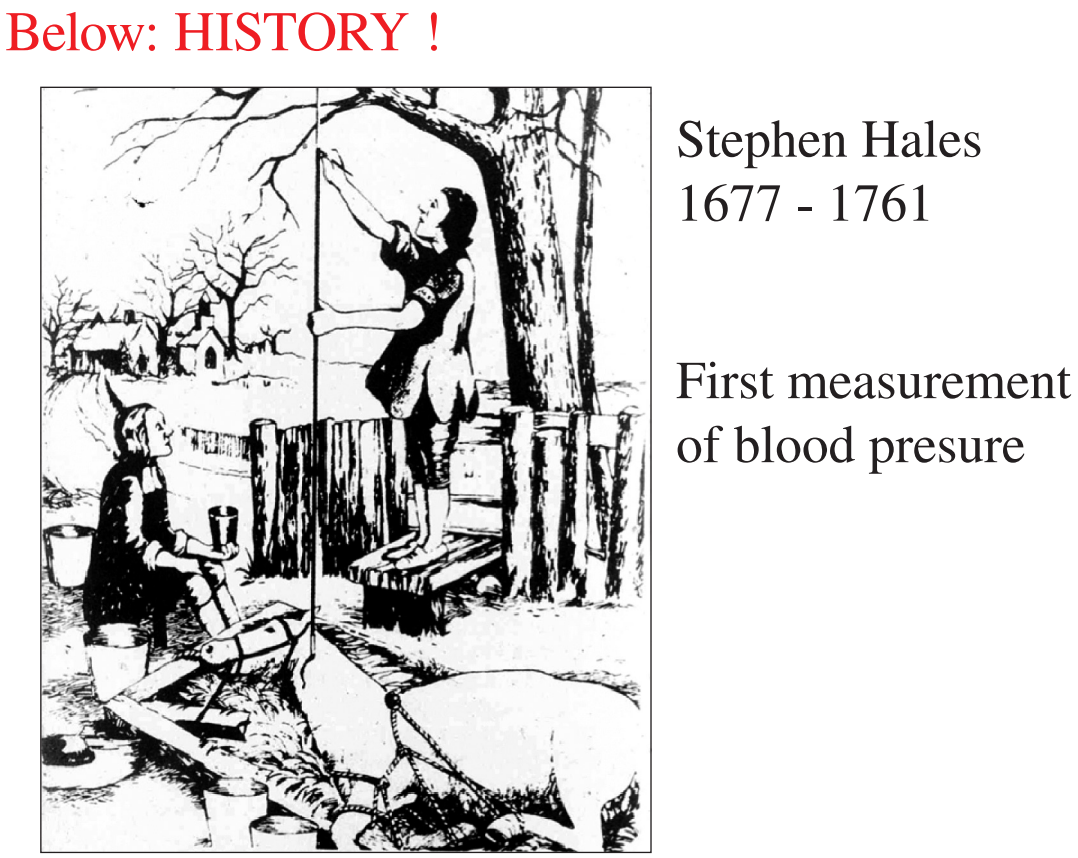


Figure 6 *Measurement of blood pressure*

As a contrast to the modern instruments: the fig. 6 shows the very first measurement of blood pressure in an animal.

Noninvasive measurement of blood pressure in the 19th century was developed by Riva - Rocci method and was used in clinic, in the 20th century Penaz developed beat by beat noninvasive measurement of blood pressure (Fig. 7).

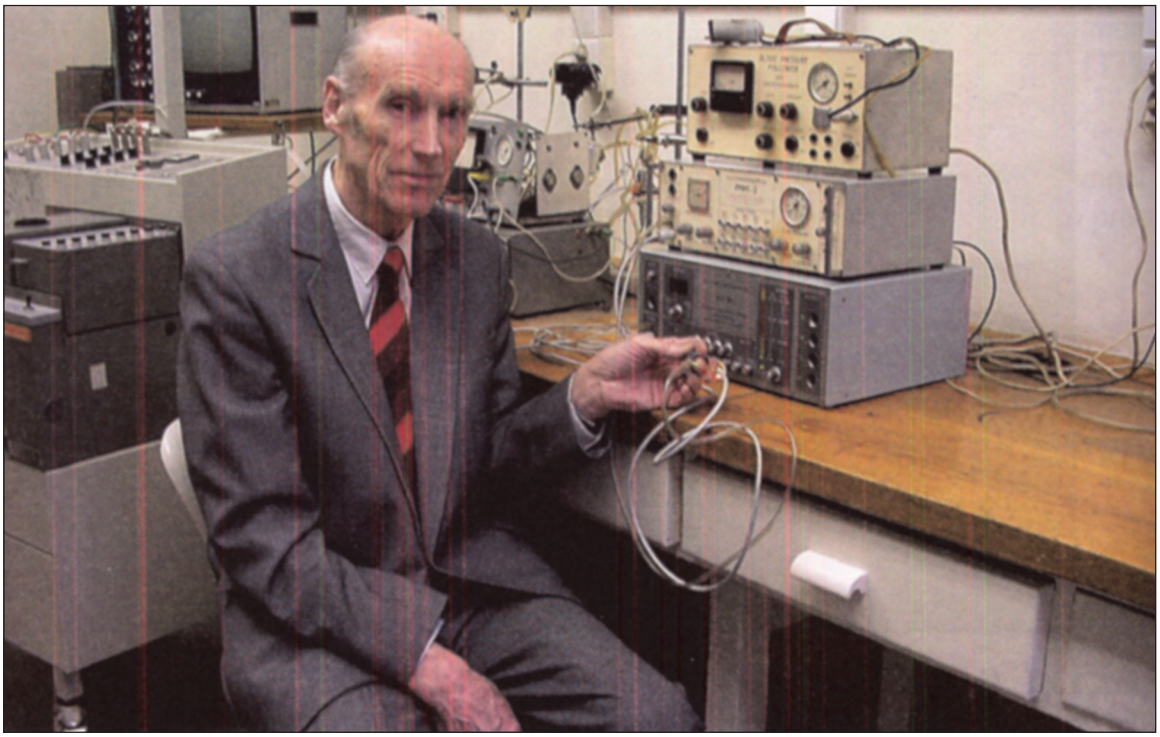
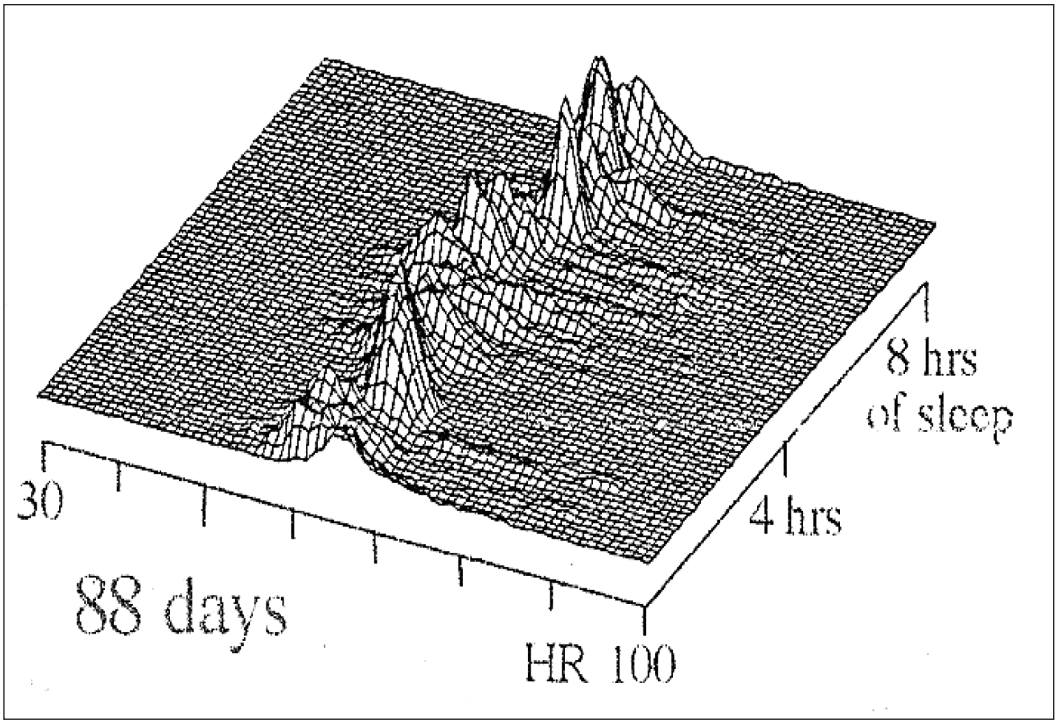


Figure 7 *Prof. J. Penaz with finger-cuff blood pressure in 1966*

Prof. PENAZ, who is still living in BRNO has invented the FINGER_CUFF-Method to measure blood pressure. It seem to me important, that his name should not be forgotten.

In the 1980th in University of Graz under the guidance of professor Kenner the heart rate variability measurement was developed. Figure 8 shows an example of heart rate record.



HR...Heart Rate / hrs of sleep per day

Figure 8 *Heart rate measurement in man*

Using evaluation of continuous recordimg of ECG, the heart rate was measured. The horizontal line indicates HR = Heart rate during sleep (line up showns the time of sleep = to 8 hours).

AUSTROMIR project also reflected older methods from 19th century of investigations in circulation blood flow and used that for complex measurement of circulation in space (Fig. 9, 10, 11)

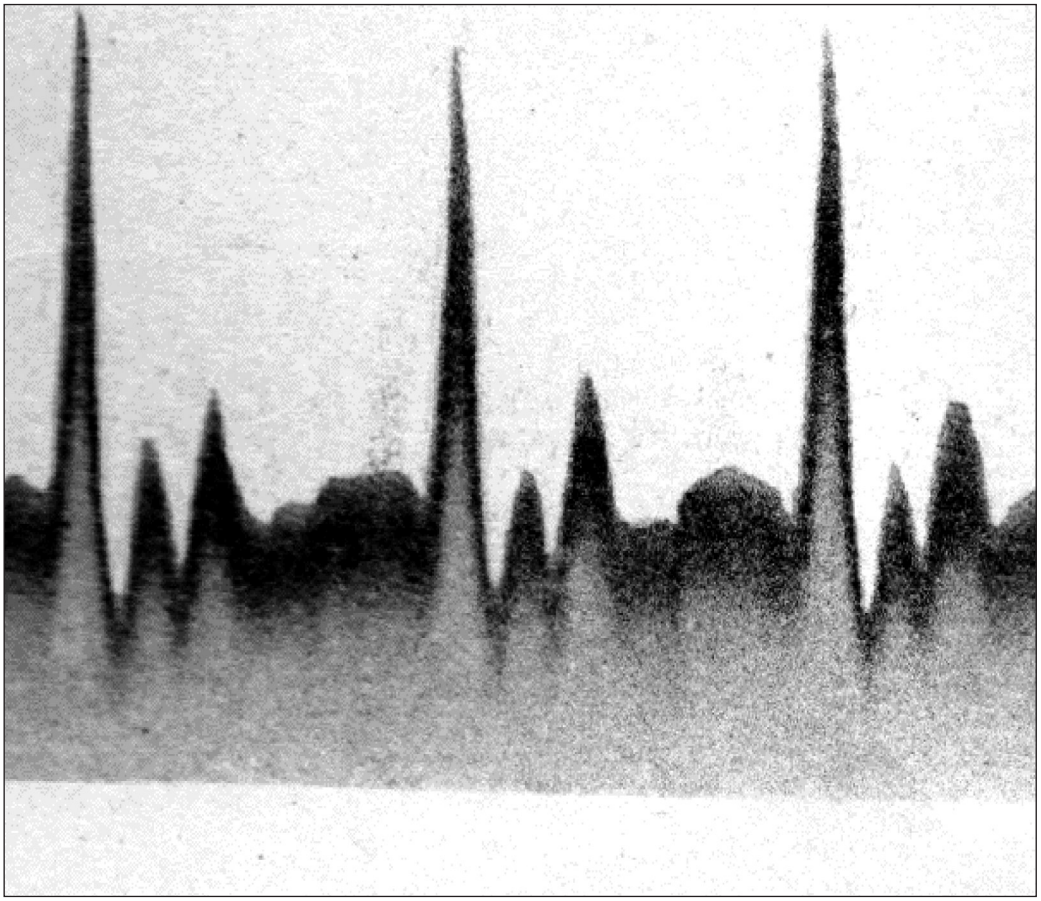


Figure 9

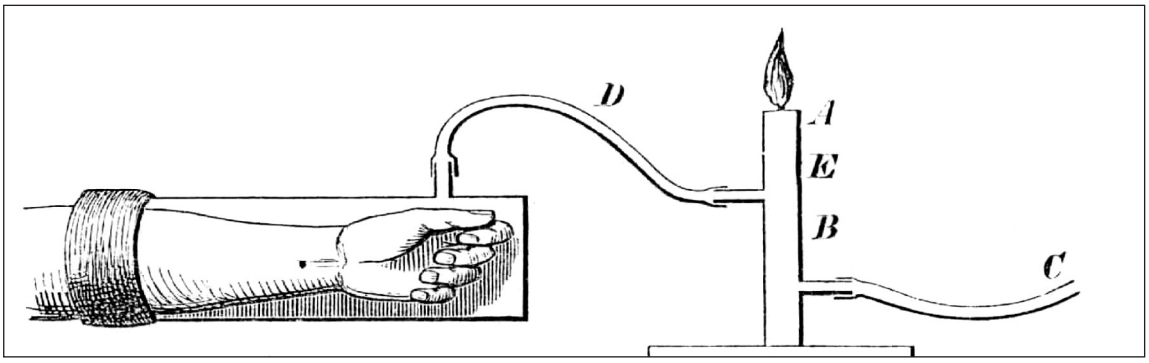


Figure 10 *FLAME-Flowmeter described by J. von Kries (1887)*

First measurement of blood flow in the arm of a person. The pulsation by the flow of blood through the arteries in the arm can be seen on the hight of a simple gas-flame. (upper record shows the pulsation and the oscillations of the flow).

This record was published by the famous physiology Johannes von KRIES in 1887.

FURTHERAPPLICATIONS OF DEVICES:

Accelerometer recordings (E. Gallasch):

Muscle movements of a baby during 5 1/2 hrs sleep

REM - Phases!

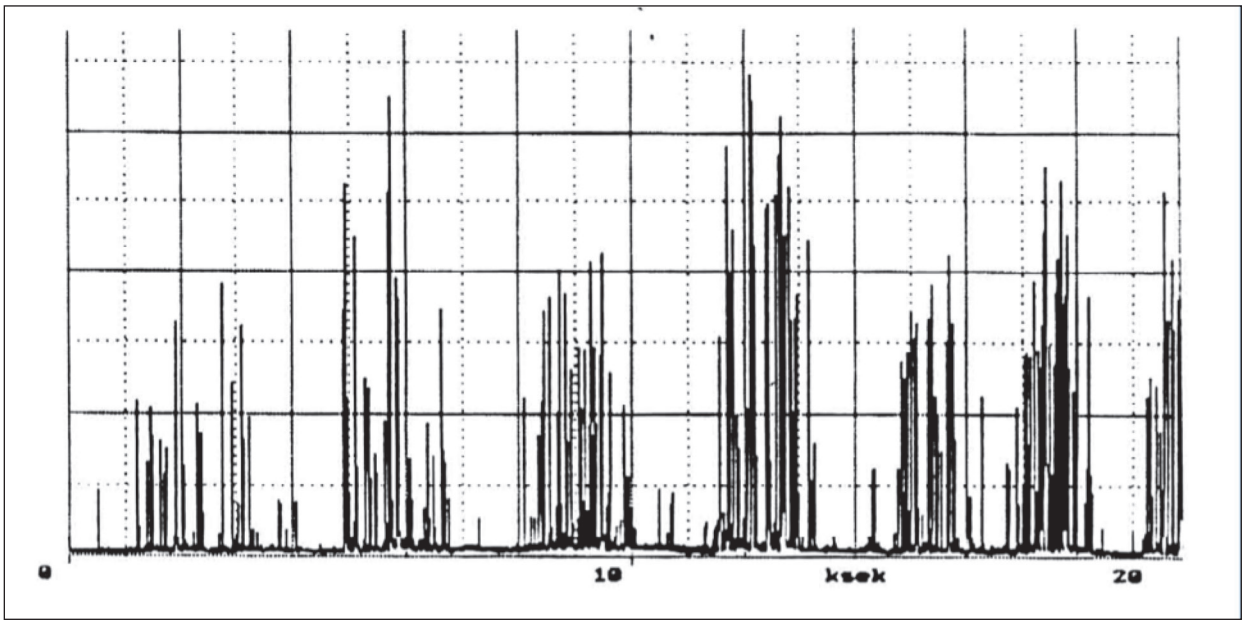


Figure 11 *Measurement from a baby the resolution of the „MICRO-VIBRATIONS“ of muscle movements*

Application of the measurement of the microvibration on a baby skin - in a hospital in Graz. In a baby the micovibrations are much finer recordable. One can see: the vibrations indicate the socalled REM- sleep phases. (The baby was sleeping)

In this example, from a baby the resolution of the „MICRO-VIBRATIONS“ of muscle movements is increased.

All measurement of heart rate and blood pressure and blood flow were developed for AUSTROMIR project which was used for AUSTROMIR project in space 1991 (Fig. 12).

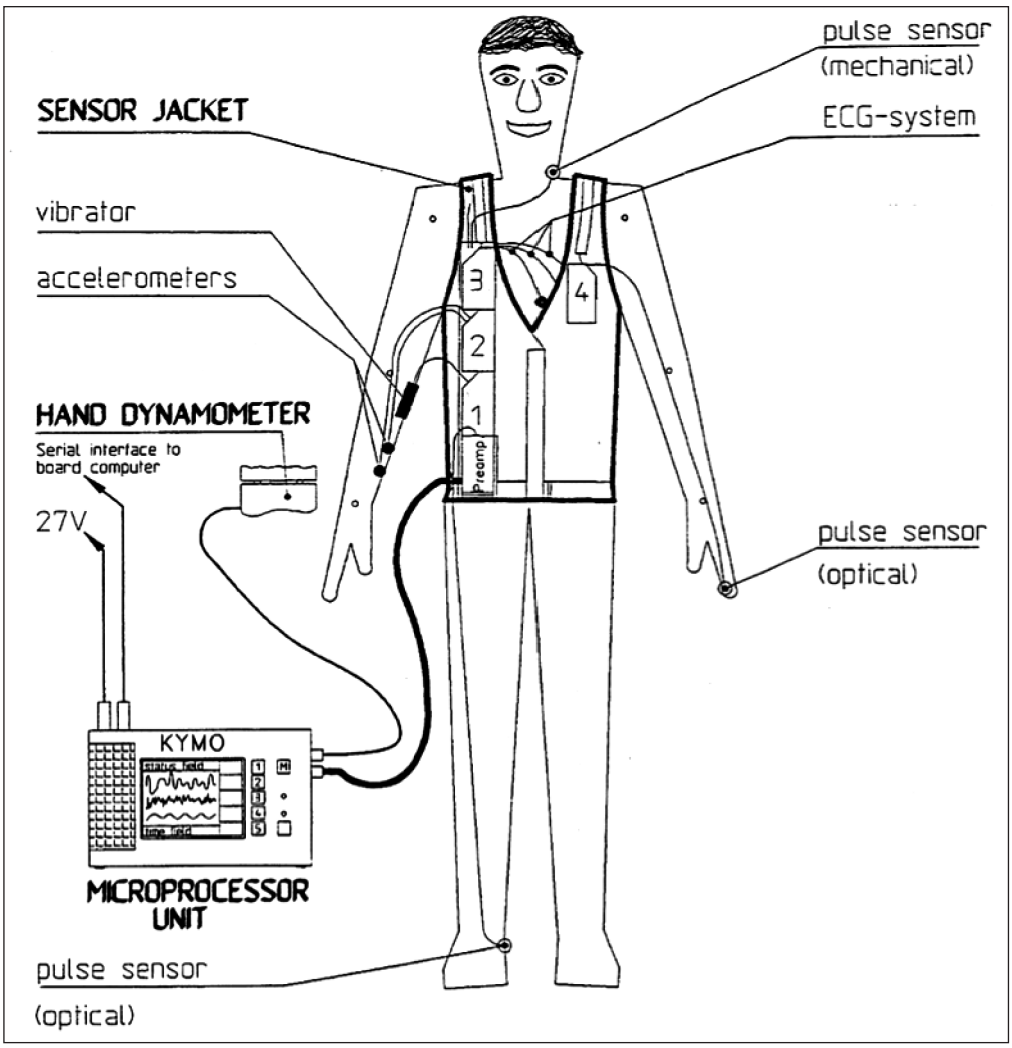


Figure 12 *AUSTROMIR project: our man in space 1991*

Austromir project: location and type of recordings are seen in fig. 12. The sensor jacket is necessary. Sensors and wires would otherwise float around during weightlessness.

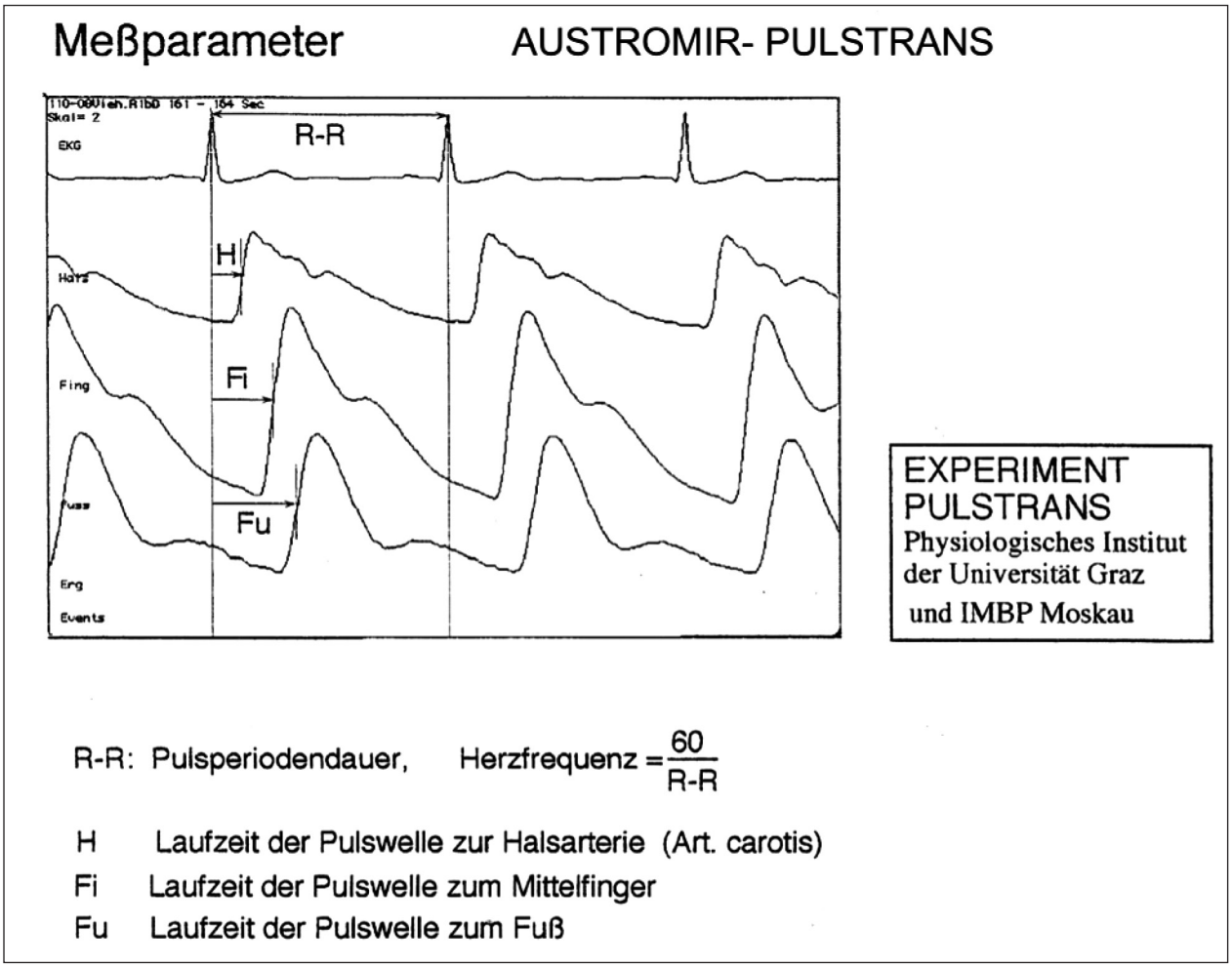


Figure 13 *Recording of pulses*

The example in Fig. 13 is from a Cosmonaut in the AUSTROMIR-PROJECT.

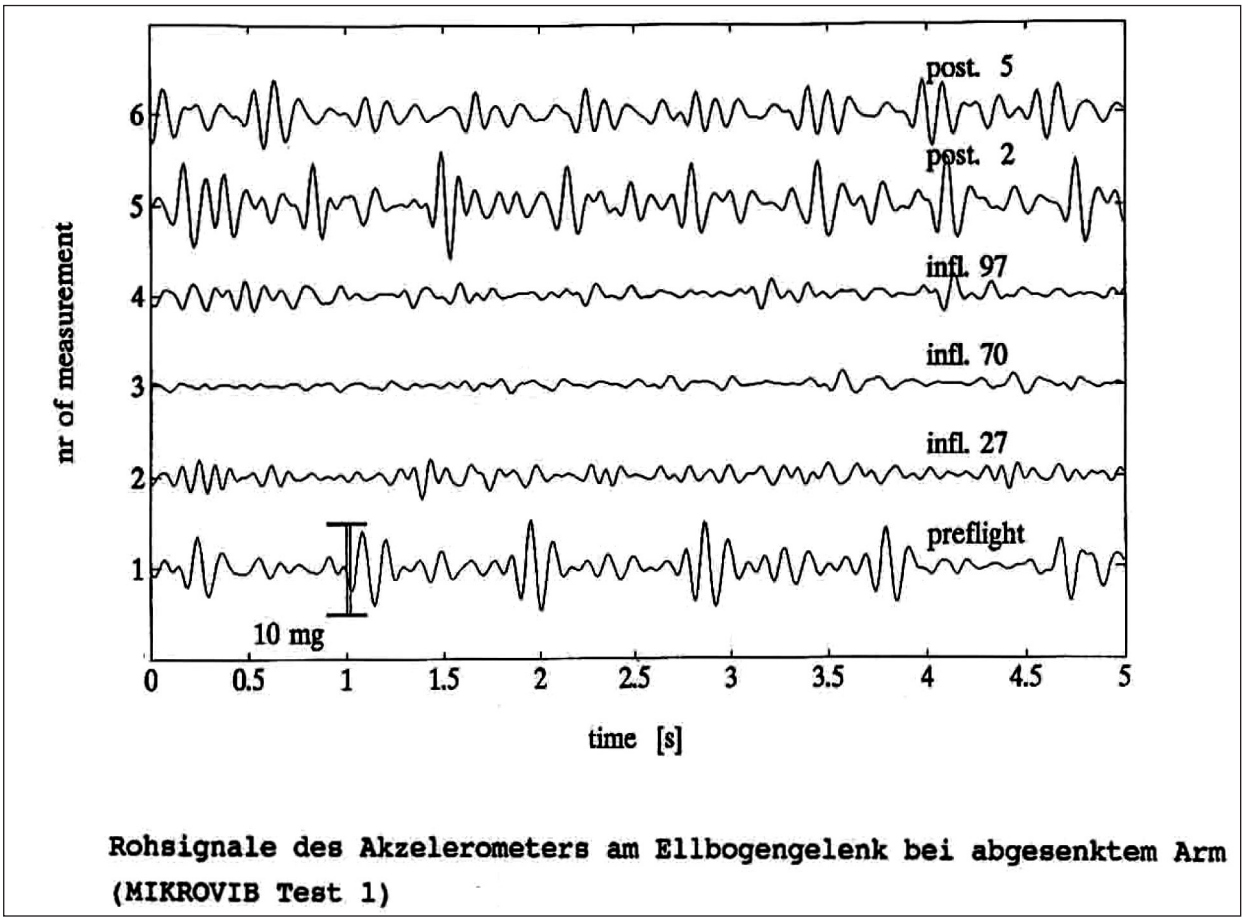


Figure 14 *Recording of the microvibration. During the phase of weightlessness is the microvibration markedly smaller*

Figure 15 *Picture of the Russian space-ship AUSTROMIR, cover of a book in german (1991)*

The picture shows the cover of a book (in German) about the Austromir Project. (1991). The Pulse wave analysis and literature can be also found in the Book DYNAMIK DES ARTERIENPULSES by E. Wetterer and T. Kenner, Sprinfer Verlag , 1968. In this book are abundant earlier literature (before 1968).

References

1. Kenner T: Neue Gesichtspunkte und Experimente zur Beschreibung und Messung der Arterienelastizität. Arch. Kreislauff. 54: 68-139 (1967)
2. Wetterer E, Kenner T: Grundlagen der Dynamik des arteriellen Pulses. Springer-Verlag, Berlin-Heidelberg-New York (1968)

3. Kenner T, Busse R, Hinghofer-Szalkay H (eds): Cardiovascular System Dynamics, Models and Measurements. Plenum Press, New York - London 1982

4. Kenner T: Small arteries and the interaction with the cardiovascular system. In: Rodkiewicz CM (ed) "Arteries and the Arterial Blood Flow", Springer Verlag, Berlin - Heidelberg (1983)

5. Kenner T: Dynamik arterieller Pulse. In: F Unger (eds) "Herzerkrankungen und Interventionsmöglichkeiten", pp. 105 - 124, Springer-Verlag Berlin Heidelberg 1998

6. Kenner T: Physiology of Circulation. In: Dalla Volta S et al. (eds) "Cardiology", pp.15 – 25 McGraw-Hill Clinical Medicine Series 1999

7. Halberg F, Kenner T, Fiser B, Siegelova (eds): Chronobiology and non-invasive methods in cardiology. Faculty of Medicine, Masaryk University Brno (1999)

8. Kenner T: Introduction to the physiology of the circulation of blood. pp 1 – 25, In: Verdonck P and Perktold K (eds): Intra- and extracorporeal fluid dynamics. WIT-Press, Southampton, Boston, 2000

9. Kenner T: Medizin und Tiere. In: Goltschnigg DB, Müller-Kampel (ed): „Die Katze des Propheten", pp. 107 – 115, Passagen Verlag, Wien, 2002

10. Proceedings of the 1st Int.Fair of med.Technology and Pharmacy. Brno: Eds T.Kenner, J.P.Martineaud, P.Mayer, B.Semrád, J.Siegelová, B. Fišer. 1993.

11. Halberg F, Kenner T, Fiser B, Siegelova J(eds): Faculty of Medicine, Masaryk University, Brno (1996).

12. Halberg F, Kenner T, Fiser B, Siegelova J(eds): Chronobiology and non-invasive methods in cardiology. Brno : IDV PZ, MU, 1999. ISBN 80-7013-279-5.Faculty of Medicine, Masaryk University, Brno (1999).

13. Halberg F, Kenner T, Fiser B (eds): The importance of chronobiology in diagnosis and therapy of internal diseases. Faculty of Medicine, Masaryk University, Brno (2002)

14. Halberg F, Kenner T, Siegelova J (eds): The importance of chronobiology in diagnosis and therapy of internal diseases. Faculty of Medicine, Masaryk University, Brno (2003)

15. Cornelissen G, Kenner T, Fiser B, Siegelova J (eds): Chronobiology in medicine. Faculty of Medicine, Masaryk University, Brno (2004)

16. Halberg F, Kenner T, Fiser B, Siegelova J (eds): Nonivasive methods in cardiology 2006. Faculty of Medicine, Masaryk University, Brno (2006)

17. Halberg F, Kenner T, Fiser B, Siegelova J(eds): Nonivasive methods in cardiology 2007. Faculty of Medicine, Masaryk University, Brno (2007)

18. Halberg F, Kenner T, Fiser B, Siegelova J (eds): Nonivasive methods in cardiology 2008 Faculty of Medicine, Masaryk University, Brno (2008)

19. Halberg F, Kenner T, Fiser B, Siegelova J (eds): Nonivasive methods in cardiology 2009 Faculty of Medicine, Masaryk University, Brno (2009)

20. Halberg F, Kenner T, Fiser B, Siegelova J(eds): Nonivasive methods in cardiology 2010; Faculty of Medicine, Masaryk University, Brno (2010)

21. Halberg F, Kenner T, Siegelova J (eds): Nonivasive methods in cardiology 2011; Faculty of Medicine, Masaryk University, Brno (2011)

22. Kenner, T., Moser, M. Systems physiology and chronobiology and their relation to music (2010) Scripta Medica Facultatis Medicae Universitatis Brunensis Masarykianae, 83 (1), pp. 33-37. http://www.scopus.com/inward/record.url?eid=2-s2.0-77953844777&partnerID=40&md5=816ec4ce022dccc97a55ff36393c18d7DOCUMENT TYPE: Short SurveySOURCE: Scopus

23. Kenner, T. The evaluation of arterial pulses, role and clinical importance(2008) Scripta Medica Facultatis Medicae Universitatis Brunensis Masarykianae, 81 (3), pp. 131-140. http://www.scopus.com/inward/record.url?eid=2s2.064949125914&partnerID=40&md5=afe9ab068f5f6447d03ef788a8f56aabDOCUMENT TYPE: Article SOURCE: Scopus

24. Moser, M., Frühwirth, M., Kenner, T. The symphony of life (2008) IEEE Engineering in Medicine and Biology Magazine, 27 (1), pp. 29-37. Cited 5times.http://www.scopus.com/inward/record.url?eid=2-s2.038549135455&partnerID=40&md5=a6c90fe91cb68b5abf5d220b08a0a51cDOCUMENT TYPE: ArticleSOURCE: Scopus

25. Kenner, T. The significance of oscillations in scaling, ageing, and biological time(2007) Scripta Medica Facultatis Medicae Universitatis Brunensis Masarykianae, 80 (4), pp. 167-174. http://www.scopus.com/inward/record.url?eid=2-s2.0-62649124655&partnerID=40&md5=5742a1903e64ec654e6f5881d74fd316DOCUMENT TYPE: ArticleSOURCE: Scopus

26. Kenner, T. An observation on chronopathology of peptic ulcer revisited(2006) Scripta Medica Facultatis Medicae Universitatis Brunensis Masarykianae, 79 (3), pp. 155-162. http://www.scopus.com/inward/record.url?eid=2-s2.0-33947722719&partnerID=40&md5=1615be9e937ea0710a736a8966851543DOCUMENT TYPE: ArticleSOURCE: Scopus

27. Kenner, T. Reform and remodeling of the university as a complex living system(2004) Scripta Medica Facultatis Medicae Universitatis Brunensis Masarykianae, 77 (5-6), pp. 247-254. http://www.scopus.com/inward/record.url?eid=2-s2.0-21244452270&partnerID=40&md5=c82006554bb652687a1deb13beaa9fcaDOCUMENT TYPE: ArticleSOURCE: Scopus

28. Kenner, T., Cornélissen, G., Katinas, G., Schwartzkopff, O., Kenner, B., Halberg, F.Population cycle in sudden infant death syndrome (SIDS)?(2003) Neuroendocrinology Letters, 24 (SUPPL. 1), pp. 96-100. Cited 1 time.http://www.scopus.com/inward/record.url?eid=2-s2.0-0242577751&partnerID=40&md5=38587f8baf75e40614e6c0980892310dDOCUMENT TYPE: ArticleSOURCE: Scopus

29. Kenner, T. Structural asymmetry and the optimisation of transport function in the circulation. Review 2002) Scripta Medica Facultatis Medicae Universitatis Brunensis Masarykianae, 75 (2), pp. 81-86. Cited 3 times.http://www.scopus.com/inward/record.url?eid=2-s2.0-0036072621&partnerID=40&md5=480e84c8a6fdecf6c093c25a2bc06dacDOCUMENT TYPE: Review SOURCE: Scopus

30. Siegelová, J., Kenner, T. The 2000 symposium on non-invasive diagnostic methods in kardiology (2002) Scripta Medica Facultatis Medicae Universitatis Brunensis Masarykianae, 75 (2), pp. 69-70.http://www.scopus.com/inward/record.url?eid=2-s2.0-0036072699&partnerID=40&md5=265c2df44f98e16e44ecba184632ac75 DOCUMENT TYPE: Conference PaperSOURCE: Scopus

31. Kenner, T., Kenner, L. Risk factors, protective factors and medical decisions (2001) Scripta Medica Facultatis Medicae Universitatis Brunensis Masarykianae, 74 (1), pp. 5-10. http://www.scopus.com/inward/record.url?eid=2-s2.0-0035184775&partnerID=40&md5=1a12eefed3756d1ea71f20b4f227e58f DOCUMENT TYPE: Review SOURCE: Scopus

32. Kenner, T., Moser, M., Tanev, I., Ono, K. The Liebau-effect or on the optimal use of energy for the circulation of blood (2000) Scripta Medica Facultatis Medicae Universitatis Brunensis Masarykianae, 73 (1), pp. 9-14. Cited 13 times.http://www.scopus.com/inward/record.url?eid=2-s2.0-0033760074&partnerID=40&md5=d166e257339c48b35c3c1030d1e0c784 DOCUMENT TYPE: Article SOURCE: Scopus

33. Gallash, E., Kenner, T. Microvibrations: An interrelation between heart beat, muscle tremor and resting muscle tone (1998) Scripta Medica Facultatis Medicae Universitatis Brunensis Masarykianae, 71 (4), pp. 165-169. Cited 1 time. http://www.scopus.com/inward/record.url?eid=2-s2.0-0032438267&partnerID=40&md5=54f66524137fac3db072c9ffa88c71f7 DOCUMENT TYPE: Conference Paper SOURCE: Scopus

34. Muhry, F., Moser, M., Kenner, T. Weak health indicators. Their meaning and their time course during rehabilitation (1997) Scripta Medica Facultatis Medicae Universitatis Brunensis Masarykianae, 70 (4-5), pp. 183-185. http://www.scopus.com/inward/record.url?eid=2-s2.0-0031452470&partnerID=40&md5=2d34464d5e01a995e693b091c6ca3aaf DOCUMENT TYPE: Conference Paper SOURCE: Scopus

35. Niederl, T., Kenner, T. Optimization of cardiac function (1997) Scripta Medica Facultatis Medicae Universitatis Brunensis Masarykianae, 70 (4-5), pp. 187-189. http://www.scopus.com/inward/record.url?eid=2-s2.0-0031466922&partnerID=40&md5=dc67c59336ed0e86d01ea8f1ea1ab34a DOCUMENT TYPE: Conference Paper SOURCE: Scopus

36. RONNIGER R.: Über eine Methode der übersichtlichen Darstellung hämodynamischer Zusammenhänge. Arch. Kreislauf-Forschung 21, 127 – 160 (1954)

DECADAL CHANGE IN HEART RATE VARIABILITY

YOSHIHIKO WATANABE[1], KUNIAKI OTSUKA[1], JARMILA SIEGELOVA[2], GERMAINE CORNÉLISSEN[3]

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

Abstract

Decreased heart rate variability (HRV) has been associated with increased cardiovascular disease risk. Several studies have also shown that HRV is decreased in association with magnetic storms. The incidence and severity of magnetic storms, in turn, are usually higher at times of high solar activity, which follows an about 11-year cycle. An effect of magnetic storms on HRV, first found by us in ECG data from one of us, led to studies by the Asian (or rather International) Chronome Ecology study group on Heart Rate Variability (ACEHRV). It also led us to examine whether the counterpart of the solar activity cycle could also be detected in longitudinal records of heart rate and/or blood pressure. Herein, we examine whether this first demonstration in 1998, in a record covering but a single solar activity cycle, could be validated in the updated record from the same person now covering 26 years.

Introduction

Decreased heart rate variability (HRV) has been associated with increased mortality after acute myocardial infarction [1] and after coronary artery bypass grafting surgery [2]. A one-standard deviation (SD) drop in the SD of total normal R-R intervals was associated with a hazard ratio of 1.47 (95% CI: 1.16, 1.86) in the Framingham Heart Study [3]. Together with increased sympathetic tone, it has been related to poor prognosis in several patient populations [4] and an increased risk of sudden cardiac death in patients with myocardial infarction, congestive heart failure or hypertension [5]. A decreased nighttime HRV was reportedly a strong marker for the development of stroke in apparently healthy subjects [6]. In healthy young adults, reduced HRV indices were independently associated with increased CRP concentrations [7]. It is thus important to gain a better understanding of factors in the environment which affect HRV.

A reduced HRV on days of high magnetic activity versus quiet days was first observed by us in the longitudinal electrocardiographic (ECG) record of a clinically healthy man, both in terms of the coefficients of variation of R-R intervals and of the total spectral power [8]. In the frequency domain, the decrease in HRV was statistically significant in the very-low frequency region (periods in the range of 25 to 333 s) but not in the low-frequency (periods of about 10.5 s in the range of 6.7 to 25 s) or high-frequency (periods of about 3.6 s in the range of 2.5 to 6.7 s) region (Figure 1), suggesting an underlying physiological mechanism other than the parasympathetic system as responsible for changes in HRV in response to magnetic activity [8, 9]. These results led to studies by the Asian (or rather International) Chronome Ecology study group on Heart Rate Variability (ACEHRV), which added much supportive evidence to the finding [10-12].

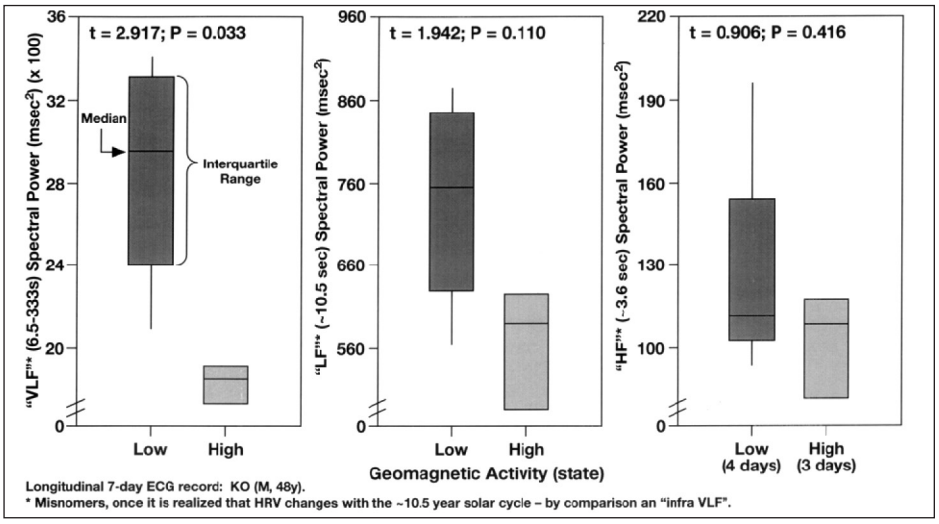


Figure 1 *During days of high magnetic activity, HRV is reduced to a different extent in different spectral regions. © Halberg Chronobiology Center.*

A decrease in HRV and an increase in heart rate in association with solar activity, as gauged by Wolf numbers, was also observed in an 11-year longitudinal record of around-the-clock data collected mostly at 30-minute intervals by a clinically healthy man [13, 14]. The subject (YW) was 35 years old when he started to measure his blood pressure (BP) and heart rate (HR) by ABPM in August 1987. The data were summarized monthly as arithmetic means and standard deviations (SD) for comparison with Wolf's numbers (WN) gauging solar activity. As seen in Figure 2, HR correlated positively, whereas HR-SD correlated negatively with WN. An about 11-year cycle was detected nonlinearly with statistical significance for both HR and HR-SD. The period estimate and its 95% confidence interval (CI) was 12.93 (CI: 9.54, 17.91) years for HR and 11.52 (CI: 8.27, 16.22) years for HR-SD, compared to 10.80 (CI: 10.26, 11.42) years for WN [13].

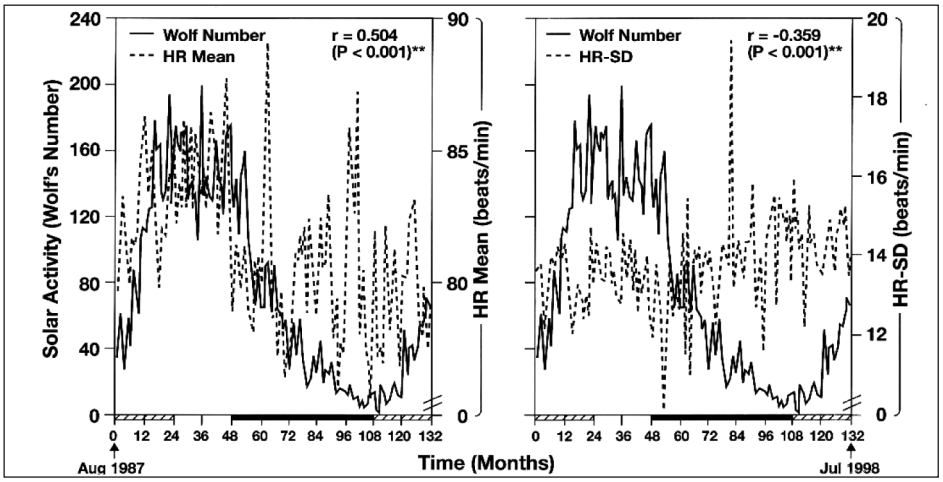


Figure 2 *Time course of HR (left) and HR-SD (right) on healthy man (YW) compared with time course of solar activity gauged by Wolf's numbers. © Halberg Chronobiology Center.*

Subject and Methods

As of August 2013, YW had collected a 26-year record of BP and HR measurements, sampled automatically around the clock, mostly at 30-minute intervals by ABPM, with occasional short interruptions.

Monthly means and SDs were computed and analyzed by the extended cosinor [15-18]. Least squares spectra were obtained for BP and HR time series, as well as for monthly WN data over the same 26-year span. Using a trial period of 10.5 years, nonlinear least squares assessed the decadal period with its CI for each data series.

Results

In view of a decreasing trend in HR as a function of age, the monthly HR means were detrended by removing a linear trend. An increase in HR and a decrease in HRV in association with solar activity are observed in the 26-year longitudinal record, as it was previously in the shorter 11-year record, Figures 3 and 4. The data are modeled by the least squares fit of cosine curves with periods of about 1.0 and 10.5 years. Nonlinearly, the periods and their CIs are estimated as 1.02 [95%CI: 1.00, 1.04] and 10.60 [95%CI: 9.21, 11.98] years for the monthly means and as 0.98 [95%CI: 0.96, 1.00] and 10.44 [95%CI: 8.85, 12.03] years for the monthly SDs of HR. In both cases, the about 11-year solar cycle length is included in the 95% CI.

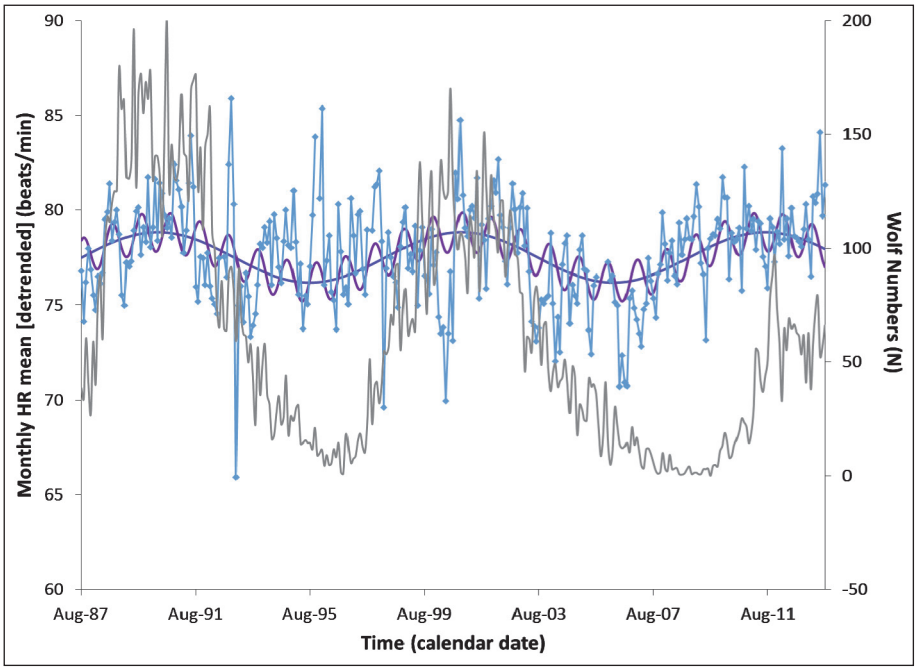


Figure 3 *Decadal cycles in HR (blue curve) and WN (grey curve) vary in phase. © Halberg Chronobiology Center.*

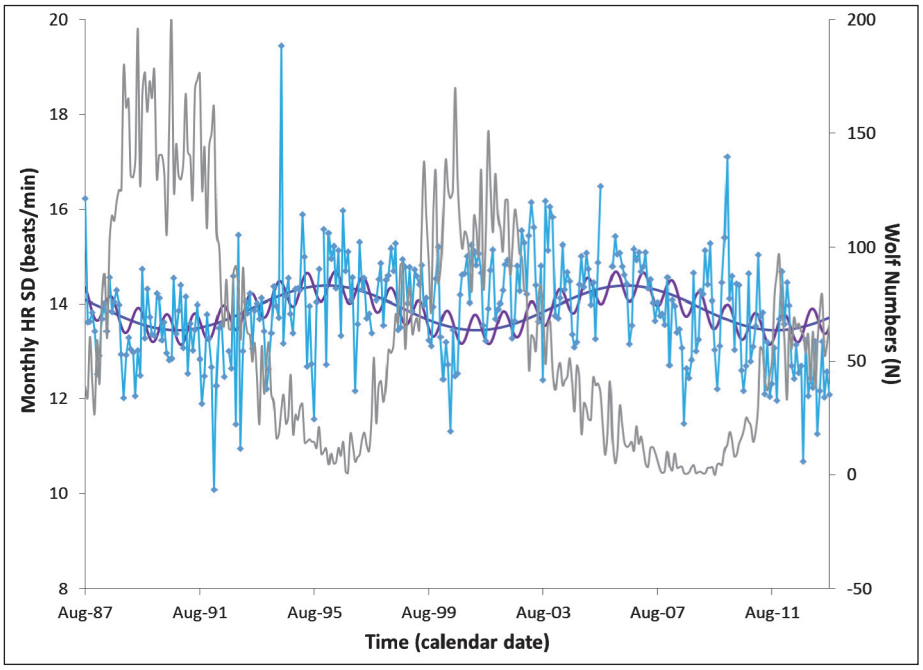


Figure 4 *Decadal cycles in HR-SD (blue curve) and WN (grey curve) vary out of phase. © Halberg Chronobiology Center*

Discussion and Conclusion

Since the early observation of a decadal cycle in HRV, gauged by the SD of HR assessed in consecutive monthly intervals in a longitudinal record of around-the-clock data collected automatically by a clinically healthy man, here corroborated in this subject's now 26-year record, decadal cycles have been detected in other longitudinal records [19-22]. As reported earlier [23], cycles with periods clustering around 10 years have been found in longitudinal records of blood pressure and heart rate from several individuals spanning several decades. Summarizing the periods of the cycles detected in these longitudinal records in a histogram reveals a sharp peak around 10 years [23]. Decadal cycles are not trivial since they also characterize the incidence patterns of major vascular conditions such as myocardial infarctions [24, 25].

About 10-year cycles described here for a clinically healthy man, and also found in longitudinal records from other individuals [23] can only be assessed after years of monitoring, and their replication takes an even longer time. The uncertainties of the periods involved, dependent on the length of the time series available for analysis, constitute a major problem in extending the lessons from circadians to long-period cycles. In order to address the challenge that this problem represents, a repository of data and maps of photic and non-photic cycle characteristics derived therefrom is being built in an "atlas of chronomes" [26, 27], as a first step toward a systematic documentation of coperiodisms linking environmental cycles to cycles in biology and human affairs more generally, in an attempt to gain a better understanding of how humans interact with their environment.

References

1. Kleiger RE, Miller JP, Bigger JT Jr, Moss AJ, Multicenter Post-Infarction Research Group. Decreased heart rate variability and its association with increased mortality after acute myocardial infarction. Am J Cardiol 1987; 59: 256-262.
2. Lakusic N, Mahovic D, Sonicki Z, Slivnjak V, Baborski F. Outcome of patients with normal and decreased heart rate variability after coronary artery bypass grafting surgery. Int J Cardiol 2013; 166(2): 516-518.

3. Tsuji H, Larson MG, Venditti FJ Jr, Manders ES, Evans JC, Feldman CL, Levy D. Impact of reduced heart rate variability on risk for cardiac events. The Framingham Heart Study. Circulation 1996; 94(11): 2850-2855.

4. Jensen-Urstad K, Reichard P, Jensen-Urstad M. Decreased heart rate variability in patients with type I diabetes mellitus is related to arterial wall stiffness. J Int Med 1999; 245(1): 57-61.

5. Wolk R. Central origin of decreased heart rate variability in patients with cardiovascular diseases. Medical Hypotheses 1996; 46(5): 479-481.

6. Binici Z, Mouridsen MR, Kober L, Sajadieh A. Decreased nighttime heart rate variability is associated with increased stroke risk. Stroke 2011; 42(11): 3196-3201.

7. Haarala A, Kahonen M, Eklund C, Jylhava J, Koskinen T, Taittonen L, Huupponen R, Lehtimaki T, Viikari J, Raitakari OT, Hurme M. Cardiovascular Risk in Young Finns Study. Eur J Clin Invest 2011; 41(9): 91-957.

8. Otsuka K, Yamanaka T, Cornélissen G, Breus T, Chibisov SM, Baevsky R, Halberg F, Siegelova J, Fiser B. Altered chronome of heart rate variability during span of high magnetic activity. Scripta medica (Brno) 2000; 73: 111-116.

9. Cornélissen G, Halberg F, Schwartzkopff O, Delmore P, Katinas G, Hunter D, Tarquini B, Tarquini R, Perfetto F, Watanabe Y, Otsuka K. Chronomes, time structures, for chronobioengineering for "a full life". Biomed Instrum Technol 1999; 33: 152-187.

10. Otsuka K, Cornélissen G, Shinagawa M, Kubo Y, Yamanaka T, Omori K, Ohkawa S-i, Zhao ZY, Delyukov A, Gorgo Y, Wang ZR, Shankaraiah K, Tarquini B, Weydahl A, Halberg F. Weekly variation of time domain measures of heart rate variability and geomagnetics in Asian Chronome Ecological Study of Heart Rate Variability (ACEHRV). Therapeutic Research 1999; 20: 388-395.

11. Otsuka K, Cornélissen G, Weydahl A, Holmeslet B, Hansen TL, Shinagawa M, Kubo Y, Nishimura Y, Omori K, Yano S, Halberg F. Geomagnetic disturbance associated with decrease in heart rate variability in a subarctic area. Biomed & Pharmacother 2001; 55 (Suppl 1): 51s-56s.

12. Oinuma S, Kubo Y, Otsuka K, Yamanaka T, Murakami S, Matsuoka O, Ohkawa S, Cornélissen G, Weydahl A, Holmeslet B, Hall C, Halberg F, on behalf of the "ICEHRV" Working Group. Graded response of heart rate variability, associated with an alteration of geomagnetic activity in a subarctic area. Biomed & Pharmacother 2002; 56 (Suppl. 2): 284s-288s.

13. Watanabe Y, Cornélissen G, Sothern RB, Nikityuk B, Bingham C, Grafe A, Halberg F. Numerical counterparts to sunspot cycles in human blood pressure and heart rate variability. In: Proc. 3rd International Symposium of Chronobiology and Chronomedicine, Kunming, China, October 7-12, 1998. Chengdu, China: Chinese Society for Chronobiology and Chronomedicine; 1998. p. 145.

14. Cornélissen G, Halberg F, Schwartzkopff O, Delmore P, Katinas G, Hunter D, Tarquini B, Tarquini R, Perfetto F, Watanabe Y, Otsuka K. Chronomes, time structures, for chronobioengineering for "a full life". Biomed Instrum Technol 1999; 33: 152-187.

15. Halberg F. Chronobiology: methodological problems. Acta med rom 1980; 18: 399-440.

16. Cornélissen G, Halberg F. Chronomedicine. In: Armitage P, Colton T. (Eds.) Encyclopedia of Biostatistics, 2nd ed. Chichester, UK: John Wiley & Sons Ltd 2005; 796-812.

17. Refinetti R, Cornélissen G, Halberg F. Procedures for numerical analysis of circadian rhythms. Biological Rhythm Research 2007; 38 (4): 275-325.

18. Cornélissen G. Cosinor-based rhythmometry. Theoretical Biology and Medical Modelling 2014; 11: 16. doi:10.1186/1742-4682-11-16. 24 pp.

19. Halberg F, Powell D, Otsuka K, Watanabe Y, Beaty LA, Rosch P, Czaplicki J, Hillman D, Schwartzkopff O, Cornélissen G. Diagnosing vascular variability anomalies, not only MESOR-hypertension. Am J Physiol Heart Circ Physiol 2013; 305: H279-H294. doi: 10.1152/ajpheart.00212.2013.

20. Haus E, Halberg F, Sackett-Lundeen L, Cornélissen G. Differing paradecadal cycles, semidecadal/decadal amplitude ratios and vascular variability anomalies in the physiology of a physician-scientist. World Heart J 2012; 4 (2/3): 141-163.

21. Watanabe Y, Cornélissen G, Hillman D, Otsuka K, Halberg F. Decadal and multidecadal periods in human blood pressure and pulse. In: Proceedings, Natural Cataclysms and Global Problems of the Modern Civilization, Istanbul, 19-21 September 2011. London: SWB International Publishing House 2012; 325-328.

22. Syutkina EV, Cornélissen G, Mitish MD, Krylova OS, Narogan MV, Masalov AV, Halberg F. Decadal solar activity cycles modulate neonatal health. In: Grigoriev AI, Zeleny LM. (Eds.) Space Weather Effects in Humans: In Space and on Earth, Space Research Institute, Moscow, Russia, June 4-8, 2012. Moscow: IKI RAN 2013; 782-788.

23. Halberg F, Cornélissen G, Schwartzkopff O, Khasigawala P, Hillman D, Sothern RB, Katinas G, Hong S, Siegelova J. Decadal and multidecadal cycles in the cardiovascular system relating to diagnosis and treatment? In: Kenner T, Cornélissen G, Siegelova J, Dobsak P. (Eds.) Noninvasive Methods in Cardiology 2013. Masaryk University, Brno, Czech Republic 2013; 69-78.

24. Cornélissen G, Halberg F, Breus T, Syutkina EV, Baevsky R, Weydahl A, Watanabe Y, Otsuka K, Siegelova J, Fiser B, Bakken EE. Non-photic solar associations of heart rate variability and myocardial infarction. J Atmos Solar-Terr Phys 2002; 64: 707-720.

25. Cornélissen G, Halberg F, Breus T, Ivanova PK, Ozheredov VF, Kleimenova NG, Kozireva OV, Agarwal RK. Congruence of mortality from myocardial infarction in Bulgaria and Pc1 pulsations. Proc. 9th International Congress „Health and Education Millennium“, 27-30 November 2008, People‘s Friendship University of Russia, Moscow, Russia. Moscow: People‘s Friendship University of Russia 2008; 609-610.

26. Cornélissen G, Beaty LA, Siegelova J, Gierke CL, Otsuka K, Watanabe Y, Syutkina EV, Masalov A, Gumarova L, Halberg F. An atlas of chronomes to map broad time structures. In: Kenner T, Cornélissen G, Siegelova J, Dobsak P. (Eds.) Noninvasive Methods in Cardiology 2013, Masaryk University, Brno, Czech Republic 2013; 102-116.

27. Cornélissen G, Beaty LA, Gierke CL, Gumarova L, Otsuka K, Watanabe Y, Wang ZR, Siegelova J. Atlas of chronomes: a work in progress. This volume.

Correspondence:
Germaine Cornélissen
Halberg Chronobiology Center
University of Minnesota, Mayo Mail Code 8609
420 Delaware St. S.E. Minneapolis, MN 55455, USA
TEL +1 612 624 6976 FAX +1 612 624 9989
E-MAIL corne001@umn.edu
Website: http://www.msi.umn.edu/~halberg/

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CHRONIC KIDNEY DISEASE: A NEW TARGET OF CARDIAC REHABILITATION

MASAHIRO KOHZUKI, OSAMU ITO, YOSHIKO SAKATA, NOBUYOSHI MORI

Department of Internal Medicine and Rehabilitation Science, Tohoku University Graduate School of Medicine, Japan

Abstract

Levels of physical activity and exercise tolerance among chronic kidney disease (CKD) patients with hemodialysis are low. Increased physical activity in this population 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. In contrast, the effect of regular exercise in pre-dialysis CKD patients has not been fully elucidated. In our laboratory, we have been demonstrated that renal protective effects of regular exercise in various animal models of pre-dialysis CKD. Moreover, we have established the Japanese Association of Renal Rehabilitation in 2011 to evaluate and promote renal rehabilitation (RR). RR is a feasible, effective and safe secondary prevention strategy following CKD, and offers a promising model for new field of rehabilitation. Therefore, RR does not simply aim to "Adding Life to Years" but "Adding Life to Years and Years to Life", which is a new rehabilitation concept. Future randomized controlled trials 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.

Introduction

Chronic kidney disease (CKD) is a worldwide public health problem. In patients with CKD, exercise endurance, measured as maximal oxygen uptake (VO_2 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. Together, these factors result in a progressive downward spiral of deconditioning. The importance of renal rehabilitation is addressed in this review.

Physical inactivity in CKD patients.

Physical inactivity is well recognized 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 hemodialysis 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].

The effect of regular exercise in dialysis CKD patients.

Results from an international study of hemodialysis 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. In DOPPS study, overall, 47.4% of participants were categorized as regular exercisers. The odds of regular exercise was 38% higher for patients from facilities offering exercise programs (P = 0.03) [3].

In DOPPS study, regular exercisers had higher health-related quality of life, physical functioning and sleep quality scores; reported fewer limitations in physical activities; and were less bothered by bodily pain or lack of appetite. Regular exercise was also correlated with more positive patient affect and fewer depressive symptoms. In models extensively adjusted for demographics, comorbidities and socio-economic indicators, mortality risk was lower among regular exercisers (hazard ratio = 0.73 [0.69–0.78]; P < 0.0001) and at facilities with more regular exercisers (0.92 [0.89–0.94]; P < 0.0001 per 10% more regular exercisers) (Figure 1) [3].

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 [4]. 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 [4]. 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 [4].

Moreover, a growing evidence base suggests that exercise training in patients with hemodialysis improves in VO_2max, 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 [5,6].

Barriers to exercise participation among dialysis patients

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" (Table 1) [7].

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, intra-dialysis programs have been found to achieve higher adherence rates compared to home exercise programs or supervised programs on non-dialysis 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 generalizable interventions can be developed.

The effect of regular exercise in pre-dialysis CKD patients.

There is increasing evidence of the benefit of regular physical exercise in a number of long-term 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 pre-dialysis CKD patients.

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 [10,11]. Therefore, exercise therapy could be an effective clinical strategy to improve renal function.

The effect of exercise training in animal pre-dialysis CKD models.

Also, there are few reports about the effect of exercise on renal function in animal models of chronic renal failure. We have been published several papers in this field recently.

First, we assessed the renal effects of moderate chronic treadmill exercise in a remnant kidney model of spontaneously hypertensive rats (SHR) with 5/6 nephrectomy and also assessed the effects of exercise and antihypertensive therapy on renal function [12]. The rats were divided into four groups: (i) no exercise (Non-EX); (ii) moderate exercise with treadmill running (20 m/min, 0 grade incline for 60 min) (EX); (iii) EX with an angiotensin converting enzyme (ACE) inhibitor, enalapril (2 mg/kg per day, i.p.); and (iv) EX with an angiotensin receptor antagonist, losartan (5 mg/kg per day, i.p.), for 4 weeks. Chronic EX significantly attenuated the increase in proteinuria and significantly protected against increases in the index of glomerular sclerosis (IGS). Both enalapril and losartan with EX significantly decreased blood pressure, and further decreased the IGS. In the stepwise multiple regression analysis, only antihypertensive drug remained in the model as a significant predictor of IGS. In contrast, exercise, antihypertensive drug and mean systolic blood pressure remained in the model as a significant predictors of mean proteinuria. These results suggest that exercise does not worsen renal function and has renal-protective effects in this model of rats. Moreover, the antihypertensive therapy has additional renal-protective effects in this model of rats.

Second, we assessed the renal and peripheral effects of moderate to intense chronic exercise as well as the effects of the combination of chronic exercise and enalapril (ENA) in 5/6-nephrectomized Wistar-Kyoto rats [13]. The rats were divided into six groups according to the following treatment: 1) no exercise (C); 2) ENA (2 mg/kg/day, subcutaneously); 3) moderate exercise with treadmill running (20 m/min for 60 min/day, 5 days/week) (EXm); 4) intense exercise with treadmill running (28 m/min for 60 min/day, 5 days/week) (EXi); 5) EXm+ENA; and 6) sham operation (S). The rats were then treated for 12 weeks. Both chronic exercise and ENA blocked the development of hypertension, blunted increases in proteinuria, reduced serum creatinine and blood urea nitrogen, and improved IGS and the relative interstitial volume of the renal cortex (RIV). Moreover, IGS and RIV in the EXm+ENA group were the lowest among all other nephrectomized groups. Furthermore, EXm+ENA enhanced capillarization as well as the proportion of type-I fiber in the soleus muscle. These results suggest that EX and ENA have renoprotective effects. The findings also suggest that EXm+ENA provided greater renoprotective effects than those of ENA alone, and that EXm+ENA had some additional peripheral effects without any complications in this rat model.

These results suggest that exercise training may have renal protective effects in various animal models of predialysis CKD.

What is renal rehabilitation?

Moreover, we have established the Japanese Association of Renal Rehabilitation in 2011 to evaluate and promote renal rehabilitation (RR). We published the first book titled “Renal Rehabilitation” as RR in the world (Figure 2) [14]. We define RR as, “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." [6,14]. 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.

Adding Life to Years and Years to Life

As super-aged society has come, the number of persons with multimorbidity and multiple disabilities (MMD) and their needs of rehabilitation have increased rapidly more than we had expected [15]. 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 (Figure 3) [16]. 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 [16].

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, urgent efforts should be made urgently to increase the implementation rate of the RR.

References

1. O'Hare AM, Tawney K, Bacchetti P, Johansen KL (2003) Decreased survival among sedentary patients undergoing dialysis: Results from the dialysis morbidity and mortality study wave 2. Am. J. Kidney Dis. 41: 447–454
2. Johansen KL (2007) Exercise in the End-Stage Renal Disease Population. J. Am. Soc. Nephrol. 18: 1845–1854.
3. Tentori F, Slder SJ, Thumma J (2010) Physical exercise among participants in the Dialysis Outcomes and Practice Patterns Study (DOPPS): correlates and associated outcomes. Nephrol. Dial. Transplant. 25: 3050–3062.
4. Smart N, Steele M (2011) Exercise training in haemodialysis patients: A systematic review and meta-analysis. Nephrology 16: 626–632.
5. Kohzuki M (2011) Exercise therapy for dialysis patients. Jap. J. Clin. Dial. 27: 1291-1298. (in Japanese with English abstract)
6. Kohzuki M (2013) Renal rehabilitation: present and future perspectives. Hemodialysis (ed. Suzuki H) Intech, pp. 743-751.
7. K/DOQI Workshop (2005) K/DOQI clinical practice guidelines dor cardiovascular disease in dialysis patients. Am. J. Kidney Dis. 45(Supple 3):S1-S153.
8. Delgado C, Johansen KL (2012) Barriers to exercise participation among dialysis patients. Nephrol. Dial. Transplant. 27: 1152–1157.

9. Konstantinidou E (2002) Exercise training in patients with end-stage renal disease on hemodialysis: comparison of three rehabilitation programs. J. Rehabil. Med. 34: 40-45.

10. Toyama K, Sugiyama S, Oka H. et al (2010) Exercise therapy correlates with improving renal function through modifying lipid metabolism in patients with cardiovascular disease and chronic kidney disease. J. Cardiol. 56:142-146.

11. Takaya Y, et al. Impact of cardiac rehabilitation on renal function in patients with and without chronic kidney disease after acute myocardial infarction. Circ J 78: 377-384, 2014.

12. Kohzuki M, Kamimoto M, Wu XM. et al (2001) Renal protective effects of chronic exercise and antihypertensive therapy in hypertensive rats with chronic renal failure. J. Hypertens. 19:1877-82.

13. Kanazawa M, Kawamura T, Li L et al (2006) Combination of exercise and enalapril enhances renoprotective and peripheral effects in rats with renal ablation. Am. J. Hypertens. 19:80-6.

14. Kohzuki M (2012) Definition of Renal Rehabilitation. In "Renal Rehabilitation" Edited by Kohzuki M Ishiyaku Publishers, Inc., Tokyo.

15. Kohzuki M. Paradigm shift in rehabilitation medicine in the era of multimorbidity and multiple disabilities (MMD). Physical Medicine and Rehabilitation International 1(2): id1006, 2014.

16. Kohzuki M, Sakata Y, Kaweamura T et al (2012) A Paradigm Shift in Rehabilitation Medicine: From "Adding Life to Years" to "Adding Life to Years and Years to Life". Asian J .Human Services 2: 1-8.

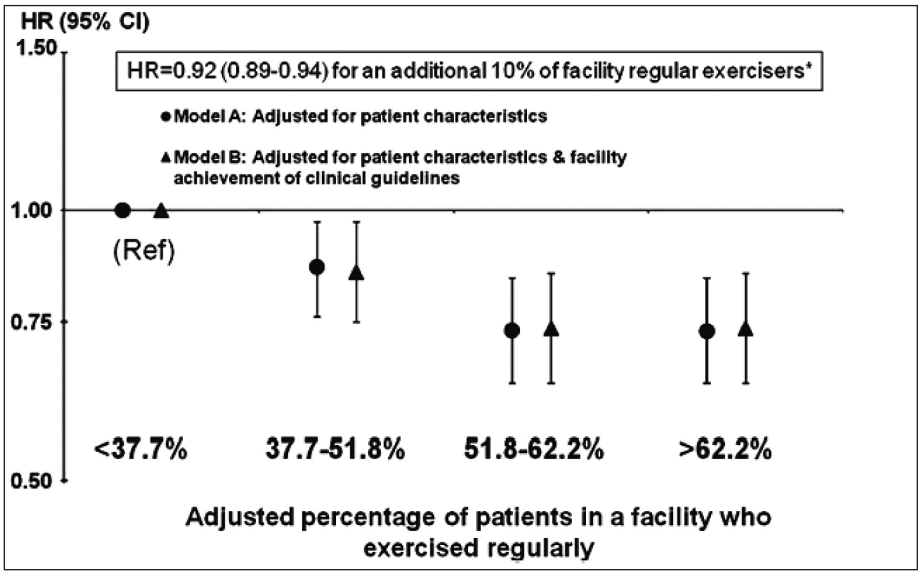

Figure 1 *Association between Facility Percentage of Regular Exercisers and Patient Mortality (Ref. [3])*

Table 1. K/DOQI Clinical Practice Guidelines 2005 for Cardiovascular Disease in Dialysis Patients (Ref. [7])

14.2 All dialysis patients should be counseled and regularly encouraged by nephrology and dialysis staff to increase their level of physical activity.

14.2.a Unique challenges to exercise in dialysis patients need to be identified in order to refer patients appropriately (e.g., to physical therapy or cardiac rehabilitation) and to enable the patients to follow regimens successfully. Such challenges include orthopedic/musculoskeletal limitations, cardiovascular concerns, and motivational issues.

14.3 Measurement of physical functioning:

14.3.a Evaluation of physical functioning and re-evaluation of the physical activity program should be done at least every 6 months.

14.3.b Physical functioning can be measured using physical performance testing or questionnaires (e.g., SF-36).

14.3.c Potential barriers to participation in physical activity should be assessed in every patient.

14.4 Physical activity recommendations:

14.4.a Many dialysis patients are severely deconditioned and therefore may need a referral for physical therapy to increase strength and endurance to the point where they are able to adopt the recommended levels of physical activity.

14.4.a.i Patients who qualify for cardiac rehabilitation should be referred to a specialist.

14.4.a.ii The goal for activity should be for cardiovascular exercise at a moderate intensity for 30 minutes most, if not all, days per week. Patients who are not currently physically active should start at very low levels and durations, and gradually progress to this recommended level.

14.4.b Follow-up:

14.4.b.i Physical functioning assessment and encouragement for participation in physical activity should be part of the routine patient care plan. Regular review should include assessment of changes in activity and physical functioning.

Figure 2 *The First Book on "Renal Rehabilitation" (Edited by Kohzuki M, Ishiyaku Publishers, Inc., Tokyo) (Ref. [14])*

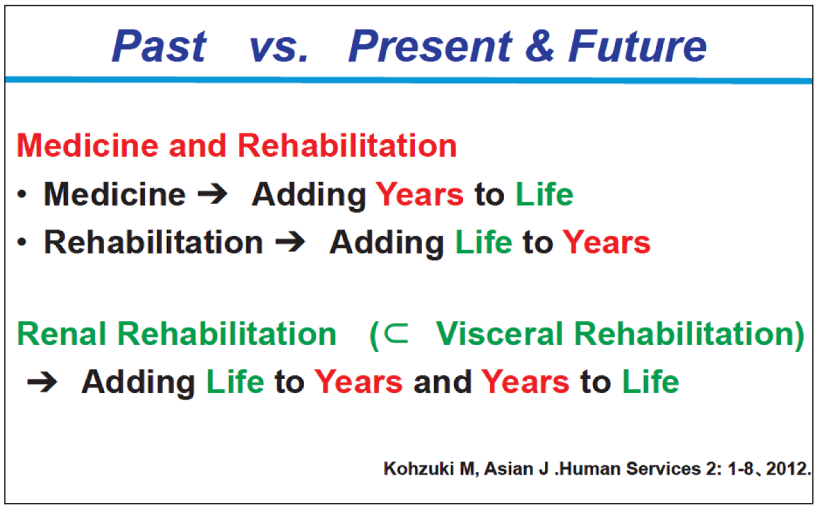

Figure 3 *Paradigm shift in rehabilitation medicine (Ref. [16])*

Address for Correspondence:
Masahiro Kohzuki M.D., Ph. D.,
Associate Dean,
Professor and Chairman
Department of Internal Medicine and Rehabilitation Science,
Tohoku University Graduate School of Medicine, 1-1 Seiryo-cho, Aoba-ku, Sendai 980-8574 Japan.
Tel +81-22-717-7353, FAX +81-22-717-7355
e-mail: kohzuki@med.tohoku.ac.jp

CIRCADIAN AND CIRCASEPTAN RHYTHM IN BLOOD PRESSURE AND HEART RATE IN NEWBORNS

JARMILA SIEGELOVA, GERMAINE CORNÉLISSEN*, JIRI DUSEK, PETR DOBSAK, OTHILD SCHWARZKOPFF*

*Dept. of Physiotherapy and Rehabilitation, Dept. of Sports Medicine and Rehabilitation, St. Anna Teaching Hospital, Medical Faculty, Masaryk University, Brno; *Halberg Chronobiology Center, University of Minnesota, USA*

Introduction

The recent research in genetic brought the evidence that mutations in five genes have been implicated in the pathogenesis of human high blood pressure (1). The influence of genes is in an interaction with environmental and demographic factors (2, 3, 4, 5, 6,7,8). According to studies of familial aggregation of blood pressure in newborns and their mothers (9) and of infant twins (10), among others (11) genetic factors that determine within-family similarities of blood pressure may be detected early in life. The role of nature (genetics) as well as culture (environment) is reflected in blood pressure and was described in twin studies (3,10).

Kellnerová (12) first documented by cosinor analysis a circadian rhythm in neonatal blood pressure. The expression of the human newborn‘s circadian rhythm is more readily demonstrated, despite its relatively small amplitude, when blood pressure (and heart rate) can be monitored (and analysed) automatically (13). A genetic and/or congenital influence on the circadian pattern of blood pressure is suggested by the fact that differences in circadian amplitude are found between babies with a positive vs. negative family history of high blood pressure and/or related vascular complications (13,14).

As compared to circadians, multiseptans (components with a period of 7 days and/or multiples and submultiples thereof) are particularly prominent in neonates (15). The multiseptan-to-circadian prominence of blood pressure and heart rate of neonates followed up longitudinally in several studies in Minnesota and elsewhere was reported by Halberg et al. (16).

In this study we tested the hypothesis that neonatal blood pressure has an about 7-day circaseptan rhythm as prominent or even larger in amplitude than 24-h component, described and quantified as the major component in human adults (17).

Material and Methods

Blood pressure and heart rate were monitored automatically for 14 to 45 days, mostly at 30 minutes intervals from a total of 86 babies.

All babies were cared for in the intensive care unit of the Teaching Hospital in Brno, Czech republic. Eighty six premature newborn babies were examined in the intensive care unit in continuous light of 201.3 ± 35.6 (mean ± SD) Lux at the eye level. Feeding was every 3 hours through an oesophageal tube or consisted of continuous parenteral infusion 6 weeks. The oscillometric method was used for blood pressure monitoring every hour. Eighty six premature newborns (850 to 3250 g of body weight) were seriously ill, 27 of them died later, 12 of them were diagnosed as having intra-cranial hemorrhage.

The values of systolic blood pressure (SBP), diastolic blood pressure (DBP) and heart rate (HR) were analysed using the computation of autocorrelation functions and power spectral density and Halberg cosinor method.

The periodicity was revealed by means of the calculation of autocorrelation function and of power-spectral densities function (18,19). The autocorrelation function of random data describes the general dependence of the value of the data at one time on the values of another time. An autocorrelation measurement provides a tool for detecting deterministic structure in data which might be masked in a random process.

The delay which corresponds to the minimal value of the autocorrelation function indicates a half of the period of the most prominent rhythm.

The power spectral density function, also called auto-spectral density function, of random data describes the general frequency composition of the data in terms of the spectral density of its mean square value. We computed power spectral density function from the autocorrelation functions using the Hanning spectral window (18).

The principal application of a power spectral density function measurement of data is to establish the frequency composition of the data.

All cardiovascular data were also analysed using the Halberg cosinor analysis (17). Each data series was analysed by single cosinor testing, involving the least-squares fit of curves, with trial periods of 24, 84 and 168 hours. In each case, the following parameters were estimated: the MESOR, a rhythm-adjusted mean; the double amplitude, a measure of the extent of predictable change within a cycle; and the acrophase, a measure of the timing of overall high values recurring in each cycle. The acrophase is expressed in (negative) degrees, with 360o equated to the trial period length. Results of cosinor analysis from individual series were further summarized by population mean cosinor. The analysis considered two different reference times: the time of birth and midnight between Saturday and Sunday. Whereas reference to the time of birth assumes that the tested component is endogenous, reference to a fixed calendar date assumes that it may be socially imposed. While these choices of reference time do not affect rhythm detection and parameter estimation on an individualized basis, they play a critical role in a population summary, which depends on the extent of synchronization of accrophases among the different neonates.

In order to explore the relative roles of a degree of endogenicity and social synchronization of the circadian and multiseptan components, the individual estimates of the circadian, circasemiseptan and circaseptan parameters of the 86 neonates monitored for 14 to 45 days, used as imputations, were separately summarized by population-mean cosinor in relation to each of the two reference times. Individual ratios of circasemiseptan to circadian and circaseptan to circadian amplitudes, averaged across were computed in order to assess the relative prominence of multiseptans vs. the circadian component during the first extra-uterine week of life. Before averaging, these amplitude ratios were log-transformed in order to preserve the symmetry of the distribution and to assure that the distribution would remain closer to a normal one. The nonlinear least squares fit of cosine curves with anticipated periods of 168, 84 and 24 hours was also applied to obtained point-and-interval estimates of the period.

The study was approved by local ethical committee.

Results

Mean values of mean blood pressure (MAP) and heart rate (HR) obtained during the time of measurement at various birth weights are seen in Table 1.

Relation between the mean values of mean blood pressure (MAP) and heart rate (HR) and gestational age are seen in Table 2. Whereas MAP increases with body weight ($r = 0.845$; $P = 0.072$) and gestational age ($r = 0.958$; $P = 0.010$), HR decreases (BW: $r = -0.891$; $P = 0.42$; GA: r is – 0.820; $P = 0.089$). The data indicate a positive correlation between blood pressure values and birth weight or gestational age.

Fig. 1 shows the record of systolic and diastolic blood pressure of high risk baby. Original blood pressure record (systolic BP and diastolic BP) is presented in the time of the postnatal days (from the five to the 41days). Non-linearly circaseptan periods estimated in systolic blood pressure to be 195.0 hours (95% confidence interval; 187.4 - 203.9 hours), in diastolic blood pressure 190.3 hours (95% confidence interval;

181.8 - 199.4 hours). The non-linear confidence intervals for the circaseptan amplitude of both systolic and diastolic blood pressure do not overlap zero, attesting to their statistical significance.

Fig. 2 shows the data of heart rate of high risk baby. The original heart rate record is presented versus time of the postnatal days from the day one to the 21days. Results from the non-linear analysis validate an increasing linear trend and the presence of circaseptan component. The period is estimated to be 165.9 hours (95% confidence interval: 157.4 – 175.2 hours). The amplitude of 9.9 does not overlap zero (95% confidence interval: 6.0- 13.8 beats per minutes), attesting the statistical significance of the circaceptan component.

We computed the autocorrelation function and power spectral density of systolic (SBP) and diastolic blood pressure (DBP) and heart rate (HR) in each newborn. Fig. 3 and Fig. 4 show the examples of the autocorrelations functions in two different newborn babies.

An example of power spectral density of heart rate, systolic and diastolic blood pressure in one newborn baby is seen in Fig.5 in newborn baby.

From our results using the computation of the autocorrelation functions and power spectral densities of heart rate, systolic and diastolic blood pressure:

In an overall summary for all 86 newborn babies , this approach indicates the presence of slow oscillations in a frequency range of one cycle in five to ten days, which is in the circaseptan range. These were found for heart rate and for blood pressure in all newborn babies investigated ($p< 0.05$). By contrast, the circadian periodicity was found in 50% in the heart rate and in systolic and diastolic blood pressure only in 43% in in all recordied series of 86 newborn babies.

Fig. 6 compares the prominence of the about –weekly, half weekly and daily variations in a plot and amplitude of heart rate, systolic and diastolic blood pressure derived from cosinor analysis. The circaseptan to circadian amplitude ratios of all three variables component is associated with the largest amplitude. The circaseptan-to-circadian amplitude ratio of all three variables are larger than one, similar results were found in diastolic blood pressure and heart rate earlier (16, 17).

Population-mean cosinor summaries of the circaseptan component were futher prepared in relation to the date and time of birth, that is by analysing data as a function of postnatal sage, or by reference to midnight between Saturday and Sunday preceding the start of data collection, that is by analysing data as a function of calendar time.

In relation to birth, the circaseptan component was statistically significant on a group basis, showing high synchronization among all babies, with higher values occurring between the third and sixth day of age, and at intervals of about 7 days thereafter. Any social synchronization of the circaseptan component was not appearent, the acrophases not differing with statistical significance from a random distribution when 00:00 on Sunday was used as reference. These data are presented in Fig. By contrast, a circadian rhythm is demonstrable with statistical significance on a population basis when midnight is used as the reference time, suggesting some degree of synchronization with the daily routine, perhaps perceived from maternal clues in the womb.

Discussion

Prominent circaseptan variations were found by spectral analysis and by cosinor for neonatal heart rate, systolic and diastolic blood pressure. Some degree of endogenicity of the circaseptan component was suggested indirectly by the population-mean cosinor results relative to a biological- birth rather than an environmental- week-day reference. The endogenicity of the circaseptan component was first postulated on the basis of free-running; in a 15-year record, the urinary excretion of 17-ketosteroids assumed a period statistically significantly shorter than 7 days during the lat 3 years, following massive androgen treatment, whereas urine volume remained 7-day synchronized (24,25).

This study found multiseptans to be more prominent than circadians, for the case for blood pressure and heart rate. These results apply to critically ill babies monitored in the Czech Republic at interval ranging from 30 to 240 minute for span 1 to 4 weeks (26). They are in keeping with results obtained in premature and thick babies (18, 27). Circaseptans have also been documented in clinically healthy babies born at term (16, 18, 29). Analysis of the non-linearly assessed circaseptan period by inra-classcorrelations of Minnesotan twins suggest a congenital if not a genetic influence in the case of heart rate, diastolic blood pressure and body weight (18). For these variables, the ciraseptan period was more similar between the twins in a pair than among twin pairs. In terestingly, circaseptans are also very prominent in unicells, as shown, for instance, for the electrical potencial of Acetabularia recorded in continuous light (30). This gigant alga was presumably present on the surface of the earth 500 million years ago (30).

Halberg et al. (32) found a counterpart for the biological week in the physical environment, namely in geomagnetics. In 1972, Fraser- Smith (33) reported that fluctuations in geomagnetic activity were characterized by a precise weekly pattern, as a weekend fenomenon. About a decade later, however, in analysing the planetary geomagnetic index Kp for the span from 1932 to 1990, a spectral peak was found to correspond to a period of about 6.74 days (32), rather than a precisely 7 days. The near week component was also observed in rainfall (34).

Pioneering work by Theodeor Hellbrugge described the circadian and ultradian rhythms in premature babies and newborns. The development of circadian rhythm was found to depend on the maturity of the child at the time of birth, periodicity developing later in premature than in full-term babies (35- 37). The results of the present investigations add an ultradian aspect to the chronome of neonatal blood pressure and heart rate.

We can summarize our findings that a circadian component is in our newborn babies statistically significant on a population basis when the reference time is related to 00:00 on Sunday but not when it is related to the exact hour of birth. The circadian component of borderline statistical significance was found in cardiovascular parameters. By contrast, the circaseptan and circasemiseptan components of blood pressure are statistically significant in relation to time of birth, but not in relation to calendar date. Our results provides the relative prominence of the circaseptan and circasemiseptan components by reference to the circadian component. In each case, the multiseptans are more prominent than the circadians.

The spectra are usually presented in two forms, in absolute units as for example mmHg.mmHg or in relative units. When the spectra are expressed in absolute units, the magnitude of peaks is increased at increased variation usually expressed in the form of standard deviation. In individual subjects the standard deviation is correlated with the mean value. For example if the blood pressure is decreased during night the standard deviation of blood pressure and also spectral peaks magnitude are decreased. We prefer the presentation in relative units. The spectral peaks magnitudeare interrelated in this case. An increase of one peak is connected with a decrease of other because the sum of all spectral values is equal to one. The relative spectra can better express the division of variability of signals into frequency range.

The Halberg cosinor analysis and spectral analysis are two alternative approaches. The advantage of calculations of power spectral density functions is to demonstrate various distinct peaks of varies frequency not only in various subjects, but also in various variables in the same subject (20).

In this study we found the larger prominence of multiseptans as compared to circadians for the case of blood pressure and heart rate and these results were documented recently for critically ill babies in Czech republic, monitored at intervals ranging from 30 to 240 minutes for spans of 1 to 4 weeks (21).

An endogenous aspect of the biological day had been documented by the demonstration of desynchronisation in adults in isolation of society (20). A heritability of the circaseptan period in diastolic blood pressure and heart rate and body weight was found in Minnesotan newborn twins (22). Cornélissen et al.(23) documented the heritability of the circaseptan component by intra-class correlation coefficient, comparing the intra- vs. the inter – twin variability in the non-linearly assessed circaseptan period, for data on diastolic blood pressure, heart rate and body weight, recorded in neonatal intensive care unit. For these

three variables, the circaseptan period was more similar between the twins in a pair than among twin pairs. The evidence on newborn twins removes any doubt for the case of humans.

The case of Acetabularia´s "week rhythm" showed that circaseptan in continuous light characterize the electrical potential of a unicellular giant alga that was presumably present on the surface of the earth 500 million years ago (24,25).

Halberg et al.(26) found a counterparts for the biological week rhythm in physical environment, namely in geomagnetics .

In 1979, Fraser- Smith (27) reported that fluctuations in geomagnetic activity are characterized by a precise weekly pattern, as a weekend phenomenon. About a decade later, in analysing the planetary geomagnetic index Kp for the span from 1932-1990, however, found a spectral peak at a period of 6.74 days (26), but no at precisely 7 days. The near week component was also observed in rainfall (28).

In summary, this study shows that a circadian rhythm in blood pressure and heart rate is expressed durng the first week of extra-uterine life, with an acrophase peaking the early morning hours. The circaseptan component in our results is more prominent than the circadian variation, with an amplitude ratio statistically significantly larger than unity. The circaseptan component in the circulation is partly endogenous, as suggested by a synchronization among babies in relations to the time of birth, which carries 7-day information rather than in relation to the calendar date, to which societal factors are related.

Conclusion

Slow oscillations with a different period between 5 to 10 days were found either in HR or in BP in all newborns. An identical period in HR, SBP and DBP was found in 31%. The peak of 24-hour periodicity in HR was found in 50% of newborns, in SBP and DBP only in 43%. The peak of 24-hour periodicity was always smaller than those found with circaseptan rhythm. Mean power spectra revealed a significant peak ($p<0.05$, Student t-test) at 0.16 cycles per day in HR, SBP and DBP. The results of this study brought the evidence: 1. the expression of a circadian rhythm during the first week of extra-uterine life, with an acrophase peaking in the early morning hours; 2. the larger prominences of the circaseptan vs. the circadian component of blood pressure and heart rate, with amplitude ratios larger than 1.5 and 95% confidence intervals not overlapping; 3. the endogenicity of the circaseptan component, suggested by a synchronization among babies in relation to the time of birth, which carries no 7-day information, rather than relation to a calendar date, to which societal factors are related.

Summary

Objective: The aim of the study was to prove the hypothesis that blood pressure and heart rate in newborns have the circaseptan and circadian variability.

Material and Methods: Long-lasting blood pressure and heart rate monitoring was applied using oscillometric sphygmomanomoter automatically every 30 minutes in 86 premature babies. All babies were cared for in intensive care unit in the Teaching Hospital Brno, Czech Republic. The premature newborn babies were monitored in continuous light of 201.3 ±35.6 (mean ±SD) Lux and fed every 3 hours through an oesophageal tube or by continuous parenteral infusion for 6 weeks. 86 premature babies (850 to 3250 g.b.w) were seriously ill, 27 of them died later, 12 of them were diagnosed as having intracranial hemorrhage. The values of systolic blood pressure (SBP), diastolic blood pressure (DBP) and heart rate (HR) were analyzed using the computations of spectral analysis and Halberg cosinor analysis.

Results: On the basis of our results we acquired using the computation of the autocorrelation functions and power spectral densities of blood pressure and heart rate, calculated in each newborn baby, we have found slow significant oscillations ($p<0.05$) with a different period between 5 to 10 days (an about-weekly component, circaseptan) either in HR, SBP or DBP in all newborn babies (100 percent). Cosinor analysis

showed that circaseptan rhythms are more prominent in blood pressure and heart rate than the circadian rhythms.

Conclusion: From our results we can conclude that the circaseptan rhythm in blood pressure and heart rate is inborn and is probably determined by the nature. Our results were also confirmed in healthy newborn babies in Minnesota, USA and Spanish La Corona.

Table 1 *Neonates with various birth weights: Number of neonates (N), mean values (± S.D.) of arterial pressure (MAP) and heart rate (HR).*

body weight	N	MAP	HR
g	number	mmHg	cpm
> 1000	15	33.8 ± 6.5	146.6 ± 8.7
1001 - 1500	17	44.1 ± 6.5	148.3 ± 7.9
1501 - 2000	22	50.1 ± 8.0	137.2 ± 10.1
2001 - 3000	15	54.1 ± 6.3	139.8 ± 8.1
3001 <	17	51.0 ± 8.2	129.3 ± 19.5

Table 2 *Gestation age of neonates: Number of neonates (N), mean values (± S.D.) of arterial pressure (MAP) and heart rate (HR).*

pregnancy	N	MAP	HR
weeks	number	mmHg	Cpm
< 29	17	40.2 ± 8.2	153.5 ± 9.6
29 - 31	15	46.1 ± 6.4	143.2 ± 11.8
32 - 34	23	47.5 ± 7.6	144.2 ± 16.2
35 - 37	17	53.4 ± 8.2	143.4 ± 17.4
37 <	14	52.3 ± 8.3	121.5 ± 16.2

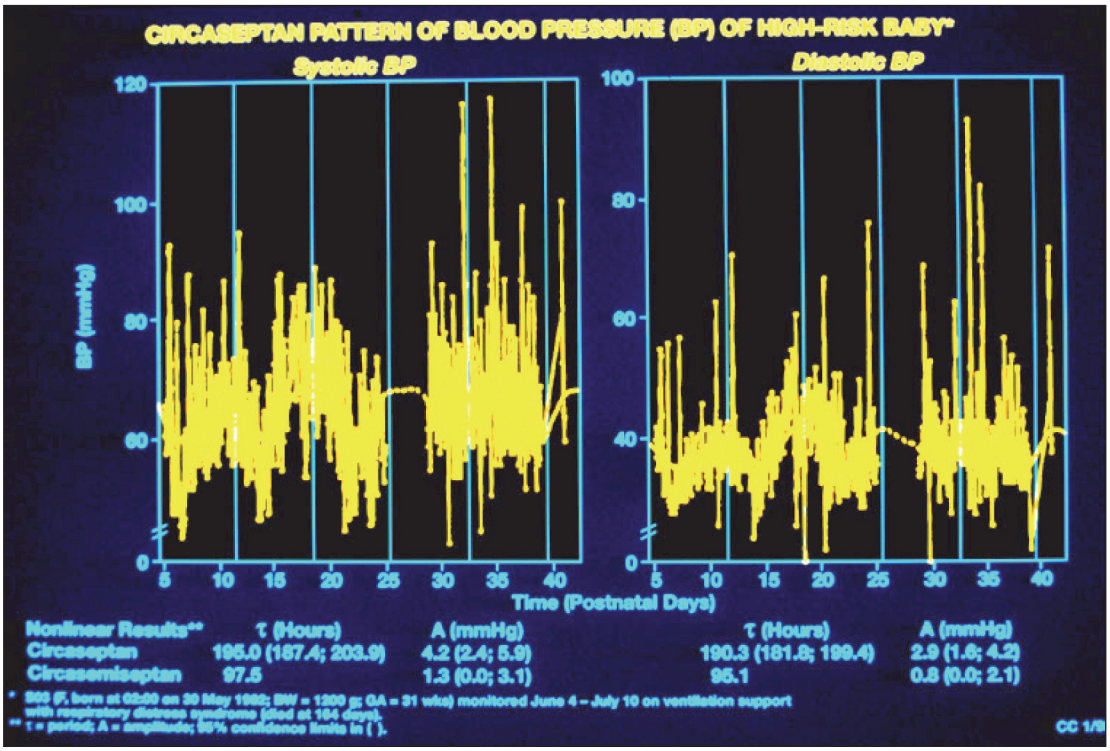

Figure 1 *Blood pressure data of a high risk baby. Original record presented as a function of time from postnatal day 5 to 41. Note prominence of about-weekly variation, validated by nonlinear least squares analysis.*

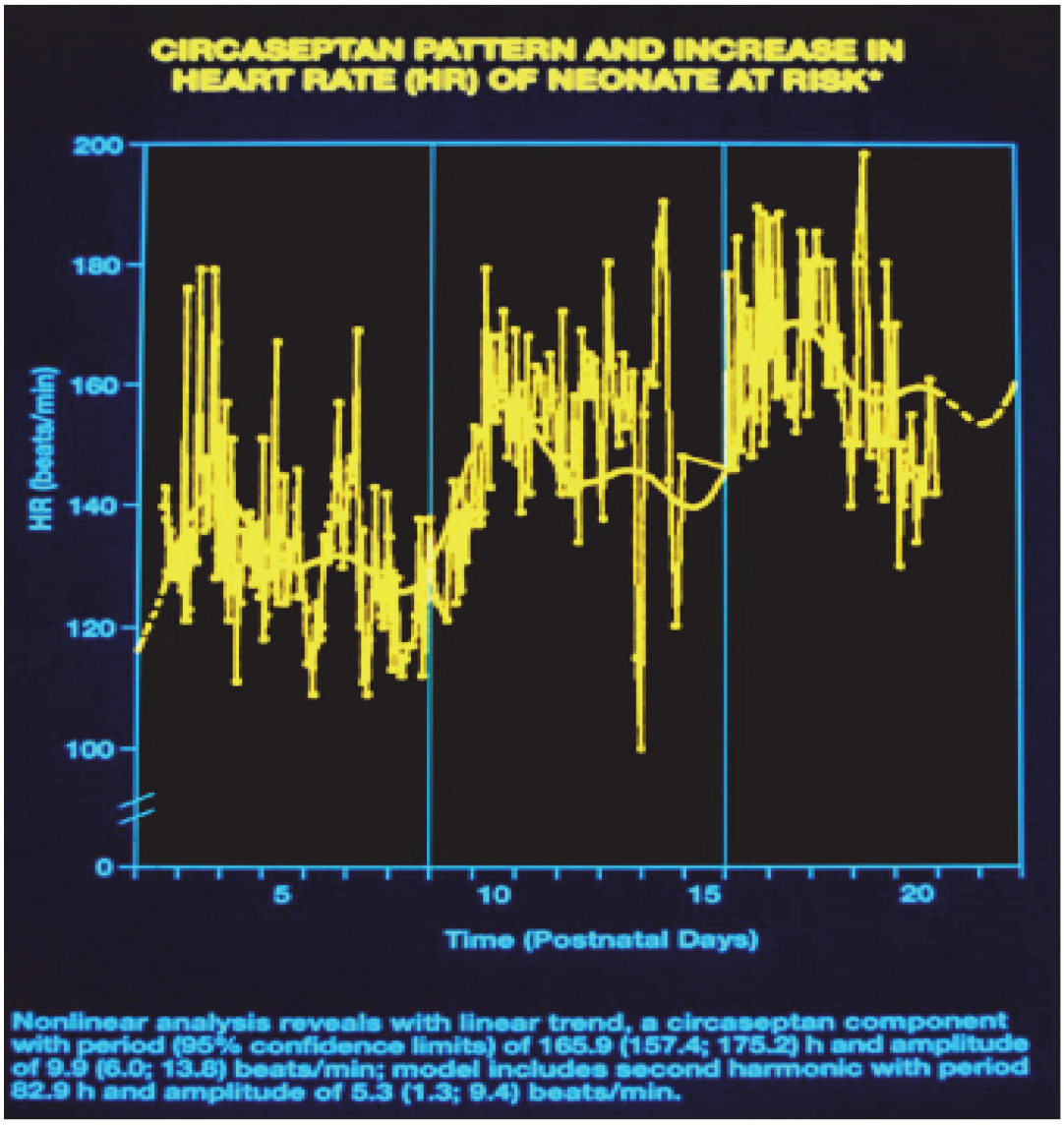

Figure 2 *Heart rate data of a high risk baby. Original record presented as a function of time from postnatal day 1 to 21. Note statistically significant circaseptan and semi-ciraseptan components superposed on increasing trend.*

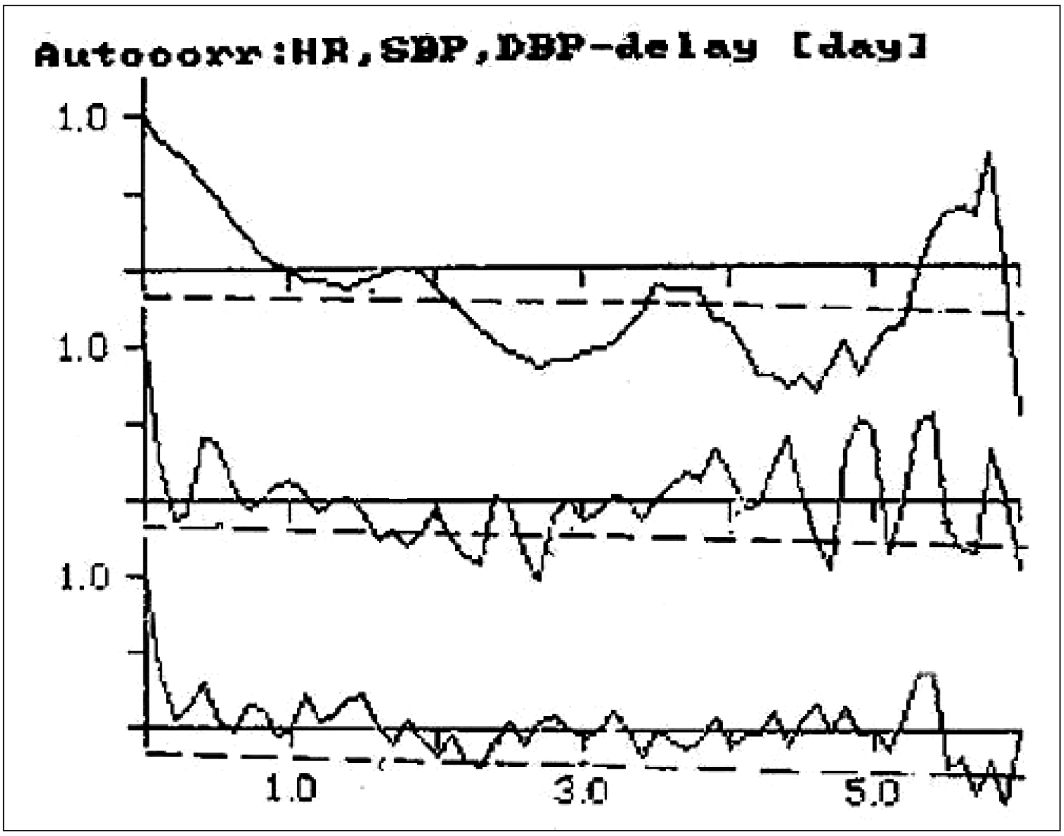

Figure 3 *Autocorrelation functions of heart rate, systolic and diastolic blood pressure of a newborn risk baby.*

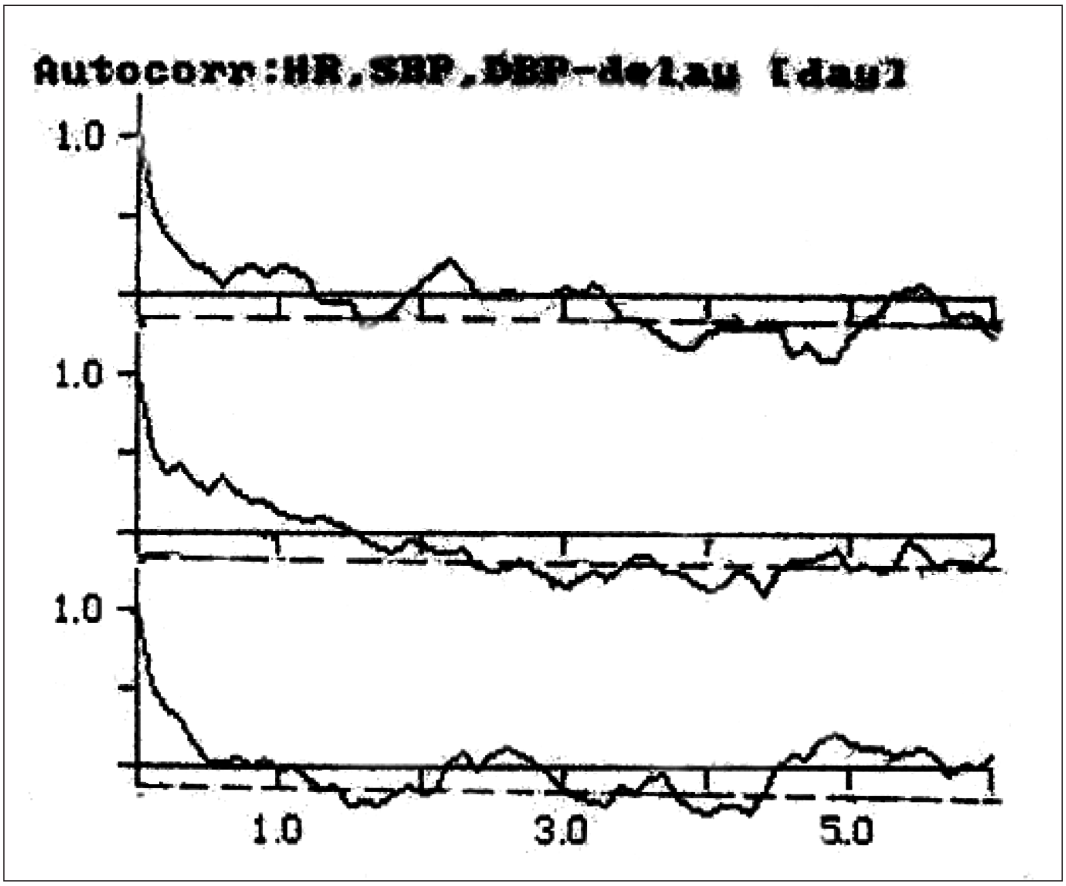

Figure 4 *Autocorrelation functions of heart rate, systolic and diastolic blood pressure of a newborn risk baby.*

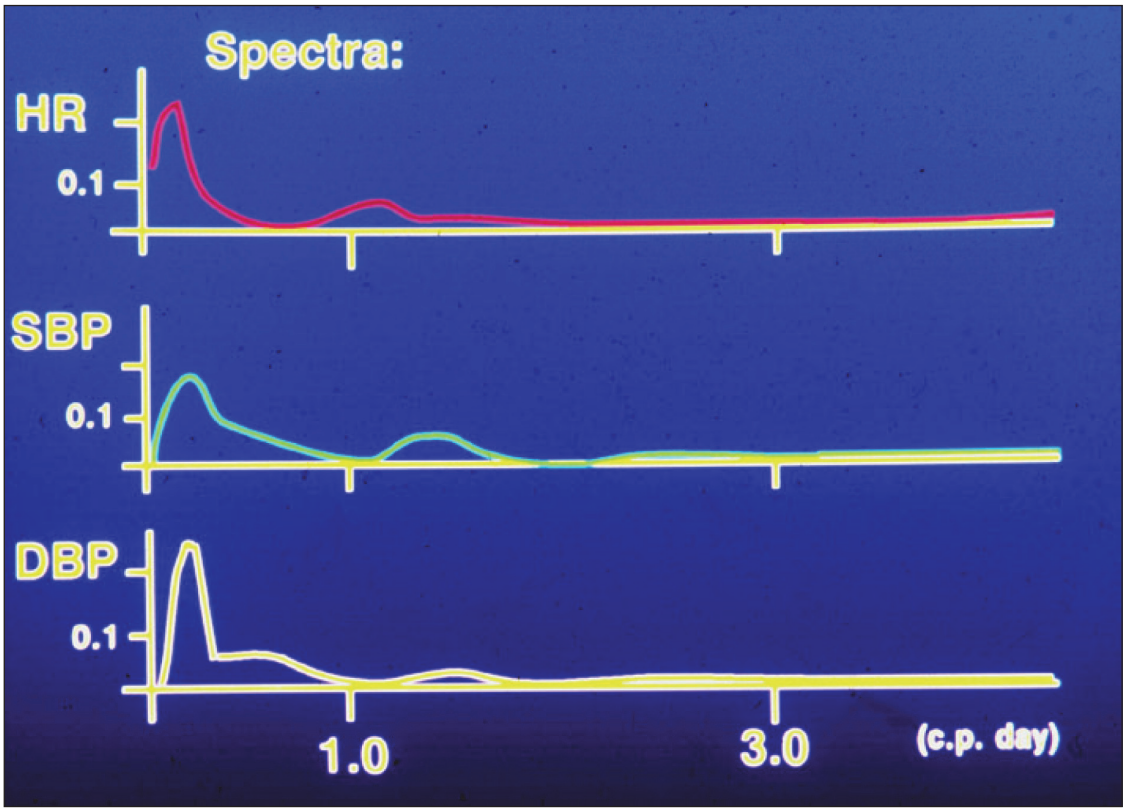

Figure 5 *Power spectra of heart rate, systolic and diastolic blood pressure of a newborn risk girl (birth weight 1150 g). Spectral peaks correspond to a component with a period 7.2 days for heart rate and 4.8 and 5.0 days for systolic and diastolic blood pressure. A circadian component is only observed for the heart rate.*

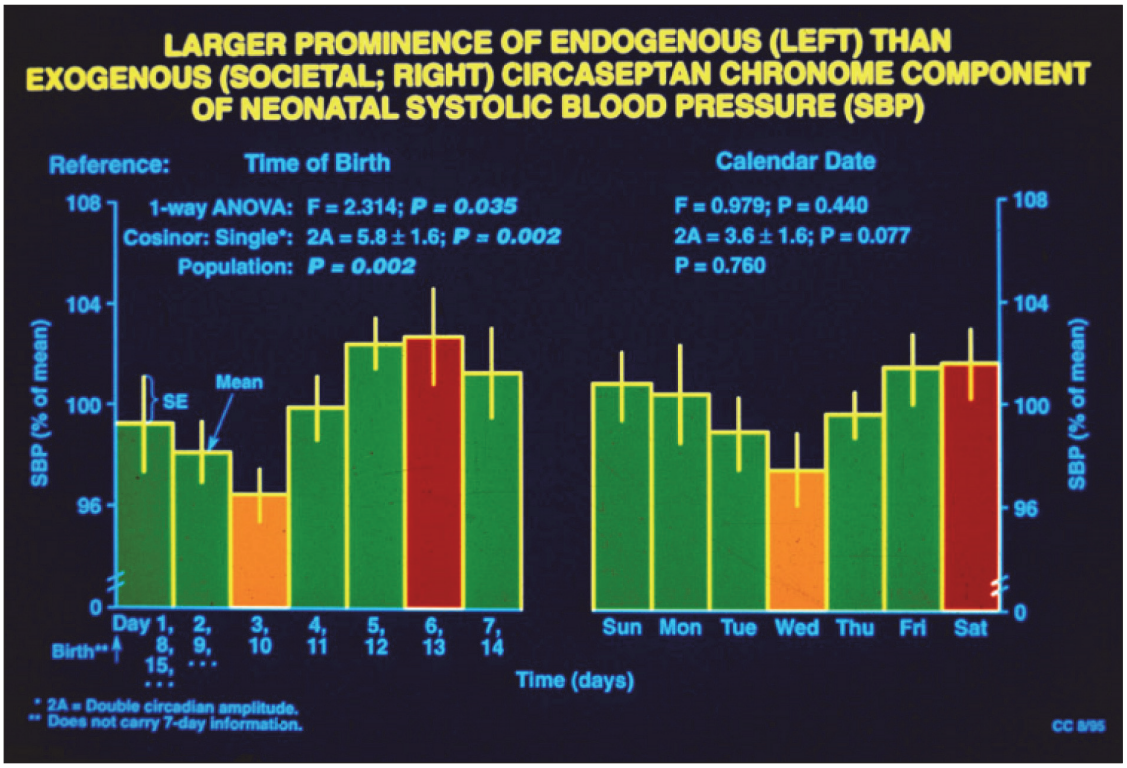

Figure 6 *Population-mean cosinor of the circaseptan component of systolic blood pressure in relation to the date and time of birth (that is by analyzing data as a function of postnatal age) on the left side of the Fig.6, and population mean cosinor of the circaseptan component of systolic blood pressure by reference to midnight between Saturday and Sunday preceding the start of data collection (that is by analyzing data as a function of calendar time) on the right side of the Fig. 6.*

In relation to birth, the circaseptan component was statistically significant on a group basis. Any social synchronization of the circaseptan component of systolic blood pressure was not appearent.

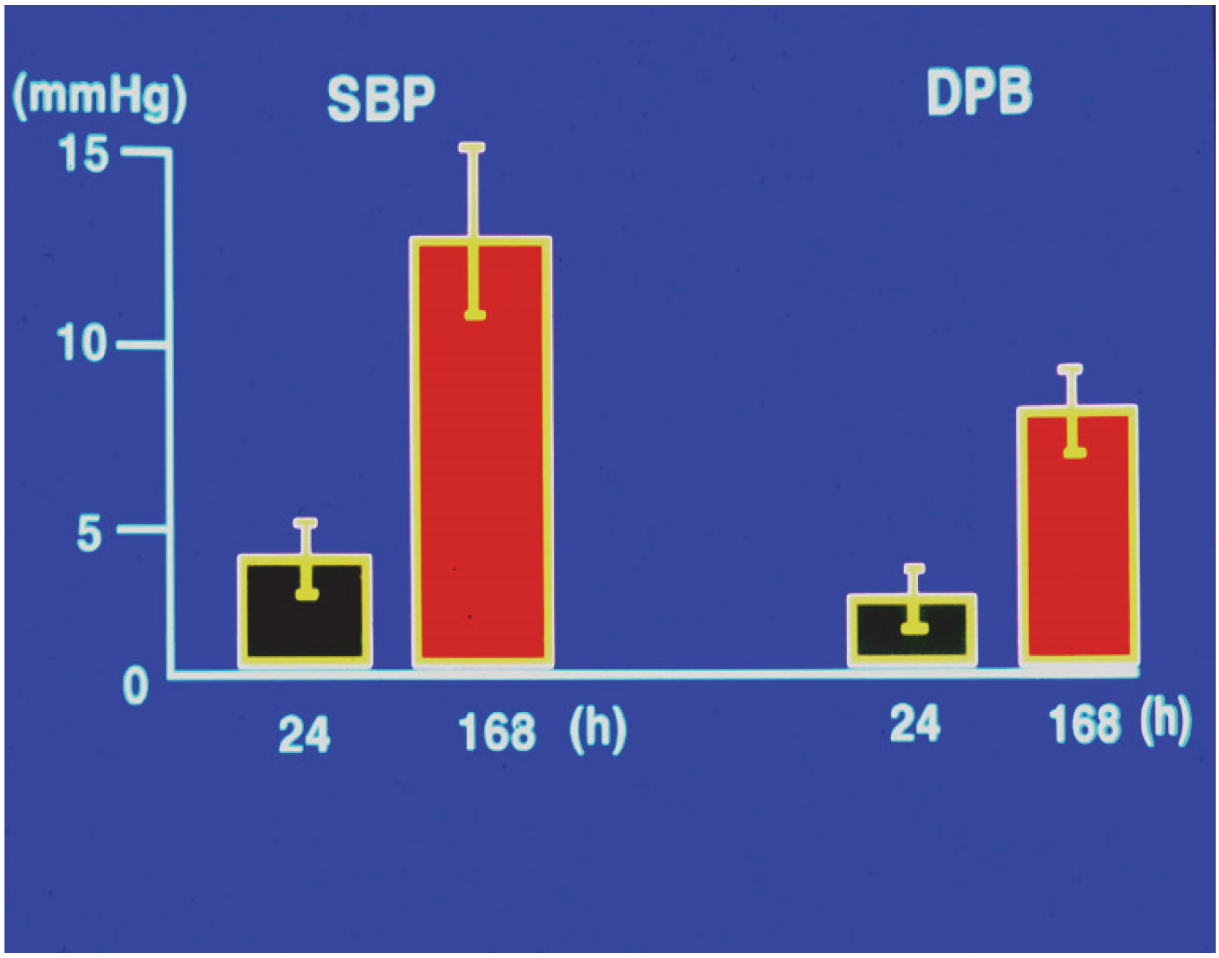

Figure 7 *Comparison of double amplitude of circadian (24 hours) and ciraseptan of the circaseptan component (168 hours) of systolic blood pressure in relation to the date of birth derived by cosinor analysis. Note large prominence of crcaseptan component vs. cikrcadian variation. Bars represent the double amplitude (means plus/minus 95% confidence limit) of cicaseptan and circadian components. Amplitudes of the two components differ with statistical significance (p<0.01, Kruskal-Wallis test).*

References

1. Longini IM, Higgins MW, Hinton PC, Moll PC, Keller JB: Am J Epidemiol 120, 131-144, 1984.
2. Biron P, Mongeau JG, Bertrand D: Can Med Assn J 115, 773-774, 1976.
3. Christian JC: Twin studies of blood pressure. In: L.J. Filer, R.M. Lauer (eds.): Children‘s Blood Pressure: Report of 88th Ross Conference on Pediatric Research. Columbus: Ross Laboratories, 1985, pp.51-55.
4. Longini IM, Higgins MW, Hinton PC, Moll PC, Keller JB: Am J Epidemiol 120, 131-144, 1984.
5. Perusse L, Moll PP, Sing CR: Am J Hum Genet 49, 94-105, 1991.
6. Rice T, Bouchard C, Borecki IB, Rao DC: Am J Hum Genet 46, 37-44, 1990.
7. Zaslavskaja RM., Chronodiagnosis and chronotherapy of cardiovascular diseases. Moskow, 1993, 397pp.

8. Zaslavskaya RM: Circadian rhythms of blood clotting in norm and pathology and therapy problems. Moscow: Quartet Scientific Publ., 1995, 444 pp.

9. Lee YH, Rosner B, Gould JB, Lowe EW, Kass EH: Familial aggregation of blood pressures of newborn infants and their mothers. Pediatrics 58, 722-729, 1976.

10. Levine RS, Hennekens CH, Duncan RC, Robertson EG, Gourley JE, Cassady JC, Gelband H: Blood pressure in infant twins, birth to 6 months of age. Hypertension 2(4 Pt 2), I29-I33, 1980.

11. Thomas CB, Cohen BH: The familial occurrence of hypertension and coronary artery disease with observations concerning heredity and diabetes. Ann Int Med 126, 90-127, 1955.

12. Kellerová E: Physiological responses of blood pressure and heart rate in neonates and infants. Adv Physiol Sci 9, 367-375, 1981.

13. Halberg F, Cornélissen G, Bingham C, Tarquini B, Mainardi G, Cagnoni M, Panero C, Scarpelli P, Romano S, März W, Hellbrügge T, Shinoda M, Kawabata Y: neonatal monitoring to assess risk for hypertension. Postgrad Med 79, 44-46, 1986.

14. Halberg F, Cornélissen G, Bakken E: Caregiving merged with chronobiologic outcome assessment, research and education in health maintenance organizations (HMOs). Prog Clin Biol Res 341B, 491-549, 1990.

15. Cornélissen G, Halberg F, Tarquini B, Mainardi G, Panero C, Cariddi A, Sorice V, Cagnoni M: Blood pressure rhythmometry during the first week of human life. In: Social Diseases and Chronobiology. Proc. IIIrd Int. Symp. Social Diseases and Chronobiology (Florence, November 29, 1986). B. Tarquini (ed.), Bologna: Societa Editrice Esculapio, 1987, pp. 113-122.

16. Halberg F, Cornélissen G, Wrbsky P, Johnson D, Rigatuso J, Tarquini B, Mainardi G, Breus T, Syutkina EV, Grigoriev AE, Abramian A, Mitish M, Wakasugi K, Tamura K: About 3.5-day (dircasemiseptan) and about 7-day (circaseptan) blood pressure featyres in human prematurity. Chronobiologia 21, 146-151, 1994.

17. Halberg F: Chronobiology. Ann Rev Physiol 31, 675-725, 1969.

18. Blackman RB, Tuckey J: The measurement of power spectra. New York: Dower, 1959

19. Benedat JS, Piersol AG: random Data: Analysis and measurement procedure. London: Wiley Intersciences,1971.

20. Halberg F, Cornéllissen G, Watanabe Y, Otsuka K, Fiser B, Siegelova J, Mazankova V, Maggioni C, Sothern RB, Katinas GS, Syutkina EV, Burioka N, Schwartzkopff O, Near 10-year and longer periods modulate circadians: intersecting anti-aging and chronoastrobiological research. J Gerontol A Biol Sci Med Sci 2001, 56: M304-M324.

21. Siegelová J, Cornélissen G, Wrbsky P, Johnson D, Halberg F: Chronomes of blood pressure (BP) and heart rate (HR) in prematurity: bases for environmental optimization? The Physical and Developmental Environment of High-Risk Infant, Orlando, January 19-21, 1995, p. 106.

22. Schwartzkopff O., Cornélissen G., Bingham C., Homolka P. Katinas G., Sonkowski RP, Halberg F., International BIOCOS Project Team. Longterm, when needed lifelong monitoring concerns governments, ethics, committees and everybody. Laudatio, Jarmila Siegelová´s 60th Birthday, Brno, Czech Republic, January 2002. In: Halberg F, Kenner T, Fiser B (eds). Proceedings, Symposium: The importance of chronobiology in diagnosing and therapy of internal diseases. Faculty of Medicine, Masaryk University, Brno, Czech Republic, Jan 10-13, 2002, Brno, Masaryk University, 2002, pp 97 – 121.

23. Cornélissen G, Halberg F: Introduction to Chronobiology. Medtronic Chronobiology Seminar #7, 1994, 52 pp. Zaslavskaya RM: Chronodiagnosis and chronotherapy of cardiovascular diseases. Moscow, 1993, 397 pp.

24. Berger S, Kaever MJ. Dasycladates. Stuttgart: Thieme-Verlag, 1992.

25. Halberg F, Cornélissen G, Katinas G, Hillman D, Schwartzkopff O. Season´s Appreciations 2000: Chronomics complement, among many other fields, genomics and proteomics. Neuroendocrinol Lett 2001; 22 : 53 - 73 .

26. Halberg F, Breus TK, Cornélissen G, Bingham C, Hillman DC, Riqutuso J,Delmore P, Bakken E, International Womb-to-Tomb Chronome Initiative Group: Chronobiology in space. Keynote, 37 gh Ann. Mtg. Japan Soc. for Aerospace and Enviromental Medicine, Nagoya, Japan, November 8-9, 1991. University of Minnesota/Medtronic Chronobiology Seminar Series, #1, December 1991, 21 pp. Of text, 70 figures.

27. Fraser-Smith AC, A weekend increase in geomagnetic activity. J Geophys Res A (Spaace Physics) 1979; 84 : 2089 - 2096.

28. Abbot CG. Solar variation and weather, a summary of the evidence, completely illustrated and documented. Smithsonian Miscellaneous Collections 146, No. 3 (Publ. 4545), Washington DC, 1963, 67 pp. + 4 plates.

29. Siegelova J., Cornelissen G., Schwarzkopff O., Halberg F. Time structures in the development of children. Neuroendocrinol. Letters Vol. 24, Supl. 1, 2003,120-131.

30. Cornélissen G, Engebretson M, Johnson D, Otsuka K, Burioka N, Posch J, Halberg F. The week, inherited in neonatal human twins, found also in geomagnetic pulsation in isolated Antarctica. Biomedicine and Pharmacoterherapy 2001; 55 (Suppl) 1:32-50.

31. Halberg F, Chronobiology, Annu Rev Physiol 1969; 31; 675-725.

32. Cornélissen G, Halberg F. Chronomedicine. In: Armitage P, Colton T. (editors-in-chief). Encyklopedia of Biostatistics, v.1.Chichester, UK:John Wiley ånd Sons Ltd.,1998: 642-649.

33. Turti , Syutkina EV, Cornélissen G, Grigoriev AE, Mitish MD, Abrahamian AS Siegelova J, Fiser B, Dusek J, Al-Kubati M, Muchova L, Uhlir M, Halberg F. Multiseptan-over-circadian prominence of neonatal blood pressure and heart rate in Moscow, Russia. Scripta medica (Brno) 1996; 67 (Suppl.2):85-92.

34. Garcia L., Hermida RC, Ayala DE, Vasquez A. Reproducible endogenous circaseptan variation in neonatal blood pressure. Biological Rhythm Research 1995; 26: 392-393.

35. Watanabe Y,. Cornélissen G, Hellbrügge T, Watanabe F, Otsuka K, Schwartzkopff O, Halberg F., Partial spectral element of the time structure or chronome of a human neonatal heart rate at term. Biomedicine and Pharmacotherapy 2002; 56: (Suppl 2) 374s-378s.

36. Hellbrügge T., The develoment of circadian rhytms in infants. Cold Spr Harb Symp quant Biol 1960; 25: 311-323.

37. Hellbrügge T, Lange JE, Rutenfranz J, Stehr K. Cirkadian periodiscity of physiological functions in different stages of infancy and childhood. Ann NY Acad Sci 1964; 117: 361-373.

38. Hellbrügge T. The development of circadian and ultradian rhytms of premanture and full-term infants. In: Scheving LE, Halberg F, Pauly JE eds. Chronobiology, Proc.Int.Soc. for the Study of Biological Rhythms, Little Rock, Ark. Stuttgart: Georg Thieme Publishers/Tokyo: Igaku Shoin Ltd., 1974: 339-341.

ATLAS OF CHRONOMES: A WORK IN PROGRESS

GERMAINE CORNÉLISSEN[1], LARRY A BEATY[1], CATHY LEE GIERKE[1], LYAZZAT GUMAROVA[1,2], KUNIAKI OTSUKA[3], YOSHIHIKO WATANABE[3], ZHENGRONG WANG[4], JARMILA SIEGELOVA[5]

[1] Halberg Chronobiology Center, University of Minnesota, [2] Al-Farabi Kazakh National University, Almaty, Kazakhstan, [3] Tokyo Women's Medical University, Daini Hospital, Tokyo, Japan, [4] West China Medical Center, Sichuan University, Chengdu, China, [5] Masaryk University, Brno, Czech Republic

Abstract

Within the scope of chronobiology, the study of non-random changes as a function of time in biology, charts have been prepared in several publications, consisting notably of maps of circadian, circaseptan (about-weekly), and circannual acrophases (phases of maxima of cosine curves with known periods fitted to data by least squares) shown with their 95% confidence intervals. Within the scope of chronomics, the study of cycles in us and around us, charts catalog information about cycles with counterparts in space weather. As these cycles are usually wobbly, focus is placed on maps of non-photic periods, shown with their 95% confidence intervals and aligned with corresponding results on matching environmental variables. The envisioned atlas of chronomes (broad time structures) should serve as a repository of results in chronobiology and chronomics assembled since the mid-1940s at the Halberg Chronobiology Center, and as a tool to enable new and renewed interpretations of and application of those results. Some of its design features are presented herein.

Introduction

Earlier, we reviewed uses for an atlas of chronomes [1]. Emphasis was placed on non-photic cycles, less well-known in biology, their detection in physiology and pathology to be aligned with a set of environmental variables aiming at a better understanding of environmental influences on humans and living matter more generally. It was noted that, particularly when dealing with long cycles, period and acrophase charts would be most useful to discriminate between apparent short-term trends and periodicities that cannot be assessed when sampling covers only a fraction of a cycle, thus enabling to better plan a roadmap for future studies.

Of course, acrophase charts and tables of rhythm characteristics for the circadian, circaseptan and circannual components are also to be included in the atlas, their usefulness recognized long ago [2, 3]. Applications include first and foremost the optimization of treatment by timing (chronotherapy), not only along the scale of the day [4, 5], but also along the scale of the week [6-9].

The merit of compiling information on circadian rhythms in time (acrophase) and space (organ, tissue) is becoming recognized, notably since a molecular and genetic basis to the circadian system has been established [10]. Recently, RNA-sequencing and DNA arrays were used to profile the transcriptomes of 12 different mouse organs, resulting into a circadian gene expression atlas [11]. By generating high-resolution multi-organ data, the authors showed that nearly half of all genes in the mouse genome are circadian periodic in one or the other organ and/or tissue. By applying pathway analysis, they observed new clock-mediated spatiotemporal relationships of direct relevance to chronotherapy [11].

The merit of mapping a broad time structure, beyond the circadian system, has been long recognized in Russia, where an atlas of natural processes in 3 volumes has already been published [12-14]. The atlas envisioned here has dynamic characteristics, as a searchable electronic document, containing not only charts but also stories linking results from different lines of inquiries reported in different publications, thus extending the atlas into an encyclopedia.

Table 1. *Fields to be filled in for each entry into the atlas of chronomes.*

I. Aim
   1. Brief description (free text field)
   2. Primary endpoints
   3. Category - subcategories
   4. List of related studies (either here or in last section: highlights or in both locations)

II. Materials and Methods
   1. Variable name(s) (e.g., blood pressure), and for each variable:
   2. Measurement technique (e.g., oscillometric)
   3. Site of measurement (e.g., wrist)
   4. Measurement kind (automatic, manual, rating, …)
   5. Study
      a. Design (longitudinal, transverse, hybrid, Latin square, …)
      b. Study span (calendar dates and times; specify reference time)
      c. Observation span (length of record)
      d. Sampling interval (e.g., every 30 minutes or 5-6/day)
      e. How many stages
      f. How many groups
   6. Experimental conditions: For each group:
      a. Description of group (descriptor: e.g., high vs. low breast cancer risk)
      b. How many "experimental units"
      c. Specify what they are (humans, mice, specimens, …)
      d. Ethnicity/Strain/Kind
      e. Gender (if appropriate)
      f. Age (if appropriate)
      g. Synchronizer(s) (Light/dark, Rest/activity, Feeding schedule, …)
      h. Geographic location
   7. Experimental conditions: For each stage:
      a. Description of stage (descriptor: e.g., low-salt diet vs. usual salt intake)
      b. Duration of stage
      c. Synchronizer(s) (Light/dark, Rest/activity, Feeding schedule, …)
      d. Geographic location
      e. Age (if appropriate)

III. Analysis (check all that apply)
   1. Parametric tests (Student t test, Paired t test, One-way ANOVA, Multiple-way ANOVA, Linear regression, Multiple regression)
   2. Non-parametric tests (Wilcoxon signed-rank test, Mann-Whitney, Spearman's rank correlation coefficient, Sign test, …)
   3. Odds ratio, Survival time analysis (Kaplan-Meier, Logrank test)
   4. Plots (Actigraph, Chronogram, Plexogram, Bland-Altman plot)
   5. Spectral analysis (Auto-correlation, Cross-correlation, Periodogram, Cross-spectrum, Spectral coherence, Wavelets)
   6. Cosinor methodology (Single-component single cosinor, Multiple-component cosinor, Least squares spectrum, Population-mean cosinor, Population-mean cosinor spectrum, Parameter tests, Single- or multiple-component Chronobiologic Serial Section, Gliding Spectrum, Nonlinear cosinor for an estimation of the period length)
   7. Superposed epoch analysis, Remove-and-replace
   8. Cluster analysis
   9. Jackknife, Bootstrap, Monte Carlo

IV. Results

   Attach one or several graphs pertinent to the study described under this heading

V. Highlights

   Include text with bullets (including tables and graphs) listing major conclusions from the study under this heading and provide a list of references where the study is described (eventually using citations to references inside the bullets).

Design of Entry Forms

One important aspect of building the atlas of chronomes consists of entering information pertinent to each study in a standardized fashion, making sure that the information provided is as complete as it can be. Another desideratum is that the atlas should be searchable. In order to accommodate these features, a form has been designed providing guidelines for the entry of any given study into the atlas. Table 1 lists the categories that would be filled within each entry into the atlas, which should have a designated overall title that states the aim of the study being described (categorized). Although Table 1 suggests the format to follow a certain sequence, its electronic counterpart does not have such a strict structure. To facilitate searches within the atlas, much of the information is entered via drop-boxes with multiple-choice entries to choose from. Other information, notably related to the main results and conclusions from a study, can be entered as free text.

Illustrative example

To illustrate how results from a given study are entered into the atlas, we turned to a publication by Siegelova et al. presented at the 2013 meeting on Noninvasive Methods in Cardiology in Brno, Czech Republic [15]. Together with the title, a document identifier (ID) is added for easy referencing. The aims, endpoints, and fields of interest are clearly indicated to situate the scope of the study, Figure 1. As the atlas becomes populated with additional studies (entries), those that are related to this study can be listed under "related Studies" with their citation. Once a study has been related to another entry in the atlas, all links can be automatically updated, so that the user does not need to go back to studies already entered into the atlas to add a link to the new entry.

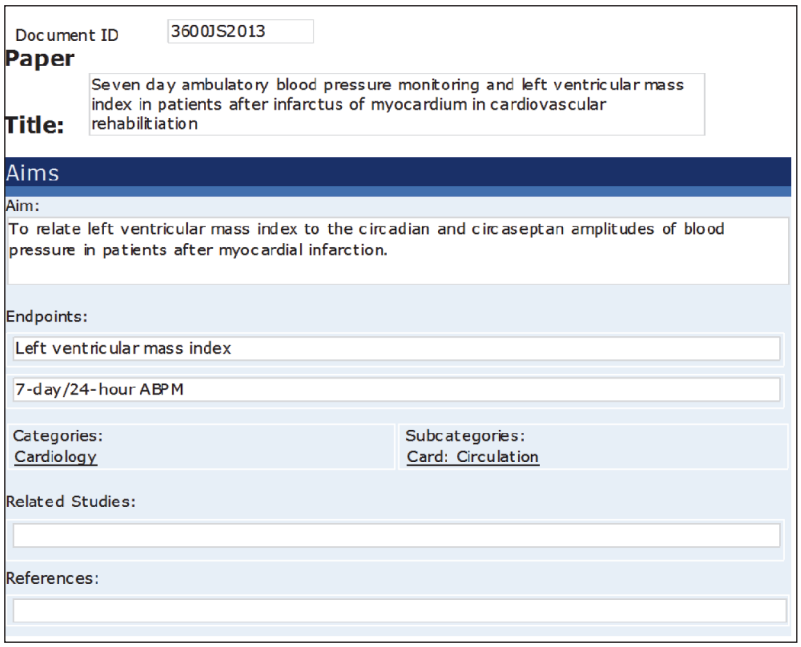

Figure 1 *With the title and study ID, aims are succinctly stated. Fields of study are chosen to facilitate the later search of information within the atlas. © Halberg Chronobiology Center.*

Under Materials and Methods, the number of stages and groups is listed, together with general information regarding when the study was conducted and which variables were measured, Figures 2-4. For each variable, sampling rate and observation span are listed, as is the site of measurement and measurement technique, as well as an indication whether the data were obtained manually or automatically, Figures 3-4. When multiple variables have been measured, there is the possibility to design the form to fill in the information entered for the first variable to be replicated for the other variables, so that only information differing from that already provided would need to be entered. It is indeed often the case that sampling remains the same for all variables examined in a given study.

In this study, there were two groups, each group undergoing the same protocol (single stage). Entry of information for each of the two groups is illustrated in Figures 5 and 6. As there was only one stage in the study, no additional information needs to be entered on the form, Figure 7, and one can immediately proceed to select which methods of analysis were applied to derive the results, Figure 7.

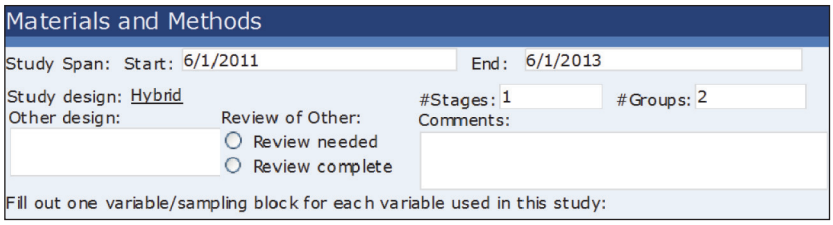

Figure 2 *Basic information regarding the study design. © Halberg Chronobiology Center.*

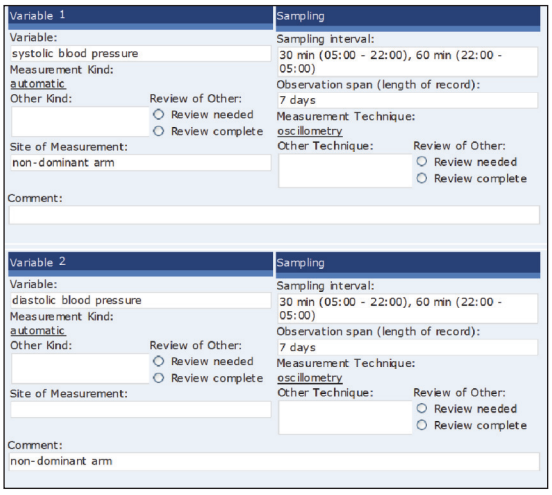

Figure 3 *Sampling information of 2 of the 4 variables examined in this study. © Halberg Chronobiology Center.*

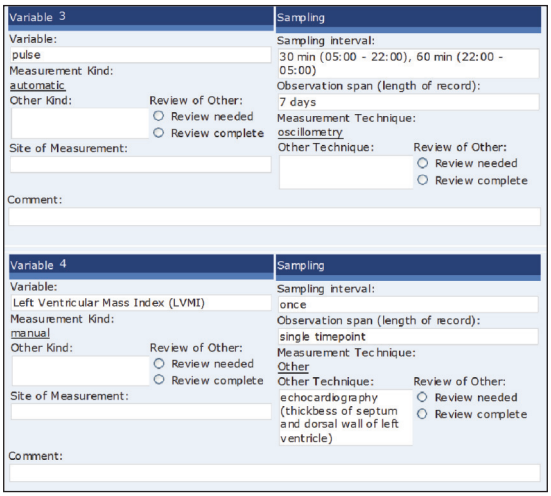

Figure 4 *Sampling information of the other 2 variables examined in this study. © Halberg Chronobiology Center.*

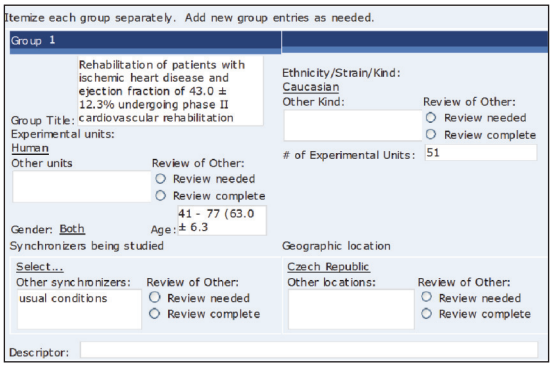

Figure 5 *Description of Group 1.*
© Halberg Chronobiology Center.

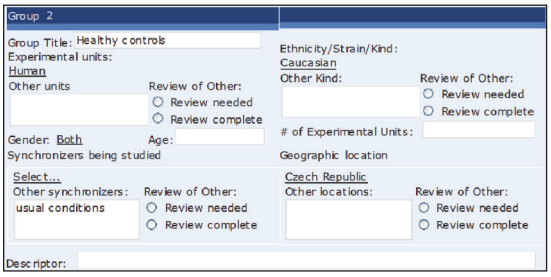

Figure 6 *Description of Group 2.*
© Halberg Chronobiology Center.

As seen in Figures 8 and 9, results and conclusions are presented in a concise way in an attempt to enable users to more easily search through what may eventually become a relatively large number of entries.

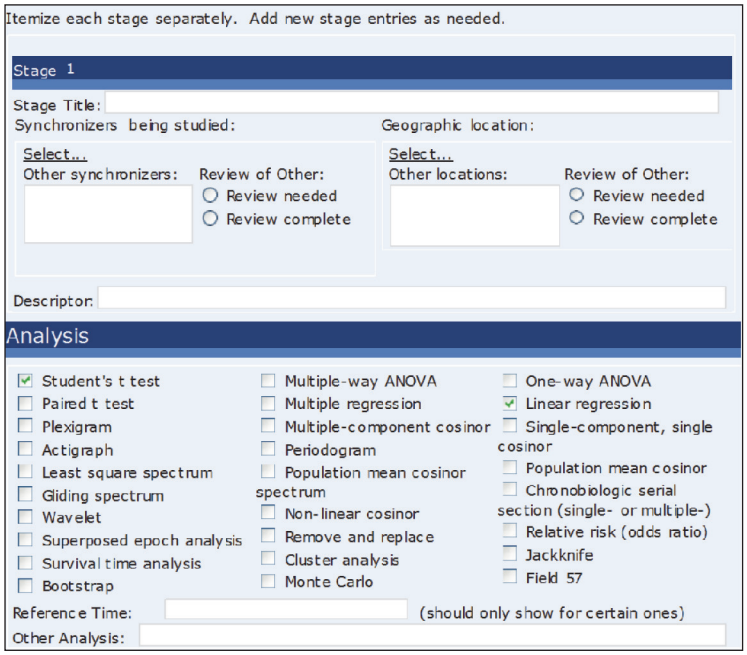

Figure 7 *No additional information needs to be entered under Stage as there is only one stage in this study, and one can proceed to select methods used for data analysis. © Halberg Chronobiology Center.*

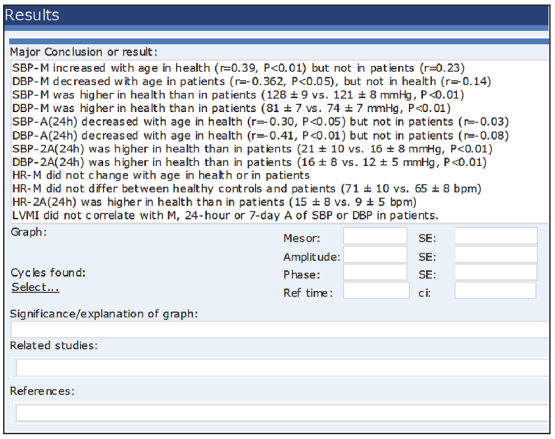

Figure 8 *Succinct presentation of major results. © Halberg Chronobiology Center.*

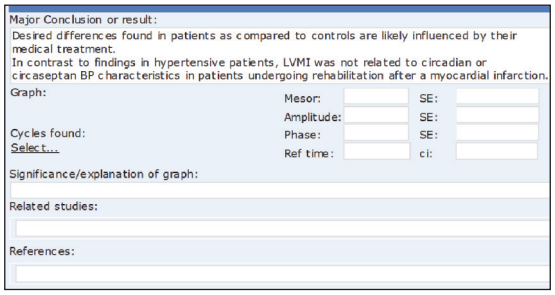

Figure 9 *Succinct presentation of major conclusions. © Halberg Chronobiology Center.*

Status quo

As seen above, we are well into the work of defining specifically what the atlas will contain and how it will be constructed. We are also starting to record information about research at the Halberg Chronobiology Center from the past few decades as the first type of information to be displayed in the atlas, Franz Halberg's legacy.

As outlined earlier [1], we expected to follow four product development steps. We find ourselves bouncing back and forth between the definition/specification steps and early product construction steps. This commonly happens when the requirements are not clear to the implementation group at the outset, and has been more-or-less formalized into what are now called "agile" product development methodologies. While we do not employ a specific agile method, we know we are benefiting from the iterative approach of building small parts of the atlas, some of us meeting weekly to share what we learned by doing so, and improving our detailed understandings of what we want the atlas to be after seeing each small bit of implementation before building or re-building the building blocks of our "product".

We expect to construct the atlas from (at least) three types of records: records of previously published studies [16], records of "chronome maps" such as previously published acrophase and period charts [17], and yet-to-be-written "stories" that tie records of related research and/or chronome maps together in a cohesive narrative explaining the usefulness of the collection of research results to healthcare or a field of science. A combined physical and conceptual XML schema has been written for the records of previously published studies. The project has not been complex enough to require the data storage details (physical schema) to be separated from the conceptual schema (the union of all the project members' visions of how the atlas will present the data to its readers).

Though we often think in terms of a traditional database as we work, we recognize that we are ultimately authoring a complex document, not a database, and that structured document authoring tools typically store data in an XML or other SGML-derived format. We have started recording studies using Microsoft InfoPath and storing the resulting XML data in simple disk files containing one study record each, as our group already had the expertise required for that. We have not completed tool selection, and specifically have not selected the authoring tools we shall need later. The relatively easy-to-use XML format gives us many practical data-conversion paths as we move forward. Microsoft has announced that InfoPath will not be a stand-alone product in the future, and that the functionality of InfoPath will be incorporated into their

other products in some way that is not yet described publicly. Hence, converting away from the InfoPath XML schema and data files into some other format might be a future task for us.

The small size of our XML database (expected to be a few thousand records) and the high level of expertise of the few data entry people we have means that we do not have to make extensive use of an XML DTD or other input validation mechanisms. All fields in the data entry forms are currently optional (not required to have values) to support saving partially-completed records, and some fields are restricted to lists of valid values to ensure consistency of spelling and granularity in the final product. The number of records entered at this time is on the order of a half-dozen, but those first few records were selected to give us experience in the usability of the data entry form, designing the schema, and constructing the valid-value lists (which are presented in the data entry form as drop-down lists). The lack of input validation will save us some programming effort (and software bugs) early in the project, and will likely be balanced by human reviews of the data later in the project. The usability of the data entry form is improved as we progress based on the mistakes made during data entry, and includes shading fields that are not yet filled in, organizing drop-down lists either alphabetically, hierarchically, or topically, special values to mark entries that someone must return to and update later in the data entry phase, programmatically making links to other records, and defining the intention of fields with text that appears when the computer mouse cursor hovers over the field.

An illustrative example of the discussions we have that lead to an important schema decision revolved around the sections of the study that record the number of groups and stages in experiments. We had to decide between recording data for each combination of group and stage (resulting in Ngroups x Nstages subrecords to be entered), or more simply for each group separately and each stage separately (resulting in Ngroups + Nstages records to be entered). We explicitly analyzed the expected use of the group and stage information, and determined that the simpler mechanism of treating group and stage separately was sufficient. A subrecord for information about variables in the experiment is similarly independent of the rest of the overall record. These analyses have taken place for almost every part of the schema and data entry form.

We discussed the merit of trying to record judgments about the value of the research in these records, variously labelling fields as “strength”, or “usefulness”, “trustworthiness”, or something similar. In the end, we decided that in every case a positive value judgment in one situation would simultaneously be a negative value judgment in some other situation, and made a strong commitment to not make such judgments in these records. Such judgments might well be made in the stories written later for another section of the atlas.

The collection of research papers (studies) that form the basis for the atlas has a formal document identifier convention, which acts as a shorthand for formal full references, as would be done in any conventional document management system. These document identifiers are used in constructing links between records that will ultimately appear in various places in the atlas (therefore are sometimes visible to readers of the atlas). Document identifiers for papers published by Franz Halberg follow their numbering in his bibliography [16] followed by the initials of the first author and the year of publication. In the illustrative example above [15], the identifier is 3600JS2013 as it is the 3600th paper in the bibliography, published by Jarmila Siegelova et al. in 2013.

Quo vadis?

A recurring discussion about who the target audience for the atlas is will soon drive us to record our use cases more formally. While we already have informal use cases recorded, we have not analyzed them for completeness, nor recorded the “Actors” (users of some part of the atlas) and other pieces normally recorded in a formal description of use cases. The list of Actors that appear in all the use cases is a formal definition of the target audience. The review of the use cases should resolve any differences between the project members’ informal vision of the target audience and the formal list of Actors. Any “person” that

appears in the informal definition of target audience but is not in the Actors list means that either a use case (with its Actor) has not been described, or that the person is not really part of the desired target audience.

will know that we have finished is in the final review of any product being developed, including an atlas such as ours: the final test of the product before it is released to its users is to run through the entire list of use cases and demonstrate that the product performs as needed for each of its potential users. Any use case that cannot be performed by real people on the real atlas that we ultimately produce would be an indication of a problem or missing feature. When all use cases can be tested successfully, we will know that we have finished the job we started out to do.

Some off-the-shelf software tools and small programs of our own will be needed soon. We expect to find or write a program to convert the XML data to prototype displayable HTML pages so we can analyze usability and usefulness (now fashionably called "user experience" or "UX" amongst experts who do this kind of work for a living) of the final atlas. While we are not looking for people to help us with designing new ways to present the information in the atlas (we think that the style of charts and tables we have to work with in the collection of studies that underlies the atlas is sufficient), we might consult with usability experts on the display of the charts and tables that we already have.

Another tool we expect to prepare at some time will build chronome "maps" such as acrophase and period charts for the atlas. This is another driver for that currently-incomplete use case work – we will need to know whether this chart-making tool would be used only by data-entry people, or by end-users of the web version of the atlas. Writing a web-based tool can be considerably different than writing a tool for a few local data-entry personnel.

If such a chronome-map making tool were to be used on the web version of the atlas, it would be in the third of three forms of searches that we might implement. The first and second types of searches are those typical of many websites, a "simple" search based on text and pattern matching, and an "advanced" search where the end user specifies values to be found in specific fields of the records in the atlas. The third form of search we envision would be an advanced search also, but tuned specifically to find records useful in creating a chronome map. If we make this third form of search available to end users of the web version of the atlas, the search web page could invoke the chronome map making tool dynamically and generate a chronome map from the specific search results just obtained, rather than displaying a chronome map previously created and entered into the atlas by data-entry people.

The interesting problem of finding study records that, taken together, support a story to be written might drive the implementation of another software tool. These records would presumably be related to each other in some way, a way that is possibly not well-defined, neither in the original studies nor in the study records. No author of atlas stories has all the relevant research papers memorized. The author could potentially make use of a machine learning or data mining / knowledge discovery technique such as a classification or clustering algorithm on the data and metadata that we will have entered to help find those papers. A request to go beyond the capabilities of "advanced search" with this kind of tool has been made and duly noted, but has not progressed to the discussion stage yet. And the idea that such a tool could theoretically be made available to users of the web atlas in addition to story authors is so far into the future that it has not entered our collective consciousness.

Concluding Remarks

Whereas determining use cases remains a task ahead, one can already point to the usefulness of an atlas of chronomes in several aspects. First and foremost, it will assemble over 60 years of research in

chronobiology and chronomics by the founder of these disciplines into a single searchable resource of interest to the broad scientific community. By extracting the essence of each study or publication and providing a concise objective interpretation of the results obtained, the legacy of Franz Halberg will become widely available without any copyright infringement as would be the case by posting all original papers online. By linking studies on a given topic, from which stories can be written, it will be possible to reach a broad-scale integration of results from the Halberg Chronobiology Center not feasible thus far. Both these features will also greatly facilitate the search for information on a given topic, while also pointing the user to the original source, as the reference to the publication being summarized is part of the entry form.

The stories, together with the separate study entries, are anticipated to be most useful to point to important methodological aspects, such as the role of competing synchronizers in determining circadian and other rhythm characteristics, and the availability of methods to deal with non-stationary time series as well as factual information on characteristics of non-photic cycles mapped at different times in different geographic locations [1].

One dividend from our endeavors will be to objectively document the birth of chronobiology and chronomics. Comparing study designs, results and interpretations from early works in the 1950s and 1960s with the latest works of Franz Halberg in the 2010s, the historian of sciences may note how chronobiology was founded on his documentation on an inferential statistical basis of free-running and the implication of a partly endogenous nature of circadian rhythms. Indeed, Franz showed that circadian rhythms are partly endogenous and can be manipulated by environmental synchronizers, notably the lighting and feeding schedules [18, 19]. Chronomics, in turn, recognizes the important influence of the non-photic as well as the photic environment on physiology, psychology and pathology [20]. The ubiquity of non-photic cycles and their persistence in biology when they are no longer detected in the environment even led Franz to postulate a partly endogenous nature of most, if not all, cycles shared between biota and its environment. For him (and some of us), rhythms are life itself [21].

References

1. Cornélissen G, Beaty LA, Siegelova J, Gierke CL, Otsuka K, Watanabe Y, Syutkina EV, Masalov A, Gumarova L, Halberg F. An atlas of chronomes to map broad time structures. In: Kenner T, Cornélissen G, Siegelova J, Dobsak P. (Eds.) Noninvasive Methods in Cardiology 2013. Masaryk University, Brno, Czech Republic 2013; 102-116.
2. Halberg F. Quo vadis basic and clinical chronobiology: promise for health maintenance. Am J Anat 1983; 168: 543-594.
3. Haus E, Nicolau GY, Lakatua D, Sackett-Lundeen L. Reference values for chronopharmacology. Annu Rev Chronopharmacol 1988; 4: 333-424.
4. Halberg F. Chronopharmacology and chronotherapy. In: Carpenter DO. (Ed.) Cellular Pacemakers. New York: John Wiley and Sons Inc. 1982; 261-297.
5. Halberg F, Halberg E. Chronopharmacology and further steps toward chronotherapy. In: Pharmacokinetic Basis for Drug Treatment, Benet LZ, Massoud N, Gambertoglio JG. (Eds.), Raven Press, New York, 1984; 221-248.
6. Levi F, Halberg F, Chihara G, Byram J. Chronoimmunomodulation: circadian, circaseptan and circannual aspects of immunopotentiation or suppression with lentinan. In: Takahashi R, Halberg F, Walker C. (Eds.) Toward Chronopharmacology, Proc. 8th IUPHAR Cong. and Sat. Symposia, Nagasaki, July 27-28, 1981. Oxford/New York: Pergamon Press; 1982; 289-311.
7. Liu T, Cavallini M, Halberg F, Cornélissen G, Field J, Sutherland DER. More on the need for circadian, circaseptan and circannual optimization of cyclosporine therapy. Experientia 1986; 42: 20-22.

8. Ulmer W, Cornélissen G, Revilla M, Siegelova J, Dusek J, Halberg F. Circadian and circaseptan dependence of the beta-ATP peak of four different cancer cell cultures: implications for chronoradiotherapy. Scripta medica (Brno) 2001; 74: 87-92.
9. Halberg Francine, Cornélissen G, Halberg F, Ulmer W, Sanchez de la Peña S, Siegelova J, Schwartzkopff O, BIOCOS project. Reasons for a protocol for radiation treatment aimed at exploiting weekly rhythms. In: Halberg F, Kenner T, Fiser B, Siegelova J. (Eds.) Proceedings, Noninvasive Methods in Cardiology, Masaryk University, Brno, Czech Republic, October 4-7, 2008; 63-73.
10. Lowrey PL, Takahashi JS. Genetics of circadian rhythms in Mammalian model organisms. Adv Genet 2011; 74: 175-230.
11. Zhang R, Lahens NF, Balance HI, Hughes ME, Hogenesch JB. A circadian gene expression atlas in mammals: Implications for biology and medicine. PNAS early edition. doi: 10.1073/pnas.1408886111.
12. Gamburtsev AG, Nikolaev AV. (Eds.) Atlas of natural processes. Vol. 1. Order and chaos in lithosphere and other spheres. Moscow: UIPE; 1994. 176 pp. [Supported by Russian Ministry of Science.]
13. Gamburtsev AG, Nikolaev AV. (Eds.) Atlas of temporal variations of natural, anthropogenic and social processes. Vol. 2. Cyclical dynamics in the nature and society. Moscow: Scientific World; 1998. 432 pp. [Supported by Russian Foundation for Basic Research.]
14. Gamburtsev AG, Nikolaev AV. (Eds.) Atlas of temporal variations of natural, anthropogenic and social processes. Vol. 3. Nature and social spheres as parts of environmental and as objects of influence. Moscow: Janus-K; 2002. 676 pp. [Supported by Russian Foundation for Basic Research.]
15. Siegelova J, Havelkova A, Dusek J, Vank P, Pohanka M, Cornélissen G, Halberg F. Seven-day ambulatory blood pressure monitoring and left ventricular mass index in patients after infarctus of myocardium in cardiovascular rehabilitation. In: Kenner T, Cornélissen G, Siegelova J, Dobsak P. (Eds.) Noninvasive Methods in Cardiology 2013. Masaryk University, Brno, Czech Republic 2013; 123-137.
16. Halberg F, Cornélissen G, Sonkowsky R, Schwartzkopff O. A bibliography: toward a chrononoosphere (from Gk chronos = time, Attic Gk nous = mind and Gk sphairos = globe). World Forum „Natural Cataclysms and Global Problems of the Modern Civilization“, 19-21 September, 2011, Istanbul, Turkey. http://2011.geocataclysm.org/pdf/franz_halberg_220811.pdf
17. Halberg F, Cornélissen G, Katinas GS, Hillman D, Otsuka K, Watanabe Y, Wu J, Halberg Francine, Halberg J, Sampson M, Schwartzkopff O, Halberg E. Many rhythms are control information for whatever we do: an autobiography. Folia anthropologica 2012; 12: 5-134. http://ttk.nyme.hu/blgi/Knyvek%20kiadvnyok/FOLIA%20ANTHROPOLOGICA/folia12.pdf
18. Halberg F. Some physiological and clinical aspects of 24-hour periodicity. Journal-Lancet (Minneapolis) 1953; 73: 20-32.
19. Halberg F, Visscher MB, Bittner JJ. Eosinophil rhythm in mice: Range of occurrence; effects of illumination, feeding and adrenalectomy. Amer J Physiol 1953; 174: 109-122.
20. Halberg F, Cornélissen G, Otsuka K, Schwartzkopff O, Halberg J, Bakken EE. Chronomics. Biomed & Pharmacother 2001; 55 (Suppl 1): 153s-190s.
21. Halberg F, Cornélissen G, Sothern RB, Katinas GS, Schwartzkopff O, Otsuka K. Cycles tipping the scale between death and survival (= „life“). Progress of Theoretical Physics 2008; Suppl. 173: 153-181.

Correspondence:
Germaine Cornélissen
Halberg Chronobiology Center
University of Minnesota, Mayo Mail Code 8609
420 Delaware St. S.E. Minneapolis, MN 55455, USA
TEL +1 612 624 6976 FAX +1 612 624 9989
E-MAIL corne001@umn.edu
Website: http://www.msi.umn.edu/~halberg/

Dedicated to the memory of Franz Halberg who first envisioned an atlas of chronomes, with the pledge to endeavor fulfilling our dear teacher's dream.

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University of Minnesota Supercomputing Institute

BLOOD PRESSURE VARIABILITY AT REST AND DURING EXERCISE IN HEALTHY MEN: SEVEN DAY AMBULATORY BLOOD PRESSURE MONITORING

JARMILA SIEGELOVÁ, ALENA HAVELKOVÁ, JIŘÍ DUŠEK, MICHAL POHANKA, LEONA DUNKLEROVÁ, PETR DOBŠÁK, GERMAINE CORNÉLISSEN*

*Department of Physiotherapy, Department of Sport Medicine and Rehabilitation, Faculty of Medicine, Masaryk University, St. Anna Teaching Hospital, Brno, CZ, *University of Minnesota, USA*

Introduction

Franz Halberg in his chronobiologic studies from Halberg University Center in Minnesota described the circadian rhythm and analyzed the risk of high blood pressure in appearence of cardiovascular diseases (1-8). In a 6 years prospective study of Kunaiki Otsuka on 297 patients, ambulatory monitored for 48 hours, circadian hyperamplitude tension (CHAT) was found to represent the largest increase in the risk of cerebral ischemic events, greater than increase in mean blood pressure, so called MESOR – hypertension, old age, a positive family history of high blood pressure, smoking, alcohol consumption (5). A reduced standard deviation (SD) from 24-hour measurement of heart rate was also associated with an increase of vascular morbidity, coronary artery disease and cerebral ischemic events (8).

Because the diagnosis of hypertension (9-18) is generally based on casual measurement of blood pressure in general practitioner office and these values of blood pressure are higher than values of ambulatory blood pressure monitoring, the table of blood pressure thresholds for definition of hypertension with different types of measurement is included in the Guidelines for Management of Hypertension (2007).

According to this table the threshold for systolic blood pressure is 140 mmHg in the office or clinic, 125 – 130 mmHg during 24 hours, 130 -135 mmHg during day and 120 mmHg during night.

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

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The corresponding values for diastolic blood pressure are 90 mmHg in the office and clinic, 80 mmHg during 24 hours, 85 mmHg during day and 75 mmHg during night.

The values for home measurement are the same as for ambulatory monitoring during day.

The condition for reliability of diagnosis is low day-to-day variation of night-time and day-time pressure values.

The purpose of the study

The aim of the study was to compare 24-hour profile from the 7-day blood pressure monitoring at rest and during exercise. We compared the blood pressure 24 h profile in the day with exercise (0-24 h) and in the day without exercise (25-48 h after exercise).

Subjects

We examined 21 man, healthy subjects, mean age 29±4.9 years (from 23 to 39).

For exercise training we used bicycle ergometer Kettler, type X7, Germany, 2x during week, constant load 120 W, lasting 60 min. Every exercise unit was compose from warm-up period 3 min., load 54 min. and cool-down period 3 min.

Methods

Healthy subject

The subjects were recruited for seven-day blood pressure monitoring. Medical Instruments (A&D, Japan) were used for ambulatory blood pressure monitoring (oscillation method, Fig. 1). One-hour means of systolic and diastolic blood pressure and 24 hour mean in every day were evaluated. We calculated mean systolic and diastolic blood pressure for seven days from every seven day blood pressure monitoring too.

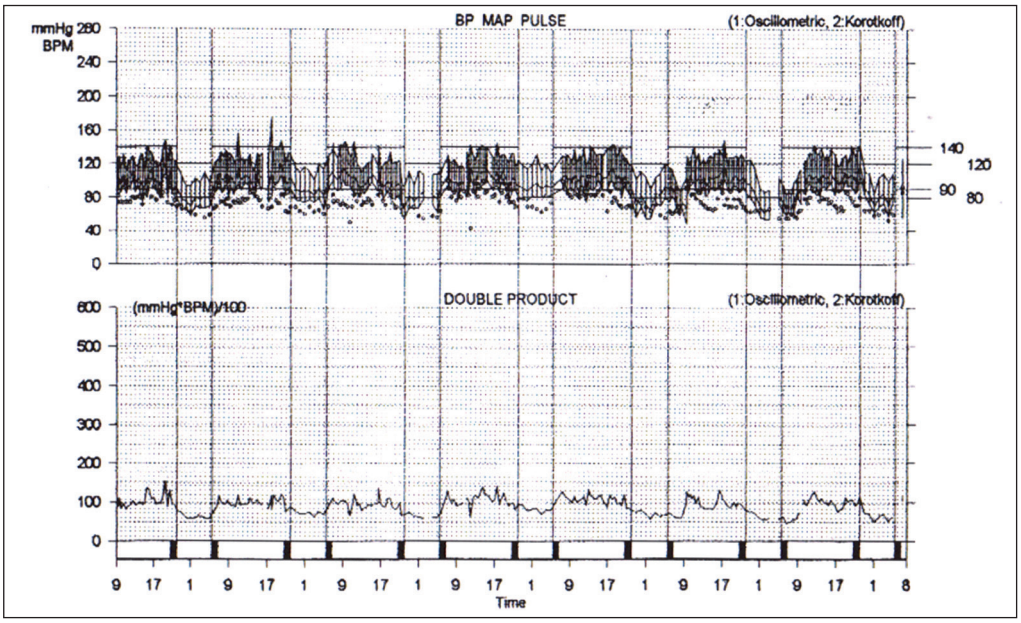


Figure 1 *Seven-day blood pressure profile in one healthy subject*

The regime of measurement of blood pressure was done for 7 days repeatedly every 30 minutes from 5 to 22 h during the day time and once in an hour from 22 to 5 h at night (Siegelová et al. 2006).

The average SBP and DBP and their standard deviations (SD) in the given days (24-h means) were determined by the calculation of arithmetic mean of these values.

To made comparison among the 24-h profile of blood pressure we used Bland-Altman statistical method (19).

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

Results

The healthy subjects (men) were ordered according mean 7-day SBP (subject No 1: 107 mmHg, subject No 21: 121 mmHg; median value: 121 mmHg).

The variability of 24-hours means of SBP values during 7-day monitoring is seen in Fig. 2 in resting days without exercise. In Figure 3 we can see the variability of 24-hour means of systolic blood pressure and 7-day mean systolic blood pressure during exercise in every 21 healthy subjects, ordered according to the SBP values.

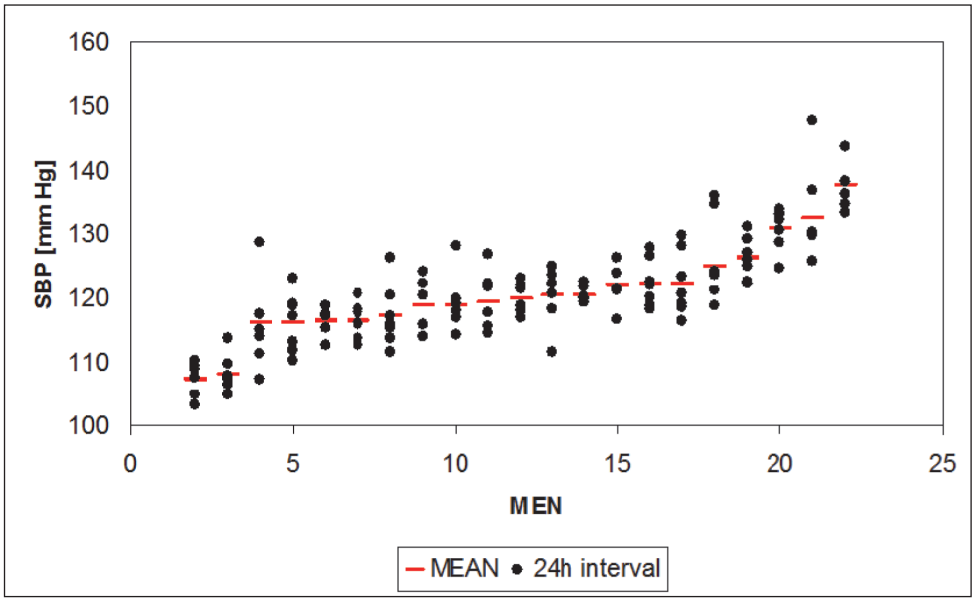


Figure 2 *The variability of 24-hour mean systolic blood pressure (black points), and 7-day mean systolic blood pressure (red line) at rest in 21 healthy subjects ordered according to the SBP values.*

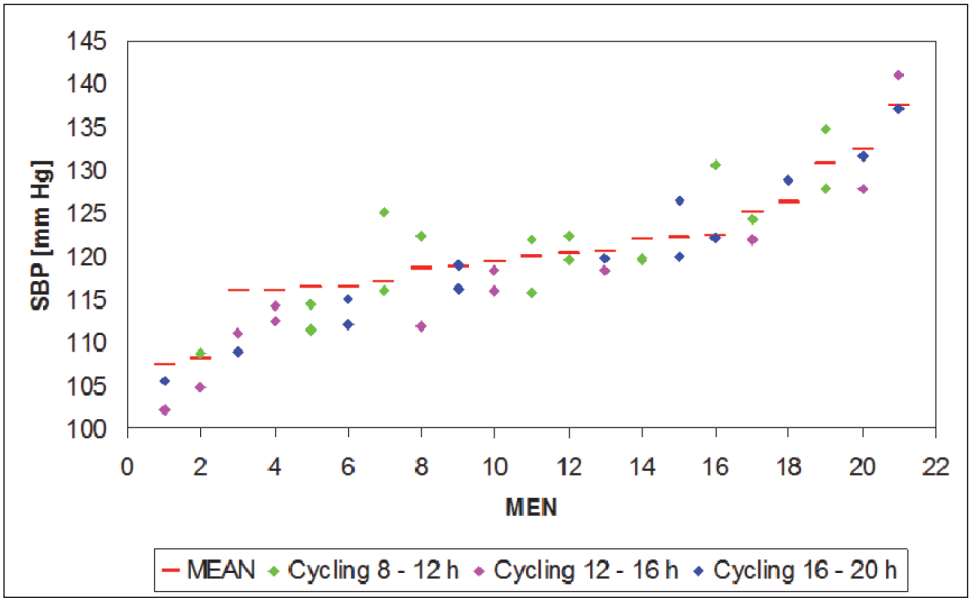


Figure 3 *The variability of 24-hour means of systolic blood pressure (points in color) and 7-day mean systolic blood pressure (red line) in the days with exercise in 21 healthy subjects.*

The variability of 24/hour means of diastolic blood pressure values during 7-day monitoring is seen in Fig. 4 at rest and in Fig. 5 in the days with exercise.

Mean 7-day values of DBP (subject No 1: 61 mmHg, subject No 21: 85 mmHg; median value: 70 mmHg).

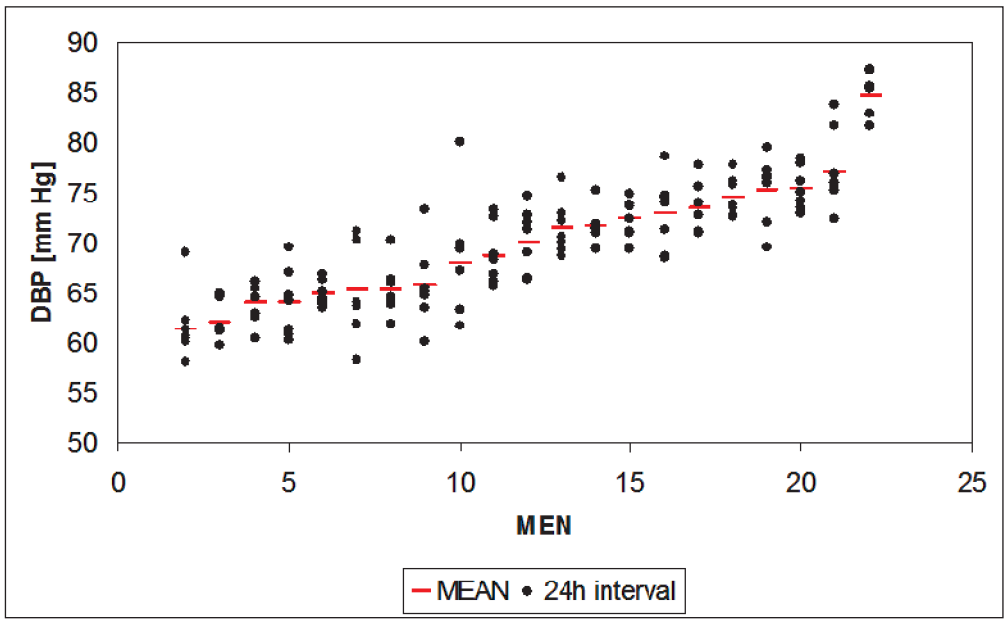


Figure 4 *The variability of 24-hour mean diastolic blood pressure (black points), and 7-day mean diastolic blood pressure (red line) at rest in 21 healthy subjects*

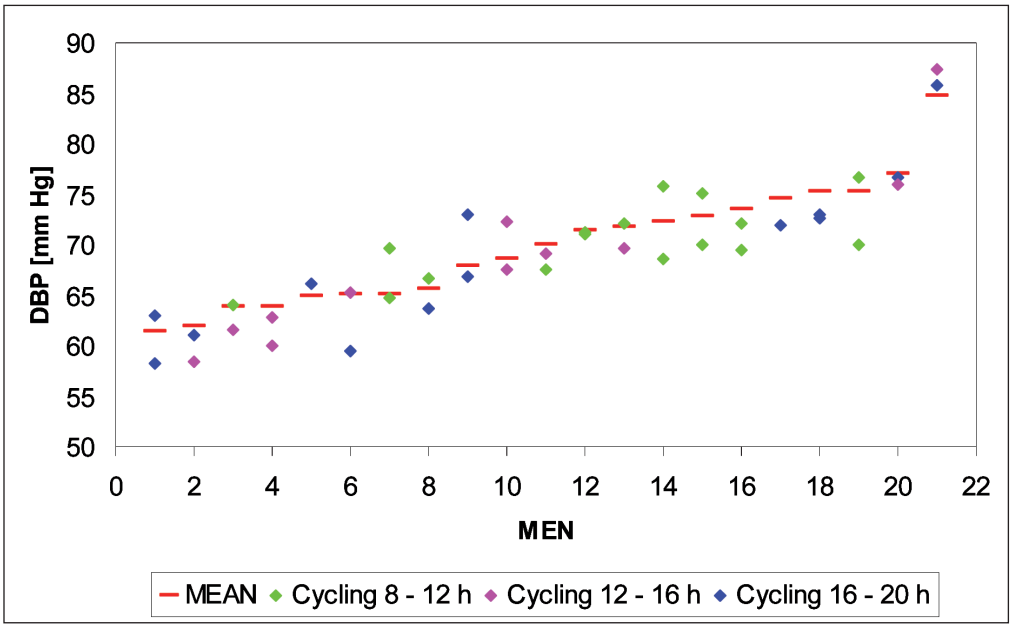


Figure 5 *The variability of 24-hour mean diastolic blood pressure (points in color), and 7-day mean diastolic blood pressure (red line) during exercise in 21 healthy subjects.*

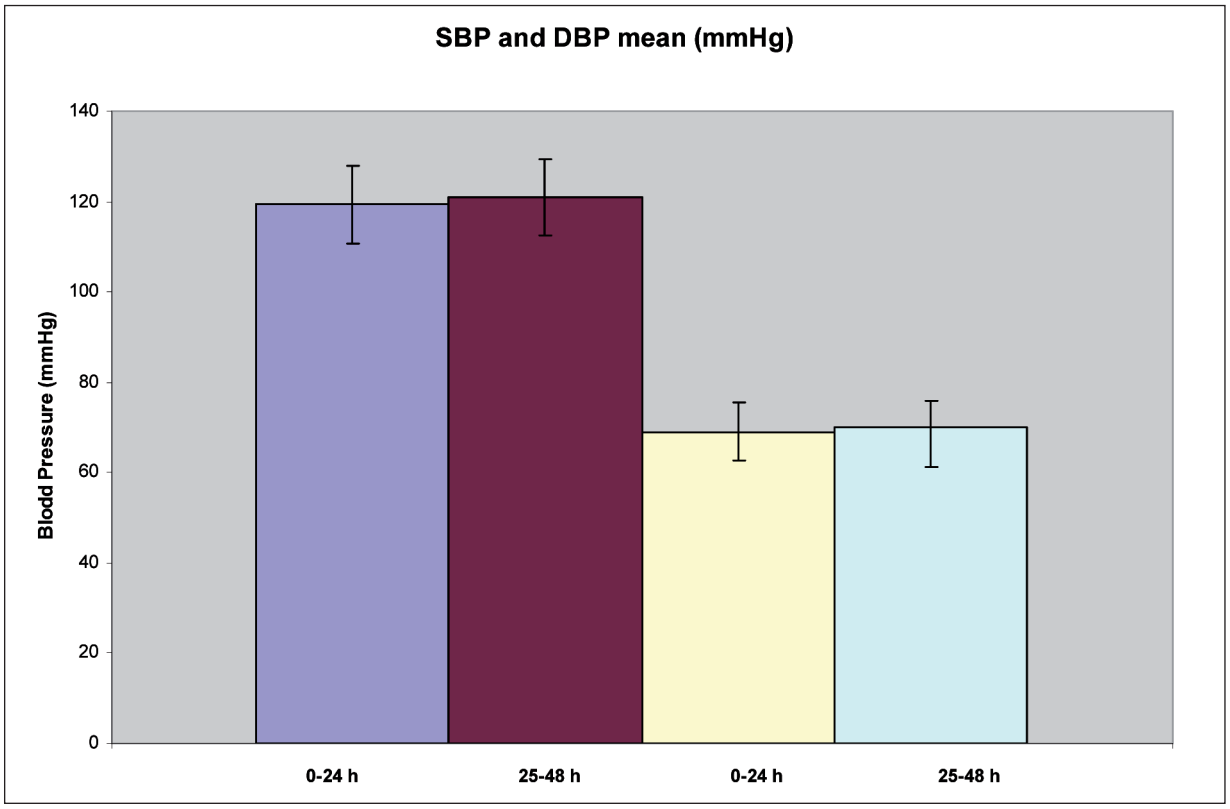


Figure 6 *The 24-hour mean systolic blood pressure in the day with exercise (0-24 h) and in the day without exercise (25-48 h) and the 24-hour mean diastolic blood pressure in the day with exercise (0-24 h) and in the day without exercise (25-48 h) in 21 healthy subject.*

Fig. 6 shows the 24-hour mean systolic blood pressure in the day with exercise (0-24 h) and in the day without exercise (25-48 h) and the 24-hour mean diastolic blood pressure in the day with exercise (0-24 h) and in the day without exercise (25-48 h) in 21 healthy subject. In mean values of systolic blood pressure and diastolic blood pressure are not differences in the days (0-24 h) with exercise and in the days (25-48 h) without exercise.

For comparison of 24-hour means and 7-day mean in SBP and DBP we constructed the Bland-Altman plots of systolic and diastolic blood pressure in the day with exercise and without exercise in 21 subjects; each subjects was exercising in two days during the week of seven day ambulatory blood pressure monitoring (19).

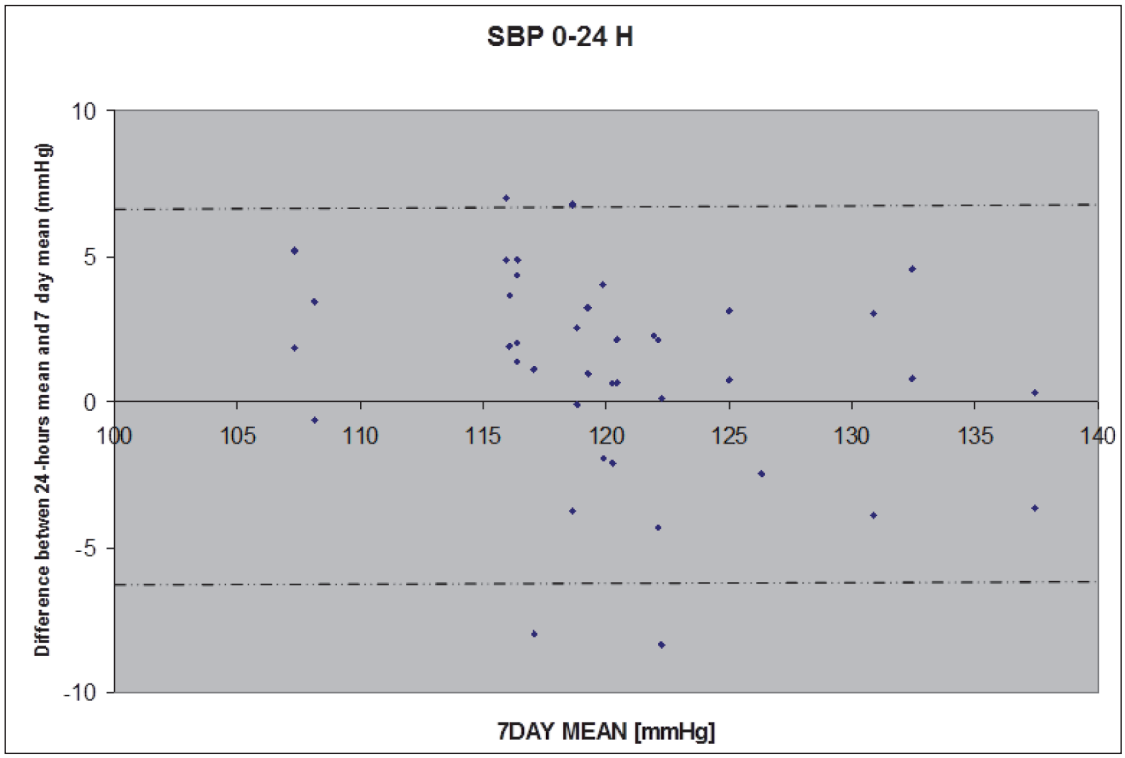


Figure 7 *Bland-Altman plot. Comparisons between 7-days mean and 24-hour means systolic blood pressure in the days with exercise. The ±1.96 standard deviations of the difference in 24-hour means of SBP (0-24 h) was 6.85 mmHg and is indicated in the figure (dashed line).*

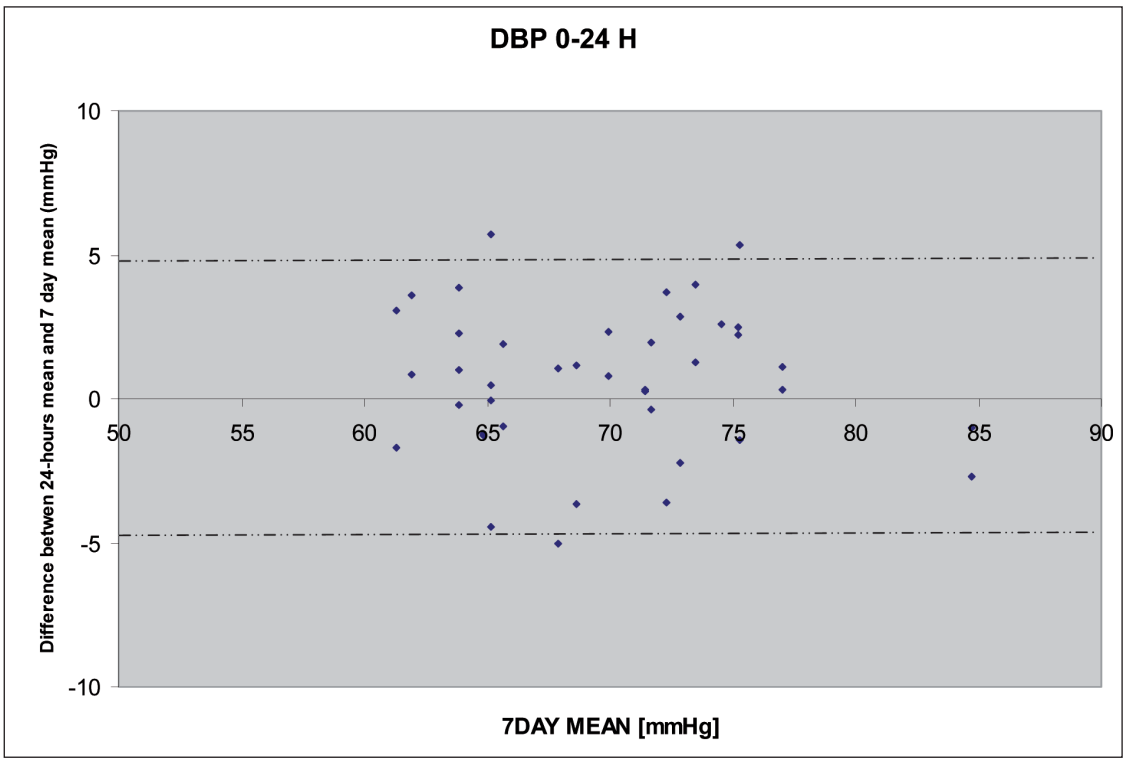


Figure 8 *Bland-Altman plot. Comparisons between 7-days mean and 24-hour means diastolic blood pressure in the days with exercise. The ±1.96 standard deviations of the difference in DBP (0-24 h) was 4.95 mmHg and is indicated in the figure (dashed line).*

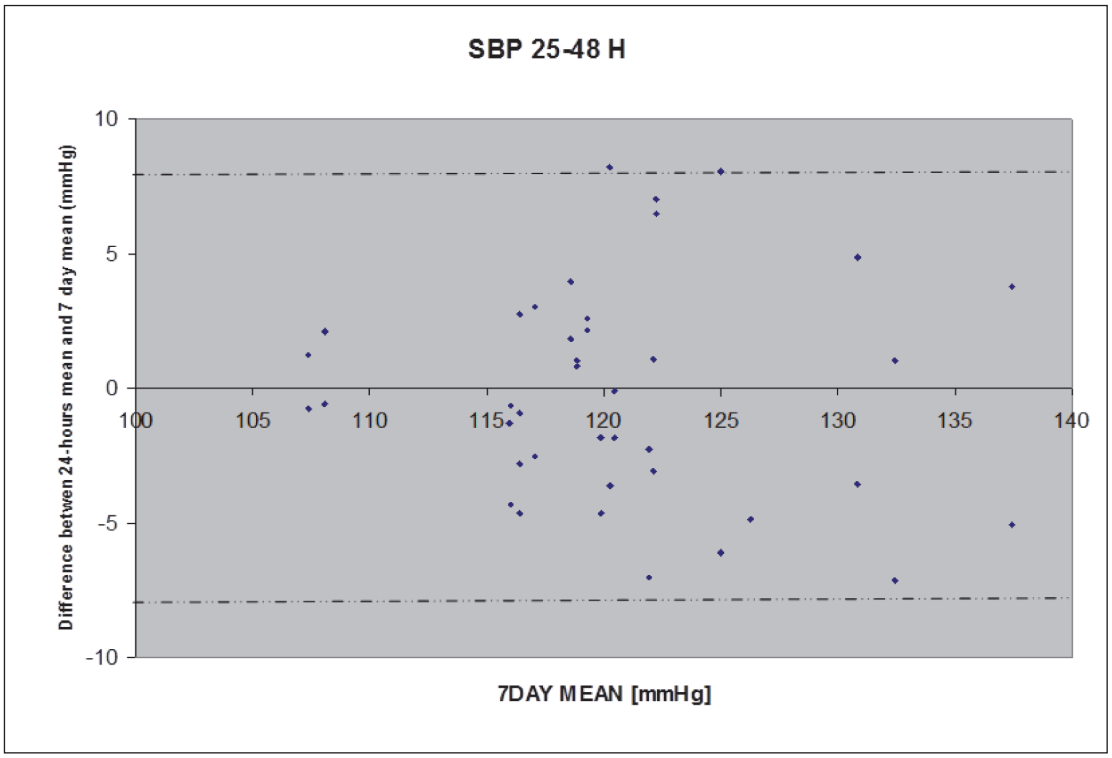


Figure 9 *Bland-Altman plot. Comparisons between 7-days mean and 24-hour means systolic blood pressure in the days without exercise (25-48h). The ±1.96 standard deviations of the difference in SBP (25-48 h) was 8.59 mmHg and is indicated in the figure (dashed line).*

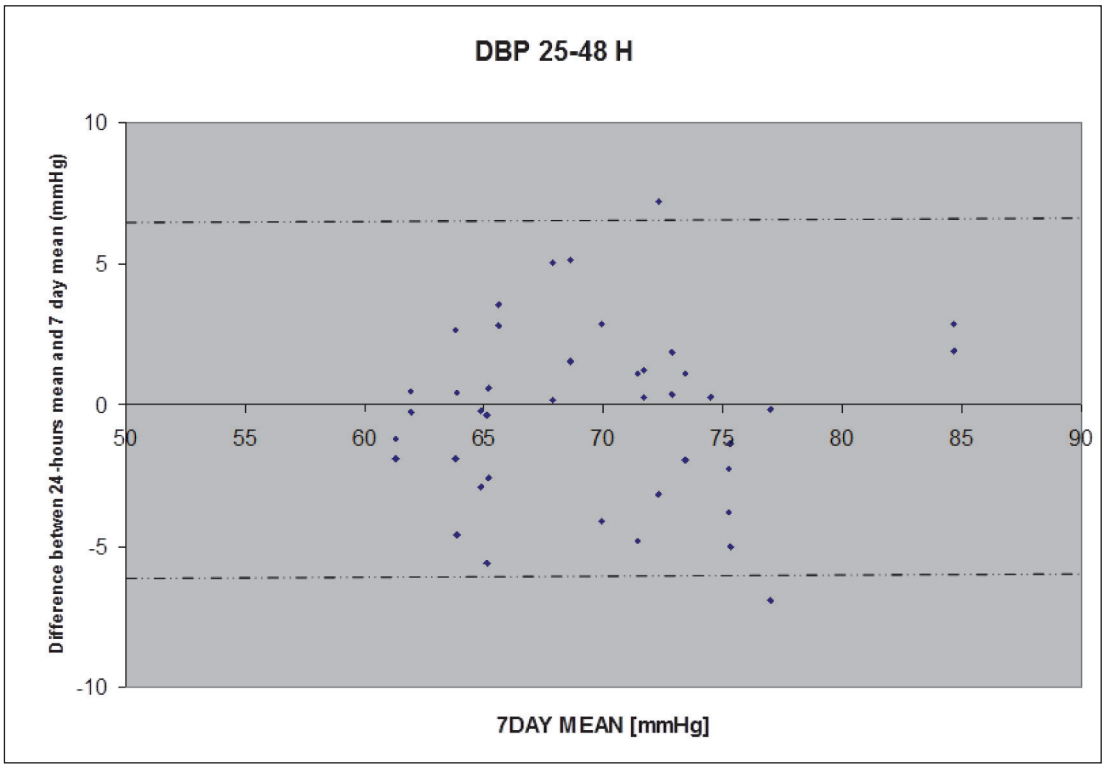


Figure 10 *Bland-Altman plot. Comparisons between 7-days mean and 24-hour means diastolic blood pressure in the days without exercise (25-48 h). The ±1.96 standard deviations of the difference in DBP (25-48 h) was 6.06 mmHg and is indicated in the figure (dashed line).*

Discussion

Seven-day ambulatory blood pressure monitoring demonstrates large day-to-day variability of blood pressure at rest. Our studies indicate with ambulatory blood pressure monitoring, that longer monitoring, preferably for 7 days, is recommended (20-26).

In our presentation we show a large variability of 24-hour profile at rest in 5 days and in 2 days with exercise in healthy subjects and in patients.

The variability in healthy subjects (day-to-day in 24-hour profile) was presented at rest and during exercise in 21 healthy subjects. During exercise, even that these data were measured only 2 days, we observed similar variability as it was described in the days without exercise.

It is clear that 24-hour monitoring is better than a single or a few measurements, but for avoiding misdiagnosis is not sufficient. Our results show that 7-day blood pressure monitoring is best way for blood pressure real values and it is in agreement with the results of BIOCOS project, under the guidance of late professor Halberg and professor Cornélissen (27-28).

Self-measurement of blood pressure at home can also provide very important blood pressure values that, when averaged over a period of a few days, are more reproducible and predict the presence and progression of organ damage as well as the risk of cardiovascular events better than office values. Home blood pressure measurement for suitable periods can be recommended before and during treatment also because this relatively cheap procedure may improve patient adherence to treatment.

Conclusion

From the results we can conclude that 24-hours blood pressure profile at rest and during exercise from day-to-day vary in healthy subjects and we have not found any differences in the day with exercise and in the day without exercise.

References

1. Halberg F, Cornélissen G, Siegelova J, Fiser B, Dobsak P, Kenner T, Placheta Z, Dusek J, Homolka P, Al-Kubati M, Schwartzkopff O, Blagonravov MB, Chibisov SM, Agarwal RK. Blood pressure or, rather, blood pressure variability disorders, VVDs, discussed in Brno on October 6, 2008. Bulletin of People‘s Friendship University of Russia: Series Medicine 2008; (7): 26-30.
2. Halberg F, Cornélissen G, Otsuka K, Sanchez de la Peña S, Schwartzkopff O, Watanabe Y, Pati AK, Wall DG, Delmore P, Borer K, Beaty LA, Nolley ES, Adams C, Siegelova J, Homolka P, Dusek J, Fiser B, Prikryl P. Why and how to implement 7-day/24-hour blood pressure monitoring? Int J Geronto-Geriatrics 2005; 8 (1): 1-31. [Dated 2005 but published in June 2008.]
3. Halberg F, Cornélissen G, Otsuka K, Watanabe Y, Singh RB, Revilla M, Sanchez de la Pena S, Gonzalez C, Siegelova J, Homolka P, Dusek J, Zeman M, Singh RK, Johnson D, Fiser B. Home C-ABPM for preventive and curative health care and transdisciplinary science. World Heart J 2008; 1 (3): 233-261.
4. Halberg F, Cornélissen G, Siegelova J, Fiser B, Dobsak P, Kenner T, Placheta Z, Dusek J, Homolka P, Al-Kubati M, Schwartzkopff O, Blagonravov MB, Chibisov SM, Agarwal RK. Blood pressure or, rather, blood pressure variability disorders, VVDs, discussed in Brno on October 6, 2008. Bulletin of People‘s Friendship University of Russia: Series Medicine 2008; (7): 26-30.
5. Halberg F, Schwartzkopff O, Cornélissen G, Hardeland R, Müller-Bohn T, Katinas G, Revilla MA, Beaty L, Otsuka K, Jozsa R, Zeman M, Csernus V, Hoogerwerf WA, Nagy G, Stebelova K, Olah A, Singh RB, Singh RK, Siegelova J, Dusek J, Fiser B, Czaplicki J, Kumagai Y, Chibisov SM, Frolov VA. Vaskuläres Variabilitäts-Syndrom (VVS) und andere Chronomik 2005-2007. In: Hardeland R,

ed. Sonderdruck aus Abhandlungen der Leibniz-Sozietät der Wissenschaften, Band 23: Facetten der Chronobiologie. Berlin: trafo verlag; 2008. p. 89-154.

6. Siegelova J, Fiser B, Havelkova A, Dobsak P, Dusek J, Pohanka M, Cornélissen G, Halberg F. Ambulatory arterial stiffness index in patients monitored for 6 consecutive days. In: Halberg F, Kenner T, Fiser B, Siegelova J, eds. Proceedings, Noninvasive Methods in Cardiology, Brno, Czech Republic, October 4-7, 2008. p. 233-237. Proceedings volume downloadable free of charge from: http://www.med.muni.cz/index.php?id=1376
7. Siegelova J, Fiser B, Havelkova A, Dobsak P, Pohanka M, Dusek J, Cornélissen G, Halberg F. Seven-day ambulatory blood pressure monitoring and ambulatory arterial stiffness index. Scripta medica (Brno) 2008; 81 (3): 181-184.
8. Halberg F, Cornélissen G, Otsuka K, Siegelova J, Fiser B, Dusek J, Homolka P, Sanchez de la Pena S, Singh RB, BIOCOS project. Extended consensus on means and need to detect vascular variability disorders (VVDs) and vascular variability syndromes (VVSs). Leibniz-Online Nr. 5, 2009 (http://www.leibniz-sozietaet.de/journal). 35 pp, AND World Heart J.
9. E O'Brien, J Sheridan and K O'Malley, Dippers and non-dippers, Lancet 332 (1988), p.397.
10. T Ohkubo, A Hozawa and J Yamaguchi et al., Prognostic significance of the nocturnal decline in blood pressure in individuals with and without high 24-h blood pressure: the Ohasama study, J Hypertens 20 (2002), pp. 2183–2189.
11. TW Hansen, J Jeppesen, F Rasmussen, H Ibsen and C Torp-Pedersen, Ambulatory blood pressure monitoring and mortality: a population-based study, Hypertension 45 (2005), pp. 499–504.
12. E Ingelsson, K Björklund, L Lind, J Ärnlöv and J Sundström, Diurnal blood pressure pattern and risk of congestive heart failure, JAMA 295 (2006), pp. 2859–2866.
13. G Mancia, R Facchetti, M Bombelli, G Grassi and R Sega, Long-term risk of mortality associated with selective and combined elevation in office, home, and ambulatory blood pressure, Hypertension 47 (2006), pp. 846–853.
14. P Verdecchia, C Porcellati and G Schillaci et al., Ambulatory blood pressure. An independent predictor of prognosis in essential hypertension, Hypertension 24 (1994), pp. 793–801.
15. José Boggia, Yan Li, Lutgarde Thijs et all. Prognostic accuracy of day versus night ambulatory blood pressure: a cohort study. Lancet 370 (2007), p.1219-1229.
16. The Task Force for the Management of Arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). 2007 Guidelines for the Management of Arterial Hypertension. J Hypertension 2007, 25:1105-1187.
17. J. Siegelová, J. Dusek, B. Fiser, P. Homolka, P. Vank, M. Kohzuki, G. Cornellisen, F. Halberg. Relationship between circadian blood pressure variation and age analyzed from 7-day ambulatory monitoring. J Hypertension, 2006, vol. 24, Suppl.6, p. 122.
18. Redón J, Vicente A, Alvarez V et. al. Circadian rhythm variability of arterial pressure: methodological aspects for the measurement. Med Clin, 1999 112:258-289.
19. Altman DG, Bland JM. Measurement in medicine: the analysis of method comparison studies. The Statistician 1983; 32, 307-317.
20. Cornélissen G, Delcour A, Toussain G et al. Opportunity of detecting pre-hypertension: world wide data on blood pressure overswinging. Biomedicine and Pharmacotherapy 59 (2005) S152-S157.
21. Management Committee, Australian National Blood Pressure Study: The Australian Therapeutic Trial in Mild Hypertension. Lancet 1980, (June 14)i(8184):1261-7.

22. Zarnke KB, Feagan BG, Mahon JL et al. A randomized study comparing a patient-directed hypertension management strategy with usual office-based care. Am J. Hypertension 1997, 10:58-67.

23. Halberg F,Cornelissen G,Hillman D,Beaty lA,Hong S, Schwarzkoppf O, Watanabe Y,Otsuka K,Siegelova J.Chronobiologically interpreted ambulatory blood pressure monitoring in health and disease. Global Adv Health Med 2012;1(2):66-123

24. Halberg F, Cornelissen G, Katinas GS, Watanabe Y, Siegelova J. Follow-up to the Cornelissen-series: Inheritance of form in space from parents and of form in time from the cosmos: From Brno´s Mendel and Siegelova, respectively. Cosmic inheritance rules.in eds. 3.Halberg F, Kenner T,Fiser B, Siegelova J. Noninvasive methods in cardiology 2009.Masaryk University, Brno. 2009,p.13-39,ISBN 978-80-7013-501-3.

25. Siegelova J, Fiser B. Day-today variability of 24-h mean values of SBP and DBP in patients monitored for 7 consecutive days. J Hypertens,2011;29,4:818-819.

26. Halberg F, Cornelissen G, Otsuka K, Siegelova J, Fiser B, Dusek J, Homolka P, Sanches de la Pena S, Singh RB and the BOCOS project. Extended consensus on means and need to detect vascular variability disorders and vascular variability syndrome. World Heart J 2010; 2,4:279-305 (cf. Leibnitz-online Nr.5 ,2009, http:www2hu-berlin.de/Leibnitz-sozietaet/journal/archive _5_09.html. 35 pp).

27. Halberg F, Cornelissen G, Dusek J, Kenner B, Kenner A, Schwarzkoppf O, Siegelova J. Bohumil Fiser (*22.10.1943-21.3.2011):Chronobiologist, Emeritus Head of the Physiology Department at Masaryk University (Brno, Czech Republic), Czech Minister of Health, an d Executive Board Member of World Health Organization: His Legacies for Public and Personal Health Care. World Heart J 2011; 3,1:63-77.

28. Siegelova J, Dusek J, Otsuka K, Cornélissen G. Mathematical Model of Cardiovascular Disease Risk Based on Vascular Variability Disorders. World Heart J, 2014, Vol. 6, No 1, p. 57-62. ISSN 1556-4002.

SEVEN DAY AMBULATORY BLOOD PRESSURE MONITORING: CIRCADIAN AND CIRCASEPTAN RHYTHM IN ADULTS

JARMILA SIEGELOVA, GERMAINE CORNÉLISSEN*, ALENA HAVELKOVA, JIŘÍ DUSEK, PAVEL VANK, PETR DOBSAK

*Masaryk University, Brno, Czech Republic, *University of Minnesota, Minneapolis, MN, USA*

Introduction

The clinical everyday management of blood pressure (BP) and heart rate (HR) can be greatly improved by the mapping of time structures in home ambulatory BP and HR assessment Thereby, we change focus from the BP and the HR to the dynamics of these variables. This change is achieved by computer-implemented chronomics, the mapping of chronomes, consisting of cyclicities (our concern herein) along with chaos and trends, in the service of cardiologists, general health care providers and the educated public. We here further illustrate the yield of chronomics in research on long BP and HR series covering years, some several decades long, and on archives of human sudden cardiac death and coronary heart disease (1-8).

Variabilities, a formidable foe and confounder (9-15) when ignored, can be computer-resolved into chronomes - clinically informative time structures (16-21). As yet, any variability is currently largely ignored in countries with resources. There, research on high BP is largely dominated by the pharmaceutical industry and the National Institutes of Health, providing funds for clinical trials and guidelines derived from these trials are used for the public at large (22-25). At entry into a trial, the BP of very many adults is usually measured without any recording of timing, without any specific consideration of age group or ethnicity, and often ignoring gender even at the most renowned clinics (22-25). Measurements may be made only on a few occasions, if not only once.

A chronobiologic approach to variability by sphygmochrons is already implemented in locations with limited resources, such as Armenia, China and India, with measurements beyond 24 hours, the target being 7-day records.

In cooperation with Halberg Chronobiology Center of University of Minnesota USA, between the years 1988 and 2014, the Brno chronobiology team consisting of Prof. Fiser, Dr. Dusek and Prof. Siegelova collected 75 029 sets of seven day ambulatory blood pressure monitoring and data from blood pressure and heart rate measurements were in the following day send and analyzed by Prof. G. Cornélissen from University of Minnesota, USA.

Aim

From these data the aim of the present publication analyses two samples: one sample of measurement on healthy subjects and another on patients with essential hypertension and healthy subjects.

Subjects and methods

In 145 healthy subjects blood pressure and heart rate profiles at 30-min intervals from seven day ambulatory blood pressure monitoring were analyzed. The oscillometric method was used for blood pressure monitoring every hour. From 7-day ambulatory blood pressure monitoring in adults we will assess

the chronome of 7-day/24-hour blood pressure (BP) and heart rate (HR) using Halberg cosinor analyses (Fig. 1). The values of systolic blood pressure (SBP), diastolic blood pressure (DBP) and heart rate (HR) were analyzed using the computation of autocorrelation functions and power spectral density.

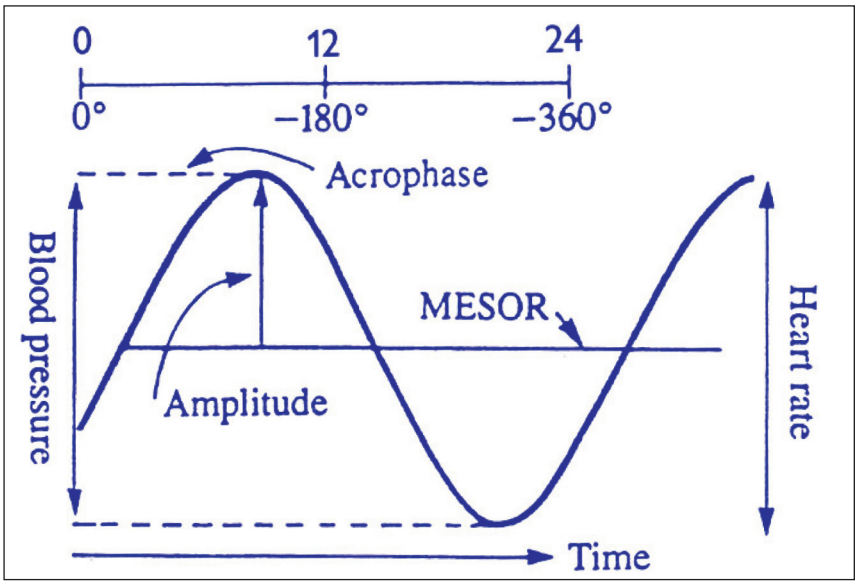
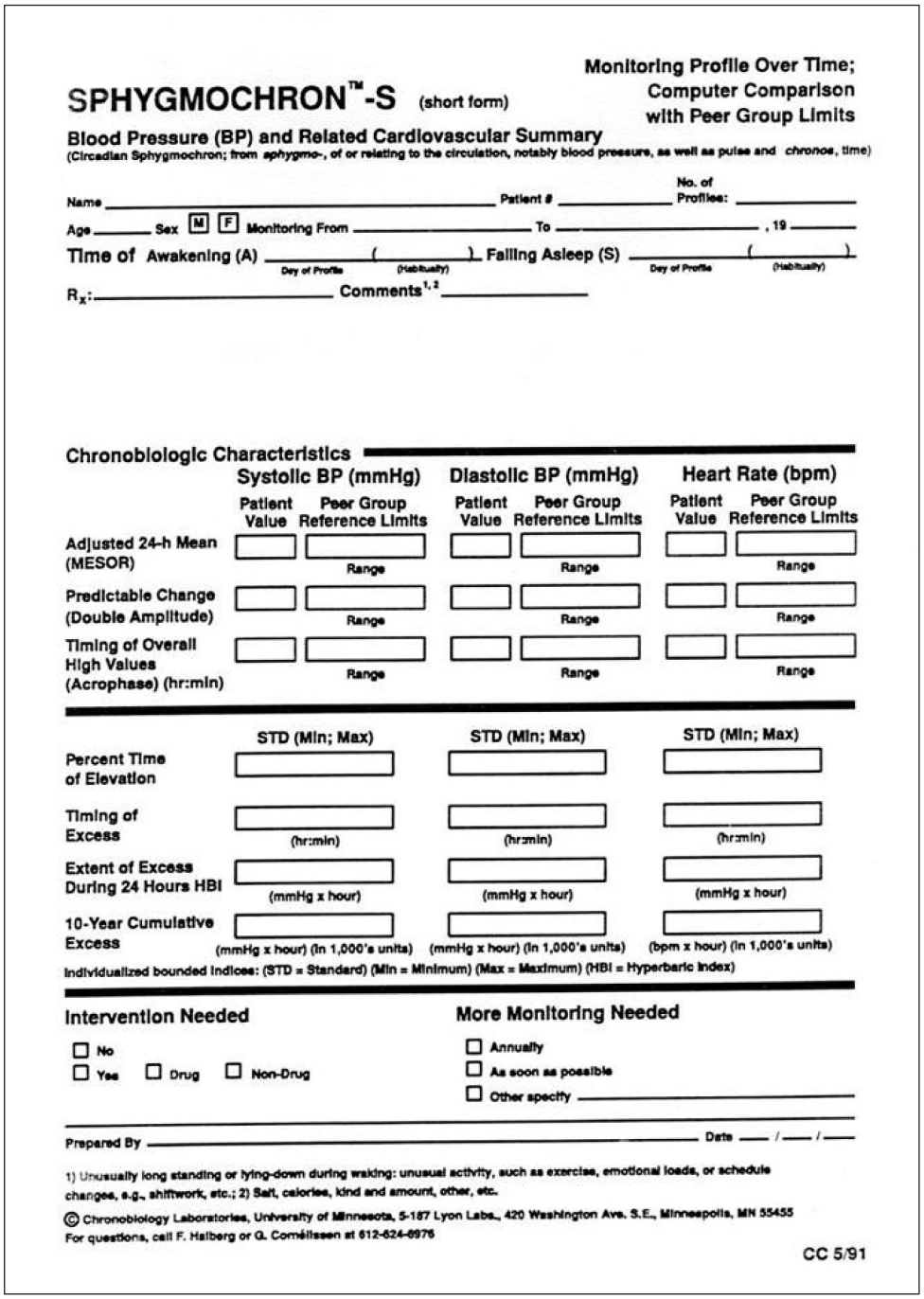


Figure 1 *Halberg cosinor analyses (1)*



SPHYGMOCHRON™-S (short form)

Monitoring Profile Over Time; Computer Comparison with Peer Group Limits

Blood Pressure (BP) and Related Cardiovascular Summary

(Circadian Sphygmochron; from *sphygmo-*, of or relating to the circulation, notably blood pressure, as well as pulse and *chronos*, time)

Name _____ Patient # _____ No. of Profiles: _____

Age _____ Sex [M] [F] Monitoring From _____ To _____, 19 _____

Time of Awakening (A) _____ (Day of Profile) _____ (Habitually) Falling Asleep (S) _____ (Day of Profile) _____ (Habitually)

R_x: _____ Comments[1,2] _____

Chronobiologic Characteristics

	Systolic BP (mmHg)		Diastolic BP (mmHg)		Heart Rate (bpm)	
	Patient Value	Peer Group Reference Limits	Patient Value	Peer Group Reference Limits	Patient Value	Peer Group Reference Limits
Adjusted 24-h Mean (MESOR)		Range		Range		Range
Predictable Change (Double Amplitude)		Range		Range		Range
Timing of Overall High Values (Acrophase) (hr:min)		Range		Range		Range

	STD (Min; Max)	STD (Min; Max)	STD (Min; Max)
Percent Time of Elevation			
Timing of Excess	(hr:min)	(hr:min)	(hr:min)
Extent of Excess During 24 Hours HBI	(mmHg x hour)	(mmHg x hour)	(mmHg x hour)
10-Year Cumulative Excess	(mmHg x hour) (ln 1,000's units)	(mmHg x hour) (ln 1,000's units)	(bpm x hour) (ln 1,000's units)

Individualized bounded indices: (STD = Standard) (Min = Minimum) (Max = Maximum) (HBI = Hyperbaric Index)

Intervention Needed

☐ No
☐ Yes ☐ Drug ☐ Non-Drug

More Monitoring Needed

☐ Annually
☐ As soon as possible
☐ Other specify _____

Prepared By _____ Date ___ / ___ / ___

1) Unusually long standing or lying-down during waking: unusual activity, such as exercise, emotional loads, or schedule changes, e.g., shiftwork, etc.; 2) Salt, calories, kind and amount, other, etc.

For questions, call F. Halberg or G. Cornélissen at 612-624-6976

CC 5/91

Figure 2 *Sphygmochron, the computer-generated form set to summarize results from the combined parametric and nonparametric assessment of the blood pressure and heart rate profile. Results from both approaches are compared with reference values specified by gender and age, given in boxes next to the subject estimates for the rhythm characteristics.*

Results

Measurement on healthy subjects

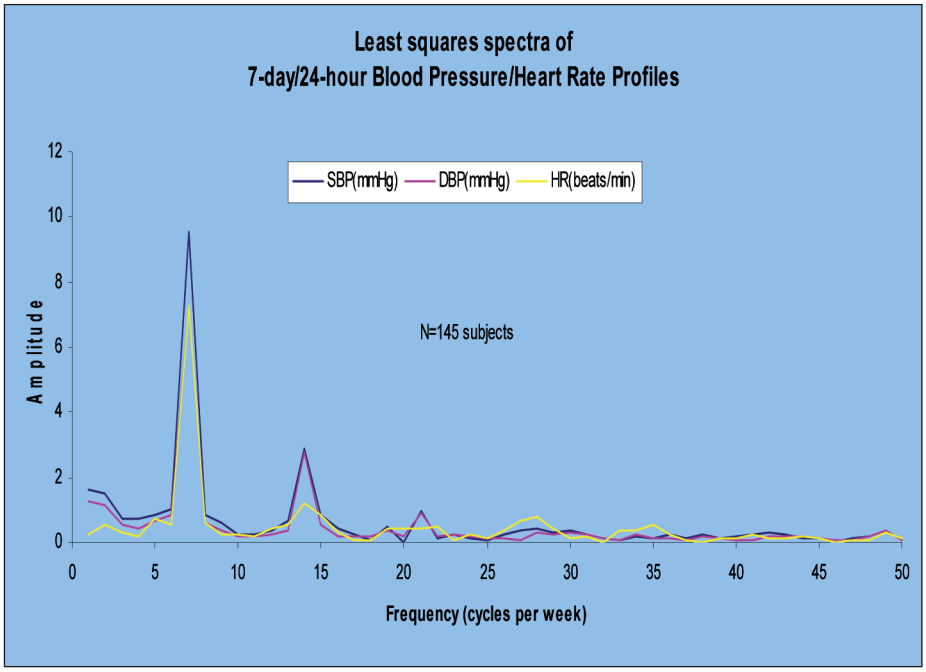


Figure 3 *Power spectra of heart rate (yellow), systolic (blue) and diastolic (red) blood pressure of 145 healthy subjects. Spectral peaks correspond to a component in cycles per week.*

Figure 3 shows Power spectra of heart rate (yellow), systolic (blue) and diastolic (red) blood pressure of 145 healthy subjects. Analyzed special frequencies are circaseptan - 1 (168 h), half week - 2 (84 h), circadian - 7 (24 h), and twelve-hour 14 (12 h). Table 1 shows the corresponding frequencies of the circaseptan, circasemiseptan, circadian, and circasemidian components, respectively. The amplitudes of the circaseptan, circasemiseptan, circadian, and circasemidian components are in Table 1.

Table 1

Freq	Component	SBP-A	DBP-A	HR-A
1	CS	1.609	1.285	0.227
2	CSS	1.498	1.119	0.555
7	CD	9.549	7.258	7.253
14	CSD	2.895	2.775	1.211

In 145 healthy subjects circaseptan component is statistically significant for systolic and diastolic blood pressure but not for heart rate. The half-week is significant for all 3 cardiovascular variables, as is the circadian rhythm. The acrophases are around mid-week and mid-afternoon for the week and day, respectively.

Patients with essential hypertension and healthy subjects

We assess the chronome of 7-day/24-hour blood pressure (BP) and heart rate (HR), blood pressure and heart rate profiles at 30-min intervals from 201 subjects and patients were analyzed by sphygmochron. In

our results blood pressure overswinging (circadian hyper-amplitude-tension, CHAT), was found. Circadian hyper-amplitude-tension, a vascular disease risk factor, was detected in 8.5% (SBP) and 7.0% (DBP) in the population in the Czech Republic (Fig. 4, 5).

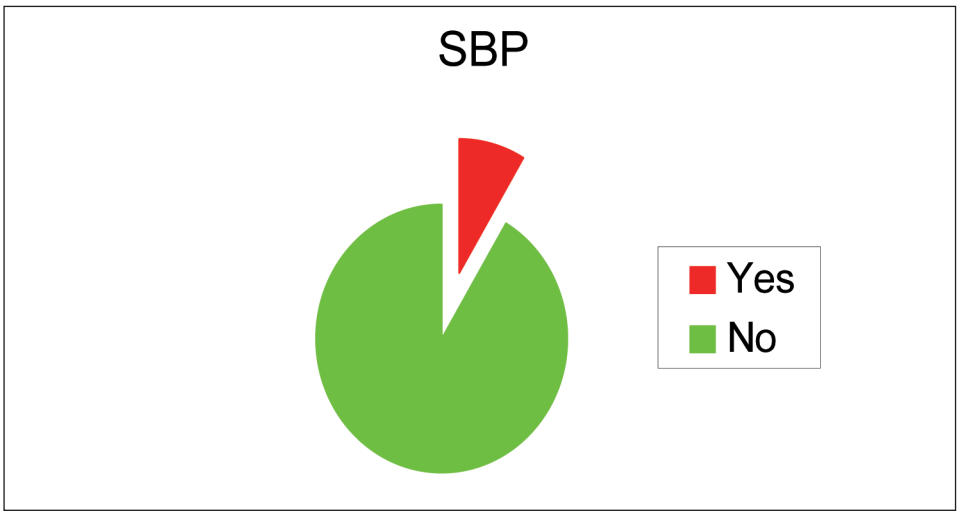


Figure 4 *Circadian hyper-amplitude-tension in systolic blood pressure in 201 subjects*

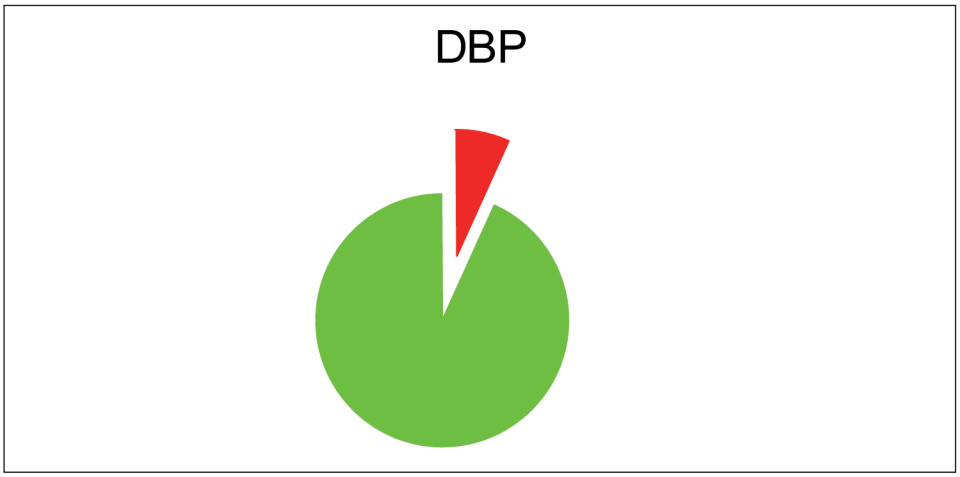


Figure 5 *Circadian hyper-amplitude-tension in diastolic blood pressure in 201 subjects*

Circadian hyper-amplitude-tension (CHAT) was associated with evening exercise in one subject. An other risk factor, increased sympathetic activity, detected as decreased heart rate variability (HRV) occurred in 2.2% of the 201 subjects (Fig. 6).

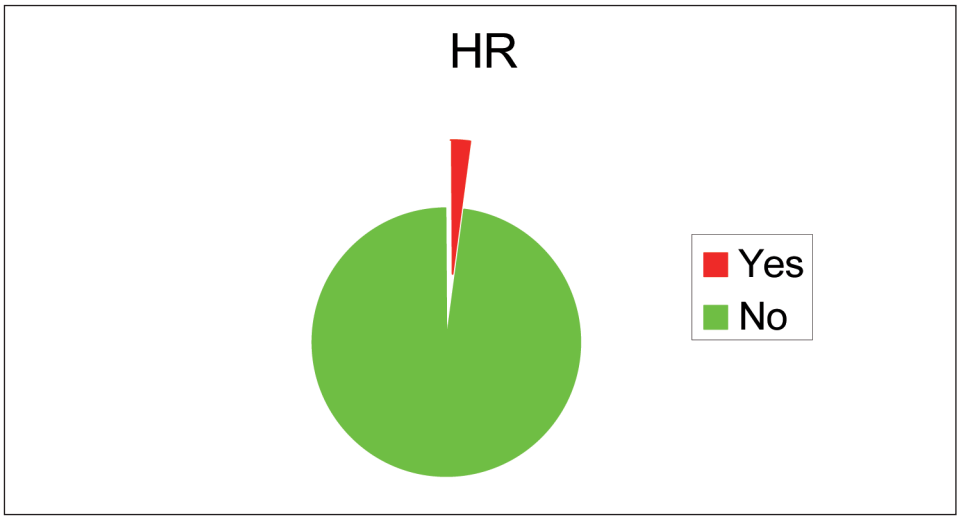


Figure 6 *Decreased heart rate variability of the 201 subjects*

Table 2 *Circadian, circaseptan and circasemidian rhythms in systolic blood pressure*

SBP	Age	M	CS-PR	CS-A	CSS-PR	CSS-A	CD-PR	CD-A	CSD-PR	CSD-A	CS-A/CD-A	LogAratio
Age	1.000	**<0.001**	**0.003**	**0.001**	0.119	**0.003**	**0.038**	0.863	**0.009**	**0.002**	**0.000**	**0.000**
M	**0.348**	1.000	0.457	0.130	0.227	0.081	**0.010**	0.860	0.070	**0.009**	0.057	0.072
CS-PR	**0.221**	0.056	1.000	**<0.001**	**<0.001**	**<0.001**	0.476	0.682	0.622	0.602	**<0.001**	**<0.001**
CS-A	**0.238**	0.114	**0.790**	1.000	**<0.001**	**<0.001**	0.769	0.067	0.605	0.087	**<0.001**	**<0.001**
CSS-PR	0.117	0.091	**0.362**	**0.501**	1.000	**<0.001**	0.389	0.572	0.171	0.392	**0.001**	**0.007**
CSS-A	**0.223**	0.131	**0.292**	**0.514**	**0.853**	1.000	0.587	**0.004**	0.124	0.346	**0.033**	**0.011**
CD-PR	**-0.156**	**-0.192**	-0.054	0.022	0.065	0.041	1.000	**<0.001**	**0.000**	**0.001**	**<0.001**	**<0.001**
CD-A	-0.013	-0.013	-0.031	0.138	0.043	**0.214**	**0.834**	1.000	**<0.001**	0.106	**<0.001**	**<0.001**
CSD-PR	**0.194**	0.136	-0.037	-0.039	-0.103	-0.116	**-0.287**	**-0.317**	1.000	**<0.001**	0.159	0.139
CSD-A	**0.227**	**0.195**	0.039	0.129	-0.065	0.071	**-0.256**	-0.122	**0.862**	1.000	0.177	**0.030**
CS-A/CD-A	**0.282**	0.143	**0.531**	**0.512**	**0.245**	**0.160**	**-0.363**	**-0.373**	0.106	0.102	1.000	**<0.001**
LogAratio	**0.279**	0.135	**0.698**	**0.643**	**0.203**	**0.191**	**-0.482**	**-0.422**	0.111	**0.162**	**0.756**	1.000

Table 3 *Circadian, circaseptan and circasemidian rhythms in diastolic blood pressure*

DBP												
	Age	*M*	*CS-PR*	*CS-A*	*CSS-PR*	*CSS-A*	*CD-PR*	*CD-A*	*CSD-PR*	*CSD-A*	*CS-A/CD-A*	*LogAratio*
Age	1.000	**<0.001**	0.409	0.134	0.389	0.334	**0.045**	0.113	0.339	0.990	**0.009**	**0.008**
M	**0.386**	1.000	0.129	**0.013**	**0.031**	**0.026**	0.065	**0.019**	0.550	0.922	0.089	0.581
CS-PR	0.062	0.114	1.000	**<0.001**	**<0.001**	**<0.001**	0.970	0.481	0.179	0.721	**<0.001**	**<0.001**
CS-A	0.113	**0.186**	**0.817**	1.000	**<0.001**	**<0.001**	0.216	**0.046**	0.227	0.982	**<0.001**	**<0.001**
CSS-PR	0.065	**0.161**	**0.320**	**0.509**	1.000	**<0.001**	0.993	0.965	0.303	0.665	**<0.001**	**0.000**
CSS-A	0.073	**0.167**	**0.289**	**0.488**	**0.902**	1.000	0.371	0.127	0.414	0.619	**<0.001**	**0.002**
CD-PR	**-0.150**	0.138	-0.003	0.093	0.001	0.067	1.000	**<0.001**	**0.000**	**0.014**	**<0.001**	**<0.001**
CD-A	-0.119	**0.175**	0.053	**0.150**	-0.003	0.115	**0.953**	1.000	**<0.001**	**0.049**	**<0.001**	**<0.001**
CSD-PR	0.072	-0.045	-0.101	-0.091	-0.078	-0.062	**-0.282**	**-0.306**	1.000	**<0.001**	0.685	**0.047**
CSD-A	-0.001	-0.007	-0.027	-0.002	-0.033	0.038	**-0.184**	**-0.148**	**0.918**	1.000	0.969	0.066
CS-A/CD-A	**0.196**	0.128	**0.610**	**0.678**	**0.507**	**0.343**	**-0.332**	**-0.334**	0.031	-0.003	1.000	**<0.001**
LogAratio	**0.197**	0.042	**0.689**	**0.647**	**0.282**	**0.232**	**-0.472**	**-0.437**	**0.149**	0.138	**0.725**	1.000

Table 4 *Circadian, circaseptan and circasemidian rhythms in heart rate variability*

HR	Age	M	CS-PR	CS-A	CSS-PR	CSS-A	CD-PR	CD-A	CSD-PR	CSD-A	CS-A/CD-A	LogAratio
Age	1.000	0.728	0.775	0.506	0.275	0.581	0.838	0.052	0.136	0.557	0.508	0.681
M	0.026	1.000	0.095	0.862	0.882	0.240	**<0.001**	**<0.001**	**0.025**	0.661	0.241	**0.000**
CS-PR	-0.022	-0.125	1.000	**<0.001**	**0.020**	0.137	**0.018**	**0.004**	0.217	0.057	**<0.001**	**<0.001**
CS-A	-0.050	-0.013	**0.778**	1.000	**0.000**	**<0.001**	0.573	0.917	0.208	0.930	**<0.001**	**<0.001**
CSS-PR	0.082	-0.011	**0.174**	**0.284**	1.000	**<0.001**	0.462	0.279	0.375	0.901	0.934	0.060
CSS-A	-0.042	0.088	0.112	**0.318**	**0.802**	1.000	0.402	**0.013**	0.736	0.256	0.228	0.921
CD-PR	-0.015	**0.377**	**-0.176**	-0.043	-0.056	0.063	1.000	**<0.001**	0.149	0.420	**<0.001**	**<0.001**
CD-A	-0.146	**0.382**	**-0.214**	-0.008	-0.082	**0.186**	**0.900**	1.000	**0.018**	0.165	**<0.001**	**<0.001**
CSD-PR	0.112	**-0.167**	-0.093	-0.095	0.067	-0.025	-0.108	**-0.177**	1.000	**<0.001**	0.996	0.339
CSD-A	-0.044	0.033	-0.143	0.007	-0.009	0.086	0.061	0.104	**0.748**	1.000	0.542	0.737
CS-A/CD-A	0.050	-0.088	**0.437**	**0.301**	0.006	-0.091	**-0.321**	**-0.395**	0.000	-0.046	1.000	**<0.001**
LogAratio	0.031	**-0.269**	**0.665**	**0.641**	0.141	0.007	**-0.548**	**-0.605**	0.072	-0.025	**0.669**	1.000

In data from the first 179 profiles of seven day ambulatory blood pressure monitoring, composed from 49 women and 130 men, aged 20-77 years, women had a lower systolic blood pressure MESOR (P=0.026) and a higher heart rate MESOR (P=0.005) than men. Figure 7 and 8 systolic blood pressure MESOR

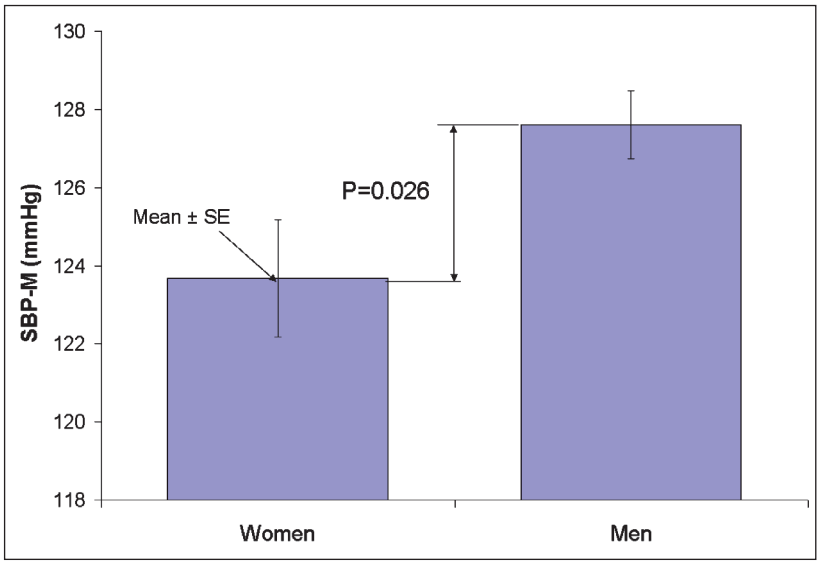


Figure 7 *Systolic blood pressure MESOR in the set of 179 profiles in the Czech Republic*

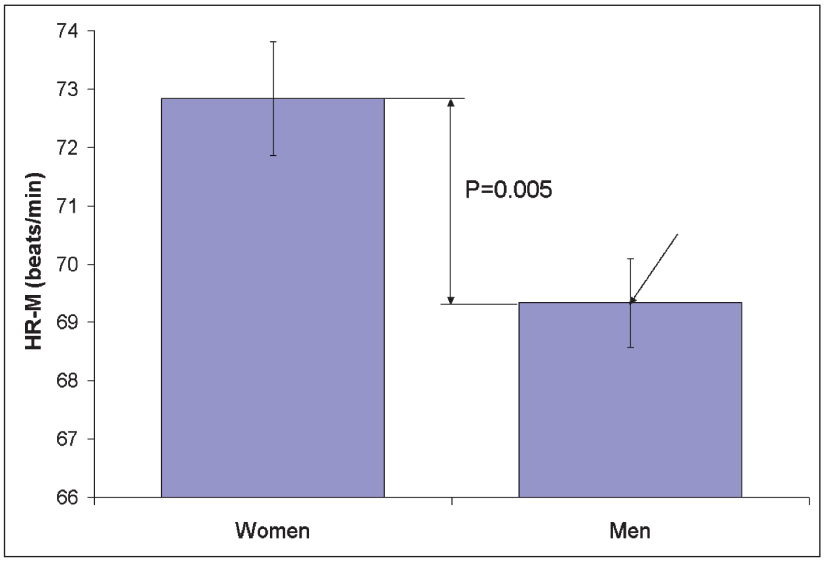


Figure 8 *Heart rate MESOR in the set of 179 profiles in the Czech Republic*

Systolic blood pressure MESOR in the set of 179 profiles in the Czech Republic increased linearly with age (r=0.341, P<0.001). It is documented in Fig. 9.

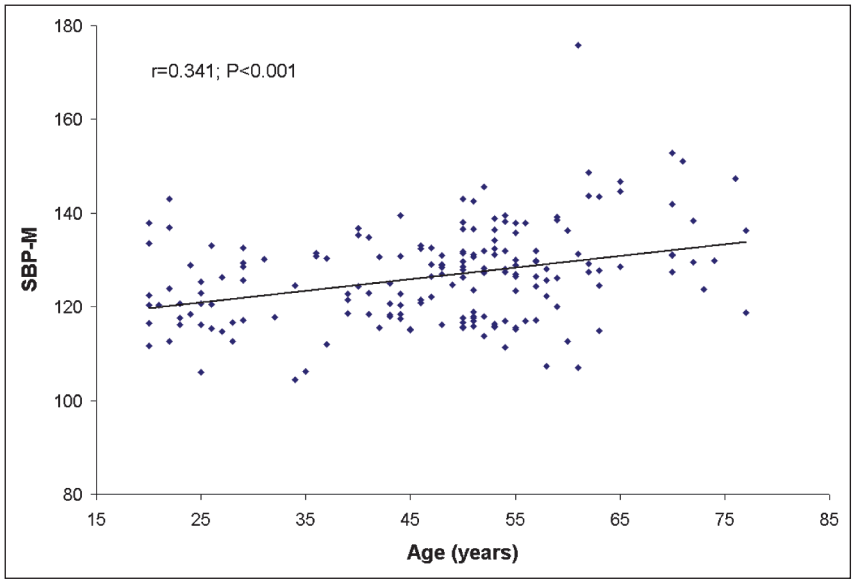


Figure 9 *Relationship between age and systolic blood pressure MESOR in 179 profiles of BP*

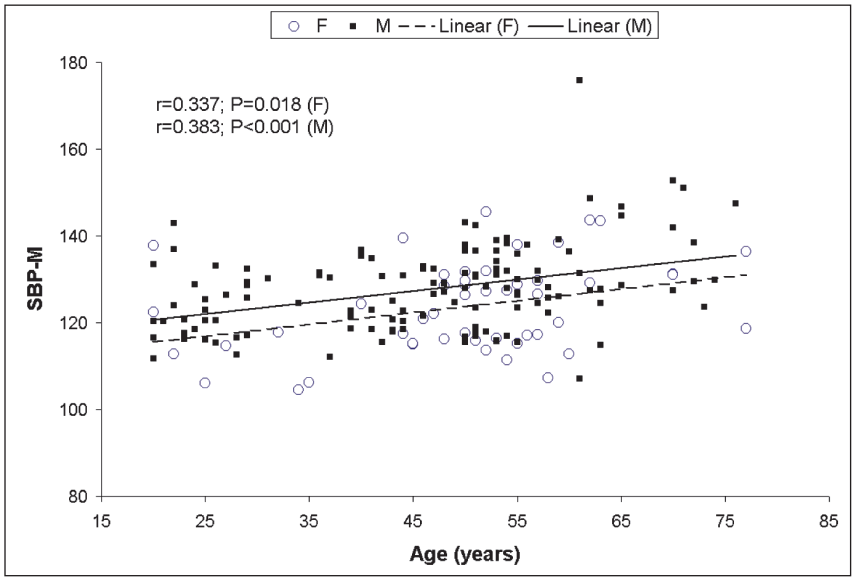


Figure 10 *Relationship between age and systolic blood pressure MESOR in 179 profiles of blood pressure, divided between men and women*

Relationship between age and systolic blood pressure MESOR in 179 profiles of BP, divided between men and women is shown in Fig. 10.

The MESORs of diastolic blood pressure and heart rate and the circadian amplitudes of blood pressure followed a quadratic model, reaching maximal values around 40-60 years of age.

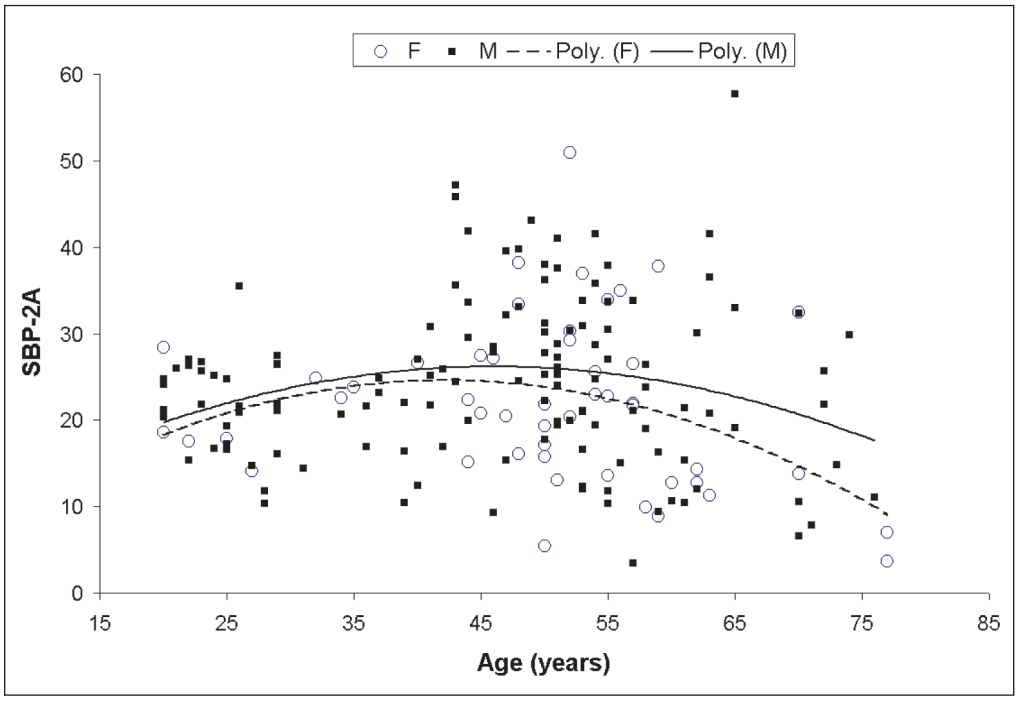


Figure 11 *Systolic blood pressure double amplitude (2A) in 179 profiles of blood pressure, divided between men and women*

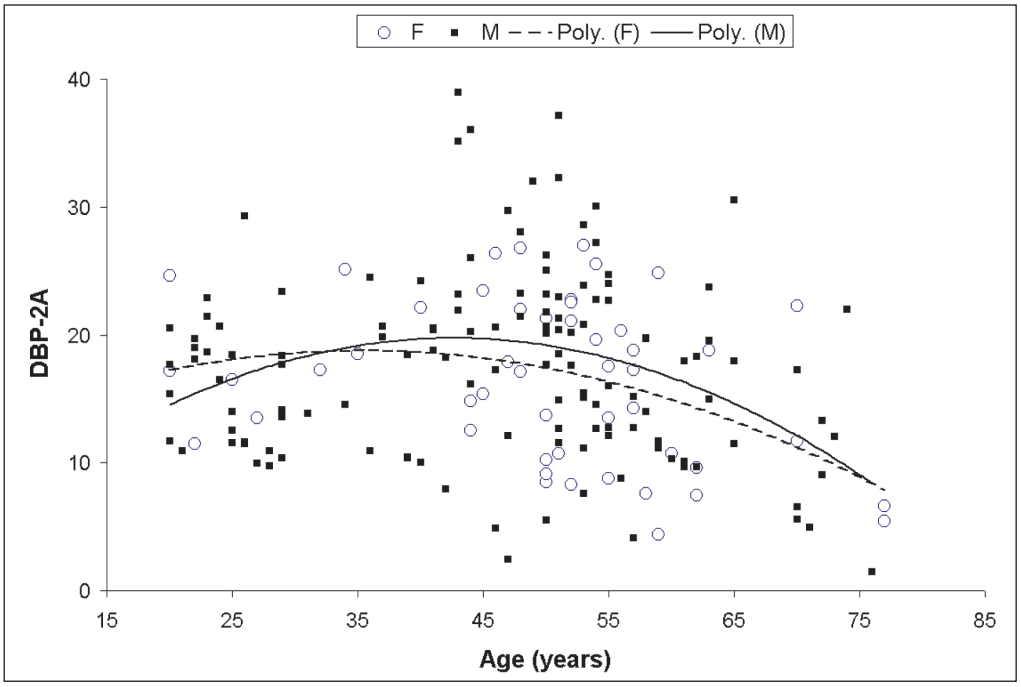


Figure 12 *Diastolic blood pressure double amplitude (2A) in 179 profiles of blood pressure, divided between men and women*

The circaseptan (P=0.092) and circasemidian (P=0.007) amplitudes of SBP were higher in patients than in healthy subjects in the blood pressure profiles in the Czech Republic. Figure 13 and 14 document the circaseptan and circasemidian amplitude of systolic blood pressure.

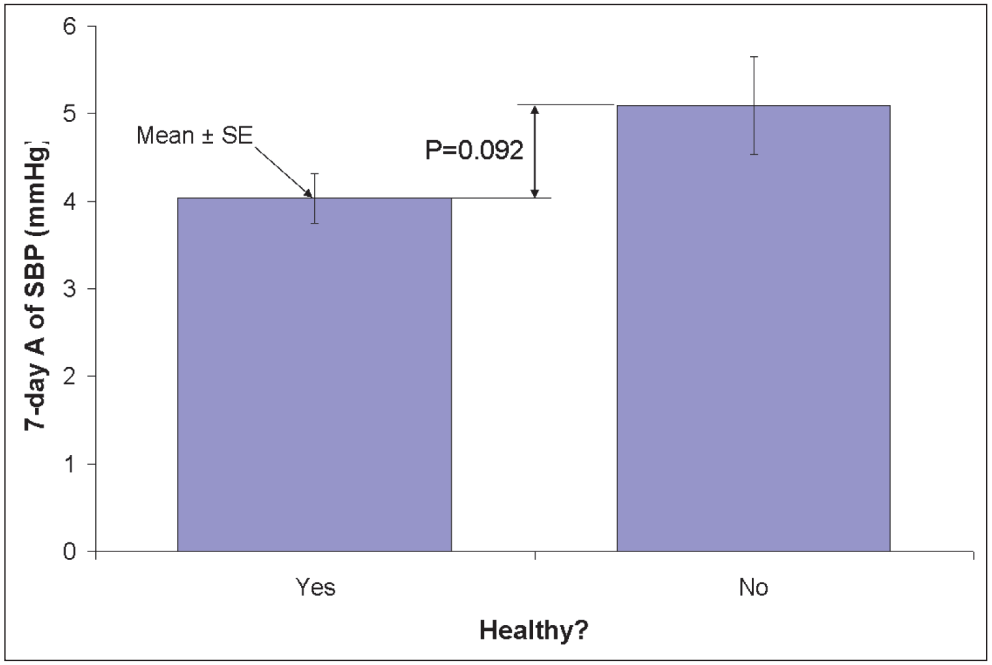


Figure 13 *The circaseptan double amplitude of systolic blood pressure were higher in patients than in healthy subjects in the blood pressure profiles in the Czech Republic*

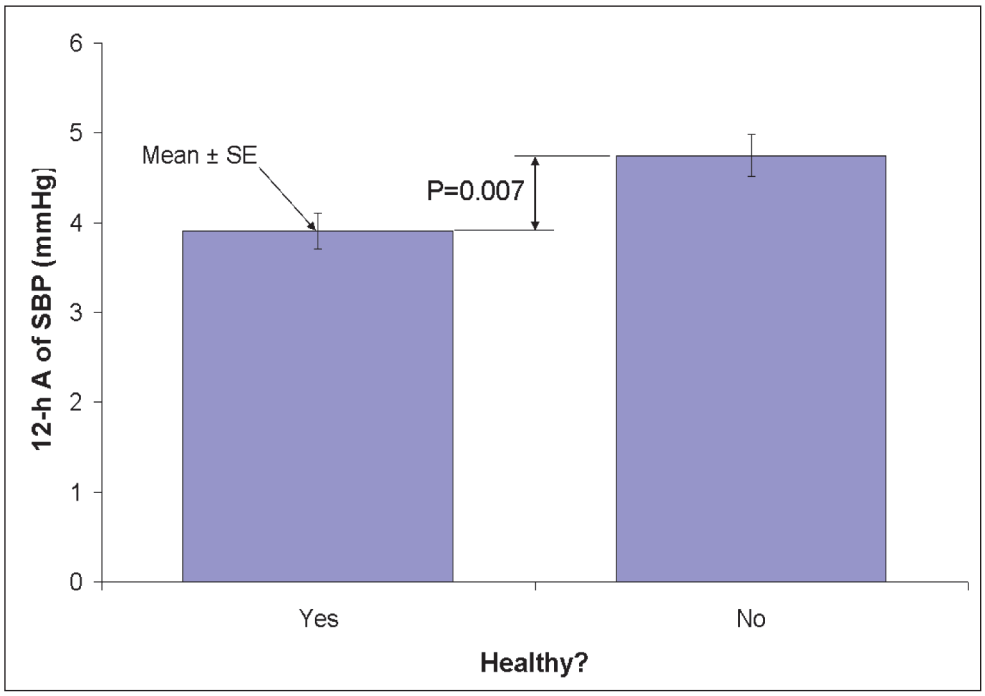


Figure 14 *The circasemidian double amplitude of systolic blood pressure were higher in patients than in healthy subjects in the blood pressure profiles in the Czech Republic*

The 7-day and 3.5-day amplitudes of BP and HR were correlated (P<0.001), as were the 3.5-day and circadian amplitudes of SBP (P=0.004) and HR (P=0.013). The 7-day and circadian amplitudes of SBP (P=0.067) and DBP (P=0.046) were weakly associated.

Gender differences and changes with age are in keeping with earlier independent investigations.

Conclusion

The larger 7-day and 0.5-day amplitudes in patients may reflect the increase in extra-circadian variation in older subjects who are more likely to have MESOR-hypertension.

The study provides on 50 clinically healthy adults the first multiseptan-to-circadian reference values for Caucasians in Europe.

The increase in multiseptan-to-circadian amplitude ratio of BP after 40 years of age in all subjects (healthy or treated for high BP) is similar to that seen transversely in health and longitudinally in a clinically healthy subject who monitored himself for 38 years.

Health care changes from a spot check evidence-based approach relying on large clinical trials to one of chronomically analyzed individualized time series.

Results from 145 patients showed circaseptan component, statistically significant for blood pressure but not for heart rate. The half-week is significant for all 3 variables, as is the circadian rhythm.

References

1. Halberg F, Cornélissen G, Katinas G, Syutkina EV, Sothern RB, Zaslavskaya R, Halberg Francine, Watanabe Y, Schwartzkopff O, Otsuka K, Tarquini R, Perfetto F, Siegelova J. Transdisciplinary unifying implications of circadian findings in the 1950s. J Circadian Rhythms 2003; 1: 2. 61 pp. www.JCircadianRhythms.com/content/pdf/1740-3391/1/2.pdf
2. Halberg F, Cornélissen G, Stoynev A, Ikonomov O, Katinas G, Sampson M, Wang ZR, Wan CM, Singh RB, Otsuka K, Sothern RB, Sothern SB, Sothern MI, Syutkina EV, Masalov A, Perfetto F, Tarquini R, Maggioni C, Kumagai Y, Siegelova J, Fiser B, Homolka P, Dusek J, Uezono K, Watanabe Y, Wu JY, Sonkowsky R, Schwartzkopff O, Hellbrügge T, Spector NH, Baciu I, Hriscu M, Bakken E. Season's Appreciations 2002 and 2003. Imaging in time: The transyear (longer-than-the-calendar year) and the half-year. Neuroendocrinol Lett 2003; 24: 421-440.
3. Sheps SG, Canzanello VJ. Current role of automated ambulatory blood pressure and self-measured blood pressure determinations in clinical practice. Mayo Clin Proc 1994; 69: 1000-1005.
4. Halberg F, Bingham C, Cornélissen G. Clinical trials: the larger the better? Chronobiologia 1993; 20: 193-212.
5. Cornélissen G, Halberg F, Prikryl P, Dankova E, Siegelova J, Dusek J, International Womb-to-Tomb Chronome Study Group: Prophylactic aspirin treatment: the merits of timing. JAMA 1991; 266: 3128-3129.
6. Halberg F, Cornélissen G, Otsuka K, Schwartzkopff O, Halberg J, Bakken EE. Chronomics. Biomedicine and Pharmacotherapy 2001; 55 (Suppl 1): 153-190.
7. Stinson SM, Cornélissen G, Scarpelli PT, Halberg F. Self-measurement and ambulatory monitoring of blood pressure: a subject's chronobiological perspective. Biomed Pharmacother 2002; 56 (Suppl 2): 333s-338s.
8. Halberg F, Cornélissen G, Schack B. Self-experimentation chronomics for health surveillance and science; also transdisciplinary civic duty? Behavioral and Brain Sciences 2004; 27 (2): 267-269.

9. Verdecchia P, Schillaci G, Guerrieri M, Gatteschi C, Benemio G, Boldrini F, Porcellati C. Circadian blood pressure changes and left ventricular hypertrophy in essential hypertension. Circulation 1990; 81: 528-536.

10. Otsuka K, Cornélissen G, Halberg F. Predictive value of blood pressure dipping and swinging with regard to vascular disease risk. Clinical Drug Investigation 1996; 11: 20-31.

11. Halberg F, Cornélissen G, Wall D, Otsuka K, Halberg J, Katinas G, Watanabe Y, Halhuber M, Müller-Bohn T, Delmore P, Siegelova J, Homolka P, Fiser B, Dusek J, Sanchez de la Peña S, Maggioni C, Delyukov A, Gorgo Y, Gubin D, Carandente F, Schaffer E, Rhodus N, Borer K, Sonkowsky RP, Schwartzkopff O. Engineering and governmental challenge: 7-day/24-hour chronobiologic blood pressure and heart rate screening. Biomedical Instrumentation & Technology 2002; 36: Part I, 89-122; Part II, 183-197.

12. Cornélissen G, Bakken E, Delmore P, Orth-Gomér K, Åkerstedt T, Carandente O, Carandente F, Halberg F. From various kinds of heart rate variability to chronocardiology. Am J Cardiol 1990; 66: 863-868.

13. Halberg F, Cornélissen G, Otsuka K, Watanabe Y, Wood MA, Lambert CR, Zaslavskaya R, Gubin D, Petukhova EY, Delmore P, Bakken E. Rewards in practice from recycling heart rate, ectopy, ischemia, and blood pressure information. J Medical Engineering & Technology 1997; 21: 174-184.

14. Halberg F, Cornélissen G, International Womb-to-Tomb Chronome Initiative Group: Resolution from a meeting of the International Society for Research on Civilization Diseases and the Environment (New SIRMCE Confederation), Brussels, Belgium, March 17-18, 1995: Fairy tale or reality? Medtronic Chronobiology Seminar #8, April 1995, 12 pp. text, 18 figures. URL http://www.msi.umn.edu/~halberg/

15. Cornélissen G, Halberg F, Bakken EE, Singh RB, Otsuka K, Tomlinson B, Delcourt A, Toussaint G, Bathina S, Schwartzkopff O, Wang ZR, Tarquini R, Perfetto F, Pantaleoni GC, Jozsa R, Delmore PA, Nolley E. 100 or 30 years after Janeway or Bartter, Healthwatch helps avoid "flying blind". Biomedicine & Pharmacotherapy 2004; 58 (Suppl 1): S69-S86.

16. Watanabe Y, Cornélissen G, Halberg F, Otsuka K, Kikuchi T. Long-acting carteolol lowers circadian and circaseptan blood pressure (BP) amplitude (A) as well as MESOR. Abstract, X National Symposium, Indian Society for Chronobiology, B.J. Medical College, Pune, India, August 21-22, 1995. p. 14-15.

17. Shinagawa M, Kubo Y, Otsuka K, Ohkawa S, Cornélissen G, Halberg F. Impact of circadian amplitude and chronotherapy: relevance to prevention and treatment of stroke. Biomedicine and Pharmacotherapy 2001; 55 (Suppl 1): 125-132.

18. Halberg F, Smith HN, Cornélissen G, Delmore P, Schwartzkopff O, International BIOCOS Group. Hurdles to asepsis, universal literacy, and chronobiology—all to be overcome. Neuroendocrinol Lett 2000; 21: 145-160.

19. Cornélissen G, Halberg F, Hawkins D, Otsuka K, Henke W. Individual assessment of antihypertensive response by self-starting cumulative sums. J Medical Engineering & Technology 1997; 21: 111-120.

20. Halberg F, Cornélissen G, Regal P, Otsuka K, Wang ZR, Katinas GS, Siegelova J, Homolka P, Prikryl P, Chibisov SM, Holley DC, Wendt HW, Bingham C, Palm SL, Sonkowsky RP, Sothern RB, Pales E, Mikulecky M, Tarquini R, Perfetto F, Salti R, Maggioni C, Jozsa R, Konradov AA, Kharlitskaya EV, Revilla M, Wan CM, Herold M, Syutkina EV, Masalov AV, Faraone P, Singh RB, Singh RK, Kumar A, Singh R, Sundaram S, Sarabandi T, Pantaleoni GC, Watanabe Y, Kumagai Y, Gubin D, Uezono K, Olah A, Borer K, Kanabrocki EA, Bathina S, Haus E, Hillman D, Schwartzkopff O, Bakken EE, Zeman M. Chronoastrobiology: proposal, nine conferences, heliogeomagnetics, transyears, near-weeks, near-decades, phylogenetic and ontogenetic memories. Biomed Pharmacother 2004; 58 (Suppl 1): S170-S186.

21. Cornélissen G, Halberg F, Schwartzkopff O, Delmore P, Katinas G, Hunter D, Tarquini B, Tarquini R, Perfetto F, Watanabe Y, Otsuka K. Chronomes, time structures, for chronobioengineering for "a full life". Biomed Instrum Technol 1999; 33: 152-187.

22. Watanabe Y, Cornélissen G, Halberg F, Bingham C, Siegelova J, Otsuka K, Kikuchi T. Incidence pattern and treatment of a clinical entity, overswinging or circadian hyperamplitudetension (CHAT). Scripta medica (Brno) 1997; 70: 245-261.

23. Halberg F, Cornélissen G, Spector NH, Sonkowsky RP, Otsuka K, Baciu I, Hriscu M, Schwartzkopff O, Bakken EE. Stress/strain/life revisited. Quantification by blood pressure chronomics: benetensive, transtensive or maletensive chrono-vasculo-neuro-immuno-modulation. Biomed Pharmacother 2003; 57 (Suppl 1): 136s-163s.

24. Halberg F, Cornélissen G, Katinas G, Sampson M, Schwartzkopff O, members of the BIOCOS project, Spector NH, Faraone P, Tomescu S, Hriscu M. In memoriam: Ion Baciu. Mutually supporting neartransyears in solar and terrestrial magnetics, microbial and cell biology, physiology and pathology. In: Cornélissen G, Kenner R, Fiser B, Siegelova J, eds. Proceedings, Symposium: Chronobiology in Medicine. Dedicated to the 85th Anniversary of Professor Franz Halberg. Brno: Masaryk University; 2004. p. 78-86.

25. Halberg F, Cornélissen G, Otsuka K, Watanabe Y, Katinas GS, Burioka N, Delyukov A, Gorgo Y, Zhao ZY, Weydahl A, Sothern RB, Siegelova J, Fiser B, Dusek J, Syutkina EV, Perfetto F, Tarquini R, Singh RB, Rhees B, Lofstrom D, Lofstrom P, Johnson PWC, Schwartzkopff O, International BIOCOS Study Group. Cross-spectrally coherent ~10.5- and 21-year biological and physical cycles, magnetic storms and myocardial infarctions. Neuroendocrinol Lett 2000; 21: 233-258.

SALT, BLOOD PRESSURE, AND CARDIOVASCULAR DISEASE RISK

GERMAINE CORNÉLISSEN[1], KUNIAKI OTSUKA[2], KEIKO UEZONO[3], JARMILA SIEGELOVA[4]

[1] Halberg Chronobiology Center, University of Minnesota, [2] Tokyo Women's Medical University, Daini Hospital, Tokyo, Japan, [3] Second Department of Internal Medicine, Kyushu University, Fukuoka, Japan, [4] Masaryk University, Brno, Czech Republic

Abstract

Reducing salt intake has emerged as a leading target to reduce the burden of cardiovascular disease worldwide. Prospective cohort studies evaluating the association between sodium intake and adverse cardiovascular outcomes have been inconsistent, however. The evidence for an across-the-board low-salt diet recommendation is reviewed herein from a chronobiologic perspective, with focus on effects of sodium intake on blood pressure.

Introduction

Sodium restriction is recommended based on the assumption that heart attacks and strokes would be prevented from a lowering effect on blood pressure (BP) [1]. The effect of sodium intake on population health remains controversial, however. On the one hand, a recent review concluded that most people are likely to benefit from reducing sodium intake [2]. A sodium-restricted DASH diet was reportedly associated with favorable changes in ventricular diastolic function, arterial elastance, and ventricular-arterial coupling [3]. Another study investigated the effect of chronic sodium loading from a low-sodium diet to a Western diet [4]. The authors concluded that dietary salt loading increased pulse wave velocity and BP in hypertensive volunteers, and that salt loading may have an effect on vascular wall function independently of an effect on BP, thus supporting the importance of dietary sodium restriction in the management of hypertension [4]. Based on costs related to health outcomes measured in disability-adjusted life years averted over a lifetime in Australia, it was concluded that programs to encourage the food industry to reduce salt in processed foods are highly recommended for improving population health [5].

On the other hand, while meta-analyses of randomized controlled trials of salt reduction report a reduction in BP, an effect on adverse cardiovascular events could not be clearly demonstrated [6]. Evidence based on 665 deaths among 6,250 participants still had insufficient power to find an effect of dietary salt intake on cardiovascular morbidity or mortality [6]. Estimates of benefits from dietary salt restriction were consistent with the anticipated small effects on clinical events attributable to the small reduction in BP achieved [6]. A number of recent studies have reported an association between low sodium intake and an increased risk of cardiovascular death [7]. A J-shaped association between sodium intake and cardiovascular disease death and heart failure has been reported [8, 9]. The comment has also been made that while dietary sodium restriction may be of value in hypertensive patients, available evidence does not support the current recommendations of a generalized and indiscriminate reduction of salt intake at the population level [10]. Moreover, reductions in sodium associated with a lowering of BP have been noted to increase plasma renin activity and aldosterone secretion, insulin resistance, sympathetic nerve activity, serum cholesterol, and triglyceride concentrations [11]. Health consequences of reducing sodium thus cannot be predicted by its impact on any single physiologic variable. One has to take into consideration the net of conflicting effects [11].

Against this background, we review evidence for an effect of salt intake on BP from a chronobiologic viewpoint. Results are interpreted in the light of recently published results on the association between dietary sodium intake and actual outcomes.

Effect of Salt Intake on the Circadian Rhythm of Blood Pressure

The epidemiology of salt-induced hypertension has been explored in animal studies, revealing an acute (rapid) BP response occurring over days to weeks, and a slow and progressive BP response that develops over a long time [12]. Assessing changes in the circadian rhythm characteristics of BP in relation to salt loading reveals an additional effect on the circadian amplitude of BP, often overlooked even in studies relying on telemetry to monitor BP and other physiological variables around-the-clock longitudinally. In the DOCA-salt model of hypertension [13], an increase in the circadian amplitude of BP was observed before the BP MESOR increased in intact or unilaterally nephrectomized male Sprague-Dawley rats (unpublished).

A similar finding has been reported in humans, as illustrated in Figure 1 [14, 15]. The study included 13 volunteers with untreated borderline hypertension and a body weight at least 10% over the desired weight. The study comprised 3 stages (a: reference, b: salt intake reduced by at least 30 mEq/day without reducing calorie intake, and c: weight loss of at least 2 kg while remaining on low salt diet), each lasting 2 months. A 24-hour ABPM profile was obtained at the end of each stage. As seen in Figure 1 for a 60-year old subject who participated in the study, a low-salt diet was associated with a small decrease in the MESOR and an increase in the circadian amplitude of systolic BP, while weight loss brought about a further larger decrease in the MESOR and a substantial decrease in the circadian amplitude of systolic BP [14, 15].

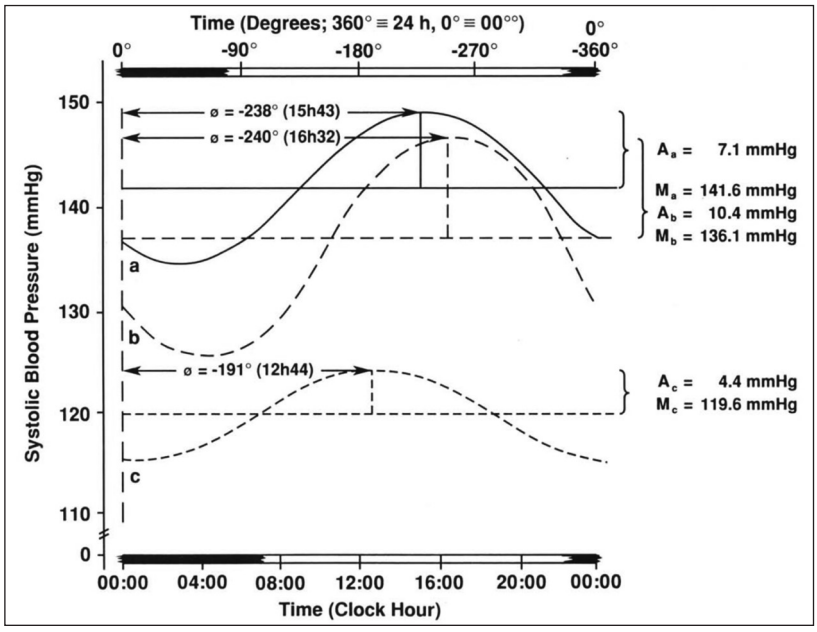


Figure 1 *Increased circadian amplitude of systolic BP associated with reduced sodium intake. © Halberg Chronobiology Center.*

Individual Differences in the Response to Dietary Salt

Not everybody responds to sodium restriction with a lowered BP. Some people even increase their BP in association with sodium restriction, as evidenced from three independent studies. One study included 50 (45 with idiopathic hypertension and 5 normotensive) subjects 35 to 65 years of age [16]. After discontinuing anti-hypertensive medication for at least 1 week, they adhered to a constant metabolic diet containing 9

mEq of sodium per day and 50-70 mEq of potassium per day for 7 days, followed by 7 days on a high sodium diet (249 mEq per day). On the last day of the low-salt and high-salt diet, their BP was monitored around-the-clock by ABPM, and the data were analyzed by cosinor [17-20]. Parameter tests [21] were applied to compare the individual response to sodium loading by each subject. The authors of the study [16] reported that 25% of the subjects were found to be salt-sensitive with a statistically significant increase in their BP MESORs with sodium loading. A subpopulation of non-salt-sensitive subjects reportedly responded to sodium loading with a statistically significant decrease in their BP MESOR [16].

Three kinds of BP response to changes in sodium intake were also observed in two other studies [22, 23]. Not all of the subjects participating in these studies had an elevated BP. Some of them were found to be MESOR-normotensive by ABPM. In both studies, tests of the equality of BP MESORs found that in response to low-sodium intake, some (salt-sensitive) subjects decreased their BP MESOR, and other (non-salt-sensitive) subjects showed no statistically significant change in their BP MESOR. In addition to these two kinds of responses, there were other subjects who increased their BP MESOR in association with sodium restriction (indirect response), Figures 2 and 3 [24, 25]. An indirect response was also found in association with sodium loading, Figure 4 [24, 25]. The extent to which day-to-day variability in circadian rhythm characteristics of BP contributed to the three kinds of response remains to be investigated.

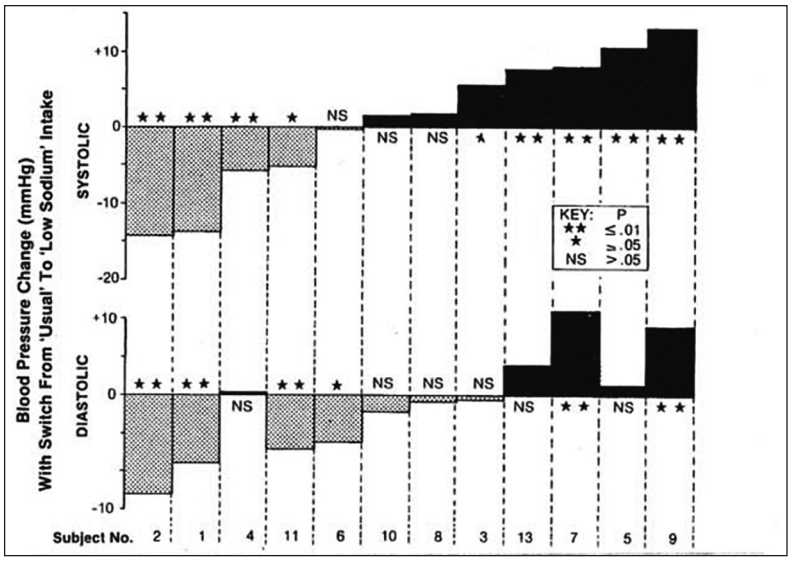


Figure 2 *Decrease, no change, or increase in BP MESOR in association with salt restriction [14, 15, 22]. © Halberg Chronobiology Center.*

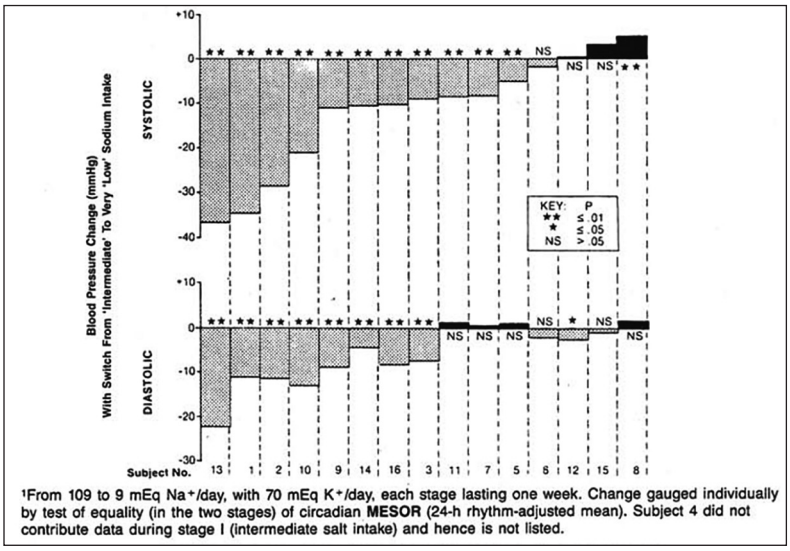


Figure 3 *Decrease, no change, or increase in BP MESOR in association with salt restriction [23]. © Halberg Chronobiology Center.*

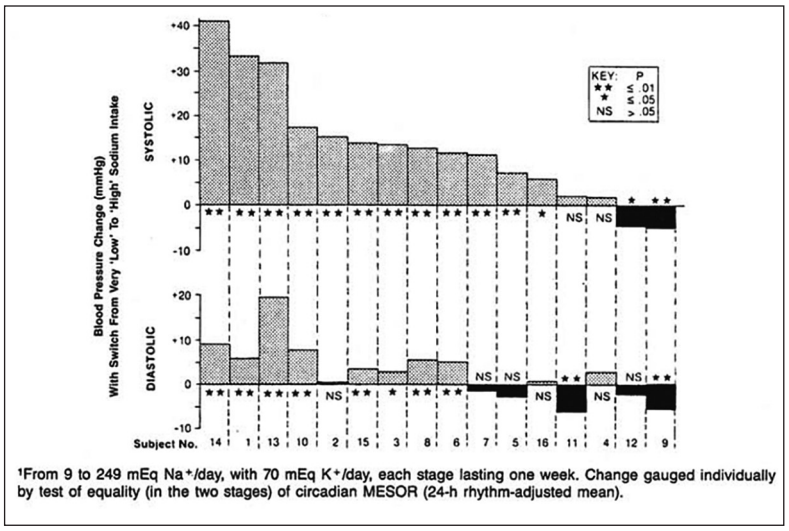


Figure 4 *Increase, no change, or decrease in BP MESOR in association with salt loading [23]. © Halberg Chronobiology Center.*

Circadian Stage-Dependent Effect of Dietary Salt on Blood Pressure

As for many other stimuli, the effect of salt intake is circadian stage-dependent. This was demonstrated in a small but elegant study of seven clinically healthy normotensive young women (20-21 years of age) [26, 27]. BP was measured around the clock by ABPM for 2 consecutive days at the end of each 9-day stage during which the subjects consumed their usual daily salt intake (12 g/day), either distributed over the three daily meals as usual (Reference), or consuming two thirds of dietary salt at lunch time (Stage LH), or consuming two thirds of dietary salt at dinner time (Stage DH). The daily amount of nutrients was similar during each stage [26]. As seen in Figure 5, with no difference in the daily amount of salt intake, the 48-hour mean value of BP did not differ between stage LH and the reference stage, but it was statistically significantly decreased during stage DH.

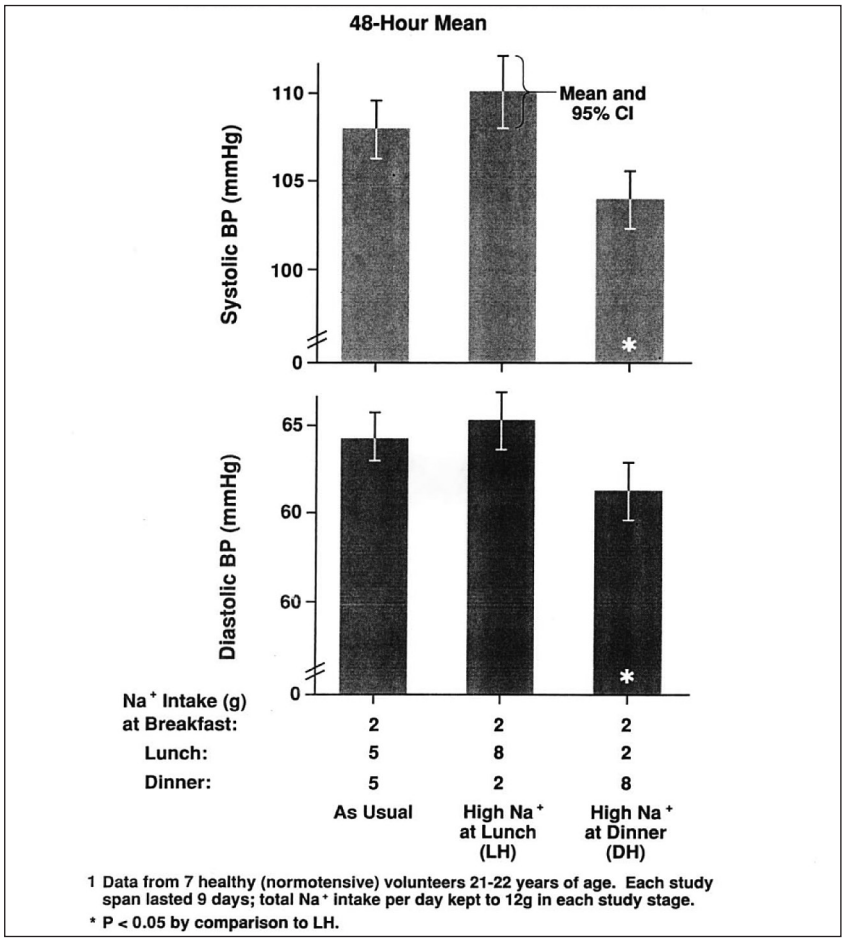


Figure 5 *The effect of dietary salt intake on BP is circadian stage-dependent [26, 27]. © Halberg Chronobiology Center.*

Discussion

On the average, the benefit of reducing salt intake in hypertensive patients has been widely examined epidemiologically [28]. In most patients, however, the specific defect causing salt-dependent hypertension has not been discerned. The importance of accounting for rhythms in this respect has also been noted by others [29]. Largely based on short-term studies of responses to high salt intake, homeostatically, dietary sodium is thought to be rapidly eliminated into urine, thereby achieving constant total-body sodium and water content. Using a reverse experimental approach, salt intake was fixed at 12 g, 9 g, and 6 g per day in men participating in space flight simulations. They were tested over 105 and 205 days for the predicted constancy in urinary excretion and total-body sodium content [29]. The authors report aldosterone-dependent circaseptan changes in daily sodium excretion, which resulted in rhythmic sodium storage. Total-body sodium changed according to monthly and longer cycles without corresponding changes in body weight and extracellular water [29]. A circaseptan rhythm in sodium and potassium excretion had been reported earlier in salt-sensitive and salt-resistant Dahl rats [30].

Any benefit from reducing dietary salt intake seems to be less clear for healthy individuals. A meta-analysis of unconfounded randomized trials aimed at reducing sodium intake in healthy adults over at least 6 months examined effects on mortality, cardiovascular events, blood pressure, and urinary sodium excretion [31]. Results at 13- to 60-month follow-up, based on 11 trials (3 on normotensive subjects, 5 on untreated and 3 on treated hypertensive subjects) including a total of 3514 individuals, indicated a 35.5 [95% CI: 23.9, 47.2] mmol/24h reduction in urinary sodium excretion, and reductions of 1.1 [95% CI: 0.4,

1.8] and 0.6 [95% CI: 0.3, 1.5] mmHg in systolic and diastolic BP, respectively. The 17 deaths were equally distributed between the reduced salt and control groups. These results led the authors to conclude that intensive interventions, unsuited to primary care or population prevention programs, provide only small reductions in BP and sodium excretion, while effects on mortality and cardiovascular events are unclear [31].

Similar conclusions were reached in a subsequent meta-analysis of 7 randomized controlled trials [6]. Urinary sodium excretion was reportedly reduced by 27 to 49 mmol/24h and systolic BP by 1 to 4 mmHg. The relative risk of mortality among normotensive subjects was 0.90 [95% CI: 0.58, 1.40] (non-significant) based on 79 deaths. For hypertensive individuals, the relative risk of mortality was 0.96 [95% CI: 0.83, 1.11] (non-significant) based on 565 deaths. Results were also non-significant in terms of cardiovascular events, with a relative risk of 0.71 [95% CI: 0.42, 1.20] (200 events) among normotensive subjects, and a relative risk of 0.84 [95% CI: 0.57, 1.23] (93 events) among hypertensive individuals [6]. Moreover, salt restriction was associated with an increased risk of all-cause mortality among patients with heart failure, with a relative risk of 2.59 [95% CI: 1.04, 6.44] (statistically significant) based on 21 deaths [6].

A more recent meta-analysis [1] also addressed the question of a J-shape relation between outcome and dietary salt intake [8, 9]. The incidence of all-cause mortality and of cardiovascular disease events was compared in populations exposed to dietary intakes of low sodium (<115 mmol or <2645 mg), usual sodium (115-165 mmol and 166-215 mmol; 165 mmol represents 3795 mg), and high sodium (>215 mmol or >3795 mg). Results are based on data from 23 cohort and 2 follow-up randomized controlled trials, involving 274,683 subjects [1]. As compared to usual sodium intake, the risks of all-cause mortality and of cardiovascular disease events was increased both in populations exposed to high sodium and in those exposed to low sodium: the hazard ratios for high sodium exposure were 1.16 [95% CI: 1.03, 1.30] and 1.12 [95% CI: 1.02, 1.24] for mortality and cardiovascular events, respectively; the hazard ratios for usual versus low sodium exposure were 0.91 [95% CI: 0.82, 0.99] and 0.90 [95% CI: 0.82, 0.99] for mortality and cardiovascular events, respectively. These results call into question the validity of the current recommendation from the US Food and Drug Administration that individuals consume no more than 2,300 mg sodium per day, and that certain groups limit intake to 1,500 mg per day [32].

Conclusions

As shown in Figures 2-4, there are three kinds of BP response to sodium restriction/loading: in addition to the salt-sensitive individuals who decrease their BP in association with reduced dietary salt intake and the non-responders, there are also some people who increase their BP with a reduced sodium intake. It is thus important to determine on an individualized basis whether a reduction in dietary salt intake may have a desirable BP lowering effect when such an effect is warranted. A review of the literature indeed suggests that some hypertensive patients may benefit from reducing their dietary salt intake.

Assessing the circadian variation in BP is recommended, since reducing dietary salt intake can be associated with an increased circadian amplitude of BP (Figure 1), which, if it becomes excessive, may bring about an increase in cardiovascular disease risk, as reviewed elsewhere in this volume. Assessing other rhythmic components is desirable as well, as illustrated by the study of Rakova et al. [29] who call into question the concept of sodium homeostasis.

The timing of sodium intake matters. Consuming the same amount at lunch or at dinner may be associated with no change or a decrease in BP, respectively, Figure 5.

As apparent from three meta-analyses [1, 6, 31], any effect of reducing dietary salt intake on BP may not necessarily translate into a decrease in the incidence of adverse cardiovascular events or all-cause mortality. A J-shape relationship between outcome and the daily amount of dietary salt intake [1, 8, 9] should be taken into consideration in making recommendations for optimal daily consumption, which are best tailored to the individual in the light of a chronobiologic assessment of circadian and other parameters of markers such as BP.

References

1. Graudal N, Jürgens G, Baslund B, Alderman MH. Compared with usual sodium intake, low- and excessive-sodium diets are associated with increased mortality: a meta-analysis. Am J Hypertens 2014; 27(9): 1129-1137.
2. Aburto NJ, Ziolkovska A, Hooper L, Elliott P, Cappuccio FP, Meerpohl JJ. Effect of lower sodium intake on health: systematic review and meta-analyses. BMJ 2013; 346:f1326.
3. Hummel SL, Seymour EM, Brook RD, Sheth SS, Ghosh E, Zhu S, Weder AB, Kovacs SJ, Kolias TJ. Low-sodium DASH diet improves diastolic function and ventricular-arterial coupling in hypertensive heart failure with preserved ejection fraction. Circulation: Heart Failure 2013; 6(6): 1165-1171.
4. Todd AS, Macginley RJ, Schollum JB, Johnson RJ, Williams SM, Sutherland WH, Mann JI, Walker RJ. Dietary salt loading impairs arterial vascular reactivity. American Journal of Clinical Nutrition 2010; 91(3): 557-564.
5. Cobiac LJ, Vos T, Veerman JL. Cost-effectiveness of interventions to reduce dietary salt intake. Heart 2010; 96(23): 1920-1925.
6. Taylor RS, Ashton KE, Moxham T, Hooper L, Ebrahim S. Reduced dietary salt for the prevention of cardiovascular disease: a meta-analysis of randomized controlled trials (Cochrane review). American Journal of Hypertension 2011; 24(8): 843-853.
7. O'Donnell MJ, Mente A, Smyth A, Yusuf S. Salt intake and cardiovascular disease: why are the data inconsistent? European Heart Journal 2013; 34(14): 1034-1040.
8. Thomas MC, Moran J, Forsblom C, Harjutsalo V, Thorn L, Ahola A, Waden J, Tolonen N, Saraheimo M, Gordin D, Groop PH. The association between dietary sodium intake, ESRD, and all-cause mortality in patients with type 1 diabetes. Diabetes Care 2011; 34: 861–866.
9. O'Donnell MJ, Yusuf S, Mente A, Gao P, Mann JF, Teo K, McQueen M, Sleight P, Sharma AM, Dans A, Probstfield J, Schmieder RE. Urinary sodium and potassium excretion and risk of cardiovascular events. JAMA 2011; 306: 2229–2238.
10. Stolarz-Skrzypek K, Bednarski A, Czarnecka D, Kawecka-Jaszcz K, Staessen JA. Sodium and potassium and the pathogenesis of hypertension. Current Hypertension Reports 2013; 15(2): 122-130.
11. Alderman MH, Cohen HW. Dietary sodium intake and cardiovascular mortality: controversy resolved? American Journal of Hypertension 2012; 25(7): 727-734.
12. Van Vliet BN, Montani JP. The time course of salt-induced hypertension, and why it matters. International Journal of Obesity 2008; 32: S35-S47.
13. Osborn JW, Jacob F, Hendel M, Collister JP, Clark L, Guzman PA. Effect of subfornical organ lesion on the development of mineralocorticoid-salt hypertension. Brain Research 2006; 1109(1): 74-82.
14. Lee JY, Gillum RF, Cornélissen G, Koga Y, Halberg F. Individualized assessment of circadian rhythm characteristics of human blood pressure and pulse after moderate salt and weight restriction. In: Takahashi R, Halberg F, Walker C. (Eds.) Toward Chronopharmacology, Oxford/New York, Pergamon Press 1982; 375-390.
15. Halberg F, Cornélissen G, Halberg E, Halberg J, Delmore P, Shinoda M, Bakken E. Chronobiology of human blood pressure. Medtronic Continuing Medical Education Seminars, 4th ed. Minneapolis: Medtronic Inc. 1988; 242 pp.
16. Bittle CC, Molina DJ, Bartter FC. Salt sensitivity in essential hypertension as determined by the cosinor method. Hypertension 1985; 7: 989-994.
17. Halberg F. Chronobiology: methodological problems. Acta med rom 1980; 18: 399-440.
18. Cornélissen G, Halberg F. Chronomedicine. In: Armitage P, Colton T. (Eds.) Encyclopedia of Biostatistics, 2nd ed. Chichester, UK: John Wiley & Sons Ltd. 2005; 796-812.

19. Refinetti R, Cornélissen G, Halberg F. Procedures for numerical analysis of circadian rhythms. Biological Rhythm Research 2007; 38 (4): 275-325.
20. Cornelissen G. Cosinor-based rhythmometry. Theoretical Biology and Medical Modelling 2014; 11: 16. doi:10.1186/1742-4682-11-16. 24 pp.
21. Bingham C, Arbogast B, Cornélissen Guillaume G, Lee JK, Halberg F. Inferential statistical methods for estimating and comparing cosinor parameters. Chronobiologia 1982; 9: 397-439.
22. Koga Y. Gillum RF. Kubicek WG. An impedance cardiographic study of the mechanism of blood pressure fall after moderate dietary sodium restriction. Japanese Heart Journal 1985; 26(2): 197-207.
23. Kawasaki T, Delea CS, Bartter FC, Smith H. The effect of high-sodium and low-sodium intakes on blood pressure and other related variables in human subjects with idiopathic hypertension. Am J Med 1978; 64: 193-198.
24. Halberg F, Cornélissen G. I: Rhythms and blood pressure. Ann Ist Super Sanità 1993; 29: 647-655.
25. Cornélissen G, Kawasaki T, Uezono K, Delea C, Halberg F. II: Blood pressure rhythms and salt. Ann Ist Super Sanità 1993; 29: 667-677.
26. Kawasaki T, Itoh H, Cugini P. Influence of reapportionment of daily salt intake on circadian blood pressure pattern in normotensive subjects. J Nutr Sci Vitaminol 1994; 40: 459-466.
27. Itoh K, Kawasaki T, Cugini P. Effects of timing of salt intake to 24-hour blood pressure and its circadian rhythm. Annals of the New York Academy of Sciences 2006; 783: 324-325.
28. Ortiz-Melo D, Coffman TM. A trip to inner space: insights into salt balance from cosmonauts. Cell Metab 2013; 17(1): 1-2.
29. Rakova N, Jüttner K, Dahlmann A, Schröder A, Linz P, Kopp C, Rauh M, Goller U, Beck L, Agureev A, Vassilieva G, Lenkova L, Johannes B, Wabel P, Moissl U, Vienken J, Gerzer R, Eckardt KU, Müller DN, Kirsch K, Morukov B, Luft FC, Titze J. Long-term space flight simulation reveals infradian rhythmicity in human Na+ balance. Cell Metab 2013; 17(1): 125-131.
30. Uezono K, Sackett-Lundeen LL, Kawasaki T, Omae T, Haus, E. Circaseptan rhythm in sodium and potassium excretion in salt-sensitive and salt-resistant Dahl rats. Prog Clin Biol Res 1987; 227A: 297–307.
31. Hooper L, Bartlett C, Davey Smith G, Ebrahim S. Systematic review of long term effects of advice to reduce dietary salt in adults. BMJ 2002; 325(7365): 628-636.
32. http://www.health.gov/dietaryguidelines/dga2005/document/html/chapter8.htm

Correspondence:
Germaine Cornélissen
Halberg Chronobiology Center
University of Minnesota, Mayo Mail Code 8609
420 Delaware St. S.E. Minneapolis, MN 55455, USA
TEL +1 612 624 6976 FAX +1 612 624 9989
E-MAIL corne001@umn.edu
Website: http://www.msi.umn.edu/~halberg/

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REHABILITATION OF THE TEMPOROMANDIBULAR JOINT

PETR KONECNY[1,2,3,4], MILAN ELFMARK[4,5], STANISLAV HORAK[4], ROBERT MIKULIK[3], JARMILA SIEGELOVA[2], PETR DOBSAK[2]

[1]Department of Rehabilitation SMN Prostejov Agel, [2]Department of Physiotherapy and Rehabilitation,Masaryk University, Brno, [3]ICRC-USA Brno, [4]Department of Neurology and Rehabilitation Palacky University Olomouc, [5]Department of Natural Sciences in Kinanthropology, Palacky University Olomouc.

Abstract

Aim: Comparison of the therapeutic effects of complex rehabilitation therapy with standard stomatological treatment of the temporomandibular joint (TMJ).

Methodology: A prospective study of the cases and the controls compares the effects of 2-month complex conservative rehabilitation therapy including physiotherapy – post-izometic relaxation (PIR) and re-education exercise and the effects of standard stomatological conservative treatment. A TMJ dysfunction, namely hypermobility, became an indication for including the above-mentioned issue in the study. The experimental group (rehabilitation) included 25 subjects whose average age was 30, and the control group of 30 subjects whose average age was 31. The parameters of the TMJ dysfunction were evaluated on an input and output basis and they included the following – pain, sound phenomena, associated symptoms, ranges of mouth opening and the kinetic 2D video analysis of the lower jaw was carried out. Then the results were analysed and the statistics evaluated.

Results: The measured values in the experimental group showed statistically significant improvements in the sound phenomena, associated symptoms and mobility alteration evaluated by the 2D video analysis. The parameters of evaluating the pain and mouth opening ranges showed changes in both of the research groups, but the difference between the experimental group and the control group was not statistically significant.

Conclusion: Rehabilitation plays an important role in the therapy of the TMJ dysfunctions within the complex approach.

Introduction

The TMJ disorders are accompanied by pain, sound phenomena (clicking) and dysfunction. The causes of such discomfort can include the TMJ structural disorders (arthrosis, injury, arthritis, etc.) or dysfunctions (e.g. joint blockade, hypermobility, muscle spasm or insufficiency). Rehabilitation is recommended for the therapy of dysfunctions [1, 2].

Methods

The aim of our study was to compare the therapeutic effects of two therapies – complex rehabilitation therapy with the TMJ targeted physiotherapy versus standard stomatological conservative treatment.

The study was carried out as a prospective randomized study. It evaluated the effects of 2-month complex conservative rehabilitation therapy with the TMJ physiotherapy including the targeted post-isometric relaxation (PIR) of the short neck extensors, PIR mm. pterygoides laterals, and the re-education exercise

of the optimum mouth opening with the use of rhythmic stabilization and also standard stomatological conservative treatment (pharmaceuticals and repositioning splint).

A TMJ dysfunction, namely hypermobility (with disc dislocation without reduction, according to X-ray, without any signs of degenerative changes), became an indication for including the above-mentioned issue in the study. The division into the experimental group (25 subjects, 20 women, whose average age was 30) and the control group (30 subjects, 24 women, whose average age was 31) was carried out at random based on an independent parameter. The parameters of the TMJ dysfunction were evaluated on an input and output basis after 2 months of either therapy and they included the following: pain, sound phenomena, associated symptoms (dysphagia, vertigo, etc.) and mouth opening ranges (interincisor distance); furthermore, the data processing of the video records of mouth opening in the sagittal and frontal planes, based on the kinetic 2D video analysis, was performed. Then the results were analysed and the statistics evaluated.

Results

The measured values in the experimental group showed statistically significant changes in the sound phenomena, associated symptoms and mobility alteration evaluated by the 2D analysis. The parameters of evaluating the pain and mouth opening ranges showed changes in both of the research groups, but the difference between the experimental group and the control group was not statistically significant (see the table 1).

Discussion

As we proved in our study, the rehabilitation exercise is seems to be more suitable to improve the function (range of jaw movement). The difference between the two group is statistically significant in this aspect (see the table 1). The vertical jaw mobility was evaluated on the basis of measuring the interincisor distance in maximum abduction and by means of video analysis. The mobility in the research sample increased from the initial value of 42.7 mm to 46.25 mm, whereas in the control sample it only increased from 43.25 mm to 44.0 mm. Significant changes of the experimental group are seen in the results of the 2D video analysis too (see graph 1 and graph 2). Some studies of other authors show similar results [3]. The TMJ secondary sound phenomena disappeared most frequently after the post-isometric relaxation m. pterygoideus lateralis (in 44 % of cases). In 46 % of patients there was only a partial improvement, i.e. the clicking sound was less “loud”, occasional or not irritating. Some authors, however, have reported that the influence of long-term exercise on the disappearance of these sound phenomena is much more significant [3, 4]. What we find quite interesting is the fact that in 98 % of patients the TMJ disorder was associated with a dysfunction of the cervical spine, especially the cervicocranial junction, conditioned by the hypertonic short neck extensors or asymmetrical mobility of the atlanto-occipital joint. This factor may partially explain the higher efficiency of the rehabilitation therapy in the patients’ final subjective evaluation [5].

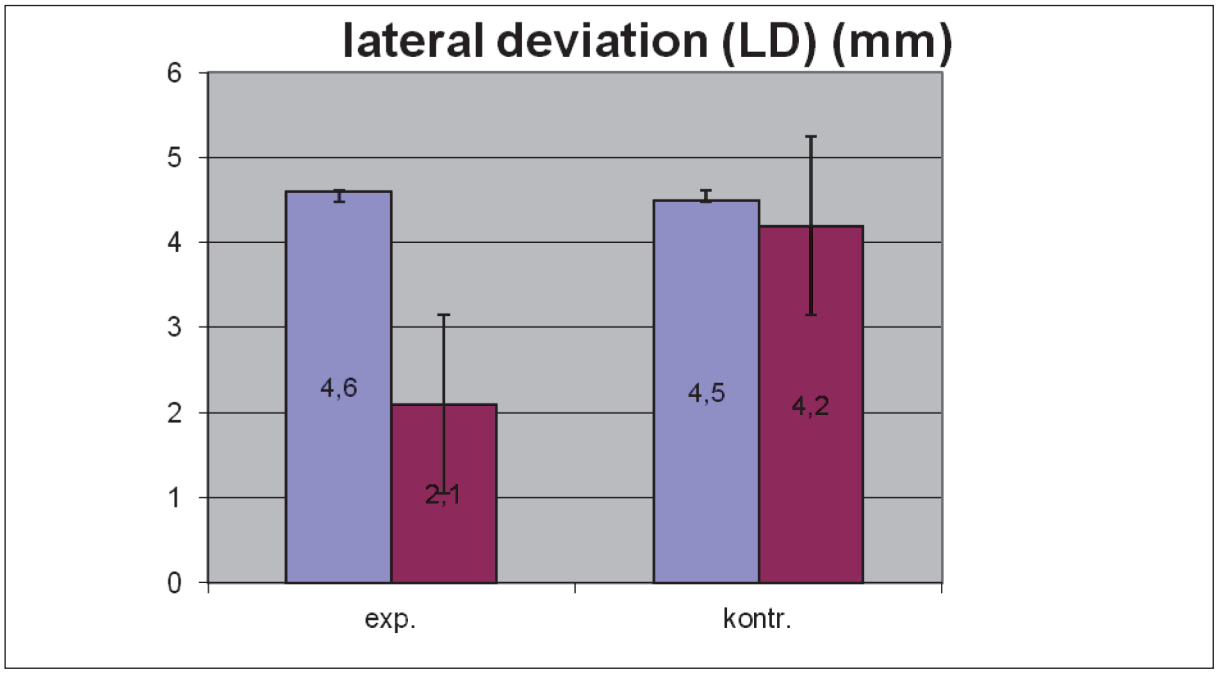
The reduction of the pain intensity during the therapy is quite apparent in both of the research groups (see the table1). However, the difference between the two samples is not statistically significant in terms of statistical analysis. The most significant relief appears at the beginning of the therapy within the first two weeks [3].

Conclusion

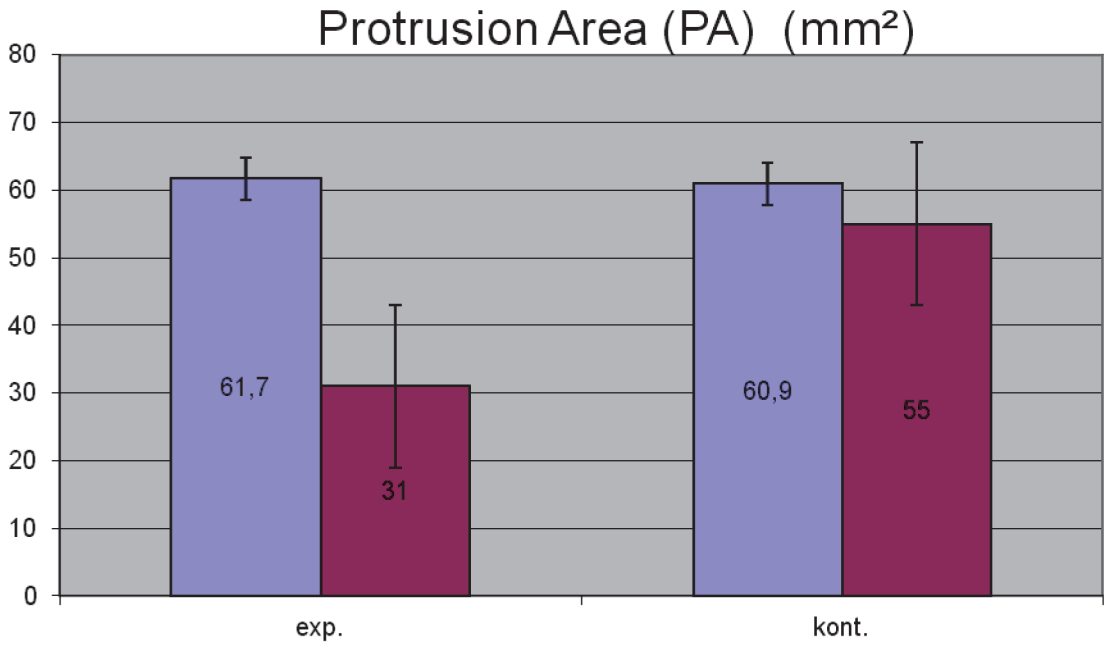
Physiotherapy has an important role in the therapy of the TMJ dysfunctions within the complex approach. In particular, physiotherapy has a demonstrable effect on reducing the sound phenomena, associated symptoms and movement optimization of the lower jaw and TMJ in respect to the patients suffering from the TMJ hypermobility with disc dislocation with reduction.

Table 1 *Changes (difference) after the rehabilitation (EXP-experimental group) and the standard treatment (CON-control group)*

	pain - VAS (1-10)			sound phenomena (1-3)			accompanying symptoms (%)		
	Input (SD)	Output (SD)	Difference (SD)	Input (SD)	Output (SD)	Difference (SD)	Input (SD)	Output (SD)	Difference (SD)
EXP.	3,6 (0,9)	1,3 (0,2)	2,3 (0,75)	2,4 (0,5)	0,8 (0,31)	1,6 (0,57)	41 (5,4)	10 (3,2)	30 (6,5)
CON.	3,5(0,95)	1,1 (0,17)	2,4 (0,7)	2,5 (0,44)	1,9 (0,42)	0,6 (0,32)	38 (6,1)	35 (5,3)	2 (0,21)
P-value			p=0,734			p=0,023			p=0,017
	inter-incisor distance (mm)			2D: lateral deviation (LD) (mm)			2D: Protrusion Area (PA) (mm²)		
	Input (SD)	Output (SD)	Rozdíl	Input (SD)	Output (SD)	Difference (SD)	Input (SD)	Output (SD)	Difference (SD)
EXP.	43 (5)	44,5 (6)	1,5 (0,55)	4,6 (0,2)	2,1 (0,15)	2,5 (0,21)	61,7 (11,7)	31,0 (7,2)	30,7 (6,6)
CON.	42,5 (4)	43,5 (4,5)	1,0 (0,4)	4,5 (0,18)	4,2 (0,21)	0,3 (0,11)	60,9 (12,1)	55,0 (6,8)	5,9 (8,1)
P-value			p=0,86			p=0,0063			p=0,0041



Graph 1 *Results of the 2D video analysis - lateral deviation (LD) in mm between experimental group and control group before (blue) and after (red) treatment.*



Graph 2 *Results of the 2D video analysis – protrusion area (PA) in mm² between experimental group and control group before (blue) and after (red) treatment*

References

1. Konečný P. Temporomandibulární kloub. In: Kolektiv autorů. Rehabilitace. Triton: Praha 2010. s. 128-154. ISBN 978-80-7387-299-1.
2. Zemen J. a kol. Konzervativní léčba temporomandibulárních poruch. Galen: Praha 1999, 213 s. ISBN 807-26-200-53
3. Hanáková D, Jureček B, Konečný P. Zhodnocení efektu propriosenzitivního reedukačního cvičení při terapii temporomandibulárních poruch.Čes Stomat 2005; 1: 30-34.
4. TMJ Syndrome Treatment [online]. Dostupné na World Wide Web: http://www.emedicinehealth.com/temporomandibular_joint_tmj_syndrome/page6_em.htm#tmj_syndrome_treatment. [Cit.22.11.2O14].
5. Konečný P, Havlíčková J, Elfmark M, Tvrdý P, Hanáková D, Jureček B. Efekty rehabilitace pacientů s poruchou temporomandibulárního komplexu. Rehabilitace a fyzikální lékařství 2007; 3: 95 - 100.

IMPORTANCE OF INTRA-DIALYTIC EXERCISE TRAINING IN HEMODIALYZED PATIENTS

[A]PETRA PALANOVÁ, [A]VERONIKA MRKVICOVÁ, [B]ANNA REICHERTOVÁ, PAVEL VANK, [B]JAN SVOJANOVSK, [B] PAVEL STUDENÍK, JARMILA SIEGELOVÁ, [B]MIROSLAV SOUČEK, [C]MASAHIRO KOHZUKI, MICHAELA SOSÍKOVÁ, PETR DOBŠÁK

Department of Functional Diagnostics and Rehabilitation (KFDR), St.Anna Faculty Hospital and Masaryk University, Brno, Czech Republic, [A] Department of Public Health, Faculty of Medicine, Masaryk University, Brno, Czech Republic, [B] 2nd Department of Internal Medicine, St.Anna Faculty Hospital and Masaryk University, Czech Republic, [C] Department of Internal Medicine and Rehabilitation Science, Tohoku University Graduate School of Medicine, Sendai, Japan

Abstract

Regular exercise is an essential part of life in both healthy and chronically ill subjects. In hemodialyzed (HD) patients the properly dosed physical activity has been shown to prevent the onset of functional disorders and somatic impairment. Objective. The aim was to assess the impact of aerobic short-term intra-dialytic training on bed-side ergometers combined with stretching and releasing exercises on functional parameters, subjective perception of exertion and quality of life in patients with end-stage renal disease (ESRD). **Patients and methods.** Eight patients (6 men and 2 women; mean age 42.4±16.1 years) completed 10-weeks of supervised intra-dialytic exercise program (frequency 2 - 3 times a week). Each training session was also combined with stretching and releasing exercises of large muscle groups. At baseline and after end of exercise program all patients underwent 6-min corridor walk test for evaluation of distance walked and of ratio of perceived exertion (RPE). Questionnaires KDQOL and FACIT (Czech versions) were used to assess the quality of life (QoL). **Results.** Ten weeks of intra-dialytic exercise training lead to statistically significant increase of distance walked assessed by 6-CWT ($P<0.05$) and also to statistically significant decrease of the RPE during the 6-CWT ($P<0.05$). Evaluation of KDQOL showed statistically significant improvement of the subscale "staff support" ($P<0.05$). Similarly, the evaluation of FACIT questionnaire demonstrated a significant improvement of the subscale "social welfare" ($P<0.05$). **Conclusion.** This study documented the beneficial effect of 10-weeks intra-dialytic aerobic training on functional performance, subjective perception of effort and quality of life in patients participating in regular HD program. However, this study also showed that 10 weeks of training is too short to achieve more significant changes in other key parameters.

Introduction

Chronic renal disease (CRD) is a serious and prevalent worldwide health problem that substantially reduces quality of life and significantly affects patient's survival (1). CRD is characterized by a gradual loss in renal function which progress to end-stage renal disease (ESRD) requiring regular dialysis or kidney transplantation. The number of patients being treated for ESRD globally was estimated to be 3.010.000 at the end of 2012 and, with a ~7% growth rate, continues to increase at a significantly higher rate than the world population. Of these 3.010.000 ESRD patients, approximately 2.358.000 were undergoing dialysis treatment (hemodialysis or peritoneal dialysis) and around 652.000 people underwent kidney transplantation. CRD patients are at high risk of serious cardiovascular (CV) complications, such as hypertension and diabetes, which are the main cause of mortality (2). In addition, CRD patients suffer from a variety of other co-morbidities creating a vicious circle enhancing the inactivity which in turn reduces physical function and increases mortality (3). To reduce CRD progression and to decrease the

number of concomitant disorders, exercise training has been shown to induce important beneficial effects (4, 5). Moreover, physical activity may also prevent general deconditioning by increasing aerometabolic capacity (6). Physical training benefits in CRD patients have been extensively studied regarding physical function either evaluated by objective laboratory tests (i.e. cardio-respiratory fitness through peak oxygen uptake (VO_{2peak}) and/or physical performance tests (i.e. field test as the six-minute walk test-6MWT – 7). However, although the intra-dialytic exercise in ESRD patients was first introduced 30 years ago, it is still only offered in a minority of hemodialysis units worldwide. The situation in the Czech Republic is even worse – there is only few hemodialysis centers providing this type of rehabilitation. The aim of the present study was to evaluate the impact of an intra-dialytic aerobic exercise training program (cycling) on selected functional parameters and quality of life (QoL) in patients on regular hemodialysis (HD).

Patients and methods

This study was carried out in regularly hemodialyzed patients in Hemodialysis center of the IInd Department of Internal Medicine of St. Anne's Faculty Hospital (Brno, Czech Republic, EU) using the Fresenius 4008 S hemodialysis unit (Fresenius Medical Care®, Bad Homburg, Germany) and Fresenius F70S or Fresenius F8HPS capillary dialyzers. All subjects included in this study underwent standard hemodialysis treatment 3 times a week (Monday, Wednesday and Friday).

Inclusion criteria: minimally 12 months of regular hemodialysis, symptomatical stability, and optimized pharmacological treatment unchanged 1 month before the start of the study.

Exclusion criteria: uncontrolled hypertension, history of venous thromboembolism, implanted cardiac pacemakers, unstable angina pectoris, heart failure, severe neurological diseases (epilepsy, multiple sclerosis, parkinsonism), severe orthopedic complications (after.total hip or knee replacement), chronic broncho-pulmonary disease, and urea clearance (spKt/v) >1.2.

Before beginning of the intra-dialytic RHB program, all patients underwent standard spiroergometric test on bicycle for the evaluation of exercise performance and aerometabolic capacity (peak O_2 uptake and peak workload) and 6-min corridor walk-test (6-CWT) to evaluate the distance walked (Fig.1).

Figure 1

Czech versions of two standard clinical questionnaires (KDQOL and FACIT) were used for evaluation of the impact of exercise training on the QoL. Exercise intensity was set at 50% of the peak workload rate achieved during the pre-training incremental ergometric test. After baseline testing, patients underwent 10-weeks intra-dialytic aerobic exercise training program consisting of bicycling 3 days/week on programmable bicycle ergometers (MOTOmed letto2, RECK® Co., Germany), adapted on the subject's dialysis chair or bed. Training was done always between the 2nd and the 3rd hour of HD. One complete session of RHB training consisted of initial stretching of leg muscles before connecting to dialyzer (5 min), releasing exercises of leg muscles (5 min), passive cycling on bed-side ergometer (1 min forward + 1 min backward), active aerobic training on ergometer (30 min), passive cycling on ergometer (1 min forward + 1 min backward), releasing exercise of leg muscles (5 min) and of terminal stretching of leg muscles after disconnection to dialyzer (5 min – Fig.2 and 3).

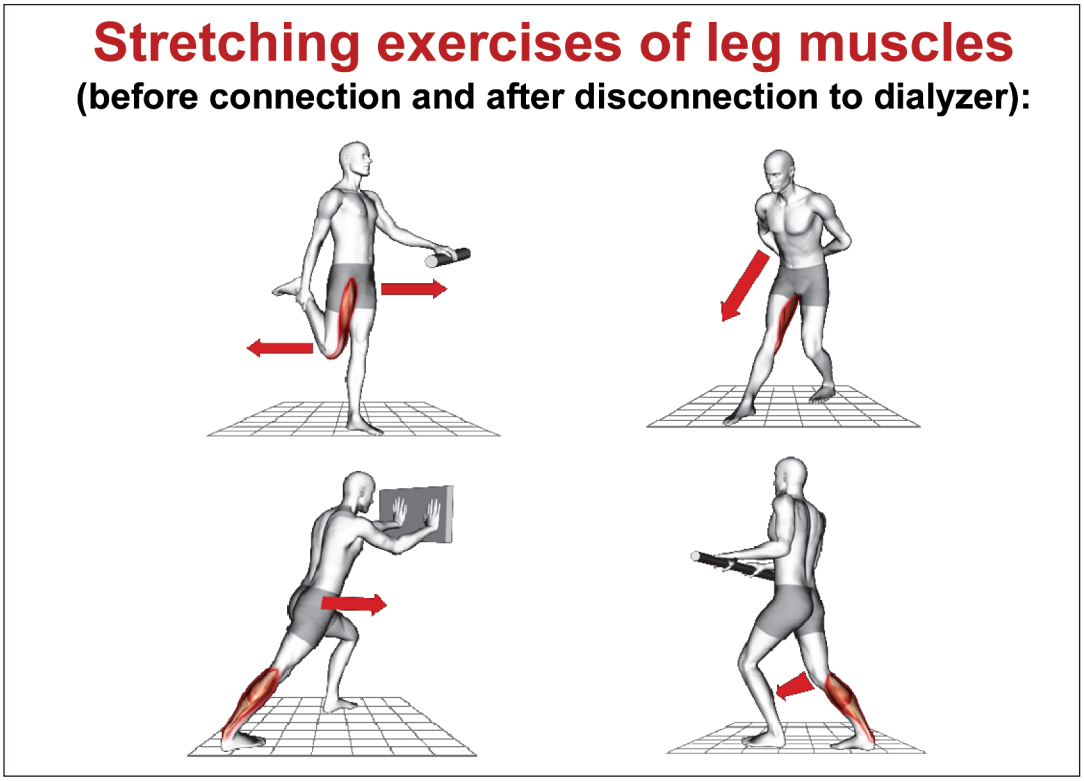


Figure 2

Figure 3

Total length of the training session lasted approximatively 54 minutes. All training sessions were supervised by a professional staff (physiotherapists and nurses).

Statistics

Microsoft Office Excel 2007 software for Windows Statistics and program version 10 MR1 were used for data processing. All data are presented as mean and standard deviation. Non-parametric Wilcoxon paired test was used for statistical analysis in order to exclude possible errors in normal data distribution. The value $P<0.05$ was considered as statistically significant.

Ethics

All patients 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 (as revised in Fortalezza, 2013) and to the GCP guidelines of the European community.

Results

Eight patients (6 men and 2 women; mean age 42.4±16.1 years) completed 10-weeks of supervised intra-dialytic exercise program (frequency 2 - 3 times a week). Basic characteristics of all the subjects are summarized in Table 1 and 2.

Patient	Age	Height	Weight	BMI	Number of HD sessions per week	Length of HD session (hours)	Frequency in ID-RHB participation (%)
S. O.	31	162	50	19.05	3	3	90
M. B.	20	156	47	19.31	2	4	80
B. V.	66	167	98	35.13	2	5	95
E. U.	57	179	85	26.53	2	4	100
L. B.	35	173	119	39.76	3	5	80
J. B.	61	174	100	33.03	2	4	95
V. P.	43	187	65	18.59	3	4	77
T. F.	26	173	50	16.70	3	4	87
Mean	**42.38**	**171.38**	**76.75**	**26.01**	**2.50**	**4.00**	**87.92**
SD	*16.09*	*9.07*	*25.74*	*8.34*	*0.50*	*0.56*	*7.94*

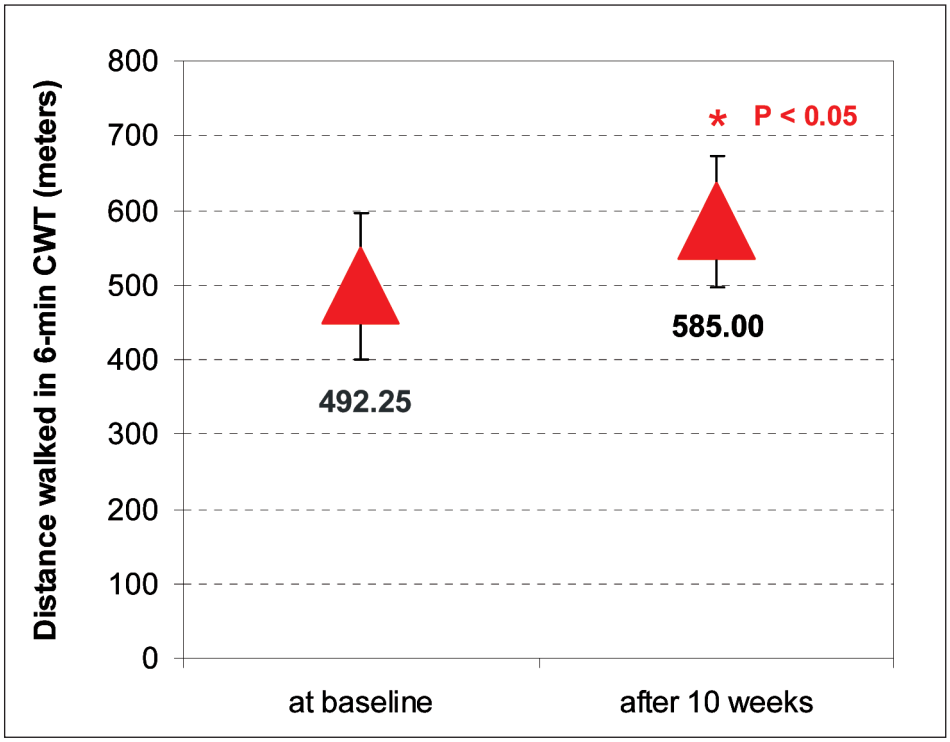
Table 1

Type of comorbidity:	Number:	Incidence (%):
anemia	6	75
hyperparathyreoidism	4	50
hypertension	3	37.5
hyperuricemia	3	37.5
dyslipidemia	2	25
hypoacusis	2	25
peripheral artery disease (PAD)	1	12.5
renal osteodystrophy	1	12.5
thrombosis	1	12.5
hyperhomocysteinemia	1	12.5

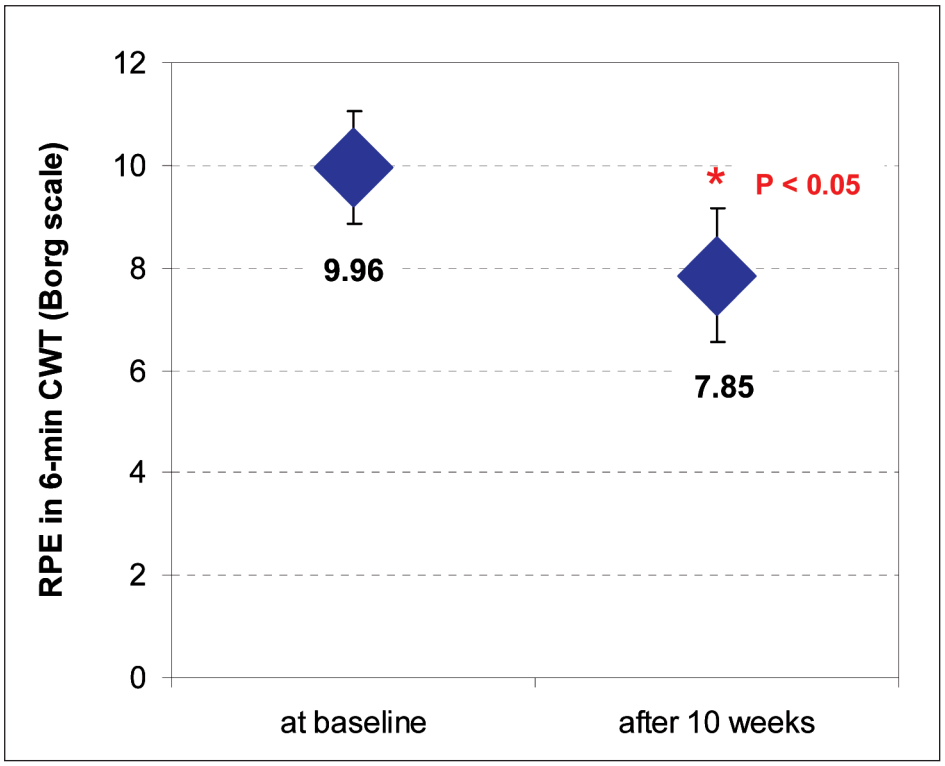
Table 2

Ten weeks of supervised intra-dialytic aerobic exercise program led to significant increase of the distance walked in 6 minutes, assessed by 6-CWT (from 492.25 ± 52.51 to 585.0m ± 86.25; *P<0.05 – Graph 1). Also After completion of intra-dialytic RHB program also significant reduction of fatigue and dyspnea (RPE) assessed by Borg scale was present (from 9.96 ± 1.94 to 7.85 ± 1.49; *P<0.05 – Graph 2). Analysis of the parameters of quality of life showed only weak significant improvement: in the questionnaire KDQOL (specific part) there was an improvement in subscale „staff support“ (from 81.25 ± 15.31 to 93.75 ± 10.83; *P<0.05 – Graph 3), and in the questionnaire FACIT in the subscale „social satisfaction“ (from 20.67 ± 5.14 to 22.67 ± 4,72; *P<0.05 – Graph 4). Only a trend to improvement was observed in other subscales of both questionnaires, however, without reaching statistical significance. Intra-dialytic exercise training in this study

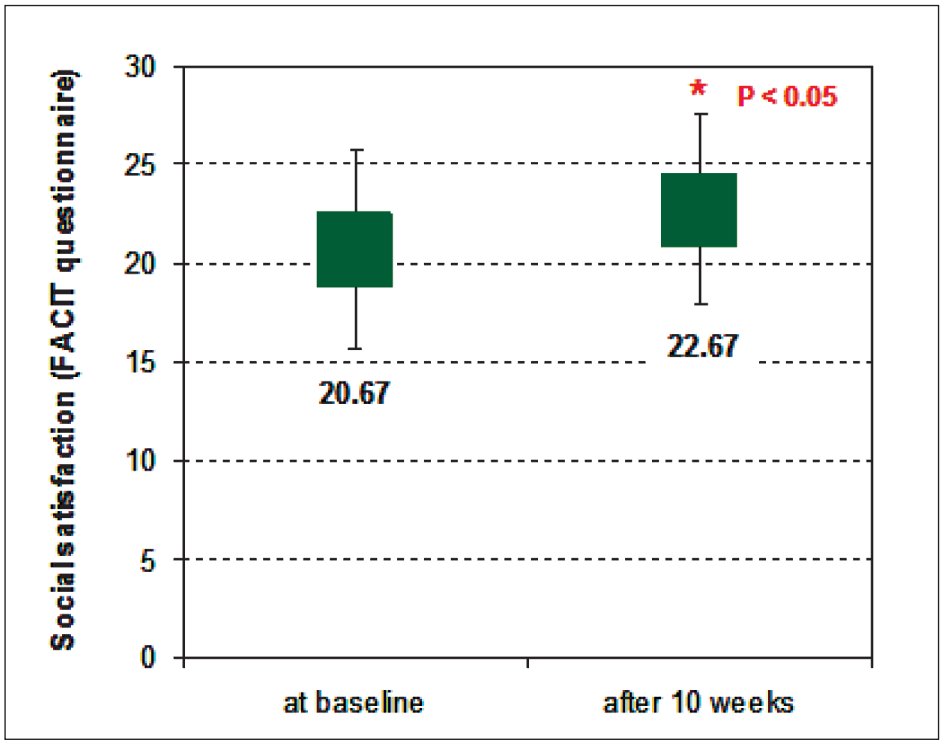
was well tolerated by all patients and in neither case were recorded complaints of discomfort or pain related to training procedure.



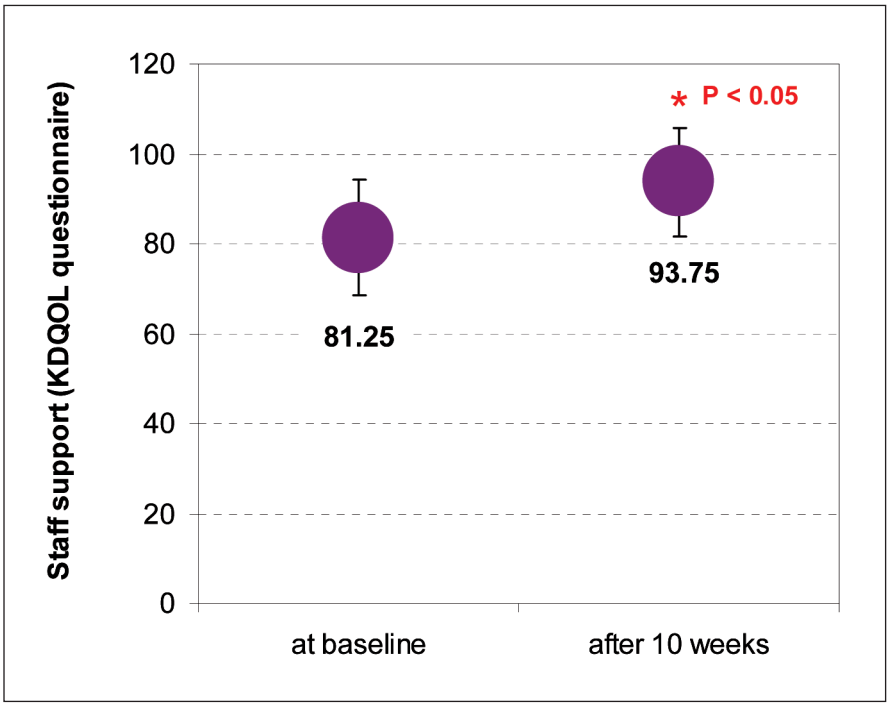
Graph 1



Graph 2



Graph 3



Graph 4

Discussion

According to the statement of the American College of Sports Medicine (ACSM) and the American Heart Association (AHA) the increase in physical activity should be one of the priorities for improving the physical fitness, reducing the risk of chronic disease or preventing unhealthy weight gain in adults (8, 9). Dialysis patients commonly have poor exercise tolerance and debilitation symptoms and impaired quality of life. Functional capacity is mainly limited by fatigue, but dyspnea on exertion is also a contributing factor (10). Aerobic capacity, peripheral skeletal muscle strength, and endurance in hemodialysis patients are approximately half that of the corresponding healthy sedentary aged-matched men (11). Anemia, deconditioning, cardiac dysfunction, impairment of autonomic balance, and mainly skeletal muscle weakness and fatigue, primarily because of uremic myopathy and neuropathy, are the main predisposing factors for their low functional ability (12). Moreover, the deleterious influence of both small and middle molecular weight uremic retention solutes, known as uremic toxins, plays an important role in these morphological and functional abnormalities (13). Johansen et al. reported that physical activity as measured by accelerometer was significantly lower in HD patients than in age-matched sedentary controls (14). Furthermore, it was demonstrated that the physical activity level in HD patients declined at a rate of 3.4% per month during an observation period of 12 months or more (15). These reports indicate that HD patients are more inactive compared to healthy adults and that their physical activity levels decline gradually. Typical exercise-training program during hemodialysis session usually contains a combination of exercises, consisting of up to 30 min cycling on bed-side ergometer and up to 10-20 min exercises for flexibility, coordination, and muscle strength (16, 17). Similar protocol was used also in the present study. We demonstrated that 10 weeks of intra-dialytic aerobic exercise training combined with strength and releasing exercises can significantly improve the submaximal physical capacity in HD patients. In concordance with several previously published reports we have shown that there are functional and psychological benefits from using regular intra-dialytic exercise training as adjunctive therapy in the treatment of dialysis patients (18, 19). Exercise training was shown to improve skeletal muscle endurance and strength and, thus, peak exercise performance in hemodialysis patients (20). Biopsy studies have demonstrated an increase in both Type I and Type II muscle fiber cross-sectional areas after both endurance and strengthening training in chronic uremic patients (21). In addition, regeneration of degenerated fibers, increase in capillary density, and favorable changes in the structure and number of mitochondria were also described (22). Mental health needs, especially episodes of depressed mood and even clinical depression, are prevalent among CRD patients (23). One of the key components of depressed mood is loss of interest in doing things. Depressed mood is often associated with decreased behavioral compliance with therapy, and non-adherent patients may be viewed by staff as “unmotivated” or “self-destructive” (24). Importantly, the increase in exercise tolerance seems to be correlated with symptomatic improvements in health-related quality-of-life measurements (19). Depressed patients with CRD had the greatest profit from exercise training, including significant improvement of QoL (18). Aerobic training decreases the prevalence of depression in patients with advanced CRD and also in patients on HD participating in the intra-dialytic exercise program (26). Exercise program improves anxiety symptoms as well as the physical and mental health scores of the SF-36 questionnaire (27, 28). Intra-dialytic training enhances also the appetite as well as calorie and protein in patients on HD (29). Exercise during the hemodialysis sessions seems to be most convenient and time-efficient way of training in patients on hemodialysis (30). An advantage of this method is that it does not create a need for extra time because patients are in the hospital 3 times per week anyway. Therefore, this mode of training is more applicable and preferable from the patient’s point of view, because the reported compliance with exercise training during hemodialysis is high (31). The outcome is more pronounced in patients who participate in an outpatient supervised program, because a greater dose and variety of exercises are applied (31). However, each patient should be encouraged to participate in any exercise-training program according to his or her needs and time schedules. Initial improvements in functional capacity in traditional programs occur at 4 weeks, and peak adaptations are seen at 16–26 weeks of training (12). Patients should be motivated and incited to include physical activity in their lifestyle, because

all exercise benefits are lost within a few weeks of non-training, and those who receive no exercise seem to deteriorate over time (12). There are some limitations to the present study. First, the training program lasted only 10 weeks and it seems that this is not enough to achieve more statistically significant results (usual length of such types of intra-dialytic RHB is at least 20 weeks). Thus, further examination will be needed to investigate the optimal length of intra-dialytic training. Finally, the absence of control group in the present study reduces somewhat the importance of the results.

Conclusion

This study proved beneficial effect of intra-dialytic supervised aerobic training on functional performance, subjective perception of exertion and quality of life in patients on HD. However, it is likely that only 10 weeks of training is too short period to achieve more important statistical significance to change key parameters. We strongly recommend that staff responsible for the care of dialysis patients should include exercise training as an integral part of the long-term management. We confirm that patients undergoing maintenance HD should engage intra-dialytic aerobic exercise training for at least 30 min per HD session to prevent deterioration of their physical performance. Moreover, participation in the intra-dialytic exercise program is effective for maintenance of a good QoL. There is an acute need to support future clinical research trials appropriately designed to further study this potentially efficacious intervention on outcomes such as quality-adjusted life expectancy, morbidity, health care and transportation costs.

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Disclosure

The authors declare no conflicts of interest.

References

1. Tonelli M, Wiebe N, Culleton B, House A, Rabbat C, Fok M, et al. Chronic kidney disease and mortality risk: a systematic review. J Am Soc Nephrol 2006; 17: 2034-47.
2. Baigent C, Burbury K, Wheeler D. Premature cardiovascular disease in chronic renal failure. Lancet 2000; 356: 147-52.
3. O'Hare AM, Tawney K, Bacchetti P, Johansen KL. Decreased survival among sedentary patients undergoing dialysis: results from the dialysis morbidity and mortality study wave 2. Am J Kidney Dis 2003; 41: 447-54.
4. Bird SR, Hawley JA. Exercise and type 2 diabetes: new prescription for an old problem. Maturitas 2012; 72: 311-6.
5. Hawley JA, Holloszy JO. Exercise: it's the real thing. Nutr Rev 2009; 67: 172-8.
6. Storer TW, Casaburi R, Sawelson S, Kopple JD. Endurance exercise training during haemodialysis improves strength, power, fatigability and physical performance in maintenance haemodialysis patients. Nephrol Dial Transplant 2005; 20: 1429-37.
7. Painter P. Physical functioning in end-stage renal disease patients: update 2005. Hemodial Int 2005; 9: 218-35.

8. Nelson ME, Rejeski WJ, Blair SN et al. Physical activity and public health in older adults: recommendation from the American College of Sports Medicine and the American Heart Association. Circulation 2007; 116: 1094–105.

9. Haskell WL, Lee IM, Pate RR et al. Physical activity and public health: updated recommendation for adults from the American College of Sports Medicine and the American Heart Association. Circulation 2007;116:1081–93.

10. Johansen KL. Physical functioning and exercise capacity in patients on dialysis. Adv Ren Replace Ther 1999; 6: 141–48.

11. Painter P, Messer-Rahak D, Hanson P, Zimmerman SW, Glass NR. Exercise capacity in hemodialysis, CAPD, and renal transplant patients. Nephron 1986; 42: 47–51.

12. Kouidi E. Central and peripheral adaptations to physical training in patients with end-stage renal disease. Sports Med 2001; 31: 651–65.

13. Vanholder R, Argiles A, Baurmeister U et al. Uremic toxicity: present state of the art. Int J Artif Organs 2001; 24: 695–725.

14. Johansen KL, Chertow GM, Ng AV et al. Physical activity levels in patients on hemodialysis and healthy sedentary controls. Kidney Int 2000; 57: 2564–70.

15. Johansen KL, Kaysen GA, Young BS, Hung AM, Da Silva M, Chertow GM. Longitudinal study of nutritional status, body composition, and physical function in hemodialysis patients. Am J Clin Nutr 2003; 77: 842–6.

16. Painter P, Nelson-Worel J, Hill M, Thornbery D, Shelp W, Harrington A, Weinstein A. Effects of exercise training during hemodialysis. Nephron 1986; 43: 87–92.

17. Konstantinidou E, Koukouvou G, Kouidi E, Deligiannis A, Tourkantonis A. Exercise renal rehabilitation: comparison of three exercise programs. J Rehabil Med 2001; 34: 40–5.

18. Kouidi E, Iacovides A, Iordanidis P, Vassiliou S, Deligiannis A, Ierodiakonou C, Tourkantonis A. Exercise renal rehabilitation program (ERRP): Psychosocial effects. Nephron 1997; 77: 152–8.

19. Painter PL. The importance of exercise training in rehabilitation of patients with end-stage renal disease. Am J Kidney Dis 1994; 24(Suppl 1): 2–9.

20. Cappy CS, Jablonka J, Schroeder E. The effects of exercise during hemodialysis on physical performance and nutrition assessment. J Renal Nutrition 1999; 9: 63–70.

21. Castaneda C, Gordon PL, Uhlin KL, Levey AS, Kehayias JJ, Dwyer JT, Fielding R, Roubenoff R, Singh MF. Resistance training to counteract the catabolism of a low-protein diet in patients with chronic renal insufficiency. Ann Intern Med 2001; 135: 965–76.

22. Kouidi E, Albani M, Natsis K, Megalopoulos A, Gigis P, Guiba-Tziampiri O, Deligiannis A, Tourkantonis A. The effects of exercise training on muscle atrophy in hemodialysis patients. Nephrol Dial Transpl 1998; 13: 685–99.

23. Finkelstein FO, Wuerth D, Troidle LK, Finkelstein SH. Depression and end-stage renal disease: a therapeutic challenge. Kidney International 2008; 74: 843-845.

24. Johnstone S. Wellness programming: nephrology social work expands its role in renal disease management. Nephrology News & Issues 2005; 19(12): 59-71.

25. Painter P, Carlson L, Carey S, Paul SM, Myll J: Physical functioning and health-related quality-of-life changes with exercise training in hemodialysis patients. Am J Kidney Dis 2000; 35: 482–492.

26. Ouzouni S, Kouidi E, Sioulis A, Grekas D, Deligiannis A: Effects of intradialytic Exercise training on health-related quality of life indices in haemodialysis patients. Clin Rehabil 2009; 23: 53–63.

27. Oh-Park M, Fast A, Gopal S: Exercise for the dialyzed: aerobic and strength training during hemodialysis. Am J Phys Med Rehabil 2002; 81: 814–821.

28. Dobsak P, Homolka P, Svojanovsky J et al. Intra-dialytic electrostimulation of leg extensors may improve exercise tolerance and quality of life in hemodialyzed patients. Artif Organs 2012; 36(1): 71-8.

29. Frey S, Mir AR, Lucas M: Visceral protein status and caloric intake in exercising versus nonexercising individuals with end-stage renal disease. J Ren Nutr 1999; 9: 71–77.

30. Painter P, Nelson-Worel J, Hill M, Thornbery D, Shelp W, Harrington A, Weinstein A. Effects of exercise training during hemodialysis. Nephron 1986; 43: 87–92.

31. Konstantinidou E, Koukouvou G, Kouidi E, Deligiannis A, Tourkantonis A. Exercise renal rehabilitation: comparison of three exercise programs. J Rehabil Med 2001; 34: 40–5.

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