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NONINVASIVE METHODS IN CARDIOLOGY 2015

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THE PROPERTIES OF BLOOD AND ITS MODIFICATIONS BY BODY POSITION AND BY VASCULAR REACTIONS

THOMAS KENNER AND DIETER PLATZER
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Overview

In 1977 we had the opportunity to use a so called oscillator technique for the continuous measurement of the mechanical density of fluids. The device was developed by O. Kratky and coworkers (1969) and constructed by A. Paar KG in Graz. The working group at the department of physiology performed measurements of blood in animal experiments and also in a patient during hemodialysis. A summary of the first results were published at the 13th International Conference on Medical and Biological Engineering (1982). Here I report about the doctoral dissertation by F. Vauti in 1984. Body temperature, heart rate, blood pressure, blood density, plasma density and hematocrit, hematocrit, number of erythrocytes and of leucocytes were measured in capillary blood during day and night for 48 hours. In addition to the results in Dr. Vauti's dissertation [1], measurements performed in a healthy person in a laboratory of the Surgical Clinic have been made. The most surprising result was that the oscillations of the arterial blood density were synchronized with the respiration. In summary, all measurements demonstrated synchronizations. This could be observed between blood density and time of day and between blood density and respiration.

Blood Density and Vascular Reactions

Many physiological as well as pathological processes of life exhibit periodic patterns. As repeatedly presented and discussed by Professor Franz Halberg these processes exhibit characteristic interconnections as well as frequencies. Chronobiological research has therefore important diagnostic as well as therapeutic relevance. Also in daily life with its circadian rhythms effects of environmental changes strongly depend on the specific timing. Additional influences include the body position and gravitational changes e.g. during space flight.

As mentioned above, data from blood density measurements reveals respiration as significant determinant of blood density fluctuations. Registrations from the cubital artery of a human person demonstrate the influence of the breathing on the arterial blood density. Figure 1 shows that the amplitude of the density changes depends on the breathing period: in this case the amplitude exhibits a maximum at a period of 20 seconds.

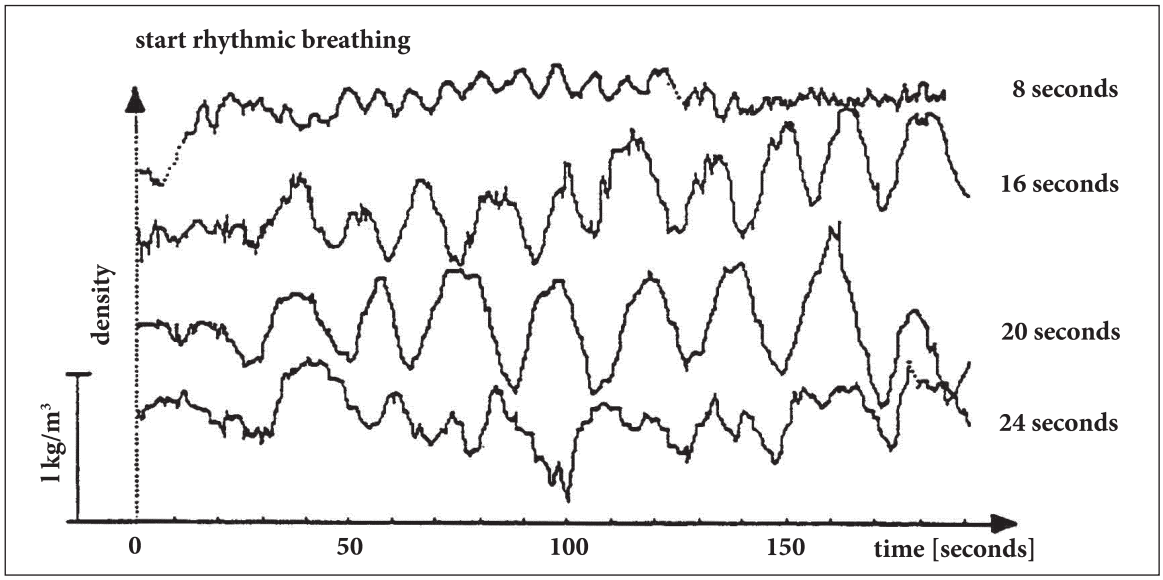

Figure 1: *Density of arterial blood in the cubital artery during rhythmic breathing. (4 experiments in one person.)*

Evans and Lee (1987) [2] reported equivalent results from measurements on artificially ventilated dogs. They deduced from the density fluctuations the percentage volume change of pulmonary capillaries. Both investigations indicate the potential of blood density measurement technique for in vivo assessment of the viscoelastic properties of the pulmonary capillaries. A comprehensive overview of density measurement applications can be found in Kenner (1982) [3].

Body Position and Gravitation

Many physiological parameters are influenced by gravitation and its direct effect on the body fluids. Tilting a person from horizontal into upright position induces hemoconcentration and increase of the hematocrit as a consequence of the increased fluid filtration in the lower body (Figure 2).

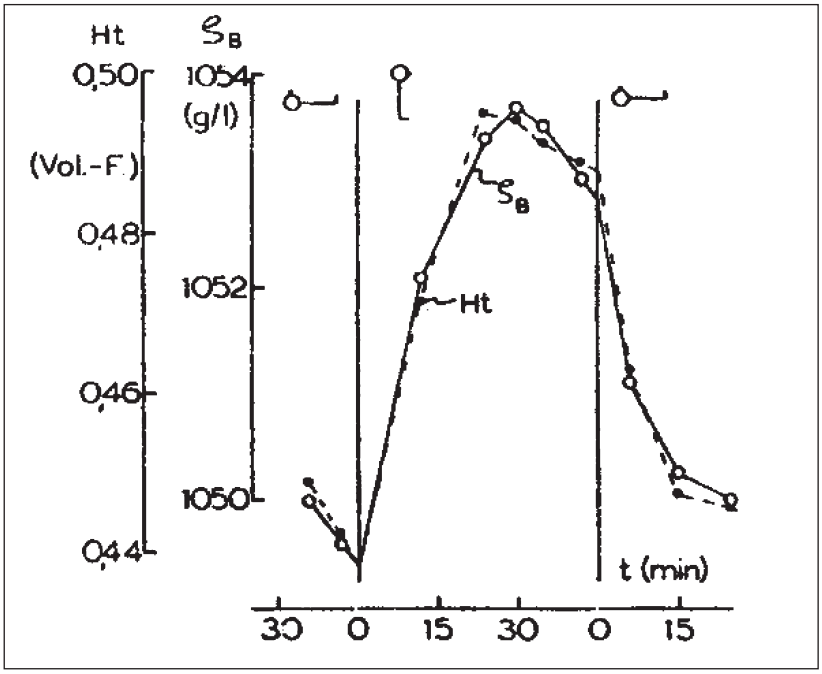

Figure 2: *Time course of Ht (hematocrit, dashed line) and ρ (blood density, dottet line) – during changes the body position.*

Vauti [5] sampled capillary blood from the earlobes of six healthy young men in supine (0°) and upright (70°) head up tilt position. The subjects rested on a tilt table in supine position for 50 minutes. Subsequently blood was sampled 4 times in intervals of 10 minutes. Tilting the body into upright position, blood was taken after 30 and 40 minutes of orthostatic load. The subjects were instructed to minimize tonus in the respective muscles. The protocol was repeated every three hours over a period of 48 hours (Figure 3)

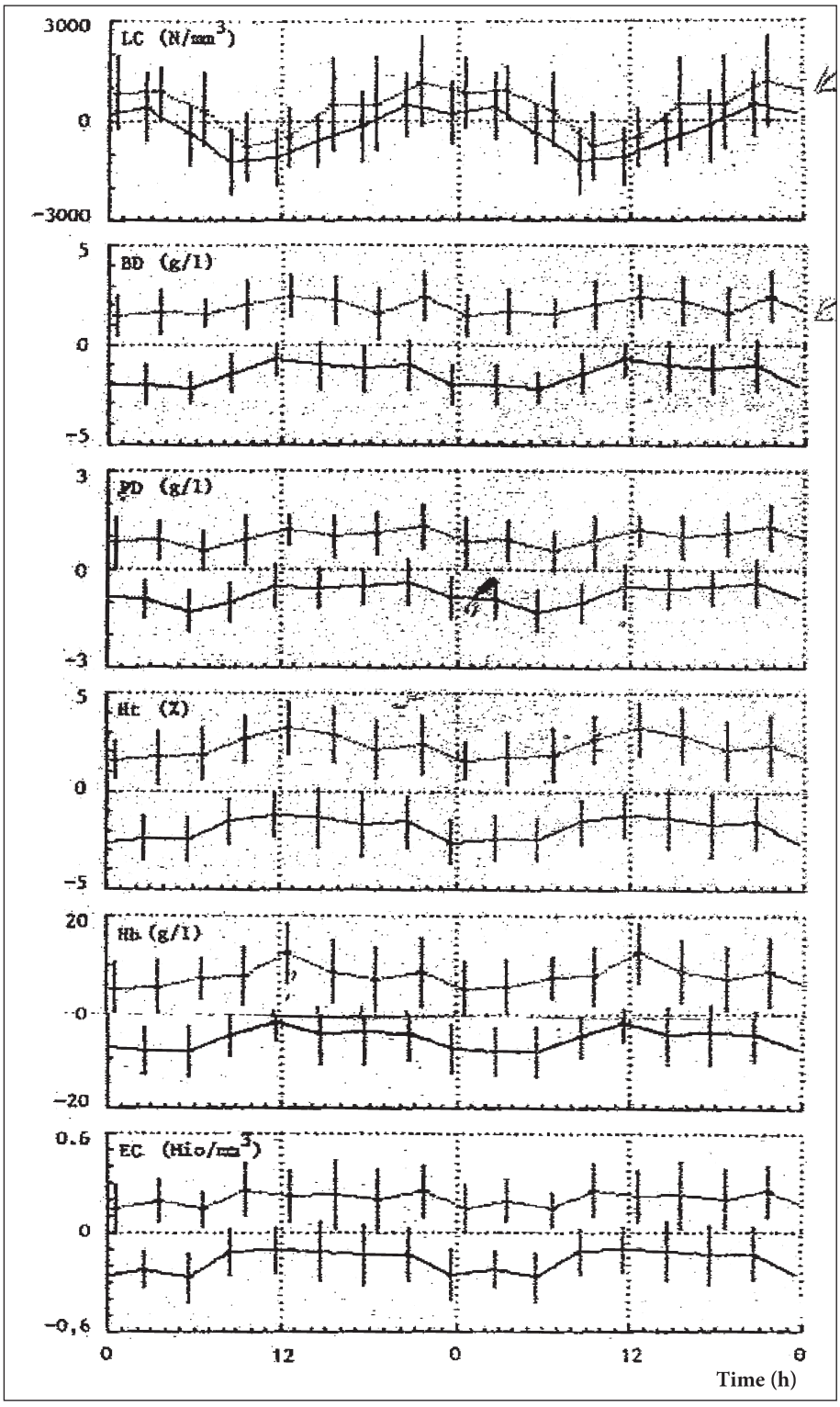

Figure 3: *Circadian rhythms of blood values in supine (continuous line) and standing (dotted line) position. Data are plotted as deviations from the 24h average.*

Blood samples were used for the determination of hemoglobin (Hb), hematocrit (Ht) and erythrocyte count (EC), whole blood density (BP) and plasma density (PD). The observed variations of parameters can be explained by corresponding changes of water content in the plasma. It has to be noted that the investigations by Vauti also reveal a pronounced circadian modulation of the hematological parameters. This finding underlines the importance of chronobiological research.

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WHY 7-DAY/24-HOUR AMBULATORY BLOOD PRESSURE MONITORING? DAY-TO-DAY VARIABILITY IN BLOOD PRESSURE AND THE NOVELTY EFFECT

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Dedicated to the memory of Franz Halberg and Bohumil Fiser

Abstract

Blood pressure (BP) and heart rate (HR) vary greatly, from one individual to another and from moment to moment in any longitudinal record. Variability in BP and HR can be accounted for by genetics, epigenetics, and in response to a variety of stimuli. Reference values in health provide guidelines to distinguish between usual and abnormal variability in BP and/or HR, in terms of deviant circadian characteristics and/or excess/deficit relative to time-specified limits of acceptability. This investigation examines the day-to-day variability in circadian rhythm characteristics determined from analyses of 7-day/24-hour records obtained by ambulatory BP monitoring (ABPM) in Brno, Czech Republic. A novelty pressor effect is quantified by comparing circadian parameters in consecutive days of monitoring. Results interpreted in terms of clinical implications indicate the need to monitor BP around the clock for longer than 24 hours, preferably for 7 days at the outset, in keeping with recommendations from the 2008 consensus meeting held in Brno.

Introduction

Blood pressure (BP) and heart rate (HR) vary greatly, from one individual to another and from moment to moment in any longitudinal record [1-4]. An example is illustrated in Figure 1. A 24-hour ABPM profile of systolic (S) BP is shown from two different patients. The circadian variation is present in both cases, with lower values by night and higher values by day. Despite a similar 24-hour MESOR (Midline Estimating Statistic Of Rhythm, a rhythm-adjusted mean), the two profiles differ greatly in their circadian amplitude. Inter-individual differences are found not only in MESOR but also in terms of their circadian variation, among others.

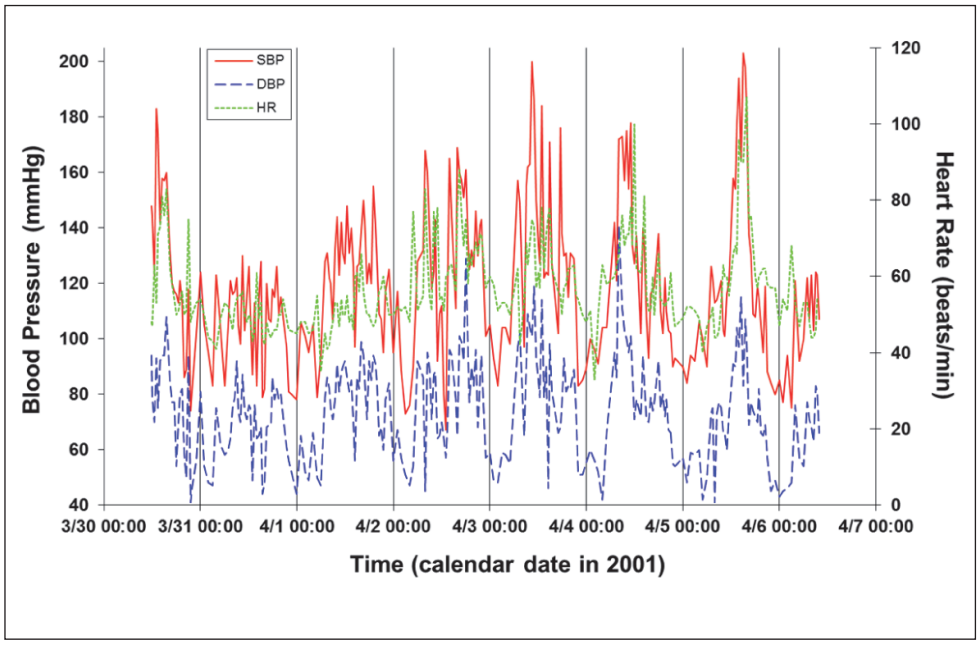

Figure 1: *Different circadian patterns of systolic blood pressure (SBP) in two clinically healthy men. © Halberg Chronobiology Center.*

As documented in detail previously [5-7] and illustrated in Figure 2, 7-day/24-hour ABPM records allowed the demonstration of a great deal of day-to-day variability in circadian rhythm characteristics observed in the same subject. In part, this variability can be accounted for by differences between work days and weekends/holidays [8].

Inter-individual differences in BP and HR can be accounted for genetics [9-12] and epigenetics [13]. BP and HR are also greatly influenced by a variety of stimuli (diet, exercise, emotions, temperature, cosmic radiation, etc.) [14-21].

Elevated BP is asymptomatic, as are other abnormal patterns of BP variability, until there is target organ damage. Like high BP, abnormal circadian characteristics of BP and HR variability are associated with increases in cardiovascular disease risk, as documented by several outcome studies that led to the 2008 Brno consensus document [22].

For these reasons, it is important to accurately assess the circadian variation in BP and HR, and to determine the extent of day-to-day variability in their circadian rhythm characteristics. This is the purpose of this investigation which focuses more specifically on any novelty pressor effect, that is an elevated BP at the start of monitoring, related to the habituation to repeated cuff inflation that may bring about anxiety and inability to fully relax. The definition given in Wikipedia is “The novelty effect is the tendency for an individual to have the strongest stress response the first time that individual is faced with a potentially threatening experience”.

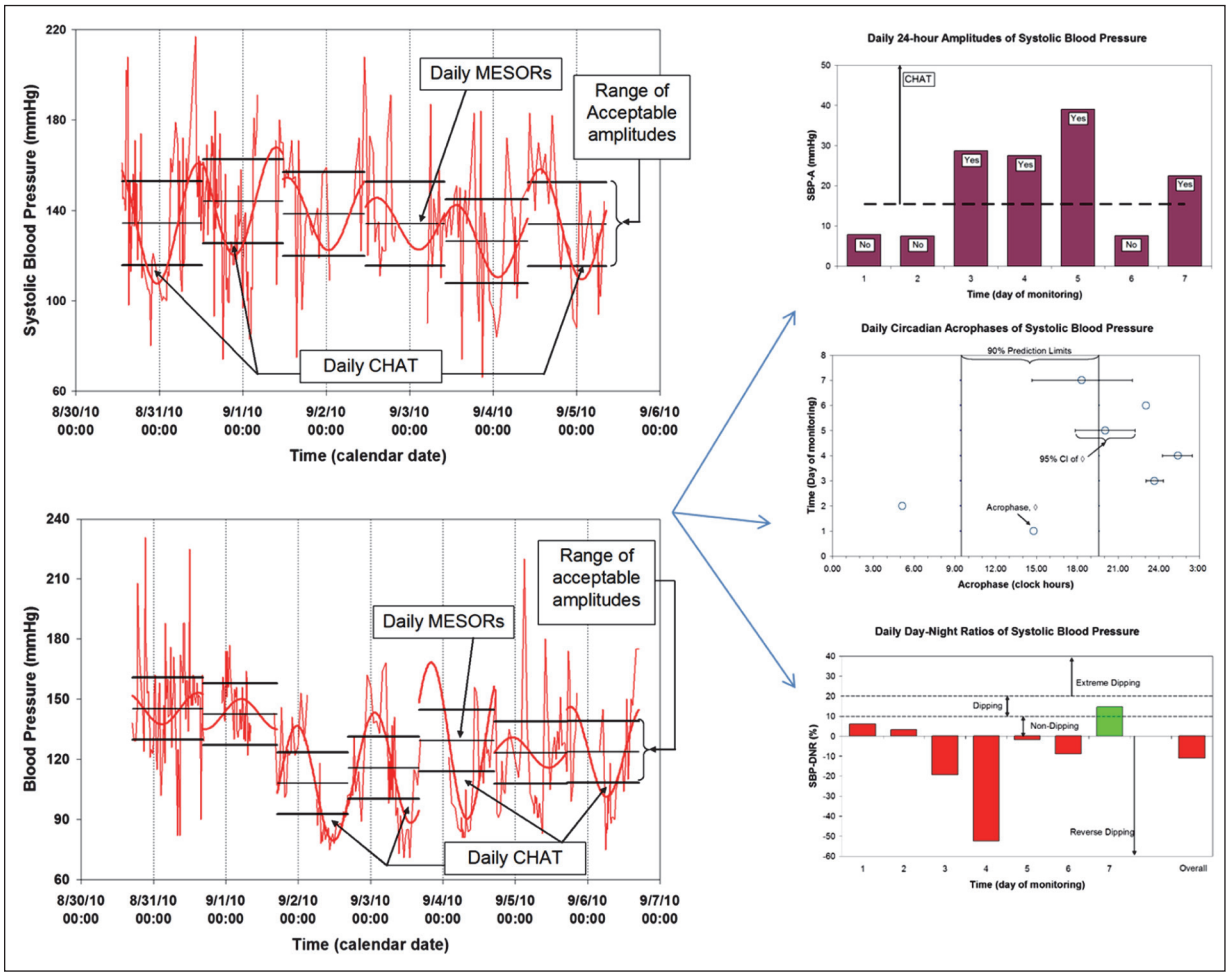

Figure 2: *Extent of day-to-day variability in the circadian characteristics of systolic blood pressure from two different subjects [6]. Data are shown with 24-hour cosine model fitted separately to consecutive days (left). Daily estimates of the circadian amplitude (top, right), acrophase (middle, right), and day-night ratio (bottom, right) are interpreted in the light of reference values from clinically healthy subjects matched by gender and age. © Halberg Chronobiology Center.*

Subjects and Methods

BP and HR were measured around the clock, mostly at 30-minute intervals for 7 days by 297 subjects in Brno, Czech Republic. The oscillometric readings from the TM-2421 ABPM monitor (A&D, Tokyo, Japan) were used for analysis, as outlined previously [23]. Each record was analyzed by sphygmochron [24] over the entire record, and separately during consecutive days. Specifically, a 2-component model consisting of cosine curves with periods of 24 and 12 hours was fitted to the data by cosinor [25-28]. To assess the novelty pressor effect, the parameters of the 24-hour component on days 2-7 were compared to those of day 1 by paired t-test.

Results

Because not all subjects monitored for 7 days, and in view of interruptions preventing a reliable estimate of circadian parameters on some days, the reference group on day 1 differed slightly for

comparison with results on days 2-7. Data from 262, 258, 253, 246, 242, and 231 subjects were available for comparisons on days 2-7 vs. day 1. Average estimates of circadian parameters on day 1 did not differ whether all subjects or only subjects providing sufficient data on days 2-7 were considered. The MESOR of SBP, diastolic (D) BP, HR, pulse pressure (PP, difference in MESOR between SBP and DBP), the 24-hour amplitude of SBP, DBP, and HR, and the standard deviation (SD) of HR were compared.

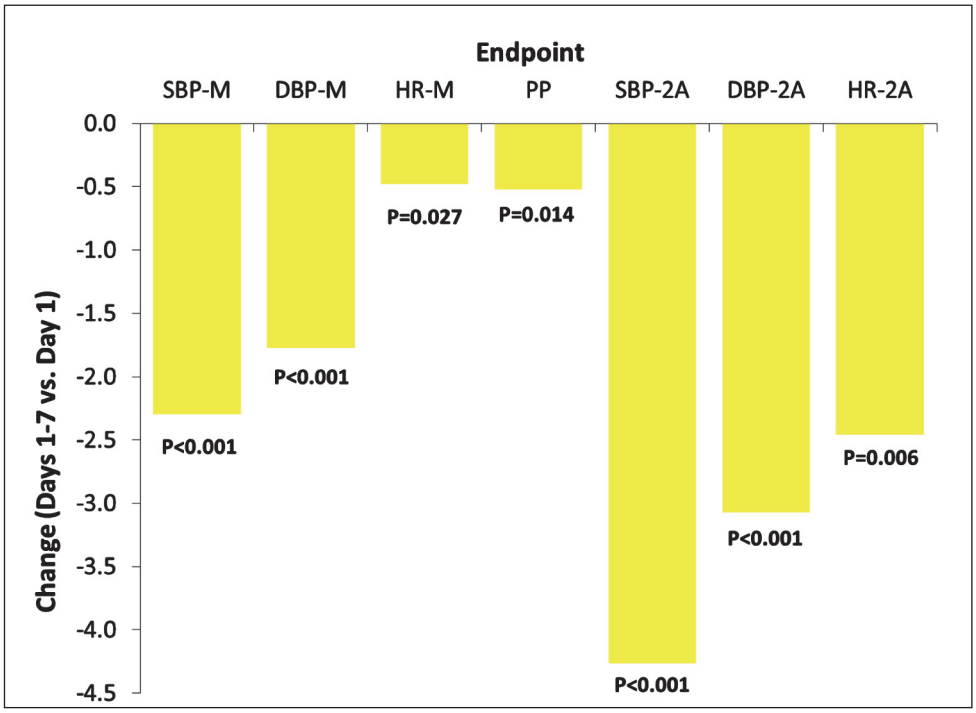

Figure 3: *As compared to estimates on day 1 (used as reference; equated to 0), all circadian parameters are lower when they are estimated on the entire record. SBP: Systolic BP; DBP: Diastolic BP; PP: Pulse Pressure; -M: MESOR; -2A: double 24-hour amplitude (extent of predictable change within one cycle). SBP, DBP, PP in mmHg; HR in beats/min.*
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By contrast, all circadian parameters are elevated on day 1 as compared to estimates obtained from the entire record, Figure 3. Moreover, all circadian parameters are elevated on day 1 as compared to estimates obtained on subsequent days. As shown in Figure 4, the extent and duration of the novelty effect depends on the circadian parameter considered. The MESOR of SBP and DBP is consistently lower on days 2-7 as compared to day 1 ($P<0.001$). In the case of DBP, the MESOR continues to decrease from day 2 to day 4, suggesting that the novelty effect may last more than one day. Pulse pressure is also consistently lower on days 2-7 as compared to day 1 ($P<0.05$), but the difference is small on average (about 1 mmHg or less). Only a small decrease in the MESOR of HR is observed on days 2 and 3 (about 1 beat/min) before returning toward values similar to those of day 1.

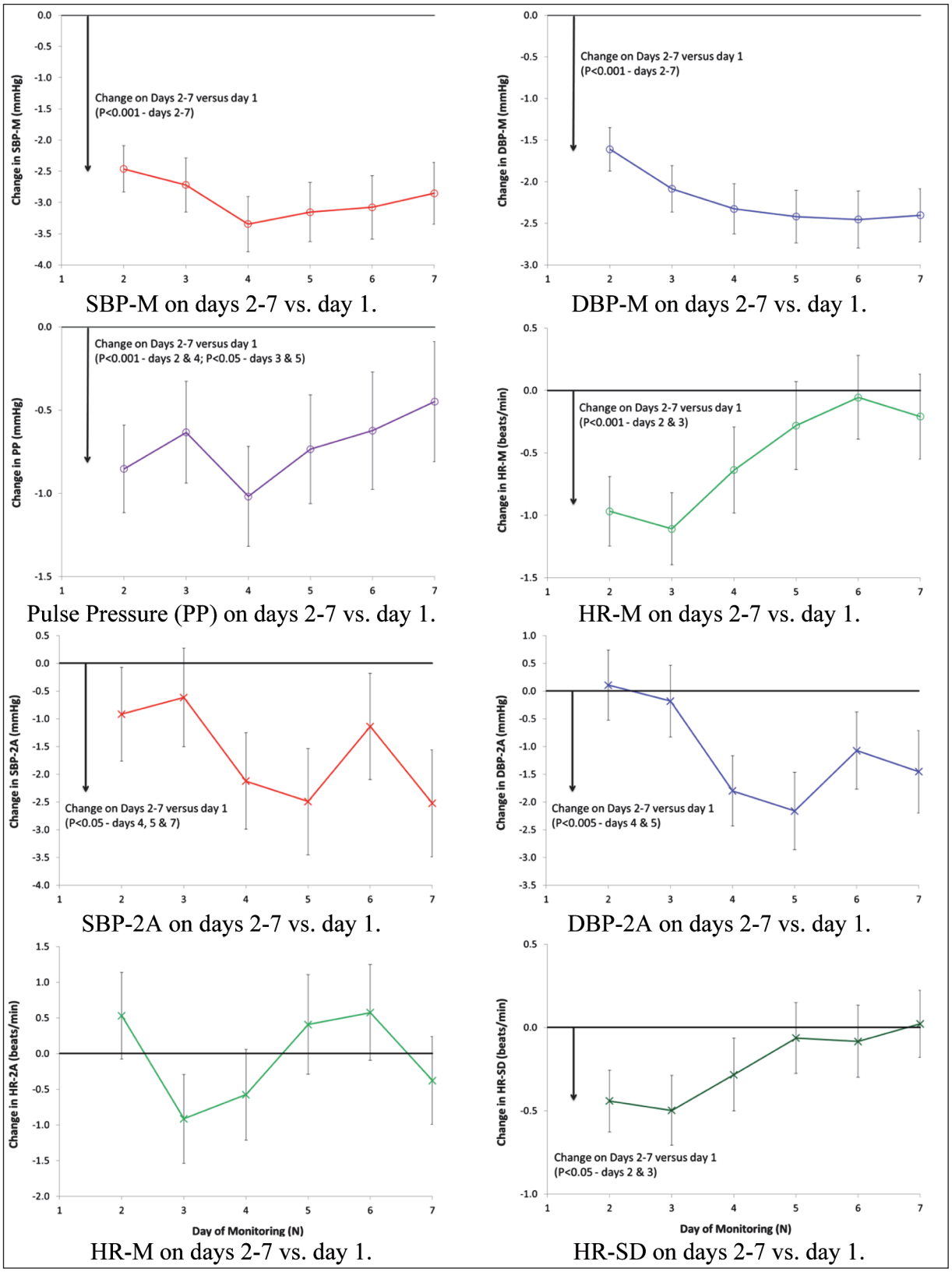

Figure 4: *Estimates of circadian characteristics on day 1 are used as reference (zero) to assess change on days 2-7, on the average across all subjects.*
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The circadian double amplitude of SBP and DBP is also larger on day 1 as compared to subsequent days. By contrast, no statistically significant change is found for the double amplitude of HR. The initial decrease in the SD of HR observed on days 2 and 3 is small and is followed by a progressive increase toward values assumed on day 1, Figure 4.

Part of the day-to-day variability in BP and HR is contributed by the about-weekly (circaseptan) and half-weekly (circasemiseptan) variation, invariably detected (N=276 subjects) with statistical significance by population-mean cosinor (P<0.005). Maxima occur on Mondays with a secondary peak toward the end of the week, as illustrated in Figure 5 for SBP, DBP, and HR.

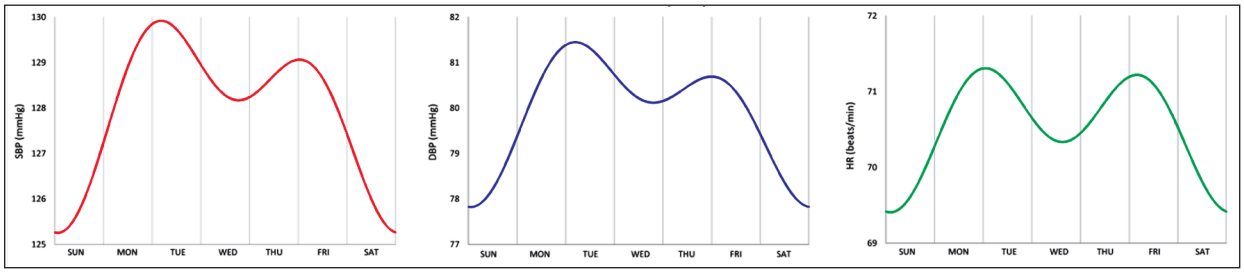

Figure 5: *Model about-weekly variation in SBP (left), DBP (middle), and HR (right) based on results from the population-mean cosinor (N=276 subjects). © Halberg Chronobiology Center.*

Clinical Implications

Whereas there is consensus that 24-hour ABPM is superior to clinic measurements in terms of diagnosis and prognosis [25], the limitations of 24-hour ABPM are not widely recognized. Both the novelty pressor effect and the circaseptan variation contribute to these limitations, as do the many events in everyday life. As shown herein, not only is the 24-hour average (MESOR) BP affected, so are the circadian rhythm characteristics. From a clinical point of view, this means that a bias from the novelty pressor effect can be expected to affect not only the diagnosis of MESOR-hypertension, but also that of CHAT (Circadian Hyper-Amplitude-Tension, defined as an excessive circadian amplitude of BP, a condition associated with an increased cardiovascular disease risk [22]).

In order to gain a better understanding of the actual limitations associated with ABPM limited to 24 hours, the data from the Brno database were further analyzed by sphygmochron to compare results of analyses of data collected on consecutive days with those considering the entire record. We found that abnormality on at least 1 day was found in all but 7 subjects. Different kinds of abnormalities of BP, HR and their variabilities, known as Vascular Variability Anomalies (VVAs) were detected. They include systolic MESOR-hypertension (S-MH), diastolic MESOR-hypertension (D-MH), excessive pulse pressure (EPP: PP>60 mmHg), systolic CHAT (S-CHAT), diastolic CHAT (D-CHAT), deficient HR variability (DHRV: HR-SD<7.5 beats/min), systolic ecphasia (S-ecPhi: an odd timing of the circadian variation of BP but not of HR), and diastolic ecphasia (D-ecPhi). These conditions were found to occur on at least 1 day in 33, 30, 14, 51, 46, 26, 56, and 68% of subjects, respectively. By comparison, only 15, 14, 5, 8, 6, 4, 7, and 6% of subjects were found to have these VVDs when the whole 7-day record was analyzed. The ability to accurately diagnose these VVAs is important since they were predictive of overall mortality in this population [26].

A novelty pressor effect has been reported in other studies [27-30]. It may account for the fact that in another database of 7-day/24-hour records obtained in a Japanese town, the diagnosis of MESOR-

hypertension based on the first day of a 7-day record could not predict the occurrence of adverse cardiovascular events with statistical significance, but it did when the diagnosis was made based on the 7-day record [31].

Discussion and Conclusion

The usefulness of ABPM has been recognized for the evaluation of white-coat hypertension, masked hypertension, and BP responses during exercise and laboratory stress [32]. ABPM, however, is often limited to a single 24-hour record, interpreted in the light of conventional fixed limits. Herein, we showed that a novelty pressor effect affects not only the estimation of the BP MESOR, but also the estimation of the circadian pattern of BP. The diagnosis of MESOR-hypertension is therefore biased, as is the diagnosis of other VVAs. To obtain a more accurate diagnosis, it is thus necessary to monitor BP around the clock for longer than 24 hours.

Results herein indicate that the novelty pressor effect may last longer than 24 hours, notably in relation to the MESOR of DBP and to the circadian amplitude of SBP and DBP. In view of the statistically significant circaseptan rhythm characterizing BP and HR that accounts for differences of a similar extent as that observed in relation to the novelty pressor effect, it is recommended to monitor BP for at least 7 days at the outset. This recommendation is in keeping with guidelines outlined during the 2008 Brno consensus meeting [22].

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APPLICATIONS OF CHRONOBIOLOGICALLY-INTERPRETED 7-DAY/24-HOUR AMBULATORY BLOOD PRESSURE MONITORING: FROM HEALTH MAINTENANCE AND PRIMARY PREVENTION TO CHRONOTHERAPY

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Dedicated to the memory of Franz Halberg and Bohumil Fiser

Abstract

Since ambulatory blood pressure monitoring (ABPM) became feasible, around-the-clock data have been collected in health and disease by an international team of investigators within the scope of the project on the BIOsphere and the COSmos (BIOCOS). The derivation of time-specified reference values in health, qualified by gender, age, and whenever possible, ethnicity, led to the definition of Vascular Variability Disorders (VVDs), abnormal patterns of blood pressure and/or heart rate variability. Outcome studies documented their association with an increased cardiovascular disease risk. These results served as the foundation for a consensus document agreed upon at the October 6, 2008, meeting held at St. Anna Hospital, Masaryk University, Brno, Czech Republic. Much added data have accumulated since then. In their light, herein we review evidence underlying the need for 7-day/24-hour ABPM and for their chronobiologic interpretation (C-ABPM).

Introduction

Circadian rhythms prominently characterize blood pressure (BP) and heart rate (HR), as well as a host of other physiological variables [1]. Their characteristics differ as a function of gender and age [2-8] as well as ethnicity [9] and health status [10-12]. The mapping of circadian rhythms in BP and HR in health from neonates [13, 14], adolescents [15], adults of different ages [10, 11], and even centenarians [16] led to the derivation of time-specified reference standards [17] in men and women of different age groups [6].

Within the scope of our project on the BIOsphere and the COSmos (BIOCOS), BP and HR have been monitored around the clock for 7 days or longer in different geographic locations [18-27]. These data shed light on the extent of day-to-day variability in the circadian characteristics of BP and HR

[28-30]. They also provide an opportunity to better understand how events in everyday life affect the circadian variation in BP and HR [28, 31, 32].

All data collected within our BIOCOS project are analyzed in a standard fashion by sphygmochron (in addition to any other analyses relative to each specific investigation). The sphygmochron is a two-pronged approach consisting of a parametric and non-parametric evaluation of the data. Parametrically, a two-component model consisting of cosine curves with periods of 24 and 12 hours is fitted by least squares to the data by cosinor [33-36], yielding estimates of the MESOR (Midline Estimating Statistic Of Rhythm, a rhythm-adjusted mean, usually more precise and more accurate than the arithmetic mean), and of amplitude (measure of half the extent of predictable change within a cycle) and acrophase (measure of the timing of overall high values recurring in each cycle) of each component, for comparison with reference norms (90% prediction limits from healthy peers matched by gender and age [17]). This model was selected based on the observation that the 24- and 12-hour components contributed most to the circadian waveform, on the average [12]. Non-parametrically data stacked over an idealized 24-hour day are compared to the reference time-specified 90% prediction limits in health to obtain the percentage time elevation, extent of blood pressure excess, and timing when most excess occurs [6]. Deviations from norms are known as Vascular Variability Anomalies (VVAs), or Disorders (VVDs) when they persist upon repeating the monitoring [37].

VVAs include an elevated MESOR of BP (MESOR-hypertension) when the BP MESOR exceeds the upper 95% prediction limit of clinically healthy peers matched by gender and age; an elevated pulse pressure (PP) when the difference between the MESOR of systolic (S) BP and the MESOR of diastolic (D) BP exceeds 60 mmHg; an excessive circadian amplitude of BP (CHAT, brief for Circadian Hyper-Amplitude-Tension), when the circadian amplitude of BP exceeds the upper 95% prediction limit of clinically healthy peers matched by gender and age; an odd phase of the circadian rhythm of BP, but not HR (ecphasia); a deficient HR variability (DHRV, brief for Deficient Heart Rate Variability), when the standard deviation of HR is below 7.5 beats/min; and too high a systolic BP x HR product (above 100 mmHg.beats/min.%) [37].

We here review evidence for 7-day/24-hour C-ABPM serving several purposes: surveillance for health maintenance, refined diagnosis and prognosis, personalized optimization of treatment by timing (chronotherapy), and as a tool to gain a better understanding of environmental influences on human physiology and pathology.

Surveillance and Health Maintenance

Routine monitoring may help us know ourselves better and improve our lifestyle. The transient occurrence of VVAs such as CHAT has been related to loads in everyday life, as documented from longitudinal records interpreted in the light of a diary in several individuals. As seen in Figure 1, a mental task may be associated with higher elevations of BP than driving in a storm during a tornado watch, or playing tennis [11]. Psychophysiological responses of BP, such as grief, anxiety and anger, have also been reported, which were associated with abnormal circadian profiles for the first 5 days of monitoring while no abnormalities were noted during a subsequent 11-day profile [38].

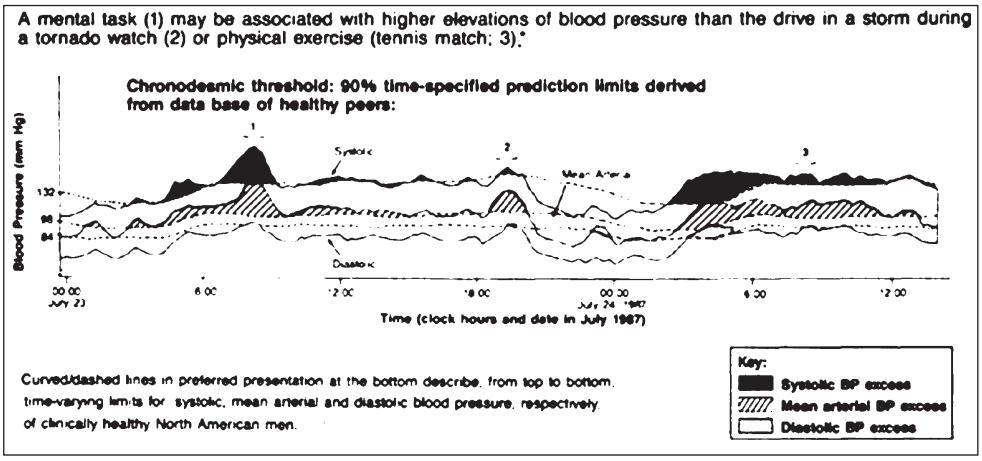

Figure 1: *Different factors influence blood pressure, contributing to the large day-to-day variability in circadian characteristics. © Halberg Chronobiology Center.*

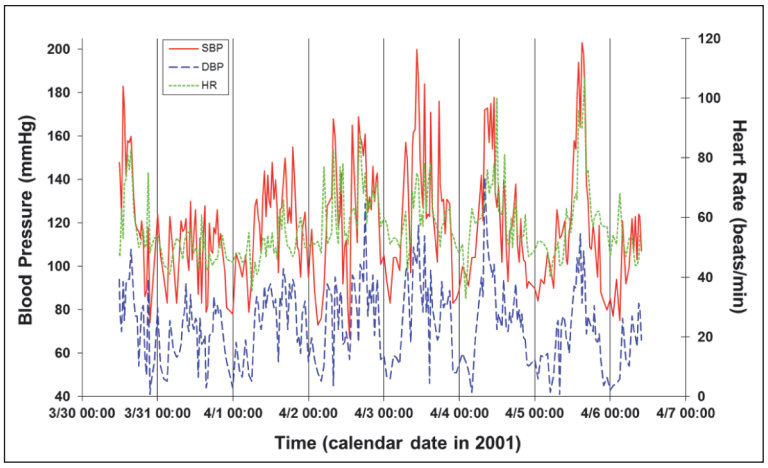

Figure 2: *Large variability in circadian BP and HR. © Halberg Chronobiology Center.*

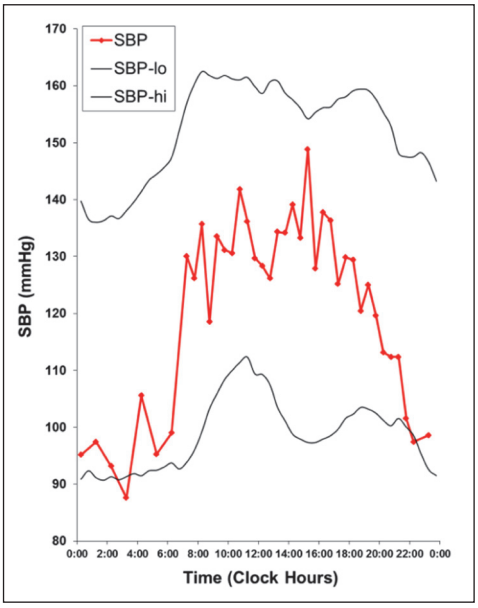

Figure 3: *Average SBP profile © Halberg Chronobiology Center.*

As shown in Figures 2 and 3, BP variability can be very large and affect all circadian parameters. When interpreted in the light of conventional fixed limits of acceptability, even the mean circadian profile includes average measurements corresponding to contradictory diagnoses of normotension or hypertension. The data stem from a 77-year old man treated with benidipine (4 mg/day in the morning). In addition to a novelty effect observed at the beginning of the record when BP is higher, variability in BP and the presence of CHAT may have been contributed by emotions as he was following a competitive championship for the next 5 days [39]. Longitudinal monitoring over years and even decades has also been invaluable for the early detection of the development of high BP, which was more pronounced on work days than on weekends and holidays, thereby indicating how loads of everyday clinical duties may contribute to the elevation in BP in this case [40].

These examples illustrate how much can be learned from data collected automatically as a function of time. Information can thus be obtained to serve several purposes:

- ❖ To indicate whether there is a change in health well before there is abnormality in relation to conventional thresholds;
- ❖ To indicate whether there is a change while on treatment, prompting adjustment in medication, dosage and/or timing;
- ❖ To aid in diagnostic accuracy;
- ❖ To distinguish changes which are part of healthy aging versus the development of BP disorders. (In clinical health, SBP was found to reach a maximum around 80 years of age, whereas DBP starts decreasing after 50 years of age [8, 41, 42]; the circadian amplitude dampens and the circadian acrophase becomes more labile in the elderly [11].)

Diagnosis and Prognosis

Whereas the relationship of the BP MESOR with cardiovascular disease risk is linear, that of the circadian amplitude of BP and the standard deviation of HR is nonlinear: a threshold needs to be exceeded for risk to increase [43]. Conditions such as CHAT were found to be associated with a large increase in cardiovascular disease risk, notably in the case of cerebral ischemic events and hypertensive nephropathy [44-46].

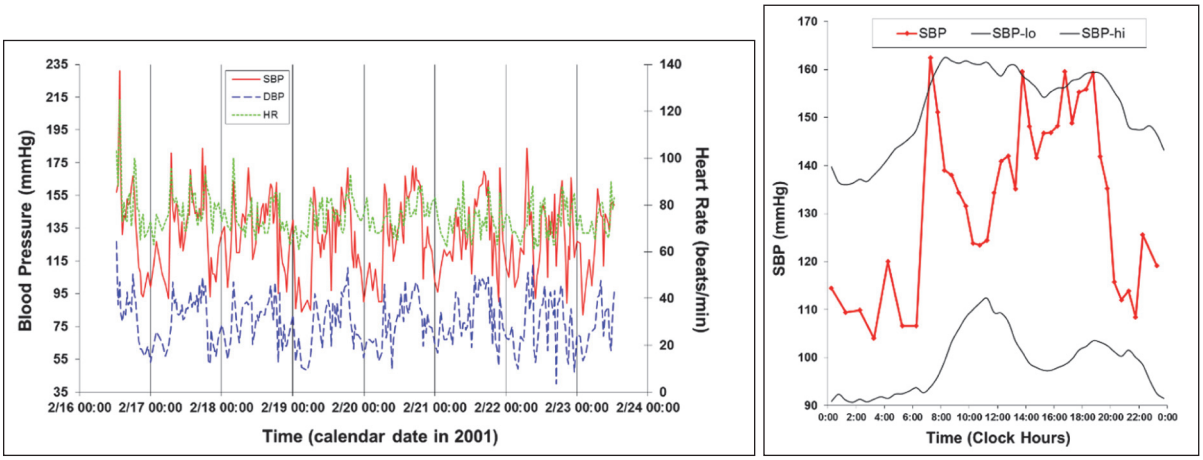

Figure 4: *CHAT complicated by morning BP surge in 68-year old man treated for high BP. Despite successful emergency operation for aneurysm, this patient died a few years later because of decreased renal function. © Halberg Chronobiology Center.*

One example is illustrated in Figure 4 which shows the case of a 68-year old man treated with benidipine (4 mg/day taken in the morning). His hepatic and renal functions were normal at the time of monitoring. His BP profile indicates the presence of a consistent morning surge. The circadian amplitude of BP is also excessive (CHAT). After being monitored, an aneurysm of the abdominal aorta was discovered, which ruptured before surgery. Several years after a successful emergency operation, this subject passed away from a slowly progressively decreased renal function on a cold winter morning [39]. Modalities need to be developed to treat not only an elevated BP, but also to restore a healthy circadian BP profile by eliminating VVDs such as CHAT. Indications that such a strategy may work stems from a cross-over study comparing treatment with benidipine in the morning versus nifedipine twice a day, in the morning and evening: whereas benidipine lowered BP to a lesser extent than nifedipine, it also reduced the circadian amplitude of BP, thereby being more likely to

eliminate or at least reducing the severity of CHAT, while nifedipine did not affect the circadian amplitude of BP. Such a differential action of the two treatments is likely to have accounted for the fewer adverse outcomes of patients treated with benidipine versus nifedipine according to the two regimens tested, strokes in particular, in two large clinical trials comparing these two treatments [47].

Except for the BP x HR product [48], VVAs are mostly independent and additive [27, 41, 49]. In one outcome study, an adverse event occurred within 6 years of the monitoring in only 8.7% of the subjects diagnosed with uncomplicated MESOR-hypertension, but it occurred in 29.1% and in 53.3% of the subjects with one or two additional VVAs complicating MESOR-hypertension; all 3 subjects with 3 additional VVAs suffered an adverse event [37, 50].

Uncomplicated MESOR-hypertension was found in 34.7% of the subjects, with 18.5%, 5.1% and 1.0% having 1, 2 or 3 additional VVAs in addition to MESOR-hypertension. Subjects diagnosed only with CHAT or DHRV, accounting for 2.4% and 1.7% of the population, would not be treated under the current standard of care [37].

In several outcome studies based on actual adverse events or on biomarkers such as the left ventricular mass index, the circadian amplitude and acrophase interpreted in the light of reference values qualified by gender and age, are better predictive of cardiovascular disease risk than the day-night ratio used for a classification in terms of "dipping" [51].

Vascular Variability Disorders and Other Biomarkers

Several outcome studies have shown that an excessive pulse pressure (PP > 60 mmHg) is associated with an increase cardiovascular disease risk [48]. A positive correlation has been documented between pulse pressure and body mass index (BMI), as shown in Figure 5 for the Brno database and in Figure 6 for an American data set [52, 53]. In the latter study, PP correlated positively with BMI both in obese (BMI > 30 kg/m2) (slope = 0.513±0.275, r=0.283, P=0.069) and non-obese (BMI < 30 kg/m^2) (slope = 0.726±0.183, r=0.348, P<0.001) subjects. As PP correlates positively with body mass index, obese people may be more likely to develop cardiovascular disease, in part because of an excessive PP.

Pulse pressure also correlates with markers of inflammation, such as C-reactive protein (CRP) and TNF-α [52, 53], Figure 7.

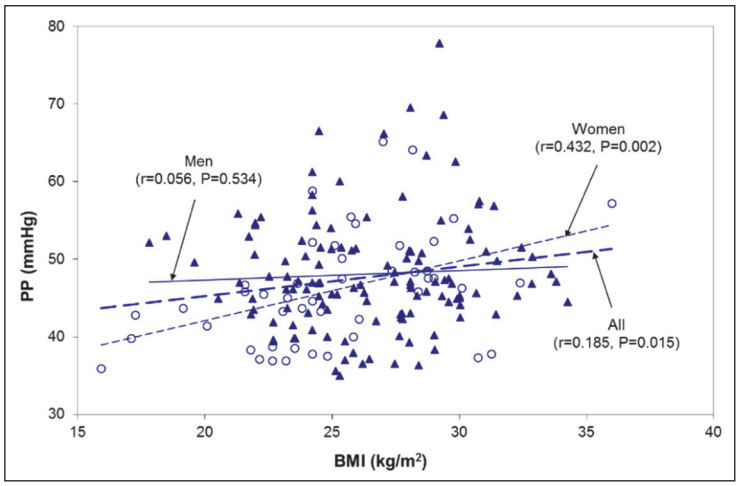

Figure 5: *Positive correlation of pulse pressure (PP) with body mass index (BMI). Data from J Siegelova. © Halberg Chronobiology Center.*

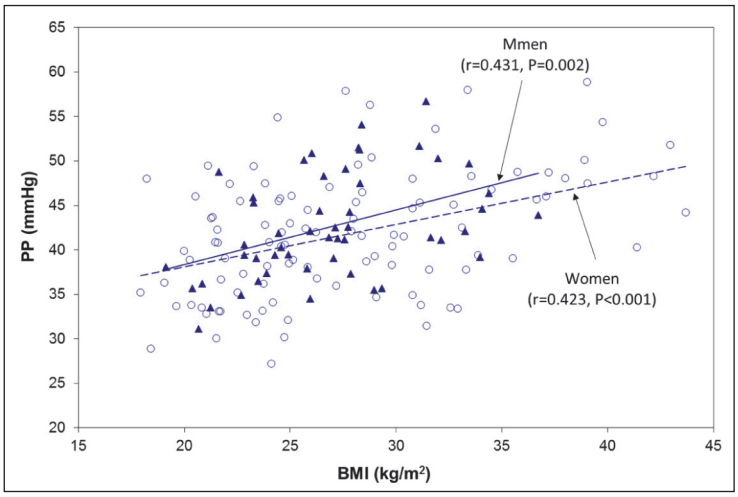

Figure 6: *Positive correlation of pulse pressure (PP) with body mass index (BMI). Data from J Abramson et al. [52, 53].*
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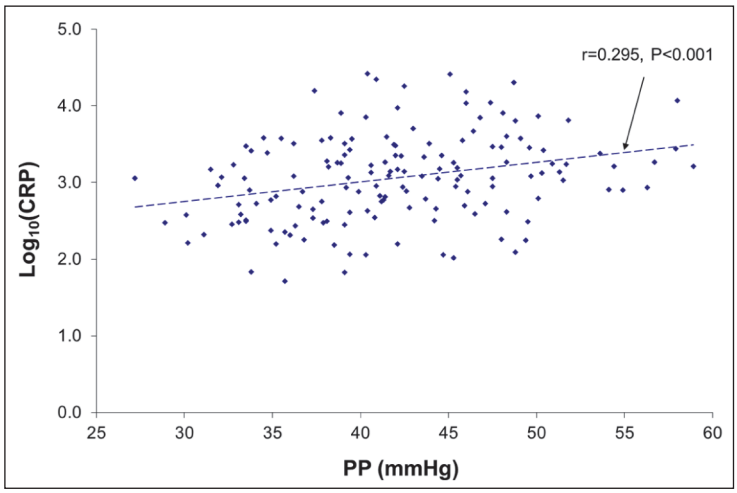

Figure 7: *Positive correlation of pulse pressure (PP) with C-reactive protein (CRP), an index of inflammation. Data from J Abramson et al. [52, 53].*
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Another reason why obese people may be at a higher risk for cardiovascular disease may relate to their having a lower heart rate variability. In the Brno database, the standard deviation (SD) of HR, here used as an index of heart rate variability, was found to correlate negatively with BMI, Figure 8.

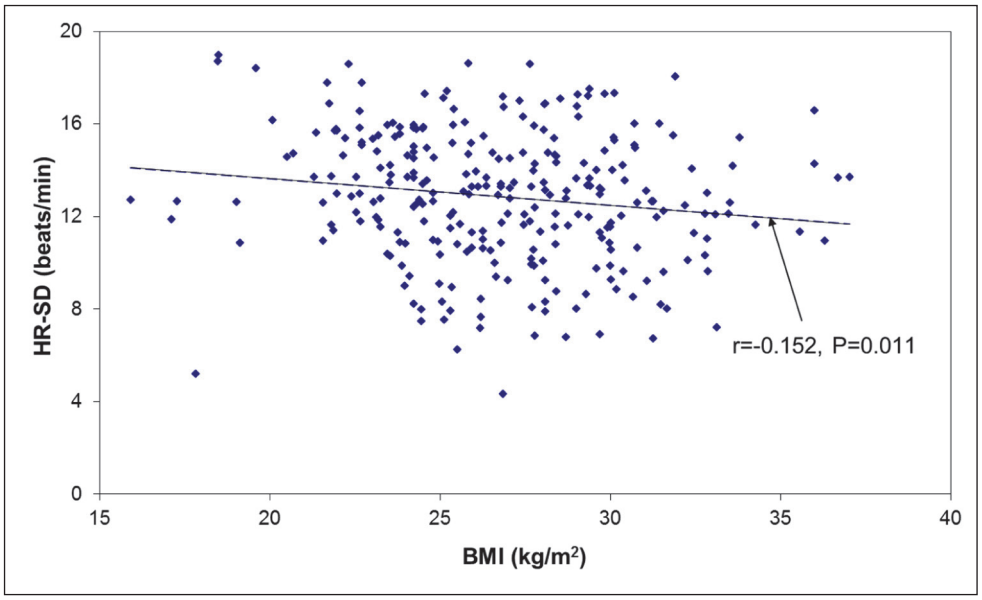

Figure 8: *Heart rate variability decreases with increasing BMI. Data from J Siegelova.*
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Ecphasia usually consists of a reversed circadian variation of BP peaking by night rather than by day, while HR assumes higher values by day than by night. This condition has been reported for patients with type-2 diabetes [54]. Its occurrence has also been associated with an increased cardiovascular disease risk, gauged by the left ventricular mass index [51]. Subjects with SBP ecphasia have been found to have a higher fasting blood glucose ($F=13.938$, $P<0.001$) and a higher glycosilated hemoglobin ($F=7.644$, $P=0.007$) [55, 56], Figure 9. As seen in Figure 10, BP ecphasia is also associated with a reduced heart rate variability (Student $t = 6.138$, $P<0.001$). These results suggest that BP ecphasia may be more prevalent among patients with type-2 diabetes with autonomic nervous dysfunction. These results [55, 56] have since been confirmed independently [57].

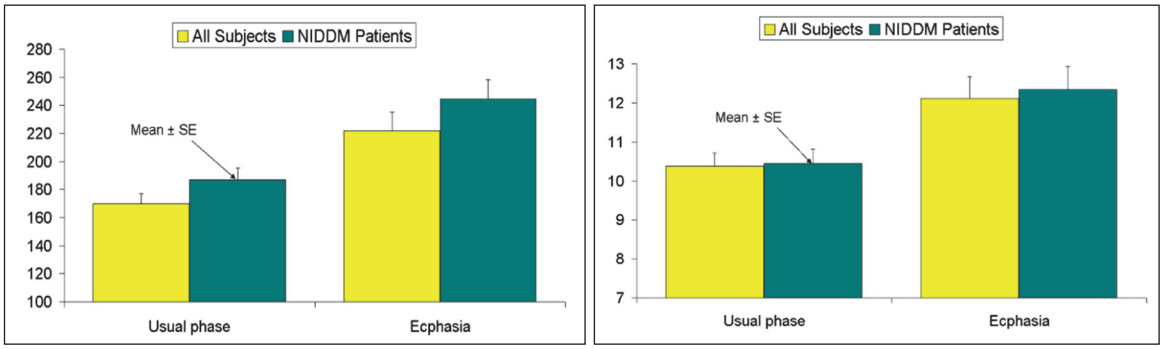

Figure 9: *SBP ecphasia is associated with higher fasting glucose (left) and higher glycosylated hemoglobin (right). Data of C Gonzalez et al. [55, 56].*
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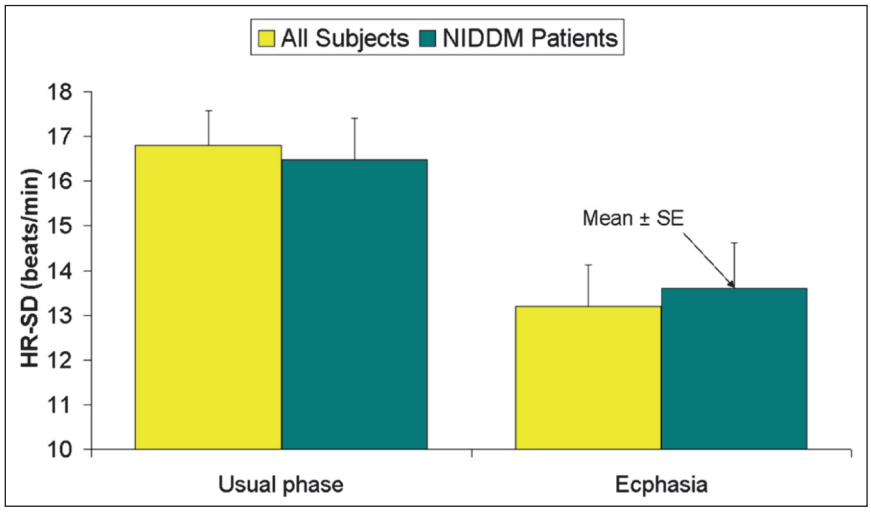

Figure 10: *BP ecphasia is associated with a lower heart rate variability. Data of C Gonzalez et al. [55, 56].*
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Chronotherapy

Treatment can be optimized by timing, using non-pharmacologic agents such as coQ10 [58] or antihypertensive medication. They do not all have an effect on the circadian amplitude [59, 60]. Several protocols have been designed. Timing treatment administration to when it is most needed, based on the drug's pharmacokinetics and the timing of BP excess, was compared to treating three times a day in a study of propranolol, clonidine and α-methyldopa [61, 62]. Chronotherapy reduced BP more with smaller doses, resulting in fewer side effects [61, 62], Figure 11.

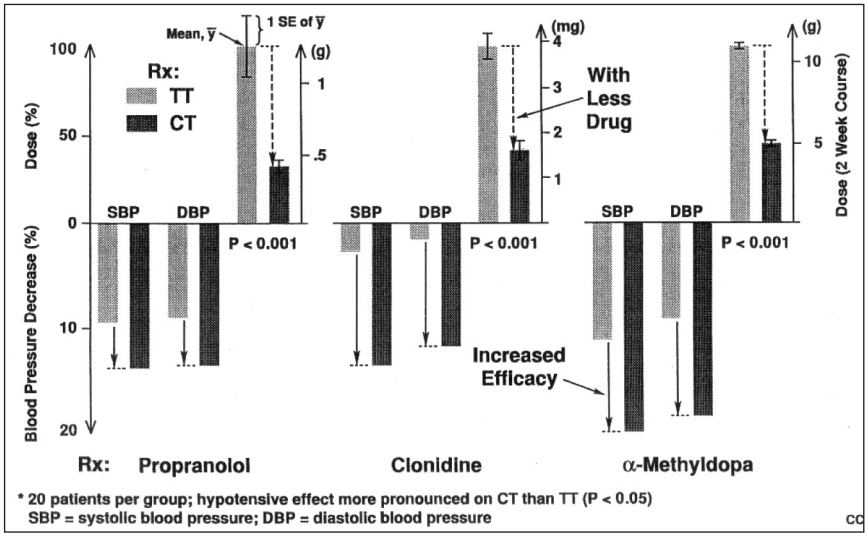

Figure 11: *Efficacy, safety and cost-effectiveness of chronotherapy (CT) compared with traditional treatment (TT) 3 times a day. Data of R Zaslavskaya.*
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Chronotherapy has also been applied by systematically testing the same dose of the same drug regimen in the same patient studied longitudinally at 6 different treatment times. Different studies used different spans during which treatment timing was kept the same in relation to the time of awakening,

varying from just one day [63] (Figure 12), to one week [64], and even one month or longer [65]. These protocols present the advantage that the optimization of treatment by timing can be individualized. It has indeed been demonstrated that optimal times of treatment can differ drastically from one patient to another [65]. Personalized chronotherapy benefits from the development of statistical techniques such as parameter tests [66] (Figure 13) and the self-starting cumulative sum (CUSUM) control chart [67, 68] (Figure 14).

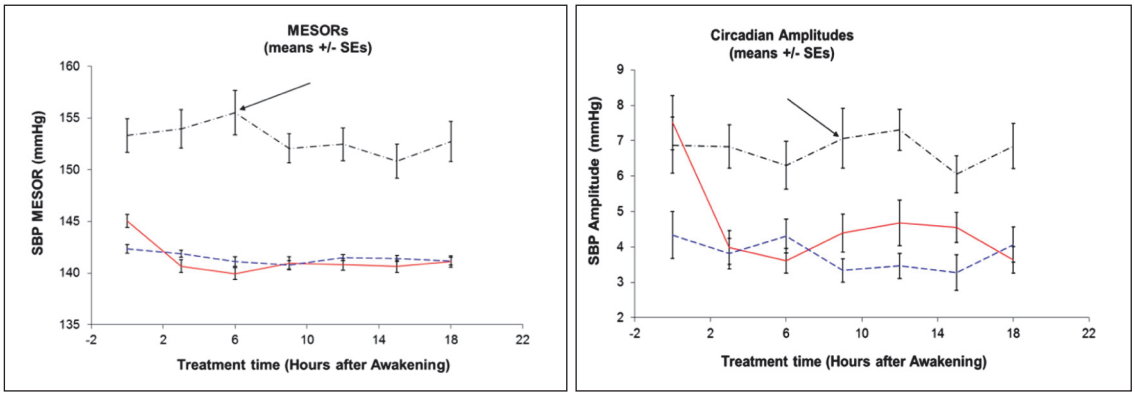

Figure 12: *Effect of Telmisartan, administered at 6 different circadian stages, on the MESOR (left) and circadian amplitude (right) of SBP. As compared to placebo (black, dashed line), Telmisartan alone (red, solid line) or with low-dose aspirin (blue, dotted line) decreases SBP-M and SBP-A to a different extent depending on the time of its administration. Data of P Prikryl [63].*
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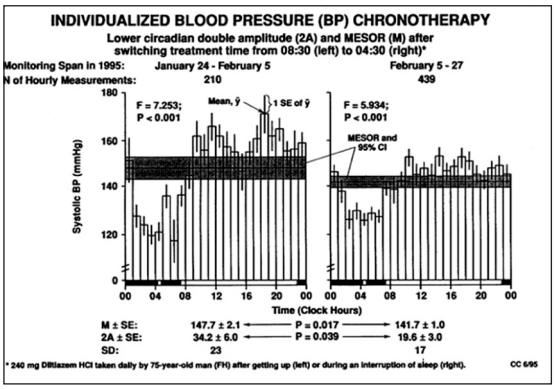

Figure 13: *Parameter tests decrease in MESOR and circadian amplitude of SBP associated with a change in timing of the same dose of the same anti-hypertensive drug to the same patient,*
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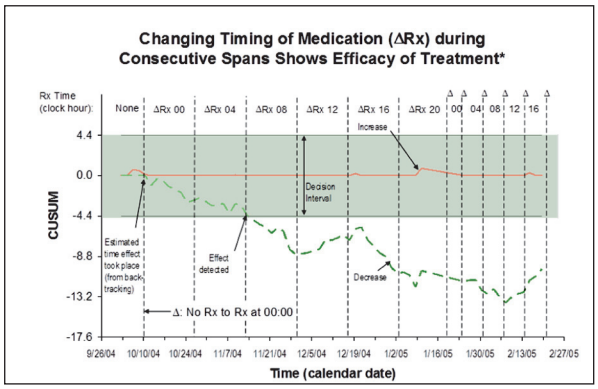

Figure 14: *Self-starting CUSUM detects lowering of BP starting approximately at the time of treatment start.*
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One lesson learned is the need to adjust treatment timing in the light of the diagnosis, a concept known as chronotheranostics [69]. Indeed, patients with the same average BP may differ greatly in terms of their BP variability that places them at different cardiovascular disease risk, Figure 15. Personalized chronotherapy was shown to benefit more than 2/3 of patients examined. Treating VVAs as well as an elevated BP can cut in half the number of strokes and overall cardiovascular events [47].

Environmental Influences

Longitudinal records spanning a decade or longer have shown the presence of cycles with periods characterizing solar activity. About 5-month [70], about 16-month [71], and even about 11-year [72-75] cycles have been found to characterize BP, HR and indices of variability in BP and HR. Figure 15 illustrates the about 11-year cycle modulating SBP. A histogram of nonlinearly-assessed spectral components found in all longitudinal records available for analysis shows that an about 11-year component is often present and detected with statistical significance, Figure 16 [75]. As reviewed elsewhere [76-84], magnetic storms have also been associated with a decrease in HR variability and in nocturnal melatonin.

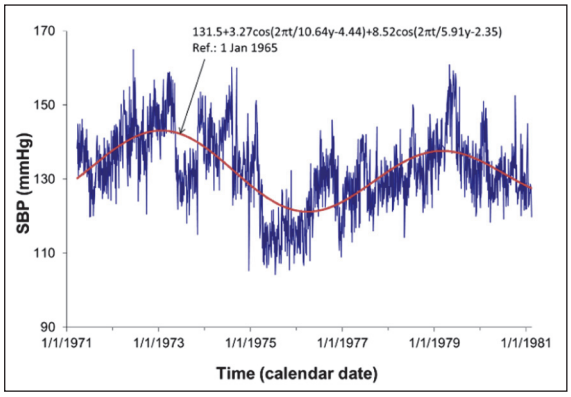

Figure 15: *About 11-year cycle modulates SBP self-measured several times a day by a clinically healthy man (EH) [73].*
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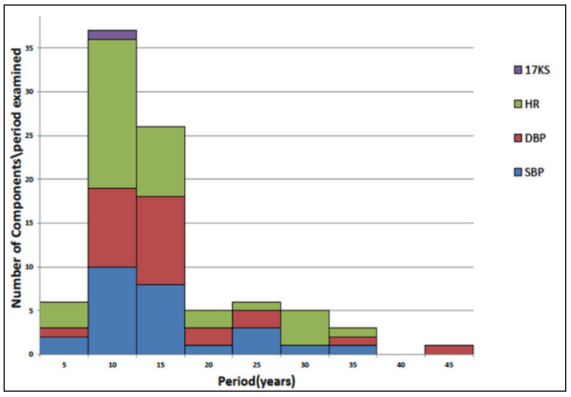

Figure 16: *About 11-year cycles are often present in longitudinal records, in preference to other periods [75].*
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Discussion and Conclusion

Awareness of the merits of a chronobiological approach versus single clinic measurements should be spread more widely, notably now that newer monitoring devices are addressing issues of comfort and convenience, which have been deterrents to longer-term monitoring. Data collected automatically as a function of time can

- ❖ Indicate whether there is a change in health well before there is abnormality in relation to conventional thresholds;
- ❖ Indicate whether there is a change while on treatment, prompting adjustment in medication, dosage and/or timing;
- ❖ Improve diagnostic accuracy; and
- ❖ Distinguish changes that are part of healthy aging versus the development of BP disorders.

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DEMONSTRATION OF COSINOR-BASED ANALYSES USING THE CHRONOMICS ANALYSIS TOOLKIT IN R

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Abstract

A network of cell-based oscillators coordinates cardiac as well as other biological systems. Understanding these rhythms demands versatile software than can characterize all aspects of an oscillation in quantitative terms. The Chronomics Analysis Toolkit (CAT), an R package for analysis of periodicities in time series, is a free and open source suite of rhythm analysis tools that runs on UNIX, Windows and Macintosh platforms. Thus it is easy to acquire. It is also versatile, capable of performing an array of simple to complex rhythm analysis techniques. It is illustrated herein to quantitatively assess changes in the time structure (chronome) of heart rate (HR) of a Japanese infant during the first 40 days of his life. Focus is placed on the development of the circadian rhythm in HR.

Introduction

Studying biological oscillations is a rapidly growing field. Some of the most accessible tools for analysis, such as actograms, autocorrelation and periodograms, each have drawbacks. Some give only subjective estimates of period; others do not assess statistical significance of the result. Researchers are moving toward quantitative analyses that can fully characterize a rhythm, and provide a measure of statistical significance. A rhythm is characterized by its period, phase, amplitude, and MESOR (Midline Estimating Statistic of Rhythm, a rhythm-adjusted mean). A rigorous analysis will quantify and consider all aspects of a rhythm. Scripting environments such as R [1], Mathematica, and MATLAB contain extensive signal processing libraries, as well as other functions that can be used for custom development of analytical tools, for those who want to do the programming themselves. For the general-purpose analysis of biological cycles in time series data, there are only a few full-featured, user-friendly packages aimed at the non-programmer [2].

Analytical Tools Available in the Chronome Analysis Toolkit (CATkit)

The Chronomics Analysis Toolkit (CATkit) package is written in R, a statistical programming language and environment [1]. CATkit is a flexible general-purpose time-series analysis suite aimed at the non-programmer, but easily modified and extended by the programming-inclined. Techniques implemented in CATkit allow data that has gaps, and in the case of the cosinor, non-equidistant data. It includes visual analysis tools to get an overview of the data, as well as tools that provide complete numeric rhythm characterization. CATkit tools are listed in Table 1.

Table 1: *Rhythm analysis tools in CATkit*

Qualitative functions. Equidistant data required	Quantitative functions. Applicable to non-equidistant data
Actogram	Single-component cosinor
Smoothing	Least squares spectrum by cosinor
Autocorrelation	Multiple-component cosinor
Crosscorrelation	Single- or multiple-component cosinor serial section
Periodogram *	Gliding spectrum

**The periodogram gives a quantitative estimate of power (or amplitude) and phase at Fourier frequencies.*
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Smoothing, Autocorrelation, and Periodogram

The first step is to get an overall idea of what the data look like. The CATkit smoothing function plots the heart rate (HR) data from the first 40 days of life, and overlays it with a smoothed curve that helps see the major features present in the data [3]. Figure 1 illustrates the procedure, where data are averaged over 11 consecutive values, using interpolated HR data rendered equidistant with filled gaps in CATkit.

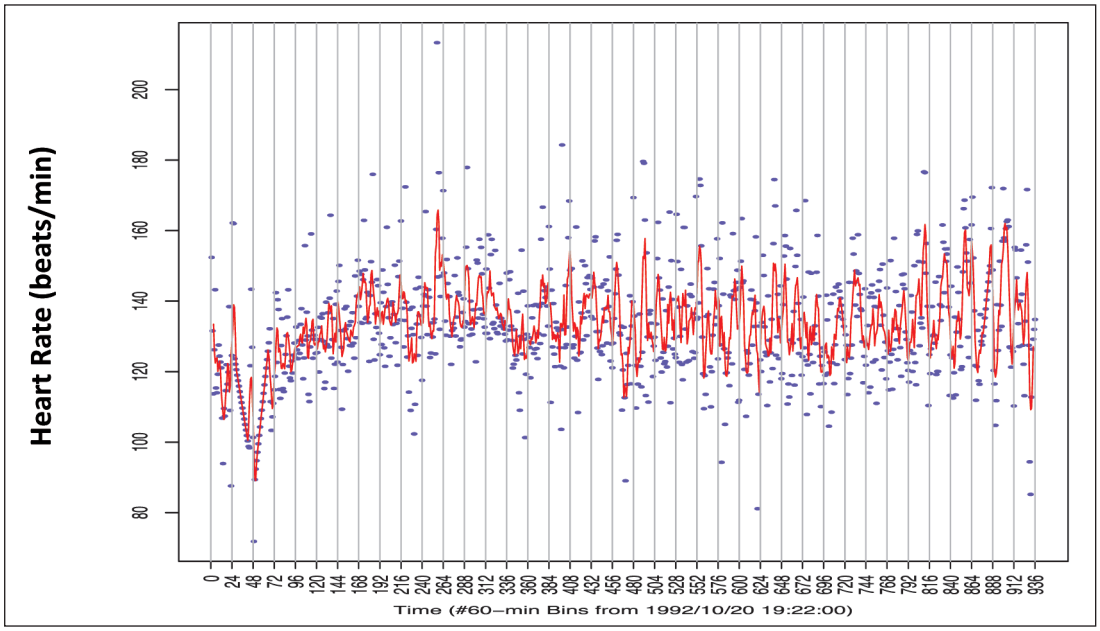

Figure 1: *Smoothing curve of data from first 40 days post-natally. 1992/10/20 - 1992/11/28*
Eleven data points averaged for smoothing. Data from Y Watanabe.
© Halberg Chronobiology Center.

As apparent from Figure 1, HR is changing over time, notably at the beginning of the record. In other words, the time series is non-stationary [4]. Since the data appear to be more stable toward the end of the record, focus is first placed on the last 7 days, Figure 2. While a circadian variation can be discerned, its full characterization requires several additional analytical steps.

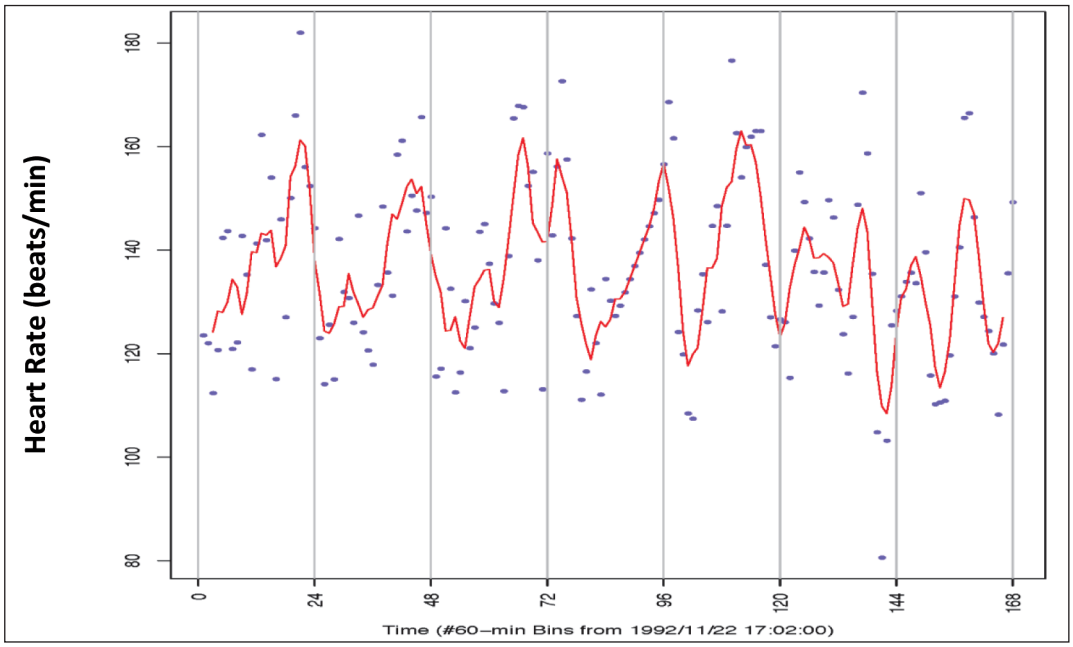

Figure 2: *Smoothing curve days 33 - 40. 1992/11/22 17:02:00 to 1992/11/29 16:02:00 Eleven data points averaged for smoothing. © Halberg Chronobiology Center.*

The periodogram of Figure 3 views the data in the frequency domain. In addition to this plot, CATkit also produces a file with quantitative output for each spectral line, including power, amplitude, phase, and corresponding period. The CATkit periodogram reports the four largest amplitudes and their corresponding periods. For days 33-40 of the HR record (Figure 3), these periods are 10.5, 24, 7.6, and 28 hours. The dotted line represents the noise level, drawn at the 95% probability level, assuming white noise. A single anticipated component that rises above this noise level can be considered statistically significant ($P<0.05$) as long as underlying assumptions are met. In the case of Figure 3, the anticipated 24-hour component has an amplitude exceeding the noise level: it is significant ($P<0.05$). As for the other 3 spectral lines listed in Figure 3, they should be interpreted with caution. The 28-hour component is likely part of the circadian signal as the actual period of a developing circadian system may not be 24-hour synchronized yet. If so, the 7.6-hour component may be a harmonic term qualifying the waveform of the circadian rhythm. The 10.5-hour component is somewhat problematic but may correspond to the half-day that may constitute a component in its own right shortly after birth. If there is evidence supporting this interpretation and it can be anticipated to be present with the circadian rhythm, albeit not in harmonic relation with it, it may also be significant as its P-value would remain below 5% after adjustment for multiple testing (e.g., Bonferroni).

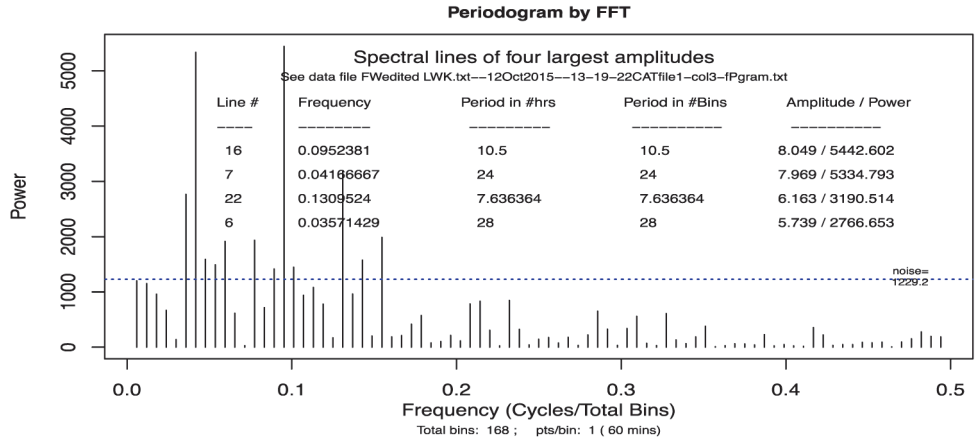

Figure 3: *Periodogram days 33 - 40. 1992/11/22 17:02:00 to 1992/11/29 16:02:00 Top largest amplitude lines given by CATkit at periods of: 10.5, 24, 7.6, and 28 hours. Experienced interpretation required. © Halberg Chronobiology Center.*

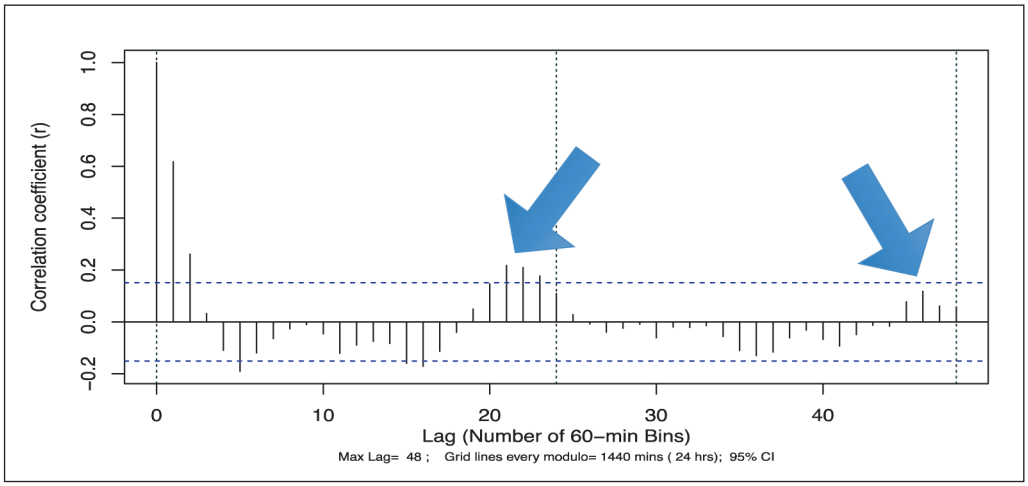

Figure 4: *Autocorrelation days 33 - 40. A period of about 22 rises above the 95% confidence interval. Multiple fluctuations in the cycle envelope indicate more than one frequency. © Halberg Chronobiology Center.*

Whereas the periodogram has the advantage of preserving the variance between the time and frequency domains, one limitation of the periodogram is the fact that Fourier frequencies are fixed by the record's length and the sampling interval. As a result, spectral lines may not correspond to periods anticipated to be present in the data.

The autocorrelation is another method available to assess periodicity. The autocorrelation of Figure 4 shows recurring higher correlation coefficients for lags about 22-24 hours apart. The correlation coefficient at a lag of 22 hours rises above the 95% confidence interval shown as horizontal dashed lines around zero. It indicates the presence of a circadian rhythm, in keeping with the results of the periodogram. The shape of the envelope of the autocorrelation function has multiple regular fluctuations that are indicative of the presence of at least another component with a period shorter than 24 hours. A quantitative characterization of the rhythm parameters cannot be obtained by this approach, however. In all of the techniques described above, the data must be equidistant.

The Single-Component Single Cosinor and Least Squares Spectrum

The single cosinor was first developed as a regression technique to handle short and sparse series of non-equidistant data [5]. Fitting a single cosine curve to the data, using trial periods corresponding to the Fourier frequencies, reproduces results from the periodogram when the data are equidistant. The analysis is known as a least squares spectrum. Results in Figure 5 are obtained on the original non-equidistant data during a slightly shorter record than that used for the analysis in Figures 3 and 4. Nevertheless, results are quite similar, with peaks corresponding to periods of 23.1, 10.5, and 7.7 hours. The least squares spectrum can use as record length (fundamental period) a value slightly different from its actual length, thereby changing the discrete trial frequencies. It can also use a harmonic increment different from 1, thereby assessing additional (in-between) frequencies.

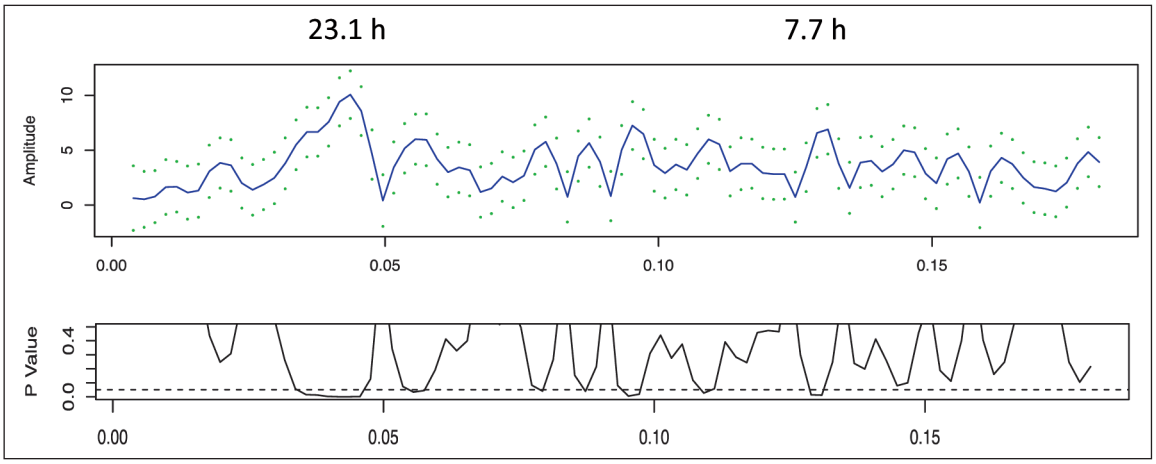

Figure 5: *Least squares spectrum of non-equidistant data. 23.1, 10.5 and 7.7 hours are significant at <.001, .0048 and .0138, respectively.*
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At each trial period, estimates of the amplitude and acrophase (phase of the maximum) are obtained. The proportion of the variance accounted for (percentage rhythm, PR) is also determined. The corresponding P-values from the zero-amplitude (no-rhythm) test are only of relative value. They are shown with a plot of amplitudes in Figure 5 for the last week of the HR data.

Because the least squares spectrum can assess frequencies intermediate to Fourier frequencies, we were able to determine more closely the period at which the amplitude was maximal. The circadian period was estimated as being 23.1 hours, suggesting that the circadian rhythm may not have been 24-hour synchronized yet. The peak at 7.7 hours may then represent the third harmonic of the circadian rhythm and modify its waveform. Figure 6 is a sample excerpted from the output file. For each trial period, PR, P, MESOR and its standard error (SE), amplitude and acrophase and their SEs are reported. Slightly different estimates for the MESOR are obtained at different trial periods because the data are non-equidistant.

Rhythmometric Summary

Err	Y	Time Pts	hours from RefDateTim	#Pts	Period in hrs	PR	P	Mesor	Mesor SE	Amp	Amp SE	PHI	PHI SE
	5	199211230001 - 199211291701	818.1333 - 986.1333	1 - 161 (161)	14.824	0.1712	0.8734	136.82808	1.620	1.19044	2.289	-63.9	110.4
	5	199211230001 -	818.1333 -	1 - 161	14.400	0.2783	0.8024	136.83810	1.619	1.51977	2.289	-114.7	86.2
	5	**199211230001 - 199211291701**	**818.1333 - 986.1333**	**1 - 161 (161)**	**24.000**	**10.4773**	**<.001**	**136.95418**	**1.533**	**9.41920**	**2.190**	**-196.2**	**13.0**
	5	**199211230001 - 199211291701**	**818.1333 - 986.1333**	**1 - 161 (161)**	**22.909**	**12.0136**	**<.001**	**137.18257**	**1.520**	**10.06293**	**2.167**	**-95.2**	**12.1**
	5	199211230001 - 199211291701	818.1333 - 986.1333	1 - 161 (161)	12.923	3.1175	0.0819	136.74885	1.595	5.06282	2.246	-56.8	25.6
	5	**199211230001 - 199211291701**	**818.1333 - 986.1333**	**1 - 161 (161)**	**10.500**	**6.5442**	**0.0048**	**136.64038**	**1.566**	**7.24489**	**2.180**	**-97.4**	**17.8**
		199211291701	986.1333	(161)									
	5	199211230001 -	818.1333 -	1 - 161	12.000	0.0687	0.9472	136.84850	1.619	0.75427	2.294	-315.0	174.3
	5	**199211230001 - 199211291701**	**818.1333 - 986.1333**	**1 - 161 (161)**	**7.754**	**5.2784**	**0.0138**	**136.93428**	**1.580**	**6.58262**	**2.219**	**-71.4**	**19.5**
	5	199211230001 - 199211291701	818.1333 - 986.1333	1 - 161 (161)	11.455	4.0090	0.0395	136.89551	1.586	5.65135	2.200	-216.3	23.2
	5	199211230001 - 199211291701	818.1333 - 986.1333	1 - 161 (161)	11.200	1.9230	0.2157	136.90475	1.604	3.95236	2.246	-150.6	33.2
	5	199211230001 - 199211291701	818.1333 - 986.1333	1 - 161 (161)	10.957	0.0855	0.9347	136.81677	1.620	0.82674	2.249	-189.6	161.7

Figure 6: *Data output excerpts. For each period, PR, P, MESOR, MESOR se, Amplitude, Amplitude se, Acrophase and Acrophase se are reported. © Halberg Chronobiology Center.*

Chronobiologic Serial Section

In days 33 – 40, the circadian rhythm is detected with statistical significance, but it is not yet 24-hour synchronized. The chronobiologic serial section helps visualize how the circadian component evolves during the first 40 days of life.

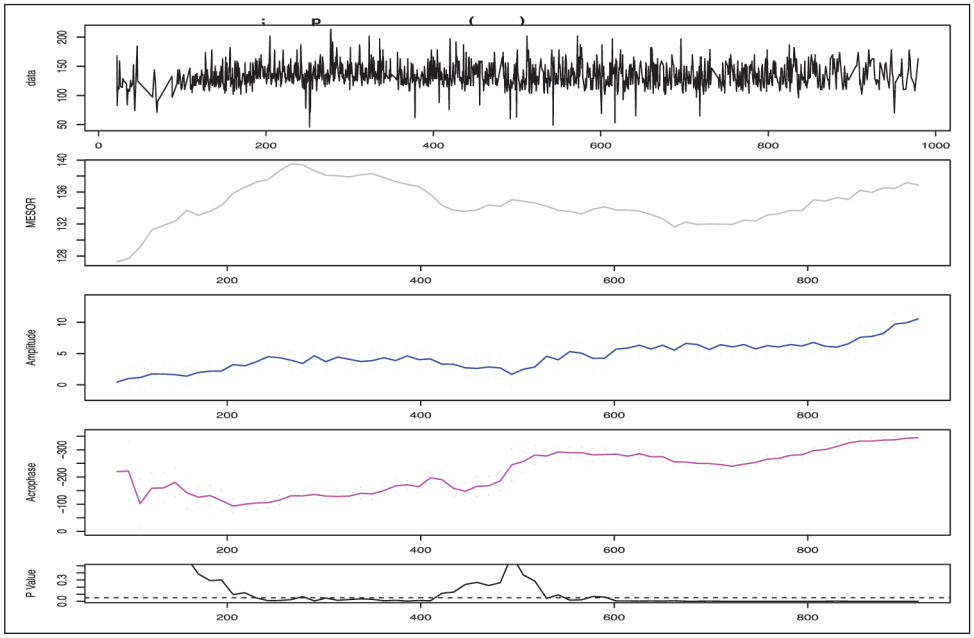

Figure 7: *Chronobiologic serial section of HR from birth to 40 days, assessed for a period of 23.1 hours. A series of overlapping spans, 168 hours long and offset by 12 hours each are estimated and results are plotted. © Halberg Chronobiology Center.*

The chronobiologic serial section analyzes data in a span (interval) shorter than the entire record and moves it progressively throughout the record by a given increment. In the case of the 40-day HR record, a 23.1-hour cosine curve has been fitted to data in a week-long span (168 hours), progressively incremented by 12 hours throughout the 40-day record. CATkit produces several graphs to help

visualize the changes taking place, as seen in Figure 7. The raw data are plotted in the first graph. MESOR, amplitude and acrophase are plotted with their SEs around the curves, followed by a plot of the P-values from the zero-amplitude test in each span.

The MESOR varies between 140 and 128 beats/min, and is fairly stable after an initial swing up. The circadian amplitude varies from 0 to 10 beats/min, and gradually increases with time. The increase in the amplitude shows that the infant's circadian rhythm is becoming stronger. P-values are below 0.05 during most of the 40 days, indicating that the circadian rhythm is present already at birth, albeit with changing characteristics as a function of age. Early measurements were sparse, perhaps accounting for the lack of statistical significance in the first few days after birth.

Multiple-Component Cosinor

To this point a single cosine curve has been used to model the data. Multiple-component models can also be fitted in CATkit to better approximate more complex signals. Figure 8 illustrates a two-component model consisting of cosine curves with periods of 23.1 and 7.7 hours fitted to data recorded on days 33-40. It approximates the developing circadian variation, including the fundamental 23.1-hour component and its third harmonic term with a period of 7.7 hours.

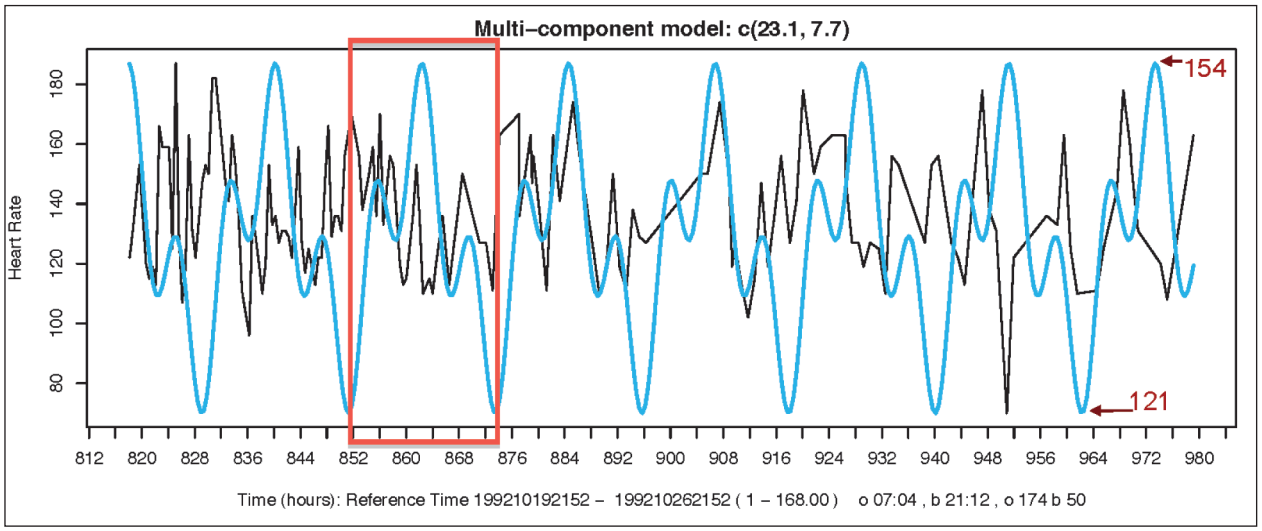

Figure 8: *Multi-component cosinor comprising 23.1 and 7.7 hours. One cycle shown in box; slightly more than 7 cycles of 23.1-hour periodicity present in HR record (days 33-40). (model and data are on different scales.)*
© Halberg Chronobiology Center.

Rhythmometric Summary

column 5 : MESOR= 137.195 MESOR s.e.= 1.482

Time Pts= 199211230001 - 199211291701 hours from RefDateTime= 818.1333 - 986.1333 #Pts Period in hrs= 1 - 161 (161)

Err	Period in Hrs	newPR	P	P(Ger)	P(Bin)	Amp	Amp SE	PHI	PHI SE
	23.10	11.855	<.001	0.00002658	0.00003161	9.905	2.105	-343.0	12.0
	7.70	5.997	0.0047	0.00486319	0.00482699	6.991	2.105	-359.0	17.0

LCM 3251035981008077 Overall: PR= 17.851 P= <.001 Magnitude= 33.0537672080761 Orthophase -186 Bathyphase= -310

Figure 9: *Rhythmometric summary for multiple-component cosinor using 23.1 and 7.7 hours. Magnitude 33, P < .001, indicate this is a good model for heart rate on days 33-40.*
© Halberg Chronobiology Center.

Numeric results for the multi-component model are shown in Figure 9. In addition to estimates for the amplitude and acrophase of each component in the model, the multiple-component cosinor also provides estimates for the magnitude, orthophase and bathyphase, parameters that describe the complex waveform from the composite model: the magnitude is the extent of predictable change within one cycle; the orthophase and bathyphase are the times of overall high and low values recurring in each cycle. In the case of the HR data on days 33-40, the magnitude is 33 beats/min. It is slightly larger than the double amplitude from the single-component model as the 7.7-hour harmonic term contributes to the extent of predictable variation within a cycle. As seen from Figure 9, the model is statistically significant (P<0.001), both components contributing to the model with statistical significance (23.1-hour: P<0.001; 7.7-hour: P=0.005).

Gliding Spectrum

The chronobiologic serial section showed how the characteristics of the 23.1-hour cosine model changed over time, from birth to 40 days. It is likely that frequency components other than the circadian variation also changed during the first few weeks of life. About-weekly variations have indeed been reported to be prominent at birth by several investigators [6-14]. The gliding spectrum is a cosinor technique that can visualize any changes in amplitude and frequency (period) as a function of time in a broader frequency range, not limited to a single trial period. Figure 10 shows the results for HR during the first 40 days of life of a full-term healthy boy. A 1-week interval is progressively displaced by 12 hours. In each weekly span, a least squares spectrum is performed in the frequency range of 1 to 90 cycles in 252 hours, using a fractional harmonic increment of 0.5.

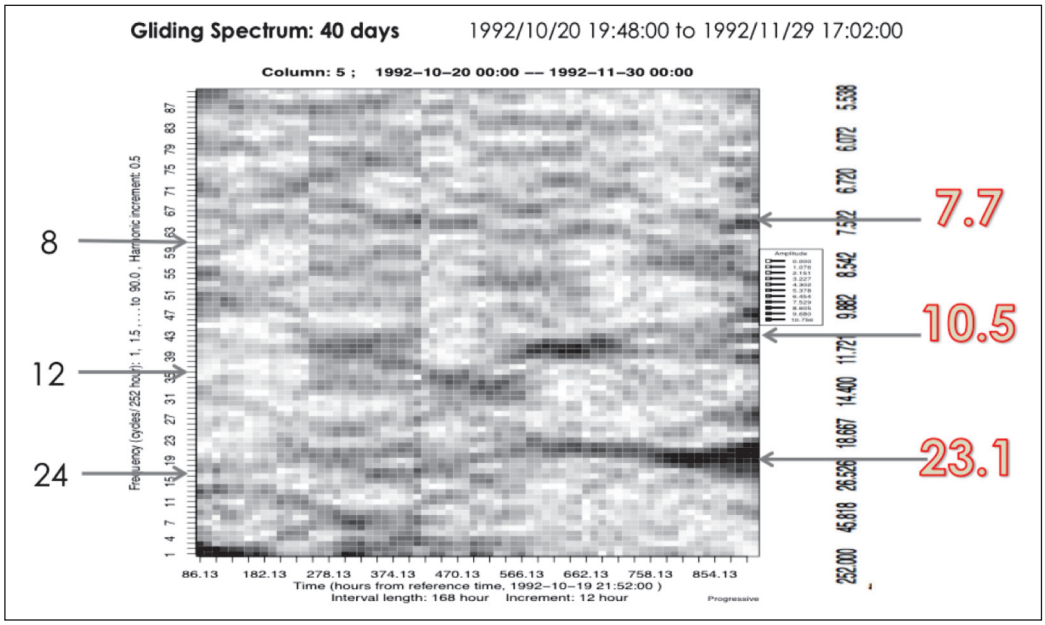

Figure 10: *Gliding Spectrum on 40 days of heart rate since birth. Few dark areas are visible on the left side, but over time a few bands resolve around 23/24 h, 10.5 h and 7.7 h. Data from Y Watanabe.*
© Halberg Chronobiology Center.

Immediately after birth, there is no coherent rhythmicity, except perhaps around the week which is not rigorously assessable with the parameters chosen for this analysis. We see only unresolved shadings. But toward the middle of the plot we begin to see bandings coalesce at specific periods. Eventually,

bands appear near 23 hours and 10.5 hours, as well as around 7.7 hours. This graph provides a view of how and when the circadian component develops in a healthy, full-term baby boy.

CATkit

These analyses have all been performed with CATkit, written in R. The call to CATkit is put into a .r script file, and can be put on the desktop. Double clicking will run the script, and produce the output displayed in the figures and tables herein, as well as additional files containing tab-delimited computer readable output. Interpolated data can also be exported for later use.

```
CATCosinor
TimeCol=1,Y=c(2,5), Components=1,

RefDateTime="199210192152",
timeFormat="%Y%m%d%H%M", RangeDateTime=list(Start="199211230000",
End="199211300000"), fileName=fileName, functionName="FWeditedLWK-HRsp"

Progressive=list(Interval=0, Increment=0),

Period=list(Set=0,Start=168,Increment=.5,End=5.5),
```

Figure 11: *Call to CATkit in .r script file. This script performs a least squares spectrum on columns 2 and 5 using a single- component cosinor model.*
© Halberg Chronobiology Center.

Each of these analyses uses only slightly different call lines in the .r script. Figure 11 is one example of a call to CATkit. This particular call line performs a least squares spectrum using a single-component cosinor. TimeCol identifies the column(s) containing the time. Any format can be used by setting timeFormat. Y is used to indicate the column or columns containing data to be analyzed. Components is set to the number of cosine components to use in the model. RangeDateTime can be used to limit the rows of data used to only those times specified as Start and End of range. Progressive Interval and Increment configure the program for serial section, or gliding spectrum. Period is used to determine which periods should be considered for analysis. Set indicates the trial period or periods. Any valid R structure can be used, so a single value can be used (Set=24), or a vector can be used (Set=c(24 12, 8)). R allows ranges to be specified as well, so a range from 24 to 12, and also 8 [hours] could be specified (Set=c(24:12,8). If Set=0 a least squares spectrum is performed using Start, Increment and End. Start and End are given in hours. These will be the starting and ending trial periods. Increment refers to frequency (harmonic increment).

CATkit produces a variety of output files (Figure 12). For each function, one or more plots are produced. Also, for each column of data acted upon by a function, quantitative results are produced in two formats, human-readable as well as tab-delimited computer-consumable. The functions that require equidistant data, and therefore use interpolation when needed, will also export the interpolated (and binned) data in tab-delimited format.

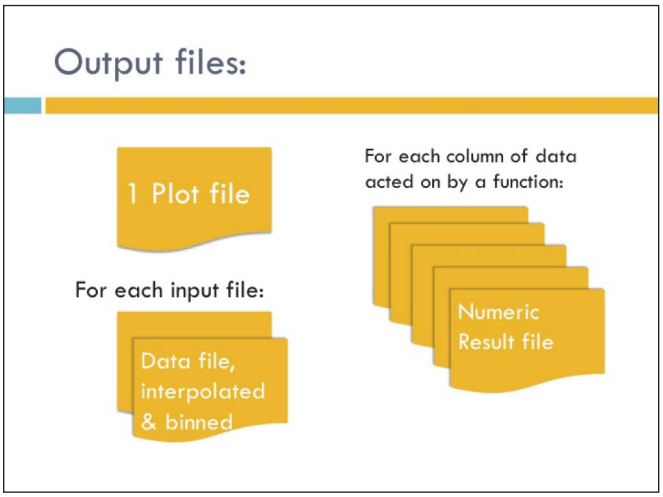

Figure 12: *Output files produced by CATkit. © Halberg Chronobiology Center.*

Discussion and Conclusion

CATkit is used at the Halberg Chronobiology Center, and by other investigators worldwide. It has been used, among other applications, for studying the day-to-day variability in circadian characteristics of blood pressure [15], for determining the best timing to take daily anti-hypertensive medication, extending results already published [16], and to assess the time structure of the incidence of cardiovascular conditions in a comprehensive database of ambulance calls in Siberia.

R is freely available from the Comprehensive R Archive Network http://cran.r-project.org/ [1], and can also be used as a scripting language, facilitating the creation of scripts to run CATkit iteratively for multiple data files, or build other custom automations in the broader R environment. CATkit, and instructions for installation and use, can be found at http://z.umn.edu/CATkit.

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RECENT PROGRESS IN THE STUDY OF THE CARDIO-ANKLE VASCULAR INDEX (CAVI)

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[3]Fukuda denshi Co

To measure the stiffness of the aorta, femoral artery and tibial artery noninvasively, cardio-ankle vascular index (CAVI) which was independent of blood pressure had been developed in cooperation of the Tohoku University and Fukuda denshi Co. The reproducibility had been studied, and the Independence from blood pressure have been studied till now. The results suggested that CAVI could reflect arteriosclerosis of the aorta, femoral artery and tibial artery. Furthermore we can evaluate the baroreflex sensitivity of an artery by the use of arterial tone. International cooperation study are ongoing now. So various scientific reports are easily found in pubmed. Medical device maker is now gathering these international papers for the presentation to the every doctors in the world for the achievements of better medical care. If the evaluation by this methodology in not so good, all doctors have a chance to use another devices. So, it is not necessary to use this method when the scientific papers showed another device had been good. Every doctors in all over the world must check recent progress in medical device in the scientific fields. By the use of the scientific, physical, quantitative methodology, evaluation of the atherosclerosis will be embodied in near future based on the normal value of every people in every country.

Key words
Cardio Ankle Vascular Index, Baroreflex, Pulse wave velocity, International cooperation

Introduction

In order to diagnose arteriosclerosis in any part of the body, pulse wave velocity (PWV) measurement is a useful approach1-3). However, it is considered that the technique of PWV measurement should be simplified. A new method for measuring PWV has therefore been proposed in Japan. The PWV of the brachial artery and the ankle was measured by applying air pressure with the aid of a volume plethysmograph3-5). Comparisons between the baPWV measurement method and the conventional method are currently being performed. Since satisfactory results have been obtained to date, baPWV has gained popularity throughout Japan.

Since this method measures PWV in the arm and foot, it may be said that aortic PWV is not reflected though a large amount of past PWV measurements. BaPWV is influenced by blood pressure. With the baPWV technique, blood pressure compensation is not carried out. Furthermore, the pulse pressure is measured by air pressure; therefore any stimulus that exerts pressure on an artery may influence these results. Due to these reasons, a cardie-ankle vascular index (CAVI) has been proposed in which the pressure wave form indicating the closing of the aortic valve appears in the form of an arterial pressure wave after a fixed delay time6-9).

Formula for measuring this index is; CAVI=a{(2rho/DeltaP) x ln(Ps/Pd)PWV(2)} + b where, Ps and Pd are systolic and diastolic blood pressures respectively, PWV is pulse wave velocity between the heart and ankle, DeltaP is Ps - Pd, rho is blood density, and a and b are constants. This equation was derived from Bramwell-Hill's equation, and stiffness parameter.

Measurements of stiffness parameter of the Aorta and arteries are of course important in developed countries, because progression of the atherosclerosis causes a chronic artery disease that develops over many years without clinical symptoms.

Furthermore, it is an important point that the progression of atherosclerosis may be decelerated by intensive treatment of the main cardiovascular risk factors. Various kinds of medical studies has been carried out in all over the world. Soska V, Dobsak,P, et al. always have noted the importance of obesity in the prevention of the stiffness parameter progression, and a lot of researchers in many countries including Japan, USA, China, have showed the data concerning the obesity and CAVI in pubmed base.

International cooperative study

In the world, the Russian data was the most interesting thing. Because the worst obese population in EU has been observed in Russia and Malta. In Smolensk, a lot of patients had been evaluated in the Smolensk State Medical Academy. 1733 peoples had been measured and evaluated. For example, 390 healthy subjects without heart attack, stroke, hypertension, HCM, DM and smoking had been compared with Aging.

Everybody knows that DM has been the worst risk factor in metabolic disorder. Of course, the Russian data had supported the existence of this phenomenon.

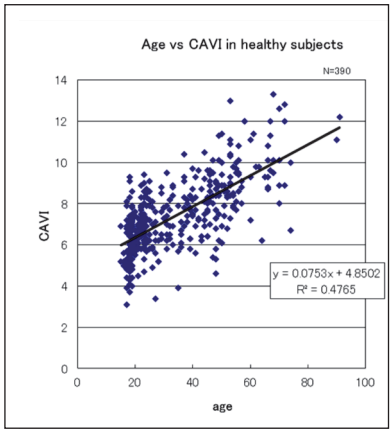

Figure 1: *CAVI in the Russian healthy subjects*

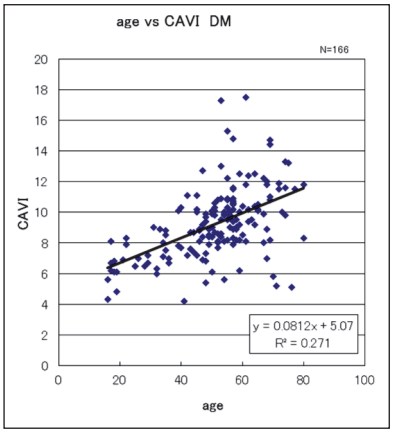

Figure 2: *CAVI in DM patients in Russia*

Baroreflex sensitivity of vascular tone

Baroreflex system is one of the most important regulatory systems to maintain the homeostasis of the circulation. When blood pressure (BP) was increased, baroreceptor sensed this increase. Neural information concerning the BP change was evaluated in the central control system. Heart rate (HR) was reduced and resistance vessels were dilated by the autonomic control system. BP was returned to the normal range by the reduction of the pump out put and vascular resistance. Sensitivity of the baroreflex system was evaluated by the various methodologies. Quantitative evaluation by the slope

of the regression line between BP change and HR change was one of the typical method to evaluated the baroreflex sensitivity of the heart. However, we could not evaluate the baroreflex sensitivity of the vascular system by this method.

Autonomic nervous system control of the each internal organ was different. So, we must evaluate the sensitivity of the baroreflex system of an artery. However, it is very difficult to evaluate the tonus of the artery in the human body during awaking condition. Recently, brachial ankle pulse wave velocity (baPWV) and cardio ankle vascular index (CAVI) were invented and commercialized. These methodologies measured the pulse wave velocity of the human body and calculate the tonus of the artery. So, if we use these methodologies to measure the tonus of the artery, we can measure the characteristics of the baroreflex system of an artery.

New diagnosis tool to evaluate the baroreflex sensitivity of an artery was invented.

In order to evaluate the baroreflex sensitivity of an artery, we used the information of the pulse wave velocity of the human body. Time series data of the ECG, pulse wave of the radial artery, and finger tip pulse wave were recorded in the data recorder and analyzed in the personal computer system.. Pulse wave velocity was calculated from the time lag between the R wave and pulse wave. Changes of the pulse wave transmission time were plotted against the changes of the blood pressure. Slopes of the regression line showed the baroreflex sensitivity of the peripheral resistance artery.

Quantitative evaluation of the baroreflex sensitivity may be useful when we consider the ideal treatment of the patients with hypertension12-13)

Recent progress of CAVI

Further international cooperative studies are undergoing now. So various scientific reports are easily found in pubmed. Medical device maker is now gathering these international papers for the presentation to the every doctors in the world for the achievements of better medical care. If the evaluation by this methodology in not so good, all doctors have a chance to use another devices. So, it is not necessary to use this method when the scientific papers showed another device had been good. Every doctors in all over the world must check recent progress in medical device in the scientific fields.

For example, Schillaci et al. had reported the usefulness of CAVI compared with cf PWV in LV mass detection14). We need the further examination in future, but comparison of the various methodology is always important.

Otsuka et al. reported the changes in CAVI after management of atherosclerotic risk factors15), and the impact of these changes on future CVD outcomes. CAVI improved in 50% patients after 6 months, but remained high in 50% patients. CVD outcomes were worse in patients with persistently impaired CAVI than in those with improved CAVI ($P < 0.001$). His study was the first to demonstrate that persistent impairment of arterial stiffness was an independent risk factor of future CVD events.

Long time follow up is the most important issue. We must continue this kind of studies. Of course, the obesity in one of the most important factors in Metabolic syndrome when we consider the healthy population in every countries. Sato asahara et al. reported the incidence of cardiovascular events in obese patients. And their study demonstrates for the first time that CAVI is an effective predictor of CVD events in obese patients.

More and more studies are carried out now in all over the world.

There may be a possibility that another new diagnosis method will be invented.

We must continue our study for the more good treatment of the patients

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CURRENT PROGRESS OF A NON-INVASIVE PERIPHERAL PERFUSION EVALUATION DURING MECHANICAL CIRCULATORY SUPPORT

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Centrifugal blood pumps have been commonly applied to the patients with severe heart failure in recent years. Due to the extension of assisting period in patients with the reduced pulsation, the prevention of long-term adverse effects in end-organs has been focused to keep the healthy conditions in peripheral perfusion under the mechanical circulatory support conditions. We have been developing novel approaches from the mechanical circulatory point of view, such as artificial myocardial assist systems or pulmonary circulatory assist devices, which could represent and promote either the ventricular contraction or the hemodynamic pulsatility delivered to peripheral organs. In order to achieve the quantitative examination of these effects on perfusions on hemodynamics, a new non-invasive approach to diagnostic procedures using a high-speed CCD image analyses has been accomplished to estimate peripheral blood flow in animal experiments with centrifugal blood pumps. Consequently, the sequential image-based analysis corresponding to the peripheral circulation may permit detrimental and comprehensive validation in each patient during the low pulsatility condition without direct measurement of blood flow.

Keywords
mechanical circulatory support, animal experiments, centrifugal blood pump, high-speed image analysis, peripheral perfusion

Introduction

In recent years, many types of rotary blood pumps have been clinically and widely employed for the surgical treatment as ventricular assist devices (VADs) in the patients with severe heart failure1–5. As rotary blood pumps are mainly supplied as the implantable VAD, there might be reduction or elimination of pulse in the patients with mechanical circulatory support. To overcome a trend in the lack of donors for heart transplantation, the trajectory of surgical treatment with the use of VADs are shifting from the bridge-to-transplant or the bridge-to recovery to the destination therapy or to the bridge-to-decision as an alternative course. The long-term use of the rotary VADs causes mechano-

physiological changes in cardiovascular systems, especially in end-organ peripheral function that might be induced by adverse effects during the extensive mechanical circulatory support.

Steering the pressure-flow relations by the total artificial heart (TAH) is one of the control methods for physiological regulation in the end-stage of heart failure by the use of pulsatile or non-pulsatile TAHs6. Although the complication according to the circulatory balance might be reduced by using the intellectual artificial control algorithm, the physiological response could be rearranged for the maintenance of end-organ function en passant.

We have been developing several types of cardiovascular mechanical contractile support devices as shown in Figure 1. Each system outputs a contraction force that is initially placed outside of the ventricle or vascular vessels to support native blood pumping action without direct contacting surface of blood. We proposed these mechanisms by combining the small components and the Ni-Ti alloy fibers to achieve the miniature implantable design and highly flexible structure for the installation into the small sized thoracic cavities. These novel artificial cardiovascular support systems could provide the effective hemodynamic assistance with respect to the physiological demands. However, the direction of the control design should include an alternative circumvented way preventing the functional dislocation of artificial contraction and the afterload mismatch.

In order to obtain the peripheral perfusion data non-invasively and quantitatively, we applied a pulse detection method by using a charge-coupled device (CCD) that provides RGB color absorbance information of the region of interests of the skin surface7–9.

A new approach to indirect diagnostic methods using a set of high-speed sequential images involves regional surveillance of surfaces of end-organs, such as skin, kidney, lung, heart, etc. This study presents the design and capabilities of an evaluation method that could exhibit the rate of pulsatility in peripheral perfusion during the mechanical circulatory support condition. The proof-of-concept was examined on the ability to represent comprehensive variation of the pulse detected by using the high-speed images obtained from the end-organ surfaces.

Materials and Methods

The current procedure of the estimation of peripheral perfusion involves the installation of a centrifugal blood pump and the analyses of color changes of each organ by indirect measurements.

a) Installation of a centrifugal blood pump

Prior to the measurement of peripheral perfusion, we performed the left VAD installation using a centrifugal blood pump (EVAHEARTTM, Sun Medical Technology Research Corporation, Suwa, Japan). Saanen goats were used for the investigation of peripheral circulation. We operated the device installation and the measurements via left thoracotomy under the normal anesthesia by the administration of 2.5% isoflurane and by 0.2μg/kg/min remifentanil. The animal experimental procedure was approved by the Institutional Animal Experiment Committee of Tohoku University, Sendai, Japan.

b) Measurement of high-speed sequential images

High-speed image recordings were performed during the rotary blood pump support as well as the control condition without the VAD support. The operating speed of the pump was varied from 1,000 to 2,200 rpm, providing a mean flow rate of 1 to 5 L/min, approximately. We recorded the images by a digital video camera (NEX-FS100JK, Sony, Japan) at the rate of 480 fps under the white-colored

LED lighting condition (VL-1600C, LPL Co. Ltd., Tokyo, Japan) as shown in Figure 2. Numerical separation of RGB color components and regional averaging of color levels in root mean square values were calculated (Mathematica V10, Wolfram Research, IL, USA). We also carried out the simultaneous measurement of tissue perfusion by a Laser flowmeter (FLO-C1, Omegawave Co. Ltd., Tokyo Japan) for the comparison of the direct measurement of end-organ surfaces.

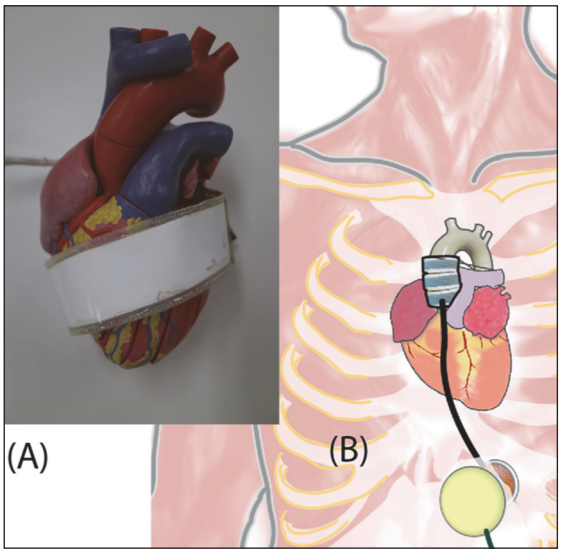

Figure 1: *Small-sized implantable mechanical circulatory devices to generate additional contractile function from outside of the heart and the vessels: A) an artificial myocardial assist system, and B) an extra aortic kinetic support device.*

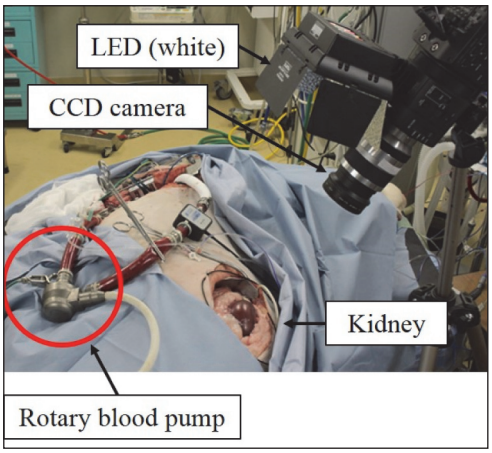

Figure 2: *An example of the measurement of high-speed sequential images by the digital video camera (CCD) under the rotary blood pump support focusing to the kidney perfusion.*

Results and Discussion

Sequential images obtained in previous studies using a CCD indicated that the absorbance of green color exhibited end-organ pulse at the face skin during the mechanical blood pump support (Figure 3). We compared the results of the conventional Laser tissue blood flow and the fluctuation of the data obtained by the indirect measurement by the CCD at the surface of left kidney. As can be seen, base

frequencies calculated by the data in each method had a close similarity that was equivalent to the heart

rate. Moreover, the oscillation of estimated pulse by the CCD corresponded to the changes in amplitude of tissue perfusion (Figure 4, 5). Therefore, a quantitative analysis to detect peripheral perfusion could be applied based on the green color component absorbance on end-organ surfaces by using a high-speed DVC/CCD. Using this method, regional physiological changes might be predicted in the failure heart hemodynamics with rotary blood pumps non-invasively. The method applied in the study provides the simplified information of levels in green color absorbance by the blood based on previous pulse detection methods. Nevertheless, these results suggest that data obtained using CCD images may provide peripheral perfusion information as well, and it can be useful for assessing the effects of end-organ blood supply. The simplified device could also provide an interactive system, where there would be practical oversight by doctors for the patients at home via tele-communication. More generally, employing these non-invasive diagnostic measurements to other organs' physiological function could improve the quality of care for patients with severe heart failure.

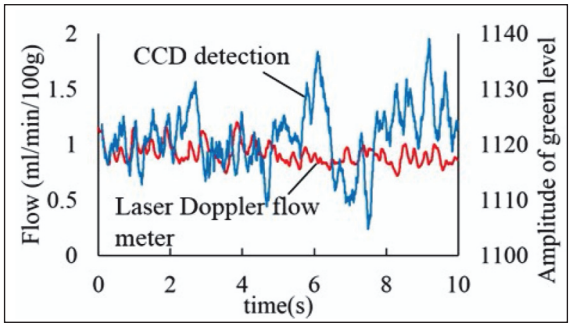

Figure 3: *Changes in the waveform obtained by the Laser tissue flowmeter and the data calculated by the CCD data from the surface. of a goat face skin*

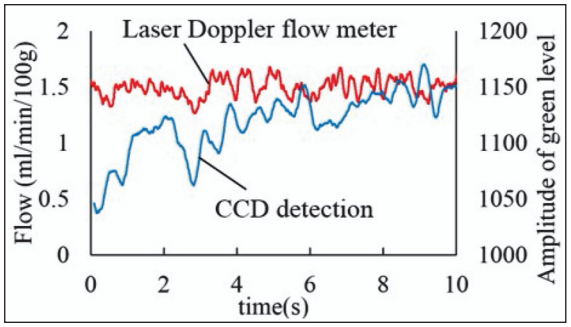

Figure 4: *Changes in the waveform obtained by the Laser tissue flowmeter and the data calculated by the CCD data from the kidney surface.*

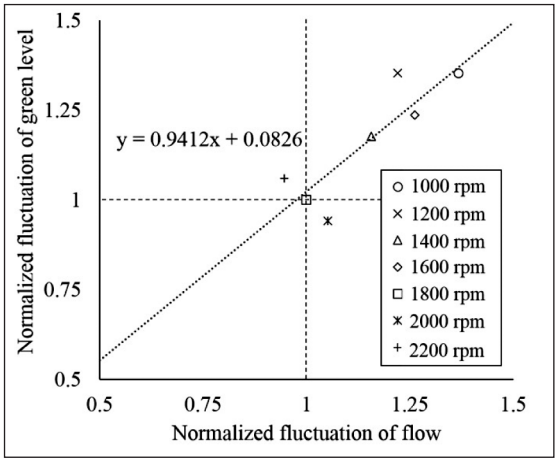

Figure 5: *Comparison of normalized fluctuations obtained by the CCD and the Laser tissue flowmeter under the different driving condition of the EVAHEART device from 1,000 to 2,200 rpm.*

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PROF. MUDR. ZDENĚK PLACHETA, DRSC. 4. 4. 1931 - 1. 11. 2014

JARMILA SIEGELOVÁ

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Prof. MUDr. Zdenek Placheta, DrSc., died on November 1st, 2014. He will be remembered as an exceptional expert in sport medicine, professor emeritus of Masaryk University and also an active sportsman.

Prof. Placheta completed his studies of medicine in Brno in 1956 and started his medical career in the Dept. of Anatomy, Masaryk University, under the leadership of excellent professor MUDr. K. Žlabek. Later he worked in the II. Clinic of Internal Medicine, Masaryk University, under the leadership of Prof. MUDr. Polčák and he qualified in internal medicine. He moved to work in the Dept. of Sport Medicine, Masaryk University, Faculty of Medicine, St. Anna Hospital in Brno; in this time Doc. MUDr. Vladimír Dražil, CSc., was the head of the Dept. of Sports Medicine.

The choice to work in the Dept. of Sports Medicine was based on the active sports career of Prof. Placheta. He was an active sportsman, played football and in the years 1954-1960 was a member of the national league of football and took part in the representation of the Czechoslovak Republic. In the Dept. of Sports Medicine he not only taught medical students in the field of sport medicine but also started his research career in sports medicine and functional investigations of cardiovascular and respiratory system at rest and during exercise. From Masaryk University he was given an exceptional possibility to continue working abroad in the field of sport medicine, namely in East Germany in Leipzig in „Sportmedizinischem Zentrum“ in 1960, and on the basis of his thesis done in Germany he was given the title Dr. Med. in Germany. In 1966 he was given the scientific degree CSc. at the Masaryk University. His research was aimed to the physical fitness in young adults aged from 12 to 18 years. He published the results of his findings in the field of sports medicine in a lot of publications. The most important were English written monographs Youth and Physical Fitness (1980) and Submaximal Exercise Testing (1988). In 1986 he was given the title Assoc. Prof. in Charles University in Prague, in 1987 he was given the research degree DrSc. In 1988 he replaced Doc. MUDr. Vladimír Dražil, CSc., who retired, and became Head of the Dept. of Sports Medicine and in the same year he became the professor of sport medicine. Under his leadership the research in the Dept. of Sports Medicine was aimed not only to healthy sportsmen of the superior level, but also to the development of new investigation methods of functional diagnostics of cardiorespiratory functions in health and disease. In 1996 he retired and gave the head position to Prof. MUDr. Jarmila Siegelova, DrSc., but following his retirement he continued to be active in the department and in 1999 he published another important monography „ Zátěžová diagnostika v ambulantní a klinické praxi“, together with Prof. J. Siegelová and Prof. M. Štejfa, and also contributed to the teaching program of the department until his death.

Prof. MUDr. Zdenek Placheta Dr.Sc., spoke English, French and German fluently and took part in international symposia, congresses and workshops in 1996 – 2014, being organized in Masaryk University every year by our department. Some of his participations are documented in the photographs together with the speakers from abroad - Europe, USA and Japan. He was also coauthor of some publications from our Congresses of Noninvasive Methods in Cardiology.

Figure 1: *Prof. MUDr. Z. Placheta DrSc. is standing and from the left we can see Prof. Dr. med. Thomas Kenner d.h.c. mult., Graz, Austria, Brigitte Kenner, Graz, Austria, Prof. Dr. Jean-Paul Marineaud, Paris, France and Prof. MUDr. Jarmila Siegelova DrSc., at the occasion of MEFA International Symposium, Brno, in 1998.*

Figure 2: *Prof. MUDr. Z. Placheta DrSc. in Brno "Trade Fair – MEFA" International Symposium, Brno, in 2003.*

Figure 3: *Prof. Dr. Jean-Paul Marineaud, Paris, France and Prof. MUDr. Z. Placheta DrSc. in Brno "Trade Fair - MEFA" International Symposium, Brno, in 2003.*

Figure 4: *Prof. Dr. Franz Halberg, d.h.c. mult., Minnesota, USA, Prof. Dr. Jean-Paul Marineaud, Paris, France and*
Prof. MUDr. Z. Placheta DrSc. in the "Trade Fair- MEFA" International Symposium, Brno, in 2003.

Figure 5: *International Congress "Noninvasive Methods in Cardiolology in 2007", held in Faculty of Medicine, Masaryk University, Brno, Komenského nam. 2. From the left we can see Mgr. Dunklerova, Brigitte Kenner and Prof. Thomas Kenner d.h.c.mult., Graz, Austria, Prof. MUDr. Zdenek Placheta DrSc. Prof. MUDr. Petr Dobsak, CSc., and Prof. Jean Eric Wolf, Dijon, France.*

Figure 6: *International Congress "Noninvasive Methods in Cardiolology in 2007", held in Faculty of Medicine, Masaryk University, Brno, Komenského nam. 2. From the right we can see Prof. Thomas Kenner d.h.c.mult., Graz, Austria, standing in the discussion with Prof. MUDr. Zdenek Placheta DrSc. sitting Prof. MUDr. Petr Dobsak CSc., Prof. MUDr. Bohumil Fišer CSc., Prof. MUDr. Jarmila Siegelova DrSc., and from behind Brigitte Kenner.*

Figure 7: *International Congress "Noninvasive Method in Cardiolology in 2007", held in Faculty of Medicine, Masaryk University, Brno, Komenského nam. 2. From the right we can see Prof. Masario Kohzuki, Sendai, Japan, standing in the discussion with Prof. MUDr. Zdenek Placheta, DrSc. and Prof. MUDr. Petr Dobšak, CSc., both standing, and at the first table from behind Brigitte Kenner and Prof. Thomas Kenner d.h.c.mult., Graz, Austria, and at the first table sitting Prof. MUDr. Bohumil Fišer, CSc., and Prof. MUDr. Jarmila Siegelova, DrSc.*

Prof. MUDr. Zdenek Placheta, DrSc., belongs to the generation of pioneering specialists in sports medicine. He will be sorely missed because of his intellectual and scientific as well as clinical contribution. Dear Prof. Placheta, we thank you very much for your friendship, collaboration, endeavour, and for pushing ahead the frontiers of knowledge in medicine. We will continue your work in the Department of Sports Medicine and Rehabilitation in St. Anna Hospital in Faculty of Medicine, Masaryk University, Brno.

PROF. MUDR. MIROSLAV MIKULECKÝ, DRSC. 22. 6. 1927 - 25. 1. 2015

JARMILA SIEGELOVÁ

Dept. of Physiotherapy and Rehabilitation, Faculty of Medicine, Masaryk University, Brno

Prof. MUD. Miroslav Mikulecký, DrSc. finished studies of medicine in 1952.In the years 1952-1994 he worked in the I. Dept of Medicine, Medical Faculty, University of Komenius in Bratislava, now Slovakia. In 1967 he finished his scientific theses and got the scientific degree CSc., in 1974 he become associated professor, in 1980 he got scientific degree Dr.Sc. and in 1982 he got the title professor in Internal medicine. In the years 1981 -1989 he was the head of I. Dept. of Medicine, Faculty of Medicine University of Komenius in Bratislava.

In the scientific field he was the founder of gastroenterology in Slovakia. He published about 1 000 scientific publications in the internal medicine, biometrics and chronobiology of cardiovascular parameters. He had excellent knowledge in mathematical and statistical methods and cooperated with scientists in Halberg Chronobiology Center, University of Minnesota, and Bethesda USA, Liverpool, Great Britan, Australia, Japan and others. He also cooperated with the III. Dept of Medicine, Faculty of Medicine, Masaryk University, namely with Prof. MUDr. Konrad Ryšánek, Dr.Sc. and his team.

Figure 1: *International Chronobiology symposium "Erna Halberg- Sun, Moon and Live" in Bratislava in 1990, organized by Prof. MUDr. Miroslav Mikulecký, Dr.Sc., sitting in the middle of the first road, next to him to the left sitting Prof. Dr. Franz Halberg, d.h.c.mult, from Universty of Minnesota, USA, in the second road standing from the left MUDr. Jiri Dušek, CSc. and Prof. MUDr. Jarmila Siegelová, Dr.Sc., and also standing Prof. Dr. med. Gunther Hildebrand, University of Marburg, Germany in the last road (under the inscription ERNA).*

Professor MUDr. Miroslav Mikulecký, Dr.Sc. organized in Slovakia in Bratislava and in Košice some important international symposia about chronobiology and also our Brno chronobiological team took part with active participations in these symposia.

Prof. MUDr.Miroslav Mikulecký, Dr.Sc. was a talented scientist, he inspired, formed and influenced countless researchers in chronobiology. He will be remembered as an outstanding physician for his kind, open mood and great humanity.

SEVEN-DAY AMBULATORY BLOOD PRESSURE MONITORING AT REST AND DURING EXERCISE: VARIABILITY OF NIGHT-TO-DAY BLOOD PRESSURE RATIO

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**University of Minnesota, USA*

Dedicated to the memory of Franz Halberg and Bohumil Fiser

Introduction

Franz Halberg and Germaine Cornelissen using ambulatory blood pressure monitoring showed the need to account day-to-day changes of blood pressure and heart rate and the necessity to circadian assessment of the hour-to- hour variability in cardiovascular parameters. The Chronobiology center of Minnesota started with the international project BIOCOS with seven day/24 hours blood pressure monitoring in Japan, Urausu, Hokkaido by Kuniaki Otsuka, In Department of functional diagnostics and rehabilitation (Dept. of Sports medicine and Rehabilitation) St. Anna Teaching Hospital, Masaryk University, Brno, Czech Republic under the guidance of Jarmila Siegelova, in Moradabad, India, under the guidance of RB Sing, and others from Belgium, Italy, Mexico, Norway, Armenia, China as well as USA California and Minnesota (1, 2).

From 1988, when O`Brien and colleagues reported that an abnormal circadian blood pressure profile with a less marked decrease in night-time blood pressure led to an increased risk for stroke, the clinical significance of night-to-day blood pressure ratio is known (3). Subsequent studies confirmed the prognostic significance of night-to-day blood pressure ratio for prediction of a higher rate of cardiovascular complications (4-10). One of large-scale studies based on International Database on Ambulatory blood pressure monitoring in relation to Cardiovascular Outcomes was published in 2007 (11). The investigators did 24-hour blood pressure monitoring in 7458 people (mean age 56.8 years) from Denmark, Belgium, Japan, Sweden, Uruguay and China. Median follow-up was 9.6 years. They found that night-to-day ratio of systolic and diastolic blood pressure adjusted for cohort, sex, age, body-mass index, smoking and drinking, serum cholesterol, history of cardiovascular disease, diabetes mellitus, and antihypertensive drug treatment predicted total mortality, non-cardiovascular mortality and cardiovascular mortality. In fully adjusted models night-to-day ratio was additionally adjusted for 24-hour blood pressure. The results for fully adjusted night-to-day ratio were similar except systolic blood pressure and cardiovascular mortality where the hazard ratio 1.08 (0.99- 1.17) was not statistically significant. After the patients were, according the night-to-day ratio, divided in 4 categories with night-to-day ratio >1.0 (reverse dippers), 0.9-1.0 (non-dippers), 0.9-0.8 (dippers) and <0.8 (ultra-dippers), the total mortality was increased in non-dippers and reverse-dippers in comparison to

dippers. Cardiovascular mortality was significantly increased in reverse dippers, as well as incidence of all cardiovascular events.

Although the prognostic significance of night-to-day blood pressure ratio was proved in a large group of patients, the clinical significance of this value depends on variation of repeated measurement in individual patients.

In the year 2010 we evaluated the night-to-day blood pressure variability during 7 days/ 24 hour of ambulatory blood pressure measurement in the healthy subjects and we found great variability in night-to -day ratio in systolic and diastolic blood pressure in the same person in repeated 24-hour blood pressure monitoring (12). In these study was the aim to evaluated night to day blood pressure ratio in the days with exercise and compared it with the days without exercise during 7day/24hour ambulatory blood pressure monitoring in patients with ischemic heart disease.

Methods

Thirty one patients with ischemic heart disease (all males), forty nine years to eighty four years old, were recruited for seven-day blood pressure monitoring. TM 2421 A D Instruments (Japan) were used for ambulatory blood pressure monitoring (oscillation method, 30-minute interval between measurements) (13).The patients were monitored 7 days/ 24 h in the days with exercise and without exercise. One-hour means of systolic and diastolic blood pressure were evaluated, when night-time was considered from midnight to 06;00 h and day time from 10;00 to 22;00 h, avoiding the transitional periods. Mean day-time and mean night-time systolic and diastolic pressures were evaluated every day (14).

Dipper status was evaluated every day. Dippers were defined as those individuals with a 10-20 % fall in nocturnal blood pressure. Non-dipping was defined as a less than 10 % nocturnal fall, and those with no fall in blood pressure were defined as reverse-dippers (15).

The patients underwent phase II of cardiovascular rehabilitation in the Dept. of Sports Medicine and Rehabilitation two times a week, controlled ambulatory rehabilitation program, composed of aerobic and resistant training, three times a week, lasting three month.

Results

Variability of night-to-day ratio during 7-day/24 h monitoring in 31patients in the days without exercise is seen in Figure 1 for SBP and in the days with exercise in Figure 2 for SBP.

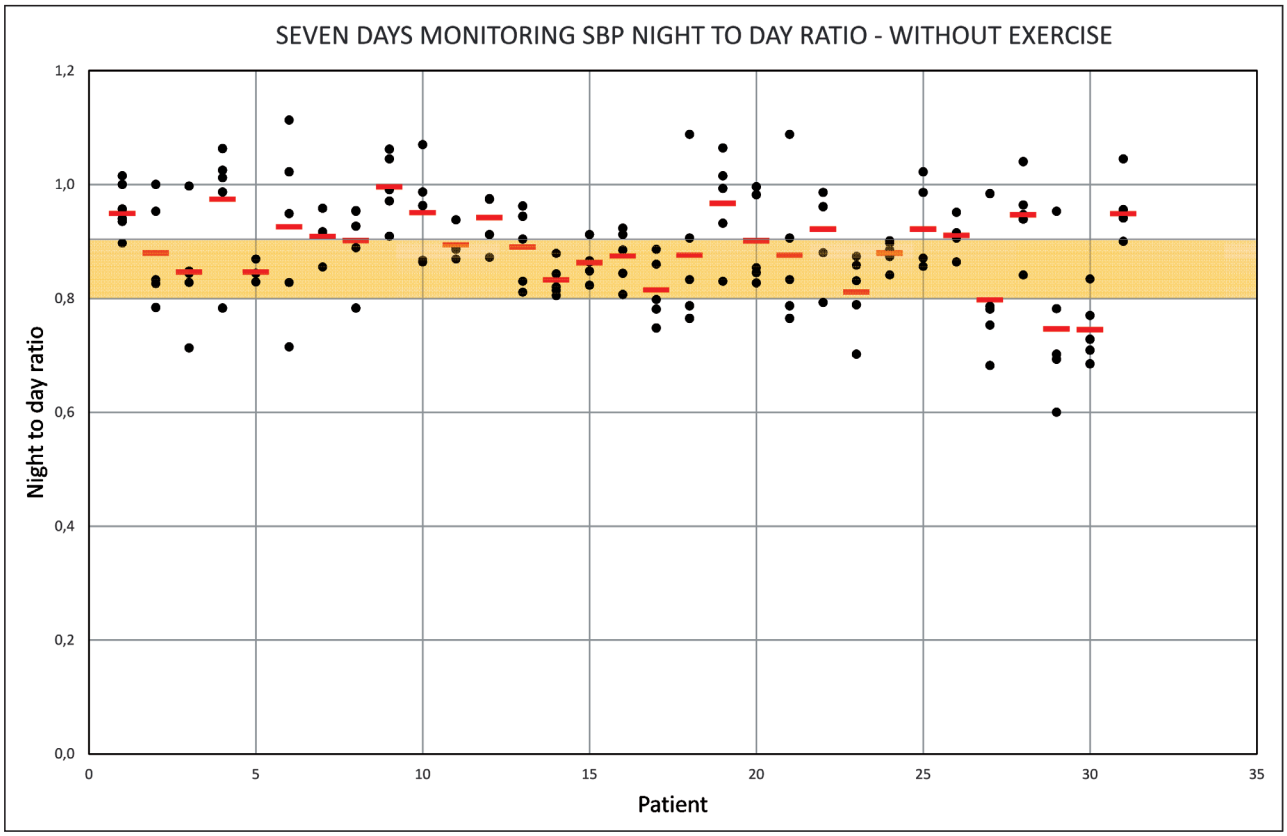

Figure 1: *Seven-day ambulatory monitoring blood pressure monitoring in patients with ischemic heart disease: variability of SBP night to day ratio in the days without exercise*

In the days without exercise in SBP only 3 subjects (10 %) were found which could be classified as SBP dippers or ultra-dippers every day. Most of the subjects were classified on various days differently, even 3 subjects (10 %) were one day classified as ultra-dippers and the other day as reverse-dippers.

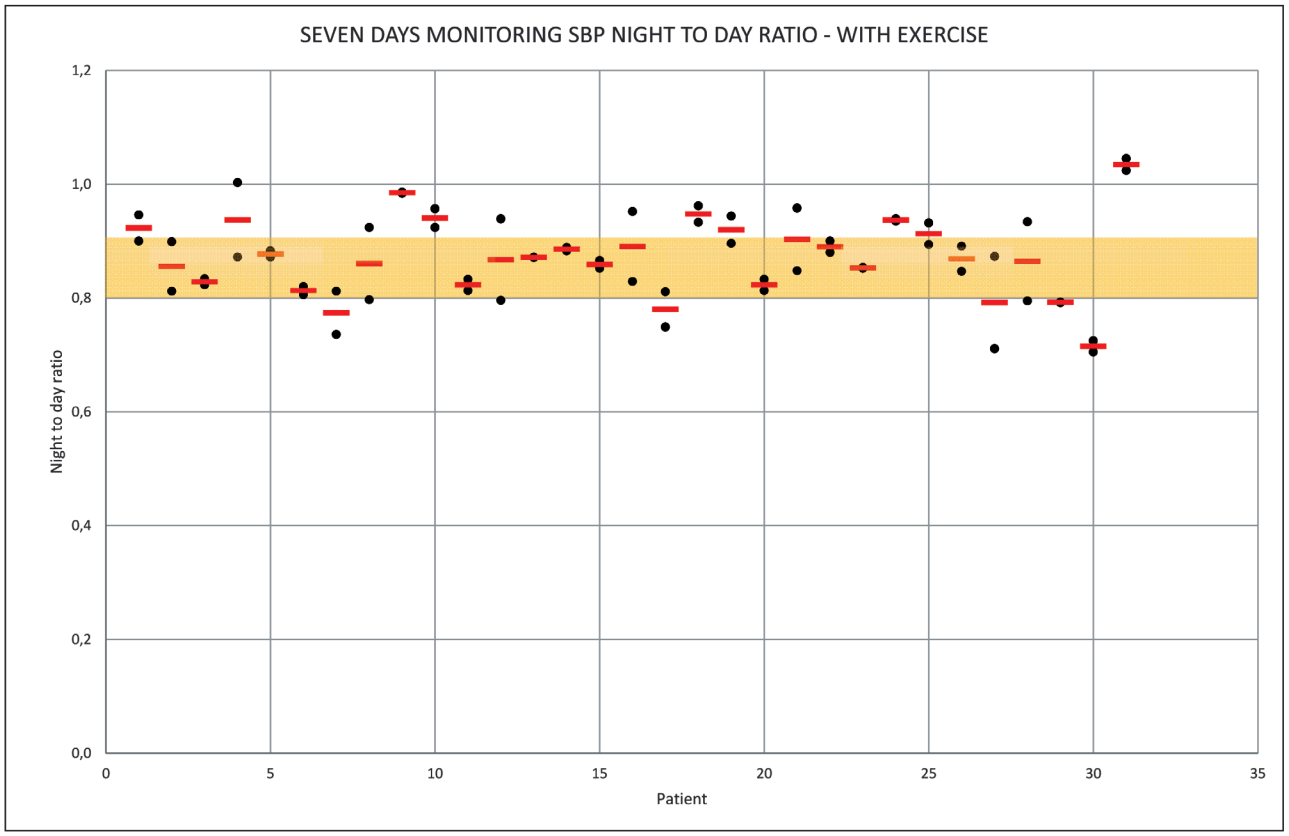

Figure 2: *Seven-day ambulatory monitoring blood pressure monitoring in patients with ischemic heart disease: variability of SBP night to day ratio in the days with exercise*

In the days with exercise in SBP only 4 subjects (13 %) were found which could be classified as SBP dippers or ultra-dippers every day. Most of the subjects were classified on various days differently, even 3 subjects (10 %) were one day classified as ultra-dippers and the other day as reverse-dippers.

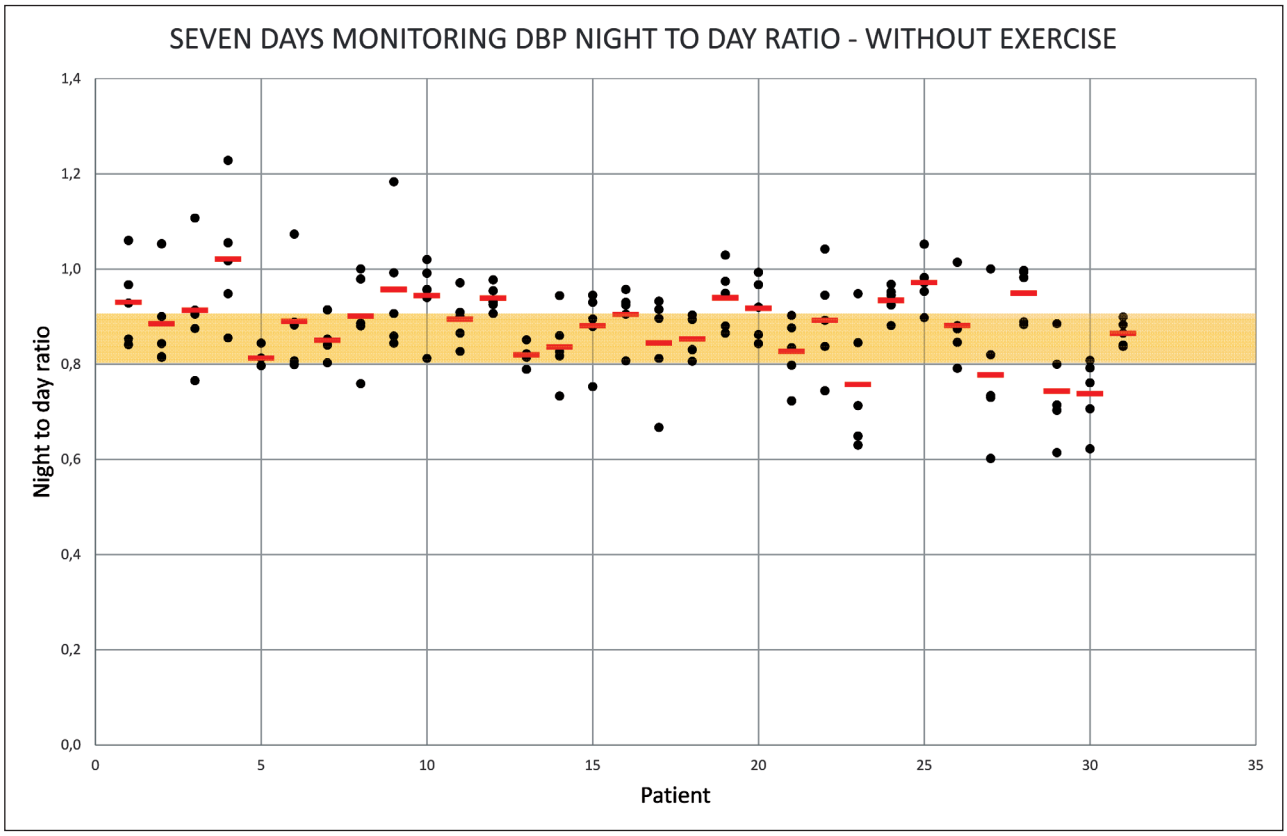

Figure 3: *Seven-day ambulatory monitoring blood pressure monitoring in patients with ischemic heart disease: variability of DBP night to day ratio in the days without exercise*

In the days without exercise, similarly no subject were classified as DBP dipper or ultra-dipper every day. Two subjects (7 %) were classified as DBP dippers, others were one day ultra-dippers and the other day as reverse-dippers.

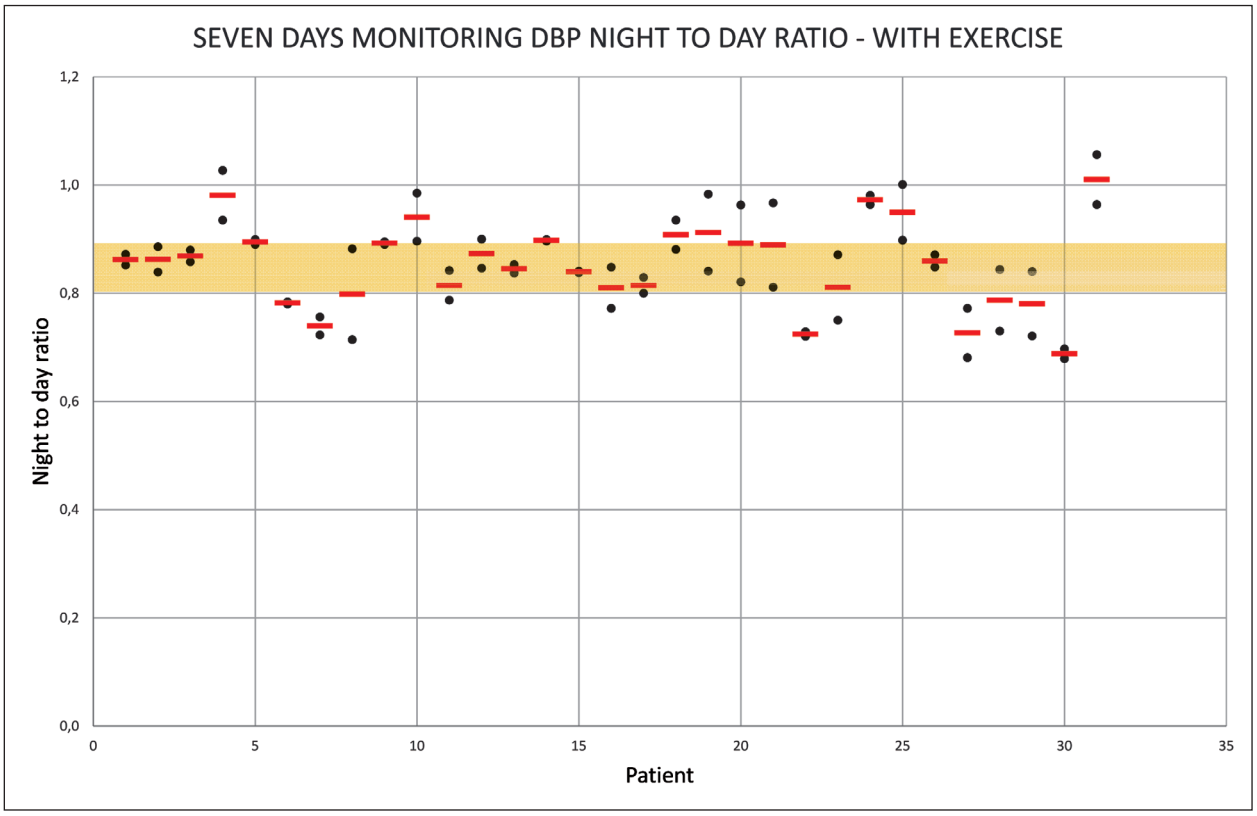

Figure 4: *Seven-day ambulatory monitoring blood pressure monitoring in patients with ischemic heart disease: variability of DBP night to day ratio in the days with exercise*

In the days with exercise, similarly no subject were classified as DBP dipper or ultra-dipper every day. Night subjects (27 %) were classified as DBP dippers, others were one day ultra-dippers and the other day as reverse-dippers.

Discussion

Our finding of large night-day ratio variability in individual subjects corresponds to the results of other studies. The night-to-day blood pressure ratio is subject to regression-to-the mean (16). In our studies with seven day blood pressure monitoring in subjects with resting condition and the presented results in patients with ischemic heart disease in the day without exercise and in the days with exercise showed also large individual variability of night to day blood pressure ratio.

Dipping status has also a low reproducibility, with up to 40 % of individuals from Europe (17) and Asia (18) changing status between repeat recordings.

In our former study we demonstrated that the relation between night-to-day ratio and risk of cardiovascular events is not linear as it is in the case of mean 24-hour systolic and diastolic pressure (19). We observed at low circadian double amplitude which roughly corresponds to the difference between night and day blood pressure (5 mmHg of systolic and 4 mmHg of diastolic pressure) about 30 % higher incidence of cardiovascular events than at circadian double amplitude of 15 to 35 mmHg systolic and of 12 to 20 mmHg diastolic pressure but at double amplitude higher than 35 mmHg in systolic and 28 mmHg in diastolic pressure the incidence was double. This indicates the existence of overswinging or Circadian Hyper-Amplitude-Tension (CHAT) syndrome which is associated with a large increase in cardiovascular disease risk. The incidence of ultra-dipping is more frequent that the

incidence of CHAT but existence of CHAT alone can lead to misdiagnosis of risk based on night-to-day blood pressure ratio (20 – 23).

In conclusion, despite the low night-to-day ratio of blood pressure predicted increased risk for cardiovascular events in large studies, the determination of this value is useless for management of arterial hypertension in individual patients.

Summary

The evaluation of night-to-day blood pressure variability during 7 days of ambulatory blood pressure measurement was the aim of the present study. Thirty subjects (18 males, 12 females), twenty one years to seventy three years old, were recruited for seven-day blood pressure monitoring. Colin Medical Instruments (Komaki, Japan) were used for ambulatory blood pressure monitoring (oscillation method, 30-minute interval between measurements). One-hour means of systolic and diastolic blood pressure were evaluated, when night-time was considered from midnight to 0600 h and day-time from 1000 to 2200 h, avoiding the transitional periods. Mean day-time and mean night-time systolic and diastolic pressures were evaluated every day.

Dipper status was evaluated every day. Dippers were defined as those individuals with a 10-20 % fall in nocturnal blood pressure. Non-dipping was defined as a less than 10 % nocturnal fall, and those with no fall in blood pressure were defined as reverse-dippers.

The day-to-day variability of night-to-day ratio is large. The dipping status classification in individual patients is not reliable.

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SEVEN DAY BLOOD PRESSURE VARIABILITY AT REST AND DURING EXERCISE IN HEALTHY MEN AND PATIENTS

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Introduction

The International College of Cardiology; American Heart Association Council on Nutrition, Physical Activity, and Metabolism; American Heart Association Council on Clinical Cardiology; and American College of Sports Medicine call on all populations of the world, and their employers to create a culture of physical activity and health for the prevention of cardiovascular diseases (CVDs) and diabetes mellitus (1-4).Usually there is no prescribed time for exercise. Regular exercise increases life expectancy, quality of life and work capability and productivity. In patients with ischemic heart disease the non-pharmacologic exercise treatment decrease morbidity and mortality of patients. In a majority of populations, some individuals work around the clock and disturb the sleep at night, what impair the circadian cardiovascular control and many of them exercise not in accordance with natural circadian rhythm. An exercise late in the evening might increase the risk of an increase of circadian hyperamplitude tension (CHAT) and can have an adverse clinical event in increase of cardiovascular disease risk, such as sudden cardiac death (SCD) or acute coronary syndrome (ACS), particularly in vulnerable subjects (3- 6). In the Dept. of Sports medicine and rehabilitation, there is cardiovascular rehabilitation for patients after coronary heart disease, organized according the guidelines of European Society of Cardiology. There are not many data about the effect of exercise on 24h values of systolic and diastolic blood pressure using ambulatory blood pressure monitoring.

The definition of hypertension with different types of measurement is included in the Guidelines for Management of Hypertension, 2007 (8).

According to this table 1 the threshold for the diagnosis of hypertension for systolic blood pressure is 140 mmHg in the office or clinic, in ambulatory blood pressure monitoring 125 – 130 mmHg during 24 hours, 130 -135 mmHg during day and 120 mmHg during night.

The corresponding values for diastolic blood pressure are 90 mmHg in the office and clinic, in ambulatory blood pressure monitoring 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.

Table 1: *From J Hypertension 2007*

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

Our previous studies on 7 day /24 h ambulatory blood pressure monitoring showed that the values of 24h blood pressure varies from day to day in the same patients (9 - 13). The cardiovascular rehabilitation program in out-patients rehabilitation includes the exercise unit, lasting 60 min, three times in a week.

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 in healthy subjects and in patients included in cardiovascular rehabilitation. From seven day ambulatory blood pressure monitoring 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). We analyzed aerobic training, resistant training, Nordic walking in healthy subjects and combined training in patients with coronary heart disease.

Methods

Healthy Subjects Aerobic Training

We examined 21 men and 20 women, healthy subjects, mean age 28±5.2 years (from 23 to 39).

For exercise training we used bicycle ergometer Kettler, type X7, Germany, two times during week, constant load 120 W in men and 80 W in women, lasting 60 min. Every exercise unit was composed from warm-up period 3 min., load 54 min. and cool-down period 3 min.

Figure 1: *Aerobic training in healthy subjects*

Healthy Subjects Combined Training

We examined 5 men and 15 women, healthy subjects, mean age 28±9 years (from 23 to 39).

For exercise training we used aerobic and resistant training, 2x during week, constant load was kept at the heart rate 70 % of heart rate maximum, lasting 25 min. and resistant training lasting 15 min. Every exercise unit was composed from warm-up period 10 min. aerobic training 25 min., resistant training 15 min. and cool-down period 10 min.

Figure 2: *Aerobic training as a part of combined training in healthy subjects*

Figure 3: *Resistant training as a part of combined training in healthy subjects*

Healthy Subjects Nordic Walking

We examined 7 men and 12 women, healthy subjects, mean age 26±7.1 years (from 23 to 39).

For exercise training we used Nordic walking, 2x during week, constant distance 4.3 km at the heart rate 70 % of heart rate maximum.

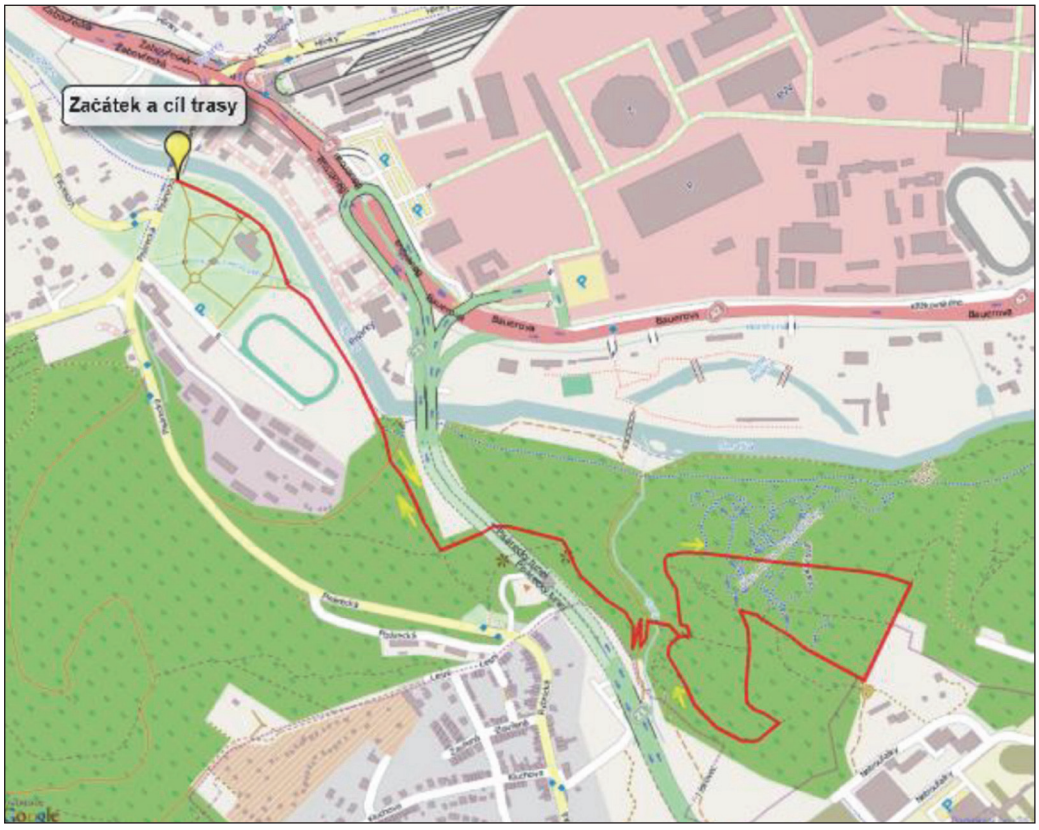

Figure 4: *Nordic walking trace in the town Brno shows the red line*

Patients with coronary heart disease

4. We examined patients with ischemic heart disease - infarctus of myocardium, mean age 62±8.9 years.

The set being monitored consisted of 53 patients after myocardial infarction in the past history more than 3 months before. Mean ejection fraction of the left ventricle 43 ± 12.3 %. The patients were diagnose and threated in the Dept. of cardio-angiology, Faculty of Medicine, Masaryk University, St. Anne Teaching Hospital. The pharmacological therapy was not changed during the period of three months during cardiovascular training.

The patients underwent phase II of cardiovascular rehabilitation (controlled ambulatory rehabilitation program) lasting three months with the frequency of three times in a week at the Department of Sports Medicine and Rehabilitation of St. Anna Teaching Hospital. Exercise unit was composed of 10 min. warm up period, 25 min aerobic training with the intensity on the level of anaerobic threshold (measured using spiroegometry), 15 min resistant training on the level of 60% one repetition maximum, 10 min cool down period.

Figure 5: *Supervised aerobic training in patients with coronary heart disease*

Figure 6: *Resistant training in patients with coronary heart disease*

Methods of blood pressure monitoring

The subjects were recruited for seven-day blood pressure monitoring. Medical Instruments (A&D, Japan) were used for ambulatory blood pressure monitoring (oscillation method). One-hour means of systolic and diastolic blood pressure were evaluated.

We calculated mean systolic and diastolic blood pressure for seven days.

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 (7).

The average SBP and DBP and their standard deviations (SD) or standard error (ER) in the given days were determined by the calculation of arithmetic mean of these values during every day and during 7 days. We evaluated the days with exercise (0-24h) and the days without exercise (25-48h).

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

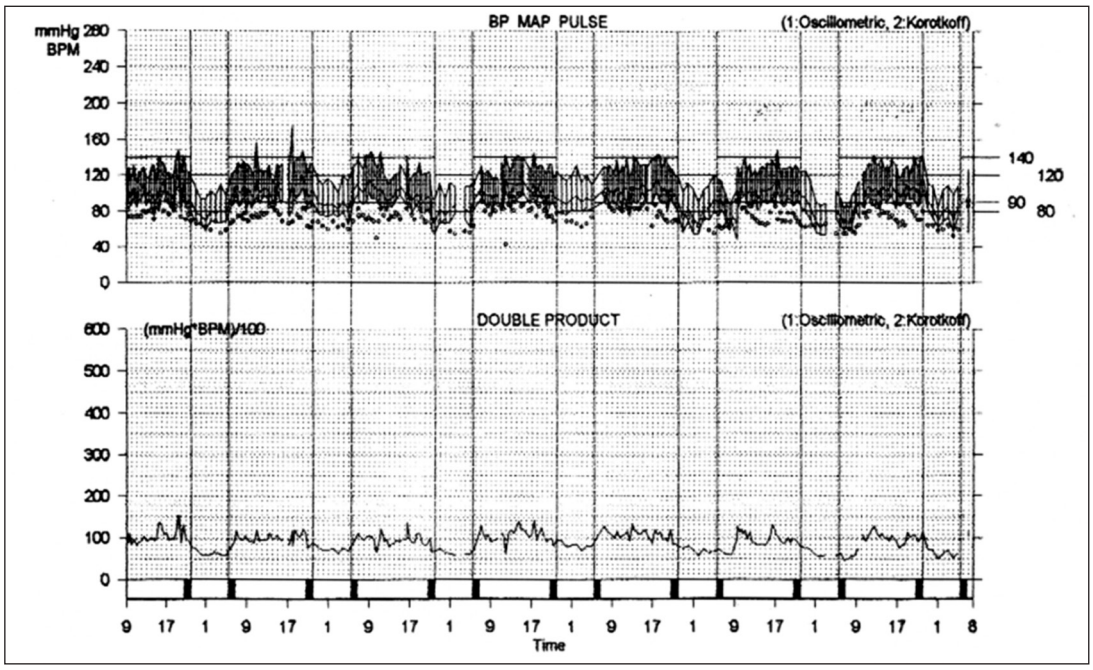

Figure 7: *Seven day ambulatory blood pressure monitoring*

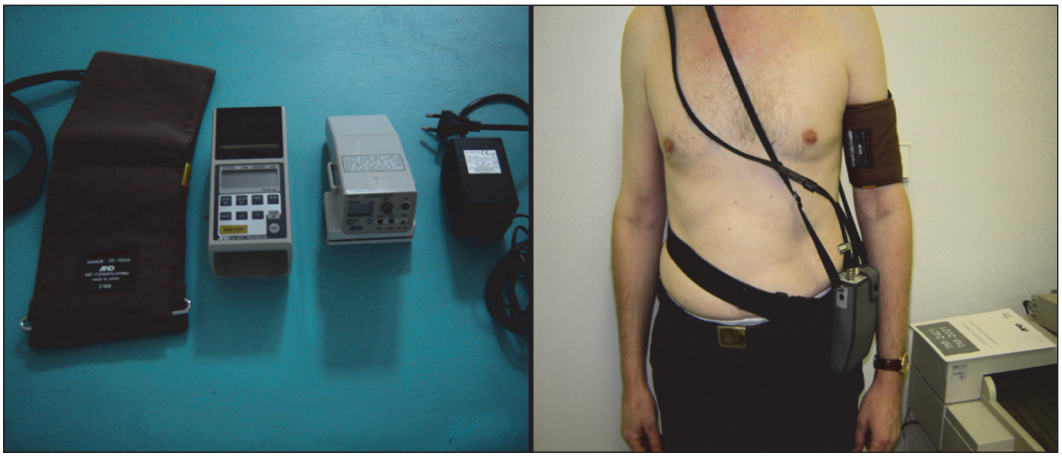

Figure 8: *Blood pressure monitoring device A and D*

Results

Healthy subject –aerobic training

In healthy subjects the seven day blood pressure mean ± SE in systolic blood pressure was 115±1.1 mmHg, in diastolic blood pressure 69±1.4 mmHg in the whole group. Figure 9 shows seven day blood pressure mean in men and women separately in systolic and diastolic blood pressure.

Figure 9: *Seven day blood pressure mean in healthy subjects with aerobic training*

In healthy subjects in the days with exercise (0-24h) blood pressure mean ± SE in systolic blood pressure was 115±2.8 mmHg, in diastolic blood pressure 69±1.7 mmHg in the whole group. Figure 10 shows in the days with exercise blood pressure mean in men and women separately in systolic and diastolic blood pressure.

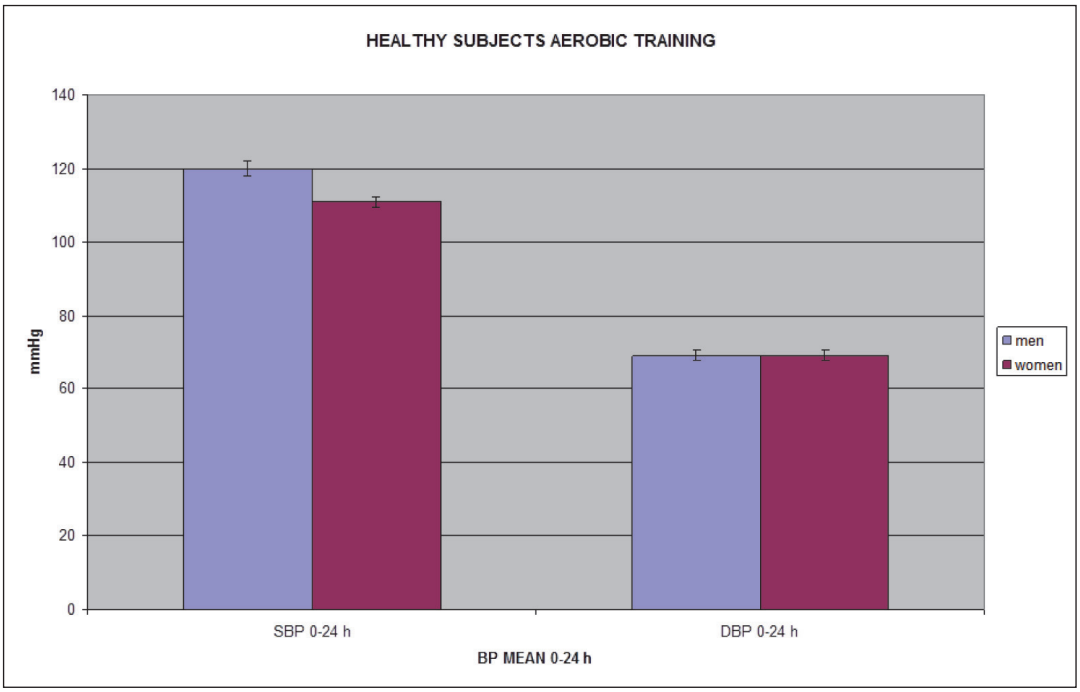

Figure 10: *Blood pressure mean 0-24 h in the days with exercise in healthy subjects with aerobic training*

In healthy subjects in the days without exercise (25-48 h) blood pressure mean ± SE in systolic blood pressure was 116±3.4 mmHg, in diastolic blood pressure 69±2.2 mmHg in the whole group. Figure 11 shows in the days without exercise blood pressure mean in men and women separately in systolic and diastolic blood pressure.

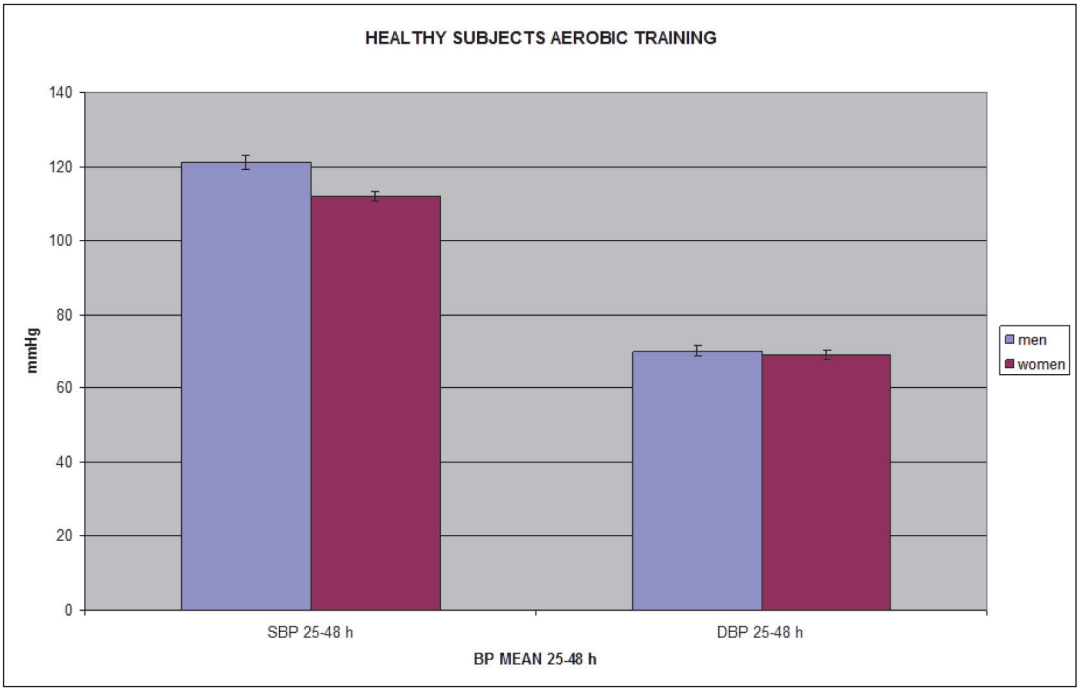

Figure 11: *Blood pressure mean 25-48 h in the days without exercise in healthy subjects with aerobic training*

Healthy subjects with combined training

In healthy subjects the seven day blood pressure mean ± SE in systolic blood pressure was 113±1.8 mmHg, in diastolic blood pressure 68±1.4 mmHg in the whole group. Figure 12 shows seven day blood pressure mean in men and women separately in systolic and diastolic blood pressure.

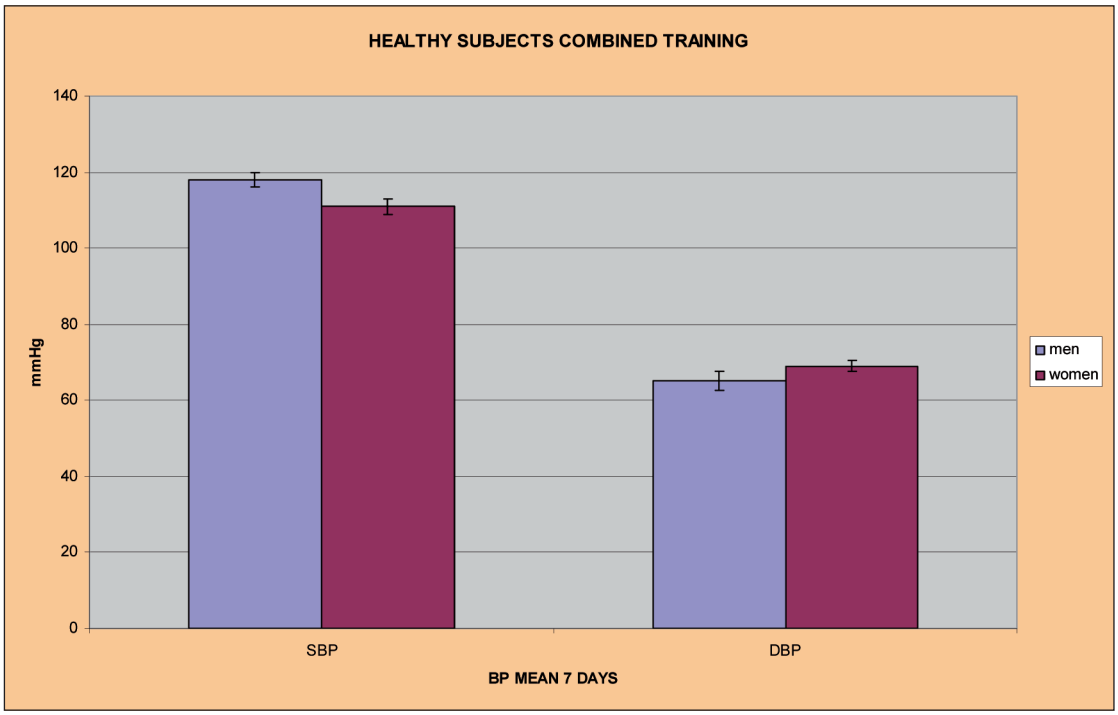

Figure 12: *Seven day blood pressure mean in healthy subjects with combined training*

In healthy subjects in the days with exercise (0-24h) blood pressure mean ± SE in systolic blood pressure was 112±1.9 mmHg, in diastolic blood pressure 69±1.5 mmHg in the whole group. Figure 13 shows in the days with exercise blood pressure mean in men and women separately in systolic and diastolic blood pressure.

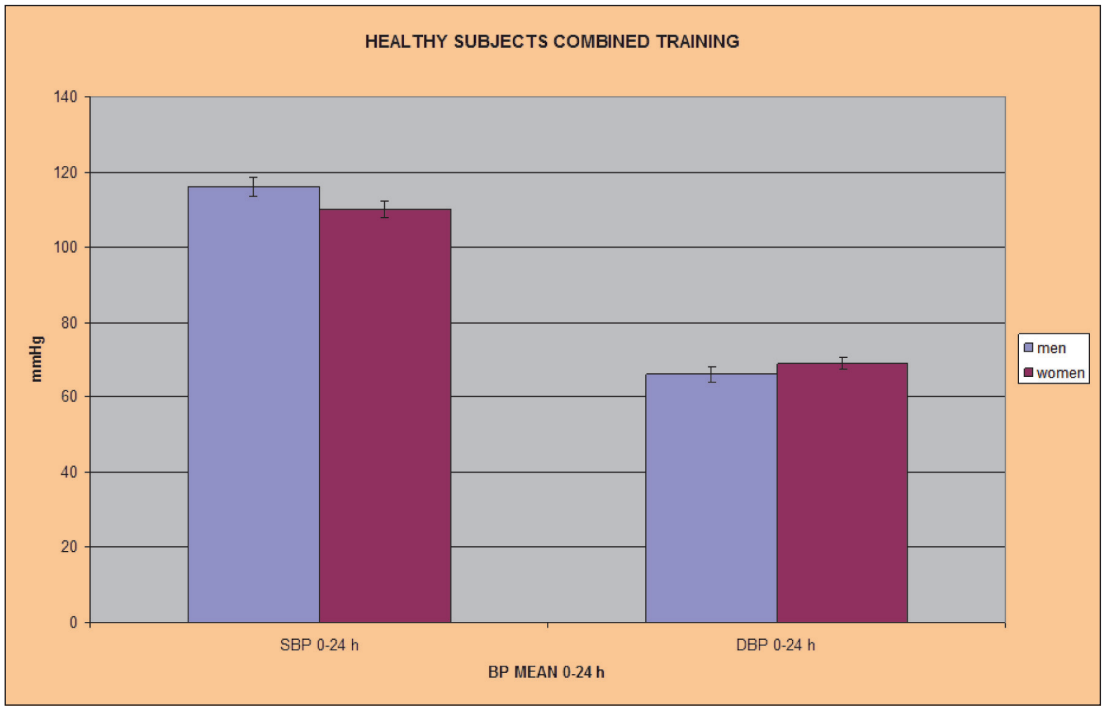

Figure 13: *Blood pressure mean 0-24 h in the days with exercise in healthy subjects with combined training*

In healthy subjects in the days without exercise (25-48 h) blood pressure mean ± SE in systolic blood pressure was 113±1.8 mmHg, in diastolic blood pressure 68±1.4 mmHg in the whole group. Figure 14 shows in the days without exercise blood pressure mean in men and women separately in systolic and diastolic blood pressure.

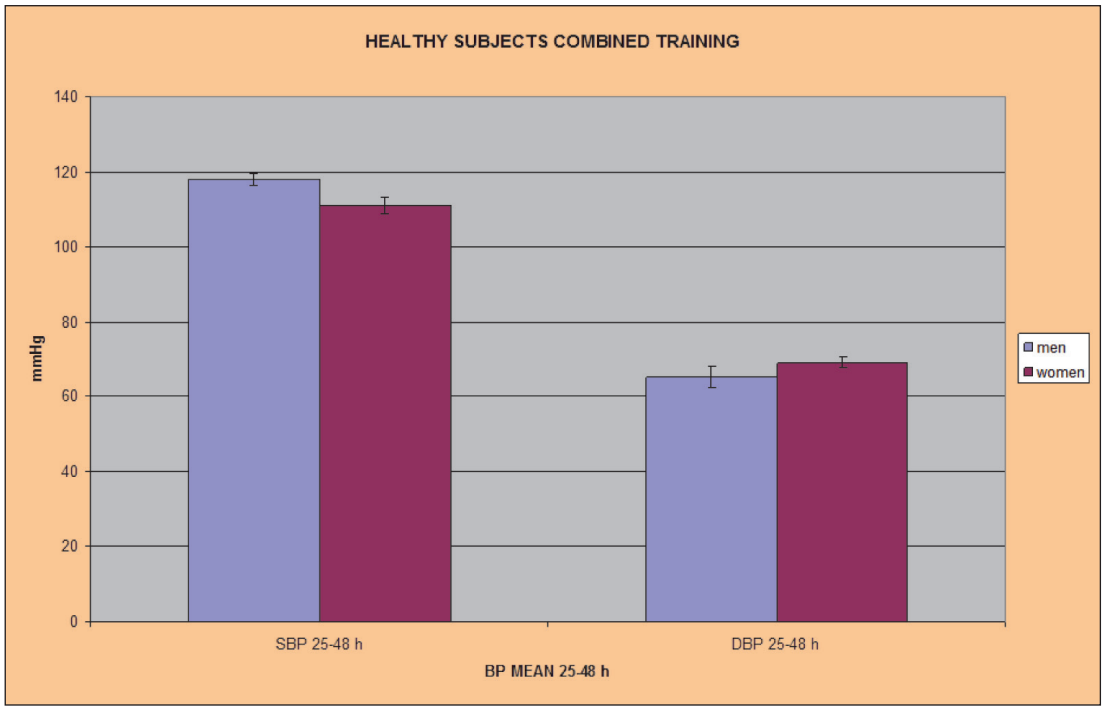

Figure 14: *Blood pressure mean 25-48 h in the days without exercise in healthy subjects with combined training*

Healthy subjects with Nordic walking

In healthy subjects the seven day blood pressure mean ± SE in systolic blood pressure was 113±1.3 mmHg, in diastolic blood pressure 69±1.3 mmHg in the whole group. Figure 15 shows seven day blood pressure mean in men and women separately in systolic and diastolic blood pressure.

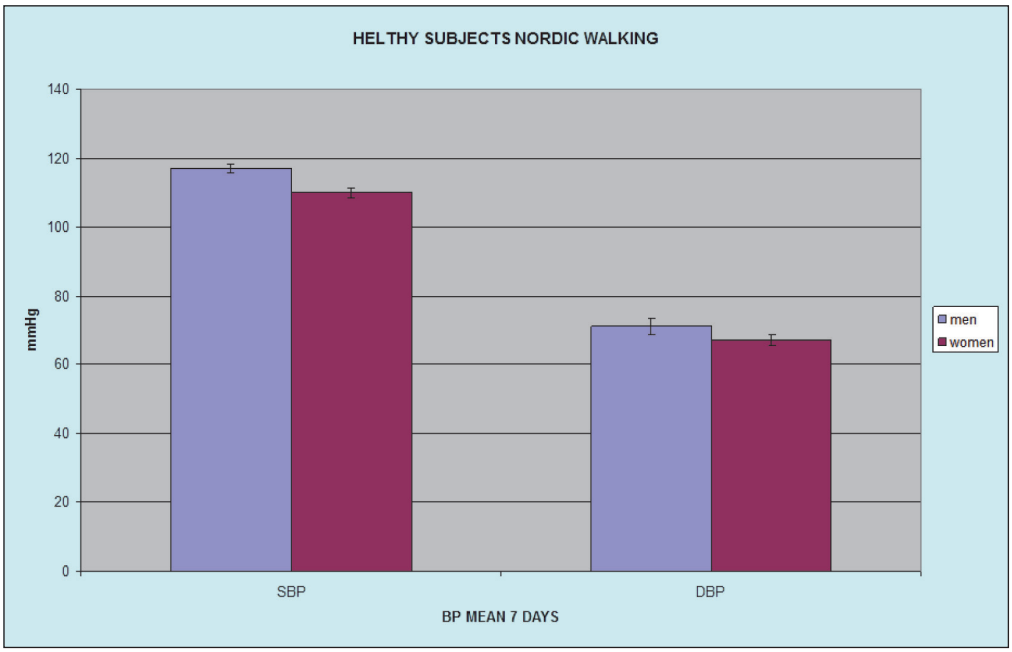

Figure 15: *Seven day blood pressure mean in healthy subjects with Nordic walking*

In healthy subjects in the days with exercise (0-24h) blood pressure mean ± SE in systolic blood pressure was 111±1.5 mmHg, in diastolic blood pressure 67±1.4 mmHg in the whole group. Figure 16 shows in the days with exercise blood pressure mean in men and women separately in systolic and diastolic blood pressure.

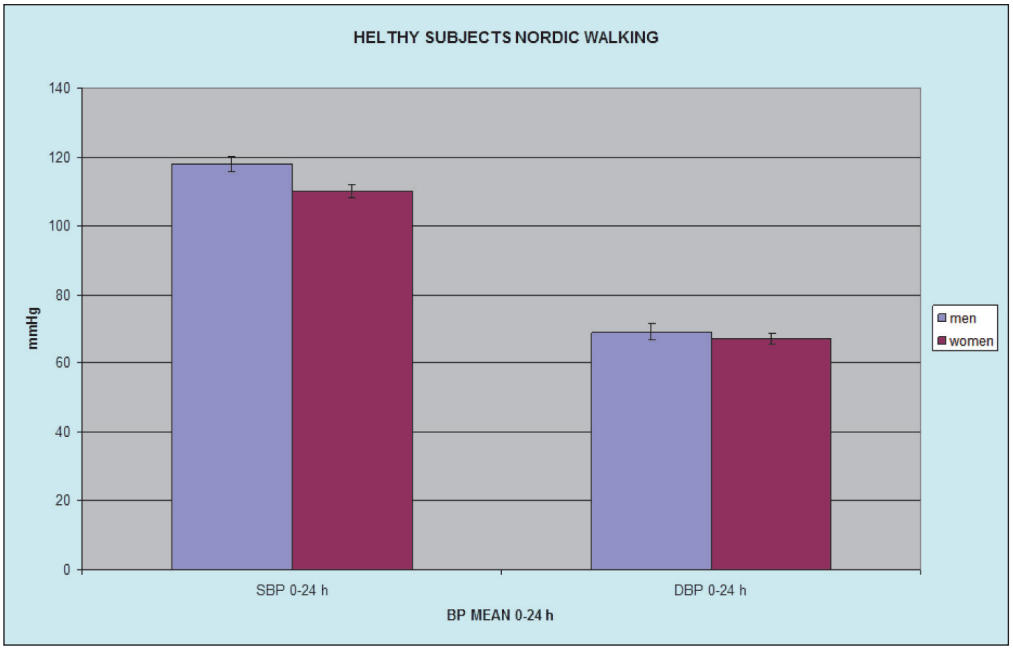

Figure 16: *Blood pressure mean 0-24 h in the days with exercise in healthy subjects with Nordic walking*

In healthy subjects in the days without exercise (25-48 h) blood pressure mean ± SE in systolic blood pressure was 113±1.8 mmHg, in diastolic blood pressure 69±1.4 mmHg in the whole group. Figure 17 shows in the days without exercise blood pressure mean in men and women separately in systolic and diastolic blood pressure.

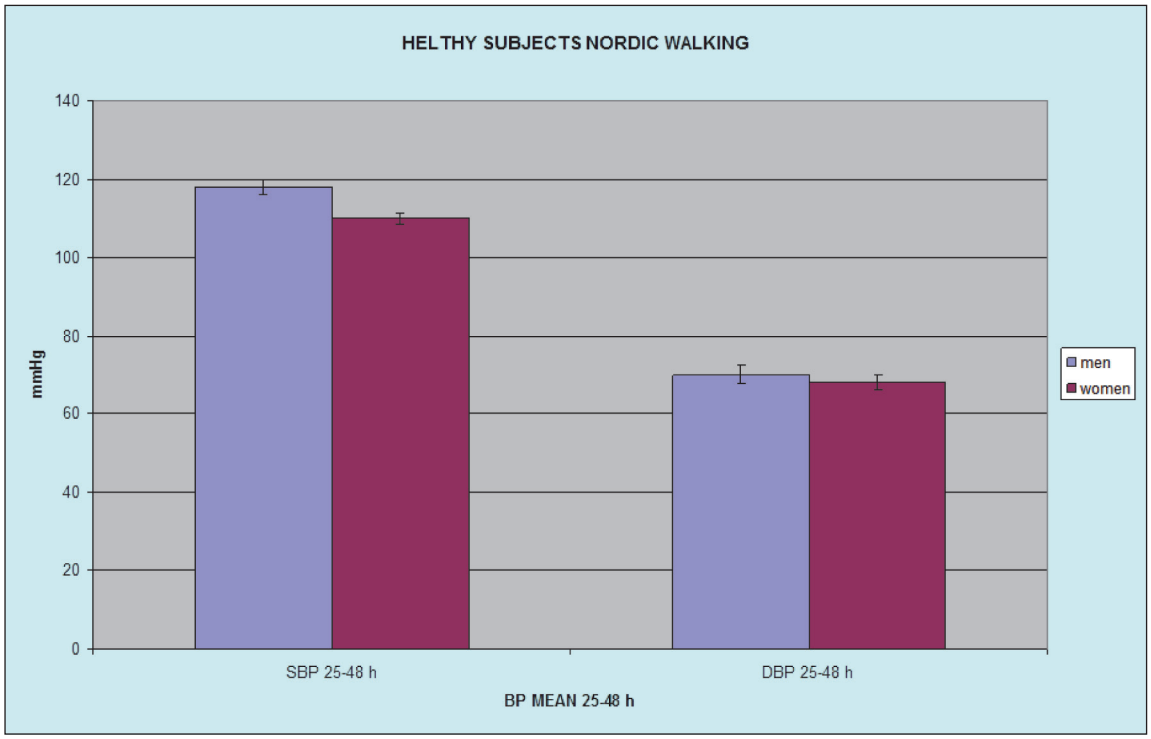

Figure 17: *Blood pressure mean 25-48 h in the days without exercise in healthy subjects with Nordic walking*

Patients with coronary heart disease

In patients with coronary heart disease the seven day blood pressure mean ± SD in systolic blood pressure was 122±12.1 mmHg, in diastolic blood pressure 74±10.4 mmHg in the whole group. Figure 18 shows seven day blood pressure mean in men and women separately in systolic and diastolic blood pressure.

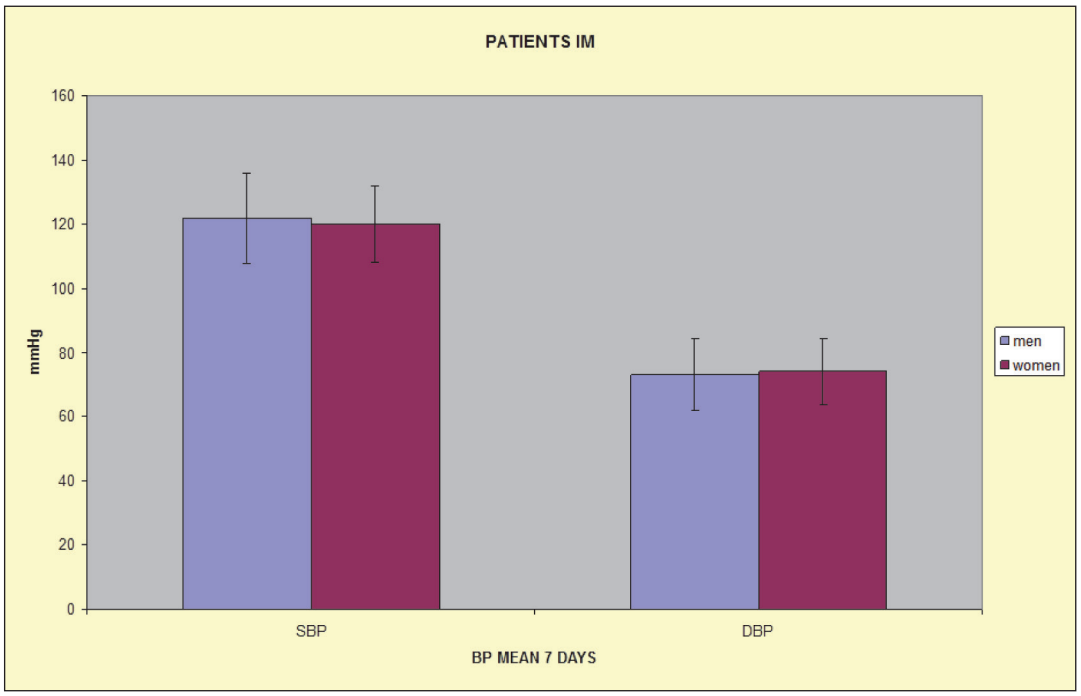

Figure 18: *Seven day blood pressure mean in patients with aerobic training*

In patients with coronary heart disease in the days with exercise (0-24h) blood pressure mean ± SD in systolic blood pressure was 121±10.1 mmHg, in diastolic blood pressure 74±7.8 mmHg in the whole group. Figure 19 shows in the days with exercise blood pressure mean in men and women separately in systolic and diastolic blood pressure.

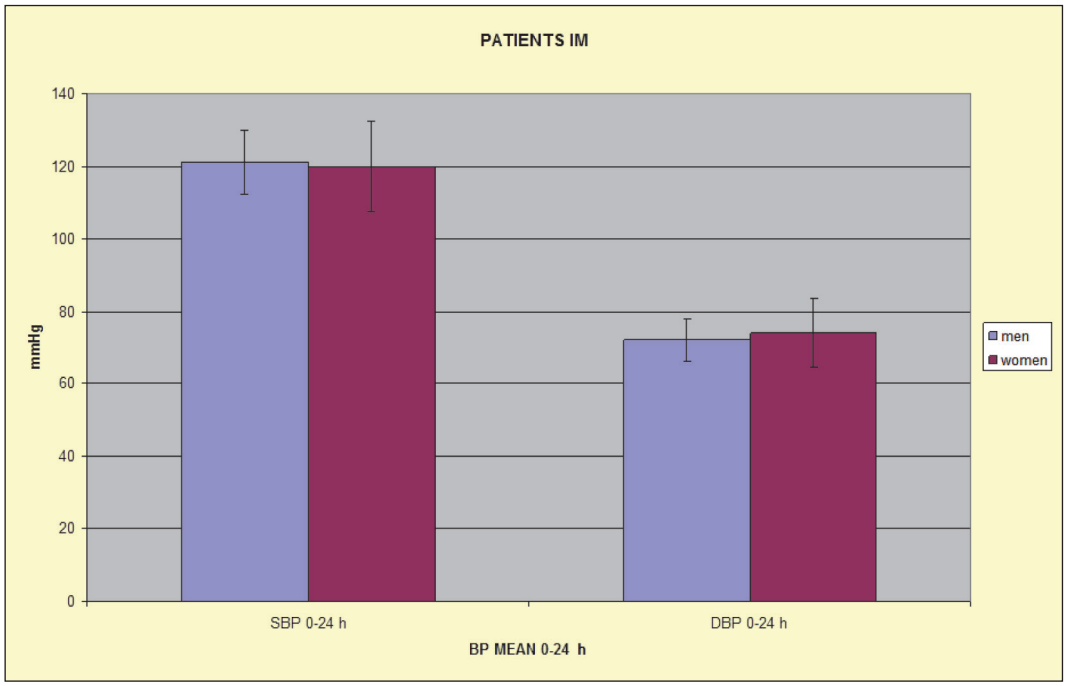

Figure 19: *Blood pressure mean 0-24 h in the days with exercise in patients with combined training*

In patients with coronary heart disease in the days without exercise (25-48 h) blood pressure mean ± SE in systolic blood pressure was 121±9.3 mmHg, in diastolic blood pressure 73±9.1 mmHg in the whole group. Figure 20 shows in the days without exercise blood pressure mean in men and women separately in systolic and diastolic blood pressure.

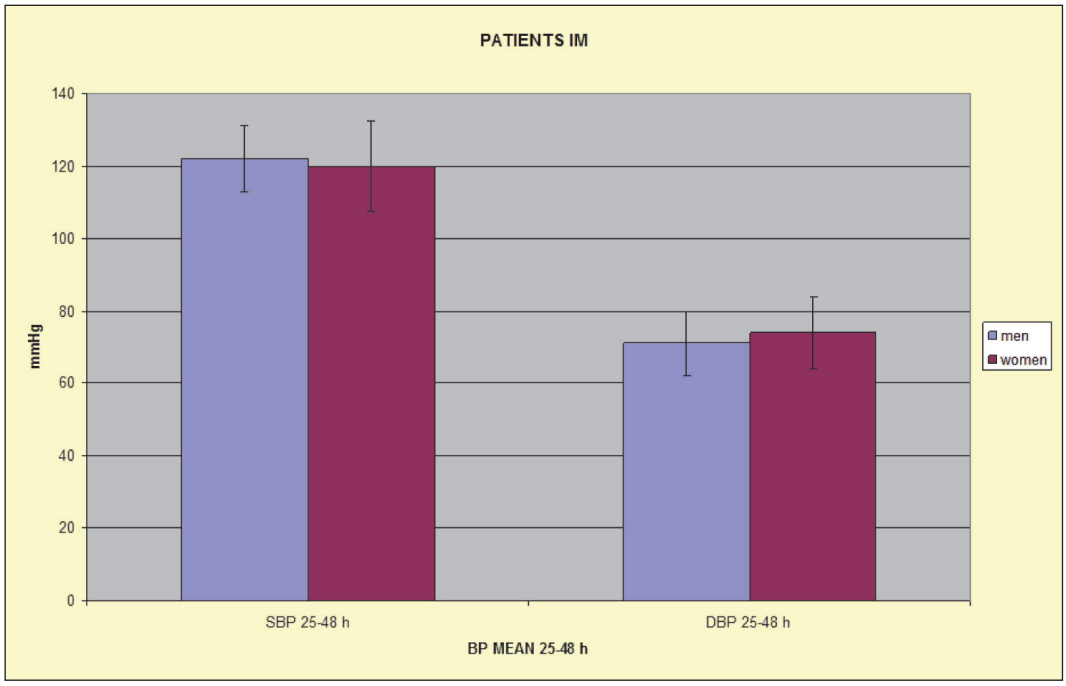

Figure 20: *Blood pressure mean 25-48 h in the days without exercise in patients with combined training*

Discussion

Franz Halberg from University of Minnesota in the in the international project of Biospere and Cosmos (BIOCOS) presented the cardiovascular parameters- blood pressure, heart rate in the rhythmical predictable variation within the physiological range of multi-frequency rhythms, trends and chaos, what he called broad chronomes, described also reference values for cardiovascular parameters for gender and age. He described also with the international study of BIOCOS Vascular Variability Disorders (14-17), which are connected with abnormal pattern of blood pressure and heart rate, identified on the basis of ambulatory blood pressure monitoring (around the clock measurement) and evaluated chronobiologically, are associated with increased cardiovascular disease risk (16). In an internationally endorsed consensus (14,15) showed that these increased blood pressure, described as MESOR hypertension, could be by Circadian Hyperamplitude tension increase (CHAT), by increased Pulse pressure (17), by decreased heart rate variability much more further complicated and risky.

In one of studies, the immediate response of blood pressure and heart rate to graded exercise was also circadian stage-dependent in an earlier study on four marathon runners (20). Exercise by a 46-year old man in the Czech Republic was associ¬ated with an increase in the circadian amplitude of BP that was more pronounced when exercise was done in the evening than in the morning, in his case leading to an abnormal circadian pattern carrying an increased cardiovascular disease risk (6). Depending on whether the circadian pattern of blood pressure tends to have too large an amplitude at the outset or not, exercise should be timed to reduce both long-term and short-term blood pressure without bringing about Vascular Variability Disorders that may be harmful and associated with a higher risk of a hard ischemic event than MESOR-hypertension. Ambulatory blood pressure monitoring and chronobilogical analysis can serve for the optimization of the timing of exercise on an individual basis (14 - 19).

High concentrations of homocysteine are associated with increased cardiovascular disease risk, by causing endothelial dysfunction and platelet aggregation. Exercise in the evening increases homocysteine more than exercise in the morning (20,21). In view of this finding, exercise may be preferred in the morning compared to midday and evening, an observation also confirmed in our study in relation to its effects on RB' BP. There may be different conditions regarding the safety and usefulness of giving priority for morning, evening or daytime exercise in different individuals. Clinical studies indicate that acute ischemic events show a circadian rhythm in their incidence which correlates with increased activity of the sympathetic nervous system and increased platelet aggregation during early morning. Increased concentrations of plasma catecholamine and cortisol following sympathetic nervous system activation can result in increased platelet aggregation (possibly by activating platelet 2-adrenergic receptors), oxidative stress and deficiency of antioxidants and magnesium which are arrhythmogenic (22). An interaction of circadian rhythm and exercise appears to be important in the pathogenesis of atherothrombosis, because abnormalities in endogenous coagulation and fibrinolysis may contribute in the development of an acute cardiovascular event (22,23). Circadian acrophases of fibrinogen and platelet rhythms have been reported in the afternoon and evening but no study was found in a review that related to the influence of exercise during morning and evening on fibrinogen and platelets (23). There is some evidence indicating increased concentration of fibrinogen and decreased platelet counts following an acute single bout of high intensity exercise (24).

Our results have shown that seven day blood pressure monitoring can give us better knowledge about blood pressure values in every individual (9 – 13). To answer the question about the effect of different kind of exercise on 24 h variability was not very easy. Our study showed in seven day blood pressure record the days with and the days without exercise repeatedly and these day were analyzed and they were compared with the seven day blood pressure results. On the basis of our results we have

found that different kind of exercise does not change 24h blood pressure profile in healthy subjects. The combined cardiovascular training in patients with coronary heart disease does not change the systolic and diastolic blood pressure profile (9 – 19).

On the basis of the results we recommend the 7-day/24 h ambulatory blood pressure monitoring or home blood pressure monitoring. The education for long-lasting self-monitoring is the best approach for management of hypertension (16).

Conclusion

Our results showed that in healthy subjects one hour lasting aerobic training, combined training and Nordic waking does not changed mean blood pressure from seven day/ 24h ambulatory blood pressure monitoring.

In patients with coronary heart disease one hour lasting combined training (aerobic and resistant) does not changed mean blood pressure from seven day/ 24h ambulatory blood pressure monitoring.

From the results we can conclude that 24-hours blood pressure profiles at rest and during exercise from day-to-day vary in healthy subjects as well as in patients with coronary heart disease and 24h blood pressure means were not different in the days with the exercise and without exercise.

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INTRA-DIALYTIC EXERCISE TRAINING COULD IMPROVE VASCULAR TONE IN HEMODIALYZED PATIENTS: A PRELIMINARY REPORT

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Abstract

We examined the effects of a 20-week intra-dialytic rehabilitation (ID-RHB) program on the physical performance and arterial stiffness in a group of patients undergoing regular ambulatory hemodialysis (14 men, 3 women; mean age: 45.4 ± 13.4 years; mean duration of dialysis: 5.9 ± 2.3 years). The patients underwent exercise aerobic training on programmable bed-side ergometers (letto2, RECK MOTOmed®, GmbH, Germany) 2-3 times weekly. Seventeen patients completed the 20 weeks of ID-RHB program. Five patients were excluded from the program for loss of motivation, 4 patients for repeated failure to fulfill the prescribed training regimen and 1 patient was transplanted. Twenty weeks of ID-RHB program led to significant increase of VO2peak (from 18.2 ± 5.8 to 19.7 ± 5.1 ml/kg/min; $P < 0.004$); distance walked in 6 minutes (from 455.2 ± 98.2 to 526.7 m ± 139.6; $P < 0.02$); muscle strength (from 271.7 ± 87.6N to 336.7 ± 97.7N; 0.02). Mean CAVI value significantly decreased from the initial 8.02 ± 1.7 to 7.32 ± 1.9 ($P < 0.02$). The training protocol and workload intensity was well tolerated by all the subjects and there were no adverse events, such as episodes of hypotension, related to exercise. We conclude that structured intra-dialytic aerobic exercise training is safe and can improve the endurance parameters and arterial stiffness in HD patients.

Key words

arterial stiffness - chronic kidney disease - functional capacity - exercise training - muscle strength

Introduction

According to the information from Institute of Health Information and Statistics (ÚZIS) there were 100 hemodialysis centers with 1.272 dialysis beds in Czech Republic by December 31, 2012. From the 7.155 treated patients, 92% were on hemodialysis and 8% on peritoneal dialysis. The number of executed treatments increased by 3.7 % compared to the previous year. More than half of these patients were older than 65 years and almost 60% were men. The most frequent comorbidities were diabetes mellitus and hypertension (1). The incidence of chronic kidney disease (CKD) shows tendency to progression also in populations of other European countries. CKD has overall bad prognosis and its diagnostics and therapy are demanding, from medical as well as economical point of view. Chronic

uremia promotes neuro-humoral disturbances, endothelial dysfunctions, vasoconstriction, oxidative and pro-inflammatory processes which potentiate one other (2, 3). These pathological changes in patients with CKD have immense impact on skeletal muscles where devastating structural and metabolic changes and extensive atrophies take place (4, 5). Quality of everyday life drops and depressive mood combined with premature muscle fatigue can be very dangerous incentive to sedentary life style (6). For years, physical activity has been shown to improve cardiovascular and metabolic parameters in healthy individuals and also in patients with a number of chronic diseases, including patients with CKD. In patients on maintenance HD, moderate intensity intra-dialytic exercise training of aerobic or resistance type have demonstrable effects, such as significant increase in functional capacity and muscle strength (7, 8, 9, 10 and 11). Increased arterial stiffness is closely related to cardiovascular mortality in patients with CKD on maintenance hemodialysis (HD). This is a direct consequence of accelerated arteriosclerosis so that accurate monitoring of the extent of vessel wall damage could play an important role (12, 13). However, still limited number of studies reported the beneficial effects of aerobic exercise training on arterial stiffness in patients on HD (14, 15 and 16). These reports were mostly based on the use of pulse wave velocity (PWV or baPWV); however, the accuracy of this conventional non-invasive arterial stiffness assessment can be confounded by the elevated blood pressure in the time of measurement (17). Cardio-ankle vascular index (CAVI) is a new parameter of evaluation of arterial stiffness which reflects stiffness of aorta, femoral and tibial arteries as a whole (17). CAVI, on the other hand, appears to be the parameter of choice because of its independence of blood pressure changes and has been shown to be superior to the traditional PWV method.

Aim

This study aimed to assess the effects of 20 weeks of intra-dialytic exercise training on arterial stiffness and on selected functional parameters in a group of patients on chronic HD.

Patients and methods

From the selected 35 regularly hemodialyzed patients with CKD only 27 started the ID-RHB program (for more details see Figure 1 and the Results). The study was carried out in the Dialysis Center at the IInd Department of Internal Medicine of St. Anne's Faculty Hospital (Brno, Czech Republic, EU) on the Fresenius 4008 S hemodialysis unit (Fresenius Medical Care®, Bad Homburg, Germany) using Fresenius F70S or Fresenius F8HPS capillary dialyzers. Patients included in the study underwent standard hemodialysis procedure 3 times a week. From the 35 selected patients 8 refused to participate and 27 patients accepted to be included in the intra-dialytic rehabilitation (ID-RHB) program (Figure 1).

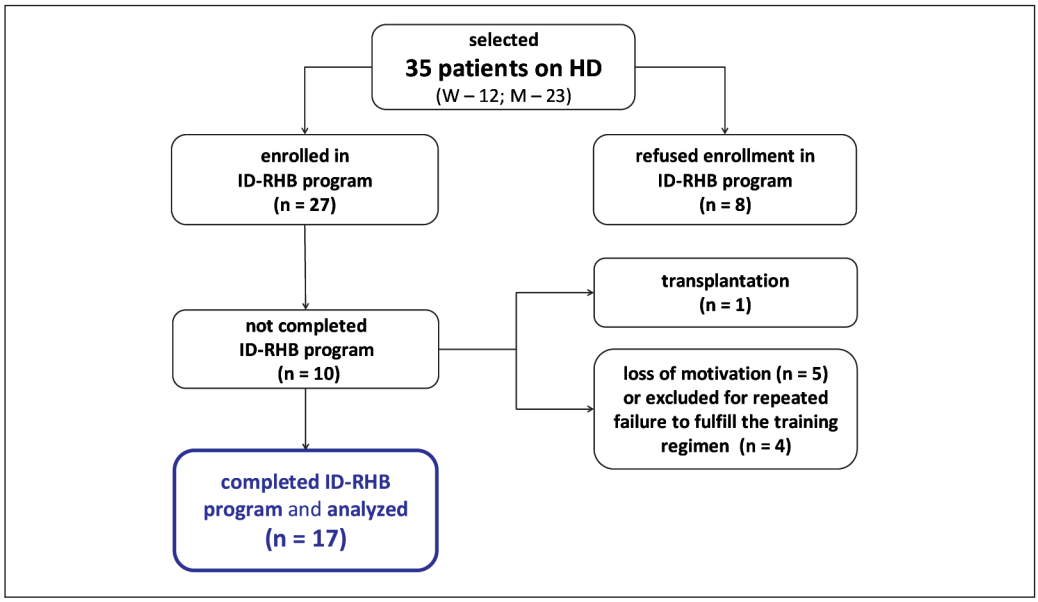


Figure 1: *Flow-chart of the selection and participation of the HD patients in the ID-RHB program.*

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 (st.p.total hip or knee replacement), chronic broncho-pulmonary disease, and urea clearance (spKt/v) >1.2. Inclusion criteria: at least 12 months of regular hemodialysis, symptomatic stability, and optimized pharmacological treatment unchanged 1 month before the start of the study.

Performance testing Before the start of intra-dialytic RHB program, all patients underwent standard spiroergometric test on bicycle for the evaluation of exercise performance and aerometabolic capacity (peak O2 uptake), 6-min corridor walk-test (6-CWT) to evaluate the distance walked and isometric dynamometry for measurement of maximal strength (Fmax) of leg extensors. To assess peak aerobic capacity (VO2peak) and to determine the training intensity, each patient completed a maximal incremental cardiopulmonary exercise test (CPX) with 12 lead electrocardiography (AT-104 PC, Schiller®, Baar, Switzerland) and blood pressure monitoring using standard methodology. CPX was performed by all patients according to a standardized protocol by Wasserman et al. (18). Spiroergometric test was done using calibrated electrically braked bicycle ergometer (Ergoselect, Ergoline®, Bitz, Germany), with work rate increments of 10 watts, so as to provide test durations of 8–12min. Minute ventilation and gas exchange were measured breath-by-breath with an automated metabolic measurement system (Power Cube, Ganshorn® Medizin Electronic, Niederlauer, Germany). Peak oxygen uptake (VO2peak) was expressed as the highest value of O2 during last 30s of the test. Maximal muscle strength of leg extensors was assessed by isometric dynamometry using the device PC-2 SDT (EXAMO®, Recens Brno, CZ) with microprocessor. Measurements were carried out in a sitting position; the chest of the examinee was fixed by 2 straps, pelvis and knees flexed at 90°. The ankle of tested limb was attached to strength converter (D.OS SBEAM-1000N, EXAMO®, Recens Brno, CZ). Subsequently, the tested subject performed 3 maximal voluntary extensions (contraction 3s - relaxation 7s); the highest value of the three attempts was recorded as the maximal strength (Fmax; N). 6-CWT is a standard diagnostic tool for assessing the physical performance at sub-maximal intensities. At baseline and after 20 weeks the patients completed the 6-min walk on 30-meter lane labeled by two plastic cones marking the turnaround points. During the test heart rate (HR) was continuously monitored using the SF-Tester Polar S725-X (Polar Electro® Oy, Finland). Subjective

fatigue and dyspnea according to Borg scale was registered at 1-min intervals. The test was carried out while respecting the principles and recommendations of the ACSM under the supervision of physician and physiotherapist (19).

Training protocol After baseline testing, patients underwent 20-weeks of intra-dialytic aerobic exercise training program consisting of cycling 3 days/week on programmable bicycle ergometers (adapted on the subject's dialysis chair or bed (Figure 2).

Figure 2: *Examples of the aerobic exercise training program on programmable bicycle ergometers letto2 (RECK MOTOmed®, GmbH, Germany) in the 2 IInd Dept. of Internal Medicine, St. Anne´s Faculty Hospital Brno).*

Training was done always between the 2nd and the 3rd hour of HD. The standard training session was designed as follows: a) initial stretching of leg muscles before connecting to dialyzer (5min), b) relaxing exercises of leg muscles (5min), c) passive cycling on bed-side ergometer (1min forward + 1min backward), d) active aerobic training on ergometer (30min), e) passive cycling on ergometer (1 min forward + 1 min backward), f) relaxing exercise of leg muscles (5min), and g) terminal stretching of leg muscles after disconnection from dialyzer (5min). Average time of 1 training session was 54 minutes. All training sessions were supervised by a professional staff (physiotherapists and nurses). During first 10 weeks the active cycling was set for 30 min at an intensity representing 50% of the peak workload rate determined by the incremental exercise test; from 11th to 20th week of ID-RHB the training intensity was increased to 75% of the initial peak workload. Such design of the training protocol enabled all the subjects to well adapt and tolerate the prescribed intensity and duration of exercise.

CAVI assessment CAVI was measured by the vascular screening system VaSera® 1500 (Fukuda Denshi Co, Tokyo, Japan) using standard protocol (17). Examination was performed in supine position; 4 pressure cuffs were placed on limbs, 1 microphone (phonocardiogram) above upper margin of sternum and 2 ECG leads on both upper limbs. CAVI was automatically calculated according to following formula:

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

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

In order to minimize adverse effects of cuff inflation on blood flow dynamics, the pulse waves were recorded only when the cuffs were inflated to the pressure lower than the diastolic one (50mmHg). Blood pressure (BP) on limbs was measured by oscillometric method; values of systolic BP (SBP),

diastolic BP (DBP) and pulse pressure (PP) were obtained from record of BP on right a. brachialis. Patients with ankle-brachial index (ABI) lower than 0.9 were excluded from the assessment.

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.

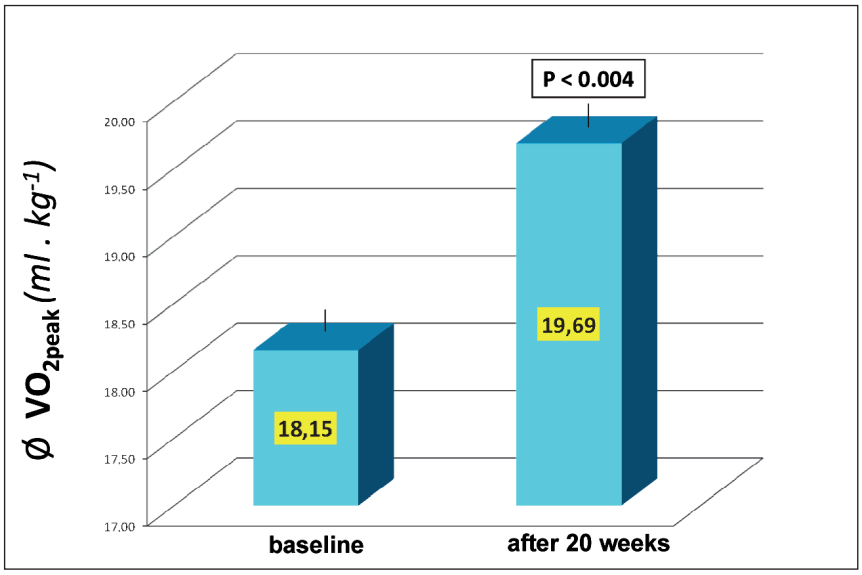
Ethics

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, Brazil 2013) and to the GCP guidelines of the European community.

Results

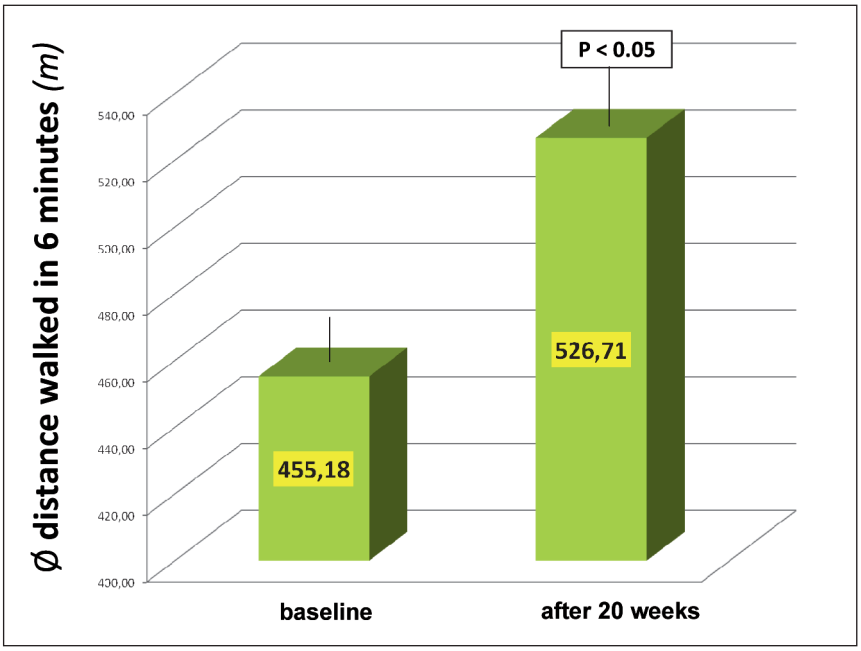
From the included 27 patients only 17 completed the 20 weeks of ID-RHB program (14 men, 3 women; mean age 45.4 ± 13.4 years; mean body weight 71.8 ± 17.6; mean height 172.3 ± 9.2; mean BMI 24.1 ± 5.0; mean duration of HD 5.9 ± 2.3 years). Summary of comorbidities in 17 analyzed patients: anemia (n=13), hypertension (n=11), hyperparathyroidism (n=8), dyslipidemia (n=4), hyperuricemia (n=3), diabetes mellitus (n=2); nephritic syndrome (n=1); coronary artery disease (n=1) and ischemic stroke (n=1). Five patients were excluded for loss of motivation, 4 patients for repeated failure to fulfill the prescribed training regimen and 1 patient was transplanted. Mean adherence of the 17 analyzed patients to the ID-RHB program was approximately 73%. The workload intensity was well tolerated, all the patients were able to engage safely the prescribed intradialytic aerobic training program, and there were no musculoskeletal, vascular access or hemodynamic complications (such as hypotension episodes) as a consequence of the exercise intervention.

Peak oxygen uptake assessment. Statistical evaluation of VO2peak showed a statistically significant increase after 20 weeks (from 18.2 ± 5.8 at baseline to 19.7 ± 5.1 ml/kg/min at the end of ID-RHB program; $P < 0.004$). Changes of mean VO2peak values before and after ID-RHB are shown in Graph 1.



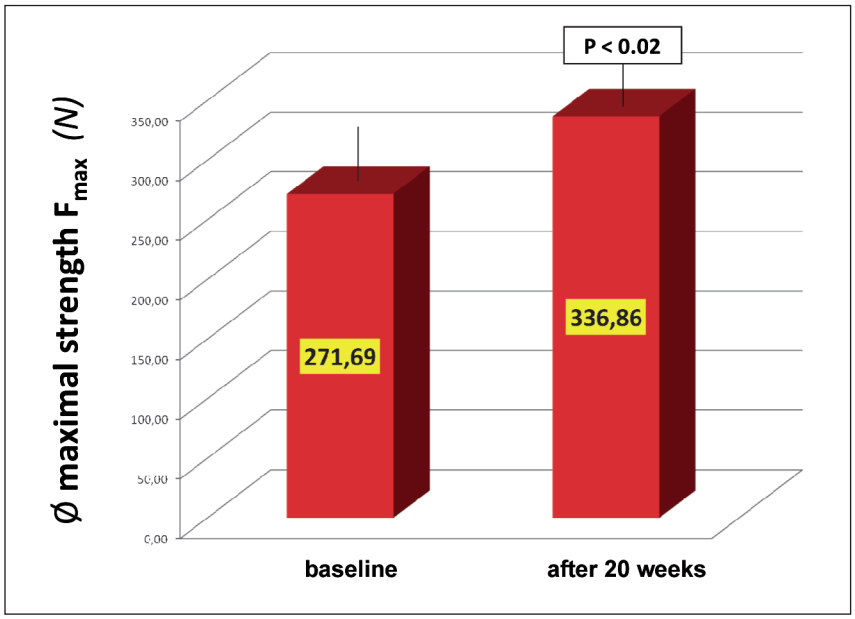
Graph 1: *Results of the peak oxygen uptake assessed by spiroergometric bicycle testing.*

6-CWT evaluation. Twenty weeks of supervised ID-RHB aerobic exercise program led to significant increase of the distance walked in 6 minutes, assessed by 6-CWT (from 455.2 ± 98.2 to 526.7 m ± 139.6; $P < 0.05$). The changes of mean distance walked in 6min before and after ID-RHB are shown in Graph 2.



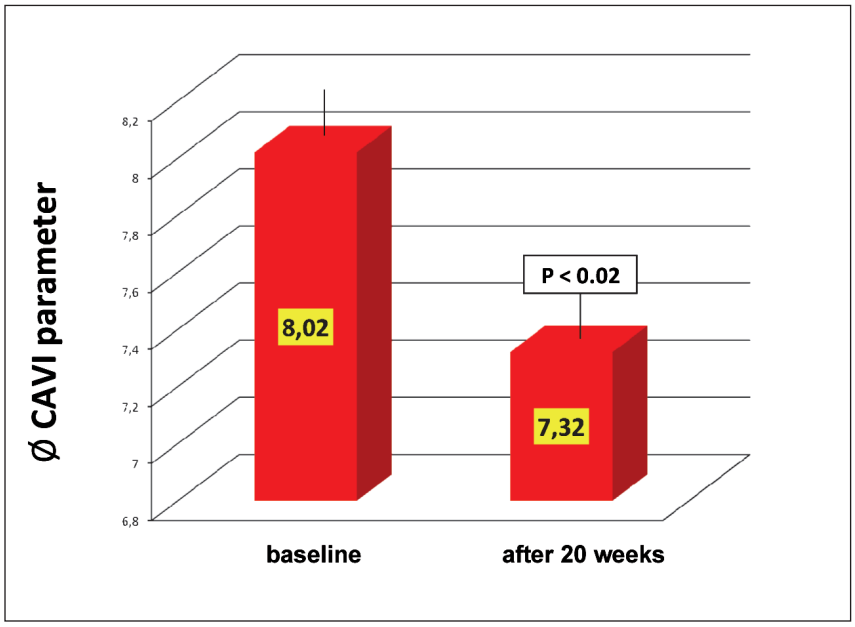
Graph 2: *Results of 6min CWT (distance walked).*

Muscle strength evaluation. The measurements of maximal muscle strength (Fmax) assessed by isometric dynamometry showed a significant increase after 20 weeks of ID-RHB (initial value 271.7 ± 87.6N vs. 336.7 ± 97.7N in the 20th week; $P < 0.02$). The changes of mean Fmax values before and after ID-RHB are shown in Graph 3.



Graph 3: *Results of maximal strength of leg extensors assessed by isometric dynamometry.*

CAVI assessment. The mean CAVI value significantly decreased after 20 weeks of ID-RHB from the initial 8.02 ± 1.7 to 7.32 ± 1.9; P < 0.02). Based on the evaluation of initial CAVI the patients were then divided into three groups according to the actual valid evaluation criteria: a) group with CAVI <8.0 (normal range; n = 7; mean CAVI = 6.63 ± 1.2); b) group with CAVI 8.0 - 9.0 (borderline; n = 4; mean CAVI = 8.2 ± 0.2), and c) group with CAVI ≥ 9.0 (arteriosclerosis suspected, n = 6; mean CAVI = 9.91 ± 0.6). After 20 weeks of ID-RHB the number of patients in the group with CAVI <8.0 (normal range) has increased to 11 (CAVI = 6.13 ± 0.9). This change was a direct result of a reduction of CAVI in all the patients of the group 8.0 - 9.0 (borderline). There were no significant changes in the group with CAVI ≥9.0 (arteriosclerosis suspected) and CAVI has remained at approximately the same average value recorded at baseline (9.91 ± 0.6 vs. 9.94 ± 0.3; NS). The changes of mean CAVI values before and after ID-RHB are shown in Graph 4.



Graph 4: *Results of vascular stiffness assessment using parameter CAVI.*

Discussion

The main problem of modern nephrology is the worldwide rapid increase in the number of patients with advanced renal disease requiring hemodialysis or peritoneal dialysis. Typical symptoms of patients on HD include extensive atrophy of skeletal muscles, decreased physical fitness and poor quality of life (20, 21). The results of a series of studies published in the past 3 decades have clearly demonstrated the positive effects of physical training on endurance, psychological well-being and quality of life (22, 23). Training on bed-side ergometers in a supine position during dialysis improves not only the cardio-pulmonary functions, but also muscle strength, fatigue, and physical ability. These results underline the importance of endurance training during a dialysis treatment (24, 25). Results of the present study showed an improvement in muscle strength of leg extensors and increase of maximal and submaximal functional capacities after completing the ID-RHB program lasting 20 weeks. These findings are in full concordance with those seen in previously published studies that used similar methodologies and training equipment such as bed-side ergometers. It is widely recognized that decreased elasticity results from structural changes which precede formation of atherosclerotic plaque or thrombus in arteries. Increased arterial stiffness is an independent predictor of death from cardiovascular disease, and cardiovascular diseases are the leading cause of death among patients with CKD. It has been showed that incidence of arterial stiffness is higher also in hemodialysis patients (26, 27). Tanaka et al. (2000) have demonstrated that regular physical activity appears to slow the loss of elasticity and compliance in the human cardiovascular system (28). Miyaki et al. (2009) reported an increase in central arterial distensibility after weight reduction by aerobic exercise training among over-weighted and obese men (29). Physical activity enhances general cardiovascular fitness and it may also delay or prevent age-related increase in arterial stiffness (30, 31). As mentioned above, only limited number of trials in patients with CKD on maintenance hemodialysis showed that long-term exercise training improves not only physical impairment and health-related quality of life but also the arterial stiffness (14, 15 and 16). CAVI, a novel parameter of evaluation of vascular wall stiffness, accurately reflects the extent of arterial fibrosis in HD patients and therefore should be considered as a useful indicator in clinical practice (32, 33). The main and in actual scientific literature still unexplored topic of this study was the evaluation of the effects of intra-dialytic aerobic exercise training on arterial stiffness in HD patients with CKD using the parameter CAVI. CAVI reflects the condition not only of elastic, but also of muscular arteries (34), and it means that CAVI value is strongly influenced by smooth muscle cells activity in arterial wall, where a large variety of vasoconstrictive (angiotensin II, thromboxane A2, endothelin, etc.) as well as vasorelaxative factors ($NO^{\bullet}$, prostacyclin, natriuretic peptide, etc.) acts. According to some recently published studies CAVI may reflect occurrence of global inflammatory reaction of vessels in whole organism. Wakabayashi et al. reported that CAVI increases with plasmatic level of C-reactive protein, amyloid A, sialic acid, fibrinogen and number of leukocytes in diabetes mellitus type 2 (35). However, the mechanisms which cause increase of CAVI under these conditions are not fully elucidated yet. Chronic uremic acidosis present in chronic renal failure is accompanied by massive production of inflammatory and vasoactive substances which can trigger smooth muscle cells reactions and initiate pathologic remodelation of vessel wall (27). Therefore it is very likely that these bio-signals may also increase CAVI in patients with CKD. One study on patients under chronic hemodialysis established a CAVI score of 7.55 as the cut-off value for suspecting the presence of cardiovascular diseases highlighting the use of CAVI as a screening parameter that would help in guiding subsequent treatment (28). The increased number of patients in the group with CAVI <8.0 (normal range) could be interpreted as a clear signal of positive effect of ID-RHB on the reduction of cardiovascular risk (the final mean CAVI in this group was 6.13 ± 0.9, far below the cut-off value of 7.55 in hemodialyzed patients as stated above). However, there were no significant changes in the group with CAVI ≥9.0 (arteriosclerosis suspected) and it seems that CAVI was not influenced by the

exercise training. In other words, in the patients with higher CAVI the increased cardiovascular risk persists. It is therefore possible to speculate about the suitability of prescribed training from the point of view of intensity and composition. The subsequent detailed analysis of both CAVI groups (low and high risk), however, showed that patients with CAVI <8 were significantly younger (mean age 39.7 ± 12 years) compared with the group with CAVI ≥9 (mean age 55.8 ± 8 years). Furthermore, younger patients with low-risk had significantly lower average number of comorbidities (2.8 comorbidities per person) compared to patients with high risk (4.2 comorbidities per person). These differences undoubtedly influenced the final results. On the other hand, however, ID-RHB program in high-risk patients (CAVI ≥9) led to significant improvement of the aerometabolic capacity and functional performance at submaximal intensities. It is therefore evident that in the future trials it will be necessary to pay more attention to the careful evaluation of the impact of physical activity on arterial stiffness in patients on HD. One possible approach might be the analysis of plasmatic levels of different vasoactive mediators (e.g., catecholamines, renin, angiotensin, endothelin, etc.) in relation to the value of CAVI, etc. However, this was not included in the design of the present study. From general point of view it is possible to conclude that the decrease of CAVI observed in this study could reflect the positive impact of regular intra-dialytic aerobic exercise and may indicate a resulting beneficial effect on overall vascular stability and endothelial functions, as well as a decrease of vasoconstrictive activity. This opinion is based on findings from some above cited clinical studies wherein this effect was distinctly demonstrated by changes of PWV. We assume that CAVI may be applicable complementary tool for monitoring of CKD development and for monitoring of beneficial changes in vascular system elicited not only by standard treatment (hemodialysis + pharmacotherapy) but also by regular exercise training as was shown in the present study.

Conclusion

This study proved beneficial effect of intra-dialytic supervised aerobic training on functional performance, muscle strength and vascular stiffness in patients on HD. We confirm that patients on maintenance HD should engage intra-dialytic aerobic exercise training for at least 30 minutes per HD session to prevent deterioration of their physical performance. Moreover, participation in the intra-dialytic exercise program could be effective for maintenance of quality of life. However, it is necessary to point out that our study provides only preliminary results because it did not deal with the changes of the concentration of important plasmatic substances, such as urea, creatinine, etc. Other limitations to be mentioned were also a limited number of analyzed patients and the absence of control (non-exercising) group. While the positive influence of ID-RHB training on vascular stiffness is certainly interesting, it is necessary to highlight one crucial point: the parameter CAVI has been introduced into clinical practice only recently, and experience with its use with regard to the influence of physical training on the human organism in healthy and unhealthy people is to date minimal. For this reason, it is necessary to consider the presented findings with caution and to further study this potentially important diagnostic methodology.

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Disclosure

The authors declare no conflicts of interest.

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THE USE OF NEUROMUSCULAR ELECTRICAL STIMULATION IN EARLY PHASE OF REHABILITATION IN PATIENTS AFTER TOTAL KNEE ARTHROPLASTY TO ENHANCE QUADRICEPS FEMORIS MUSCLE STRENGTH

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Summary

This study deals with early rehabilitation in patients after total knee arthroplasty combined with neuromuscular electrical stimulation (NMES). The aim of this study was to evaluate the effect of NMES to increase muscle strength of quadriceps femoris muscle (QFM).

Key words

rehabilitation, neuromuscular electrical stimulation (NMES), total knee arthroplasty (TKA), quadriceps femoris muscle (QFM) strength

Background

Osteoarthritis is a chronic degenerative joint disease that negatively influences the quality of life of many hundred thousands of elderly Czech people. More than 10.000 total knee arthroplasties (TKAs) are performed each year in Czech Republic. Although TKA reliably reduces pain and improves functional performance in older adults with knee OA, the recovery of QFM strength and function is not optimal and predisposes patients to disability with increasing age. One month after TKA, QFM strength declines up to 60% of preoperative levels, despite the initiation of rehabilitation early after surgery. Even many years after surgery, QFM weakness persists in people with TKA compared with healthy individuals. It has profound functional consequences – QFM weakness is associated with decreased speed of gait, deteriorated balance and stair-climbing ability, and ability to rise from a seated position, as well as with an increased risk for falls.

Effective physiotherapy strategies after TKA should focus to address QFM weakness. Impairments in QFM strength are mainly due to deficits in voluntary activation and partially due to muscle atrophy as well. Also spinal reflex activity from swelling or pain in the knee joint may modify afferent input from the operated joint and result in decreased efferent motor drive to QFM that reduces muscle strength (1 – 3).

Neuromuscular electrical stimulation (NMES) offers an innovative approach to potentially reduce QFM voluntary activation deficits and prevent muscle atrophy early after surgery. Using NMES restores

normal QFM function more effectively than voluntary exercise alone. Severe voluntary activation deficits may limit improvements in muscle strength in response to rehabilitation that utilizes voluntary exercise. It is probably because of the inability to generate muscle contractions of sufficient intensity to promote strength gains (4 – 7). NMES has the potential to override voluntary activation deficits. Early intervention with intensive NMES may offer greater benefits than the initiation of NMES 1 month and later after TKA because it may be easier to prevent the decline of muscle function after surgery than to reverse losses after they occur. It was found also in our earlier studies that NMES improves muscle function in cardiac patients (8 – 12).

Objective

The aim of the study was to evaluate the influence of NMES of QFM by the assessment of isometric strength of QFM in patients following TKA in early phase of rehabilitation The measurement was done at the beginning and at the end of one-week rehabilitation program.

Methods

Twenty-eight patients of mean age 65.7 years after a primary unilateral TKA (tricompartmental, cemented TKA with a medial parapatellar surgical approach), were randomly assigned to receive either standard (non-NMES group) rehabilitation or rehabilitation supplemented with NMES (NMES group; Figure 1). All the patients underwent surgery at The Orthopedic Clinic, and then the rehabilitation program at The Inpatient Rehabilitation Department at St. Anne´s University Hospital.

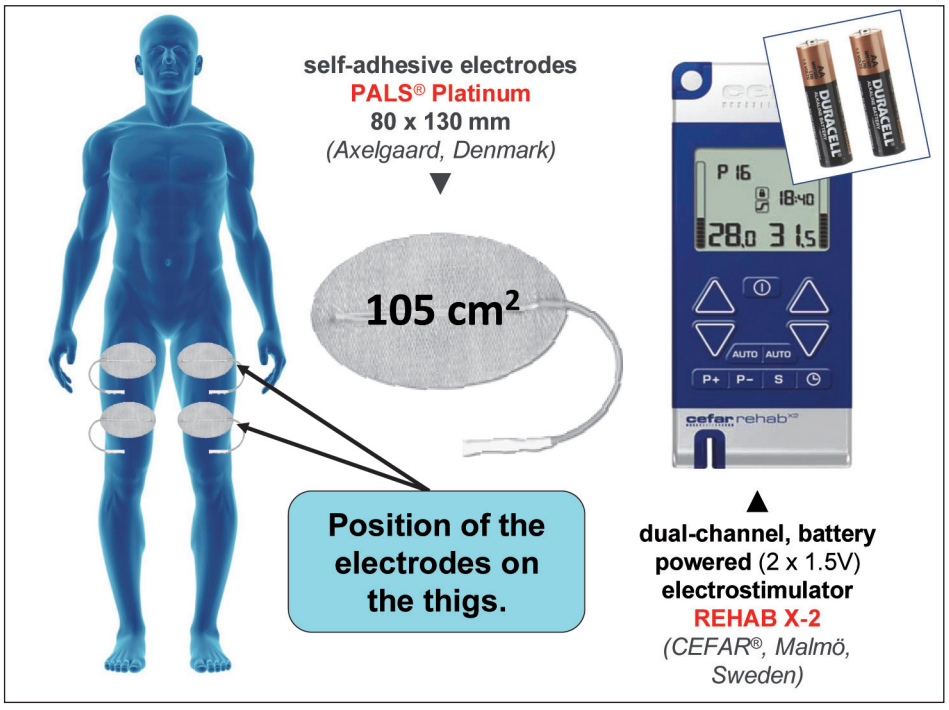


Figure 1: *Standard equipment for the application of NMES and positioning of the stimulating electrodes on the thighs.*

The stimulated muscles were the quadriceps of both legs. Self-adhesive surface electrodes 80x130mm (PALS® Platinum, Axelgaard Manufacturing Co., Lystrup, Denmark) were placed on the thighs approx. 5cm below inguinal fold and 3cm above the upper patella border. Stimulation was applied in supine position using portable, dual-channel battery-powered stimulators REHAB X-2 (CEFAR-COMPEX®, Switzerland). NMES characteristics were set up as follows: frequency 10Hz, "on-off" mode stimulus (20s stimulation, 20s rest), pulse width 200msec, rise and fall time 1s, and maximal stimulation amplitude 60mA. The intensity of NMES was always individually adjusted so that it did not cause any unpleasant feelings or pain.

The rehabilitation program (Table 1.) lasted one week, patients were divided into two groups: non-NMES group underwent a standard rehabilitation protocol with two physiotherapy sessions a day; the physiotherapy of NMES group was supplemented with NMES of QFM that was applied once a day (1 session of NMES = 60 min).

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, Brazil 2013) and to the GCP guidelines of the European community.

Table 1: *Rehabilitation program following TKA – subacute phase*

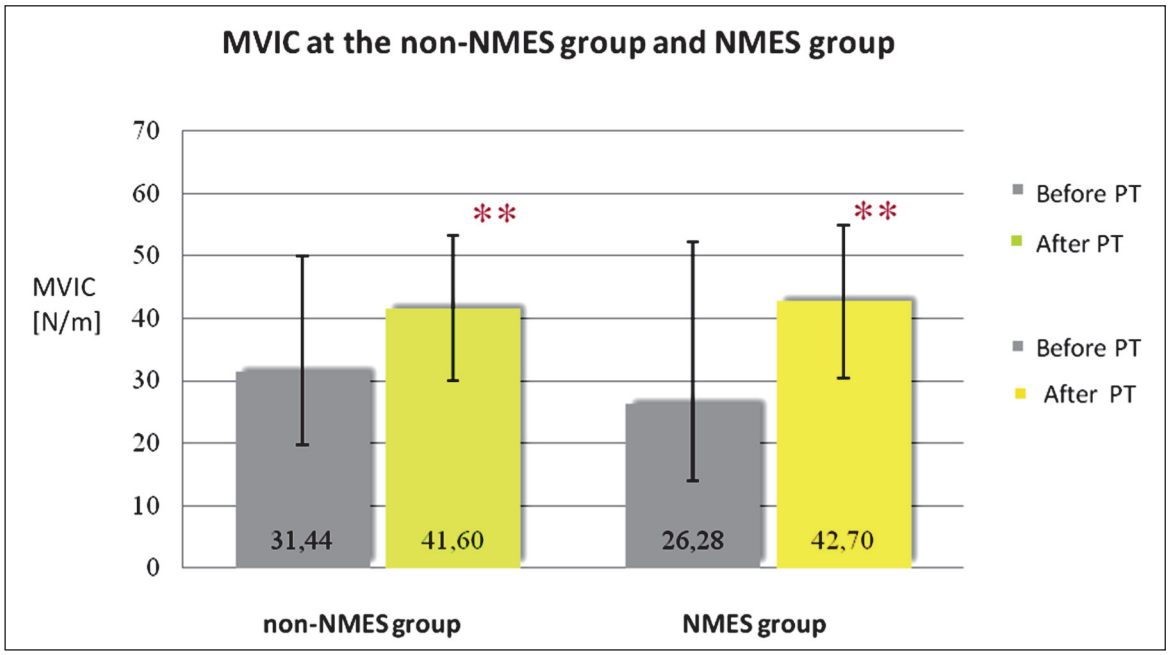
Range of motion (ROM)
• **Active-assistive ROM for knee flexion** • **Passive knee extension stretch**
Strength
• **Quad sets, straight leg raises, hip abduction, hamstring curls, isometric strengthening**
Functional activities
• **Gait training, stairs climbing**
Modalities
• **Local cooling by ice, positioning (flex-extend), NMES of QFM**
Manual techniques
• **Soft tissue techniques for scarf, patellar mobilization**

Data for QFM strength was obtained using isometric dynamometer PS-2SDT. The initial testing was done before the rehabilitation program started (12 ± 4 days after surgery); the final testing was performed at the end of rehabilitation (19 ± 1 day after surgery). We analyzed the parameter of maximal voluntary isometric contraction (MVIC).

Participants were positioned in an isometric dynamometer, stabilized with 90 degrees of flexion, isometric contraction lasted 3seconds and was repeated up to 3 times, with 4seconds of rest between attempts. The attempt with the largest MVIC output then was used for data analysis.

Results

Taking part at the rehabilitation program after TKA led to a beneficial outcome. Significant improvement of QFM strength (average 46%) was obtained in both groups. In NMES group the values of MVIC of QFM increased from initial 31.4 N/m to final 41.6 N/m (+62%; $P < 0.01$). In the non-NMES group the improvement was from 26.3 N/m to 42,7 N/m (+32%; $P < 0.01$; Graph 2.).



Graph 2: *Comparison of the initial and final values of MVIC of QFM in non-NMES and NMES group of patients following TKA rehabilitation program*

Discussion

The purpose of this study was to evaluate the efficiency of the NMES of quadriceps muscles, combined with standard rehabilitation protocol. We expected that NMES would reduce QFM strength loss by decreasing voluntary activation deficits and result in better functional performance outcomes when compared with standard rehabilitation protocol.

A lot of studies refer to the fact that intensive rehabilitation care after TKA can accelerate patients recovery and can lead in better functional outcomes (13 - 15).

Early rehabilitation programs should focus on improvement of QFM voluntary activation deficits, which is mainly due to preoperative muscle artrogeneous inhibition and worsens with the operation approach and pain (3, 13).

The addition of NMES initiated early after TKA attenuate loss of QFM strength in patients after TKA and improve their functional performance; benefits of NMES treatment persist through 1 year (6).

Conclusion

One-week rehabilitation program in patients following TKA with or without addition of NMES improves QFM strength. NMES seems to be an effective method complementary to standard physiotherapy approaches, its´ application leads to rapid improvement of QFM strength and better functional performance. Further research focused on early intervention after TKA is deserved to optimize patient's outcomes.

Disclosure

The authors declare no conflicts of interest.

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THE ROLE OF STRUCTURAL AND FUNCTIONAL ASYMMETRY IN THE CIRCULATION

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Abstract

Asymmetry is a very remarkable property of biological structures and functions. Structure and function of the human body are strong interrelated and depend on each other. Failures in structural development often imply subsequent functional failures of the organism after the developmental phase. It is the asymmetry in the cardiovascular system that plays an important role with respect to its functional optimization. The time course of the contraction of the heart and of the ejection into the large arteries is asymmetric in time in order to minimize energy consumption. The so-called Liebau effect permits valveless pumping of fluids and essentially depends on the asymmetric properties of conduits. One important example of the Liebau effect appears to be in the function of the coronary vascular system. It can be shown that there are several mechanisms of so called valveless pumping that contribute to the blood transport in the cardiovascular system. The common denominator of most of these mechanisms is the dependence of the unidirectional pumping effect on asymmetry. It appears that many additional examples of transport effects concerning fluids or gases in biology as well as in engineering have their basis in the underlying structural asymmetry.

Introduction

As summarized in an excellent review by Mainzer [1], symmetry is an important property of many systems in nature. Furthermore, as everybody knows, "the heart is on the left side of the body," which indicates that in the mammalian circulation asymmetry of structures and of functions is important (Kilner et al.) [2].

During ontogenetic as well as during phylogenetic development the structure of the heart and of the vascular system starts as a symmetric tube with symmetric branching. During phylogeny and with the development of more sophisticated animals, the cardiovascular system develops more and more asymmetric components. The same process also takes place in each individual during ontogeny.

Step by step the cardiovascular system becomes more asymmetric. Ewald Weibel in his book Symmorphosis [3] has summarized the adjustment in human beings and in animals of the adequate development of structures in relation to their function by the Greek term "symmorphosis". The term "symmorphosis" indicates that a certain structure is ideally adapted to performing specific functions.

Weibel describes "symmorphosis" as follows: "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. It is obvious that the principles of adaptation, integration and economy are satisfied if structural design is commensurate to functional needs throughout the organism."

There are many ways of economizing the function of the cardiovascular system. Of course, it cannot be denied that many ideas about biological economy and optimization are incompletely understood. Concerning the cardiovascular system, besides the heart, additional pump mechanisms help to propel the blood through the arteries, capillaries, and through the veins back to the heart and the lung. If one compares animals of different sizes, a strong indication for optimal function seems to follow clearly from the similarity of structures and functions, which obey certain rules of similarity.

Finally, it is suggested that the so-called Liebau effect may be involved in improving vascular blood transport (Kenner [4], Moser [5]).

The historic glass model of the aortic arch (Figure 1) not only shows how the fluid turns through the aortic arch, but also depicts the functional role of the arch [6].

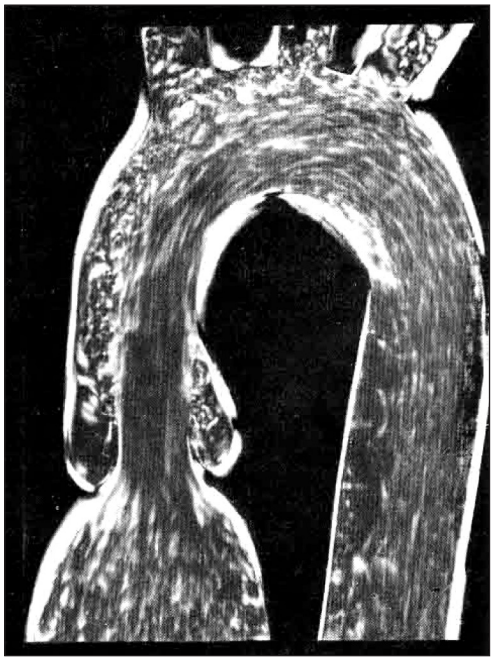

Figure 1: *Glass model of aortic arch (from: Wetterer and Kenner, 1968)*

Evolution and Development of Cardiovascular Asymmetry

The Austrian Nobel Laureate Karl von Frisch also pointed out the modification of the heart and the main vessels among vertebrates, showing a distinct evolution from symmetry to asymmetry [7], as shown in Figure 2.

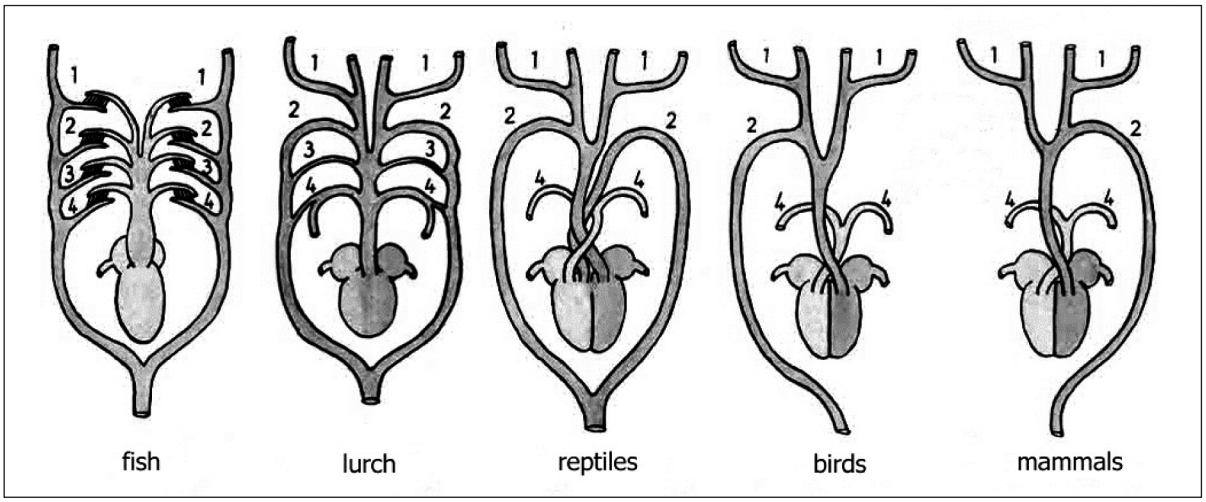

Figure 2: *Evolution of the heart and large arteries - from gills to lung (from Frisch, 1960)*

During the first weeks of embryonic life the heart as well as the vascular transport system consists of a symmetric line of elastic and contractile tubes. As shown in the textbook of embryology by Moore (1985) [8] this system is still symmetric on the 35th day of embryonic life. Therefore, the contraction of the heart chambers, which are positioned in series between the veins and the aorta, at this time mainly occurs in the circumferential direction. Even in this very early time of development, another type of asymmetry exists in the following sense: The blood in circulation flows from more distensible veins to the heart and lung and then is directed forward to less distensible arteries, and thereon circulates through the capillaries back to the veins. In the early embryonic development valves have not yet been formed. Therefore, the asymmetry in distensibilities is a condition that enables the generation of unidirectional valveless flow as proposed by Liebau (1970) [9].

During the following days of life, the contractile part of the tubes, i.e. the early structural state of the heart, folds and twists in a rather complex manner. The aortic–arterial outflow system divides, giving rise to the double outflow into aorta and pulmonary artery. Furthermore, the aorta becomes asymmetric because, from the early symmetric double arch only the left arch survives completely. Finally, the left and right pumps are positioned side by side. All these developmental processes are completed before the 49th day of embryonic life. Therefore, the two chambers of the heart are then able to contract in circumferential as well as in lengthwise direction.

In addition recent hemodynamic data from living embryos further confirm that the pumping function of the embryonic heart actually differs from a peristaltic pump in several respects and that the embryonic heart tubes act as valveless “Liebau pumps” [10].

In adults, as indicated in Figure 3, both ventricles constrict and shorten during systole. By this shortening the atria are extended. It follows that during ventricular ejection the atria are filled with blood from the large veins. This is the “mechanism of the moving plane of the valves” mentioned before. More recently, in the English literature the longitudinal shortening of the ventricles is included in the term “long axis dynamics of the heart” [11].

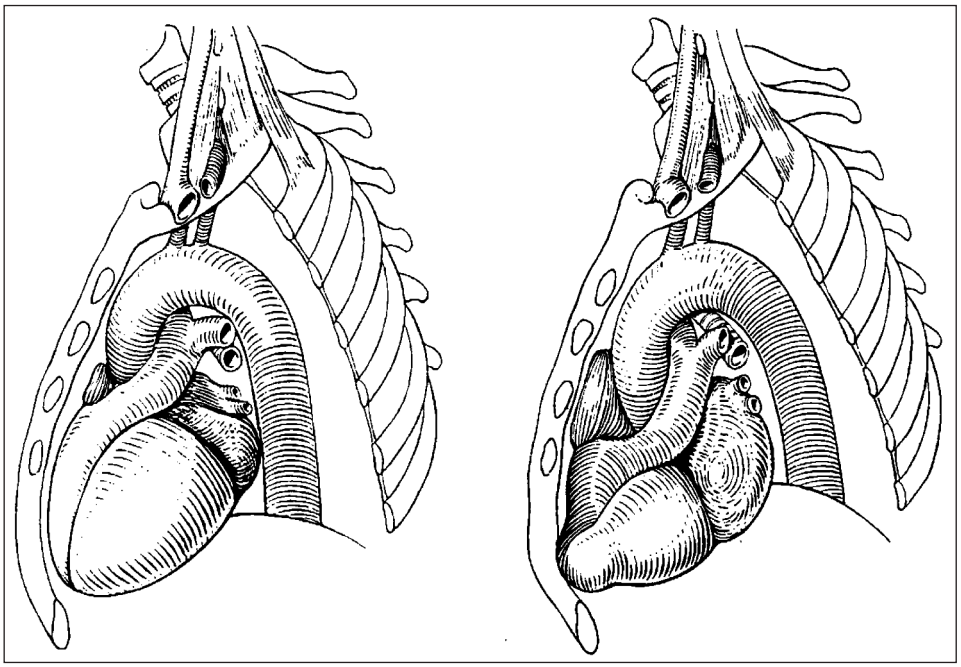

Figure 3: *The left part of the figure shows the heart in diastole, the right part shows the heart in systole—both from the left side. The movement of the plane of the valves can well be seen (from Boehme 1936) [12].*

The simultaneous pumping action of the two ventricles of the heart has such a high effectivity because of the asymmetry which is produced during early development by turning, folding, and partitioning into two tubes pulmonary system and aorta. The so-called mechanism of the moving plane of valves permits the heart to pump by combined circumferential and lengthwise contraction.

There seems to be a correlation between a highly adaptable cardiovascular transport capacity and the degree of asymmetry in the heart and large vessels. One interesting example, well known already in the 19th century is the "mechanism of the moving plane of the valves" (in German "Ventilebenenmechanismus"). This mechanism is well summarized in a paper by Henke (1872) as cited by Boehme [12]. The function of these mechanism is only possible through the asymmetric, folded, and twisted configuration of the heart that develops during embryonic life. In addition, all highly efficient fast-moving animals have an asymmetric one-sided aorta. It seems that the necessity of blood mixing in the heart chambers may also be involved in the process of optimization [2].

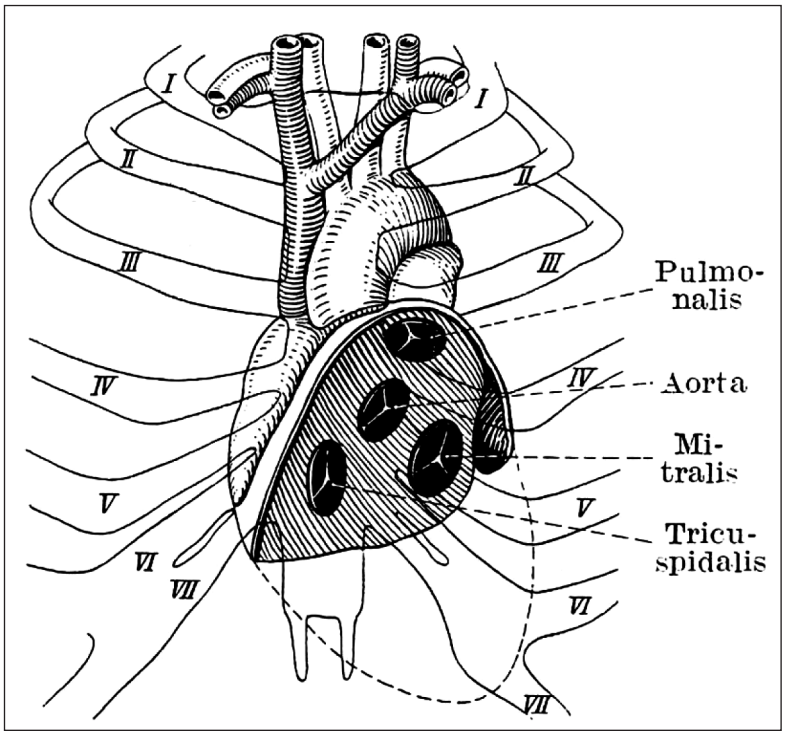

Figure 4: *The plane of the AV-valves (from Braus 1921 [13])*

Valveless Pumping, a Consequence of Structural Asymmetry

Liebau was a physician and practitioner interested in physical curiosities. He published several papers and formulated patents about the principle of valveless pumping [9]. As discussed earlier (Kenner [4], Moser [5]) there are certain conditions for the functioning of this effect. The first condition is an energy driven source of fluid movement. The second condition is asymmetry of conduits. The components of this asymmetry are inertia and compliance. The latter is a mechanism to store potential energy and fluid volume and, in stiff-walled tubes, may be due to gravitational effects. The third condition is an asymmetry of the time course of movements. An example for a model of the Liebau effect is a circular tube, half of which is made of a rigid tube. The other half is made of a distensible rubber tube. If the distensible tube is compressed periodically (with a finger) in an asymmetric location, fluid moves into the direction of the more closely located rigid tube.

Another model is a straight elastic tube, which consists of a more distensible and wider part and of a stiffer and narrower part. Compression of the wider part moves fluid from the wider to the narrower (and stiffer) part of the tube. This model was especially studied by Liebau himself and was, as an example of the effectiveness of the mechanism, depicted in one of his patent applications. This model could also serve as a possible mechanism of valveless pumping of the early embryonic heart.

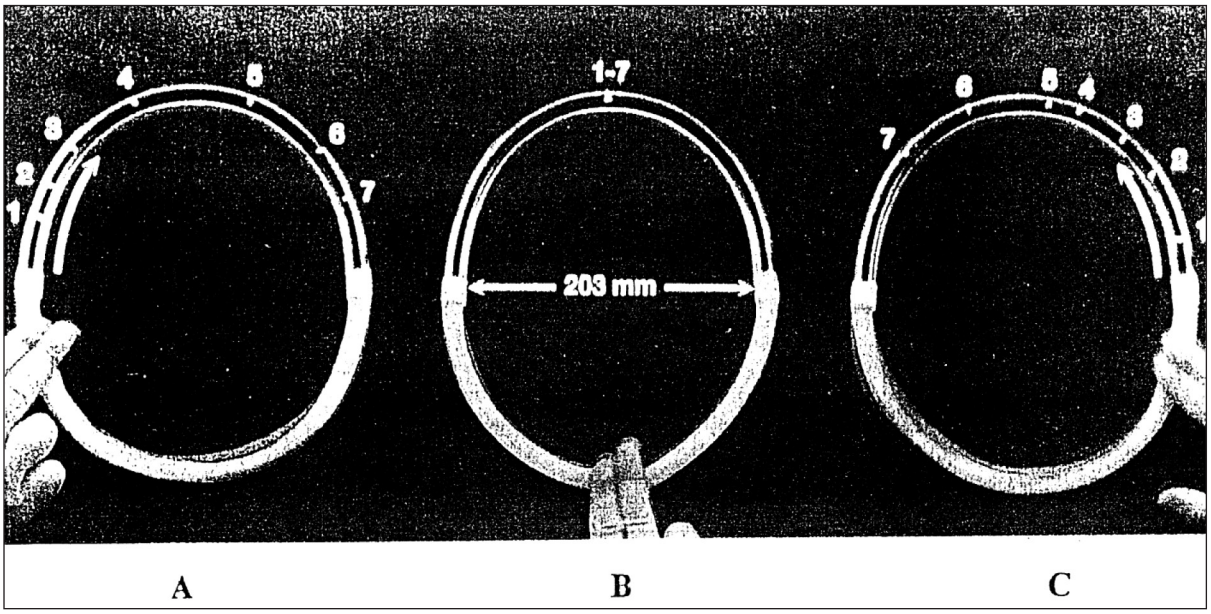

Figure 5: *Liebau-effect, a valveless pumping mechanism (from Moser, 1998 [5])*

The simplest model that can be used to demonstrate valveless unidirectional flow was already mentioned above. It consists of a fluid-filled circular tube [4,5]. The upper half of the model is a rigid glass tube. For the other half a flexible and distensible rubber tube (e.g., Penrose rubber) is used. If this distensible tube is compressed rhythmically by a finger at an asymmetric location on the right side of the circle then the fluid moves in counterclockwise direction. If the tube is compressed in the same manner in the symmetric middle of the distensible tube, then no net movement of the fluid can be observed. If the tube is rhythmically compressed at the left side, the net movement starts in counterclockwise direction.

This simple and impressive experiment, which, in different modifications, had already been performed by Liebau himself [9], raises the following questions:

(1) What are the conditions for unidirectional net motion of fluid?

(2) What determines the direction of fluid movement?

As far as the pump (the source) is concerned it is interesting to note that this pump must be able to change its characteristics during one cycle of action. We can assume that a fast and complete compression, as shown in the upper part of Figure 4, generates more or less symmetric flow pulses. Thus, the compressed site acts as a flow pump in both directions. It follows that the same volume is pushed into both directions of the compression.

Immediately after the subsequent release of the compression the pressures on both sides of the "pump" equalize (Figure 5, lower part). The location has now changed to a location with low internal resistance, i.e., a pressure pump. During the following events the backward flow to the pump through the tube with the high inertance is more delayed when compared to the flow on the other side of the pump. This process generates, on average, a preferred flow direction toward the side of higher inertance. The essential functional asymmetry in effect acts during the compression phase when the flow generating part of the stroke forcefully pushes the fluid into the part of the tube with high inertance.

Asymmetry of Time Course

Asymmetry of time course can be observed on different time scales. The time course of environmental variables as well as the wake and sleep pattern have a marked influence on physiological variables like heart rate, blood pressure and many others. This is the major area of investigation in circadian physiology.

On a fine time scale there also exist marked asymmetries e.g. as far as functions in the circulation are concerned, the time course of blood ejection from the left ventricle into the aorta. Normal ejection function starts from zero with a steep increase of the flow to reach a peak level. The flow then decreases with a slow declining downslope, which, in a typical normal example, has a small bump. 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 asymmetry regarding 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 optimal coronary perfusion.

On the level of individual cells the action potential, preceding the mechanical contraction also exhibits a marked asymmetry, with typical steep potential change at the start of each individual heartbeat.

Discussion and Conclusion

Asymmetry is an essential feature of the cardiovascular system. The Liebau effect is an interesting phenomenon the importance of which is still uncertain. The circular model first chosen by Moser [5] to analyze the Liebau effect, actually demonstrates that in an asymmetric system a net flow can be generated by a symmetric pump. There is, in addition, an asymmetry of function and time course, in particular, if the sequence of compression and release is considered. It is possible to generate valveless flow in a number of systems under the condition of an energy-consuming input by a two-phase pump: a circular model of elastic and rigid tubing and a system of rigid tubes, where the fluid surface simulates elastic effects. It follows that the principle of asymmetric flow generation plays a role in several biological or medical situations. One quite important location for the influence of asymmetry is the coronary vascular system.

A systolic activation sequence that starts from the left side and proceeds to the right side would produce a compression of the vessels similar to a peristaltic process. In addition, there is no question that further asymmetries, including nonlinearities of the system, may also add to unidirectional flow effects.

The overall efficiency of this type of pumping has been estimated by Moser [5] comparing a system without valves to a system with valves. The unidirectional flow without valves, on average, is less than half when compared to the flow generated with valves. In spite of the disadvantage of a rather small efficiency, the Liebau phenomenon of valveless unidirectional flow serves well as a source of flow in the embryonic circulation or in other valveless biological flow systems, and acts as an additional energy source for a flow in the adult circulation. Therefore, the Liebau effect most probably contributes to the optimal use of energy in the cardiovascular system. It is certain that there are more pump mechanisms in the system than the heart alone [5].

Finally it is necessary to mention the role of respiration. The periodic variation of thoracic pressure certainly is an additional source of transport energy. In needs to be noted, that this mechanism in part depends on the cardiac valves. However, the influence of a Liebau-effect type of blood transport has to be taken into account as well [14].

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WHAT WE CAN LEARN FROM MODELING CARDIAC FUNCTION?

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Abstract

Physiology has always followed an integrative approach to gain insight into the functions of the human body. The system approach considers biological processes as systems of interacting components. Mathematical and computational modeling aims to bridge the gap between experimentally gained observations of isolated components and the desired understanding of the whole living organism in health and disease. This approach requires a clear definition of the purpose, the assumptions, and the boundaries of the model. It is necessary that mathematical models have to be based on reliable experimental data. At present we witness an amazing development and refinement of biophysical methods to quantitatively describe biological phenomena with increasing accuracy. In parallel, sophisticated computational techniques enable the increasingly efficient solution of ordinary and partial differential equations, which are used to describe these systems in the language of mathematics. The hierarchical nature of causal knowledge and understanding consequently leads to "multi-scale" modeling, integrating important features across multiple levels of organizational, spatial or temporal scales. Perhaps the most advanced area of computational physiology is computational cardiac electrophysiology, investigating the electrical activity of the heart. Multi-scale cardiac modeling and simulation have been crucial in improving our understanding of ionic mechanisms of normal and abnormal heart rhythm, electrotherapy, and the electrocardiogram.

Introduction

Andreas Vesalius (+1564) not only was the father of modern anatomy, he was also an essential contributor to modern medicine with his work on the vascular and circulatory system (Figure 1).

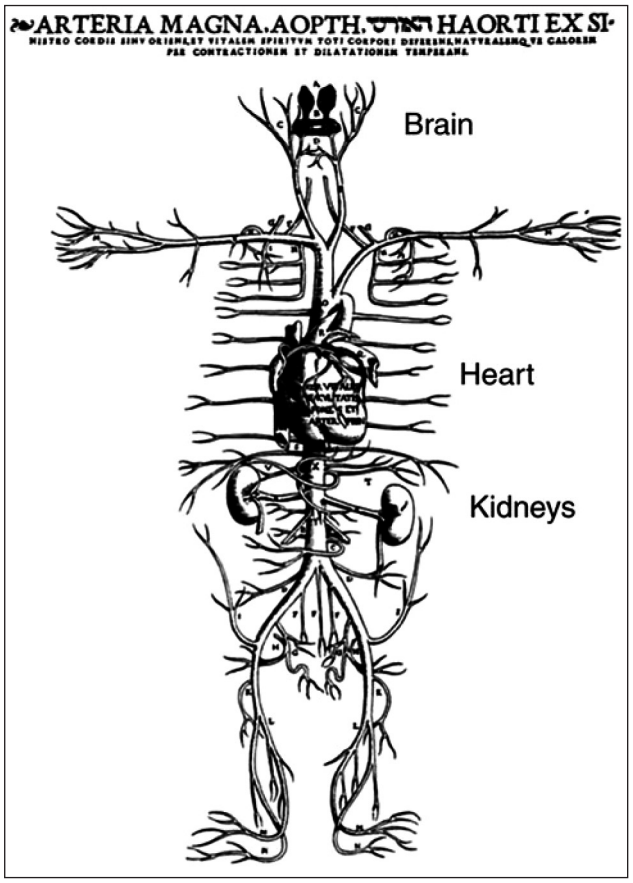


Figure 1: *The heart at the center of the circulation, Vesalius A. (1546)*

Very early, as soon as the development of experimental techniques allowed first steps, cardiac function has been in the focus of physiologists, with the ultimate aim to get more insight into one of the most essential processes found in all higher developed life forms. With the advent of increased computational capabilities, mathematical and computational modeling have become invaluable tools to better understand complex phenomena. Particularly computational modelling of essential cardiac functions (cardiac electrophysiology coupled to cardiac mechanics) is a current major effort with notable results.

Scientific models are used to explain and predict the behavior of real objects or systems and are used in a variety of scientific disciplines. Although modeling is a central component of modern science, scientific models at best are approximations of the objects and systems that they represent—they are not exact replicas. Thus, scientists constantly are working to improve and refine their models.

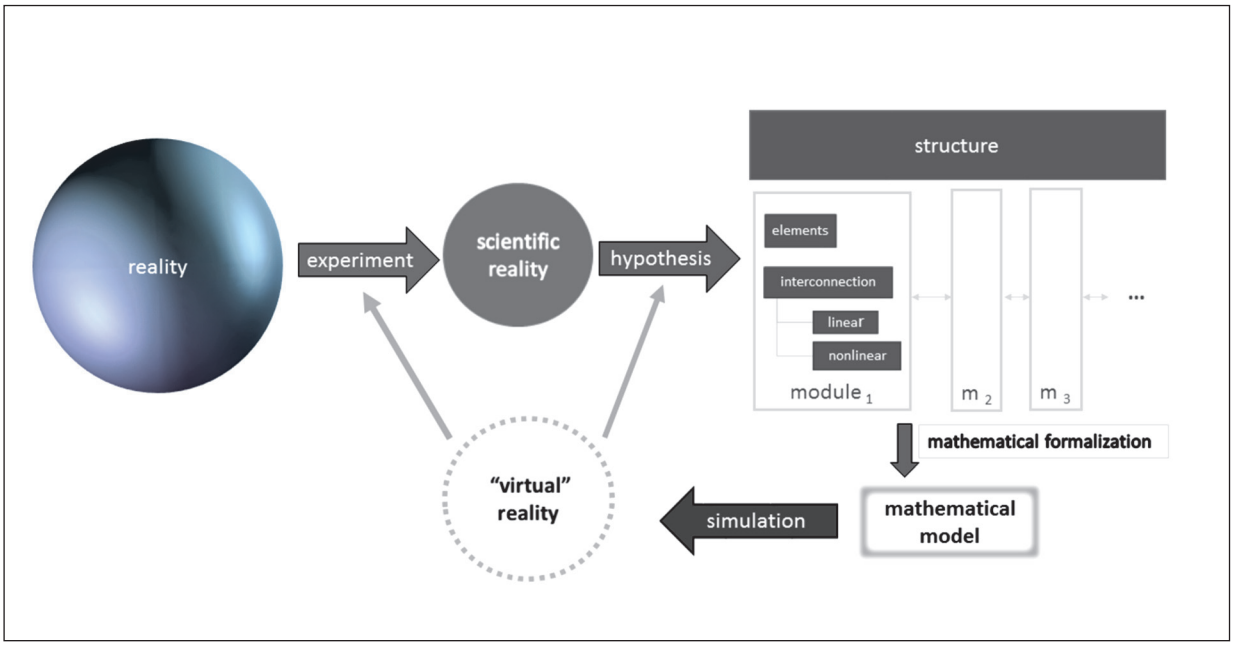


Figure 2: *Principle of scientific workflow when targeting mathematical modelling and computer simulation towards a specific aspect of reality.*

The heart of the workflow in natural sciences is the attempt to grasp reality with reproducible measurements. This has been markedly expressed by Lord Kelvin, when he said: "… when you can measure what you are speaking about, and express it in numbers, you know something about it; but when you cannot measure it, when you cannot express it in numbers, your knowledge is of a meagre and unsatisfactory kind; it may be the beginning of knowledge, but you have scarcely, in your thoughts, advanced to the stage of Science whatever the matter may be." [1]

Therefore experiments form an indispensable component in the scientific workflow to provide the observations that reveal aspects of the reality. In other words, "scientific reality" is that part of the information that natural scientists accept. However this is achieved by a reduction of dimensions (Figure 2).

CARDIAC FUNCTION: A MULTI-SCALE MULTI-DOMAIN RUSSIAN DOLL

To better understand an organism or a living system, multiple models, each representing a part of the object or system, are needed. Collectively the particular submodels may be able to provide a more complete representation, or at least a more complete understanding, of the real system.

Modular systems can be decomposed in first approximation into structurally and functionally independent parts. Obviously the human mind "is looking for" modules.

Figure 3: *Investigating the cardiac function is actually like playing with a Russian doll*

Highly sophisticated multi-scale (from cell-to-organ) computational models have been developed to reproduce the electrophysiological activity of the heart.

These models span a hierarchy of scales. When we look at cardiac function we find different levels (shells), ranging from macroscopic to microscopic scales:

a. systemic whole body/patient level
b. organ level
c. tissue level
d. cell level
e. subcellular
f. molecular

On each scale different experimental as well as modelling techniques are needed.

THE CLOSED LOOP DILEMMA: THE WHOLE IS MORE THAT IT'S PARTS

In the living organism interconnected feedback loops enable a proper adjustment to internal and external changes and provide a safety mechanism against failure of individual components (Figure 4). The cardiovascular control system effectively maintains arterial blood pressure using heart rate and heart contractility as primary regulating variables.

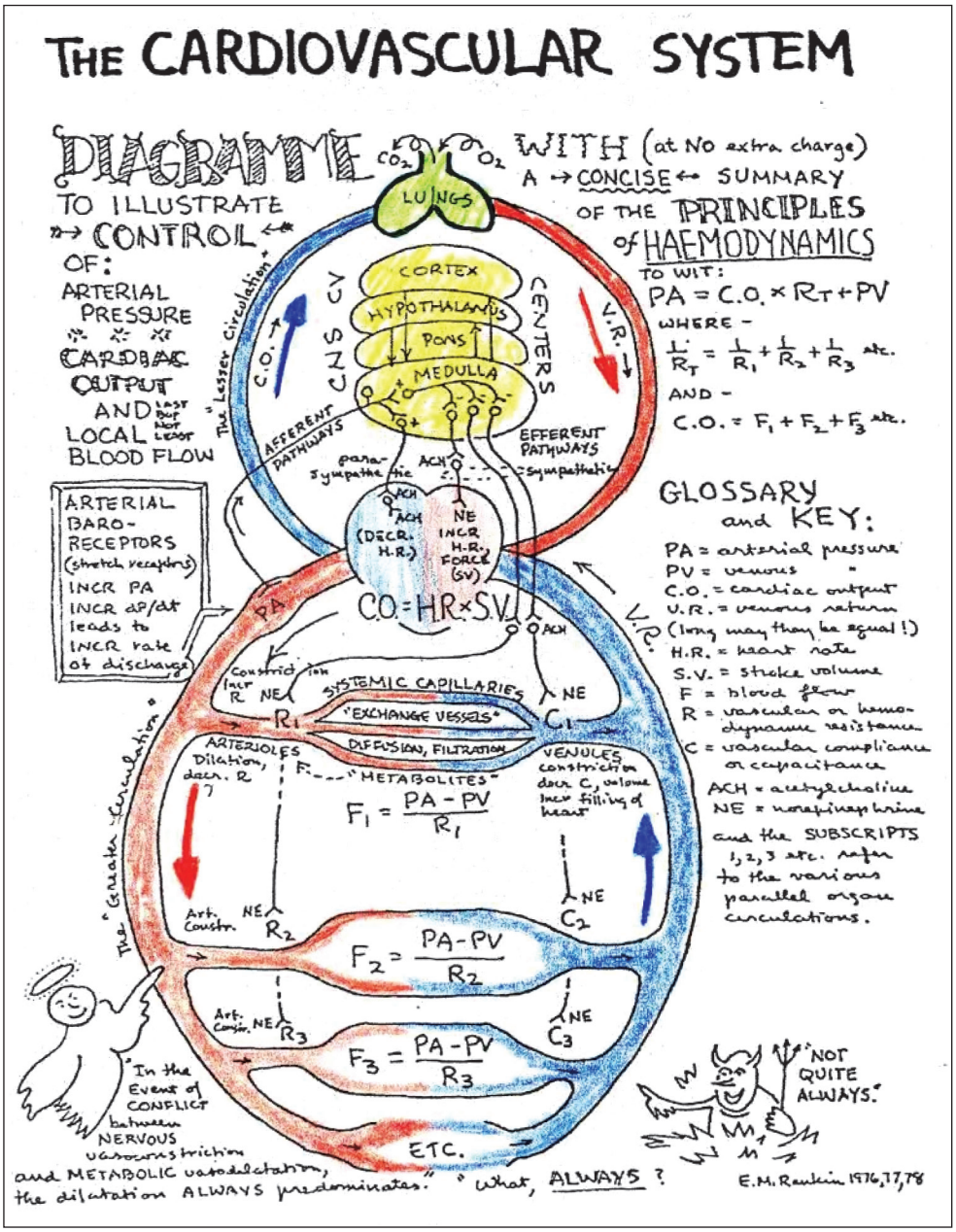


Figure 4: *The cardiovascular system as a set of interconnected feedback loops*

Very early at the advent of "System Dynamics" in the late 1950s and early 1960s it became feasible to study the circulatory system using the emerging analog computers [2].

About the same time when Hodgkin and Huxley were investigating the electrical properties of isolated squid axons and were eventually able to formulate a set of equations – actually coupled ordinary differential equations (ODEs) to adequately describe their experimental observations [3]. These formalisms have since then become the core basis for the vast majority of computational models of excitable tissue.

To enable sharing of the growing number of basically ODE-based models, CellML – originally a common model description language, has been used to establish a public model repository (https://models.cellml.org/cellml). Currently it already contains several hundred models, whose properties are encoded using a common convention of model specifications, components and annotations [4]. This collection of models is constantly expanded, using refined sophisticated experimental setups, exciting

cardiac tissue preparations and isolated cells in order to reveal cause effect relationships between specific system variables.

While these cellular models are still not first principle based, but rather heuristic, they nevertheless contribute essentially to the predictive power at the higher hierarchy level model (e.g. tissue or whole heart). This reintegration into the higher level model of course implies knowledge about the interconnections between the constituting submodels (i.e. understanding of the structure, see Figure 2).

The following experimental examples serve to illustrate the points made above. In optical mapping potential sensitive dyes and laser light excitation together with field stimulation are used to reveal hidden structural information of cardiac tissue at microscopic level.

Figure 6 and 7 show excitation experiments using either a local current stimulation or global external electric field stimulation of atrial guinea pig tissue to visualize the resulting pattern of excitation. Comparing the resulting activation maps, one can see that a tailored field stimulation experiment visualizes structural discontinuities of the tissue [5].

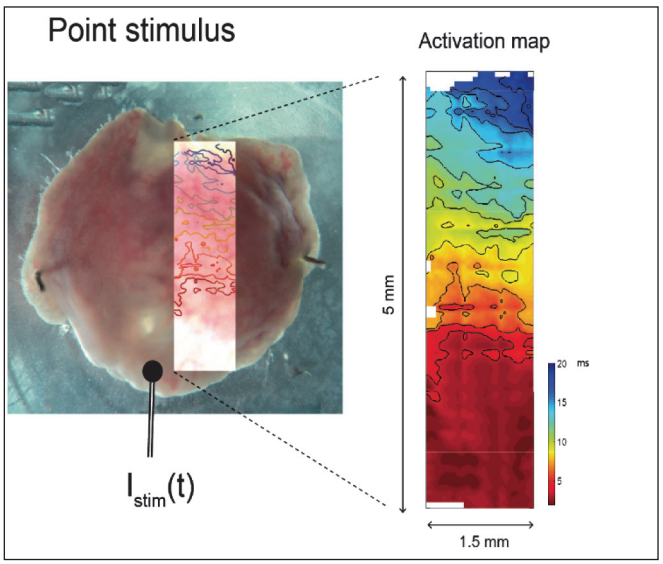


Figure 5: *Photograph of a typical adult isolated guinea pig atrium. The overlay visualizes the excitation, elicited by a suprathreshold current pulse applied at point P, as isochrones. Instant depolarization of about 1/3rd of the atrial tissue is followed by a well-defined wave front propagating at a velocity of ~0.2 mm/ms.*

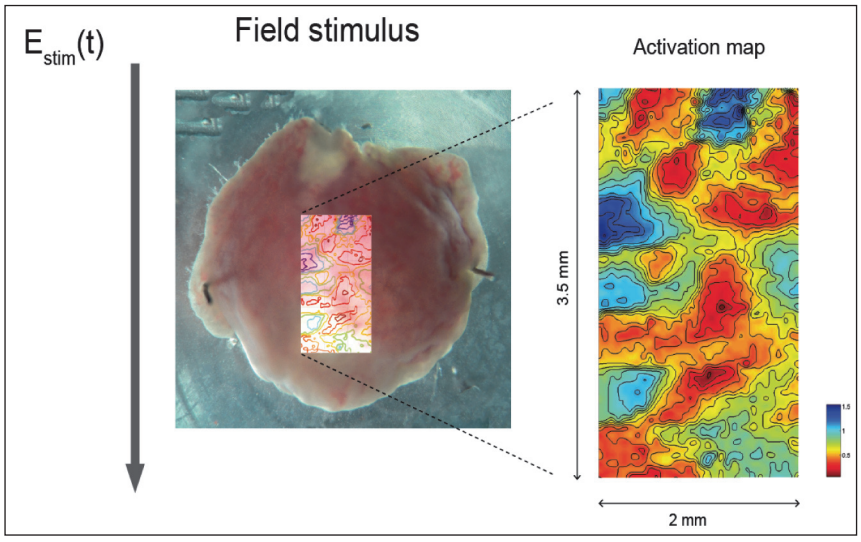


Figure 6: *Photograph shows the same preparation. The overlay depicts the isochrones of excitation, elicited by a suprathreshold electric field pulse applied across the atrium. The activation map reveals distinct multiple sources, where excitation start simultaneously. Consequently the time to excite the whole atrial tissue is reduced to ~ 1.5 ms.*

The next step towards a computational model is the translation of empirical data into the language of mathematics (i.e. formulating the adequate ordinary and partial differential equations (see Figure 2).

For simulation purpose the mathematical model has now to be turned into a computational model. Whereas time and space are continuous in the mathematical model, for computer simulations, we have to describe the system in discrete time and space. The continuous arrow of time is replaced by a sequence of discrete points in time. In additions space is discretized as well and replaced by a grid of lumped entities, whose dynamic behavior generally can be described by ordinary differential equations in time. Together with the knowledge of the coupling determined by the given spatial structure these description forms a mesh, as shown in Figure 7.

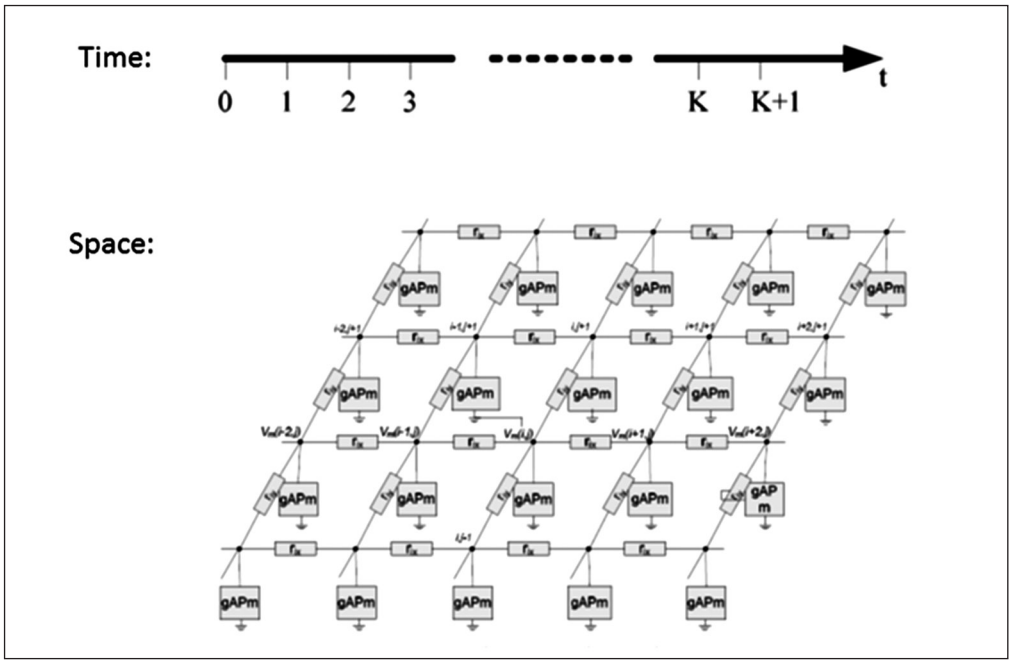


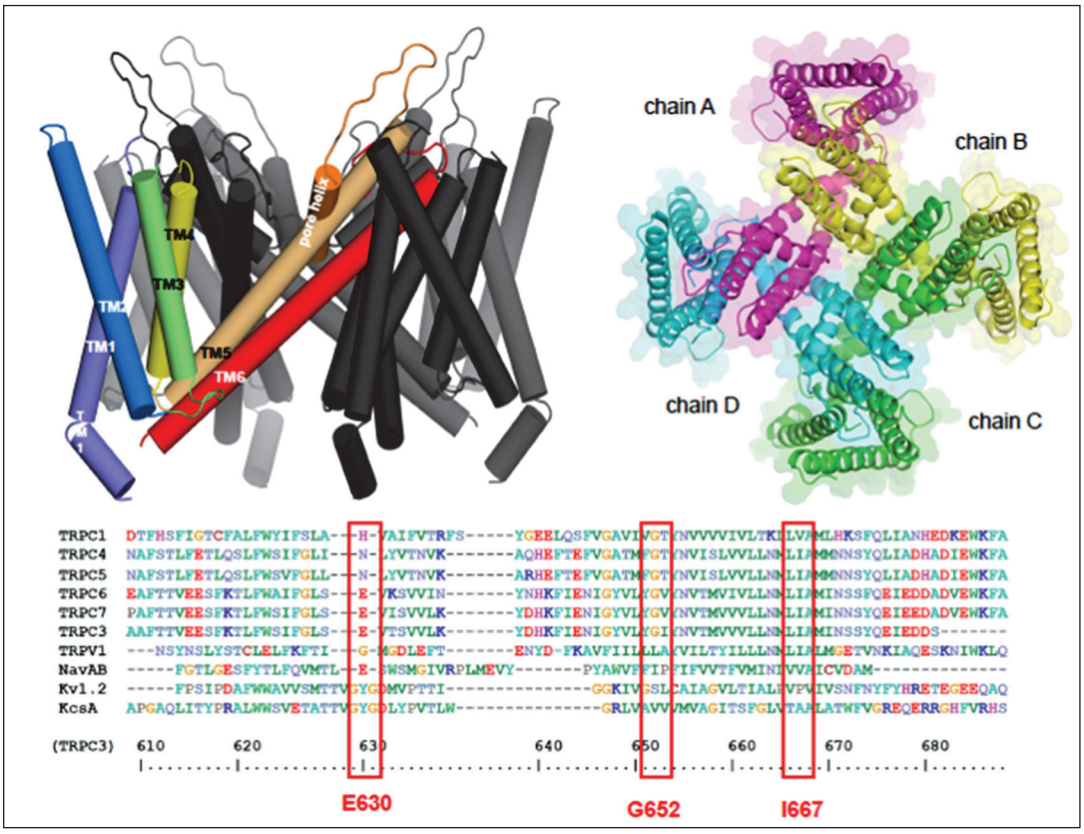
Figure 7: *Discretization of time and space by formulating an equivalent discrete electrical circuit. For a two-dimensional approximation of in this case uniform cardiac muscle sheet with gAPm designating a generalized action potential model and rx and ry being the intracellular coupling resistances in directions x and y. The time development of the resulting electrical behavior is computed for discrete points tk along the arrow of time (modified from [6]).*

At this point, we now deal with the question of whether the properties of the continuous problem are inherited to the discretized problem. Unfortunately, at the current stage of development, there is no general answer to this question.

So far experiments have driven the model generation process, culminating in numerical simulation studies. Computational modelling contains an additional potential, namely to inspire new experiments and hypothesis (see Figure 2). For example in the case of field stimulation experiments of isolated myocytes [7], the simulation experiments suggested the presence of a hitherto unknown ionic current, which is under current experimental investigation.

The ultimate goal is to unify experiment and simulation, so that they are not viewed as separate activities but that are a shared set of techniques to solve problems.

A new and exciting hierarchical level is opened by modeling the protein structures which are key components of all life processes. Every heart beat relies on proper opening and closing of specific proteins, the so called “ion channels”. Figure 8 shows computer based visualization of a yet not determined three dimensional structure of the pore forming molecule of s specific cardiac ion channel [8]. This adds new structural information to better understand ion channel functioning and also its interactions with pharmacological relevant substances.



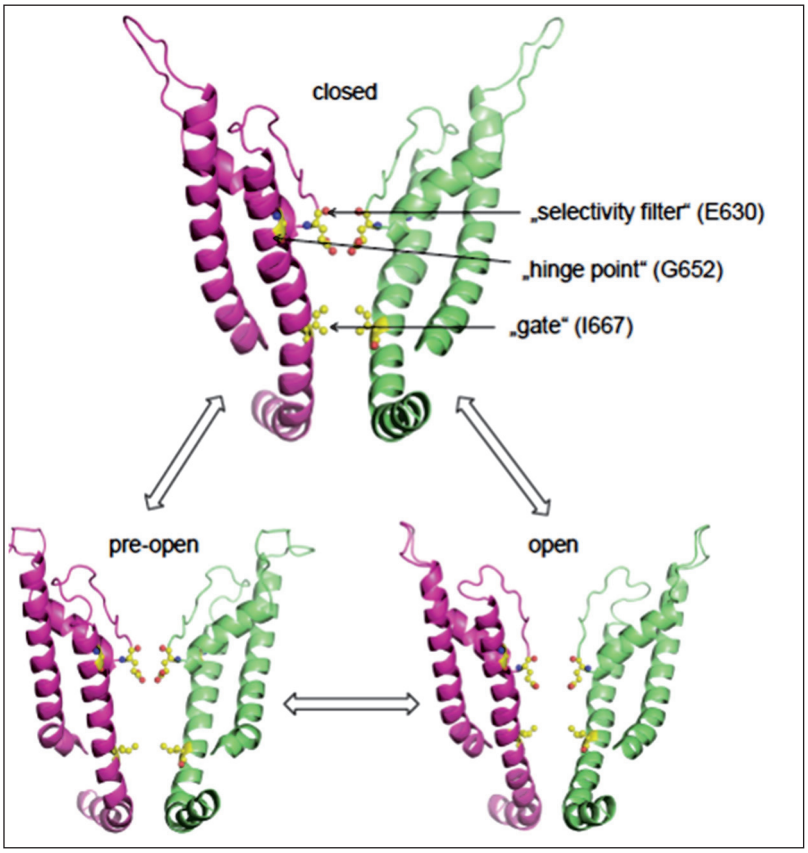


Figure 8: *Identification of residues that determine TRPC3 function based on its homology to TRPV1*

Conclusion

So, what can we learn from computational cardiac modelling? In a nutshell I would say, computational cardiac modelling allows us to evaluate the relevance of scientific hypotheses targeting complex biological phenomena and simultaneously deepens the insight into the material processes underlying these phenomena. In both aspects modelling helps to improve our understanding of scientific reality and thereby deblurring the image of reality provided by natural science.

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