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Prof. MUDr. Martin Repko, Ph.D., Dean of Faculty of Medicine Masaryk University Brno

Reviewed by: Prof. MUDr. Kamil Javorka, DrSc.
Jessenius Faculty of Medicine in Martin
Comenius University in Bratislava
Slovak Republic

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Nandu Goswami, Coordinator

Medical University Graz, Austria

On behal of the ***EndoCOVID*** Team

Austria: Goswami, N., Steuber, B., Schmid-Zalaudek, K
Norway: Fredriksen, P.M., Lundin, K.E.A.,
South Africa: Motaung, S., Nkeh Chungag, B, Hyera, F.
Nigeria: Elias, S.

Prof. Nandu Goswami
Austria

Prof. Francis Hyera,
South Africa

Prof. Knut Lundin,
Norway

Prof. Shirley Motaung
South Africa

Dr. Karin Schmid,
Zalaudek
Austria

Dr. Bianca Steuber

Austria

Prof. Simiat Elias,

Nigeria

Prof. Peter Moten,
Frederiksen
Norway

Benedicta
Nkeh Chungag
South Africa

Abstract

Background

COVID-19 has affected almost every country in the world, especially in terms of health system capacity and economic burden. People from sub-Saharan Africa (SSA) often face

interaction between human immunodeficiency virus (HIV) infection and non-communicable diseases such as cardiovascular disease. Role of HIV infection and anti-retroviral treatment (ART) in altered cardiovascular risk is questionable and there is still need to further carry out research in this field. However, thus far it is unclear, what impact the COVID-19 co-infection in people living with HIV (PLHIV), with or without therapy will have. The ENDOCOVID project aims to investigate whether and how HIV-infection in COVID-19 patients modulates the time course of the disease, alters cardiovascular risk, and changes vascular endothelial function and coagulation parameters/ thrombosis risk.

Methods:

A total of 1026 patients will be included into this study. Cardiovascular research PLHIV with (n = 114 in each of the three recruiting centers) - or without - ART (n = 114 in each of the three recruiting centers) with COVID-19 and HIV-negative with COVID-19 (n = 114 in each of the three recruiting centers) will be carried out via clinical and biochemical measurements for cardiovascular risk factors and biomarkers of cardiovascular disease (CVD). Vascular and endothelial function will be measured by brachial artery flow-mediated dilatation (FMD), carotid intima-media thickness (IMT) assessments, and retinal blood vessel analyses, along with vascular endothelial biomarkers and cogualation markers. The correlation between HIV-infection in COVID-19 PLHIV with or without ART and its role in enhancement of cardiovascular risk and endothelial dysfunction will be assessed at admission, weekly, at discharge and, 4 weeks post-discharge (if possible).

Impact of project

The ENDOCOVID project aims to evaluate in the long-term the cardiovascular risk and vascular endothelial function in PLHIV thus revealing an important transitional cardiovascular phenotype in COVID-19. The study was registered under clinicaltrials.gov (NCT04709302).

Declaration: This abstract has been presented as a protocol paper by the EndoCOVID team:

Goswami, N., Fredriksen, P.M., Lundin, K.E.A. et al. COVID-19 and its effects on endothelium in HIV-positive patients in sub-Saharan Africa: Cardiometabolic risk, thrombosis and vascular function (ENDOCOVID STUDY). BMC Infect Dis 21, 719 (2021). https://doi.org/10.1186/s12879-021-06426-8


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Chronotherapy of Blood Pressure: Beyond Comparing Morning vs. Evening Dosing

Cornelissen G[1], Havelková A[2], Siegelová J[2], Gubin D[3], Beaty LA[1], Otsuka K[1,4]

[1]Halberg Chronobiology Center, University of Minnesota, Minneapolis, MN, USA;
[2]Masaryk University, Brno, Czech Republic;
[3]Laboratory for Chronobiology and Chronomedicine, Research Institute of Biomedicine and Biomedical Technologies, Medical University, Tyumen, Russia;
[4]Executive Medical Center, Totsuka Royal Clinic, Tokyo Women's Medical University, Tokyo, Japan

Correspondence:

Germaine Cornelissen
Halberg Chronobiology Center
University of Minnesota,
420 Delaware St. S.E.
MMC8609
Minneapolis, MN 55455, USA
Tel.: +1 612 624 6976
E-mail: corne001@umn.edu
Website: https://halbergchronobiologycenter.umn.edu/halberg-chronobiology-center

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Abstract

The day-night ratio (DNR) of blood pressure (BP) is the index currently used most often by those relying on ambulatory blood pressure monitoring (ABPM) for the diagnosis and prognosis of hypertensive patients. It is also used as a gauge of the response to anti-hypertensive medication. Herein, we illustrate how ongoing debates regarding the relative merits of administering anti-hypertensive drugs in the morning or evening are misguided by trying to answer the wrong question. We review evidence showing that cardiovascular disease risk tends to be more strongly associated with a reverse dipping pattern of BP than with a non-

dipping pattern. We also offer some explanation why extreme dipping may be associated with increased risk in the elderly while it is protective in younger populations. Based on abstract models, we demonstrate that reliance on the circadian amplitude and phase interpreted in the light of chronobiologic reference values qualified by gender and age constitutes a more robust and more reliable approach than the classification in terms of dipping based on the DNR. We conclude by redefining the question to be answered in future clinical trials, leading to the suggestion of chronotherapy protocols aimed at a personalized treatment of BP disorders.

Introduction

Blood pressure (BP) in clinical health and uncomplicated hypertension undergoes a large-amplitude circadian rhythm with lower values during nightly sleep and higher values during the active daytime [1]. On average, BP is lower in women than in men in the absence of anti-hypertensive treatment [2]. While systolic (S) BP increases at least up to 80 years of age, diastolic (D) BP reaches a maximum around 40 years of age, and starts decreasing thereafter. As a consequence, pulse pressure (PP), the difference between SBP and DBP starts increasing after 40 years of age [3]. The circadian amplitude of BP also changes as a function of age, reaching a maximum around 45 years of age [3], while the circadian acrophase tends to advance in the elderly [4]. The circadian waveform of BP undergoes further changes with age in terms of the post-prandial dip in early afternoon, which is accentuated in older persons [5].

These changes in circadian characteristics of BP as a function of age were first mapped when ABPM devices became available and were used to monitor clinically healthy populations [6]. On their basis, time-specified reference values were derived [7] as well as reference values, determined as 90% prediction limits, for the parameters of the 24-hour component of BP assessed by cosinor [8, 9]. Vascular variability disorders (VVDs) were defined as conditions such that one or the other circadian characteristic of BP (or heart rate, HR) deviated from the reference range from clinically healthy peers matched by gender and age [10].

Over the years, awareness of the large extent of day-to-day variability in all parameters of the 24-hour BP rhythm emerged [11, 12]. This realization prompted our recommendation to perform ABPM for spans longer than 24 hours [10]. Current practice, however, still limits ABPM mostly to 24 hours in special cases for which a diagnosis is difficult to make, as stipulated in the guidelines [13, 14]. Clinical trials concerned with the optimization of the time of administration of anti-hypertensive medications also often rely on ABPM carried out over spans of 24 hours. Clinicians using ABPM to monitor the BP of their patients mostly rely on an index, the day-night ratio (DNR) that is intended to approximate the circadian variation in BP. Herein, we review some of the literature showing how the DNR affects cardiovascular risk. We show how the information derived from estimates of the circadian amplitude and

acrophase may be less biased than reliance of the DNR. Finally, we question whether current chronotherapy trials of BP ask the right question and suggest protocols for use in future studies that could resolve the current controversy regarding treatment in the morning or evening, while leading the way toward personalized chronotherapy.

Day-Night Ratio of Blood Pressure and Dipping Patterns - Association with CVD Risk

The day-night ratio (DNR) was introduced as a way to estimate the extent of predictable daily change in BP without having to use regression models [15]. The DNR is computed as DNR = (average daytime BP – average nighttime BP)/(average 24-hour BP), where daytime and nighttime have been defined somewhat differently by different investigators [15-18]. In order to include BP measurements during daytime or nighttime when they are most stable and not contaminated by measurements taken around the times of awakening or falling asleep when BP changes rapidly, we defined daytime as the daily span from 10:00 to 20:00 and nighttime as the daily span from 00:00 to 06:00 [19]. When the times of awakening and falling asleep are known, daytime starts 3 hours after the time of awakening and ends 3 hours before the time of falling asleep, while nighttime starts 1 hour after the time of falling asleep and ends 1 hour before the time of awakening.

ABPM results from clinical studies determined that patients for whom BP dropped by less than 10% during the night compared to daytime had a higher incidence of adverse cardiovascular events than patients with a day-night difference in BP larger than 10% [15-18]. They were called “non-dippers” and “dippers”, respectively [15]. Dipping categories based on the DNR were later extended to include reverse dippers (RD) when DNR<0%, non-dippers (ND) when 0%<DNR<10%, dippers (DP) when 10%<DNR<20%, and extreme dippers € when DNR>20% [20]. Dipping has since also been assessed based on the night-day ratio (NDR) of BP [21], defined as NDR = (average nighttime BP)/(average daytime BP). The four dipping categories defined based on the NDR are RD when NDR>1, ND when 1>NDR>0.9, DP when 0.9>NDR>0.8, and ED when NDR<0.8. These limits apply to all adults of both genders.

As illustrated in Figure 1, which summarizes results from Verdecchia et al. [20], non-dipping and reverse dipping have been associated with a higher cardiovascular risk. This study included 3012 initially untreated patients with essential hypertension. Over a mean follow-up period of 8.44 years, 268 patients developed a major cardiovascular event and 220 died. Each patient provided a 24-hour ABPM profile with measurements at 15-minute intervals, which determined that there were 3.9% RD, 27.8% ND, 54.8% DP, and 13.6% ED. RD and ND, but not ED were found to have a higher cardiovascular risk than DP [20].

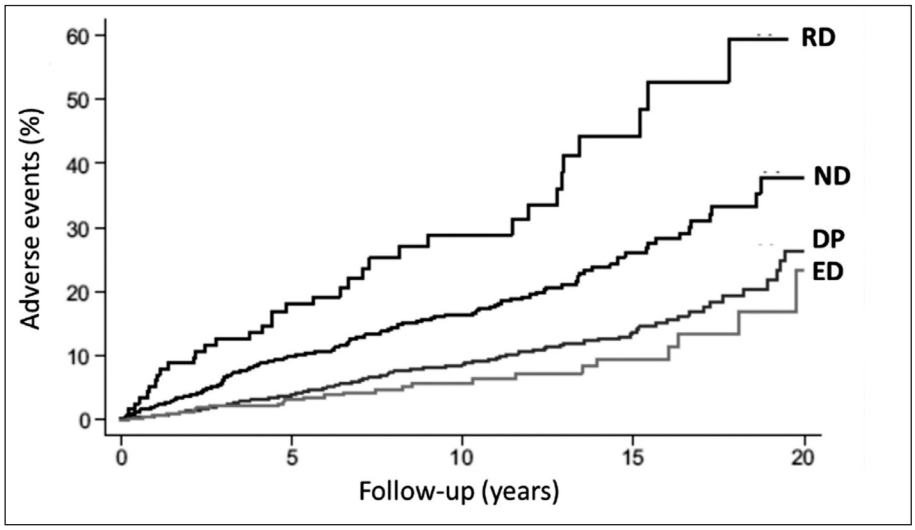

Figure 1. *Kaplan-Meier curves reporting the cumulative incidence of cardiovascular disease in the four dipping categories. Adapted from [20]*

While some studies report an increased cardiovascular risk in the absence of BP dipping, reverse dippers are generally found to carry the largest risk [22-31], as illustrated in Figure 2 based on data from Fagard et al. [21]. Conditions such as diabetes [32, 33] and kidney disease [34-36] have long been known to be associated with changes in the circadian BP acrophase, and even with a reversal of the circadian BP rhythm, which can be associated with marked changes in the DNR or NDR (and corresponding dipping category).

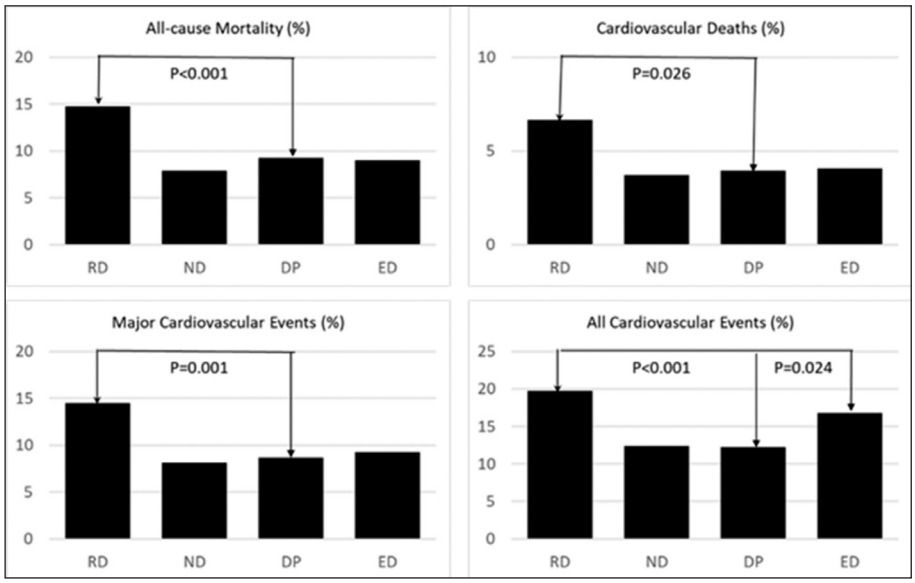

Figure 2. *Events after follow-up of 23,164 patient-years in 3,468 treated or untreated hypertensive patients from four prospective studies performed in Europe, classified by their night-day ratio as reverse dippers (RD, N=421), non-dippers (ND, N=1407), dippers (DP, N=1295), or extreme dippers (ED, N=345) based on 24-hour ABPM. Data from Fagard et al. [21].* **© Halberg Chronobiology Center**

Effect of Phase Shift on the Day-Night Ratio

To illustrate this point, Figure 3 shows how the phase of the circadian rhythm in BP can affect the DNR greatly in the absence of any change in the extent of predictable daily change assessed by the fit of a single 24-hour cosine curve or of a two-component model consisting of cosine curves with periods of 24 and 12 hours that approximates more closely the circadian waveform of BP. In all models of Figure 3, the 24-hour amplitude of systolic (S) BP is 15 mmHg around a rhythm-adjusted mean (MESOR) of 120 mmHg. When the 24-hour acrophase occurs at 6 pm, the DNR is 14.3 and the NDR is 0.87, indicative of a dipper pattern. Shifting this rhythm in SBP as a 2- to 4-hour delay results in large decreases in the DNR (or increases in the NDR) that would be interpreted as representing non-dipping or even reverse dipping patterns even though the 24-hour amplitude remained the same. Phase delays such as those modeled in Figure 3 may be due to differences in chronotype, differences in lifestyle habits, or the presence of underlying conditions such as diabetes or chronic kidney disease, even when the rest-activity schedule is unchanged.

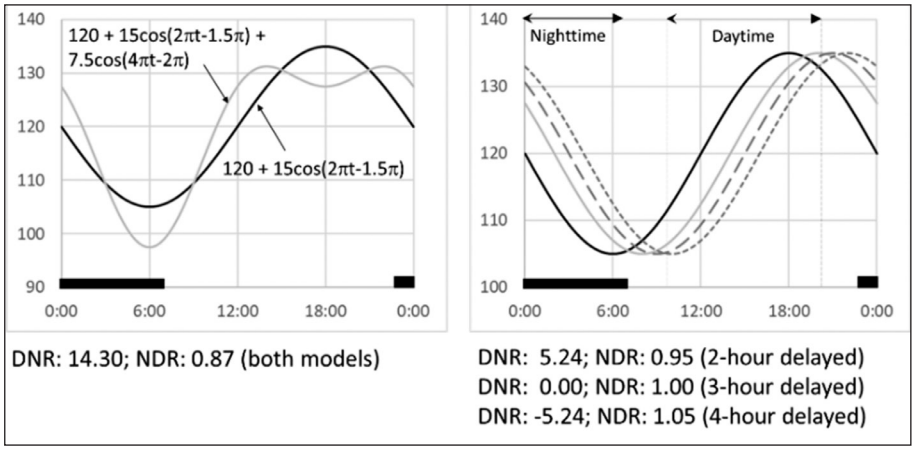

Figure 3. *Left: One- or two-component models approximate the circadian variation in SBP. The Day-Night Ratio (DNR) is between 10% and 20% and the Night-to-Day Ratio (NDR) is between 0.8 and 0.9, both corresponding to a dipper pattern. Right: As compared to the one-component model shown on the left (solid black curve), similar models delayed by 2, 3, or 4 hours (solid, dashed, and dotted gray curves, respectively) are associated with non-dipper and even reverse-dipper patterns. Similar results apply to the two-component model: after a delay of 2, 3, or 4 hours, the DNR is 2.82, -2.78, and -7.65, respectively, and the NDR is 0.97, 1.03, and 1.08, respectively.*

Effect of Post-Prandial Dip on Day-Night Ratio

Changes in the circadian waveform of BP observed with advancing age include a more pronounced post-prandial dip in the early afternoon [5]. Response to anti-hypertensive

medication can also account for similar circadian BP patterns. Such a change in the circadian waveform of BP is not necessarily associated with a change in the amplitude of the 24-hour component, but is rather contributed by additional harmonic terms in the model. Often the second and sometimes the third harmonic terms with periods of 12 and 8 hours are sufficient to approximate the post-prandial dip in BP, as shown in Figure 4. Whereas the single-component 24-hour cosine model remains compatible with a dipper pattern based on the DNR and NDR, their computation from the multiple-component model that approximates the data more closely now indicates a non-dipper pattern. The change in dipping category, however, occurred in the absence of a change in the 24-hour amplitude.

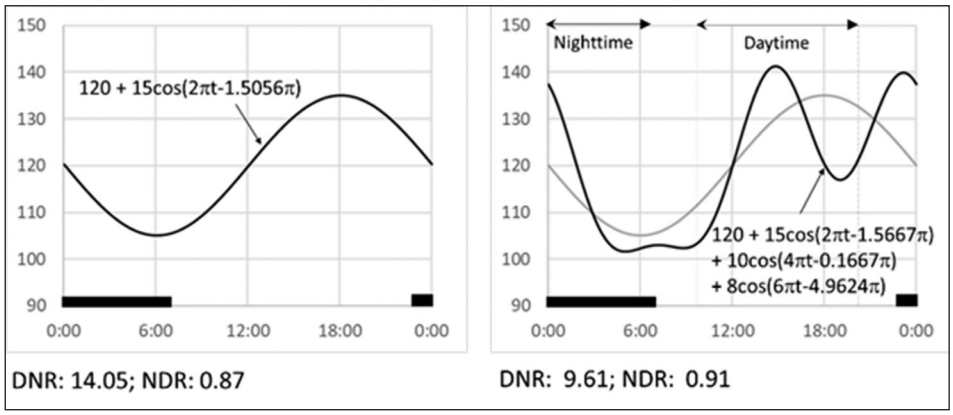

Figure 4. *Left: The single-component 24-hour cosine model, with an amplitude of 15 mmHg around a MESOR of 120 mmHg, approximates the circadian variation in SBP of young adults. The DNR is between 10% and 20% and the NDR is between 0.8 and 0.9, both corresponding to a dipper pattern. Right: A composite model, differing mostly from the model on the left by a sharp post-prandial dip in early afternoon, approximates the circadian pattern of SBP in some older individuals. The DNR is below 10% and the NDR is between 0.9 and 1.0, both corresponding to a non-dipper pattern, while the 24-hour amplitude remained unchanged.*
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Is Extreme Dipping Associated with Cardiovascular Risk?

Controversy remains regarding cardiovascular risk associated with extreme dipping. Several Japanese studies reported an increased risk of stroke and silent cerebral disease in association with extreme dipping [37-41]. An increased risk among extreme dippers tends to affect older populations, as extreme dipping is reportedly protective in the young [42-44]. Some investigators have linked the risk associated with extreme dipping to the morning BP surge [45, 46], but others refuted this relationship [47]. As apparent from Figure 2, extreme dipping relates to an increased risk for all cardiovascular events, but not for major cardiovascular events in analyses from the same databases. Our own results based on an Asian population documented a large increase in the risk of cerebral ischemic events but not to coronary artery disease in relation to

circadian hyper-amplitude-tension (CHAT), which represents too large a 24-hour amplitude of BP [19, 48, 49], Figure 5.

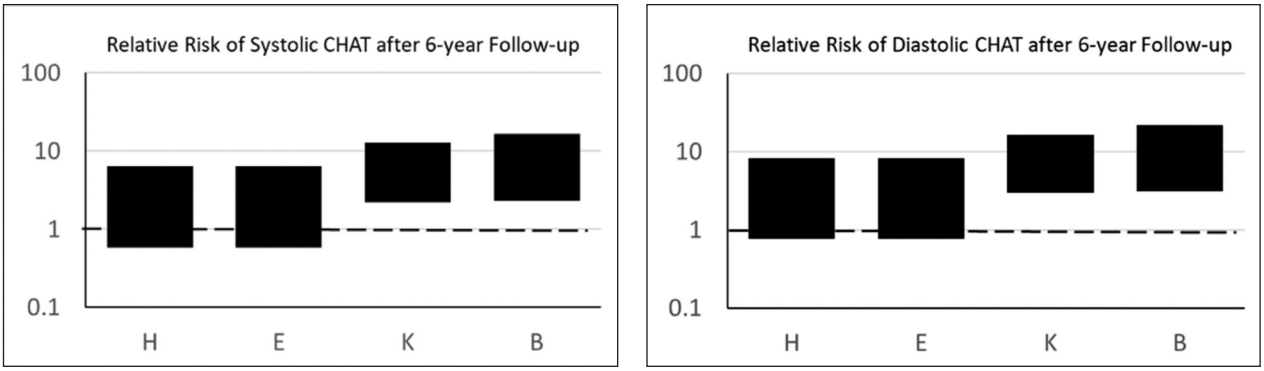

Figure 5: *Relative risk (and 95% CI) of coronary artery disease (H), retinopathy (E), nephropathy (K), and cerebral ischemic events (B) associated with too large a 24-hour amplitude of systolic (left) or diastolic (right) BP in 297 normotensive or treated hypertensive patients without any morbidity at the start of study. Patients were followed-up for 6 years at 6-month intervals.* **© Halberg Chronobiology Center**

Our results also showed that the 24-hour amplitude of BP does not have a linear relationship with cardiovascular disease risk [5, 48, 49], Figure 6. Our 7-day/24-hour monitoring of clinically healthy individuals also documented how the 24-hour amplitude of BP changes as a function of age in men and women [3, 4]. As seen in Figure 7, the 24-hour BP amplitude of a 75-year old is about half that of a 45-year old, on average. Translating these results into estimates of the DNR or NDR, the 20% or 0.8 limit delineating extreme dipping from dipping requires a larger deviation from norms for a 75-year old than for a 45-year old, thereby accounting, in part, for differences reported in the literature regarding the risk of extreme dipping in the old or the young. Modeling in Figure 8 illustrates this point.

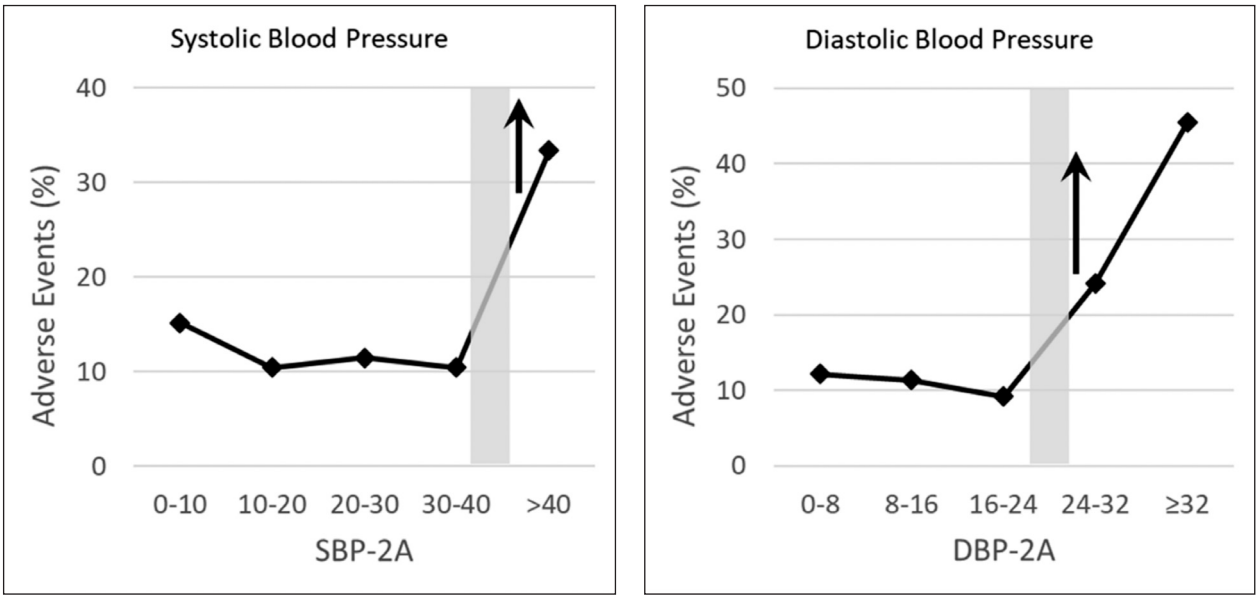

Figure 6. *The 24-hour amplitude of BP relates nonlinearly to cardiovascular disease risk. An elevation in risk occurs only after the 24-hour amplitude of BP exceeds a threshold (up arrows separate amplitude ranges where a statistically significant increase in risk occurs). These thresholds (gray areas) can be approximated by computing 90% prediction limits of parameters of the 24-hour BP rhythm from clinically healthy peers matched by gender and age.* **© Halberg Chronobiology Center**

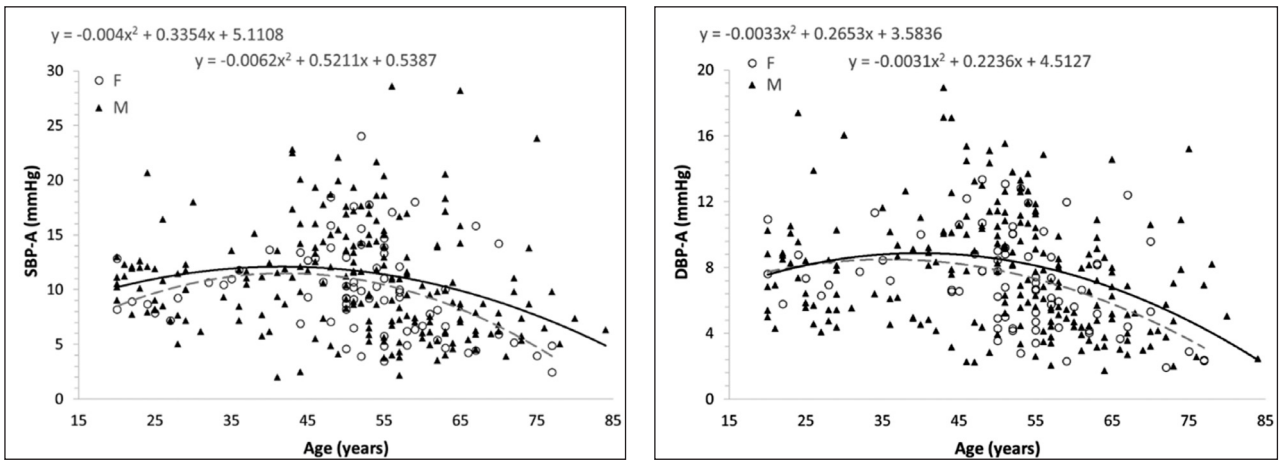

Figure 7. *Changes in the 24-hour BP amplitude with age can be approximated by a second-order polynomial, which shows maximal amplitudes around 45 years of age.* **© Halberg Chronobiology Center**

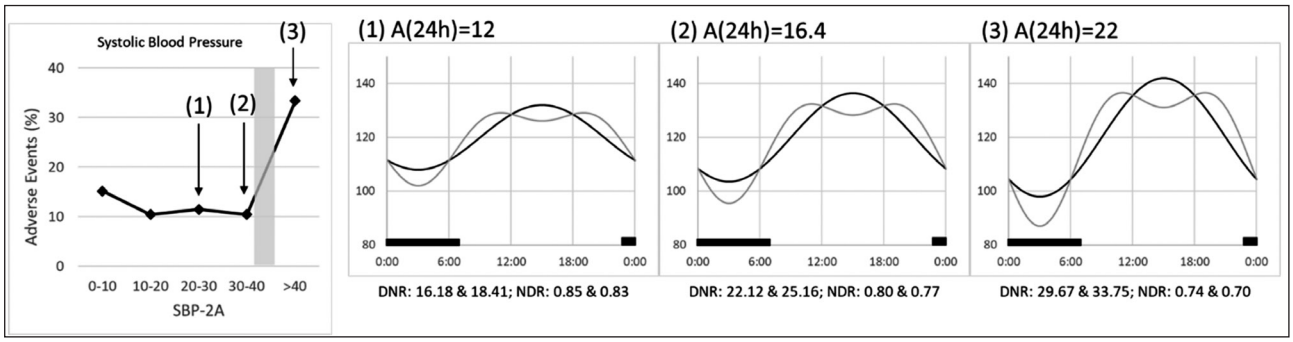

Figure 8. *The DNR and NDR computed based on one- or two-component models of the circadian BP rhythm already assume values corresponding to extreme dipping when the 24-hour amplitude is still in the acceptable range (see model in middle corresponding to a 24h-A of 16.4 mmHg). They assume values close to 30% or 0.7 for models of CHAT (last model on right), deviating markedly from the 20% or 0.8 limit delineating extreme dipping from dipping.* **© Halberg Chronobiology Center**

Implications for Chronotherapy Trials

Considering that a number of studies find a higher cardiovascular risk among non-dippers and among reverse dippers in particular, whereas extreme dipping tends to be protective in young populations, some investigators consider the additional benefit of achieving a nocturnal BP dip between 10% and 20% when treating hypertensive patients. Several trials compared outcomes between patients receiving anti-hypertensive treatment in the morning or evening [50]. Evening dosing is generally viewed as beneficial since it tends to decrease nocturnal BP, thereby increasing the DNR [51, 52]. Evening dosing achieved a reduction in adverse outcomes mostly in patients with diabetes and chronic kidney disease who tend to have a weakened circadian BP rhythm, some even showing a reverse circadian BP pattern [52-55]. There should be concern, however, for the risk of achieving extreme dipping in some patients with glaucoma, for whom nocturnal hypotension represents a known risk of optic neuropathy [56]. In our experience, similar concern should be extended to patients presenting with CHAT.

The issue of determining the optimal time of administration of anti-hypertensive medications is, however, much broader. Figure 9 illustrates the problem. It displays the average circadian pattern of SBP monitored around the clock for 7 days by ABPM for five different patients, where the data are stacked over an idealized 24-hour day. In one case (left), the circadian variation of SBP is blunted and it would make sense to time treatment aiming at amplifying its circadian rhythm. In another case, BP peaks during the night, when treatment efficacy should reach its maximum. Another case (middle) has an excessive circadian amplitude of SBP (CHAT), for whom caution should be taken not to decrease BP to values that are too low during the night. Maximal drug action may need to target the highest SBP values around mid-day in this case. BP is elevated across the entire day in another case, who would benefit from treatment acting

equally throughout the 24 hours. Another case (right) shows the characteristic pronounced post-prandial dip in BP in early afternoon. Highest efficacy of the treatment in this case should target two times of day, the morning peak and the evening peak. The point of these examples is that different patients present with different circadian BP profiles in the absence of treatment, suggesting that the optimal treatment time may also differ among them.

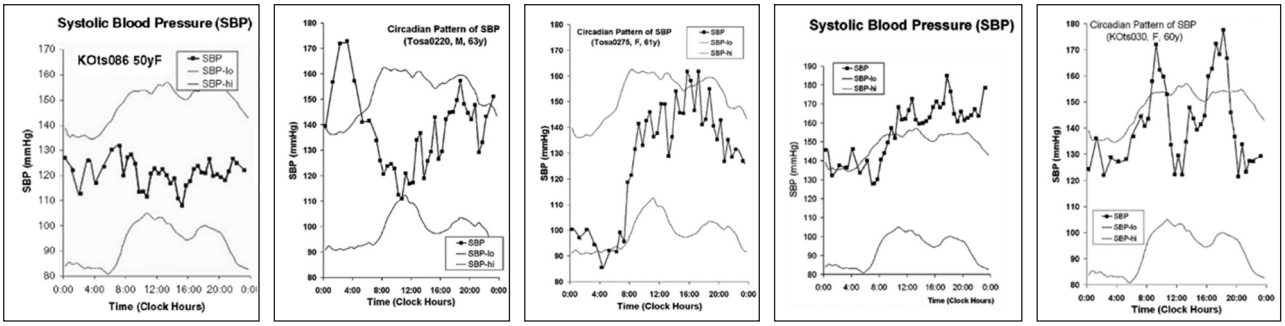

Figure 9. *The circadian profile of SBP can differ markedly among patients, suggesting that the optimal time of anti-hypertensive treatment may also differ greatly from one patient to another.*
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Rather than asking the question whether evening dosing is better than morning dosing, future clinical trials could ask a more pertinent question while also leading the way toward personalized chronotherapy. One approach could consist of using N-of-6 or N-of-1 designs [57, 58] to first determine the best treatment time for individual patients, then enter patients on that regimen to be compared with matched controls treated conventionally. Another approach could be to monitor BP around the clock for several (e.g., 7) days by ABPM, to analyze the data by cosinor, and to interpret the circadian parameters in the light of chronobiologic reference values from clinically healthy peers matched by gender and age. Based on the results thus obtained, the time when medication needs to be the most effective could be estimated and treatment timing (dosing) could be determined by accounting for the pharmacokinetics of the drug(s) used. Each patient could enter the clinical trial on the regimen that was individually optimized for comparison with a matched control to be treated conventionally. The personalized optimization of treatment timing could account for all VVDs. The 7-day/24-hour ABPM could be repeated at intervals during follow-up when outcomes are recorded prospectively. Results from such clinical trials would answer the question whether a personalized chronotherapeutic approach is superior to treatment as usual.

Discussion and Conclusion

Many factors affect BP [59]. It is not surprising then that circadian characteristics of BP fluctuate greatly from one day to another [12]. These reasons underlie the recommendation to

monitor BP around the clock for longer than 24 hours [10]. Activity [60], sleep [61], age [44, 62], and medications [63] all reportedly affect the DNR, and are likely to contribute to its poor reproducibility [64, 65]. As shown herein, a different daily routine associated with a phase shift of the circadian BP rhythm, or a more pronounced post-prandial dip in BP can drastically change the DNR and the dipping category when the 24-hour amplitude of BP remains the same. Reproducibility of a diagnosis in terms of VVDs is much higher [66] when a chronobiologic approach is used to interpret cosinor-derived parameters in the light of reference values from clinically healthy peers matched by gender and age.

The limitations of the DNR or NDR need to be better understood. The merits of assessing the circadian BP rhythm in terms of its amplitude and phase should be recognized, and means should be provided for their easy determination by clinicians. The limitations of current clinical trials comparing morning versus evening dosing to draw across-the-board recommendations for treatment timing need to be better understood. Clinical trials should be implemented that aim at personalized chronotherapy by accounting for the fact that different patients present with different circadian BP patterns in the absence of treatment (chronodiagnosis).

Monitoring the circadian variation in BP for spans longer than 24 hours is critical to address the issue of the large day-to-day variability in all parameters of the 24-hour BP rhythm. Estimates of the 24-hour amplitude and phase of BP are more robust than the computation of the DNR or NDR. The interpretation of the 24-hour amplitude and phase in the light of chronobiologic reference values from clinically healthy peers matched by gender and age renders a diagnosis in terms of VVDs more reliable (more reproducible) than a diagnosis in terms of dipping based on the DNR or NDR. Determining whether personalized chronotherapy that accounts for the chronodiagnosis is superior to conventional treatment should be the question investigated in future clinical trials instead of the misguided question whether morning or evening dosing is better, since the best treatment time cannot be the same for a patient with CHAT and for patient who is a reverse dipper.

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Application of Mathematica Toolkit to Data from Residents in the Arctic

A. Chase Turner[1], Denis Gubin[2], Larry Beaty[1], Germaine Cornelissen[1]

[1]Halberg Chronobiology Center, University of Minnesota, Minneapolis, MN, USA
[2]Laboratory for Chronobiology and Chronomedicine, Research Institute of Biomedicine and Biomedical Technologies, Medical University, Tyumen, Russia

Correspondence:

Halberg Chronobiology Center
University of Minnesota,
420 Delaware St. S.E. - MMC8609
Minneapolis, MN 55455, USA
E-mail: turn0383@umn.edu
corne001@umn.edu
Website: https://halbergchronobiologycenter.umn.edu/halberg-chronobiology-center

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Introduction

The natural photoperiodic environment is a major synchronizer of circadian rhythms [1]. At higher latitudes, it varies drastically across seasons, thereby affecting health and well-being [2]. Working in the Arctic at latitudes above the Polar circle entails month-long sojourns in the Arctic alternating with month-long stays at home in cities located within one time zone of the workplace in Yamburg [3]. For a better understanding of how photoperiodic conditions in the Arctic influence the rhythmic architecture of physiologic processes, another approach can be used, namely examining circadian rhythms of residents who have lived in this region for at least 5 years. As part of a larger investigation, this study addresses a specific methodological question concerning the modelling of circadian rhythms of physiological variables and of the residents' exposure to ambient and blue light to which the circadian system is particularly sensitive [4].

The single cosinor method [5-9] is usually well suited to model the circadian variation in physiological variables. While the 24-hour component usually accounts for the largest

proportion of the variability in the data, harmonic terms determine the shape of circadian rhythms, which can deviate markedly from a sinusoid. The question herein is whether a single 24-hour model is sufficient to describe the variables monitored in Arctic residents during the summer, or whether a multiple-component model is needed to describe the circadian variation in these variables. Cosinor methods developed in Mathematica that aim at answering this question are illustrated herein.

Subjects and Methods

The study adhered to the tenets of the Declaration of Helsinki and was approved by the Ethics Committee of Tyumen State Medical University (Protocol No. 101, September 13, 2021). Written informed consent was obtained from all participants.

The study was carried out in the nearby locations of Salekhard (66°53′ N, 66°60′ E), Aksarka settlement (66°33′ N, 67°48′ E -- during March 22-April 8, 2022), and Urengoy town (65°58′ N, 76°63′ E). It involved 32 residents, in two cohorts, one monitored from June 18 to 24, 2022, and the other from June 18 to 24, 2023, near the summer solstice. Daylight hours were 2:55 am to 9:45 pm (local), and twilight from 9:45 pm to 2:54 am.

Each resident provided 7-day actigraphy records collected by ActTrust 2 wearable devices that measured light exposure in different spectral domains in addition to skin temperature and activity at 1-minute intervals. Analyses herein focus on ambient light and blue light as well as on skin temperature and the zero-crossing mode (ZCM) of activity.

Analyses and graphic illustrations of the results were produced with Mathematica 13.2 running on an Apple macOS 14.0 host with 32 GB of RAM. Other supported Mathematica configurations are documented on the software publisher's website [10].

The following analyses were carried out in Mathematica.

1. Chronograms [11], plots of the data as a function of time, are prepared for one of the study participants as an illustration of some of the graphics generated in Mathematica.

2. Least Squares Spectral Analysis (LSSA), a cosinor-based technique that yields the same results as a Discrete Fourier Transform (DFT) when data are equidistant with no missing value [12], was first applied to all records. LSSA consists of separately fitting (by least squares) cosine curves with frequencies in the range of 1/T (where T is the record length) to 1/2Δt (where Δt is the sampling interval). In the presence of missing data or when data are not equidistant, provided the data are uniformly distributed, the LSSA still provides approximate results in the frequency range from 1/T to 1/2Δt, where Δt is less well defined and lies between the average and the longest sampling interval. In a LSSA, trial frequencies

are incremented by 1/T. Even though records spanned about a week, since the question concerned the circadian variation more specifically, a partial LSSA was performed, as a fundamental period of 24 hours instead of 7 days was considered and only the first 48 harmonic terms (shortest trial period of 0.5 hour) were computed. The LSSA was thus computed at trial periods of 24h, 24h/2=12h, 24h/3=8h, …, 24h/48=0.5h. Spectral lines with large amplitudes indicate the presence of rhythmic components, which can be validated statistically by the zero-amplitude (no-rhythm) test after adjustment for multiple testing. Herein, they are also considered as input to the next analytical step.

3. For each variable, at each trial period, the arithmetic mean and standard error of amplitudes across all 32 participants were calculated and plotted. Individual LSSA results were compared to the population average, using a logarithmic scale on the vertical axis.

4. The population-mean cosinor, which summarizes results from the single cosinor across all individuals that are randomly selected from a homogeneous population, was applied across all 32 participants for each variable at each trial period of the LSSA. In this approach, instead of computing the arithmetic mean of amplitudes, the average vectorial mean of (amplitude, acrophase) pairs is calculated. In other words, amplitudes are phase-weighted. A component is detected as being statistically significant when individuals in the population have similar phases as well as similar amplitudes. As long as participants are a random sample of a homogeneous population, results from the population-mean cosinor can be extended to the whole population they represent.

5. Based on results from the population-mean least squares spectra, components contributing a sizable amount to the overall variance were selected to model the circadian rhythm of each variable. Several models were considered in order to answer the original question whether a single 24-hour cosine curve fitted to a given variable was sufficient to depict its circadian rhythm.

Results

Data were received as a compressed file, the contents of which were unpacked into 32 individual files, each with 21 columns of measured variables. A Mathematica-based import function was written to import and process the contents of each file to produce 32 individual multiple-variable records from which the four variables of interest were extracted together with their associated date and time stamps. As an example, Figure 1 illustrates the chronogram of all 4 variables from one of the study participants (A002), shown as a ListLogPlot, where a logarithmic scale is used on the vertical axis.

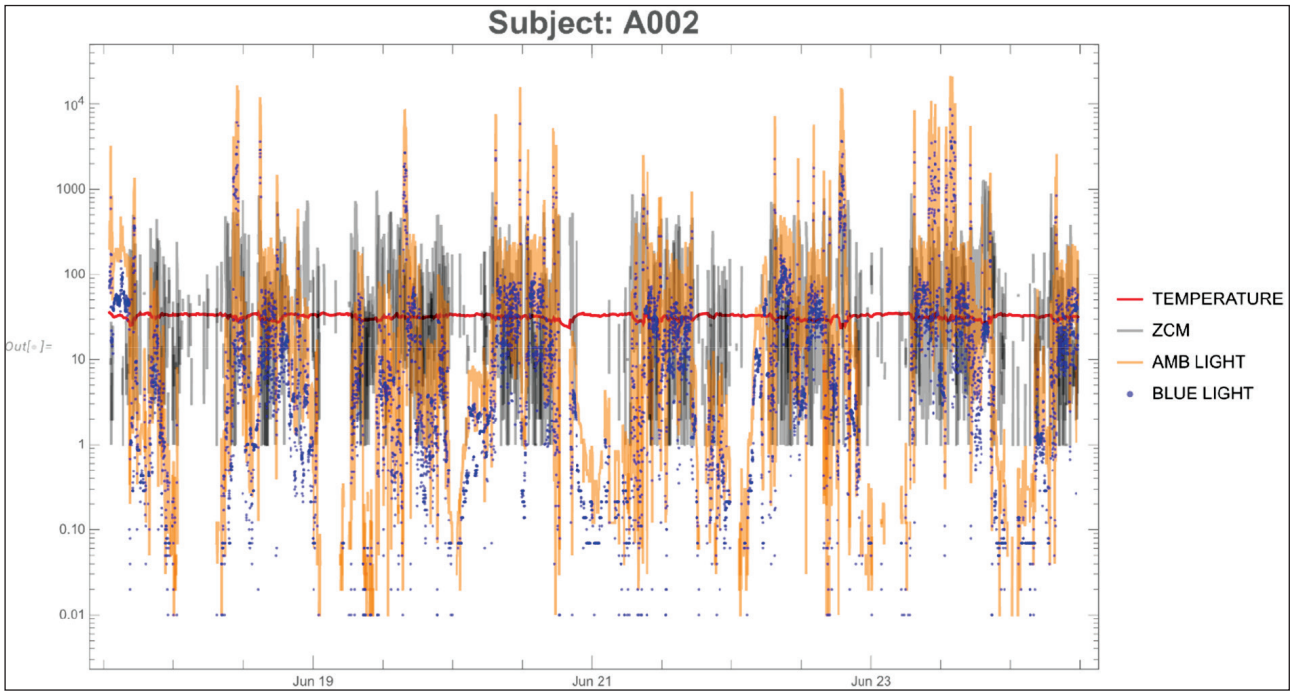

Figure 1. *Chronogram of all four variables investigated for participant A002, shown as an example of a ListLogPlot in Mathematica (vertical scale is logarithmic).*

As an example, Figure 2 shows the LSSA of activity (ZCM) for the same participant (A002), displayed as a ListLogPlot and overlaid with the phase-unweighted average LSSA across all participants (gray line).

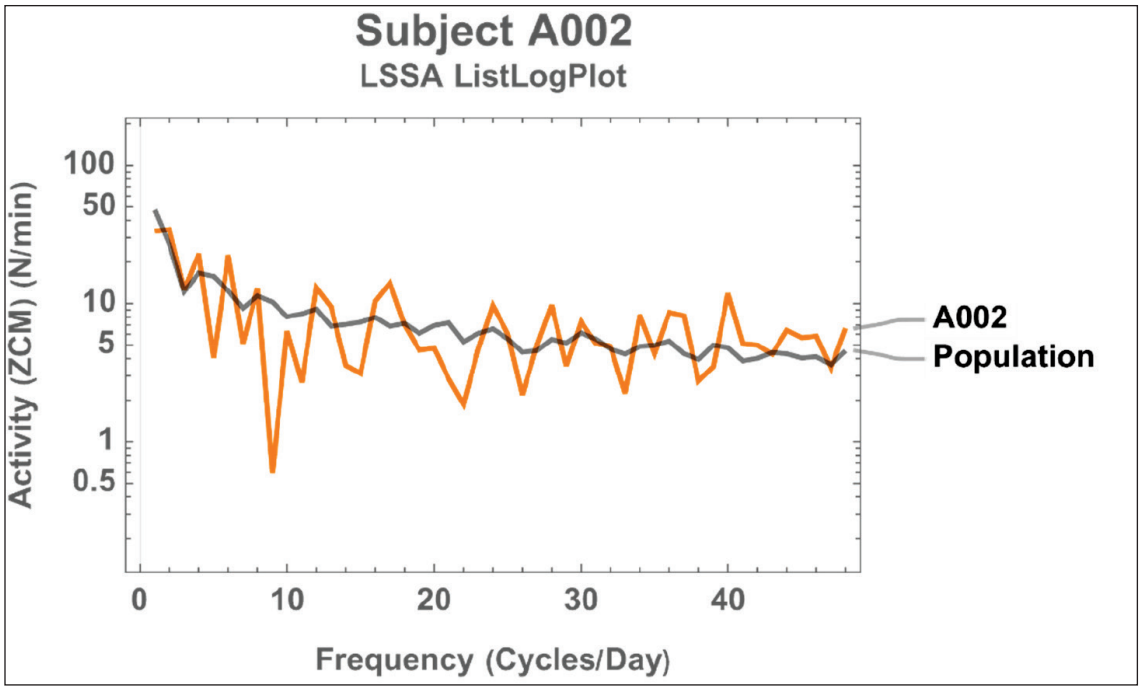

Figure 2. *LSSA of activity for A002 shown as a ListLogPlot (logarithmic vertical axis) compared to the phase-unweighted average spectrum for the whole population (gray line).*

In order to apply the population-mean cosinor to the LSSA results, a common time reference (t_R) was needed. It was set to midnight (00:00) on Wednesday, June 15, 2022 before running the individual LSSA analyses. In addition to obtaining parameter estimates and a measure of their uncertainty as standard error (SE) and 95% confidence limits, results are also shown in a polar plot. In such plots, the 360° circle is equated to the length of the trial period (τ) being considered, and 0° shown on top represents t_R. The average vector, which originates from the center of the plot is a directed line that has a length and angle corresponding to the vectorial average of individual (A, ϕ) pairs, where A is the amplitude and ϕ is the acrophase in the cosinor model

$$Y(t) = M + A\cos(2\pi(t-t_R)/\tau + \phi) + e(t).$$

The 95% confidence region of the average (A, ϕ) vector is an ellipse around the tip of the vector. Statistical significance is determined by the non-overlap of the origin (center of the plot) by the error ellipse. In Mathematica, results from the population-mean cosinor spectra include error ellipses in relation to the origin, thereby providing an immediate visual determination of components characterizing the time structure of the variable investigated.

Figure 3 displays results for the first few components from the phase-weighted least squares spectra obtained by population-mean cosinor. Since the fundamental period was 24 hours, the first few components are expected to account for most of the variance in the data. On the left are the first four harmonic terms of the circadian rhythm of activity (ZCM), with periods of 24, 12, 8, and 6 hours. Error ellipses do not cover the origin (black dot) in the case of the 24-, 12-, and 6-hour components, indicating that they all contribute to the waveform of the circadian rhythm of activity. The 8-hour harmonic, however, is not statistically significant since the error ellipse covers the origin. The fact that the error ellipse for the 24-hour component points toward the lower left indicates that, on average, activity is highest in the afternoon (sometime between noon and 6 pm). On the right, results for the 12-hour component are shown for all four variables examined. It can be readily seen from the error ellipses that this component contributes significantly to the waveform of the circadian rhythm of skin temperature and activity but not to that of ambient or blue light.

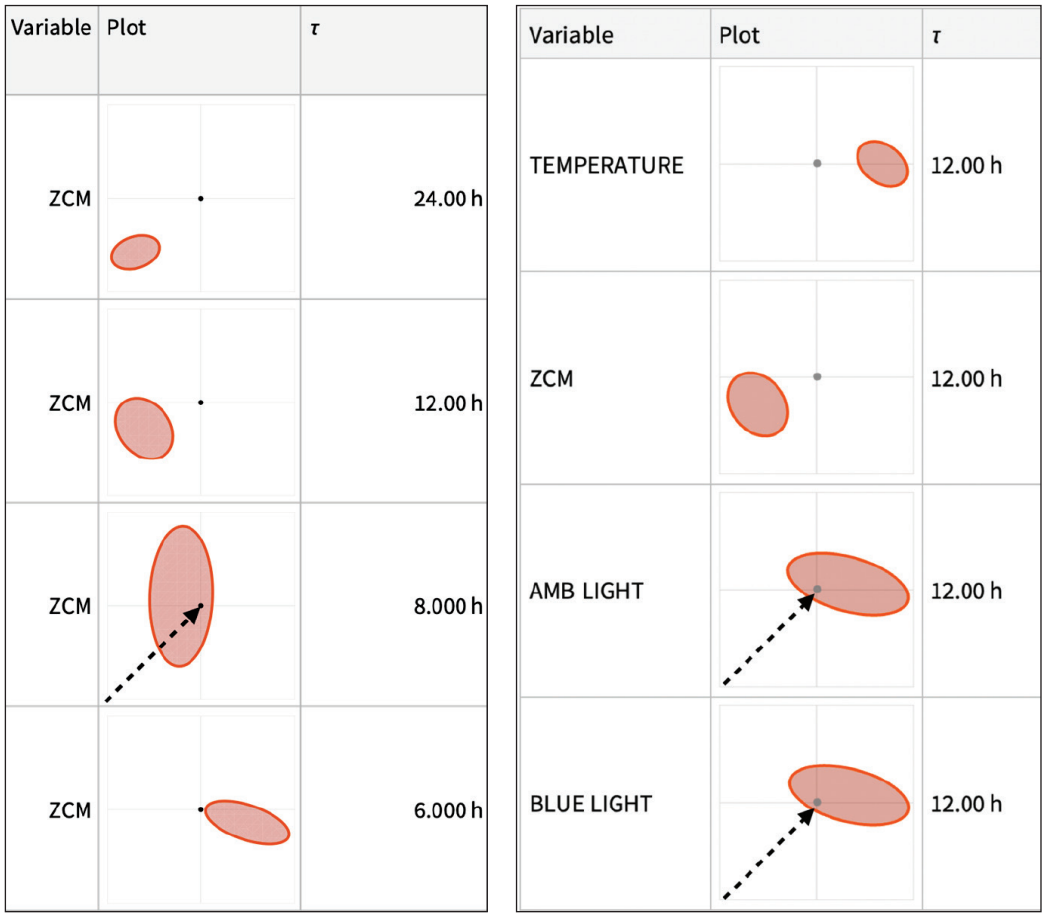

Figure 3. *Polar display of results for the first few components from the phase-weighted LSSA obtained by population-mean cosinor. Left: Results of first four harmonic terms of activity (ZCM). Right: Results of 12-hour component for all four variables. Dashed arrowhead lines indicate components that are not statistically significant (for which the 95% confidence ellipse includes the origin).*

Based on results from the phase-unweighted and phase-weighted average least squares spectra, models were derived for the four variables examined herein. As reference, single 24-hour cosine models were generated, using the parameter estimates from the population-mean cosinor spectra. To answer the original question, the second harmonic with a period of 12 hours was added to the model, since this component usually contributes most of the residual variance for these variables. Since some other harmonic terms also reached statistical significance and contributed fairly to the overall variance in the data, additional models were generated that accounted for their contribution.

Results are illustrated for all four variables in Figure 4. In each case, the single 24-hour cosine model and the composite model consisting of cosine curves with periods of 24 and 12 hours are shown. Models incorporating some additional harmonic terms are also included. A single 24-hour cosine component may be sufficient to describe the circadian rhythm of exposure to ambient light and to blue light. This is not the case, however, for activity or skin temperature. For instance, activity is higher in the evening than the morning and values during

the night are lower when a 2-component model is considered instead of the single 24-hour cosine curve. Likewise, skin temperature assumes higher night-time values and daytime values remain more similar when considering a 2-component model instead of the single 24-hour cosine curve.

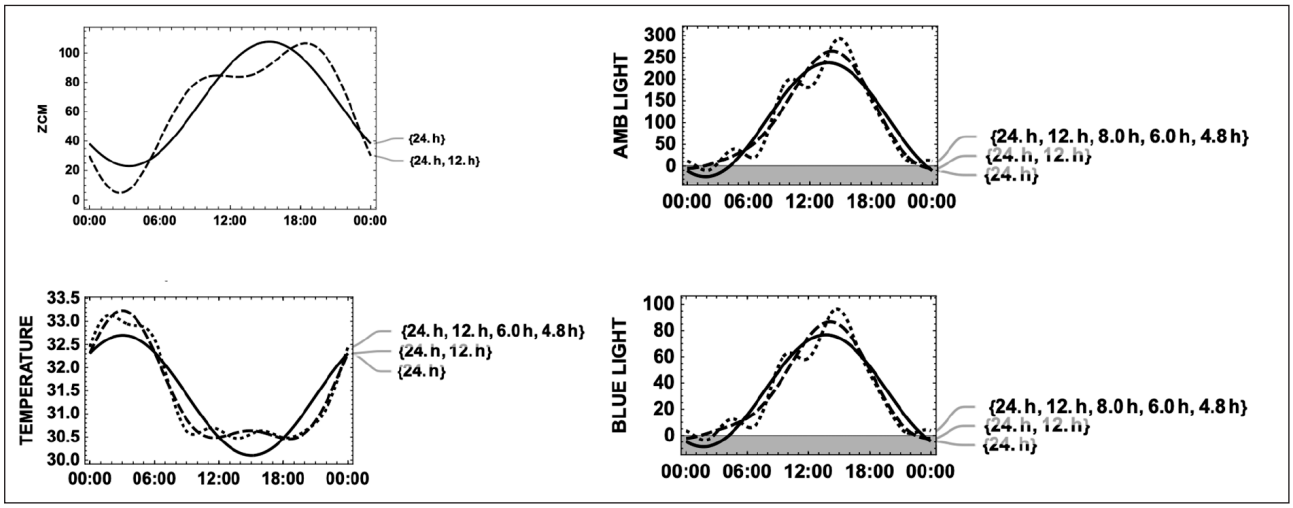

Figure 4. *Single 24-hour and multiple-component models approximating the circadian variation of activity (ZCM) (upper left), skin temperature (lower left), ambient and blue light (upper and lower right).*

Discussion and Conclusion

Analyses herein of variables automatically measured by a wearable device during the summer solstice by individuals living in the far north region of Siberia, above the Arctic Circle illustrate the ease with which results can be obtained in Mathematica.

For example, Mathematica's 30 years support of hybrid symbolic-number methodologies and multi-paradigm languages allows for coding using both TraditionalForm and InputForm interchangeably to maximize awareness of the code, as illustrated in Table 1.

	TraditionalForm	InputForm
Variance	$\frac{1}{k-1}\sum_{i=1}^{k}(s_i-\bar{s})^2$	Variance[s]
Standard Deviation	$\sqrt{\sigma^2_s}$	StandardDeviation[s]
Covariance	$\frac{1}{k-1}\sum_{i=1}^{k}(s_i-\bar{s})\left(t_i-\bar{t}\right)$	Covariance[s, t]

Table 1. *Mathematica code examples for well-known statistical functions.*

Results in Figure 4 also highlight some methodological issues that remain to be addressed. For instance, models generated for exposure to ambient and blue light assume negative values

during part of the 24-hour day. Such a result could be interpreted as having no such exposure, but negative values are nonsensical. Data should have been pre-processed, for instance by log-transformation or by square-root transformation prior to analysis, since the assumption of normality of the data is not validated in this case.

Models were determined based on results from the population-mean least squares spectra. A multiple-component model could have been fitted to the individual records before proceeding to the population-mean cosinor analyses. Results herein would not differ very much, however, since most records covered exactly 7 days and there were practically no missing data.

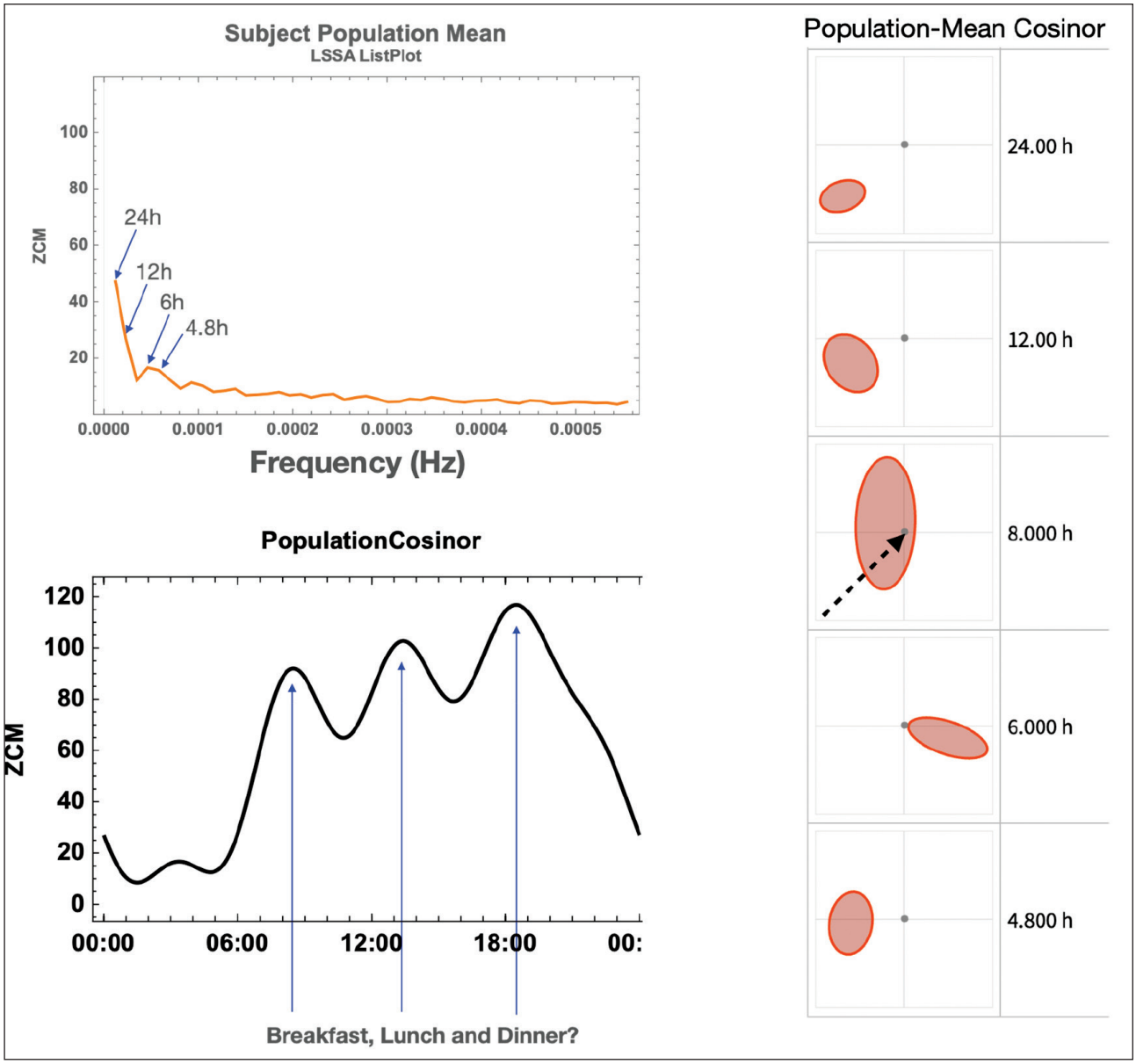

Figure 5. *The three peaks, perhaps related to the timing of breakfast, lunch and dinner, are accounted for by the addition to the model of harmonic terms with periods of 6 and 4.8 hours (they are not present when a 2-component model including cosine curves with periods of 24 and 12 hours is considered, as shown in Figure 4, top left).*

Of interest is the 4-component model approximating the circadian waveform of activity (ZCM), shown in Figure 5. It includes cosine curves with periods of 24, 12, 6 and 4.8 hours, all detected with statistical significance, and omitting the non-significant 8-hour harmonic (Figure 5, top left and right). The addition of the 6- and 4.8-hour harmonics to the model brings about three daytime peaks that perhaps correspond to breakfast, lunch, and dinner (Figure 5, bottom left) since these residents follow a similar daily routine.

The HCC is creating a Mathematica-based open-source toolkit for Chronobiologists. Utilizing cosinor methods developed in Mathematica will facilitate data analysis to assess their broad time structure, to compare rhythm parameters among individuals or populations, and to model rhythms as illustrated herein for the Arctic residents.

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Prof. MUDr. Bohumil Fišer, CSc. (October 22. 1943 – March 21. 2011)

Marie Nováková

Dept. of Physiology, Faculty of Medicine, Masaryk University

It is hard to believe that prof. Fišer left our community already 12 years ago. His decease at still productive age was unexpected by all his colleagues, students, friends. We knew he was seriously ill, however could not believe that it was true. These days we commemorate birthday anniversary of prof. Fišer. This short remembrance is dedicated to his personality rather than his scientific and political achievements.

Prof. Fišer is remembered among those who were lucky to meet him and to work with him first of all as a great teacher. His lectures represented scientifically-oriented information transfer accompanied by entertaining his students. He was for instance willing to demonstrate symptoms of various disorders, thus showing his students clearly the importance of the subject lectured. Many medical students remember his lectures at Physiology as the most interesting ones among the preclinical subjects.

Prof. Fišer naturally affected also numerous doctoral students passing the Department of Physiology, regardless it was during the years when he served as a head of the department or not. I remember him suggesting some improvements of my experimental set-up, although he was neither my supervisor nor the direct collaborator. He was always willing to give advice, to support, to help.

Bohumil Fišer was each time able to find the proper way how to talk to particular person, he knew almost immediately what kind of communication will work best, he managed to solve various problems. He showed clear social awareness, which later transformed into his engagement in political issues.

The personality of prof. Fišer was extraordinary. I personally very often come across a situation or problem which he mentioned many years ago and predicted what would happen. Not only me, but all my colleagues at the Department of Physiology miss prof. Fišer with his humour and unobtrusive support.

80 Years Anniversary of Prof. MUDr. Bohumil Fišer, CSc. (October 22. 1943 – March 21. 2011)

Jarmila Siegelová

Department of Physiotherapy and Rehabilitation, Faculty of Medicine, Masaryk University, St. Anne´s University Hospital in Brno, CZ

Figure 1: *Prof. Bohumil Fišer*

Prof. Bohumil Fišer was Head of the Department of Physiology, Faculty of Medicine, Masaryk University, Brno in the years 1995-2008, Minister of Health of the Czech Republic in 2000-2002, Member of Executive Committee of WHO in 2003-2008. He was a highly regarded scientist of worldwide renown in the field of normal and pathological physiology and

a successful organizer in health service, as it was described in the publications by Professor Franz Halberg et al. in World Heart Journal in 2011.

Scientific achievements of Professor Bohumil Fišer CSc. are still fresh in our memory and continue to inspire all who were fortunate to know him. I started working with him in Physiological Institute of Masaryk (at that time Purkynje) University in Brno in 1965. The head of the Institute, Prof. MUDr. Vladislav Kruta, DrSc. signed the Proclamation of 200 words in the year 1968, because of this I was obliged to leave the Institute of Physiology and also Prof. Fišer could not reach higher pedagogical qualification.

After the revolution in 1989 we started a very closed cooperation and also the common international activities with Prof. Dr. Franz Halberg, Dr.h.c. multi, Prof. Germaine Cornelissen, Halberg Chronobiology Center, University of Minnesota, USA, Prof. Dr. Thomas Kenner, Dr.h.c multi, Dean of Faculty of Medicine and Rector of University in Graz, Austria, and Prof. Dr. Jean Paul Martineaud, University of Paris, Hopital Lariboisier, France.

In Brno we started scientific presentations together with the international universities mentioned above and organized in Masaryk University international workshops, meetings and congresses. They presented the results in the fields of cardiology, physiology, pathology, chronobiology, neurology, rehabilitation, internal medicine and neurology which were published as full papers in Brno, as Noninvasive Methods in Cardiology (https://www.med.muni.cz/noninvasive-methods-in-cardiology).

The editors of Noninvasive Methods in Cardiology were Prof. F. Halberg, Prof. T. Kenner, Prof. B. Fišer, Prof. J. Siegelová, later prof. Cornelissen, and Prof. Dobsak. In the year 2003 the Congress of "Noninvasive Methods of Cardiology" was dedicated to the 60 years of Prof. B. Fišer anniversary. The lectures presented at the occasion of the Congress in 2003 were published all in Noninvasive Methods in Cardiology 2003. The Congress in 2003 was organized by Prof. MUDr. Jarmila Siegelová, DrSc.

The Congress in 2003 took place under the auspices of Prof. RNDr. Jiri Zlatuska, CSc., Rector of Masaryk University Brno, Prof. MUDr. Jan Zaloudik, CSc., Dean of Faculty of Medicine Masaryk University Brno, Prof. MUDr. Helena Illnerova, DrSc., President of the Academy of Sciences of the Czech Republic, Prof. MUDr. Jaroslav Blahos, DrSc., President of the Czech Medical Society and World Medical Association, Mgr. Karla Pochyla, Director of National Centre of Nursing and Other Health Professions.

The scientific lectures were presented by Prof. Dr. Franz Halberg, University of Minnesota, USA, Prof. Dr. Germaine Cornelissen, University of Minnesota, USA, Prof. Dr. Thomas Kenner, M.D., Rector of University of Graz, Austria, Prof. Dr. Falko Skrabal, University of Graz, Austria, Prof. Dr. Falko Skrabal, Dr. H. Mayer, Dr. J. Lindenmann, University of Graz,

Austria, Prof. Dr. Jean Paul Martineaud, University of Paris, France, from Masaryk University, Czech Republic Prof. MUDr. Jarmila Siegelová, DrSc., Prof. MUDr. Borivoj Semrad, CSc., Prof. MUDr. Natasa Honzikova, CSc., Prof. MUDr. Miloslav Kukleta, CSc., Prof. MUDr. Zdenek Kadanka, CSc., Prof. MUDr. Hana Hrstkova, CSc., Prof. MUDr. Petr Dobsak, CSc. and participants from abroad Dr. Itsuro Saito, Kyorin university, Tokio, Japan, Prof. Dr. Takashi Isoyama, Kyorin university, Tokio, Japan, Dr. Othild Schwartzkoppf, University Minnesota, USA, Prof. Dr. Franz Halberg, University of Minnesota, USA, Prof. Dr. Helena Rasková, DrSc., UK, Praha, Czech Republic.

The extensive bibliography of Prof. B. Fišer illustrates the active scientific career of Professor Fišer. The innovations he made in the field brought him to the Head the Department of Physiology Masaryk University and the Czech Republic also could not have chosen a better person to serve as Minister of Health. The responsibilities of Professor Fišer have been expanded even further when he served on the Executive Board of the World Health Organization.

We will continue the work of Professor Bohumil Fišer in medicine together with Professor Germaine Cornelissen, PhD, Director of Halberg Chronobiology Center, Professor of Integrative Biology and Physiology, University of Minnesota, USA and her scientific international team, with Professor Masairo Kohzuki, University Graduate School of Medicine, Japan, Assoc. Prof. PD Dr. med. Nandu Goswami, Dept. of Physiology, Medical University of Graz, Austria, the staff of Dept. of Physiology Masaryk University Professor Marie Novakova, Professor Petr Babula, Dr. Zuzana Novakova, and with the members from Department of Physiotherapy and Rehabilitation, members from Department of Sports Medicine and Rehabilitation, Masaryk University Professor Jarmila Siegelová, Professor Petr Dobsak and his team, Assoc. Professor Michal Pohanka, Dr. Jiri Dusek and others.

Figure 2: *Prof. Franz Halberg, M.D., Dr. h. c. multi and prof. MUDr. Bohumil Fišer, CSc. in Brno at the symposium Noninvasive Methods in Cardiology 2003*

Figure 3: *Professor Halberg, Dr. Souček, Professor Siegelová, B. Kenner, Professor Kenner, Professor Fišer in Brno congress*

Figure 4: *Prof. Fišer, Prof. Siegelová and Prof. Jean Paul Martineaud, M.D., Paris, France (cooperation from 1976 to 2010) in Dept. of Physiology Brno.*

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The History of the Teaching Bachelor and Magister in Physiotherapy in the Faculty of Medicine Masaryk University

Siegelová Jarmila, Dunklerová Leona, Pohanka Michal

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

At the beginning of the 90th in the Czech Republic started the teaching of the profession of non-medical professional workers in the health services in the universities and this trend started also in Masaryk University.

Prof. MUDr. Zdeněk Placheta, DrSc. as the Head of the Department of Functional Diagnostics and Sport medicine (1988 – 1996) at that time, which provided health service, education of medical students and science, was asked by a group of experts in rehabilitation and physical medicine MUDr. J. Svobodová, MUDr. B. Müllerová, doc. MUDr. I. Müller, CSc., MUDr. E. Drápelová, MUDr. J. Roubalová, MUDr. F. Trkan and physiotherapist J. Burianová, at that time president of UNIFY, to start the teaching of the bachelor's program in physiotherapy at the Faculty of Medicine, Masaryk University. With the support of the Dean of Faculty of Medicine at that time, prof. MUDr. J. Bilder, CSc. The teaching of the bachelor's program was started under the Dept. of Functional Diagnostics and Sport medicine in the school year 1994/1995.

In the year 1996 Prof. MUDr. Jarmila Siegelová, DrSc started to work as a Head of the Department of Functional Investigation and Sport Medicine and to educate the students in physiotherapy. In the year 1997, with the support of the rector Prof. Dr.Jiří Zlatuska, CSc, of Masaryk University, director of Teaching Hospital of St. Anna in Brno MUDr. A. Štětková CSc and Dean of Faculty of Medicine Masaryk University Prof. MUDr. J. Vorlíček, CSc., the health service of rehabilitation with 32 beds and ambulatory out patients was added to the Dept. of Functional Diagnostics and Sport Medicine and the name was changed to Department of Functional Investigation and Rehabilitation. The staff of the Dept. of Functional Diagnostics and Rehabilitation consisted at that time of 150 doctors of medicine, physiotherapists and nurses. In 2007 at the age of 65 years (as usual) Prof. MUDr. Jarmila Siegelová, DrSc finished as a Head of this Department and was replaced by professor MUDr. P. Dobšák, CSc who was a member of her staff of the Department from 1997. Prof. MUDr. Jarmila Siegelová, DrSc continued the work in the Department of Physiotherapy and Rehabilitation in the Medical Faculty of FNUSA.

From 2010 the department was named Dept. of Sport Medicine under professor Dobšák as its Head. Prof. Siegelová continued to work as the professor until 2022, when she was nominated professor emeritus of Masaryk University.

The Dept. of Functional Diagnostics and Rehabilitation, later Dept. of Sport Medicine and Rehabilitation provides the teaching of medical students in in the subject of internal medicine and the teaching program of different topics of bachelor studies in physiotherapy.

The first students in bachelor studies finished for the first time in 1998 and two-year master studies in physiotherapy were started; the first complete masters of physiotherapy finished in the year 2000.

In the year 2005 the Faculty of Medicine decided to form a separate Department of Physiotherapy and Rehabilitation only for the teaching of the program of physiotherapy. I was the Head of this Department until 2012.

Mgr. Leona Dunklerova has been in charge of the teaching the Bc. and Mgr. of physiotherapy, administration and accreditations of the program in physiotherapy and organizing the theoretical and practical education since the year 1998 until now.

In order to innovate and improve the teaching process in the bachelor and master study of physiotherapy it was necessary to renew the teaching. Prof. MUDr. Jarmila Siegelová, DrSc. directed the Operational Program "Modifying a system of education in the field of physiotherapy, in the topic of Education for Competitiveness, funded from European sources, from 2012 to 2014. The project has been successfully completed.

In order to increase the education of the teaching staff of the Dept. of Functional Diagnostics and Rehabilitation, now the Sports Medicine and Rehabilitation, and the Dept. of Physiotherapy and Rehabilitation, it was necessary to increase their qualifications by postgraduate study. Prof. Siegelová successfully as a supervisor completed 17 doctoral students and Prof. Dobšák as a supervisor successfully completed 7 doctoral students.

According to the law of university school studies in the Czech Republic both forms of study, bachelor's and master's, must end with the defense of the bachelor's and master's theses. Supervisors of Bc. theses and Mgr. diploma theses are both doctors and masters of physiotherapy. For carrying out of physiotherapy diploma theses, it is an indisputable benefit if the supervisors have a scientific degree CSc. or Ph.D. or have a higher scientific in pedagogical rank (associate professor, professor. In the Dept. of Functional Diagnostics and Rehabilitation - Dept. of Sport Medicine and Rehabilitation there were two members of staff, who accomplished titles assoc. prof. and one professor.

The Department of Physiotherapy and Rehabilitation in cooperation with Dept. of Sports Medicine and Rehabilitation organized every year international and national congresses, meetings and workshops, attended by leading foreign academic experts, as well as specialists from the field of rehabilitation and physiotherapy from abroad and the entire Czech Republic.

The scientific cooperation takes place namely with the following departments: Halberg Chronobiology Center, Minneapolis, USA, Department of Internal Medicine & RHB Science,

Tohoku University, Sendai, Japan, Physiologisches Institut, Karl-Franzens-Universität, Graz, Austria, Centre de Cardiologie, Université de Bourgogne, Dijon, France, Department of Internal Medicine, Tōho University, Japan, Institute of Development, Aging and Cancer, Tohoku University, Sendai, Japan.

In the Czech program of Bc. program 724 students completed their studies and these students wrote 724 Czech Bc. theses, which are presented in the archive of Information System Masaryk University. The bachelor thesis includes a case study with practical work from the Bc. Physiotherapist.

A total of 433 physiotherapy students completed their master's studies, which means 433 diploma theses. The diploma theses of our students of physiotherapy contain pilot studies on the therapeutic effects of physiotherapy in various medical fields, for example in internal medicine, surgery, traumatology, neurology, pediatrics, etc. In these works they also use statistical evaluation of the achieved results.

For these works, it is very important that the supervisors obtained a scientific qualification of at least Ph.D.

Dean of the Faculty of Medicine, MU Prof. MUDr. J. Mayer, CSc. commissioned in 2013 Prof. MUDr. P. Dobšák, CSc., Head of the Department of Physiotherapy and Rehabilitation of the Faculty of Medicine of the MU by accreditation and implementation of the bachelor's degree in physiotherapy in English. Prof. MUDr. P. Dobšák, CSc. together with Prof. MUDr. J. Siegelová, DrSc., Mgr. L. Dunklerová and other members of the Dept. of Physiotherapy and Rehabilitation, in cooperation with the Dept. of Sport Medicine and Rehabilitation successfully started this english course in 2014. The first graduates completed their studies in 2017 and also wrote bachelor theses with case studies in English, which are listed in the MU Information System and are cited in this thesis. The Dean of Faculty of Medicine, Masaryk University Prof. MUDr. Martin Repko, CSc decided to finish the program of teaching the Bc. Physiotherapy in English and the lat students fish the bachelor studies.

We completed the last year of the Bachelor of Physiotherapy in English in 2023. In references we have summarized the Bc. thesis, written in English, done by our students in the years 2017 to 2023.

On the pictures there are our students on the last day of our state exams together with the members of the State Examination Commission in all these years.

This year Professor Dobšák will complete the age of 65 years and will leave the position of Head of the Dept. of Sports Medicine and Rehabilitation in Faculty of Medicine, Masaryk University, St. Anna Teaching Hospital and his successor will be Assoc. MUDr. M. Pohanka, Ph.D.

Figure 1: *State final exams of the Bachelor of Physiotherapy program in English in 2017, committee members: Prof. MUDr. Petr Dobšák, CSc., Prof. MUDr. Jarmila Siegelová, DrSc., MUDr. Eva Drápelová, Doc. MUDr. Ivan Müller, CSc.*
graduates: Eli Odnopozov, Tessa Lynn Bell

Figure 2: *State final exams of the Bachelor of Physiotherapy program in English in 2018, committee members: Prof. MUDr. Jarmila Siegelová, DrSc., Prof. MUDr. Petr Dobšák, CSc., Doc. MUDr. Michal Pohanka, Ph.D., MUDr. Eva Drápelová, Doc. MUDr. Ivan Müller, CSc.*
graduates: Josh Tilrem, Roy Even Omlid

Figure 3: *State final exams of the Bachelor of Physiotherapy program in English in 2019, committee members: Prof. MUDr. Jarmila Siegelová, DrSc., Prof. MUDr. Petr Dobšák, CSc., MUDr. Eva Drápelová, MUDr. Vítězslav Ruber, Ph.D.*
graduates: Lilly Warhanek, Jan Ondruš

Figure 4: *State final exams of the Bachelor of Physiotherapy program in English in 2020, committee members: Doc. MUDr. Michal Pohanka, Ph.D., Mgr. Alena Sedláková, Prof. MUDr. Jarmila Siegelová, DrSc., Prof. MUDr. Petr Dobšák, CSc., Mgr. Veronika Mrkvicová, Ph.D.*
graduates: Irene Solomou, Louis Amin Lotfalla Mamdouh, Liron Neuman, Akoma Anomu Omamuli

Figure 5: *State final exams of the Bachelor of Physiotherapy program in English in 2021, committee members: MUDr. Eva Drápelová, Prof. MUDr. Petr Dobšák, CSc., Prof. MUDr. Jarmila Siegelová, DrSc., Doc. MUDr. Michal Pohanka, Ph.D.*
graduates: Marios Giannakou, Shuai Jiaqi, Ada Jacqueline Zubercova

Figure 6: *State final exams of the Bachelor of Physiotherapy program in English in 2022, committee members: MUDr. Eva Drápelová, Prof. MUDr. Petr Dobšák, CSc., Prof. MUDr. Jarmila Siegelová, DrSc., Mgr. Simona Šrubařová, Ph.D.*

Figure 7: *State final exams of the Bachelor of Physiotherapy program in English in 2022, graduates: Rana Mohammed a Ismail, Virginia Braggio, Alireza Sadeghi, Yevgen Okshyn, Ghaida Alqurayshah, Sergey Golikov*

Figure 8: *State final exams of the Bachelor of Physiotherapy program in English in 2023, committee members: Doc. MUDr. Michal Pohanka, Ph.D., Mgr. Alena Havelková, Ph.D., MUDr. Eva Drápelová, Prof. MUDr. Petr Dobšák, CSc., Prof. MUDr. Jarmila Siegelová, DrSc.*
graduates: Sebastiano Emeterio San Albino, Gina Francesca Evans, Isabelle Patricia Océane Giret, Giulio Massocco, Amina Muhanbetaman, Theresa Schwab, Supanut Thongprapai,

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Scientific International Cooperation between Masaryk University Brno and University of Minnesota

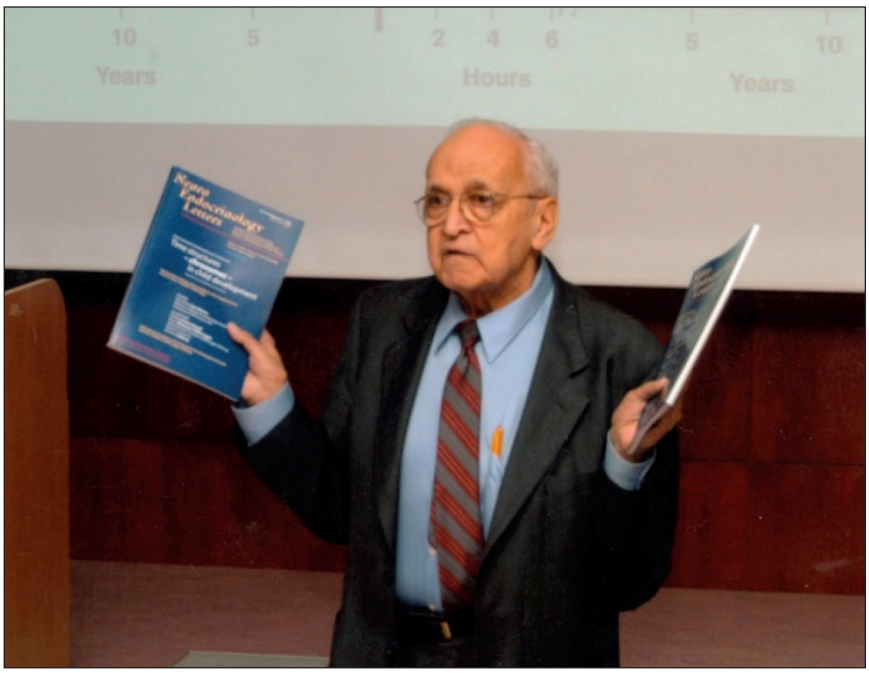
Prof. MUDr. Jarmila Siegelová, DrSc.

Department of Physiotherapy and Rehabilitation, Faculty of Medicine Masaryk University

Scientific international cooperation is possible after Velvet Revolution in the Czech Republic with the cooperation between Masaryk University and University of Minnesota.

Cooperation with Professor Franz Halberg and with Professor Germaine Cornélissen, Dr. Othild Schwartzkopff, Halberg Chronobiology Center of the University of Minnesota, USA started in 1988 with Brno team - Professor Bohumil Fišer, Jiri Dusek, M.D. and Professor Jarmila Siegelová.

The common studies of circadian variability of cardiovascular variables and baroreflex sensitivity were published in many papers as the result of this common work and our Brno team participated in international projects Womb to Tomb, later BIOCOS, under the direction of the Halberg Chronobiology Center at the University of Minnesota.



Franz Halberg, M.D., Dr. h.c. (Montpellier), Dr. h.c. (Ferrara), Dr. h.c. (Tyumen), Dr. h.c. (Brno), Dr. h.c. (L'Aquila), Dr. h.c. (People's FriendshipUniversity of Russia, Moscow), Professor of Laboratory Medicine andPathology, Physiology, Biology, Bioengineering and Oral medicine 5. 6. 1919 – 9. 6. 2013

From 80th of the last century, Prof. Franz Halberg and Prof. Germaine Cornelissen became coordinators of international chronobiology project "Womb-to-Tomb Study", now BIOCOS (The BIOsphere and the COSmos). The chronobiological team from MU was part of both projects. On November 22, 1994 BIOCOS was described for the first time. The BIOsphere and the COSmos, BIOCOS, as the task of building a novel transdisciplinary spectrum was pursued, and further periods of decades, centuries, and thousands and millions of years were documented. Much of the evidence was provided very successfully by Germaine Cornelissen, PhD, Professor of Integrative Biology and Physiology at the University of Minnesota.

Professor Germaine Cornelissen, PhD
director of Halberg Chronobiology Center (from 2013- until now)
Professor of Integrative Biology and Physiology
University of Minnesota, USA (from 2006 until now)

In the thirty years of the duration of international cooperation and every year Congresses of Noninvasive Methods in Cardiology in Masaryk University, Brno, the number of members of the Brno chronobiological team increased with Professor Petr Dobsak, Assoc. Professor Michal Pohanka, Dr. Pavel Vank, Dr. Michaela Sosikova PhD., Mgr. Alena Havelkova PhD, Mgr. Veronika Mrkvicova PhD., Mgr. Leona Dunklerova and others.

The Noninvasive Methods in Cardiology congresses and symposia in Masaryk University were visited every time by famous scientific personalities from abroad - Prof. Franz Halberg and Prof. Germaine Cornelissen from the University of Minnesota, USA, Prof. Thomas Kenner, Rector of University and Dean of Medical Faculty, University of Graz, Austria and Prof. Jean-Paul Martineaud, Medical Faculty, Hopital Lariboisiere, Paris, France, Prof. Dr. Etienne

Savin, Hopital Lariboisiere, University Paris, France, Professeur Jean-Eric Wolf, C.H.U. du Bocage, Dr. Jean-Christophe Eicher, C.H.U. du Bocage, University Dijon, France, Professor Kou Imachi, M.D., Ph.D., T.U.B.E.R.O., Tohoku University, Sendai, Japan, Professor Masahiro Kohzuki, M.D. Ph.D., Tohoku University, Sendai, Japan, Professor Yambe Tomoyuki, M.D. Ph.D., Tohoku University, Sendai, Japan. In the last year there were also new co-workers of Prof. T. Kenner, namely Prof. Dieter Platzer, University Graz, Prof. Nandu Goswami, Prof. Maxmilian Moser, University Graz, Prof. Daniel Schneditz, University Graz, Mgr. Bianca Brix, University Graz.

Since the year 2013 Professor Germaine Cornelissen has been director of the Halberg Chronobiology Center and leads international cooperation of Halberg Chronobiology Center all over the world in the project BIOCOS very successfully and many publications also together with us. She directs the international Project BIOCOS, is a member of the Phoenix Group, which comprises members of the Twin Cities chapter of the Electrical and Electronics Engineers in Minnesota, USA. Professor Germaine Cornelissen is an active member in the International Society of Chronobiology, the American Association for the Advancement of Science, the American Physical Society, the American Statistical Association, the New York Academy of Sciences, the American Physiological Society. She was the secretary of the North American branch of the International Society for Research on Civilization Diseases and the Environment (SIRMCE) and a member of the Scientific Council of SIRMCE.

In 2008, the very important Consensus meeting at St. Anna Hospital, Faculty of Medicine, Masaryk University was held. The participants under the leadership of Prof. Franz Halberg - Prof. Germaine Cornelissen, Prof. Thomas Kenner, Prof. Bohumil Fišer, Jarmila Siegelová, Dr. Jiri Dusek and others proclaimed Vascular Variability Disorders – MESOR hypertension, circadian hyperamplitude-tension, excessive pulse pressure, deficient heart variability and deviation of circadian rhythm, biomarkers of cardiovascular disease risk derived from 7-day/24-hour ambulatory blood pressure monitoring (1-7).

In the footsteps of the late prof. Franz Halberg, in the intensive collaboration with the leading personality Prof. Germaine Cornelissen, University of Minnesota in the future we plan further intensive scientific work with the University of Minnesota, USA on the BIOCOS project and other chronobiological studies.

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Night-to-day Blood Pressure Ratio from Seven Day/24 h Ambulatory Blood Pressure Monitoring by Repeated Measurements in Patients with Coronary Heart Disease

Siegelová J., Havelková A., Dusek J. Dunklerová L., Lapciková K., Pohanka M., Dobšák P., *Cornelissen G.

Dept. Physiotherapy and Rehabilitation, Dept. Sports Medicine and Rehabilitation, St. Anna Teaching Hospital, Masaryk University, Brno,
**University of Minnesota, USA*

Night-to-day blood pressure ratio with a less marked decrease in night-time blood pressure led to an increase in cardiovascular outcomes and it was described in 1988 by O‘ Brien at al. (1). In our earlier studies we have described from seven day/24 h ambulatory blood pressure measurement large variability of circadian blood pressure profile in every subject (2-10) and also large variabiliy in night-to-day ratio (11).

The aim of the present study was to examine night-to-day blood pressure variability in two repeated seven day/24 h ambulatory blood presure monitoring in patients with coronary heart disease.

Methods

20 patients with coronary heart diseases were characterized in Tab.1 and divided in two subgroups.

The 20 patients with coronary heart diseases were under pharmacological therapy with ACE inhibitors, beta blokers and statins. The ambulatory blood pressure monitoring was in every patient provided twice and every measurement, which lasted seven days/ 24 hours repeatedly with the device from A&D (Tokyo, Japan). The 20 patients were divided in subgroups 1 and 2.

Subgroup 1 was monitored before and after 3 months of our patients cardiovascular rerhabilitation 3 times a week (10 min warm-up period, 25 min aerobic training, 15 min resistant training, 10 min cool-down period.

Supgroup 2 was monitored before and after usual every day activity.

Results

We evaluated night-to-day blood pressure ratio in every day of blood pressure profile and seven day mean value before and after cardiac RHB in SBP and DBP in subgroup 1 and subgroup 2 and the results are in every individual value presented in following figures 1,2,3,4.

Tab. 1: *The characteristic of the subgroup 1 and 2 in 20 patients with coronary heart disease*

PARAMETERS	WITH REHABILITATION	WITHOUT REHABILITATION
	x ± SD	x ± SD
NUMBER OF PATIENTS [n]	10	10
AGE [years]	64,0±2,77	49,3±1,49
HEIGHT [m]	1,7±2,25	1,8±2,42
WEIGHT [kg]	89,3±4,71	89,4±7,33
BMI [kg.m^{-2}]	29,9±1,32	28,6±2,05
EJECTION FRACTION [%]	52±4,5	53±3,1

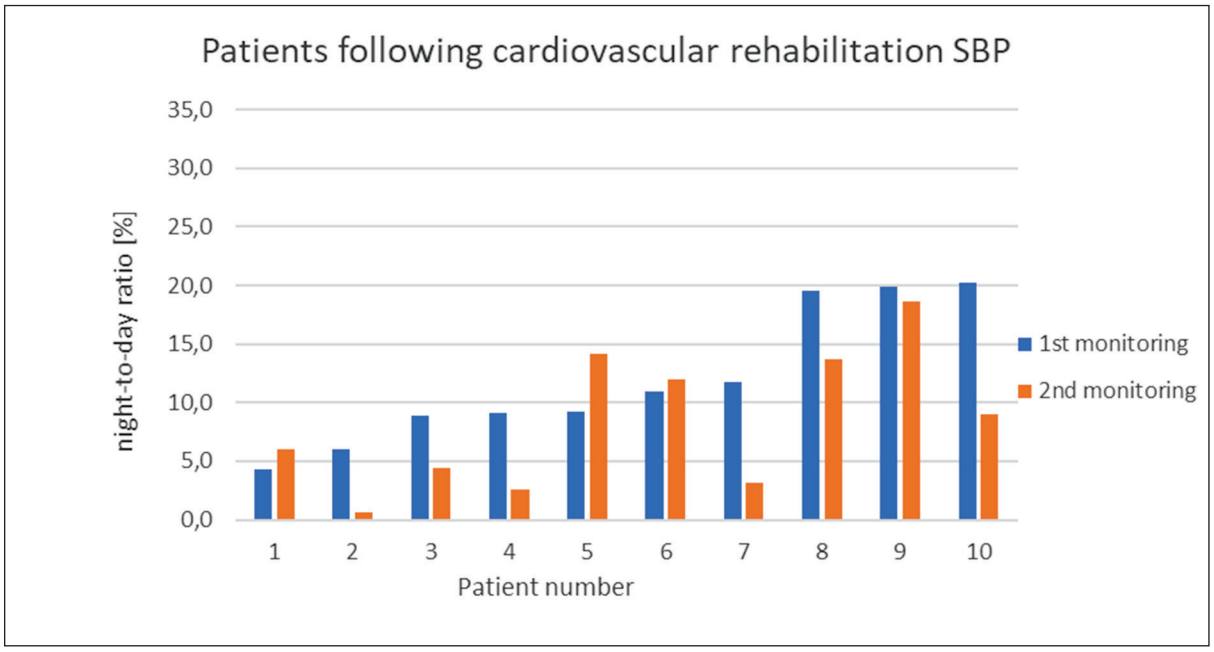

Figure 1: *Mean values of night-to-day systolic blood pressure ratio evaluated from seven day/24 h ambulatory blood pressure monitoring in subgroup of patients with coronary heart diseases and cardiovascular rehabilitation in the 1st and 2nd monitoring.*

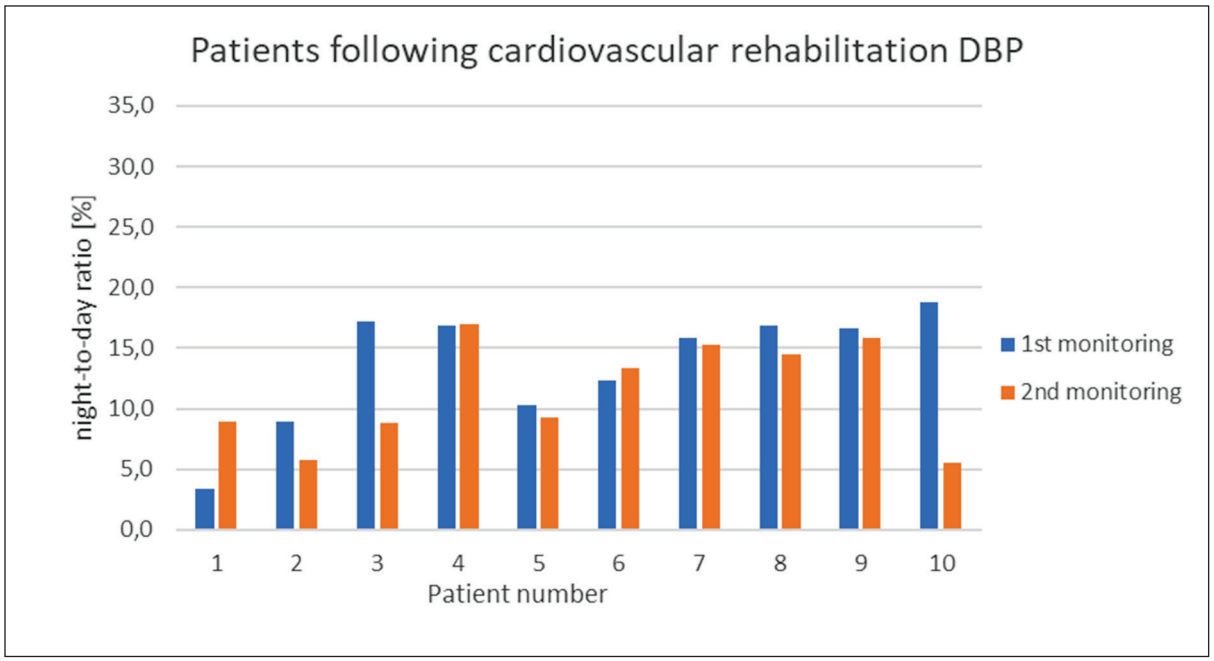

Figure 2: *Mean values of night-to-day diastolic blood pressure ratio evaluated from seven day/24 h ambulatory blood pressure monitoring in subgroup of patients with coronary heart diseases and cardiovascular rehabilitation in the 1st and 2nd monitoring.*

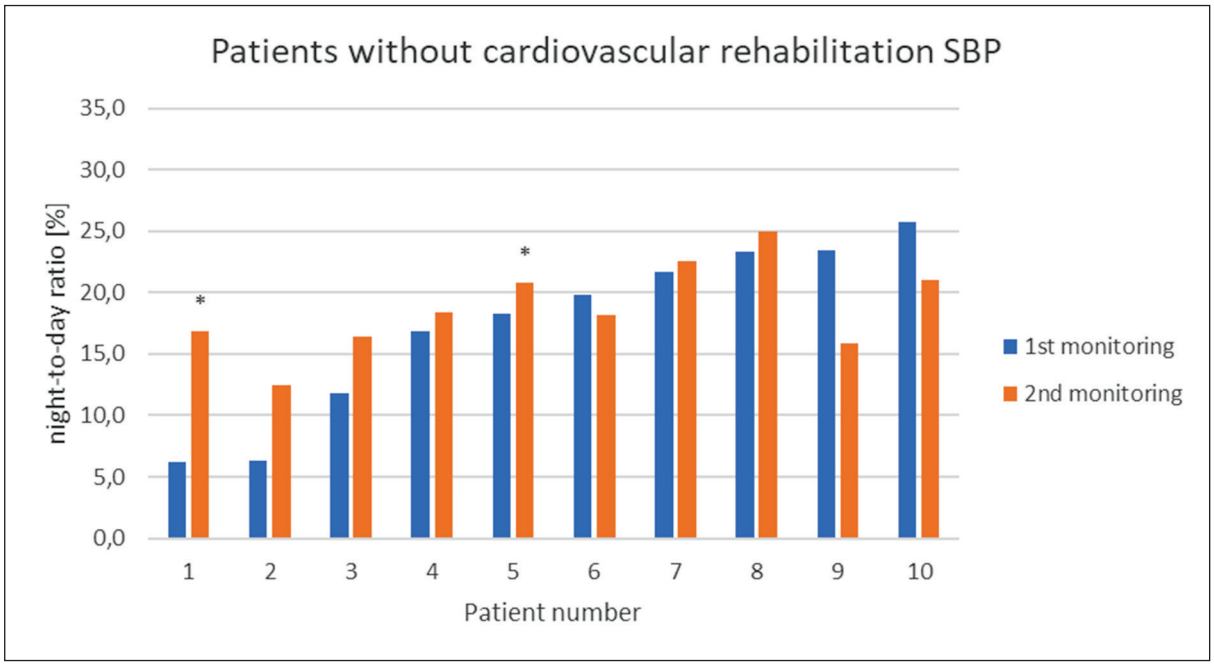

Figure 3: *Mean values of night-to-day systolic blood pressure ratio evaluated from seven day/24 h ambulatory blood pressure monitoring in subgroup 1 of patients with coronary heart diseases and with every day aktivity between i the 1st and 2nd monitoring*

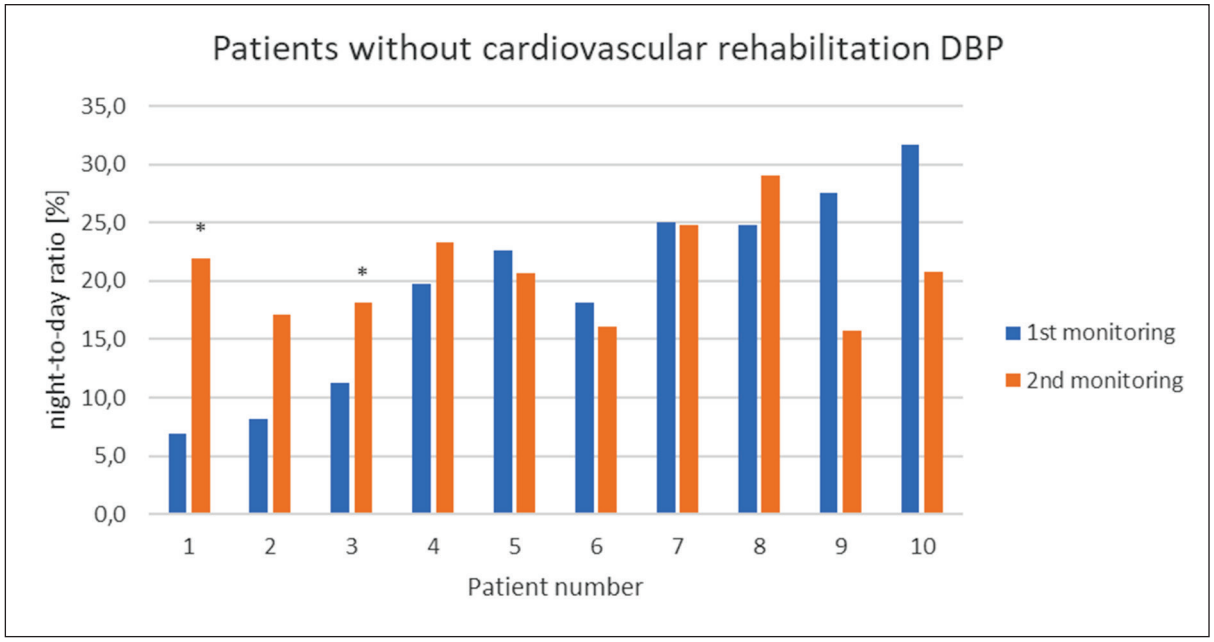

Figure 4: *Mean values of night-to-day diastolic blood pressure ratio evaluated from seven day/24 h ambulatory blood pressure monitoring in subgroup of patients with coronary heart diseases and every day aktivity between the 1st and 2nd monitoring*

The mean values of night-to-day ratio in blood pressure from seven day/24 h AMBP by repeated measurement in subgroup 1 and subgroup 2 are presented for SBP and DBP in figures 5, 6, 7, and 8.

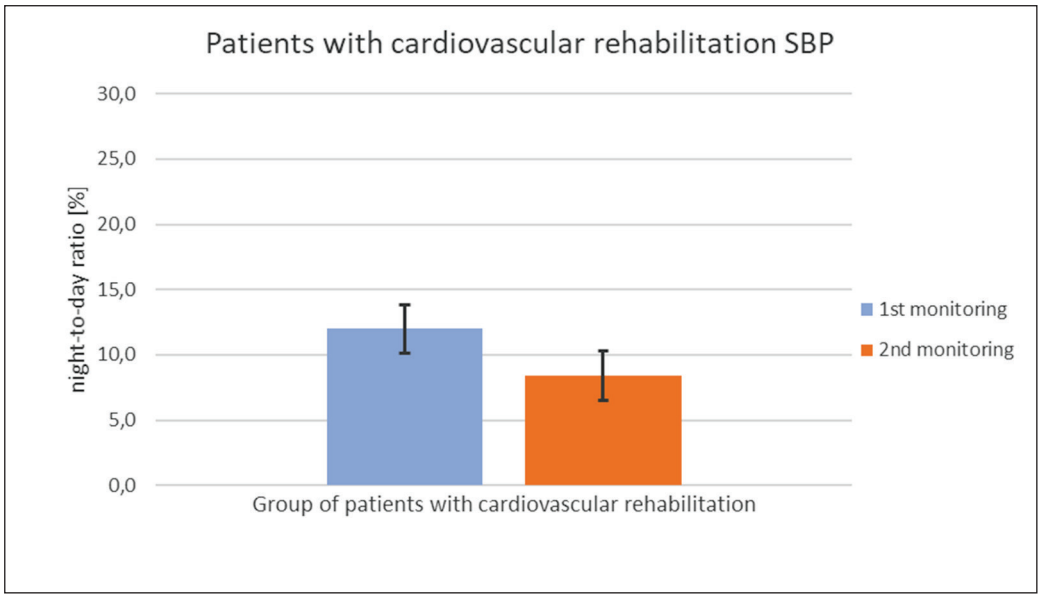

Figure 5: *Mean values of night-to-day systolic blood pressure ratio evaluated from seven day/24 hour ambulatory blood pressure monitoring in the whole subgroup 1 in patients with coronary heart disease and cardiovascular rehabilitation between the 1st and 2nd monitoring.*

The mean values of night-to-day systilic blood pressure ratio estimated from seven day/24hour ambulatory blood pressure monitoring in subgroup 1 is the 1st monitoring: 12.0±1.85 % , 2nd monitoring: 8.4±1.89 %, the difference is not statistically significant.

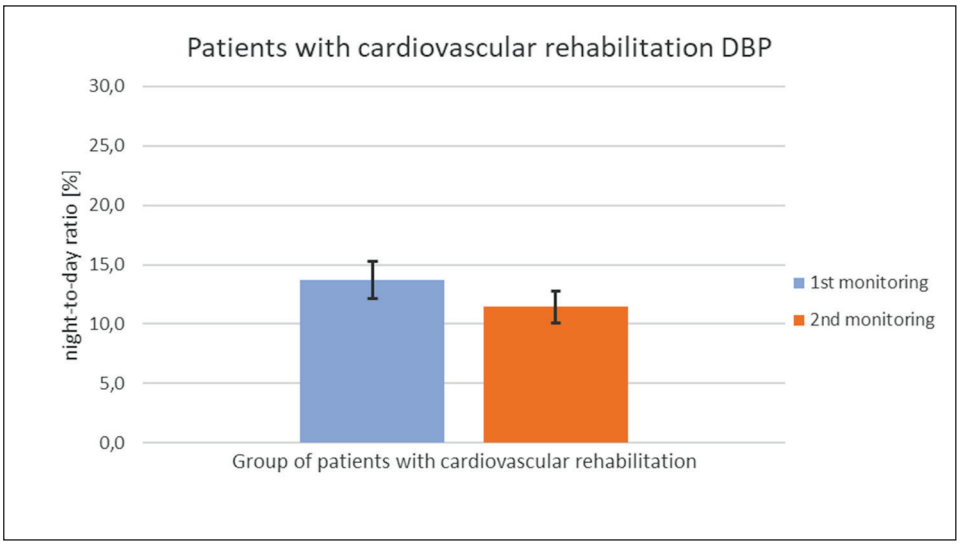

Figure 6: *Mean values of night-to-day diastolic blood pressure ratio evaluated from seven day/24 hour ambulatory blood preasure measurement in the whole subgroup 1 in patients with coronary heart disease and cardiovascular rehabilitation between the 1st and 2nd monitoring.*

The mean values of night-to-day diastolic blood pressure ratio evaluated from seven day/24 hour ambulastory blood pressure monitoring in subroup 1: 1st monitoring: 13.7±1.54 % ; 2nd monitoring: 11.4±1.34 %, the difference is not statistically significant.

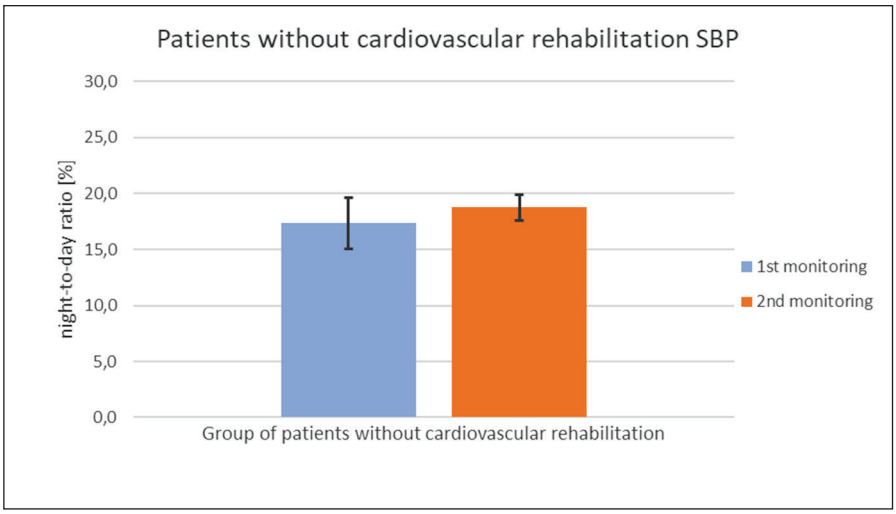

Figure 7: *Mean values of night to day systolic blood pressure ratio evaluated from seven deay/ 24 h ambulatory blood pressure monitoring in the whole subgroup 2 in patients with coronary heart disease and every day activity beween the 1st and 2nd measurement.*

The mean value of night to day systolic blood pressure ratio evaluated from seven day/24 hour ambulatory blood pressure monitoring in subgroup 2: 1st monitoring: 17.3±2.23 % ; 2nd monitoring: 18.8±1.16 %

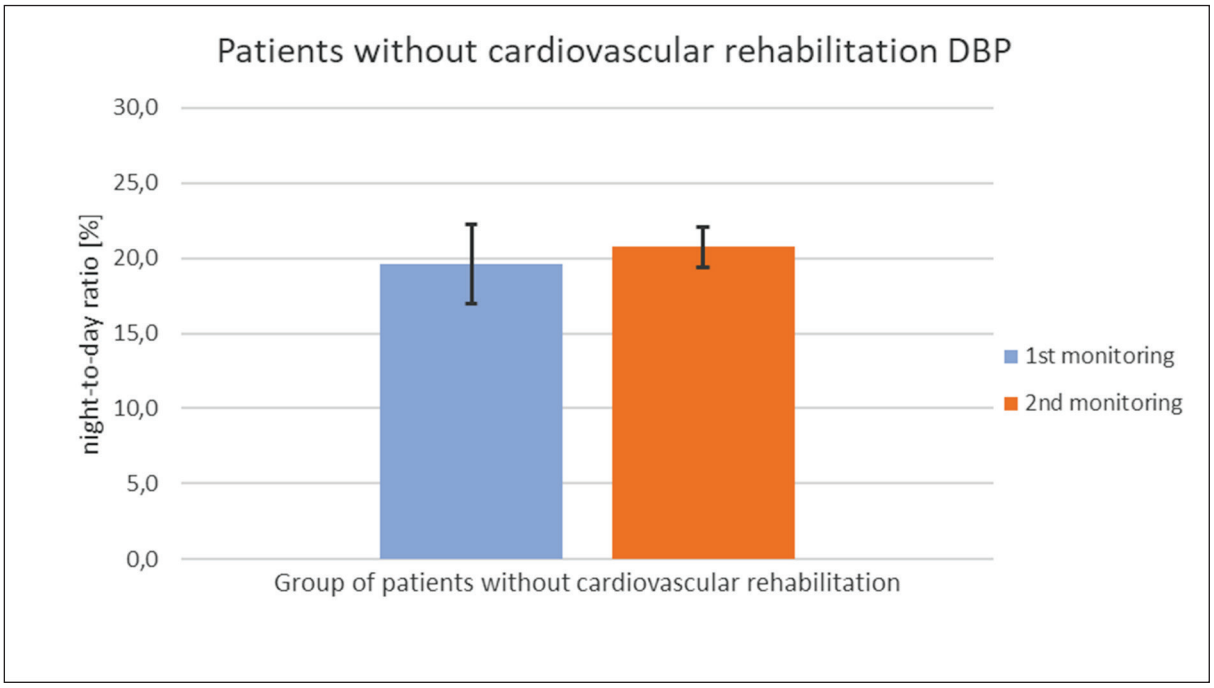

Figure 8: *Mean values of night to day ratio diastolic blood pressure ratio evaluated from seven day/ 24 hour ambulastory blood pressure monitoring in patients with coronary heart disease and every day aktivity between třhe n1swt and 2nd measurement.*

The mean values of night to day diastolic blood pressure ratio evaluated from seven day /24 hour abulatory blood pressure monitoring in subgroup 2: 1st monitoring: 19.6±2.66 % ; 2nd monitoring: 20.7±1.33 %, the difference is not statistically significant.

Discussion

Our finding of large night-to-day ratio variability in individual patients with coronary heart diseases corresponds to the results of other studies in healthy subjects. The night-to-day blood pressure ratio is subject to regression-to-the mean. Dipping status has also a low reproducibility, with up to 40 % of individuals from Europe and Asia 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 (2-10). 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-today blood pressure ratio. 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.

Conclusion

Night-to-day blood pressure ratio from seven day/24 h ABPM varied in one ambulatory blood pressure 24h profile and also in mean values from seven day/24 h ABPM in 1st and 2nd measurement.

We have not found significant difference between the subgroup 1 before and after cardiac rehabilitation. We have not found significant difference in repeated measurement in subgroup 2 with usual activities between repeated measurements.

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From Oita, Hometown Japan to Medical Care and Welfare in the Republic of Kenya Medical, Health and Welfare Improvement Project

Mitsuo Takei

CEO and Founder of Medical Corporation KOSHINKAI in JAPAN.
CEO and Founder of GRAND FOREST JAPAN HOSPITAL in KENYA.
Chairman of (NGO) DREAM WORLD HEALTHCARE PROGRAMME in KENYA

Practicing Japanese-style meticulous medical care in Africa

In March 2013, the Limited Company “Grand Forest Japan Hospital” was registered with the Government of the Republic of Kenya. We opened a medical center in Nairobi City in order to provide the people of Kenya with meticulous medical services based on Japanese

scientific evidence. With the motto of “prompt and accurate diagnosis and treatment,” we have steadily taken root in the local community and expanded our business by establishing a new rehabilitation center. While making use of our local experience and know-how, we continue to provide high quality medical services and expand and expand our business with the aim of perpetuating our activities in the future. Apart from medical services, we also established a local NGO, Dream World Healthcare Programme, in January 2013. In collaboration with Nakuru and Kaziad County, the program provides monthly mobile healthcare services to maintain and improve health and quality of life, mainly in residential areas with high poverty rates.

Introduction of Japanese medical equipment

Equipped with X-ray, CT scan, Ultrasound, gastro-camera, colonic camera, blood, urine and stool testing equipment. As much as possible, we have installed Japanese-made medical equipment that is precise and has few failures. We provide Kenyan medical professionals who visit our facility with an opportunity to learn about Japanese medical equipment, which leads to purchases.

Providing quality medical care and staff education thoughtful Japanese--style

Forest Japan Medical Center also conducts health checks, which are rare in Kenya. In addition, the level of medical care in Japan is trusted, and after the MOU was concluded, we began to receive requests for tests from local medical facilities. In the future, it is expected that needs from various fields will increase, and we are contributing to improving the quality of medical care in Kenya. In November 2020, Forest Japan Rehabilitation Centre opened in Karen District, Nairobi Province. We offer Japanese-style rehabilitation in accordance with scientific evidence. Although it was opened in the Corona Vortex, there are repeat patients. The center differentiates itself from rehabilitation centers in Kenya, where physical therapy is the mainstay of rehabilitation, and offers a wide range of rehabilitation services to help patients return to their daily lives. Our activities are in line with the policies of the Kenyan government and we have signed MOUs with provincial governments and educational institutions. We believe that by providing Japanese medical care and traveling clinic services, we can contribute to the health maintenance of Kenyan citizens, labor force improvement, and ultimately economic development. Furthermore, since 2016, we have been conducting local training programs and building relationships of trust through the development of medical professionals. Through these activities, we also introduce Japanese culture, medical conditions, and equipment.

Figure 1: *MACHAKOS Level 5 Hospital*

Present situation

Now, our organization implement a free medical camp (outreach activity) in slam area to improve a healthcare services, medical treatment and social welfare services once a month (it started from May 2013 in collaboration with Ministry of Health in Nakuru-county Republic of Kenya). Now increased to twice a month to every week. Totally, we have treated over 70.000 citizens from new born, maternity woman to aged. Nowadays obesity is a big problem not only in high-end people but also in BOP (base of pyramid) people in slam area. Because it depends on life style, cultural background and everyday food habits. They don't have an enough knowledge and not well educated about health care. So, NCD's (like a diabetes, hypertension, hyperlipidemia and obesity) will become a serious problem. Near future (2025), number of patients who are suffering from NCD's will be exceeding Communicable Disease (infectious disease). Death rate of newborn and maternity woman is also a serious problem, it is a hundred times a lot compared to Japan. At the same time, it is very important to have an educational activity to Kenyan medical staff. We have already started to educate in Nairobi-University, some technical school and some Hospitals.

Figure 2: *Meeting with vice President Ruto*

Contents of our free medical camp (list of services provided)

Height, body weight, BMI calculation, body temperature, oximetry, blood pressure, blood sugar, general urinalysis, HIV test, malaria test, parasite inspection, fungus and tuberculosis infection test, sexually transmitted disease (STD) inspection, family planning and HIV counselling, education for a prevention of infectious disease, education for prevention of a lifestyle disease, data acquisition to grasp the actual state of NCD's in the slum area, prevention education about an infection and lifestyle disease, and so on.

Another activities

A medical staff from Japan has a class, which gives a lesson about various kinds of medics regularly. We have a MOU with Nairobi University, which regulate rules between Nairobi University and Medical Corporation KOSHINKAI in Japan from 2017.

Memorandum of Understanding (MOU)

An education program for interchange of the student, research program, participation to a meeting and seminar and other cooperation.

Conclusion

With economic growth in Kenya, the disease structure is changing and becoming more Westernized, especially in Nairobi City. As a result, lifestyle-related diseases are on the rise and the number of people with disabilities is increasing, as in Japan. In addition, there are few policies for children with disabilities. We are building a medical support system that considers these factors. We are also focusing on human resource development. Good medical care, welfare, and healthcare require good human resources. Exchange between Japan and Kenya is mutually beneficial. There are many challenges ahead, but we intend to move forward slowly, one at a time. I would be very happy if our activities can help Kenyans maintain and improve their health and become a cornerstone of the country's prosperity.

With the aim of protecting the precious lives of our patients, we strive every day to provide high-quality medical services to patients who visit our center. The smiles of our patients bring us joy, and by interacting with many patients, we gain valuable experience every day.

Note

The above text provides an overview of the content of the lecture, which was held on September 19, 2023 at the Faculty of Medicine, Masaryk University in Brno.

Figure 3: *The state of Kenya on the map of Africa*

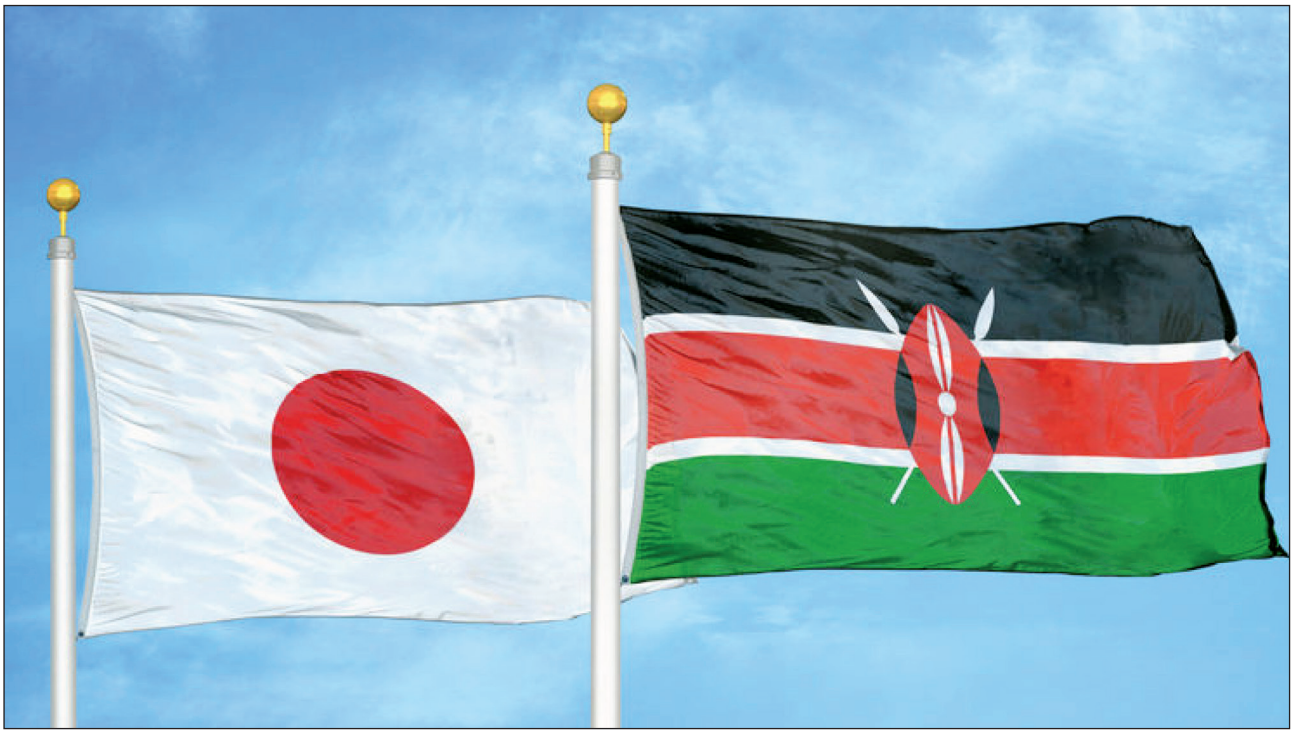

Figure 4: *A symbol of cooperation between the states of Japan and Kenya*

NONINVASIVE METHODS IN CARDIOLOGY 2023

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