NONINVASIVE METHODS IN CARDIOLOGY **2024**

Edited by: **Cornélissen G., Pohanka M., Siegelová J., Dobšák P.**

MASARYK
UNIVERSITY
PRESS

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Masaryk University Press
Brno 2024

Under the auspices of

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

Reviewed by: Prof. MUDr. Kamil Javorka, DrSc.
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Slovak Republic

ISBN 978-80-280-0668-6 (paperback)
ISBN 978-80-280-0669-3 (online ; pdf)
https://doi.org/10.5817/CZ.MUNI.M280-0669-2024

Contents

https://doi.org/10.5817/CZ.MUNI.M280-0669-2024-1

Congresses of Noninvasive Method of Cardiology in Faculty of Medicine, Masaryk University, Brno, Czech Republic and Halberg Chronobiology Center of Minnesota, USA: 35 Years of Scientific Research with Professor Germaine Cornélissen

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In eighties of the last century started the cooperation between Masaryk Unisersity and University of Minnesota, USA. University of Graz, Austria and continued the cooperation with Medical Faculty Paris, France.

In 1990 Prof. Dr.Franz Halberg, Dr. honoris causa mult. (1919-2013) and Prof Germaine. Cornélissen visited Masaryk University in Brno for the first time and presented chronobiological results in cardiovascular parameters in man in Masaryk University in Brno Congress. Immediately, an intensive cooperation started between the Brno team, consisting of Prof. MUDr. Jarmila Siegelova, DrSc. and Prof. MUDr. Bohumil Fiser, CSc. (1943-2011), former head of the Physiology Department, Czech Minister of Health and executive board member of WHO); MUDr. Jiri Dusek, CSc. with Prof. Halberg and Prof. Cornelissen, University of Minnesota, USA. In Brno at that time we carried out the beat-to-beat noninvasive measurement of blood pressure, developed by Prof. MUDr. Jan Penaz, CSc (1926-2015) and young scientist subject Prof. Fiser, as well as measurements of baroreflex sensitivity and heart rate variability and Prof. Jarmila Siegelová had the equipment for ambulatory 24-h blood pressure monitoring for adults. The University of Minnesota lent us equipment for oscillometric measurement of blood pressure in newborn children. We started common scientific work while our data of blood pressure and heart rate collected on the Czech population were at first faxed, later on line sent via e-mail to Chronobiological laboratories in Minnesota, Halberg Chronobiology Center and analyzed from prof. Germaine Cornelissen in the University of Minnesota, USA.Then for 35 years until now the ambulatory monitoring of blood pressure and heart rate data from Brno were immediately analyzed by Prof. Cornelissen and the results of these analyses served not only for scientific work, but also for therapy of the Czech population. Between the years 2000 and 2008 the Brno team consisting of Prof Jarmila Siegelova, Prof. Fiser, Dr. Dusek and we collected 73.888 sets of blood pressure and heart rate measurements and all data were analyzed by Prof. Cornelissen the following day. The daily data exchange and analysis continues until now.

Very important chronobiological findings of blood pressure control were made on newborn children's blood pressure, on blood pressure changes after the timed administration of low dose aspirin, in cardiac patients with cardiac rehabilitation, on baroreflex sensitivity in healthy subjects and patients with essential hypertension, in cardiac patients and on groups of normotensive subjects and hypertensive patients given antihypertensive therapy and without therapy. The cooperation resulted in many common publications of Brno team and Halberg Chronobiological Center.

From 1990 every year, sometimes twice a year, common meetings, symposia and workshops were organized in Brno, such as MEFA Congress or chronobiological congresses of Noninvasive methods in cardiology, presenting a lot of latest findings in chronobiology of carčdiovascular parameters in scientific lectures and the scientist visited us in Brno. Scientific meetings were organized with the participation of Prof. Cornelissen and Prof. Halberg from Minnesota; USA, Prof. Thomas Kenner, former president of the University of Graz, Austria (1932-2019); and his coworkers from University Graz, Austria and Prof. J.P. Martineaud, Hopital Lariboisiere, Medical Faculty, Paris, France¨(1931-2010) and his cooworkers from Paris, Hôpital Lariboisière, Paris France. Prof. Cornelissen prepared a lot of publications for every year congresses and symposia in Brno.

The Brno team visited USA, France, Austria many times.

One chronobiology study was undertaken in University in Minnesota in 1995, where Prof. Cornelissen and the Brno team- Prof. Siegelova, Prof. Fiser and Dr. Dusek evaluated two Japanese ambulatory blood pressure monitors. The scientists measured themselves day by day two weeks. The scientific team placed blood pressure cuffs on both arms and worn them for fourteen days. The results were evaluated using cosinor analysis and Prof. Cornelissen published them.

In 1987 Prof. Cornélissen was appointed the secretary of the North American branch of the International Society for Research on Civilization Diseases and the Environment (SRMCE). She summarized and published numerous papers on risks of civilization diseases and on morbidity and mortality of cardiovascular diseases.

In 1994 Prof. Cornelissen became coordinator of international chronobiology project Womb-to-Tomb Study, now BIOCOS (The BIOsphere and the COSmos). The Brno team is a member of both international projects. From the year 2013 prof. Germaine Cornelissen, Professor of Integrative Biology and Physiology at the University of Minnesota is the director of Halberg Chronobiological Center from University of Minnesota and cooperates with the sciences from Japan, India, Belgium, Czech Republic, Slovak Republic and Other counries,

Prof. Cornelissen's scientific capabilities were appreciated by a number of awards, citations and membership in scientific organizations. She was nominated as an honorary member of the Cardiff Scientific Society (2002), a member of the advisory board of the International College of Nutrition and International College of Cardiology, MYODEA, Moradabad, India (2005), of which she is a fellow Royal Scientist; a foreign member of the Problem Commission on Chronobiology and Chronomedicine of the Russian Academy of Medical Sciences (2006); a member of the Leibniz Society (the former Academy of Science of the German Democratic Republic) (2009), and of the International Academy of Science (2011).

In 2000 Masaryk university honored the international cooperation of Prof. Dr. Franz Halberg, University of Minnesota USA and Prof. Dr. Thomas Kenner, University Graz, Austria with Masaryk Univesity and nominated both scientists with the title Doctor honoris causa of Masaryk University Brno, Czech Republic.

Figure 1: *Doctor honoris causa award in 2000 in Masaryk University Brno of Prof. Dr. Franz Halberg, University of Minnesota, USA, Prof. Dr. Thomas Kenner, University of Graz, Austria presented by the Rector of Masaryk University Prof. RNDr. Jiří Zlatuška and promoter Prof. MUDr. Jarmila Siegelová DrSc and vicedean of Faculty of Medicine Prof. MUDr. Libor Páč, CSc.*

In Noninvasive methods in cardiolology 2008, on October 6, 2008, Prof. Franz Halberg, presented with prof. Germaine Cornélissen and with us the vascular variability abnormalities, and the Nonivasive Methods of Cardiology was known as Consensus meeting, which described MESOR hyperternsion, Excesive pulse pressure, Circadian-Hyperamplitude -Tension (night to day blood pressure dipping), Deficient Heart Rate Variability, diagnosed on seven day/24-h ambulatory blood pressure monitoring, at Masaryk University, Brno, Czech Republic, St. Anna Teaching Hospital.

The leading scientist was Prof. Dr. Franz Halberg, d.h.mult. with other participants Prof. Dr. Germaine Cornelissen, Dr. Othild Schwarzkopff, University of Minnesota, USA, Halberg Chronobiology Center, Prof. Dr. Thomas Kenner, d.h.c.mult., University Graz, Austria, from Masaryk University Prof. MUDr. Jarmila Siegelova, DrSc., Prof. MUDr. Bohumil Fišer,CSc., Prof. MUDr. Petr Dobšak, CSc., MUDr. Jiři Dušek, CSc., Prof. MUDr. Zdeněk Placheta, DrSc(1931-2014)., MUDr.Pavel Homolka, PhD., Dr. Mohamned Al-Kubati, PhD. Assoc. Prof. Michal Pohanka, PhD., Masaryk University Brno, St. Anna Teaching Hospital, CZ participated on this consensus.

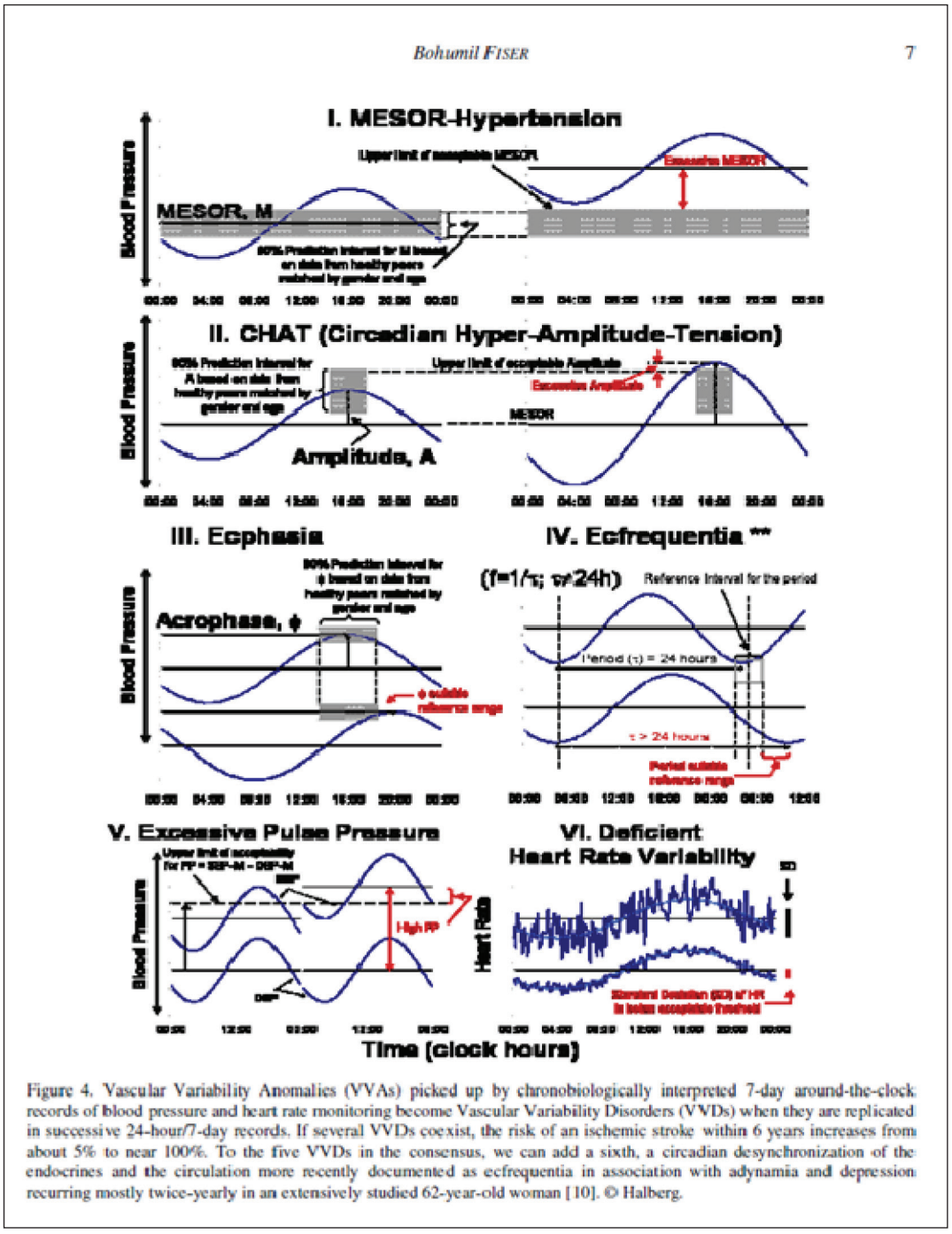

Figure 4. Vascular Variability Anomalies (VVAs) picked up by chronobiologically interpreted 7-day around-the-clock records of blood pressure and heart rate monitoring become Vascular Variability Disorders (VVDs) when they are replicated in successive 24-hour/7-day records. If several VVDs coexist, the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

Figure 2:

Figure 3: *Professor Bohumil Fišer, As. Professor Michal Pohanka, Professor Thomas Kenner, Brigitte Kenner, Dr. Othild Schwartzkopff, Professor Franz Halberg, Dr. Jiří Dušek, Professor Jarmila Siegelova, Brno Congress Noninvasive Methods in Cardiology 2008*

Figure 4: *Professor Germaine Cornelissen, PhD.,*
Director of Halberg Chronobiology Center, Professor of Integrative Biology and Physiology, University of Minnesota, USA, Noninvasive Methods in cardiology 2002

Figure 5: *Professor Masairo Kohzuki, M.D.*
Head of Department of Internal Medicine and Rehabilitation Science, Tohoku University Graduate School of Medicine, Sendai, Japan, Noninvasive Methods in Cardiology 2018

Figure 6: *Assoc. Prof. PD Dr. med. Nandu Goswami,*
Head of Dept. of Physiology, Medical University of Graz, Austria, Noninvasive methods in cardiology 2018

Figure 7: *Prof. MUDr. Jarmila Siegelová, DrSc., Dr. Biaca Brix, Professor Masairo Kohzuki M.D., Prof. PD Dr. med. Nandu Goswami. Dr. Jana Svačinová, Masaryk University, Brno 2019*

Figure 8: *Prof. MUDr. Petr Dobšák, CSc.*
Head of Dept. of Sports Medicine and Rehabilitation, University Hospital at St. Anna in Brno, Dept. of Physiotherapy and Rehabilitation, Faculty of Medicne, Masaryk University

In the thirty five years of the duration of Noninvasive Methods in Cardiology every year Congresses and proceedings of Noninvasive Methods in Cardiology in Masaryk University, Brno were poublished, and the number of participants from abroad increased in our Masaryk University.Frčom the y\ear 1997 Prof. Dr Petr Dobšák, CSc., who organized cooperation with Japan Universities and from 2002 Assoc. Professor Michal Pohanka, Phd. took part in the noninvasive Methods in Cardiology. From Masaryk University participated our colleagues Assoc. Prof. Jiri Jancik, Phd., Dr. Jitka Svobodova, Dr. Hana Svacinova, PhD, Dr. Pavel Vank, Dr. Michaela Sosikova, Dr. Alena Havelková, Dr. Petra Palanová, Dr. Veronika Mrkvicová, Mgr. Leona Dunklerová, Dr. Pavel Homolka, PhD., Prof. Dr. Pavel Bravený, CSc (1931-2018 Prof. Dr. Marie Nováková, PhD., Dr. Zuzana Novákova, PhD, Dr. Jana Svačinová. The congresses and symposia in Masaryk University were visited every time from abroad by famous scientific personalities - Prof. Franz Halberg and Prof. Germaine Cornelissen from University of Minnesota, USA, Dr. Othild Schwarzkoppf, Minnesota, USA, Cathy Lee Gierke, Minnesota, USA, Linda Sackett, Minnesota, USA, A Chase Turner, Minnesota, USA,. and their cooworkers from different countries Prof. Dr Ram B. Singh, Halberg Hospital, Morabod, India, Dr. Fabien de Master, Belgium, Prof Dr. Yoshihika Watanabe, Tokyo Womens Medical University, Japan, Prof. Kuniaki Otsuka, Tokio Universiy, Japan, Prof. Denis Gubin, Tyumen University, Rossia. Prof. Thomas Kenner, Rector of University and Dean of Medical Faculty, University of Graz, Austria and head of Dept of Physiology broat with him to Brno on Congresses of Noninvasive Methods in Cardiology in the last years also new co-workers from University in Graz Prof. Dieter Platzer, later head of the Dept of Physiology Prof. Nandu Goswami, Prof. Maxmilian Moser, University, Prof. Daniel Schneditz, and Dr. Bianca Brix, PhD. Prof. Jean-Paul Martineaud, Medical Faculty, Hopital Lariboisiere, Paris, France, brought to Masaryk University, Prof. Dr. Etienne Savin, Hopital Lariboisiere, University Paris, France, Prof. Bernard Levy, head, Hopital, Lariboisiere Paris, INSERM Paris, France. The coopration with Dijon started Prof Dobšák later with Prof. Jean-Eric Wolf, C.H.U. du Bocage, University of Dijon, France, and Dr. Jean-Christophe Eicher, C.H.U. du Bocage, University Dijon, France and Japan-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, Prof. Yambe Tomoyuki, M.D. Ph.D., Tohoku University, Sendai, Japan. From Germany Prof.Dr. Hans Rieckert, UniversitY Ulm and Prof. Dr.Nguyen-Duong, University Ulm.

We have a great luck that we could cooperate with internationally known excellent experts and scientists in the field of medicine, physiology, pathophysiology and chronobiology and we appreciate it very much that we can continue in the cooperation with famous University all over the world – USA, Europe, Asia.

We appreciate the great scientific work of Prof. Cornelissen in the chronobiology, physiology, pathology, biology, wthe expert of University of Minnesota, director of Halberg Chronobiology center with the broad international scientific and spcially the long lasting cooperation with Masaryk University. We hope in the long common scientific work between Minnesota University, USA and Masaryk University and St. Anna Teaching Hospital in Brno, Czech Republic.

Figure 9: *On the left part above of the picture Prof. Jarmila Siegelova, DrSc., Tomoyuki Yambe, Professor, Ph.D, MD, Sendai, Japan, Prof. MUDr. Petr Dobsák, CSc., MU, Masaryk University, Dr. Jiri Dusek, Yusuke Inoue, Assistan Professor, Ph.D., Sendai, Japan, Kazumasu Sasaki, D.V.M., Ph.D., Sendai, Japan, Mitsuya Maruyama, Fukuda Denshi, Tokyo, Japan.*

On the right part above of the picture is Brigitte Kenner and Prof. Thomas Kenner, Dr. M.D., Dr. h. c. mult., University Graz, Austria, Prof. Dieter Platzer, Dipl.-Ing. Dr.techn., Institut für Biophysik, University Graz, Austria.

On the right part down of the picture is Prof. Germaine Cornelissen, Dr., University of Minnesota, USA, Cathy Lee Gierke, University of Minnesota, USA

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https://doi.org/10.5817/CZ.MUNI.M280-0669-2024-2

Determinants and Reliability of the Ambulatory Arterial Stiffness Index, AASI

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Support:

Halberg Chronobiology Fund (GC)

Abstract

The Ambulatory Arterial Stiffness Index (AASI) was introduced as an easily implemented way to non-invasively assess arterial stiffness from 24-hour ambulatory blood pressure monitoring (ABPM) records. After a brief review of the literature, this investigation considers ABPM records from two clinically healthy populations to compute the AASI and assess its major determinants. The 7-day/24-hour ABPM records collected in one of the two studies served to determine the extent of day-to-day variability in the AASI estimation. In the other study, age, body mass index (BMI), systolic (S) BP MESOR, and pulse pressure (PP) correlated positively with AASI, while the magnitude (extent of predictable daily change) of SBP and the 24-hour amplitude of diastolic (D) BP correlated negatively with AASI. Although AASI computed on separate days correlates well with its value estimated from the entire 7-day record, the day-to-day variation in its estimate is quite large. The relatively large difference in estimated average AASI between the two studies, which included seemingly similar populations, can be accounted for by taking into consideration the small differences in all determinants of the AASI existing between the two samples. Novel findings from this investigation are the effect on AASI of (1) a misaligned circadian BP rhythm, and of (2) a sparser nighttime vs. daytime sampling.

Although our results agree with published results, the large uncertainty associated with the estimation of AASI may limit its clinical usefulness in guiding the treatment of individual patients.

Introduction

The Ambulatory Arterial Stiffness Index (AASI) is a simple indirect method to estimate arterial stiffness from a 24-hour Ambulatory Blood Pressure Monitoring (ABPM) record. It is defined as 1 – b, where b is the slope of the regression line of diastolic (D) on systolic (S) blood pressure (BP): DBP = a + b*SBP (Figure 1). The index expresses the notion that for a given increase in DBP, the increase in SBP is smaller in a compliant than in a stiff artery [1]. It was introduced in 2006 [2-4] as another surrogate measure of arterial stiffness capable of predicting cardiovascular mortality over and above pulse pressure (PP = SBP - DBP), even in normotensive individuals.

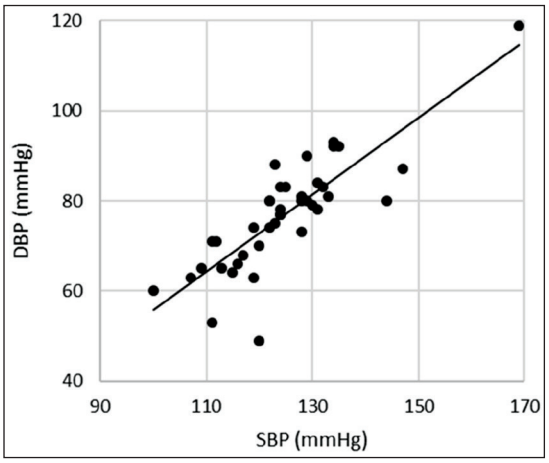

Figure 1: *Example of AASI computation from a 24-hour ABPM record, with around-the-clock measurements every 30 minutes: b = 0.856; AASI = 0.144.*

AASI was shown to correlate with established measures of arterial stiffness [3]. However, it changes with age. While the 95th percentile of AASI was 0.57 in normotensive Europeans enrolled in the International Database on Ambulatory Blood Pressure Monitoring, it ranged from 0.53 to 0.72 in adults 20 to 80 years of age [3]. A better fit of the regression line used to estimate AASI reportedly enhances its value as a marker of arterial stiffness; a sensitivity threshold R^2 value of 0.36 was suggested [5]. It has been advocated further that the median number of measurements in a 24-hour ABPM record be about 35 or more [6].

After briefly reviewing the literature, AASI is estimated retrospectively from 24-hour and 7-day/24-hour ABPM records of clinically healthy participants in two different studies to verify in these populations the effect on AASI of different factors described in the literature. The extent of reproducibility of the AASI is evaluated by comparing its estimation on separate days with that obtained by considering the entire 7-day ABPM records. In view of the difference in average AASI between the two studies, despite their seemingly similar populations, we examine whether the effect of known determinants of the AASI can account for this difference.

Brief Review of the Literature

AASI was found to predict adverse cardiovascular events, particularly stroke, in several studies. When relating mortality in 1542 Ohasama residents (40–93 years) followed-up for a median of 13.3 years to AASI and PP in a Cox regression adjusting for potential confounders, AASI predicted cardiovascular and stroke mortality over and beyond PP [7]. Similarly, AASI was a strong predictor of stroke, beyond traditional cardiovascular risk factors, including MAP and PP, in a random sample of 1829 Danes (40-70 years) followed-up for a median of 9.4 years [8]. In this population, AASI predicted stroke while aortic pulse wave velocity (aPWV) did not, whereas aPWV but not AASI predicted all cardiovascular events [9]. A recent systematic review and meta-analysis included results from 13 studies on 28,855 patients who were followed-up for 2.2 to 15.2 years. Higher AASI was associated with a significant increase in all-cause mortality, stroke, and MACE (major adverse cardiovascular events) [10]. An elevated AASI above 0.56 was also an independent predictor of MACE in women (18-75 years) who underwent 24-hour ABPM for the diagnosis of hypertension or its control and were followed-up for an average of 25.5 months [11]. In another study of 1200 treated and untreated hypertensive patients (51 ± 12 years) without previous cardiovascular events followed-up for 8.2 ± 3.0 years, AASI predicted total cardiovascular events and stroke but not coronary events [12].

AASI was also related to organ damage in some studies. Untreated patients with primary hypertension diagnosed with microalbuminuria, carotid abnormalities, or left ventricular hypertrophy had a higher AASI as compared with those without it [13]. In treated and untreated hypertensive patients, AASI was positively correlated with vascular damage gauged by the carotid intima-media thickness and with Cornell VDP gauging cardiac damage. Moreover, it was negatively correlated with glomerular filtration rate as a gauge of renal damage and with the ankle/brachial index gauging vascular damage. These results indicated that an increased AASI is associated with a greater presence of subclinical organ damage [14]. In untreated hypertensive patients, AASI correlated positively with relative wall thickness and left ventricular mass index [15], while AASI correlated inversely with estimated glomerular filtration rate in hypertensive Chinese outpatients [16].

Among the several factors that affect the AASI is the nocturnal drop in BP, notably in hypertensive patients [17]. AASI correlated positively with age, average SBP, and average PP, and negatively with the standard deviation (SD) of DBP, PP, and heart rate (HR), and with nocturnal dipping in untreated hypertensive patients [15]. AASI also correlated positively with age, SBP, and PP, and negatively with the 24-hour variation in DBP in hypertensive Chinese outpatients [16]. As noted above, PP is a major determinant of AASI, as also demonstrated mathematically [18]. In addition, BMI was an independent predictor of an abnormal AASI (≥0.50) in normotensive obese patients [19]. By considering daytime measurements only to estimate AASI, it remained elevated in hypertensive children and adults and maintained the relationship with age, PP, SBP and DBP [20]. A modified AASI, derived by symmetric regression (bisecting the line of DBP vs SBP and SBP vs. DBP), abolished the negative association with BP dipping, and was more strongly associated with age and enhanced its prediction of all-cause mortality [21].

The influence of the nocturnal BP dip on the computation of AASI led some authors to conclude that AASI is unable to estimate arterial stiffness of older hypertensive patients with a high burden of organ and vascular damage and several comorbidities, for whom the nocturnal reduction of BP is the main determinant of AASI [1, 17]. Using a computer model to vary arterial distensibility (inverse of stiffness), peripheral resistance, heart rate, maximal cardiac elastance and venous filling pressure from 80 to 120% of their initial value in steps of 10% to mimic the daily BP fluctuations in one theoretical patient, AASI was found to be normally distributed with a mean (SD) of 0.43 (0.04) [22]. Vascular

resistance and heart rate, however, had marked confounding effects that were deemed to seriously limit the use of AASI as a marker of stiffness [22]. Other simulations tested the hypothesis that nonlinear arterial elasticity underlies AASI physiological principles [23].

Methods

Study 1 used a cross-sectional design to examine whether inflammatory factors might be associated with elevated BP variability during 24-hour ABPM [24-26]. The study included 161 clinically healthy adults, 30 to 60 years of age (56 M and 105 non-pregnant F). They had no history of hypertension or cardiovascular disease, and they were not using antihypertensive medications or lipid-lowering drugs. They were also free of any other major systemic illnesses, and they were non-smokers. Questionnaires inquired about age, sex, and race (White, African American, Asian, Hispanic, or other). BMI was derived from measurements of height (Ht, in m) and weight (Wt, in kg) as $BMI = Wt/Ht^2$. Fasting blood samples from each participant were used to determine C-reactive protein (CRP) and tumor necrosis factor-α (TNFα) by ELISA. ABPM for 24 hours used a Spacelabs 90217 monitor (Spacelabs Inc., Redmond Washington), programmed to take measurements at 30-minute intervals [24].

Study 2 is observational in nature [27, 28] and is still ongoing. A random sample of 30 clinically healthy participants was considered in this investigation. They were untreated normotensive and ranged in age from 20 to 35 (N=15) and from 43 to 82 (N=15) years (11 M and 19 F). Measurements of height and weight were used to derive the BMI. Each participant underwent a 7-day/24-hour ABPM, using the TM-2430 monitor from A&D (Tokyo, Japan) programmed to take measurements at 30-minute intervals from 06:00 to 22:00 and every 60 minutes between 22:00 and 06:00.

The AASI was estimated from each ABPM record as the slope from the regression line of DBP as a function of SBP, as illustrated in Figure 1. In Study 2, AASI was estimated globally, considering the entire 7-day record, and also for each of the 7 separate 24-hour days in order to assess the extent of its reproducibility. The daily variation in BP and HR was characterized by fitting a 2-component model consisting of cosine curves with periods of 24 and 12 hours by cosinor [29, 30]. Estimates were thus obtained for the MESOR (M, rhythm-adjusted mean), the amplitude (A) and acrophase (ϕ) (measures of the predictable extent and timing of change within a cycle in relation to local midnight) of each component. In addition, the magnitude, orthophase and bathyphase were derived therefrom to reflect the total extent of predictable change within a day, and the times of maximum and minimum predicted from the composite model, respectively. Statistical analyses include assessing the equality of group means by means of the Student t test or paired t test, and determining associations of the AASI with assumed determinants by linear regression. All analyses were carried out using in-house software and Microsoft Excel 2016.

Results

In Study 1, AASI averaged 0.343 ± 0.151 (SD). Participants whose 24-hour phase was shifted or reversed had a higher AASI as compared to all other participants (0.455 ± 0.047 vs. 0.336 ± 0.012, Student $t = 2.325$, $P = 0.021$). Their CRP was also elevated (8266 ± 2092 vs. 2415 ± 357, Student $t = 3.659$, $P < 0.001$), Figure 2. As illustrated in Figure 3, AASI correlated positively with age ($r = 0.368$, $P < 0.001$), PP ($r = 0.438$, $P < 0.001$), SBP-M ($r = 0.314$, $P < 0.001$), and BMI ($r = 0.145$, $P = 0.068$), and negatively with the magnitude of SBP ($r = -0.162$, $P = 0.042$) and the 24-hour amplitude of DBP ($r = -0.458$, $P < 0.001$). A multivariate regression analysis found age, PP, SBP-magnitude, and DBP-A(24h) to independently predict AASI, Table 1.

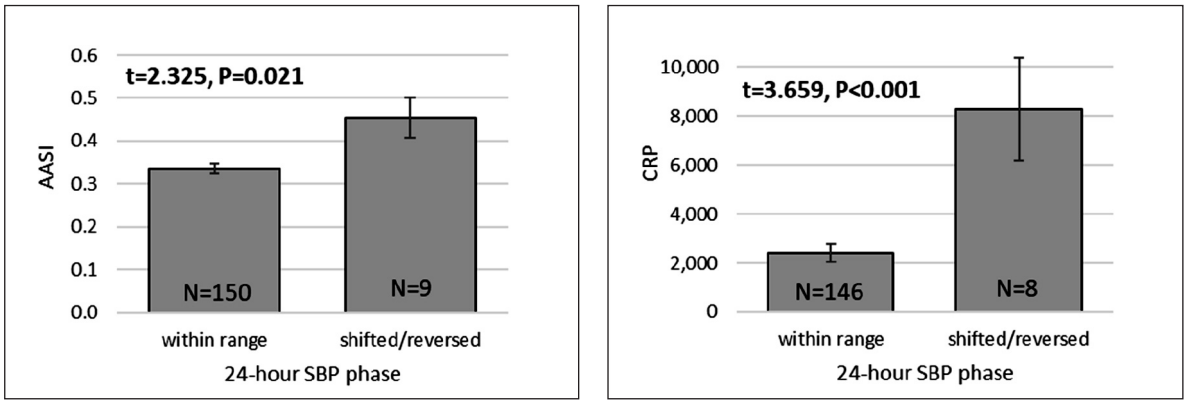

Figure 2: *A misaligned 24-hour pattern of SBP (phase occurring outside acceptable time window) is associated with a higher AASI (left) and elevated CRP (right).*

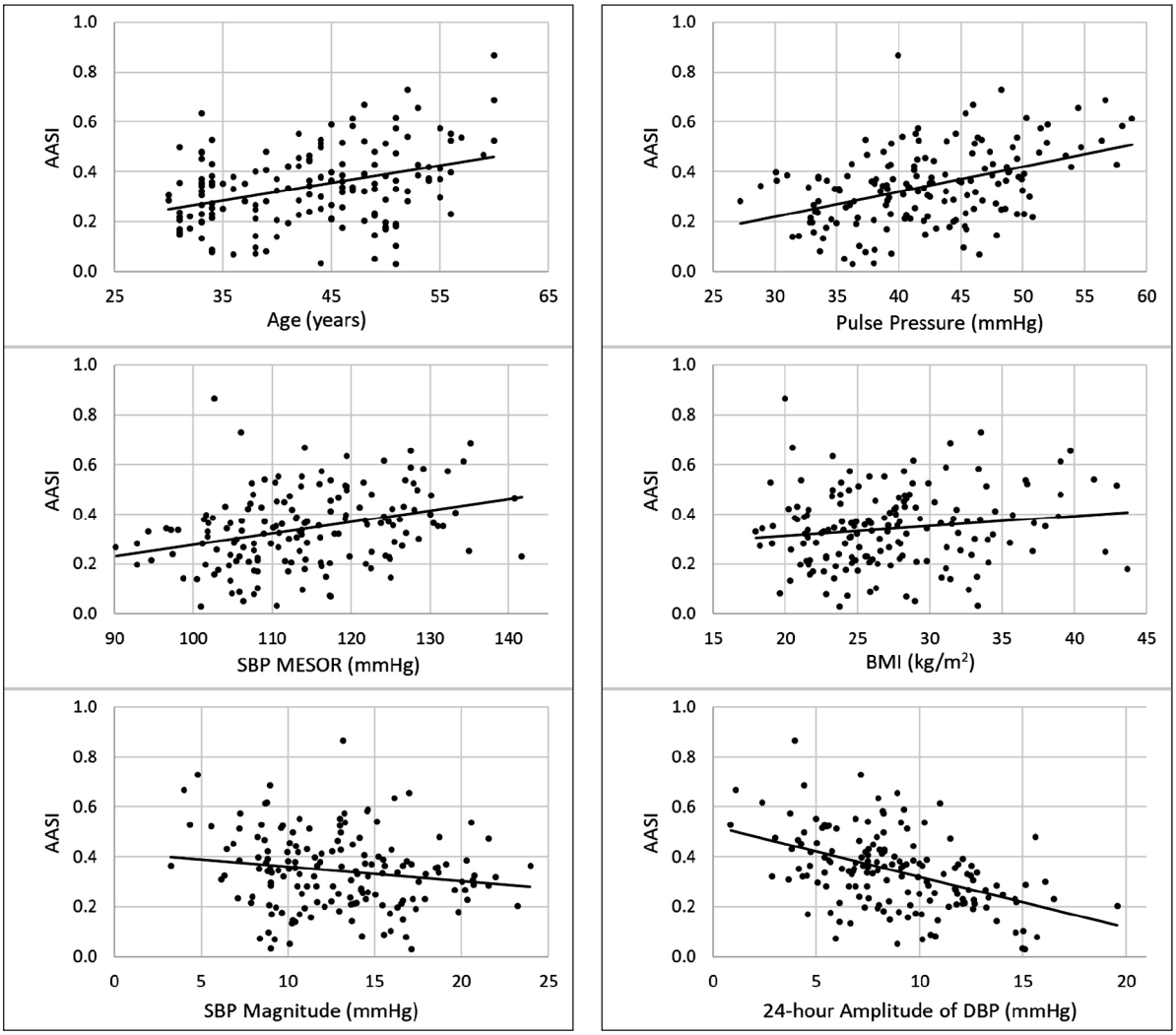

Figure 3: *AASI increases with age (0.0070/year), PP (0.0101/mmHg), SBP-M (0.0046/mmHg), and BMI (by 0.0040/(kg/m^2)) and decreases with the magnitude of SBP (-0.0057/mmHg) and the 24-hour amplitude of DBP (-0.0202/mmHg).*

Table 1: *Multiple regression analysis shows that age, pulse pressure, and variability in both SBP and DBP within 24 hours independently predict AASI (R^2 = 0.4802)*

AASI	df	SS	MS	F	P-value	
Regression	4	1.7340	0.4335	**35.5686**	**4.99E-21**	
Residual	154	1.8769	0.0122			
Total	158	3.6109				
	β	SE(β)	t Stat	P-value	(95%	CI)
Intercept	-0.1137	0.0762	-1.4935	0.1373	-0.2642	0.0367
Age (years)	0.0050	0.0011	4.4825	**1.43E-05**	0.0028	0.0072
PP (mmHg)	0.0087	0.0014	6.4558	**1.33E-09**	0.0061	0.0114
SBP-Mag (mmHg)	0.0060	0.0028	2.1684	**0.031665**	0.0005	0.0115
DBP-A24h (mmHg)	-0.0234	0.0035	-6.7450	**2.91E-10**	-0.0303	-0.0165

In Study 2, AASI averaged 0.491 ± 0.102 (SD). It did not differ significantly between men and women, between younger (20-35 years) and older (43-82 years) participants, or between participants with or without VVDs (vascular variability disorders, defined as any abnormality of the within-day BP and/or HR variability [31]). AASI was not significantly associated with age, PP, SBP MESOR, BMI, or the magnitude of SBP (P > 0.2). It only weakly correlated negatively with the 24-hour amplitude of DBP (r = -0.303, P=0.104), Figure 4.

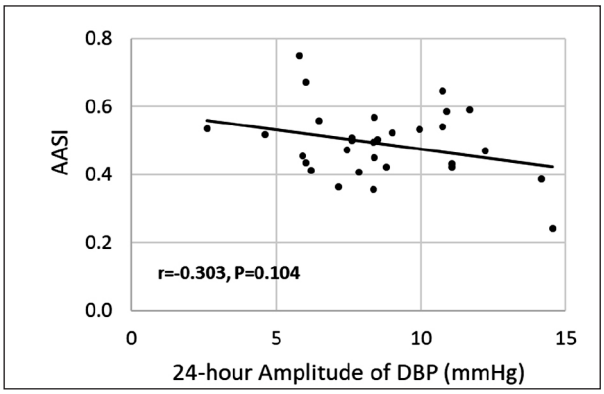

Figure 4: *Weak association of AASI with the 24-hour amplitude of DBP in Study 2. AASI is estimated to decrease by 0.0114±0.0068/mmHg.*

In this study, AASI was estimated from 7-day/24-hour ABPM records. By assessing the AASI for each of the 7 days separately, the mean AASI(24h) and its SD were computed for each participant. Overall, the SD of AASI(24h) correlated negatively with the average number of measurements per 24 hours (r = -0.467, P = 0.009). This relation, however, depended on two outliers related to participants who had fewer than 35 measurements per 24 hours on average. It was no longer significant after removing the two outliers (P > 0.2).

Each day's AASI(24h) correlated strongly with AASI computed from the 7-day/24-hour ABPM records. Moreover, the regression lines showed a good agreement between each day's AASI(24h) and the global AASI estimate, as evidenced by intercepts (a) not differing from zero and slopes (b) not differing from one, Table 2.

As shown in Figure 5, the day-to-day variability in AASI is relatively large, with an average SD of 0.159 and an average range of 0.450 across all 30 participants. The average AASI(24h) of 0.484 ± 0.106 is close to the average AASI determined from the entire 7-day/24-hour ABPM records, as is the average median AASI(24h) of 0.477 ± 0.127.

Table 2: *Agreement between each day's AASI(24h) and the global AASI estimated from the entire 7-day/24-hour ABPM records, determined by linear regression analysis*

Day	r	P	a	SE(a)	b	SE(b)
1	0.576	0.001	-0.010	0.140	1.042	0.280
2	0.389	0.033	0.124	0.159	0.711	0.318
3	0.519	0.003	0.128	0.125	0.801	0.249
4	0.731	0.000	-0.270	0.135	1.530	0.270
5	0.367	0.046	0.115	0.168	0.698	0.335
6	0.433	0.017	0.019	0.180	0.913	0.359
7	0.706	0.000	-0.113	0.116	1.216	0.230

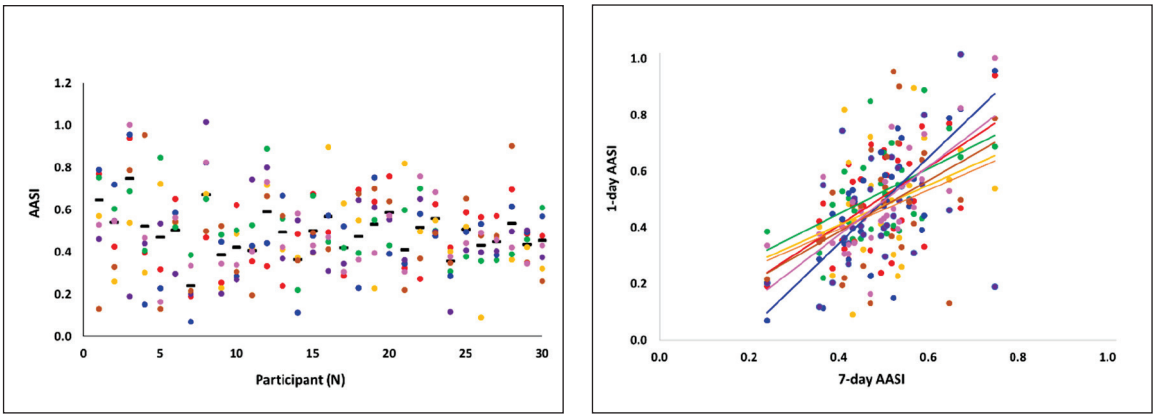

Figure 5: *Despite good agreement between each day's AASI(24h) and the global AASI estimated from the 7-day/24-hour ABPM records (linear regression analyses, right; see also Table 2), AASI(24h) varies greatly from one day to another (left). Each color represents a different day.*

Discussion and Conclusion

While both studies included clinically healthy adults of similar age and equal sex distributions, the average AASI differed greatly between the two populations (0.491 ± 0.102 in Study 2, compared to 0.343 ± 0.151 in Study 1). In order to understand the reason for this large difference in AASI, we reviewed aspects in which the two studies differed.

- Study 1 was performed in the USA, while Study 2 was conducted in the Czech Republic. Although participants were Caucasian in Study 2, Study 1 was multi-racial, but AASI did not differ among different races.

- The ABPM monitor used in Study 1 was the Spacelabs 90217 and in Study 2, it was the A&D TM-2430. Both were validated for accuracy.

- The duration of monitoring was 7 days in Study 2, compared to 24 hours in Study 1. As shown above, there was good agreement between each day's AASI(24h) with the global AASI estimated from the 7-day records.

- The two studies differed in terms of the sample size, Study 1 including 161 participants, compared to 30 in Study 2. While likely accounting for the failure of Study 2 to discern effects of potential determinants of AASI, it should not have affected the AASI.

Despite the larger number of BP measurements in Study 2 than in Study 1, a difference in the sampling schedule between the two studies might have played a role. In Study 1, sampling was kept the same throughout the 24 hours, with measurements taken every 30 minutes. By contrast, in Study 2, the 30-minute sampling interval during daytime was changed to 60 minutes during the night. In order to check whether this difference in sampling schedule affected the estimation of AASI, nighttime data of Study 1 were decimated by removing measurements collected at 00:30, 01:30, 02:30, 03:30, 04:30, and 05:30 (up to 6 measurements per record) to simulate the hourly nighttime sampling of Study 2. Although the number of readings remained mostly above 35, the AASI estimate increased by 0.017 ± 0.003 (paired $t = 5.111$, $P < 0.001$), Figure 6.

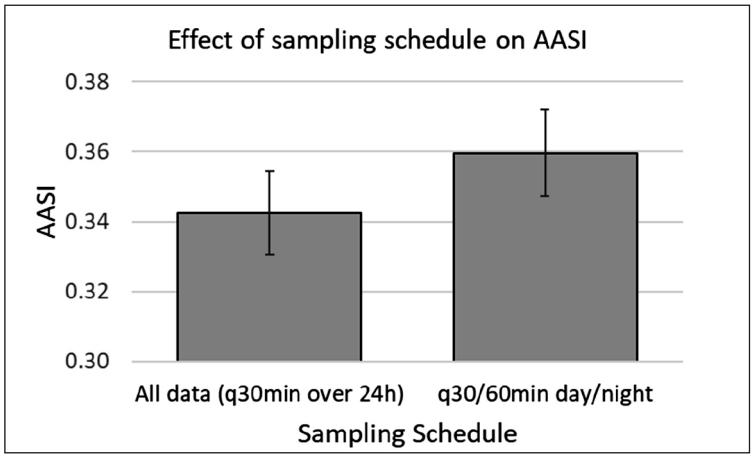

Figure 6: *Switching nighttime sampling from once every 30 minutes to once every 60 minutes affects the estimation of AASI, which increased by 0.017 ± 0.003 (paired $t = 5.111$, $P < 0.001$).*

Table 3: *Estimated effect on AASI of differences in characteristics between the two studies*

Population:	1	2	Δ(variable)	Δ(AASI)
Variable				
AASI(q30min)	0.343			
AASI(q30/60min)	0.360			
M/F(%)	34.8/65.2	36.7/63.3		
Sampling	q30min	q30/60min		0.01711
Age	43.19	44.53	1.34	0.00939
PP	42.23	48.20	5.97	0.06014
SBP-M	114.12	120.17	6.05	0.02757
DBP-M	71.89	71.97		
BMI	27.27	24.88	-2.39	-0.00949
SBP-A(24h)	9.93	10.79		
SBP-mag	12.95	14.09	1.14	-0.00651
DBP-A(24h)	8.86	8.61	-0.25	0.00502
HR-M	73.12	70.24		
HR-SD	10.12	13.96		
				Total
				0.10323

Albeit small, the two populations differed slightly in terms of mean age, PP, SBP MESOR, BMI, SBP magnitude, and 24-hour amplitude of DBP. In order to see whether these differences in factors potentially affecting AASI might account for the difference in AASI between the two studies, the slopes estimated by linear regression of AASI on each of these factors in Study 1 were used to estimate effects these small differences could have had on the estimation of AASI in Study 2. For instance, age averaged 43.19 years in Study 1 and 44.53 years in Study 2. From Figure 3, AASI increases by 0.0070 for each 1-year increase in age. The correcting factor for AASI between Study 1 and Study 2 can hence be estimated as 0.0070*(44.53 – 43.19) = 0.0094. As shown in Table 3, accounting for all variables affecting AASI, the total correction to be applied to the estimate of Study 2 based on results from Study 1 amounts to ΔAASI = 0.103:

$$AASI_{Study2}(\text{estimated}) = AASI_{Study1} + \Delta AASI = 0.360 + 0.103 = 0.463$$

As $AASI_{Study2}$ was 0.491, the difference between the two studies is reduced to 0.491 – 0.463 = 0.028. Physiological differences between the two populations thus seem to account for the difference observed in AASI between the two studies.

This result and those of Table 2 and Figure 5 are in agreement with published findings on the reproducibility of the AASI [32-35]. They point to the usefulness of the AASI as an easily determined index of arterial stiffness in population studies, but they also indicate the shortcomings of using this marker as a guide for the management of individual patients. It is hence not surprising that others concluded that the AASI response to antihypertensive treatment is only marginal and clinically uncertain, which may render its use as a therapeutic target in clinical practice questionable [36].

In summary, our results, obtained in a random sampling of clinically healthy, normotensive individuals, agree with other published studies, some of them carried out in untreated or treated hypertensive patients. Study 1 results show that AASI may serve as a marker of organ damage in view of its association with CRP. They also confirm that factors such as age, PP, and BMI influence AASI, as does BP variability within a day, as gauged by the 24-hour amplitude of DBP and the magnitude of SBP. As such, AASI reflects both arterial stiffness and BP variability, as others also concluded (see literature review above). In addition, we showed that a misaligned 24-hour variation in BP (when the 24-hour acrophase lies outside the acceptable time window) is also associated with a higher AASI (Figure 2).

The uncertainty associated with the estimation of AASI, gauged by the SD across 7 days, was larger for the few records containing fewer than 35 measurements, in agreement with published recommendations [6]. In addition, we showed that the sampling schedule also plays a role. Switching the sampling interval from 30 to 60 minutes during the night resulted in a statistically significant increase of 0.017 in the estimation of AASI (Figure 6).

Finally, we showed that, on average, AASI estimated from 24-hour ABPM records agrees well with AASI estimated from 7-day/24-hour ABPM records. The day-to-day variability in AASI estimates, however, is relatively large. The AASI may thus serve as a useful marker in population studies, while its usefulness for the management of individual patients remains questionable. The dependence of the AASI on BP variability also needs to be considered as both a blessing and a curse since it is not a specific proxy for arterial stiffness but it can capture cardiovascular disease risk also associated with circadian disruption. Whether modified estimates of the AASI such as the symmetrical AASI can provide more specific markers of arterial stiffness deserves further study.

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https://doi.org/10.5817/CZ.MUNI.M280-0669-2024-3

Off-Wrist, Off-Mark: How Off-Wrist Events Skew Estimation of Circadian Characteristics from Actigraphy Data

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Support:

Halberg Chronobiology Fund (GC)

Introduction

Ever since the discovery of molecular mechanisms responsible for the manifestation of circadian rhythms, interest has grown in understanding their involvement in processes of aging and the pathogenesis of diseases [1-4]. Chronomedicine, the investigation of biological rhythms in health and disease, has grown in interest as a way to enhance health and performance, detect impending disease risk early, and optimize treatment timing [5]. As the endogenous circadian system coordinates cellular, physiological, and behavioral processes, disruption from its natural environment has been linked to an increased risk of various diseases like obesity, diabetes, cardiovascular diseases and cancer [6].

For health surveillance and other applications in chronomedicine, various wearable technologies now exist to monitor a host of physiological variables. In particular, actigraphy lends itself well to study sleep and circadian rhythms [7], as it is able to capture data continuously in unsupervised, free-living conditions in large-scale studies [8]. Evaluating and modeling activity patterns is important for understanding disease risk and improving health outcomes [9].

One important issue related to collecting and analyzing actigraphy data, however, relates to the difficulty of distinguishing sedentary behavior from non-wear episodes that occur when the user removes the wearable device. Failure to identify non-wear episodes accurately affects downstream measures, including the volume of valid, usable data, and the amount of sleep, sedentary behavior and activity estimates [10]. The accurate detection of non-wear time is still an ongoing problem, since this issue has received little attention and studies have failed to address it adequately [11].

Several algorithms have been proposed to distinguish wear time from non-wear time. Most of them rely on a continuous stream of zeroes in intervals varying from 10 to 60 minutes to indicate a non-wear episode [12]. Two other algorithms allow for 2 minutes of interruptions within a 60- or 90-minute interval of zero counts per minute [13, 14]. Heuristic and machine learning approaches have also been developed and tested based on specific protocols mimicking contexts of actimeter wear/non-wear in real-life [15]. Without an accompanying diary, however, these algorithms are not entirely reliable, notably for detecting short non-wear intervals.

Newer devices have incorporated sensors to measure other variables in addition to activity. Most commonly, these variables are wrist temperature and light exposure, including a breakdown in different wavelength ranges. Temperature then offers itself as another approach to identify nonwear intervals. When losing contact with the skin, the temperature signal usually decreases until it reaches the surrounding temperature. Using absolute temperature thresholds, however, as some algorithms do [16, 17], risks overestimating or underestimating non-wear time. Since such a threshold would need to account for the large-amplitude circadian rhythm in temperature and for inter-individual differences in average temperature, it could not be a fixed value and would need to be adjusted, which is not practical. Vert et al. [18] proposed an algorithm, called DETACH, which uses both raw acceleration data and a rate-of-change in temperature criterion. Other algorithms using an approach based on signal processing and data-driven decision rules have also been described [11].

Our goal herein is to illustrate the critical importance of detecting non-wear data and any other outliers in chronobiological applications using actigraphy. We also discuss the merit of using changes in temperature to detect non-wear intervals.

Methods

Participants. Participants in one study were mostly teenagers in Brazil who were monitored for at least one week on several occasions over one year. Participants in the other study were Arctic residents, 12 to 59 years of age, who were monitored for 7 days each during the spring equinox as part of the "Light Arctic" study [19].

Device. We analyzed data collected with the actigraph ActTrust from Condor Instruments (Sao Paulo, Brazil), Figure 1. Volunteers in two different studies wore it on the wrist to assess cycles of rest and activity non-invasively. Movement, sensed by means of accelerometers, was recorded every 0.1 second, and measurements were aggregated over 1-minute intervals according to different modes, including the Proportional Integrating Measure (PIM) mode that measures the intensity of movement, considered herein. The device also sensed skin temperature and light exposure.

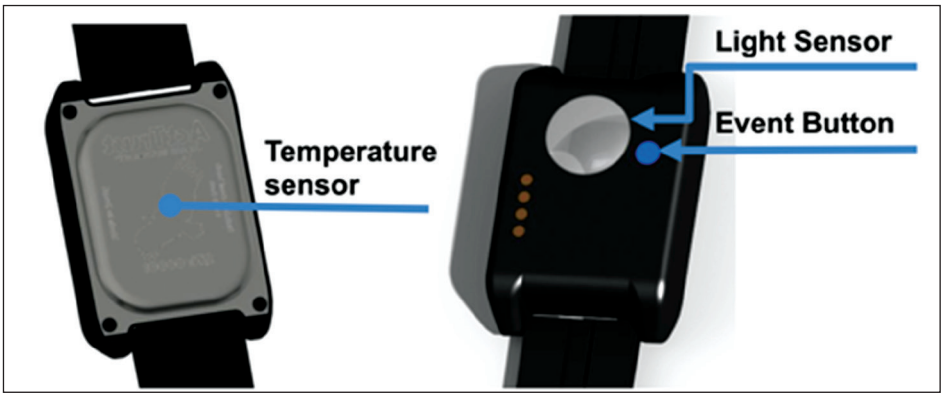

Figure 1: *Condor Instruments' ActTrust Actigraph*

Data. Data collected by the ActTrust device are saved as text files. They were imported into Excel and Mathematica. Figure 2 illustrates the beginning of such a data file. The first few lines include metadata with information about the wearer and the device used. The following rows are the data, including the date and time when measurements of wrist temperature, activity (three different modes, including PIM), and light exposure (in different wavelength ranges) were taken. In the examples considered herein, measurements were aggregated at 1-minute intervals.

Detection of non-wear episodes. Contrary to activity that can change rapidly from sedentary to active and vice versa, changes in temperature are much slower. Concomitant temperature and activity data can follow one of four different scenarios.

(1) Stable temperature and non-zero activity is the most common.

(2) Stable temperature and no (or zero) activity indicates sedentary behavior or sleep.

(3) Rapidly changing temperature and non-zero activity does not correspond to non-wear data but may deserve further attention when the temperature data qualify as outliers [20].

(4) Rapidly changing (usually decreasing) temperature accompanied by no (or zero) activity indicates the start of non-wear data. In this case, the end of the non-wear interval needs to be identified when activity returns to non-zero values and temperature starts increasing rapidly.

Figure 3 illustrates how to distinguish between two cases of no activity, one corresponding to sedentary behavior and the other to a non-wear episode.

```
+-------------+ Condor Instruments Report +-------------+
SOFTWARE_VERSION : 1.0.22
SUBJECT_NAME : xxxxxxxxxxx
SUBJECT_GENDER : Male
SUBJECT_DATE_OF_BIRTH : 30/06/2001
SUBJECT_DESCRIPTION : xxxxxxxxxxxx
DEVICE_ID : 1174
DEVICE_MODEL : ActTrust1
HARDWARE_VERSION : 3.2
FIRMWARE_VERSION : 3.7
MEMORY_SIZE : 3987712
LOG_SIZE : 2411259
MEMORY_USAGE : 60.47 %
BATTERY_VOLTAGE : 4.21875
ERROR_FLAG : 0
ERROR_CODE : 0
POWER_DOWN_FLAG : 0
TAT_THRESHOLD : 1024
ORIENTATION : 0
MODE : PIM/TAT/ZCM
INTERVAL : 60
DATA_CORRECTION : 0
DATA_CORRECTION_DESCRIPTION : Nenhum
DATE_TIME : 24/05/2022 18:44:45
+-----------------------------------------------------------+
DATE/TIME;MS;EVENT;TEMPERATURE;EXT TEMPERATURE;ORIENTATION;PIM;PIMn;TAT;TATn;ZCM;ZCMn;LIGHT;AMB LIGHT;RED LIGHT;GREEN LIGHT;BLUE LIGHT;IR LIGHT;UVA LIGHT;UVB LIGHT;STATE
22/03/2022 18:36:22;0;0;24.26;24.50;0;2533;1.53704e-06;148;8.98072e-08;77;4.6724e-08;36.83;14.92;5.64;7.07;2.97;2.08;0.00;0.00;0
22/03/2022 18:37:22;0;0;24.14;24.38;0;6346;105.767;356;5.93333;218;3.63333;12.62;5.11;1.84;2.51;0.99;0.69;0.00;0.00;0
22/03/2022 18:38:22;0;0;24.09;24.31;0;0;0;0;0;0;0.01;0.00;0.00;0.00;0.00;0.00;0.00;0.00;0
22/03/2022 18:39:22;0;0;24.04;24.25;0;0;0;0;0;0;0.01;0.00;0.00;0.00;0.00;0.00;0.00;0.00;0
22/03/2022 18:40:22;0;0;24.00;24.19;0;0;0;0;0;0;0.01;0.00;0.00;0.00;0.00;0.00;0.00;0.00;0
22/03/2022 18:41:22;0;0;23.96;24.12;0;0;0;0;0;0;0.01;0.00;0.00;0.00;0.00;0.00;0.00;0.00;0
22/03/2022 18:42:22;0;0;23.93;24.12;0;0;0;0;0;0;0.01;0.00;0.00;0.00;0.00;0.00;0.00;0.00;0
22/03/2022 18:43:22;0;0;23.90;24.06;0;0;0;0;0;0;0.01;0.00;0.00;0.00;0.00;0.00;0.00;0.00;0
22/03/2022 18:44:22;0;0;23.86;24.00;0;0;0;0;0;0;0.01;0.00;0.00;0.00;0.00;0.00;0.00;0.00;0
```

Figure 2: *Example of ActTrust data (only data over the first few minutes are shown).*

Transition from Scenario 1 to Scenario 2

Timestamp	TEMP	PIM
2022-04-01T21:19:09	33.2	578
2022-04-01T21:20:09	33.33	8
2022-04-01T21:21:09	33.38	205
2022-04-01T21:22:09	33.23	869
2022-04-01T21:23:09	33.04	0
2022-04-01T21:24:09	32.9	12
2022-04-01T21:25:09	32.79	0
2022-04-01T21:26:09	32.7	0
2022-04-01T21:27:09	32.63	0
2022-04-01T21:28:09	32.57	0
2022-04-01T21:29:09	32.51	0
2022-04-01T21:30:09	32.47	0
2022-04-01T21:31:09	32.44	0
2022-04-01T21:32:09	32.41	0
2022-04-01T21:33:09	32.4	0

Sedentary behavior: while activity (PIM) drops to zero, temperature remains stable

Transition from Scenario 3 to Scenario 4

Timestamp	TEMP	PIM
2022-04-04T19:06:09	29.61	11093
2022-04-04T19:07:09	29.36	11967
2022-04-04T19:08:09	28.98	10851
2022-04-04T19:09:09	28.1	11859
2022-04-04T19:10:09	27.39	0
2022-04-04T19:11:09	26.95	0
2022-04-04T19:12:09	26.61	0
2022-04-04T19:13:09	26.31	0
2022-04-04T19:14:09	26.04	0
2022-04-04T19:15:09	25.81	0
2022-04-04T19:16:09	25.59	0
2022-04-04T19:17:09	25.38	0
2022-04-04T19:18:09	25.18	0
2022-04-04T19:19:09	24.99	0
2022-04-04T19:20:09	24.82	0

Start of non-wear episode: PIM abruptly drops to zero and temperature decreases by 3°C in 15 minutes

Transition From Scenario 4 to Scenario 1

Timestamp	TEMP	PIM
2022-04-05T03:51:09	24.7	0
2022-04-05T03:52:09	24.69	0
2022-04-05T03:53:09	24.69	0
2022-04-05T03:54:09	24.69	0
2022-04-05T03:55:09	24.7	0
2022-04-05T03:56:09	24.69	0
2022-04-05T03:57:09	24.69	0
2022-04-05T03:58:09	24.69	0
2022-04-05T03:59:09	24.7	0
2022-04-05T04:00:09	27	4396
2022-04-05T04:01:09	29.51	3255
2022-04-05T04:02:09	30.34	2854
2022-04-05T04:03:09	30.69	3835
2022-04-05T04:04:09	30.96	3966
2022-04-05T04:05:09	31.18	2516
2022-04-05T04:06:09	31.48	5665

End of non-wear episode: PIM abruptly transitions from zero to non-zero values and temperature increases by 6.7°C in 6 minutes

Figure 3: *Distinguishing between wear and non-wear data, based on temperature and activity.*

Data analysis. Actigraphy records from 5 participants serve as examples to illustrate the need to remove non-wear data prior to analysis. Wrist temperature (wT) and activity (PIM) data from each record are analyzed using all unedited data, and after editing by removing data during the detected non-wear episodes. In each case, data are stacked over a 24-hour cycle and analyzed by cosinor [21, 22]. Specifically, a 2-component model consisting of cosine curves with periods of 24 and 12 hours is fitted by least squares to the data to yield estimates of the MESOR, a rhythm-adjusted mean, and of the amplitude and acrophase (phase of maximum in relation to local midnight) of each component. Data were analyzed using Wolfram Mathematica 14.1 running on an Apple macOS 15.1 host with 32GB

of RAM. Other supported Mathematica configurations are documented on the software publisher's website [23].

Results

For each of the five selected records, a Mathematica-based import function was written to import the data, extract the two variables of interest (wT and PIM), together with their associated date and timestamps, and analyze them as outlined above. Figure 4 illustrates how detecting non-wear data from activity alone can be difficult, and how the simultaneous consideration of temperature can help.

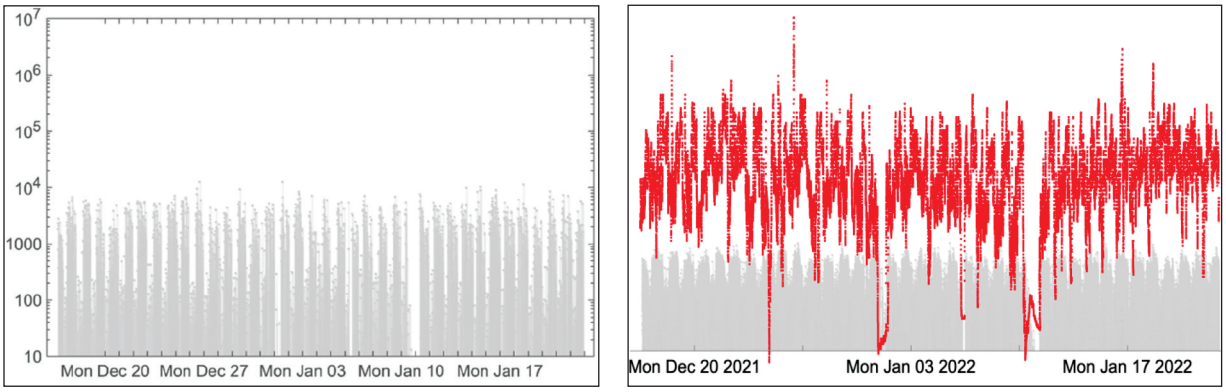

Figure 4: *Activity (PIM) data from participant Pt01: 12/16/2021 15:00 - 01/22/2022 20:47 (37 days, 5 hours and 47 minutes). Overlaying temperature data (red) over activity (grey) helps identify 12 non-wear episodes spanning a total of 6108 minutes (6.04%), validated by diary.*

Figure 5 illustrates how failing to remove non-wear data from the record prior to analysis can have a profound effect on the results and even bias conclusions derived from the study. Here, PIM has been $\log_{10}$-transformed to render its distribution closer to a normal distribution. While including non-wear data alters its average 24-hour profile, notably between 08:00 and 09:30, the effect on wrist temperature is much larger. Data during the night are consistently higher by about 0.5°C after deleting non-wear data. The even larger difference observed in the morning can be accounted for by the fact that this participant consistently removed the device while going to the gym to exercise. In this graph, the 1-minute data were first averaged over consecutive 15-minute intervals. They were then stacked over an idealized 24-hour day. Means across days at corresponding times are plotted with their standard errors.

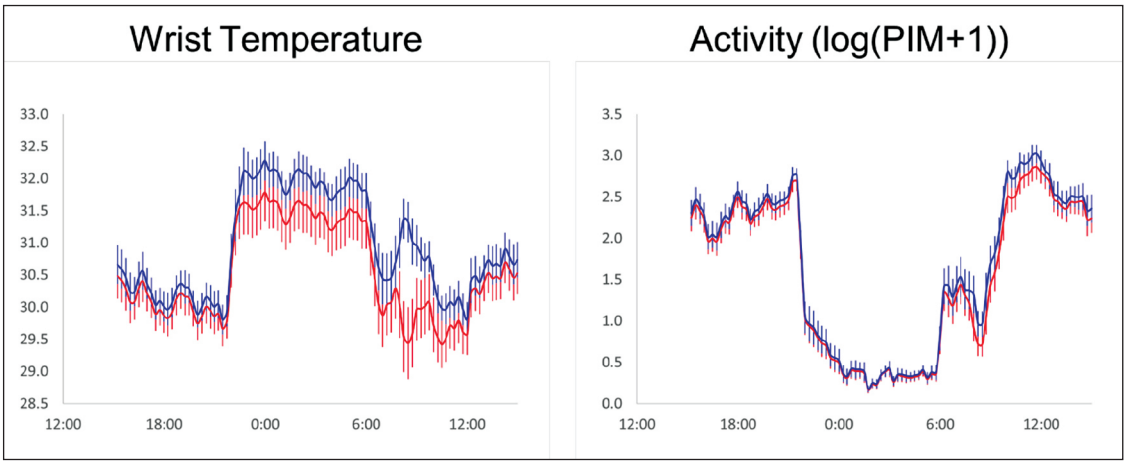

Figure 5: *Data from participant Pt01 shown in Figure 4 are stacked over an idealized 24-hour day. Results from unedited data (red) differ markedly from results obtained after removing non-wear data (blue). The effect of non-wear data is larger for wrist temperature (left) than for activity, shown here after log_{10}-transformation to normalize its distribution (right).*

In Figure 6, a 2-component model is fitted to the average 24-hour profile of wrist temperature. Parameters of the model differ markedly depending on whether non-wear data are included or excluded. In the former case, the model can be written as $wT = 30.54 + 0.74\cos(2\pi t/24h - 0.45) + 0.56\cos(2\pi t/12h - 1.24)$, whereas in the latter case, it is $wT = 30.93 + 0.87\cos(2\pi t/24h - 0.77) + 0.46\cos(2\pi t/12h - 1.13)$. The difference in MESOR between the two models is highly significant ($F=29.302$, $P<0.001$). In addition, a 73-minute difference in acrophase of the 24-hour component is also detected ($F=5.836$, $P=0.017$). The 0.13˚C difference in amplitude is not significant in this case.

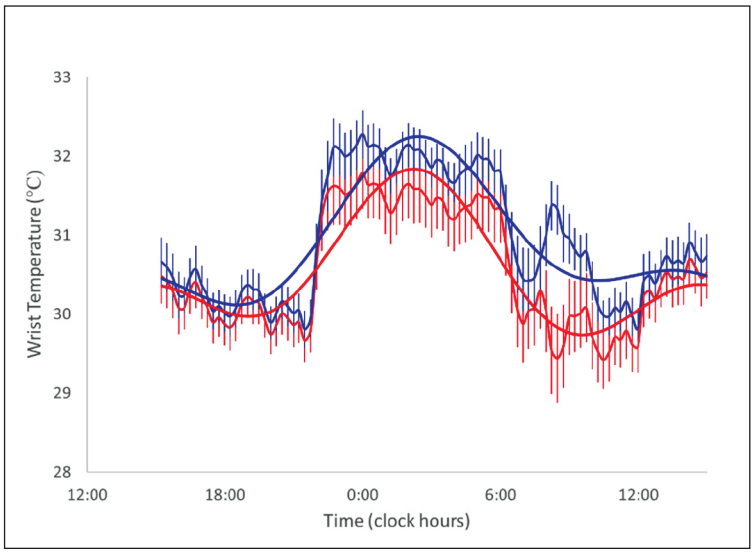

Figure 6: *Two-component model fitted to wrist temperature data of participant 01 differs markedly depending on whether non-wear data are included (red) or excluded (blue).*

A weeklong record of wrist temperature and activity (PIM) from one of the Arctic residents is displayed in Figure 7. In the absence of a diary, non-wear episodes were identified as outlined above. Despite the presence of multiple outliers in temperature, only one non-wear episode was detected.

Stacking the temperature data over an idealized 24-hour day reveals that outlying values tend to occur at similar times of day, shortly after noon and in the evening. Removing non-wear data had only a minor effect in this case, but further removal of outliers had a much larger effect in characterizing the circadian variation in wrist temperature, as seen in Figure 8. Also apparent from Figure 8 are marked differences in the 24-hour pattern of temperature from one day to another, with much higher daytime values observed during the weekend as compared to workdays.

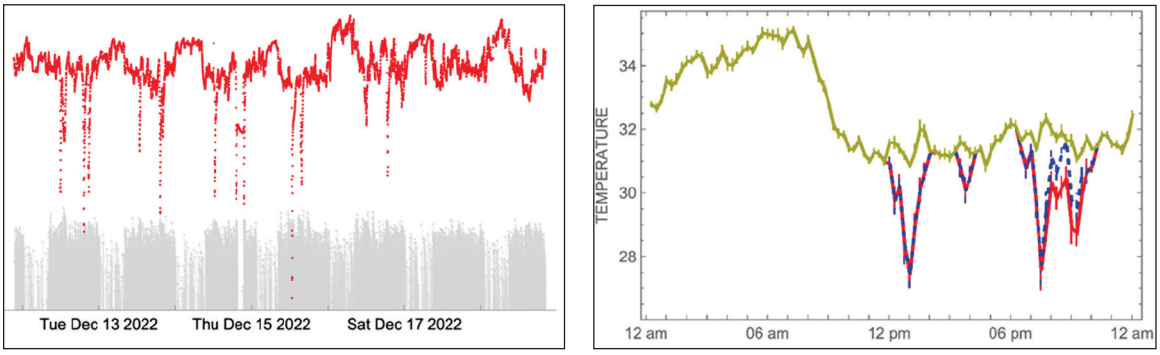

Figure 7: *Left: Weeklong record of wrist temperature (red) and activity (PIM, grey) of Arctic resident #010. Right: 24-hour profile of wrist temperature after stacking the data over a single 24-hour day (from local midnight to the next midnight), using all data (red), after removing non-wear data only (blue), as well as all outliers (yellow). Note only small difference between red and blue curves, which differ greatly from the yellow curve.*

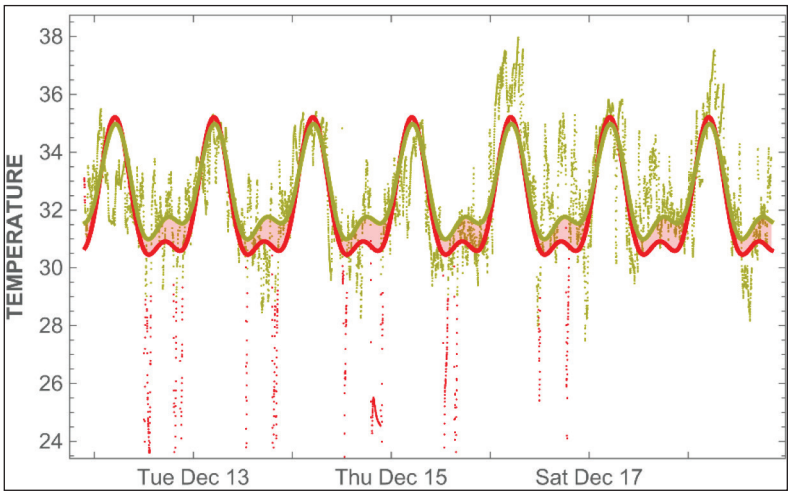

Figure 8: *Outlying values of wrist temperature of Arctic resident #010 greatly affect the characterization of its circadian variation during the daytime. Daytime values are also much higher during the weekend (last two days) as compared to workdays (first 4 days): On Saturday (Dec 17), some daytime temperatures reach values as high as the global model's predicted maximum (close to 35˚C). The unedited data are shown with the 2-component model fitted to all data (red) and after removing non-wear data and outliers (yellow).*

The effect of non-wear data on wrist temperature of three other Arctic residents is shown in Figure 9. The total duration and timing of non-wear data differ in each case, with two to five episodes detected during the weeklong monitoring session.

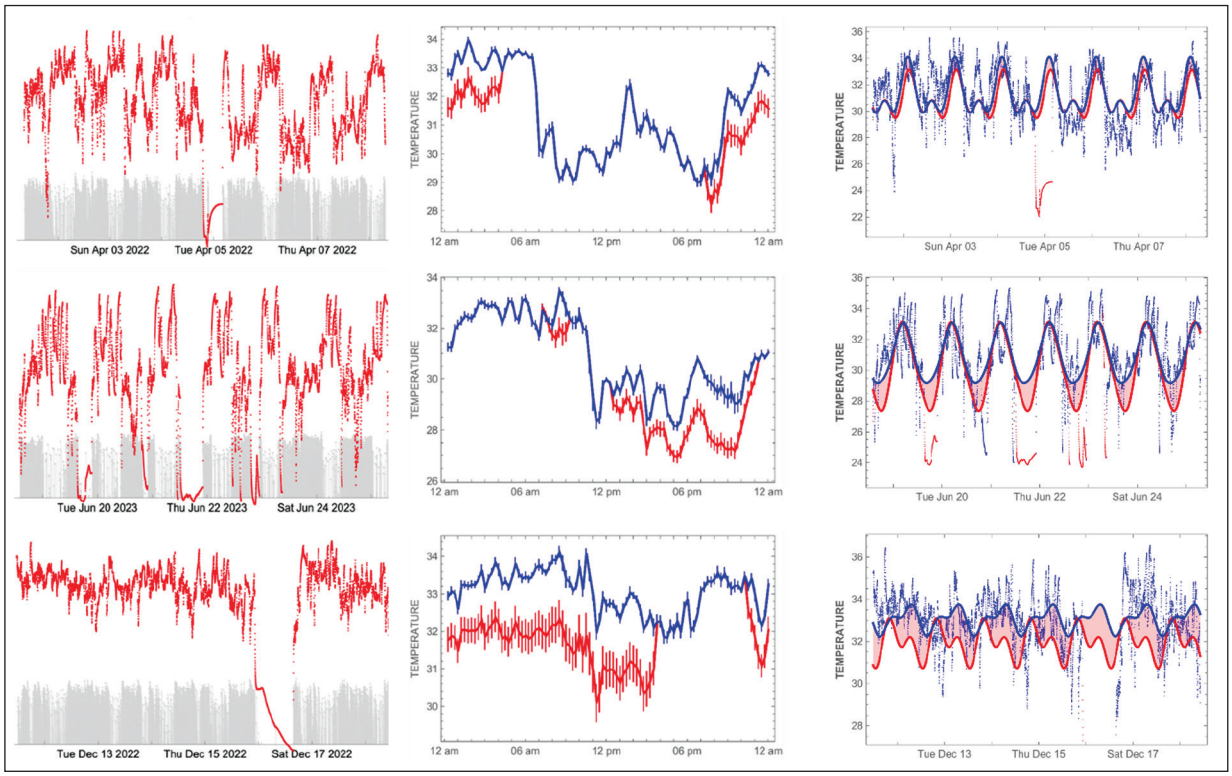

Figure 9: *Left: Weeklong records of wrist temperature (red) and activity (PIM, grey) of Arctic residents #002 (top), #154 (middle), and #144 (bottom). Center: 24-hour profile of wrist temperature using all data (red) and after removing non-wear data (blue). Right: Weeklong record of wrist temperature shown with fitted 2-component model consisting of cosine curves with periods of 24 and 12 hours.*

Discussion and Conclusion

In view of the difficulties in correctly identifying non-wear data [11, 20] and the marked effect such data can have, as illustrated above, the importance of keeping an accurate diary cannot be emphasized enough. Once non-wear intervals have been identified, it is crucial to remove these data prior to analysis, as illustrated herein. These points have direct implications in study design.

Implications of the handling of non-wear data regarding data analysis are particularly consequential in chronobiological applications. Even a small amount of non-wear data can profoundly affect the correct estimation of rhythm parameters, including the 24-hour amplitude and acrophase in addition to the MESOR that are all sensitive to outliers. This consideration applies particularly to wrist temperature, which is affected by non-wear data to a larger extent than activity (or light exposure), as illustrated herein (see Figure 5). The characterization of circadian rhythms thus requires even more attention to non-wear data than the usual concern of assessing active and sedentary times and distinguishing sleep from awake intervals. Being able to sense skin temperature and light exposure in addition to activity has great merit in chronobiology as these variables represent important markers of the circadian system and of the negative effects that circadian disruption has on health [19, 24-28].

Apart from the influence of non-wear data on the characterization of circadian rhythms, the examples reviewed herein raised two additional questions deserving further consideration. One question relates

to what needs to be done with outliers that do not correspond to non-wear data, as seen in Figure 7. Although they may be valid data, keeping them in the analysis will affect the characterization of the circadian rhythm in wrist temperature. Resulting parameters thus reflect both the 24-hour variation and the confounding effect of external factors on the 24-our variation in wrist temperature. Removing all outliers might help separate these two sources of variation. Again, information kept in a diary would be very useful in this case. For instance, one could determine whether the effect of cold exposure for a given amount of time on wrist temperature varies as a function of when during the day cold exposure took place.

Another question relates to the merit to be derived from also analyzing the data day by day. Records such as that shown in Figure 8 reveal features that may be specific to some but not all days, as may be the case between weekends and workdays. Understanding and assessing day-to-day differences in rhythm characteristics is important for determining the extent of external influences, such as daily events.

In summary, using temperature and activity data in combination, it is possible to detect even short non-wear intervals by following the different scenarios illustrated in Figure 3, without necessarily analyzing the raw 3-dimensional accelerometer data, which are sampled at a much higher frequency to generate the 1-minute aggregated activity measurements. New algorithms could be developed to detect non-wear data that do not rely on any temperature thresholds, using only activity data and the rate of change in skin temperature. Another improvement can come from newer actigraphs such as the ActLumus from Condor Instruments (Sao Paulo, Brazil) that now provides an added skin contact sensor specifically aimed at detecting off-wrist episodes. Such a development is great news in view of the critical importance of excluding non-wear data prior to analysis, as illustrated herein

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https://doi.org/10.5817/CZ.MUNI.M280-0669-2024-4

Natural Foods-based Chronotherapy of Blood Pressure

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University of Minnesota Supercomputing Institute (GC)
A&D (GC

Introduction

A healthy diet is known to help protect against non-communicable diseases, including diabetes, heart disease, stroke and cancer. Unhealthy diets and lack of physical activity were repeatedly associated with increased global risks to health [1-3]. An unhealthy diet and physical inactivity are among the most important behavioral risk factors underlying cardiovascular diseases, which are the leading cause of death globally, resulting in raised blood pressure (BP) as one of their major effects [4]. A diet rich in fruits and vegetables is generally associated with a lowered BP and decreased cardiovascular risk [5, 6].

The key ingredients of the DASH and Mediterranean-style diets responsible for their beneficial health effects are a high intake of fruits, vegetables, whole grains, legumes, nuts, seeds, and healthy fats like olive oil, which provide a rich source of fiber, vitamins, minerals, antioxidants, and unsaturated fatty acids, contributing to improved heart health and overall well-being [7]. Specific nutrients in selected fruits and vegetables also contribute to heart health. For instance, bananas, leafy green vegetables like spinach and kale, beets, berries, fatty fish like salmon, whole grains like oatmeal, low-fat dairy products like yogurt, dark chocolate, and tomatoes are foods that are considered to help lower BP, as they are rich in potassium, nitrates, fiber, and other nutrients that can help regulate BP [8].

Herein, we investigate the effects of eggplant and Kalahari watermelon on BP. Watermelon, which contains an amino acid called citrulline, is thought to also have a BP lowering effect [9]. Citrulline is converted in the body to arginine, which helps the body produce nitric oxide, a gas that relaxes blood vessels and helps arteries be more flexible. These effects aid blood flow, which can lower high BP. Eggplant is another vegetable that contains compounds that are susceptible to help lower BP [10].

The Kalahari watermelon is native to the Kalahari Desert in Southern Africa. It is known as the "miracle watermelon" because it survives in this harsh environment where it receives twice as much UV rays as in Tokyo, Japan. The fruit is about 97% water, has excellent water retention, and is extremely resistant to rotting and drying, making it a true miracle plant [9]. The Kalahari watermelon is a valuable food source that can thrive even in such environments, providing sustenance to the people and wild animals living in the desert, Figure 1.

Figure 1: *Kalahari watermelon: fruit and cross-section.*
Courtesy of Euglena Co., Ltd. (Tokyo, Japan).

Eggplant is a specialty vegetable from Kochi's Prefecture. It benefits from its warm climate and abundant sunlight. The prefecture boasts one of the highest shipment volumes of greenhouse-grown eggplants in Japan during the winter and spring seasons (October to June), Figure 2. Eggplants are rich in acetylcholine, which can have beneficial effects against high BP and negative psychological states [11]. Acetylcholine concentration is 2900-fold higher in eggplant (6.12g mg/100g) than in other agricultural products (average: 2.11×10-3 mg/100g) [12]. Two Kochi eggplants contain 2.3 mg of acetylcholine. Since heat treatment does not cause loss of acetylcholine in eggplant, it represents an excellent raw material for functional foods.

Figure 2: *Eggplants and region of origin* (Kochi Prefecture, Japan).

The large amount of choline ester in eggplant may help improve mood as well as BP by regulating nervous system activity, as shown in studies on spontaneously hypertensive rats and in humans [10]. As mentioned above, eggplant is rich in acetylcholine, which decreases BP by stimulating endothelium nitric oxide-dependent vasodilation in resistance arterioles. The biosynthetic product of choline acetyltransferase contained in normal plasma is acetylcholine. Potentially, at high-enough concentrations, it can affect BP by its action on the endothelium.

Against this background, this study examines the effect of timed consumption of eggplant or Kalahari watermelon on BP and heart rate (HR) in a few hypertensive individuals, using 7-day/24-hour ambulatory BP monitoring (ABPM).

Methods

The study included 10 participants. Three (2 women and 1 man, 44 – 71 years of age) used eggplant extracts (8 tablets, containing 2.3 mg of acetylcholine) and 7 (4 women and 3 men, 52 – 83 years of age) used extracts of Kalahari watermelon (6 tablets). All participants had high BP. All but one were untreated at the start of monitoring. One participant (KT) using eggplant supplementation started anti-hypertensive treatment (amlodipine, 5 mg/day).

Before the start of eggplant or Kalahari watermelon supplementation, each participant provided a 7-day/24-hour ABPM record of systolic (S) and diastolic (D) BP and HR measurements taken automatically at 30-minute intervals. Participant KT, originally untreated, was started on Amlodipine treatment, and after at least one month on this regimen, he provided another 7-day/24-hour ABPM record before starting eggplant extract supplementation. These records served as reference. Functional food supplementation upon awakening lasted for at least one month before another 7-day/24-hour ABPM record was obtained from each participant. Additional 7-day/24-hour ABPM profiles from 5 participants were collected after eggplant or Kalahari melon supplementation at other times (3, 6, 9, 12, 15, and/or18 hours after awakening).

Each record was analyzed by sphygmochron [13]. A 2-component model consisting of cosine curves with periods of 24 and 12 hours was fitted by cosinor [14] to yield estimates of the MESOR (Midline Estimating Statistic Of Rhythm, a rhythm-adjusted mean), and of each component's amplitude and acrophase (measures of the predictable extent and timing of maximal change within a cycle). These

parameters were compared to chronobiologic references values qualified by gender and age to determine whether they were within or outside acceptable ranges. Paired t tests compared changes in MESOR, double 24-hour amplitude (2A) and acrophase (ϕ) of SBP, DBP, and HR between supplementation and no-supplementation (reference).

Results

Eggplant supplementation

Table 1 lists 24-hour characteristics of BP and HR for each participant during each study stage. Effects of eggplant supplementation are summarized in Table 2. The response in MESOR, double amplitude, and standard deviation is assessed as a percentage of the corresponding reference value in the absence of intervention. The response in acrophase is assessed as a difference in relation to its estimate in the absence of intervention.

Irrespective of the timing of eggplant supplementation, small decreases in the MESOR of SBP and DBP do not reach statistical significance. The 24-hour acrophase of DBP is slightly advanced by about 1 hour (P = 0.062). When eggplant supplementation is administered upon awakening, a similar advance of the DBP acrophase is detected (P = 0.013). These results need to be interpreted with caution, however, in view of the limited sample size.

Table 1: *24-hour rhythm characteristics of blood pressure (BP) and heart rate (HR) before and during timed eggplant supplementation* *

ID	G	Age	Rx	SBP-M	DBP-M	PP	HR-M	SBP-2A	DBP-2A	HR-2A	HR-SD	SBP-ϕ	DBP-ϕ	HR-ϕ
KT240322	M	44	NoRx	159.775	101.237	58.537	67.375	17.115	10.650	9.019	11.042	14:55	13:13	12:27
KT240510	M	44	NoRx(*)	133.326	86.732	46.594	67.257	12.286	9.289	8.098	12.080	18:32	18:32	14:23
KT240705	M	44	AW(*)	137.851	87.975	49.876	75.081	12.983	8.634	10.521	13.192	16:05	14:46	14:04
KT240906	M	44	AW+3h(*)	134.587	85.073	49.514	71.571	4.136	5.412	5.559	12.884	15:47	12:11	18:07
OK240520	F	71	NoRx	150.910	87.274	63.636	64.815	47.509	21.830	10.843	8.575	12:03	12:39	11:10
OK240627	F	71	AW	152.939	85.597	67.342	61.858	42.657	21.712	9.312	7.712	12:08	11:39	12:12
OK240801	F	71	AW+3h	150.445	87.657	62.788	69.319	37.215	19.586	14.488	9.167	12:18	12:28	12:03
OK24926	F	71	AW+6h	143.113	83.461	59.652	61.555	28.404	14.083	12.399	7.717	12:15	13:01	12:20
UH231117	F	68	NoRx	133.411	77.083	56.328	61.701	16.420	8.783	13.982	9.712	18:22	17:38	17:07
UH230810	F	68	AW	135.524	77.771	57.753	60.864	19.065	9.827	10.420	7.757	16:09	16:11	17:13
UH230929	F	68	AW+3h	140.880	78.803	62.076	62.903	23.730	11.644	11.991	9.219	16:46	16:56	15:31
(*) Rx: Amlodipine (5 mg/d)														

Table 2: *Effect of eggplant supplementation on 24-hour characteristics of blood pressure (BP) and heart rate (HR) **

SBP-M	DBP-M	PP	HR-M	SBP-2A	DBP-2A	HR-2A	HR-SD	SBP-ϕ	DBP-ϕ	HR-ϕ	
7	7	7	7	7	7	7	7	7	7	7	N
98.42	97.34	100.01	102.26	86.43	91.29	97.43	98.17	-0.029	-0.046	0.041	Mean
4.95	4.28	6.39	6.29	37.51	26.79	26.13	12.82	0.040	0.054	0.079	SD
1.87	1.62	2.42	2.38	14.18	10.13	9.87	4.85	0.015	0.020	0.030	SE
0.844	1.642	0.003	0.950	0.957	0.860	0.260	0.378	1.926	***2.285***	1.382	t
0.431	0.152	0.998	0.379	0.375	0.423	0.804	0.718	0.102	***0.062***	0.216	P
3	3	3	3	3	3	3	3	3	3	3	N(AW)
99.00	97.53	101.08	101.87	98.07	99.32	94.44	94.63	-0.039	-0.049	0.025	Mean
4.27	3.67	5.61	8.52	15.64	12.64	25.31	17.60	0.049	0.010	0.020	SD
2.47	2.12	3.24	4.92	9.03	7.30	14.61	10.16	0.028	0.006	0.011	SE
0.406	1.167	0.333	0.381	0.214	0.094	0.380	0.528	1.370	**8.581**	2.185	t
0.724	0.364	0.771	0.740	0.851	0.934	0.740	0.650	0.304	**0.013**	0.160	P
3	3	3	3	3	3	3	3	3	3	3	N(AW+3h)
99.04	97.73	101.02	105.07	83.66	92.20	94.78	104.42	-0.032	-0.074	0.079	Mean
6.90	6.31	8.26	2.72	58.37	39.20	35.21	8.54	0.039	0.078	0.133	SD
3.99	3.64	4.77	1.57	33.70	22.63	20.33	4.93	0.023	0.045	0.077	SE
0.240	0.623	0.214	***3.226***	0.485	0.345	0.257	0.897	1.408	1.633	1.032	t
0.832	0.597	0.850	***0.084***	0.676	0.763	0.821	0.464	0.294	0.244	0.410	P

Kalahari melon supplementation

Table 3 lists 24-hour characteristics of BP and HR for each participant during each study stage. Effects of Kalahari melon supplementation are summarized in Table 4. Irrespective of the timing of intervention, Kalahari melon supplementation lowered the BP MESOR by 3 to 4% compared to its estimate in the absence of treatment (SBP: 4.2%, paired t = 2.677, P = 0.015; DBP: 3.0%, paired t = 2.176, P =0.043). The 5.9% decrease in PP is slightly larger (paired t = 2.701, P = 0.015). A small delay of less than 1 hour in the 24-hour acrophase of HR is also detected, as is a decrease in the standard deviation of HR of borderline statistical significance, Table 4.

Supplementation taken upon awakening confirms its lowering effect on the SBP MESOR by 6.6% (paired t = 3.230, P = 0.014). The effect on pulse pressure is even larger (10.6%, paired t = 3.828, P = 0.006). Deserving further study is the relatively large increase in the double amplitude of BP, which is significant for SBP when supplementation of Kalahari melon is taken 3 hours after awakening (37.7%, paired t = 12.896, P =0.049), albeit only 2 participants led to this result.

Two participants contributed a 7-day/24-hour ABPM record while taking Kalahari melon supplementation at 6 or 7 different times in relation to their time of awakening. The BP response differs depending on the timing of supplementation. It can be approximated by a model consisting of a 24-hour cosine curve with or without the addition of a 12-hour component, Figure 3. Models approximating the response of the SBP, DBP and PP, based on daily averages computed from the 7-day/24-hour records, all reach statistical significance. In the case of participant SK, the largest decrease in SBP MESOR occurs when Kalahari melon supplementation is taken upon awakening (Figure 3, left). For participant HM, the largest response occurs when supplementation is taken 6 to 9 hours after awakening, highlighting the merit of personalizing treatment timing. Other factors may also play a role in view of the different response of participant HM treated upon awakening for at least one month on two different occasions (Figure 3, right).

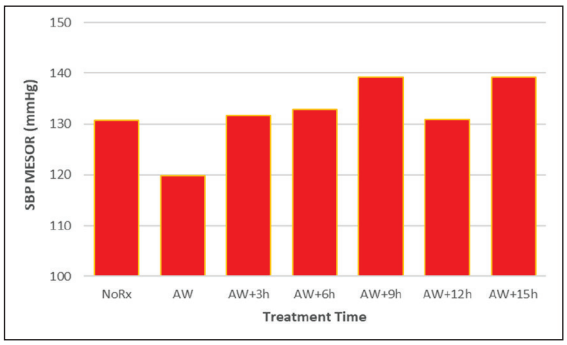
Table 3: *24-hour rhythm characteristics of blood pressure (BP) and heart rate (HR) before and during timed Kalahari melon supplementation* *

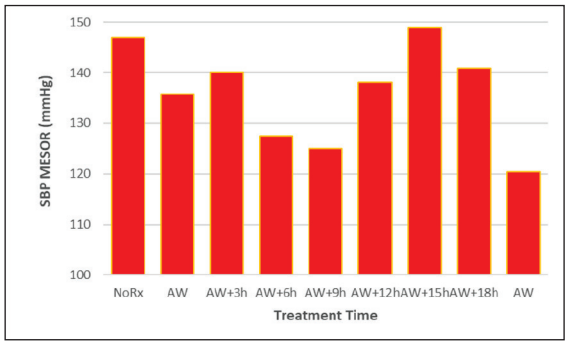
ID	G	Age	Rx	SBP-M	DBP-M	HR-M	PP	SBP-2A	DBP-2A	HR-2A	HR-SD	SBP-ϕ	DBP-ϕ	HR-ϕ
HM221114	M	68	NoRx	146.890	93.140	61.136	53.750	19.243	13.452	14.871	11.059	15:21	14:26	13:38
HM221219	M	68	AW	135.691	88.730	65.625	46.961	11.875	11.959	11.843	11.247	15:30	14:59	15:02
HM230403	M	68	AW+3h	140.020	91.596	72.013	48.425	25.932	20.584	15.803	11.677	15:22	15:08	13:36
HM230626	M	68	AW+6h	127.455	82.056	65.937	45.399	10.681	7.729	16.909	12.935	14:41	14:35	14:19
HM230911	M	68	AW+9h	124.968	81.705	63.625	43.263	17.996	12.287	10.692	11.115	13:50	13:35	14:46
HM231113	M	68	AW+12h	138.030	85.056	61.689	52.974	11.387	7.858	10.062	10.548	14:01	15:22	13:46
HM240304	M	68	AW+15h	148.797	93.054	64.393	55.743	17.454	13.231	15.310	11.567	13:58	14:44	13:55
HM240423	M	68	AW+18h	141.315	88.475	70.920	52.840	13.683	10.821	3.374	9.918	13:36	13:49	14:26
HM240521	M	68	AW	120.382	81.387	65.443	38.995	11.033	8.686	13.604	11.809	14:48	14:23	13:52
KT190729	M	83	NoRx	131.894	70.259	63.757	61.635	3.497	5.110	13.443	10.906	10:15	16:22	14:37
KT191001	M	83	AW	129.528	74.696	68.690	54.831	12.748	10.506	15.276	13.629	9:39	13:29	12:58
SK191209	F	61	NoRx	130.631	77.939	68.287	52.693	12.308	3.749	13.024	12.370	17:55	15:50	12:26
SK200210	F	61	AW	119.809	72.072	63.193	47.737	11.678	4.506	11.538	8.408	19:34	19:06	15:08
SK200518	F	61	AW+3h	131.658	79.073	64.677	52.585	17.306	3.759	14.489	9.007	18:09	14:27	14:47
SK200720	F	61	AW+6h	132.943	79.094	64.902	53.849	8.833	1.828	13.043	9.523	16:58	16:50	15:01
SK201005	F	61	AW+9h	139.137	79.766	60.040	59.371	13.378	2.173	9.740	6.185	18:01	22:21	14:30
SK210510	F	61	AW+12h	130.880	78.260	60.481	52.620	11.292	3.157	17.088	7.468	19:14	15:42	13:36
SK210927	F	61	AW+15h	139.178	83.062	63.049	56.116	22.850	6.402	14.664	8.819	16:19	15:39	15:00
UE190527	F	52	NoRx	150.815	94.998	78.219	55.817	29.541	20.872	11.806	8.650	13:24	13:22	13:50
UE190722	F	52	AW	149.984	97.198	81.031	52.786	31.083	20.489	20.945	10.47	14:41	14:05	13:54
UZ190730	F	53	NoRx	138.993	89.219	78.783	49.774	33.515	16.657	6.289	12.300	12:48	13:01	6:35
UZ191112	F	53	AW	124.760	80.975	81.505	43.785	36.633	28.232	12.294	13.250	13:14	12:54	6:36
UH231117	F	67	NoRx	140.880	78.803	62.903	62.076	23.730	11.644	11.991	9.712	16:46	16:56	15:31
UH240118	F	67	AW	138.872	77.607	62.340	61.265	28.310	13.226	7.786	7.301	17:12	17:01	17:07
Ko240722	M	56	NoRx	161.389	99.617	79.604	61.772	29.519	13.420	19.165	15.739	11:27	12:56	11:45
Ko240930	M	56	AW	153.062	94.732	76.386	58.330	20.214	8.396	11.261	13.546	11:15	9:59	10:49

Table 4: *Effect of Kalahari melon supplementation on 24-hour characteristics of blood pressure (BP) and heart rate (HR)* *

SBP-M	DBP-M	HR-M	PP	SBP-2A	DBP-2A	HR-2A	HR-SD	SBP-ϕ	DBP-ϕ	HR-ϕ	
19	19	19	19	19	19	19	19	19	19	19	N
95.84	96.99	100.80	94.08	111.09	102.61	100.28	91.35	-0.007	0.013	0.032	Mean
6.77	6.03	7.73	9.56	69.67	44.31	38.06	21.37	0.040	0.085	0.057	SD
1.55	1.38	1.77	2.19	15.98	10.17	8.73	4.90	0.009	0.019	0.013	SE
2.677	**2.176**	0.451	**2.701**	0.694	0.257	0.032	***1.765***	0.806	0.658	**2.495**	t
0.015	**0.043**	0.657	**0.015**	0.497	0.800	0.975	***0.094***	0.431	0.519	**0.023**	P
8	8	8	8	8	8	8	8	8	8	8	N(AW)
93.36	96.01	102.10	89.39	122.60	115.38	108.74	98.93	0.013	-0.007	0.018	Mean
5.81	6.19	5.68	7.84	100.50	49.95	51.03	20.71	0.034	0.084	0.059	SD
2.06	2.19	2.01	2.77	35.53	17.66	18.04	7.32	0.012	0.030	0.021	SE
3.230	1.823	1.044	**3.828**	0.636	0.871	0.484	0.146	1.120	0.238	0.857	t
0.014	0.111	0.331	**0.006**	0.545	0.413	0.643	0.888	0.299	0.819	0.420	P
2	2	2	2	2	2	2	2	2	2	2	N(AW+3h)
98.05	99.90	106.25	94.94	137.68	126.64	108.76	89.20	0.005	-0.014	0.048	Mean
3.86	2.20	16.32	6.86	4.13	37.31	3.52	23.17	0.007	0.062	0.070	SD
2.73	1.56	11.54	4.85	2.92	26.38	2.49	16.39	0.005	0.044	0.050	SE
0.712	0.065	0.542	1.042	**12.896**	1.010	3.515	0.659	1.045	0.329	0.973	t
0.606	0.959	0.684	0.487	**0.049**	0.497	0.176	0.629	0.486	0.798	0.509	P

* *See footnotes of Tables 1 and 2.*





SBP-Mean = 131.3 + 7.4cos(2πt/24h – 4.42) P<0.001

DBP-Mean = 78.5 + 3.2cos(2πt/24h – 4.69) P=0.003

PP = 52.8 + 4.4cos(2πt/24h – 4.21) P<0.001

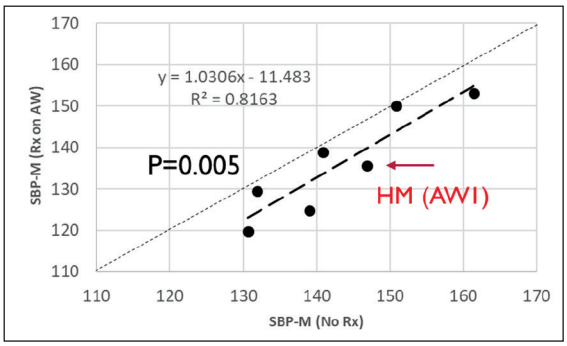
SBP-Mean = 134.5 + 6.7cos(2πt/24h – 5.60) +9.8cos(2πt/12h – 4.78) P<0.001

DBP-Mean = 86.4 + 2.2cos(2πt/24h – 6.09) + 5.3cos(2πt/12h – 4.73) P<0.001

PP = 48.1 + 4.9cos(2πt/24h – 5.39) + 4.5cos(2πt/12h – 4.85) P<0.001

Figure 3: *Response of the MESOR of systolic blood pressure (SBP) to Kalahari melon supplementation taken for at least one month at different times of the day by participant SK (F, 61y, left) and participant HM (M, 68y, right). In each case, the response of average SBP, diastolic blood pressure (DBP) and pulse pressure (PP) can be approximated by a model consisting of 24-hour with (right) or without (left) the addition of a 12-hour component, indicating that the timing of supplementation matters.*

Kalahari melon supplementation taken upon awakening had a statistically significant lowering effect on the SBP MESOR, Table 4. In view of the large difference in participant HM's response, analyses were repeated considering either one of the two estimates, Figure 4. In both cases, the BP lowering effect of Kalahari melon supplementation is confirmed, as seen by all SBP MESORs on treatment being below their corresponding estimates in the absence of treatment.



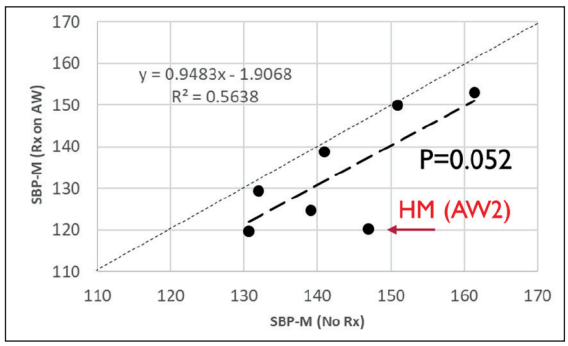


Figure 4: *Overall response of the MESOR of systolic blood pressure (SBP) to Kalahari melon supplementation taken upon awakening (all participants). All estimates on treatment are below estimates prior to treatment, whether considering the first (left) or second (right) instance of supplementation upon awakening by participant HM.*

As a potential confounder, the effect of salt intake on the SBP MESOR of both participants SK and HM was determined, Figure 5. In both cases, the association failed to reach statistical significance,

suggesting that the amount of salt consumed by participants SK and HM was not a major confounder of the timed-dependent effect of Kalahari melon supplementation on the SBP MESOR.

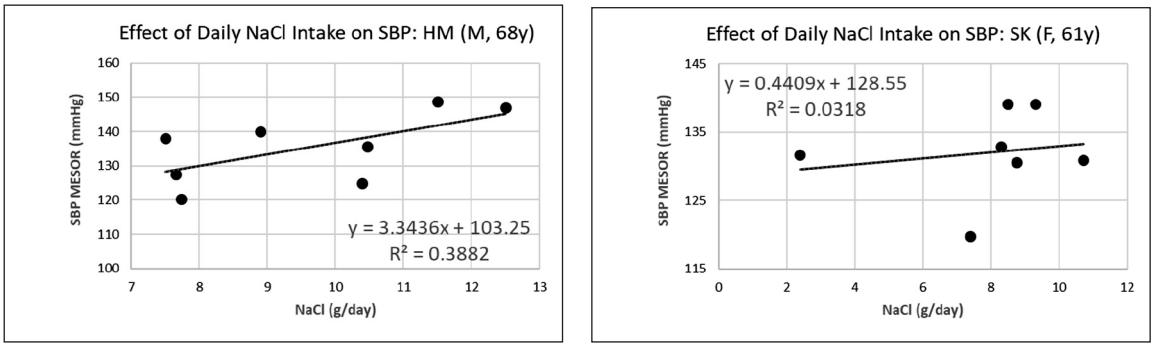


Figure 5: *Effect of daily salt intake on the MESOR of systolic blood pressure (SBP) in participants HM (left) and SK (right). The slight increase in SBP MESOR as a function of salt intake observed in both cases is not statistically significant (HM: P = 0.099; SK: P = 0.702).*

Discussion and Conclusion

Despite the small sample sizes in this ongoing study, results herein generally support the idea that some foods can have a beneficial effect in lowering BP. Effects observed in this study were relatively small, averaging about 3 to 4% overall. Deserving further investigation is the somewhat larger effect on pulse pressure, which averaged almost 6% as a response to Kalahari melon supplementation. Decreasing an excessive pulse pressure is important in view of its strong association with cardiovascular disease risk [15, 16].

By varying the time of administration of Kalahari melon supplementation, in combination with BP monitoring, it becomes possible to determine the optimal treatment time for each person, as documented in Figure 3 for two of the study participants. A time-dependent effect of anti-hypertensive medication [17] and aspirin [18] on BP have also been reported. Even globally, supplementation taken upon awakening decreased the MESOR of DBP and SBP on average by 4 to 6.6%, slightly more than the global decreases of 3 and 4% observed irrespective of treatment time. The effect of supplementation upon awakening on pulse pressure is even larger, reaching 10.6% (as compared to 6% globally).

The tentative effects based on very few participants detected herein to affect the 24-hour amplitude and acrophase of BP deserve further study. The amplification of a dampened circadian variation and any phase adjustment toward a circadian rhythm aligned more appropriately with the natural environment are likely to have beneficial effects on health, as suggested by a number of chronobiologic investigations [19, 20].

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Variability of Night-to-day Blood Pressure Ratio from Seven-day/24-h Ambulatory Blood Pressure Monitoring in Healthy Subjects and in Patients with Coronary Heart Disease

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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 variability in night-to-day ratio (11).

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

Methods

50 healthy subjects (47.8 ± 2.8 years, 172 ± 1.2 cm, 80 ± 2.2 kg) - 50 patients with ischemic coronary heart diseases (67 ± 2.7 years 170 ± 2.2 cm, 89 ± 4 kg).

The 50 patients with coronary heart diseases were under pharmacological therapy with ACE inhibitors, beta blockers and statins. They are also treated in cardiovascular rehabilitation before the ambulatory blood pressure monitoring. The ambulatory blood pressure monitoring was in every subject and patients provided seven-days/24-hours with the A&D Japan equipment. TM 2421 A&D Instruments (Japan) were used for ambulatory blood pressure monitoring (oscillation method, 30-minute interval between measurements during the time from 6 o clock to 22 o clock, one hour from 22 o clock to 6 o clock). The subjects and patients were monitored 7-days/24-h. 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. We used also evaluation of seven day mean value of dipping of night-to-day ratio.

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

Results

The group of 50 healthy subjects in the seven-day/24-h record in every day in one subject showed the different night-to-day blood pressure ratio according the clasification of dipper (D), nondipper (ND), extremer dipper (ED) and reverse dipper (RD) in systolic and diastolic blood pressure.

Individual values of seven-days/24-h of night-to-day ratio in 50 healthy subjects in systolic and diastolic blood pressure are shown in Tables 1a, 1b. 2a, 2b.

Tab 1a: Clarification accordance of night-to-day ratio in (%) in systolic blood pressure and based on evaluation D, ND, ED, RD for mean from 7 days and values for individual days in healthy subjects No 1- 25

Tab 1b: Clarification accordance of night-to-day ratio in (%) in systolic blood pressure and based on evaluation D, ND, ED, RD for mean from 7 days and values for individual days in healthy subjects No 26-50

Tab 2a: Clarification accordance of night-to-day ratio in (%) in diastolic blood pressure and based on evaluation D, ND, ED, RD for mean from 7 days and values for individual days in healthy subjects No 1- 25

Tab 2b: Clarification accordance of night-to-day ratio in (%) in diastolic blood pressure and based on evaluation D, ND, ED, RD for mean from 7 days and values for individual days in healthy subjects No 26- 50

Table 1a: *D dipper, ND-nondipper ED extrem dipper, RD reverse dipper*

No.	Night-to day ratio	Mean 7 day	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
1.	(%)	14,5	13,8	7,5	9,0	23,7	16,5	18,7	11,4
	ND-R	D	D	ND	ND	ED	D	D	D
2.	(%)	19,2	19,2	23,6	25,1	24,2	22,2	12,3	6,4
	ND-R	D	D	ED	ED	ED	ED	D	ND
3.	(%)	11,2	9,6	14,8	8,6	1,6	16,2	7,7	19,0
	ND-R	D	ND	D	ND	ND	D	ND	D
4.	(%)	15,4	26,8	7,7	14,9	13,0	21,5	9,5	12,0
	ND-R	D	ED	ND	D	D	ED	ND	D
5.	(%)	20,9	19,4	21,2	28,7	23,5	24,3	8,4	17,8
	ND-R	ED	D	ED	ED	ED	ED	ND	D
6.	(%)	18,2	16,2	19,7	19,3	25,8	17,9	15,7	12,5
	ND-R	D	D	D	D	ED	D	D	D
7.	(%)	13,4	14,3	4,1	5,8	16,8	11,1	20,2	20,6
	ND-R	D	D	ND	ND	D	D	ED	ED
8.	(%)	17,9	29,7	20,8	16,8	13,0	12,8	6,5	22,9
	ND-R	D	ED	ED	D	D	D	ND	ED
9.	(%)	14,4	27,0	13,4	18,0	9,2	14,3	14,0	2,0
	ND-R	D	ED	D	D	ND	D	D	ND
10.	(%)	16,4	22,2	20,3	26,5	16,5	9,3	8,3	10,2
	ND-R	D	ED	ED	ED	D	ND	ND	D
11.	(%)	6,5	16,5	20,6	1,9	11,8	6,9	–22,1	10,2
	ND-R	ND	D	ED	ND	D	ND	RD	D
12.	(%)	9,7	2,9	17,7	–12,1	16,6	15,1	8,3	18,4
	ND-R	ND	ND	D	RD	D	D	ND	D
13.	(%)	16,0	18,9	15,9	20,2	12,5	15,9	15,3	15,2
	ND-R	D	D	D	ED	D	D	D	D
14.	(%)	22,9	18,3	13,7	16,0	20,1	25,7	40,2	24,3
	ND-R	ED	D	D	D	ED	ED	ED	ED
15.	(%)	20,5	10,1	16,8	29,3	17,2	24,3	17,3	27,0
	ND-R	ED	D	D	ED	D	ED	D	ED
16.	(%)	19,6	33,7	24,0	18,8	3,7	3,5	26,1	22,1
	ND-R	D	ED	ED	D	ND	ND	ED	ED
17.	(%)	9,0	18,6	5,1	8,6	5,5	2,7	6,5	14,8
	ND-R	ND	D	ND	ND	ND	ND	ND	D
18.	(%)	15,3	16,2	17,9	14,9	14,0	13,7	11,6	18,8
	ND-R	D	D	D	D	D	D	D	D
19.	(%)	15,3	19,2	11,9	8,9	16,2	19,4	19,7	11,1
	ND-R	D	D	D	ND	D	D	D	D
20.	(%)	15,3	5,5	22,7	34,6	11,2		–0,7	10,8
	ND-R	D	ND	ED	ED	D		RD	D
21.	(%)	10,1	17,2	26,1	16,8	26,4	17,8	–21,9	–20,4
	ND-R	D	D	ED	D	ED	D	RD	RD
22.	(%)	19,0	13,0	24,3	16,2	15,0	21,7	16,7	25,9
	ND-R	D	D	ED	D	D	ED	D	ED
23.	(%)	6,7	7,6	–5,8	10,7	8,3	12,5	5,8	
	ND-R	ND	ND	RD	D	ND	D	ND	
24.	(%)	8,9	8,1	13,0	15,2	–2,2	15,2	8,1	4,7
	ND-R	ND	ND	D	D	RD	D	ND	ND
25.	(%)	14,4	2,2	19,6	19,1	6,2	4,1	25,6	23,0
	ND-R	D	ND	D	D	ND	ND	ED	ED

Table 1b: *D dipper, ND-nondipper ED extrem dipper, RD reverse dipper*

No.	Night-to day ratio	Mean 7 day	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
26.	*(%)* **ND-R**	*–11,1* **RD**	*–11,5* **RD**	*–19,7* **RD**	*–17,7* **RD**	*–8,2* **RD**	*1,8* **ND**	*–18,0* **RD**	*–4,7* **RD**
27.	*(%)* **ND-R**	*19,2* **D**	*23,1* **ED**	*20,4* **ED**	*18,0* **D**	*21,1* **ED**	*18,1* **D**	*17,1* **D**	*16,5* **D**
28.	*(%)* **ND-R**	*23,2* **ED**	*26,4* **ED**	*23,8* **ED**	*31,2* **ED**	*27,2* **ED**	*19,5* **D**	*13,5* **D**	*19,5* **D**
29.	*(%)* **ND-R**	*25,2* **ED**	*36,8* **ED**	*25,1* **ED**	*30,8* **ED**	*25,9* **ED**	*7,8* **ND**	*21,1* **ED**	*26,1* **ED**
30.	*(%)* **ND-R**	*9,3* **ND**	*10,4* **D**	*10,9* **D**	*7,9* **ND**	*7,3* **ND**	*10,2* **D**	*7,4* **ND**	*11,2* **D**
31.	*(%)* **ND-R**	*16,0* **D**	*2,7* **ND**	*27,4* **ED**	*20,3* **ED**	*7,1* **ND**	*16,7* **D**	*12,2* **D**	*24,5* **ED**
32.	*(%)* **ND-R**	*17,5* **D**	*21,8* **ED**	*17,1* **D**	*20,3* **ED**	*19,5* **D**	*18,9* **D**	*10,5* **D**	*13,9* **D**
33.	*(%)* **ND-R**	*15,7* **D**	*23,2* **ED**	*21,3* **ED**	*14,5* **D**	*11,0* **D**	*16,4* **D**	*7,7* **ND**	
34.	*(%)* **ND-R**	*20,6* **ED**	*19,6* **D**	*18,5* **D**	*22,6* **ED**	*23,0* **ED**	*17,1* **D**	*18,6* **D**	*24,6* **ED**
35.	*(%)* **ND-R**	*20,2* **ED**	*20,8* **ED**	*1,2* **ND**	*14,4* **D**	*27,0* **ED**	*27,5* **ED**	*28,8* **ED**	
36.	*(%)* **ND-R**	*11,4* **D**	*9,7* **ND**	*14,1* **D**	*13,5* **D**	*7,7* **ND**	*6,5* **ND**	*12,7* **D**	*15,5* **D**
37.	*(%)* **ND-R**	*12,4* **D**	*13,1* **D**	*22,7* **ED**	*7,9* **ND**	*8,3* **ND**	*18,0* **D**	*4,7* **ND**	
38.	*(%)* **ND-R**	*8,4* **ND**	*15,0* **D**	*8,1* **ND**	*2,7* **ND**	*8,3* **ND**	*6,9* **ND**	*8,6* **ND**	
39.	*(%)* **ND-R**	*18,2* **D**	*17,1* **D**	*24,0* **ED**	*6,8* **ND**	*10,0* **D**	*17,7* **D**	*25,2* **ED**	*24,7* **ED**
40.	*(%)* **ND-R**	*18,7* **D**	*24,3* **ED**	*22,1* **ED**	*15,8* **D**	*19,0* **D**	*20,0* **D**	*11,9* **D**	*16,7* **D**
41.	*(%)* **ND-R**	*16,9* **D**	*13,9* **D**	*13,5* **D**	*28,4* **ED**	*18,1* **D**	*7,5* **ND**	*26,9* **ED**	*8,0* **ND**
42.	*(%)* **ND-R**	*–3,4* **RD**	*–11,5* **RD**	*7,4* **ND**	*–9,3* **RD**	*5,3* **ND**	*1,4* **ND**	*5,2* **ND**	*–24,1* **RD**
43.	*(%)* **ND-R**	*15,4* **D**	*0,7* **ND**	*17,9* **D**	*17,6* **D**	*20,0* **D**	*14,2* **D**	*29,1* **ED**	*5,7* **ND**
44.	*(%)* **ND-R**	*16,0* **D**	*17,4* **D**	*16,7* **D**	*21,3* **ED**	*13,6* **D**	*16,3* **D**	*23,3* **ED**	*1,7* **ND**
45.	*(%)* **ND-R**	*–13,5* **RD**	*–2,4* **RD**	*–7,7* **RD**	*–10,1* **RD**	*–17,1* **RD**	*–15,4* **RD**	*–26,0* **RD**	*–16,9* **RD**
46.	*(%)* **ND-R**	*6,7* **ND**	*–2,2* **RD**	*14,4* **D**	*1,2* **ND**	*7,7* **ND**	*–4,4* **RD**	*11,4* **D**	*16,2* **D**
47.	*(%)* **ND-R**	*19,9* **D**	*17,2* **D**	*25,5* **ED**	*12,9* **D**	*23,8* **ED**	*20,0* **D**	*21,1* **ED**	*17,7* **D**
48.	*(%)* **ND-R**	*22,8* **ED**	*28,8* **ED**	*15,8* **D**	*9,0* **ND**	*33,6* **ED**	*19,9* **D**	*26,5* **ED**	
49.	*(%)* **ND-R**	*4,1* **ND**	*3,9* **ND**	*7,3* **ND**	*5,2* **ND**	*–2,3* **RD**	*5,7* **ND**	*5,2* **ND**	*4,0* **ND**
50.	*(%)* **ND-R**	*14,6* **D**	*19,1* **D**	*7,2* **ND**	*8,0* **ND**	*16,1* **D**	*25,0* **ED**	*10,3* **D**	*15,8* **D**

Table 2a: *D dipper, ND-nondipper ED extrem dipper, RD reverse dipper*

No.	Night-to day ratio	Mean 7 day	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
1.	(%) ND-R	20,7 ED	22,1 ED	13,3 D	18,2 D	29,0 ED	21,5 ED	23,0 ED	17,2 D
2.	(%) ND-R	24,6 ED	26,3 ED	23,2 ED	26,4 ED	27,4 ED	31,4 ED	14,3 D	21,7 ED
3.	(%) ND-R	9,6 ND	24,4 ED	19,1 D	−1,6 RD	−8,6 RD	−2,1 RD	9,3 ND	24,4 ED
4.	(%) ND-R	26,1 ED	34,1 ED	25,5 ED	31,7 ED	11,7 D	38,7 ED	10,2 D	25,7 ED
5.	(%) ND-R	24,8 ED	14,5 D	17,3 D	30,0 ED	36,6 ED	29,5 ED	14,0 D	26,7 ED
6.	(%) ND-R	18,9 D	17,3 D	24,7 ED	17,8 D	24,4 ED	21,0 ED	14,6 D	11,9 D
7.	(%) ND-R	18,0 D	12,1 D	17,6 D	6,1 ND	27,1 ED	9,9 ND	27,4 ED	24,0 ED
8.	(%) ND-R	22,4 ED	29,4 ED	27,2 ED	22,7 ED	23,9 ED	20,2 ED	5,6 ND	25,1 ED
9.	(%) ND-R	14,5 D	25,7 ED	17,9 D	19,5 D	9,6 ND	14,3 D	6,7 ND	5,5 ND
10.	(%) ND-R	20,1 ED	23,3 ED	26,7 ED	29,3 ED	23,4 ED	8,2 ND	13,9 D	16,3 D
11.	(%) ND-R	14,0 D	21,1 ED	27,2 ED	7,5 ND	17,3 D	22,2 ED	−5,7 RD	7,6 ND
12.	(%) ND-R	11,8 D	2,6 ND	9,2 ND	−24,5 RD	18,8 D	22,3 ED	26,9 ED	24,6 ED
13.	(%) ND-R	21,6 ED	21,8 ED	17,4 D	22,1 ED	23,2 ED	22,2 ED	21,3 ED	23,1 ED
14.	(%) ND-R	22,9 ED	20,0 D	13,3 D	17,7 D	19,7 D	28,5 ED	30,4 ED	29,4 ED
15.	(%) ND-R	25,7 ED	13,2 D	26,5 ED	34,7 ED	29,1 ED	23,8 ED	19,1 D	33,1 ED
16.	(%) ND-R	28,2 ED	40,4 ED	33,8 ED	34,0 ED	15,0 D	4,2 ND	35,5 ED	26,3 ED
17.	(%) ND-R	11,7 D	20,1 ED	11,5 D	10,0 ND	−12,5 RD	6,5 ND	6,5 ND	31,6 ED
18.	(%) ND-R	19,0 D	13,1 D	14,0 D	20,9 ED	16,2 D	21,6 ED	17,5 D	29,1 ED
19.	(%) ND-R	18,7 D	24,5 ED	15,9 D	14,1 D	20,8 ED	21,6 ED	27,1 ED	6,6 ND
20.	(%) ND-R	17,3 D	13,1 D	39,0 ED	36,8 ED	17,5 D		−20,4 RD	10,0 ND
21.	(%) ND-R	17,5 D	29,8 ED	26,0 ED	13,7 D	30,3 ED	19,7 D	−23,5 RD	21,6 ED
22.	(%) ND-R	27,9 ED	15,6 D	30,6 ED	30,8 ED	30,3 ED	30,7 ED	30,1 ED	27,5 ED
23.	(%) ND-R	9,1 ND	9,6 ND	0,4 ND	11,2 D	9,1 ND	12,4 D	11,0 D	
24.	(%) ND-R	11,5 D	8,5 ND	17,2 D	14,5 D	4,2 ND	12,2 D	7,1 ND	16,4 D
25.	(%) ND-R	16,4 D	2,1 ND	24,7 ED	18,1 D	−0,7 RD	5,8 ND	31,3 ED	28,5 ED

Table 2b: *D dipper, ND-nondipper ED extrem dipper, RD reverse dipper*

No.	Night-to day ratio	Mean 7 day	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
26.	*(%)* **ND-R**	*–10,6* **RD**	*–21,5* **RD**	*–12,8* **RD**	*–16,9* **RD**	*–3,2* **RD**	*4,5* **ND**	*–20,8* **RD**	*–5,6* **RD**
27.	*(%)* **ND-R**	*25,9* **ED**	*29,3* **ED**	*32,5* **ED**	*25,4* **ED**	*29,1* **ED**	*26,8* **ED**	*23,8* **ED**	*13,7* **D**
28.	*(%)* **ND-R**	*25,5* **ED**	*30,7* **ED**	*23,5* **ED**	*33,4* **ED**	*27,7* **ED**	*27,2* **ED**	*13,3* **D**	*21,5* **ED**
29.	*(%)* **ND-R**	*27,8* **ED**	*39,3* **ED**	*33,3* **ED**	*31,4* **ED**	*29,0* **ED**	*10,5* **D**	*18,9* **D**	*28,4* **ED**
30.	*(%)* **ND-R**	*10,6* **D**	*8,1* **ND**	*14,2* **D**	*10,7* **D**	*6,5* **ND**	*16,2* **D**	*7,0* **ND**	*11,9* **D**
31.	*(%)* **ND-R**	*24,3* **ED**	*–3,3* **RD**	*41,3* **ED**	*30,8* **ED**	*15,2* **D**	*24,0* **ED**	*19,6* **D**	*37,8* **ED**
32.	*(%)* **ND-R**	*22,3* **ED**	*27,1* **ED**	*17,8* **D**	*23,3* **ED**	*19,5* **D**	*26,2* **ED**	*18,8* **D**	*23,2* **ED**
33.	*(%)* **ND-R**	*15,6* **D**	*23,0* **ED**	*24,7* **ED**	*4,3* **ND**	*20,1* **ED**	*14,8* **D**	*5,8* **ND**	
34.	*(%)* **ND-R**	*21,0* **ED**	*21,3* **ED**	*21,4* **ED**	*20,9* **ED**	*21,0* **ED**	*19,2* **D**	*16,5* **D**	*26,1* **ED**
35.	*(%)* **ND-R**	*19,4* **ED**	*24,7* **ED**	*5,1* **ND**	*7,3* **ND**	*15,3* **D**	*29,6* **ED**	*31,9* **ED**	
36.	*(%)* **ND-R**	*16,6* **D**	*16,1* **D**	*20,1* **ED**	*22,5* **ED**	*10,5* **D**	*11,7* **D**	*14,6* **D**	*20,7* **ED**
37.	*(%)* **ND-R**	*9,4* **ND**	*13,2* **D**	*11,4* **D**	*7,7* **ND**	*–0,6* **RD**	*8,8* **ND**	*14,6* **D**	
38.	*(%)* **ND-R**	*13,6* **D**	*28,8* **ED**	*20,0* **D**	*10,7* **D**	*13,0* **D**	*4,0* **ND**	*3,0* **ND**	
39.	*(%)* **ND-R**	*18,2* **D**	*13,0* **D**	*25,2* **ED**	*–1,0* **RD**	*15,0* **D**	*11,4* **D**	*29,3* **ED**	*32,0* **ED**
40.	*(%)* **ND-R**	*15,9* **D**	*21,5* **ED**	*26,3* **ED**	*14,2* **D**	*15,1* **D**	*20,1* **ED**	*14,0* **D**	*–1,3* **RD**
41.	*(%)* **ND-R**	*20,7* **ED**	*21,9* **ED**	*15,3* **D**	*31,6* **ED**	*8,7* **ND**	*21,9* **ED**	*25,4* **ED**	*17,3* **D**
42.	*(%)* **ND-R**	*2,1* **ND**	*–10,0* **RD**	*13,5* **D**	*–3,6* **RD**	*4,4* **ND**	*17,5* **D**	*11,6* **D**	*–22,2* **RD**
43.	*(%)* **ND-R**	*13,0* **D**	*3,4* **ND**	*19,0* **D**	*26,5* **ED**	*14,3* **D**	*–1,5* **RD**	*26,9* **ED**	*–0,8* **RD**
44.	*(%)* **ND-R**	*14,1* **D**	*14,1* **D**	*24,7* **ED**	*17,1* **D**	*4,0* **ND**	*11,0* **D**	*26,2* **ED**	*–1,8* **RD**
45.	*(%)* **ND-R**	*5,3* **ND**	*14,3* **D**	*8,6* **ND**	*2,5* **ND**	*6,9* **ND**	*4,6* **ND**	*–5,4* **RD**	*4,8* **ND**
46.	*(%)* **ND-R**	*0,2* **ND**	*–11,7* **RD**	*3,1* **ND**	*–4,0* **RD**	*7,9* **ND**	*–7,5* **RD**	*6,0* **ND**	*6,4* **ND**
47.	*(%)* **ND-R**	*16,7* **D**	*17,6* **D**	*23,8* **ED**	*10,2* **D**	*17,7* **D**	*19,9* **D**	*18,4* **D**	*8,0* **ND**
48.	*(%)* **ND-R**	*28,5* **ED**	*31,9* **ED**	*18,9* **D**	*18,7* **D**	*38,4* **ED**	*28,5* **ED**	*30,6* **ED**	
49.	*(%)* **ND-R**	*7,3* **ND**	*8,2* **ND**	*12,2* **D**	*12,9* **D**	*–3,2* **RD**	*2,5* **ND**	*10,0* **D**	*7,7* **ND**
50.	*(%)* **ND-R**	*14,9* **D**	*21,0* **ED**	*2,2* **ND**	*10,5* **D**	*21,6* **ED**	*17,5* **D**	*6,9* **ND**	*20,5* **ED**

In the tables 3a, 3b, 4a,4b is presented as night-to-day ratio in seven days/24 h in 50 patients with ischemic heart disease in systolic and diastolic blood pressure.

Tab 3a: Clarification accordance of night-to-day ration in (%) in systolic blood pressure and based on evaluation D, ND, ED, RD for mean from 7 days and values for individual days in patients with ischemic heart disease No 1-25

Tab 3b: Clarification accordance of night-to-day ration in (%) in systolic blood pressure and based on evaluation D, ND, ED, RD for mean from 7 days and values for individual days in patients with ischemic heart disease No 26-50

Tab 4a: Clarification accordance of night-to-day ration in (%) in diastolic blood pressure and based on evaluation D, ND, ED, RD for mean from 7- days and values for individual days in patients with ischemic heart disease No 1-25

Tab 4b: Clarification accordance of night-to-day ration in (%) in diastolic blood pressure and based on evaluation D, ND, ED, RD for mean from 7 days and values for individual days in patients with ischemic heart disease No 26-50

Table 3a: *D dipper, ND-nondipper ED extrem dipper, RD reverse dipper*

No.	Night-to day ratio	Mean 7 day	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
1.	*(%)* **ND-R**	*12,0* **D**	*8,1* **ND**	*9,8* **ND**	*7,8* **ND**	*7,6* **ND**	*23,0* **ED**	*10,6* **D**	*16,6* **D**
2.	*(%)* **ND-R**	*8,2* **ND**	*2,9* **ND**	*−0,3* **RD**	*16,0* **D**	*4,4* **ND**	*8,9* **ND**	*12,9* **D**	*12,4* **D**
3.	*(%)* **ND-R**	*7,9* **ND**	*12,2* **D**	*−0,8* **RD**	*14,3* **D**	*17,6* **D**	*7,2* **ND**	*−0,1* **RD**	*3,1* **ND**
4.	*(%)* **ND-R**	*0,3* **ND**	*−6,0* **RD**	*3,4* **ND**	*3,7* **ND**	*9,3* **ND**	*−4,9* **RD**	*−12,1* **RD**	*6,8* **ND**
5.	*(%)* **ND-R**	*22,8* **ED**	*26,7* **ED**	*13,4* **D**	*23,7* **ED**	*29,8* **ED**	*21,9* **ED**	*20,7* **ED**	*22,1* **ED**
6.	*(%)* **ND-R**	*12,3* **D**	*11,3* **D**	*14,7* **D**	*8,9* **ND**	*15,7* **D**	*16,1* **D**	*13,7* **D**	
7.	*(%)* **ND-R**	*14,7* **D**	*17,8* **D**	*15,9* **D**	*23,4* **ED**	*19,4* **D**	*7,6* **ND**	*15,3* **D**	*3,4* **ND**
8.	*(%)* **ND-R**	*20,6* **ED**	*15,4* **D**	*24,6* **ED**	*23,4* **ED**	*17,5* **D**	*33,6* **ED**	*2,0* **ND**	*25,7* **ED**
9.	*(%)* **ND-R**	*6,3* **ND**	*1,8* **ND**	*20,4* **ED**	*8,4* **ND**	*3,6* **ND**	*10,1* **D**	*3,2* **ND**	*−4,2* **RD**
10.	*(%)* **ND-R**	*15,8* **D**	*22,7* **ED**	*19,3* **D**	*23,7* **ED**	*15,8* **D**	*3,6* **ND**	*6,7* **ND**	*16,4* **D**
11.	*(%)* **ND-R**	*10,3* **D**	*8,9* **ND**	*19,9* **D**	*16,4* **D**	*5,6* **ND**	*2,5* **ND**	*14,7* **D**	
12.	*(%)* **ND-R**	*22,5* **ED**	*23,7* **ED**	*12,8* **D**	*35,3* **ED**	*16,9* **D**	*21,2* **ED**	*25,3* **ED**	*21,5* **ED**
13.	*(%)* **ND-R**	*3,5* **ND**	*0,6* **ND**	*2,7* **ND**	*11,6* **D**	*5,8* **ND**	*7,2* **ND**	*−0,2* **RD**	*−3,3* **RD**
14.	*(%)* **ND-R**	*7,2* **ND**	*0,0* **ND**	*13,9* **D**	*7,3* **ND**	*15,2* **D**	*1,4* **ND**	*−2,4* **RD**	*13,7* **D**
15.	*(%)* **ND-R**	*19,1* **D**	*6,8* **ND**	*22,3* **ED**	*27,0* **ED**	*20,8* **ED**	*27,2* **ED**	*18,2* **D**	*10,4* **D**
16.	*(%)* **ND-R**	*21,8* **ED**	*17,7* **D**	*11,4* **D**	*24,0* **ED**	*17,3* **D**	*26,2* **ED**	*27,5* **ED**	*26,2* **ED**
17.	*(%)* **ND-R**	*23,8* **ED**	*38,5* **ED**	*18,5* **D**	*10,9* **D**	*18,0* **D**	*27,3* **ED**	*24,3* **ED**	*28,1* **ED**
18.	*(%)* **ND-R**	*8,6* **ND**	*9,5* **ND**	*0,8* **ND**	*17,7* **D**	*21,1* **ED**	*16,9* **D**	*0,6* **ND**	*−2,2* **RD**
19.	*(%)* **ND-R**	*1,0* **ND**	*6,5* **ND**	*19,0* **D**	*1,7* **D**	*−19,6* **RD**	*−3,3* **RD**	*10,4* **D**	*−11,7* **RD**
20.	*(%)* **ND-R**	*21,8* **ED**	*21,6* **ED**	*24,2* **ED**	*25,9* **ED**	*16,4* **D**	*19,7* **D**	*24,0* **ED**	*20,6* **ED**
21.	*(%)* **ND-R**	*19,4* **D**	*13,7* **D**	*22,2* **ED**	*21,0* **ED**	*18,0* **D**	*11,3* **D**	*28,5* **ED**	*19,9* **D**
22.	*(%)* **ND-R**	*16,8* **D**	*17,5* **D**	*13,1* **D**	*14,4* **D**	*21,1* **ED**	*13,0* **D**	*23,5* **ED**	*14,8* **D**
23.	*(%)* **ND-R**	*21,5* **ED**	*25,6* **ED**	*24,8* **ED**	*16,9* **D**	*18,8* **D**	*10,7* **D**	*22,5* **ED**	*30,3* **ED**
24.	*(%)* **ND-R**	*15,2* **D**	*14,2* **D**	*19,4* **D**	*30,4* **ED**	*16,4* **D**	*10,0* **ND**	*12,3* **D**	*−0,8* **RD**
25.	*(%)* **ND-R**	*18,5* **D**	*24,9* **ED**	*4,5* **ND**	*22,1* **ED**	*21,5* **ED**	*21,9* **ED**	*6,3* **ND**	*25,3* **ED**

Table 3b: *D dipper, ND-nondipper ED extrem dipper, RD reverse dipper*

No.	Night-to day ratio	Mean 7 day	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
26.	*(%)* **ND-R**	*10,3* **D**	*10,1* **D**	*19,6* **D**	*13,4* **D**	*6,2* **ND**	*4,2* **ND**	*7,0* **ND**	*11,6* **D**
27.	*(%)* **ND-R**	*9,4* **ND**	*2,4* **ND**	*12,6* **D**	*4,8* **ND**	*6,6* **ND**	*14,8* **D**	*16,7* **D**	*7,8* **ND**
28.	*(%)* **ND-R**	*15,9* **D**	*10,6* **D**	*18,4* **D**	*25,3* **ED**	*10,3* **D**	*16,0* **D**	*13,1* **D**	*16,8* **D**
29.	*(%)* **ND-R**	*17,1* **D**	*16,4* **D**	*18,8* **D**	*13,2* **D**	*15,1* **D**	*17,7* **D**	*21,6* **ED**	*16,7* **D**
30.	*(%)* **ND-R**	*7,9* **ND**	*–1,9* **RD**	*2,4* **ND**	*5,3* **ND**	*10,3* **D**	*16,9* **D**	*18,2* **D**	*3,2* **ND**
31.	*(%)* **ND-R**	*12,8* **D**	*11,6* **D**	*10,6* **D**	*20,9* **ED**	*7,3* **ND**	*6,6* **ND**	*20,3* **ED**	*11,0* **D**
32.	*(%)* **ND-R**	*4,2* **ND**	*7,3* **ND**	*7,4* **ND**	*2,6* **ND**	*6,8* **ND**	*–4,8* **RD**	*4,5* **ND**	*4,8* **ND**
33.	*(%)* **ND-R**	*17,0* **D**	*26,4* **ED**	*20,5* **ED**	*18,8* **D**	*23,1* **ED**	*11,7* **D**	*4,4* **ND**	*13,9* **D**
34.	*(%)* **ND-R**	*6,6* **ND**	*10,2* **D**	*1,0* **ND**	*18,4* **D**	*13,9* **D**	*–3,7* **RD**	*–0,4* **RD**	*5,5* **ND**
35.	*(%)* **ND-R**	*8,3* **ND**	*–3,2* **RD**	*7,8* **ND**	*7,8* **ND**	*10,0* **D**	*12,4* **D**	*14,0* **D**	*9,6* **ND**
36.	*(%)* **ND-R**	*9,4* **ND**	*17,0* **D**	*15,3* **D**	*6,5* **ND**	*3,7* **ND**	*11,7* **D**	*8,4* **ND**	*3,3* **ND**
37.	*(%)* **ND-R**	*13,4* **D**	*11,7* **D**	*8,8* **ND**	*–7,1* **RD**	*23,1* **ED**	*9,0* **ND**	*28,6* **ED**	*16,5* **D**
38.	*(%)* **ND-R**	*17,9* **D**	*22,9* **ED**	*24,6* **ED**	*23,7* **ED**	*7,7* **ND**	*16,5* **D**	*20,6* **ED**	*7,6* **ND**
39.	*(%)* **ND-R**	*11,4* **D**	*14,6* **D**	*9,6* **ND**	*17,4* **D**	*10,6* **D**	*–3,3* **RD**	*14,4* **D**	*15,3* **D**
40.	*(%)* **ND-R**	*7,9* **ND**	*9,9* **ND**	*1,3* **ND**	*4,3* **ND**	*12,4* **D**	*11,2* **D**	*9,0* **ND**	*6,9* **ND**
41.	*(%)* **ND-R**	*13,7* **D**	*22,9* **ED**	*8,6* **ND**	*9,0* **ND**	*16,7* **D**	*14,3* **D**	*6,0* **ND**	*16,2* **D**
42.	*(%)* **ND-R**	*21,8* **ED**	*13,4* **D**	*18,1* **D**	*27,6* **ED**	*19,9* **D**	*23,3* **ED**	*26,1* **ED**	
43.	*(%)* **ND-R**	*16,1* **D**	*15,0* **D**	*19,6* **D**	*14,6* **D**	*17,6* **D**	*17,3* **D**	*23,2* **ED**	*4,4* **ND**
44.	*(%)* **ND-R**	*17,0* **D**	*17,4* **D**	*20,8* **ED**	*23,0* **ED**	*17,0* **D**	*10,6* **D**	*13,4* **D**	*15,9* **D**
45.	*(%)* **ND-R**	*8,9* **ND**	*8,5* **ND**	*4,7* **ND**	*11,4* **D**	*–1,9* **RD**	*15,3* **D**	*11,7* **D**	*11,7* **D**
46.	*(%)* **ND-R**	*2,4* **ND**	*–4,8* **RD**	*8,3* **ND**	*12,1* **D**	*4,1* **ND**	*0,1* **ND**	*2,1* **ND**	*–5,2* **RD**
47.	*(%)* **ND-R**	*16,2* **D**	*17,7* **D**	*17,5* **D**	*15,3* **D**	*22,9* **ED**	*19,3* **D**	*14,8* **D**	*5,3* **ND**
48.	*(%)* **ND-R**	*17,7* **D**	*19,3* **D**	*28,1* **ED**	*17,3* **D**	*10,9* **D**	*1,3* **ND**	*20,0* **ED**	*24,2* **ED**
49.	*(%)* **ND-R**	*9,0* **ND**	*21,4* **ED**	*6,1* **ND**	*3,9* **ND**	*9,5* **ND**	*9,2* **ND**	*7,6* **ND**	*3,8* **ND**
50.	*(%)* **ND-R**	*10,7* **D**	*9,0* **ND**	*13,8* **D**	*5,1* **ND**	*12,2* **D**	*1,3* **ND**	*12,7* **D**	*20,8* **ED**

Table 4a: *D dipper, ND-nondipper ED extrem dipper, RD reverse diper*

No.	Night-to day ratio	Mean 7 day	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
1.	*(%)* **ND-R**	*13,3* **D**	*9,9* **ND**	*9,6* **ND**	*14,4* **D**	*8,5* **ND**	*3,3* **ND**	*14,0* **D**	*12,4* **D**
2.	*(%)* **ND-R**	*8,2* **ND**	*2,9* **ND**	*−0,3* **RD**	*16,0* **D**	*4,4* **ND**	*8,9* **ND**	*12,9* **D**	*12,4* **D**
3.	*(%)* **ND-R**	*11,4* **D**	*16,3* **D**	*−0,3* **RD**	*13,9* **D**	*15,4* **D**	*12,2* **D**	*17,2* **D**	*4,3* **ND**
4.	*(%)* **ND-R**	*7,0* **ND**	*4,3* **ND**	*3,2* **ND**	*15,7* **D**	*6,9* **ND**	*10,1* **D**	*−12,8* **RD**	*20,3* **ED**
5.	*(%)* **ND-R**	*23,5* **ED**	*24,2* **ED**	*19,3* **D**	*27,1* **ED**	*28,8* **ED**	*23,1* **ED**	*16,5* **D**	*23,9* **ED**
6.	*(%)* **ND-R**	*12,3* **D**	*11,3* **D**	*14,7* **D**	*8,9* **ND**	*15,7* **D**	*16,1* **D**	*13,7* **D**	
7.	*(%)* **ND-R**	*25,2* **ED**	*21,4* **ED**	*15,6* **D**	*36,0* **ED**	*21,4* **ED**	*24,5* **ED**	*33,6* **ED**	*33,0* **ED**
8.	*(%)* **ND-R**	*22,3* **ED**	*17,9* **D**	*31,8* **ED**	*21,2* **ED**	*22,6* **ED**	*29,9* **ED**	*−1,1* **RD**	*29,7* **ED**
9.	*(%)* **ND-R**	*6,3* **ND**	*1,8* **ND**	*20,4* **ED**	*8,4* **ND**	*3,6* **ND**	*10,1* **D**	*3,2* **ND**	*−4,2* **RD**
10.	*(%)* **ND-R**	*15,8* **D**	*22,7* **ED**	*19,3* **D**	*23,7* **ED**	*15,8* **D**	*3,6* **ND**	*6,7* **ND**	*16,4* **D**
11.	*(%)* **ND-R**	*10,3* **D**	*8,9* **ND**	*19,9* **D**	*16,4* **D**	*5,6* **ND**	*2,5* **ND**	*14,7* **D**	
12.	*(%)* **ND-R**	*22,5* **ED**	*23,7* **ED**	*12,8* **D**	*35,3* **ED**	*16,9* **D**	*21,2* **ED**	*25,3* **ED**	*21,5* **ED**
13.	*(%)* **ND-R**	*6,4* **ND**	*−0,1* **RD**	*4,3* **ND**	*2,8* **ND**	*15,1* **D**	*12,1* **D**	*5,4* **ND**	*4,6* **ND**
14.	*(%)* **ND-R**	*15,7* **D**	*13,0* **D**	*20,5* **ED**	*21,1* **ED**	*22,0* **ED**	*0,4* **ND**	*5,7* **ND**	*24,2* **ED**
15.	*(%)* **ND-R**	*16,3* **D**	*10,7* **D**	*14,2* **D**	*23,7* **ED**	*17,9* **D**	*19,3* **D**	*12,6* **D**	*16,3* **D**
16.	*(%)* **ND-R**	*10,8* **D**	*15,4* **D**	*9,3* **ND**	*20,5* **ED**	*7,3* **ND**	*18,4* **D**	*11,5* **D**	*−6,8* **RD**
17.	*(%)* **ND-R**	*23,8* **ED**	*38,5* **ED**	*18,5* **D**	*10,9* **D**	*18,0* **D**	*27,3* **ED**	*24,3* **ED**	*28,1* **ED**
18.	*(%)* **ND-R**	*13,0* **D**	*14,8* **D**	*6,5* **ND**	*20,3* **ED**	*14,3* **D**	*17,3* **D**	*5,4* **ND**	*5,4* **ND**
19.	*(%)* **ND-R**	*1,0* **ND**	*6,5* **ND**	*19,0* **D**	*1,7* **D**	*−19,6* **RD**	*−3,3* **RD**	*10,4* **D**	*−11,7* **RD**
20.	*(%)* **ND-R**	*21,8* **ED**	*21,6* **ED**	*24,2* **ED**	*25,9* **ED**	*16,4* **D**	*19,7* **D**	*24,0* **ED**	*20,6* **ED**
21.	*(%)* **ND-R**	*19,4* **D**	*13,7* **D**	*22,2* **ED**	*21,0* **ED**	*18,0* **D**	*11,3* **D**	*28,5* **ED**	*19,9* **D**
22.	*(%)* **ND-R**	*16,8* **D**	*17,5* **D**	*13,1* **D**	*14,4* **D**	*21,1* **ED**	*13,0* **D**	*23,5* **ED**	*14,8* **D**
23.	*(%)* **ND-R**	*23,5* **ED**	*30,0* **ED**	*23,6* **ED**	*20,9* **ED**	*20,8* **ED**	*9,6* **ND**	*25,6* **ED**	*33,4* **ED**
24.	*(%)* **ND-R**	*13,6* **D**	*22,3* **ED**	*10,5* **D**	*26,4* **ED**	*17,6* **D**	*6,0* **ND**	*9,8* **ND**	*−0,6* **RD**
25.	*(%)* **ND-R**	*67,0* **15,2**	*69,0* **17,1**	*72,2* **7,5**	*64,7* **18,1**	*67,2* **15,6**	*60,3* **54,5**	*68,3* **8,7**	*67,0* **14,1**

Table 4b: *D dipper, ND-nondipper ED extrem dipper, RD reverse dipper*

No.	Night-to day ratio	Mean 7 day	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
26.	*(%)* **ND-R**	*19,4* **D**	*24,0* **ED**	*23,2* **ED**	*17,1* **D**	*18,4* **D**	*18,5* **D**	*12,7* **D**	*21,4* **ED**
27.	*(%)* **ND-R**	*10,3* **D**	*8,5* **ND**	*18,5* **D**	*10,8* **D**	*4,8* **ND**	*7,0* **ND**	*18,0* **D**	*3,5* **ND**
28.	*(%)* **ND-R**	*21,9* **ED**	*36,6* **ED**	*15,5* **D**	*36,0* **ED**	*5,9* **ND**	*26,0* **ED**	*24,0* **ED**	*0,4* **ND**
29.	*(%)* **ND-R**	*18,7* **D**	*23,1* **ED**	*20,5* **ED**	*12,5* **D**	*13,1* **D**	*20,9* **ED**	*22,1* **ED**	*18,2* **D**
30.	*(%)* **ND-R**	*9,6* **ND**	*7,5* **ND**	*12,8* **D**	*1,3* **ND**	*8,9* **ND**	*15,5* **D**	*15,6* **D**	*5,3* **ND**
31.	*(%)* **ND-R**	*18,5* **D**	*15,8* **D**	*19,3* **D**	*24,1* **ED**	*–0,7* **RD**	*17,0* **D**	*27,1* **ED**	*23,9* **ED**
32.	*(%)* **ND-R**	*17,0* **D**	*15,4* **D**	*20,9* **ED**	*12,3* **D**	*20,2* **ED**	*9,9* **ND**	*19,5* **D**	*25,6* **ED**
33.	*(%)* **ND-R**	*24,1* **ED**	*24,5* **ED**	*33,5* **ED**	*33,4* **ED**	*26,9* **ED**	*15,6* **D**	*22,2* **ED**	*11,7* **D**
34.	*(%)* **ND-R**	*2,0* **ND**	*0,5* **ND**	*8,0* **ND**	*11,1* **D**	*4,0* **ND**	*–13,5* **RD**	*–1,8* **RD**	*4,3* **ND**
35.	*(%)* **ND-R**	*9,6* **D**	*0,9* **ND**	*15,8* **D**	*13,8* **D**	*10,0* **D**	*11,0* **D**	*11,3* **D**	*3,9* **ND**
36.	*(%)* **ND-R**	*19,1* **D**	*19,7* **D**	*19,0* **D**	*20,7* **ED**	*31,5* **ED**	*13,2* **D**	*4,4* **ND**	*22,3* **ED**
37.	*(%)* **ND-R**	*16,2* **D**	*15,1* **D**	*7,2* **ND**	*2,2* **ND**	*23,2* **ED**	*17,3* **D**	*24,6* **ED**	*22,6* **ED**
38.	*(%)* **ND-R**	*13,1* **D**	*15,6* **D**	*17,8* **D**	*16,3* **D**	*10,0* **ND**	*19,4* **D**	*9,4* **ND**	*3,3* **ND**
39.	*(%)* **ND-R**	*12,6* **D**	*16,6* **D**	*14,8* **D**	*13,0* **D**	*14,5* **D**	*–2,6* **RD**	*18,8* **D**	*17,7* **D**
40.	*(%)* **ND-R**	*13,1* **D**	*10,5* **D**	*–4,3* **RD**	*14,9* **D**	*13,7* **D**	*22,9* **ED**	*22,0* **ED**	*12,2* **D**
41.	*(%)* **ND-R**	*15,8* **D**	*24,3* **ED**	*11,2* **D**	*15,3* **D**	*9,2* **ND**	*23,2* **ED**	*18,4* **D**	*7,9* **ND**
42.	*(%)* **ND-R**	*20,4* **ED**	*14,8* **D**	*10,2* **D**	*24,1* **ED**	*19,0* **D**	*25,6* **ED**	*26,7* **ED**	
43.	*(%)* **ND-R**	*16,5* **D**	*15,8* **D**	*22,8* **ED**	*20,7* **ED**	*22,2* **ED**	*14,0* **D**	*15,0* **D**	*3,3* **ND**
44.	*(%)* **ND-R**	*24,1* **ED**	*25,5* **ED**	*23,8* **ED**	*29,4* **ED**	*23,2* **ED**	*16,8* **D**	*25,2* **ED**	*23,6* **ED**
45.	*(%)* **ND-R**	*15,1* **D**	*20,8* **ED**	*12,8* **D**	*22,6* **ED**	*4,2* **ND**	*15,5* **D**	*21,4* **ED**	*6,5* **ND**
46.	*(%)* **ND-R**	*8,5* **ND**	*6,9* **ND**	*17,9* **D**	*15,4* **D**	*10,6* **D**	*3,2* **ND**	*5,1* **ND**	*0,3* **ND**
47.	*(%)* **ND-R**	*23,4* **ED**	*15,7* **D**	*18,0* **D**	*24,1* **ED**	*27,6* **ED**	*33,6* **ED**	*21,5* **ED**	*23,0* **ED**
48.	*(%)* **ND-R**	*14,9* **D**	*24,0* **ED**	*11,2* **D**	*9,6* **ND**	*1,4* **ND**	*6,6* **ND**	*11,2* **D**	*25,4* **ED**
49.	*(%)* **ND-R**	*17,2* **D**	*26,7* **ED**	*13,7* **D**	*12,9* **D**	*19,8* **D**	*17,5* **D**	*16,2* **D**	*12,8* **D**
50.	*(%)* **ND-R**	*10,7* **D**	*9,0* **ND**	*13,8* **D**	*5,1* **ND**	*12,2* **D**	*1,3* **ND**	*12,7* **D**	*20,8* **ED**

According Brno consensus of circadian blood pressure we evaluated the seven day mean of day-to-night ratio in systolic blood pressure.

Table 5 shows the results of seven day mean of night-to-day ration in healthy subjects in systolic blood pressure in numbers and percent. in the Table 5 are presented the results of seven-day/24-h mean of diastolic blood pressure in healthy subjects.

Table 5: *Seven-day/24-h mean of night to-day systolic blood pressure ratio in healthy subjects*

Healthy subjects	Mean 7-day number	Mean 7-day %
D	30	60
ND	9	18
ED	8	16
RD	3	6

In the table classification accordance of night decrease of blood pressure based on the definition night-to-day ratio (D, ND, ED, RD) in systolic blood pressure (SBP) in healthy subject shows the differences in the seven day means in healthy subjects in SBP in categories of D, ND, ED and RD.

Table 6: *Seven-day/24-h mean of night to-day diastolic blood pressure ratio in healthy subjects*

Healthy subjects	Mean 7-day number	Mean 7-day %
D	22	44
ND	7	14
ED	20	40
RD	1	2

Table 6 Classification accordance of night-to-day ratio of blood pressure based on the definition night-to-day ratio (D, ND, ED, RD) in diastolic blood pressure (DBP) in healthy subject in subjects shows the differences in the seven day means in healthy subjects in SBP in categories of D, ND, ED and RD.

Between seven-day/24-h clasifications of night-to-day ration in systolic blood pressure and diastolic blood pressure are the differences in healthy subjects.

Table 7: *Seven-day/24-h mean of night to-day systolic blood pressure ratio in patients with ischemic heart disease*

Patients	Mean 7-day number	Mean 7-day %
D	24	48
ND	18	36
ED	8	16
RD	0	0

Table 7 Classification accordance of night decrease of blood pressure based on the definition night-to-day ratio (D, ND, ED, RD) in systolic blood pressure (SBP) in patients with ishemic heart disease in systolic blood pressure (SBP) showed the differences in the seven day means in healthy subjects in SBP in categories of D, ND, ED and RD,

Table 8: *Seven-day/24-h mean of night to-day diastolic blood pressure ratio in patients with ischemic heart disease*

Patients	Mean 7-day number	Mean 7-day %
D	31	62
ND	7	14
ED	12	24
RD	0	0

Table 8 Classification accordance of night decrease of blood pressure based on the definition night-to-day ratio (D, ND, ED, RD) in diasolic blood pressure (DBP) in patients with ischemic heart disease showed the differences in the seven day means in healthy subjects in SBP in categories of D, ND, ED and RD.

Between seven-day/24-h clasifications of night-to-day ration in systolic blood pressure and diastolic blood pressure are the differences in patients with ischemic heart disease.

Prevalence of dipper and nondipper parameters in our clinicaly healthy subjects shows differnt results in evaluation in systolic blood pressure and diatolic blood pressure. The variability in one day measurement showed the importance for evaluation the dipping and nondipping status on the basis of seven-day/24-h ambulatory blood pressure monitoring according to Brno consensus in 2008, presented on our Congress on Noninvasive methods in cardiology in Brno. Mean values of dipping status from seven-day/24-h record were in healthy subjects in systolic blood pressue 60%, in patients with ischemic heart disease 48%, nondipping status were in healthy subjects 16% ED and .6% RD, in patients with ischemic heart disease nondipping status was 16% ED .

Mean value from seven-day/24-h of dipping in diastolic blood pressue in heathy subjects was 44% and in patients with ischemic heart disease 62%, nondipping in healthy subjects were 14% ND, 40% ED, in patients with ischemic heart disease 14%ND, 24%ED.

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

Several physiological and methodological reasons may explain the poor reproducibility of the circadian blood pressure variation. The level of daytime activity and the duration and quality of sleep are major determinants of nocturnal blood pressure fall. Differences in the duration and depth of sleep may have a marked impact on their autonomic regulation of cardiovascular system during the nigh-time, leading to different changes in blood pressure and heart rate during repeated ambulatory blood pressure monitoring (12-25).

Dipping status has also a low reproducibility, with up to 40 % of individuals from Europe (28) and Asia (29) 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 (6,10,11,21). 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 (2, 3, 4, 6,8,9,10, 23- 30).

The results in our group of healthy subjects and patients with ischemic heart disease could be also effected by the fact, that the patient were under pharmacological therapy and cardiovascular rehabilitation changed their living style with regular physical activity.

Conclusion

Our result showed that the group of 50 healthy subjects and 50 patients with ischemic heart disease showed variability of seven-day/24-h mean values of night-to-day ratio in systolic and diastolic blood pressure:

Mean values from seven-day/24-h of dipping status were in healthy subjects in systolic blood pressue 60%, in patients with ischemic heart disease 48%, nondipping status were in healthy subjects 16% ED and .6% RD, in patients with ischemic heart disease nondipping status wa 16% ED .

Mean value from seven-day/24-h of dipping in diastolic blood pressue in heathy subjects was 44% and in patients with ischemic heart disease 62%, nondipping in healthy subjects were 14% ND, 40% ED, in patients with ischemic heart disease 14%ND, 24%ED.

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https://doi.org/10.5817/CZ.MUNI.M280-0669-2024-6

Muscle Preconditioning Using Electrostimulation of the Lower Limbs in Hemodialysis Patients

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Introduction

End-stage chronic kidney disease (ESRD) represents a global health problem, associated with high mortality and morbidity, a number of devastating comorbidities, and a huge economic burden on national budgets (1). According to current estimates, ESRD could become the leading cause of death in the next two decades (2). ESRD results from irreversible damage to the renal parenchyma. Very frequently, the kidney failure is the consequence of chronic pathologies such as diabetes mellitus, hypertension, glomerulonephritis, autoimmune diseases and a number of congenital abnormalities (3). Gradual loss of renal excretory and regulatory functions leads to the development of uremic syndrome (4; 5). Retention of uremic toxins is one of the main reasons of premature muscle fatigue, skeletal muscle dysfunction, malaise, anorexia, anemia, fluid retention, bone mineral loss, and numerous neurological symptoms (4; 5). Progressive deterioration of kidney function causes a general decrease in physical and psychological well-being. Most HD patients have severely limited functional capacity, as evidenced by the fact that their maximal oxygen uptake is only 60-70 % of the normal age-dependent range (6; 7). Typical clinical manifestations of functional and morphological abnormalities in dialysis patients are poor condition, weakness and muscle atrophy, especially of the muscles of the lower limbs. All this enhances tendency to sedentary lifestyle and inactivity, which greatly limits the physical and mental abilities of patients, especially when it comes to ADL (8). A number of clinical trials have reported positive effects of ambulatory or home-based exercise (mainly aerobic) in dialysis patients (9; 10; 11). The intervention methods and duration of training programs is quite variable, ranging from 8 weeks to 1 year. Most studies have shown a significant improvement in VO_{2peak} after aerobic (cardiovascular) training with an average increase of 15-16 % across studies (9; 0; 11). Although the improvement found was similar to that in healthy people, no one training modality led to full normalization of the maximal oxygen uptake, and values after the rehabilitation program sometimes remained far below age-predicted values (12; 13). In addition to improving aerometabolic capacity, improvements were also seen in renal clearance (e.g. urea removal), blood pressure control and lipid profiles. Similarly, a significant rise of the muscle strength was found after completing an aerobic exercise program alone or in combination with resistance training (12; 13, 14). However, only modest or no improvements were observed in measures of quality of life (assessed by questionnaires) or self-sufficiency (14; 15; 16).

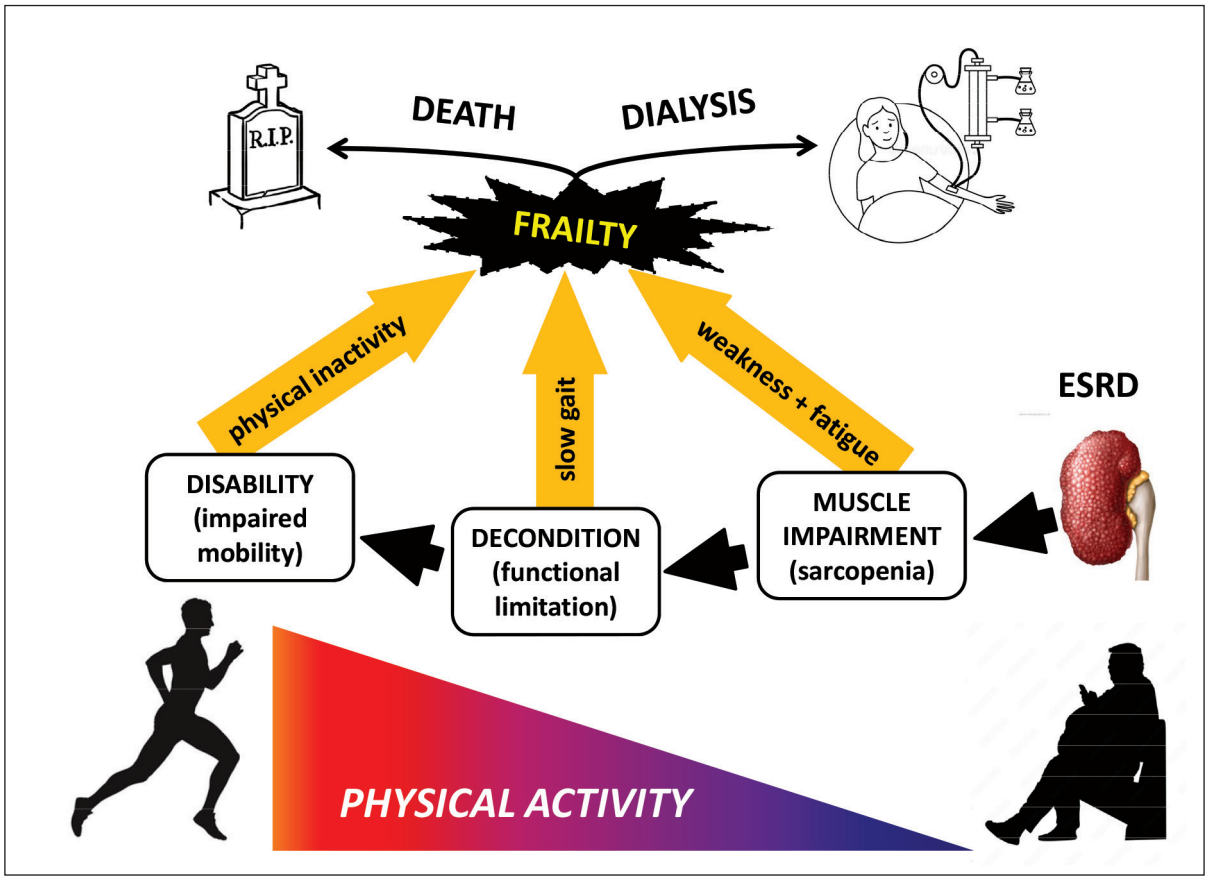

Figure 1: *ESRD leads to muscle impairment promoting loss of fitness, disability, and frailty (Source: modified scheme from 19).*

The muscle weakness at the beginning of the intradialytic aerobic training program is not only the cause of non-compliance with the training intensity, but very often leads to early dropout from the rehabilitation program. Moreover, the same limitation linked to the premature muscle fatigue of the lower limbs also applies to the result of the functional testing, such as spiroergometry (CPET), performed before the inclusion in the ID-RHB program. According to actual guidelines, the minimum time length of a valid CPET is 8, optimally 12 min (17). However, according to our own and other´s experience, a significant number of dialysis patients are too "frail" to complete the CPET within the mentioned time limit (18). "Frail" or" "frailty" – what does it mean for dialyzed people? Current bibliography often emphasizes that an individual's functional capacity is affected not only by cardiorespiratory fitness, but also by so-called "frailty" (Fig. 1), a term originally associated with the adverse consequences of aging (19) However, it is now increasingly recognized as a clinical syndrome and an important feature of severe chronic diseases, including ESRD (20; 21). The "frailty syndrome" is characterized by the presence of following criteria: unintentional weight loss (10 lbs in past year), self-reported exhaustion, weakness (grip strength), slow walking speed, and low physical activity (22). It has been proven that the presence of at least three of these criteria significantly predicts an increased risk of falls, impaired mobility, disability, hospitalization or fatal events in the elderly (22). The presence of the "frailty syndrome" in HD patients signalizes a very high risk that the full metabolic load during CPET will not be achieved, and the determination of a safe limit of training intensity will be considerably more difficult. Thus, the solution could be e.g. the strengthening of the skeletal muscle mass. In this context in the past two decades, the idea of skeletal muscle "prehabilitation" has been shown to positively influence the health status of frail HD patients awaiting transplantation (23; 24).

Therapeutic potential of electrical stimulation in HD patients

Application of electricity for therapeutic purposes dates back to thousands of years before Christ. The Ancient Egyptians and later the Greeks and Romans recognized that electrical fishes are capable of generating electric shocks for relief of pain. Murals depicting the Nile catfish (Fig. 2) have been discovered in Egyptian tombs dating from the Fifth Dynasty (25; 26). Scribonius Largus, a court physician to the Roman Emperor Tiberius Claudius, reported one of the first medical uses of electricity by torpedo rayfish to treat headache and gout (25; 26).

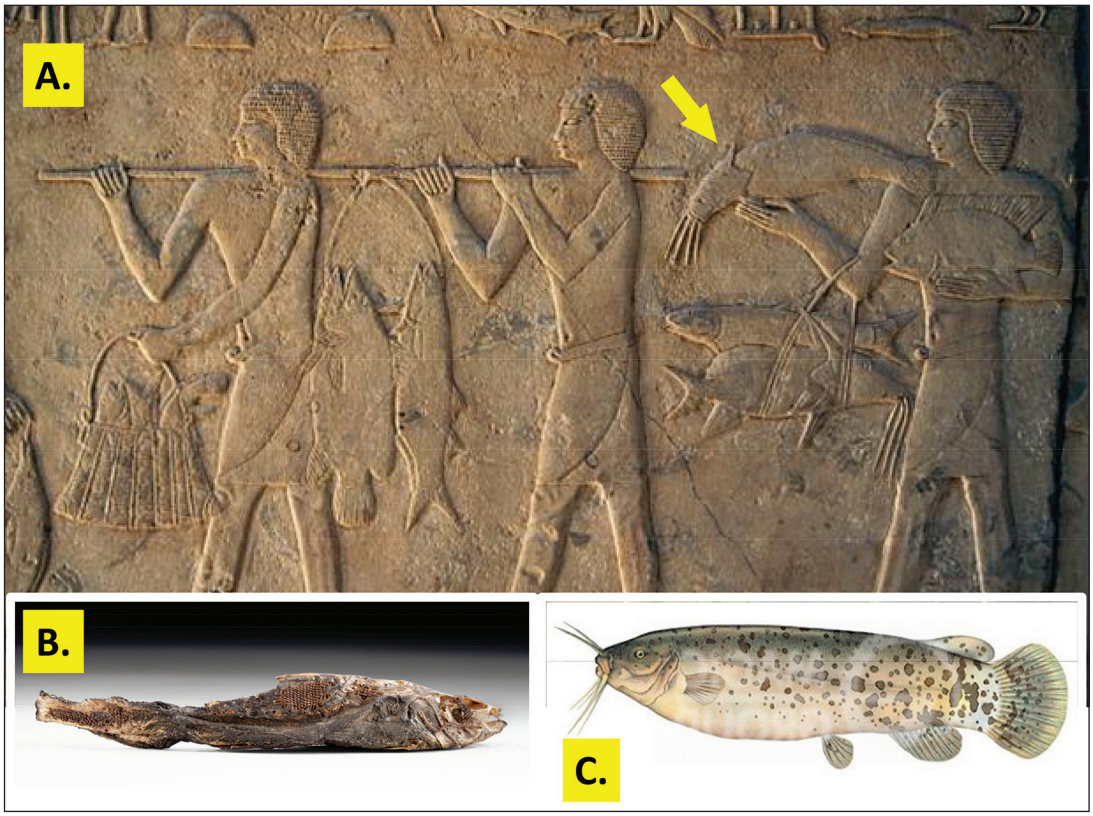

Figure 2: *A. Murals depicting the Nile catfish (arrow ➡), have been discovered in Egyptian tombs dating from the Fifth Dynasty (ca. 2400 BCE). B. Mummified catfish from Egyptian tomb. C. Nile electric catfish (Malapterurus electricus) (Sources:* https://egyptraveluxe.blogspot.com/2017/02/the-tomb-of-kagemni.html*;* https://www.liveauctioneers.com/item/89369692_egyptian-mummified-electric-catfish-and-wood-plaque*;* https://animalia.bio/malapterurus-electricus*)*

During the reign of Emperor Nero, a military surgeon in the Roman army, Pedanius Dioscorides, presented first experiences about the use of the torpedo rayfish electric discharge for muscle stimulation as a treatment of prolapsus ani (26). In the 17th century, Pieter van Musschenbroek invented the Leyden jar, which provided a platform for the progression of modern electrotherapy. In the course of the 18th and 19th centuries, manufactured electrical devices replaced the natural sources of electricity. A pivotal roles were played by Luigi Galvani (and his famous frog experiments), Benjamin Franklin and Michael Faraday (Fig. 3).

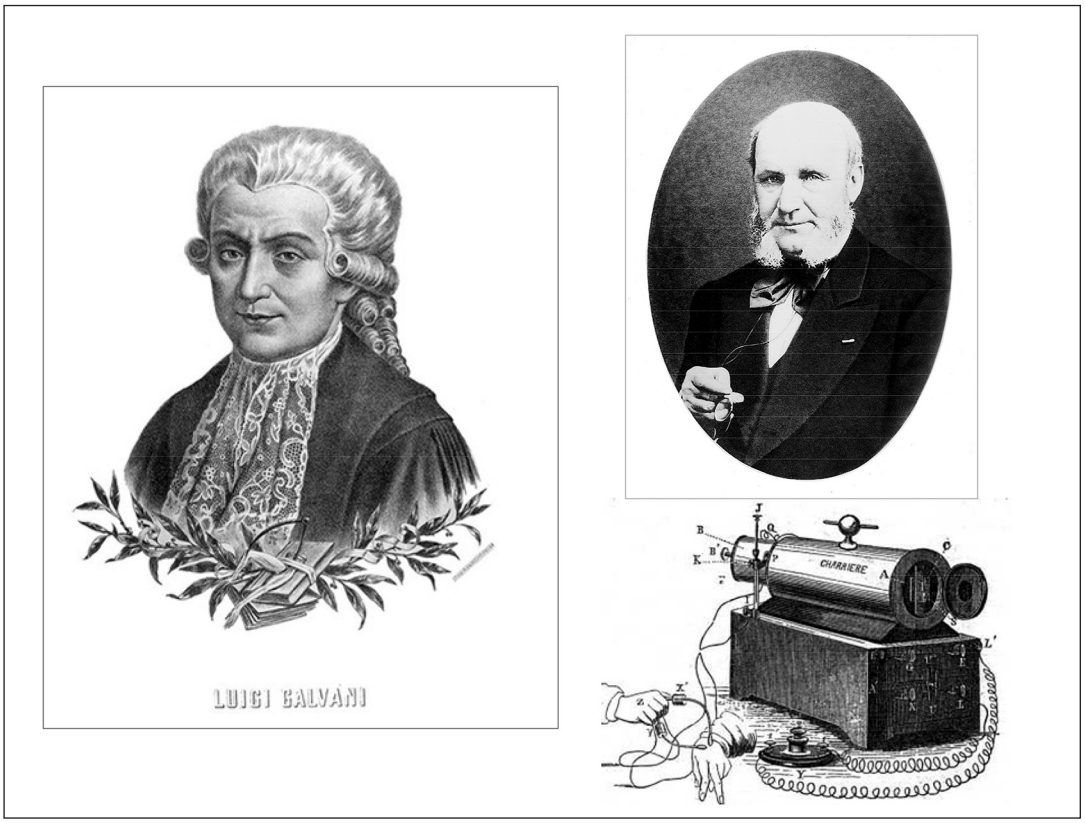

Figure 3: *Luigi Galvani (1737 - 1798), Guillaume Duchenne de Boulogne (1806 - 1875) and the original depiction of Duchenne's „appareil volta-électrique" ("volta-electric apparatus„). (Source:* https://www.bridgemanimages.com/en/french-school/volta-faradic-apparatus-used-by-guillaume-benjamin-duchenne-de-boulogne-1806-75-illustration-from/engraving/asset/207820 *)*

It should be also highlighted still a little bit omitted contribution of the French neurologist Guillaume Duchenne de Boulogne (Fig. 3), the inventor of volta-electric apparatus, who revived Galvani's research and greatly advanced the knowledge and progress in electrophysiology (26; 27). Therefore, the 19th century can rightly be called the "golden age" of electrotherapy that was used for countless dental, neurological, psychiatric and gynecological disturbances. The modern electrotherapy of neuro-musculo-skeletal disorders is based in particular on the following types: a) transcutaneous electrical nerve stimulation, b) electrostimulation strength training; c) functional electrical stimulation; d) neuromuscular electrical stimulation (NMES) and, e) and spinal cord stimulation (27). As mentioned, patients on ambulatory HD are very often limited in their physical performance by weakness of the leg muscles. This contributes to poor gait abilities and decreased degree of independence that hampers the immediate admission into the RHB programs of intradialytic aerobic training (ID-AT). For that reason, it is advisable to consider alternative rehabilitation methods, e.g. low-intensity aerobic training, yoga or local neuromuscular electrical stimulation (NMES). The positive effects of NMES have been shown in the course of the last few decades in debilitating chronic diseases accompanied by loss of skeletal muscle mass (28; 29). In 2020, a meta-analysis of eight studies including 221 patients showed that NMES applied during HD sessions enhanced functional capacity assessed by distance walked at 6MWT and increased peak workload during incremental exercise (30). The authors also suggested that NMES might be an effective strategy for maximizing training stimuli and subsequent muscle adaptations in patients who can perform volitional exercise (30).

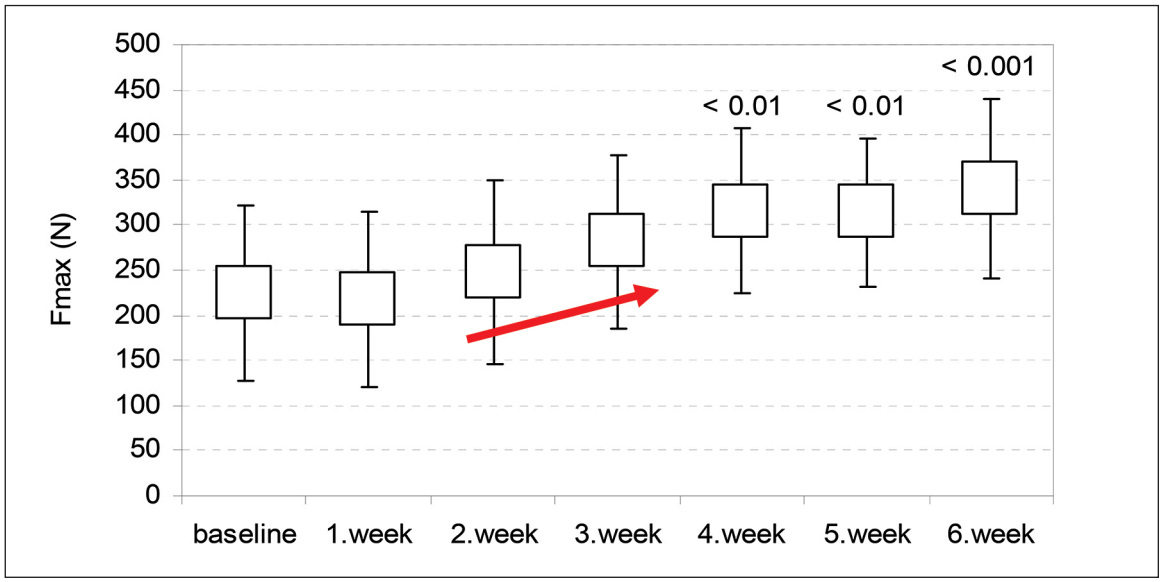

Figure 4: *Graph showing the increase of the maximal muscle power of leg extensors during 6 consecutive weeks of NMES (Source: 28).*

A significant advantage of neuromuscular electrical stimulation (NMES) is its analgesic effect, but it is also useful in the therapy of myoskeletal disorders. According to the results of large clinical trials, it seems that NMES improves the structural-metabolic properties of skeletal muscle in serious diseases, such as diabetes mellitus, chronic heart failure or chronic renal insufficiency (27). Based on our previous experience with the patients with chronic congestive heart failure NYHA IV (Fig. 4), the application of low-frequency NMES at 10Hz can considerably improve the muscle power of leg extensors already within 3 weeks (only) of daily stimulation (28). Thus, it is likely to achieve similar results in patients on ambulatory hemodialysis, where the muscle wasting can strongly limit their full inclusion into intradialytic training program. Therefore, we conducted and assessed the effect of home-based training using low-frequency NMES as a kind of prehabilitation or „muscle conditioning“.

Patient's characteristics

We enrolled 9 patients (7 men, 2 women; mean age 62.7 ± 9.1 yrs; mean BMI 27.3 ± 6.01; mean body weight 80.8 ± 15.2 kg). All were on ambulatory hemodialysis three times a week. The total number of comorbidities was 43; the most frequent pathology was hyperparathyreosis, hypertension and diabetes mellitus. The whole rehabilitation program had two phases. The first phase was the NMES prehabilitation program for three consecutive weeks. Portable battery-powered stimulators (Rehab X-2, Cefar, Sweden) and self-adhesive electrodes (80 x 130 mm; PALS Platinum, Axelgaard Manufacturing, Denmark) were used for NMES. The position of the electrodes was chosen based on the estimated places of highest density of motor points in quadriceps muscles of both legs. After the initial instruction by an experienced physiotherapist (handling the device and correct placement of the stimulation electrodes) in the hospital (in the presence of family members), the devices were distributed to the patients to realize NMES at home (Fig. 5). The stimulation protocol was compiled as follows: biphasic current of 25 Hz frequency, pulse width 200 msec, mode "on-off" (8s stimulation, 12s rest), and maximal amplitude of 60mA. NMES was performed 2 x 60min/day, 7 days a week, for three consecutive weeks (Fig. 6). The patients were asked to perform the stimulation at least one time a day and at best twice daily in supine or semi-supine position and in quiet environment. Then, the second phase started and after the entrance CPET (within 1 week after the end of the NMES) all patients were included into the standard intradialytic aerobic training.

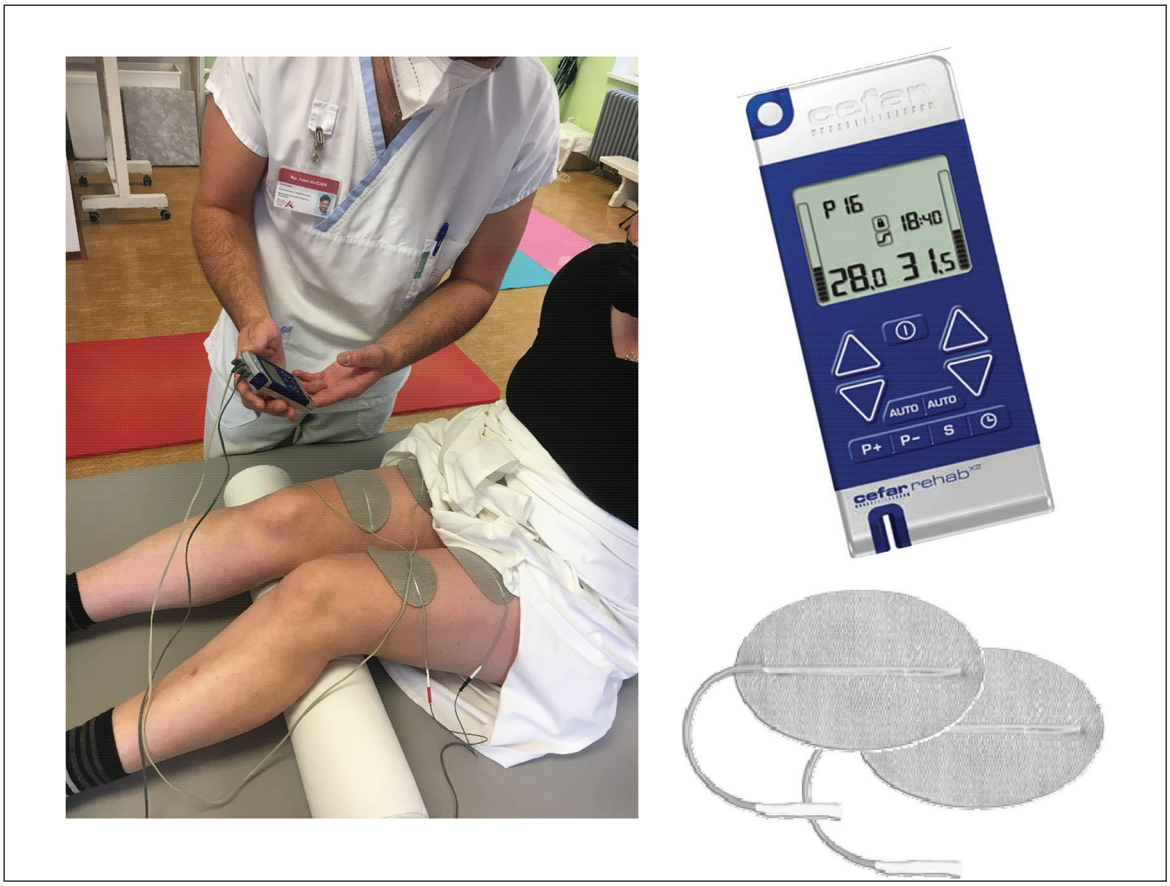

Figure 5: *In-hospital instruction of the patient about proper positioning of electrodes and the stimulator Rehab X-2 Cefar (Sweden) (Source: own material).*

Performance testing

Before the program of prehabilitation or „muscle conditioning“by NMES was started, a simple isometric dynamometry testing of the muscle power (F_{max} and M_{max}) of quadriceps muscles was performed using the PC-2 SDT dynamometric system (EXAMO® Recens, Brno, Czechia) with a microprocessor. To evaluate the actual physical performance of the enrolled patients a six minutes corridor walk test (6MWT) was done according to standard protocol (31) and the predicted distance was calculated (32). The Fig. 4 shows the detailed schematic view of „muscle conditioning“in three steps. The same tests were realized after three weeks of home-based prehabilitation by NMES.

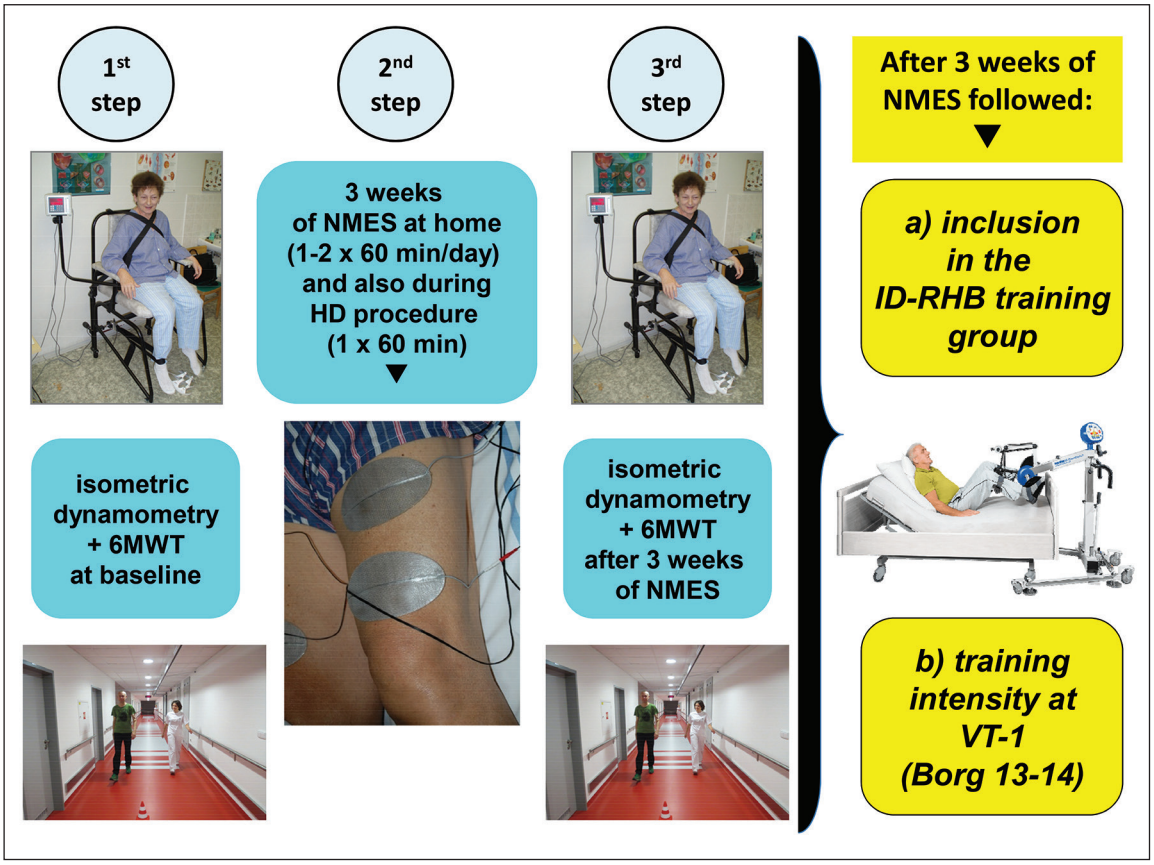

Figure 6: *Muscle „conditioning“- schematic view of the intervention protocol in 3 steps before full inclusion in the ID-RHB training program (Source: own material).*

Results

As expected, the physical performance of our subjects was quite poor – the average value of the distance walked in 6MWT was only about 50 % of predicted value (Fig. 6). Similarly, also the dynamometric testing showed a low average value of the muscle power of knee extensors, expressed as maximum force F_{max} and peak torque M_{max}. After 3 weeks of daily NMES the mean value of knee extensors inreased by 13 % (Fig. 7) and this improvement was statistically significant (from 195 ± 44.9 N to 221 ± 41.5 N; $P < 0.05$). In addition, the mean peak torque M_{max} showed an improvement (by 5 %), however without statistical significance (from 105 ± 30.1 Nm to 110 ± 29.1 Nm; NS). The control 6MWT after RHB home training by NMES was not performed to prevent too extensive physical loading of the patients, and a baseline CPET was preferred to allow patients to initiate the ID-RHB

program. However, it can be assumed that due to the improvement of muscle strength, the distance traveled would also increase.

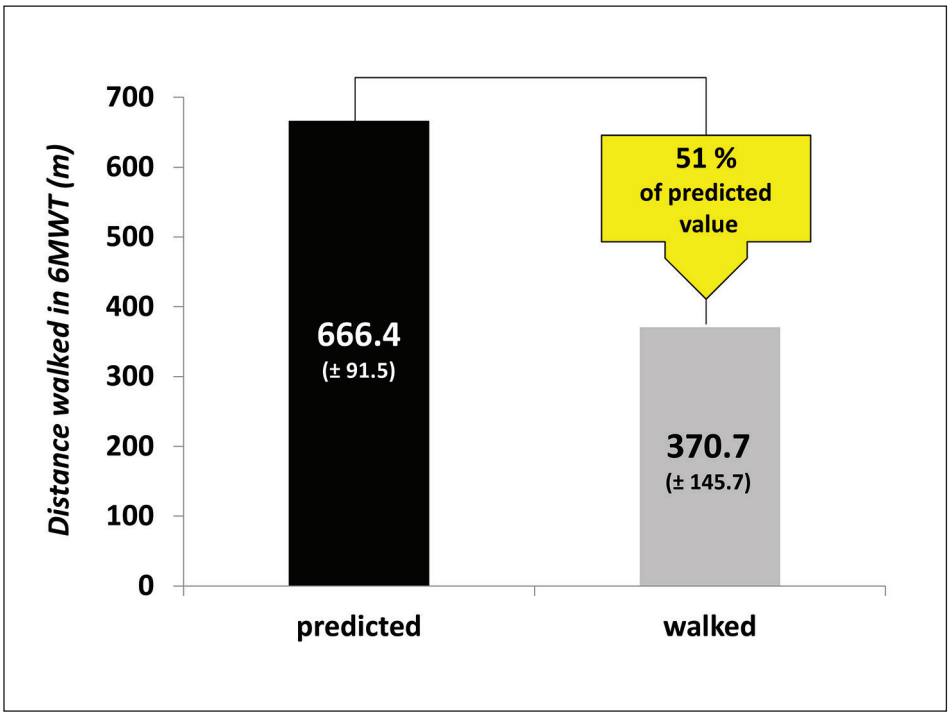

Figure 7: *Results of the 6MWT at baseline (predicted vs. real mean distance walked).*

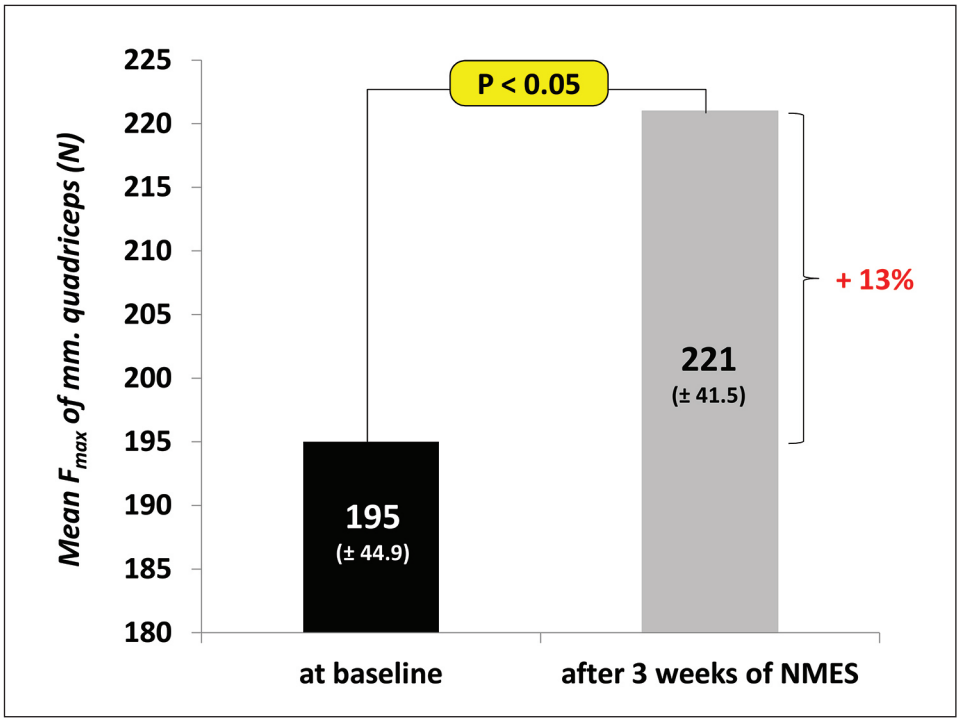

Figure 8: *Results of mean F_{max} of mm. quadriceps assessment after 3 weeks of NMES.*

Conclusion

Several „barriers“to exercising in ESRD patients still exist (33; 34; 35). First, the persistent problem in the current care of patients with ESRD is inactivity, especially present in dialysis patients. Inactivity in combination with the aforementioned effects of chronic uremia, prevailing catabolism, and systemic inflammation further deepens overall deconditioning and the development of myoskeletal dysfunction and sarcopenia (36). A sedentary lifestyle only exacerbates the manifestations of fatigue, depression, reduced physical fitness and quality of life. It is well known that sedentary dialysis patients show a higher mortality rate than those who perform some form of physical activity regularly (37). Moreover, not only countries with limited economic resources, but also the well-developed health systems of industrialized countries still struggle with insufficient capacity and infrastructure to provide appropriate exercise programs and promote physical activity in this patient´s population. The predominant reasons that HD patients consider to be the main „barriers“ to performing physical activity include fatigue, subjective discomfort, weakness, accompanying comorbidities, poor motivation and concerns about the risks of exercise, e.g. injury, worsening of condition, etc. (38; 39). It is necessary to admit, that a significant number of these “barriers” can be connected directly or indirectly with the already mentioned frailty syndrome. As already mentioned, especially frailty is an important factor influencing the level of active participation of HD patients in exercise programs. However, many „barriers“can be overcomed in this patient´s population with a proper assessment of health status, education and careful design of exercise training. Usually, the best practice is to individually start with exercises of a lower intensity and short duration, where good tolerance of the patient can be expected, and gradually increase the training doses over the course of the following weeks. However, when standard exercise programs are not available or due to patient´s incapacity or low interest, alternative strategies should be considered, first the NMES. We can conclude, three weeks of low frequency NMES applied to leg extensors increases significantly muscle power in HD patients and at least partly counterbalances the negative effects of chronic uremic pro-inflammatory milieu. NMES in this small study has been shown as an effective auxiliary tool of prehabilitation for “muscle conditioning”, increasing the power of knee extensors in patients on ambulatory hemodialysis before their full inclusion to standard intradialytic aerobic training. NMES could be a safe, practical and effective way to improve muscle power also in patients at risk of complication during intradialytic exercise, or who are unwilling to join active exercise programs (40). However, although the results of several recent clinical trials support the routine implementation of NMES during dialysis sessions, it is preferable that voluntary physical exercise should be performed whenever possible.

Due to the covid-19 pandemics in 2021, the intradialytic rehabilitation program was interrupted and relaunched only this year.

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https://doi.org/10.5817/CZ.MUNI.M280-0669-2024-7

Cardiac Rehabilitation after Cardiac Diseases

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The lecture was presented on the 13. international congress of cardiology and diabetes In Noida, India, 9-10 november 2024


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Invitation letter as a speaker ICCD 2024

To,
Dr Siegelova Jarmila
(Czech Republic)
Dear Madam,

We are pleased to inform you that we are organizing the 13th International Congress of Cardiology & Diabetes (ICCD 13) in association with the Association of Physicians of India – Noida Chapter. The event will take place on November 9-10, 2024, at the Holiday Inn, Mayur Vihar Phase-1, New Delhi-110091, India.

This Congress is part of our ongoing scientific activities aimed at enhancing our knowledge and skills through collaboration. We have invited esteemed international and national experts to participate. We would be honored to have you as one of our speakers to share your valuable knowledge and experience.

Please confirm your participation at your earliest convenience at iccd2024noida@gmail.com, and drmeenakshijain@gmail.com.You may also use this letter for visa application purposes.

Thank you and best regards,

Dr. S Chakravorty
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TOPIC - Morning surge and the circadian circa-semidian coupling in blood pressure.
OSAMA ELMARAGHI
TOPIC - SGLT2 Inhibitors
DR ALOK KUMAR SINGH
TOPIC - Evolution of Drug therapy from Digitalis to SGLT-2 inhibitors in heart failure
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TOPIC - Future Perspective of Once a Week basal Insulin therapy
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TOPIC - The novel role of circadian clock system in the transition of HFpEF to HFrEF.
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TOPIC - Noreflow after PCI: Divesity of pharmacological strategies
DR KAOROLLA RAKHIMOV
TOPIC - New approaches to pharcotherapy in diabetes mellitus
DR MAURIZIO CAMPANIELLO
DR DEVENDRA K AGRAVAL
TOPIC - Novel Treatment Strategies to Attenuate Plaque Vulnerability in Atherosclerosis
FATEME NABAVIZADEH
DR RAMESH GOYAL
DR. AMITABH YADUVANSHI
TOPIC - Renal Denervation for Management of Hypertension : Ready for Primetime?
DR FABIOLA SOZZI
TOPIC - Mitral valve imaging
DR SIEGELOVA JARMILA
TOPIC - Cardiac rehabilitation after cardiac disease
DR NASSER GHALY YOUSIF
TOPIC - Carcinogenesis as risk factor of atherosclerosis
ANDREA GIOVANNI PARATO
TOPIC - Novel approach to atrial fibrillation in cardio-oncology
13th ICCD 2024 | India

Cardiovascular rehabilitation

„Cardiovascular rehabilitation is a complex process by which patients with cardiovascular diseases are encouraged and supported to achieve and maintain optimal physical, psychosocial, emotional health.“

The goals of cardiac rehabilitation are to improve muscle strength, to prevent atrophy of skeletal muscle and to reduce risk of ischemic heart disease.

These goals should improve quality of life in patients with heart diseases!

Cardiac rehabilitation programs significantly increase the survival of cardiac patients.

According to the official Guidelines of the European Society of Cardiology and Czech Society of Cardiology is indicated cardiac rehabilitation program.

The purpose of this cardiovascular training is to facilitate the return to optimal living and to encourage patients to make lifestyle changes in order to prevent further cardiovascular events.

Psychological support is a part of the program and is also necessary to deal with psychological distress, which is common following AMI.

Cardiovascular program:

Phase 1: rehabilitation process in hospital

Phase 2: early rehabilitation program - outpatient rehabilitation

- ► ambulatory supervised rehabilitation program
- ► rehabilitation program in spa

Phase 3: stabilization period

-structured exercise program with educational and psychological support

Phase 1

- ✧ prevention of decondition and loss of muscle power
- ✧ adequate perfusion of low extremities and prevention of thrombosis
- ✧ introduction of patients for theirs daily habitual activity
- ✧ The hospitalization of AIM lasts 7 – 12 days
- ✧ Rest in bed only 12 – 24 h after AIM !!! The patients must be stabilized – lost of chest pain, HR and BP
- ✧ Rehabilitation program includes:
  - ✓ Exercise with the evaluation of the blood pressure and heart rate before, during and after exercise, monitoring of subjective feeling of patients (fatigue, dyspnoe, chest pain).
  - ✓ terapy 1 per day supervised by physioterapist
  - ✓ repetiotion by patient´s own activities 2-3 per day
  - ✓ patient´s education by physiotherapist

- ✧ The program may begin with slowly increased intensity of load and increased time of exercise.
- ✧ Exercise starts in lying position, later in sitting position, and standing up, walking, before the discharge walking in the staircase.
- ✧ The first standing up could be accompanied by orthostatic hypotension
- ✧ BP must be measured before and after standing
- ✧ Decrease systolic BP in standing to the level lower than 90 mmHg or decrease of more than 20 mmHg – patient must return in the bed and can not exercise in standing position
- ✧ Systolic BP > 90 mmHg or decrease of < 10 mmHg – patient can walk

Contraindications of cardiac rehabilitation

- ✦ Sinus tachycardia > 120 per min.
- ✦ SBP > 200 mmHg, DBP > 115 mmHg
- ✦ Hypotension
- ✦ Acute infection
- ✦ Stenosis aortae
- ✦ Aneurysma aortae dissec
- ✦ Nonstabile angina pectoris
- ✦ Heart failure
- ✦ Embolia pulmonaris
- ✦ Arrythmias

Education of patients for the change of living style

1. Nonsmoking
2. BP control
3. Diet
4. Physical activity
5. Body weight
6. Therapy
   - ✓ Antiagregation therapy
   - ✓ Betablocars
   - ✓ ACEI (dysfunction LV)
   - ✓ Statins

phase 2 Ambulatory supervised rehabilitation program

Aim:
Improvement of physical and psychical load
Improvement of aerobic capacity and muscle strenght
Improvement of healthy living style

Including in active life
Improvement of quality of life

Ambulatory supervised rehabilitation program

➢ starts within **3 weeks after discharge**

➢ recommended **by treating cardiologist**

➢ program is **fully covered** by health insurance

exercise testing (spiroergometry)

should be done to determine the **safety limits**

✓ at the beginning of RHB program

✓ in its first half

✓ after its end

Spiroergometry testing (CPX System MedGraphics®, USA)

Figure 1: *Spiroergometry*

♦ W_{SL}

♦ W_{SL}. kg^{-1}

♦ VO_{2SL}

♦ VO_{2SL}. kg^{-1}

♦ HR_{SL}, BP_{SL}

♦ 12-lead ECG

♦ $HR_{AT = training}$

♦ $W_{AT = training}$

♦ $RPE_{AT = training}$

Exercise program in phase II

Training unit Aerobic training unit	Training unit with strengthening
1. Warm-up phase 10 min	1. Warm-up phase 10 min
2. Aerobic phase 40 min	2. Aerobic phase 20 min
3. Relaxation phase 10 min	3. Strengthening 20 min
4. Relaxation phase 10 min	4. Relaxation phase 10 min

Ergosoft + (Ergoline+)

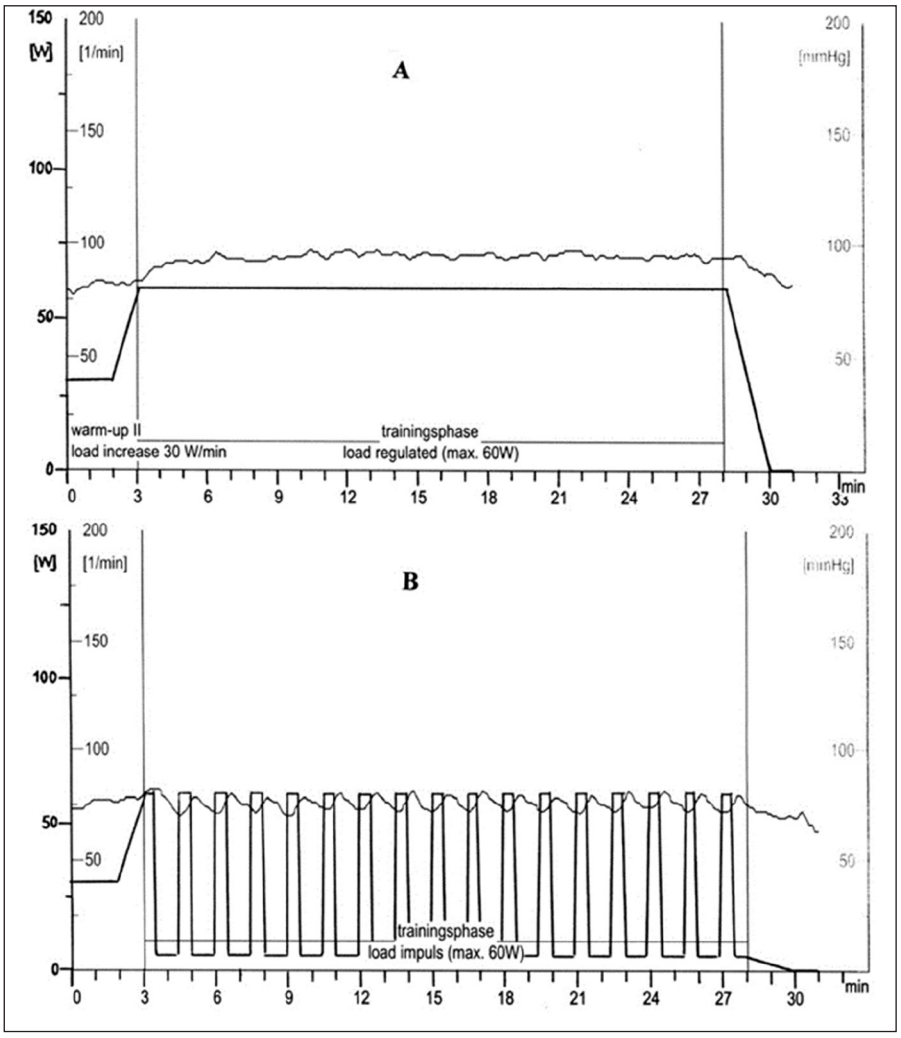

Figure 2: *Aerobic trainig*

Training Intensity of individual load is on the anaerobic thesholds (AT) HR_{AT}, W_{AT}, RPE_{AT}

A Constant load

B Interval training - in patients with high risk:

Residual ischemia
Depression of left ventricule function
Heart failure

II. phase -„warm up“ period

Figure 3: *II. phase -„warm up“ period*

II. phase - „warm up“ period

Figure 4: *II. phase -„warm up“ period*

II. phase - aerobic training period

Figure 5: *II. phase - aerobic training period*

II. phase - aerobic training period

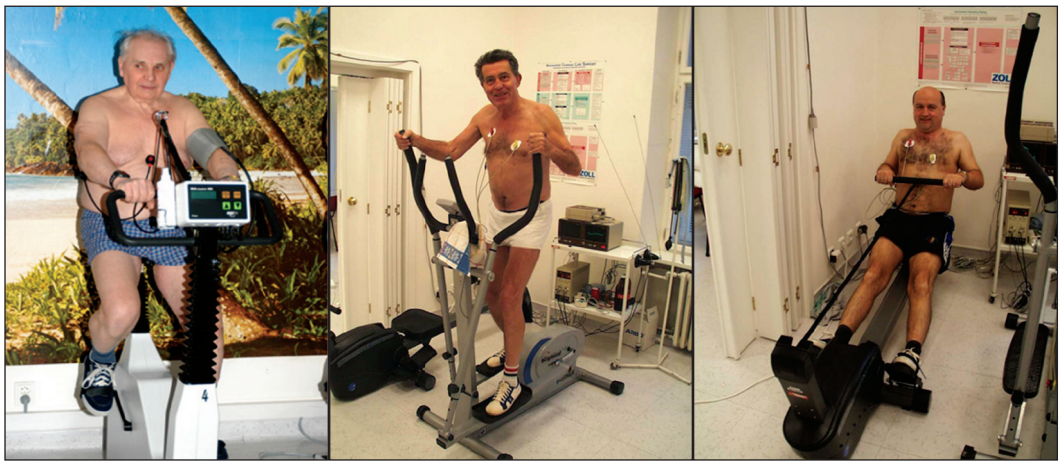

Figure 5: *II. phase - aerobic training period*

II. phase - resistance training period

- ✦ Follows after 2-4 weeks of aerobic training
- ✦ Training intensity determination using the method 1-RM
- ✦ Training intensity could be from od 25 % one repetition maximum (1-RM) to 80 % 1-RM
- ✦ 4 - 15 different exercises
- ✦ 1 - 5 series by 8 - 15 repetitions
- ✦ breaks between series 30 - 60 s

Figure 7: *II. phase - resistance training period*

II. phase - arms resistance training

Figure 8: *II. phase - resistance training period*

II. phase Relaxation phase

- ✦ Calming the body, adjusting circulatory conditions and returning HR and BP to pre-training levels.
- ✦ Schultz's autogenic training,
- ✦ Jacobson's muscle relaxation
- ✦ Resting values of BP and HR,
- ✦ Duration 10 min

„cool-down" period

Figure 9: *„Cool-down" period*

Night-to-day ratio specified by seven-day/24-h ambulatory blood pressure monitoring in second phase of cardiovascular rehabilitation

The presented results analyzed seven-day/24-h ambulantory blood pressure monitoring and cardiovascular risk analyzed from night-to-day blood pressure ratio in patients with ischemic cardiac diseases Many studies confirmed the prognostic significance of night-to-day blood pressure ratio for prediction of a higher rate of cardiovascular complications.

One of large-scale studies based on International Database on Ambulatory blood pressure monitoring in relation to Cardiovascular Outcomes was published in 2007. 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.

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.

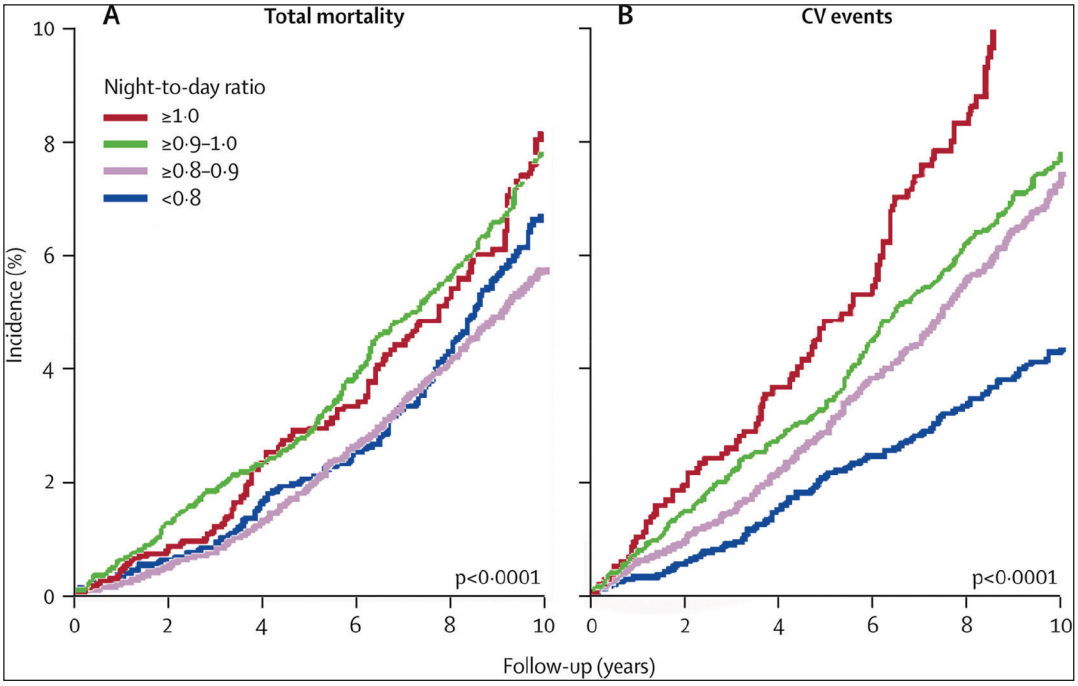

Figure 10: *International database on Ambulatory blood pressure monitoring in relation to Cardiovascular Outcomes was published in 2007 (J. Borgia et al., Lancet 370, 2007, p. 1219-1229)*

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. Our results in 2010 during seven day blood pressure monitoring shoved in repeated measurement of blood pressure changes from dippers to non-dippers from dippers to reverse dippers.

The evaluation of night-to-day blood pressure variability during 7 days of ambulatory blood pressure measurement was the aim of the present study in patients with coronary heart disease in the days with exercise and in the days without exercise.

Methods

Thirty one patients (all males), forty nine years to eighty four years old (63 ± 7.3 years), were recruited for seven-day blood pressure monitoring. TM – 2421 of the Japanese firm AD instruments 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.

Our patients were studied in the second phase of cardiovascular rehabilitation.

The patients underwent phase II of cardiovascular rehabilitation (controlled ambulatory rehabilitation program) lasting three months with the frequency of three times in a week in St. Anna Teaching Hospital.

Results

Variability of night-to-day ratio in the days with exercise and without exercise during 7-day blood pressure monitoring is seen in following slides.

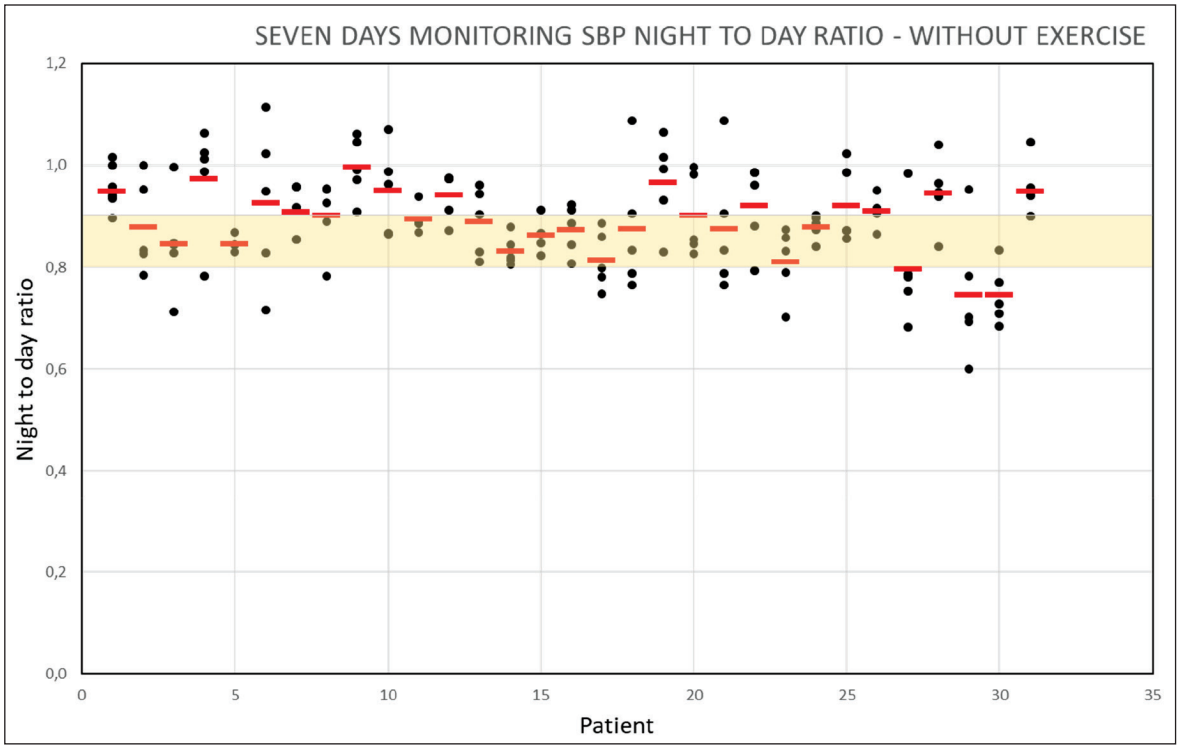

Figure11: *Seven-day ambulatory monitoring blood pressure monitoring in patients with ichemic heart disease: SBP night to day ratio in the days without exercise*

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.

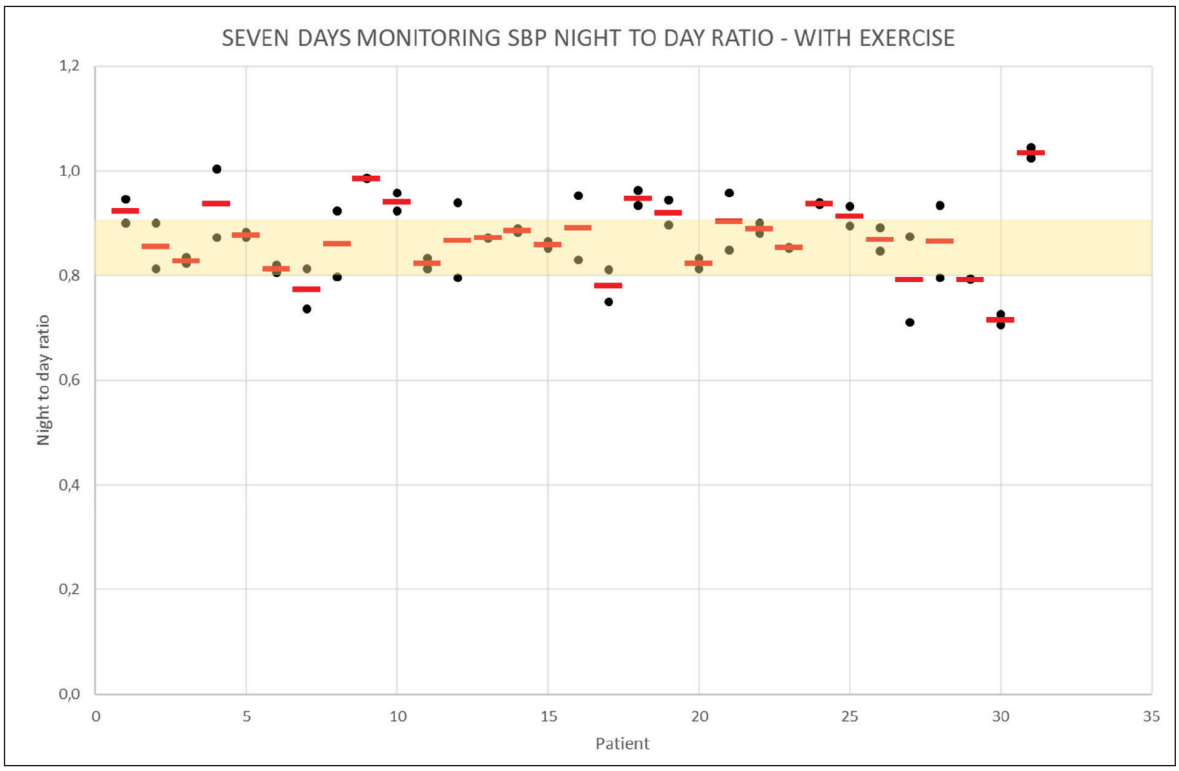

Figure12: *Seven-day ambulatory monitoring blood pressure monitoring in patients with ichemic heart disease: SBP night to day ratio in the days with exercise*

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.

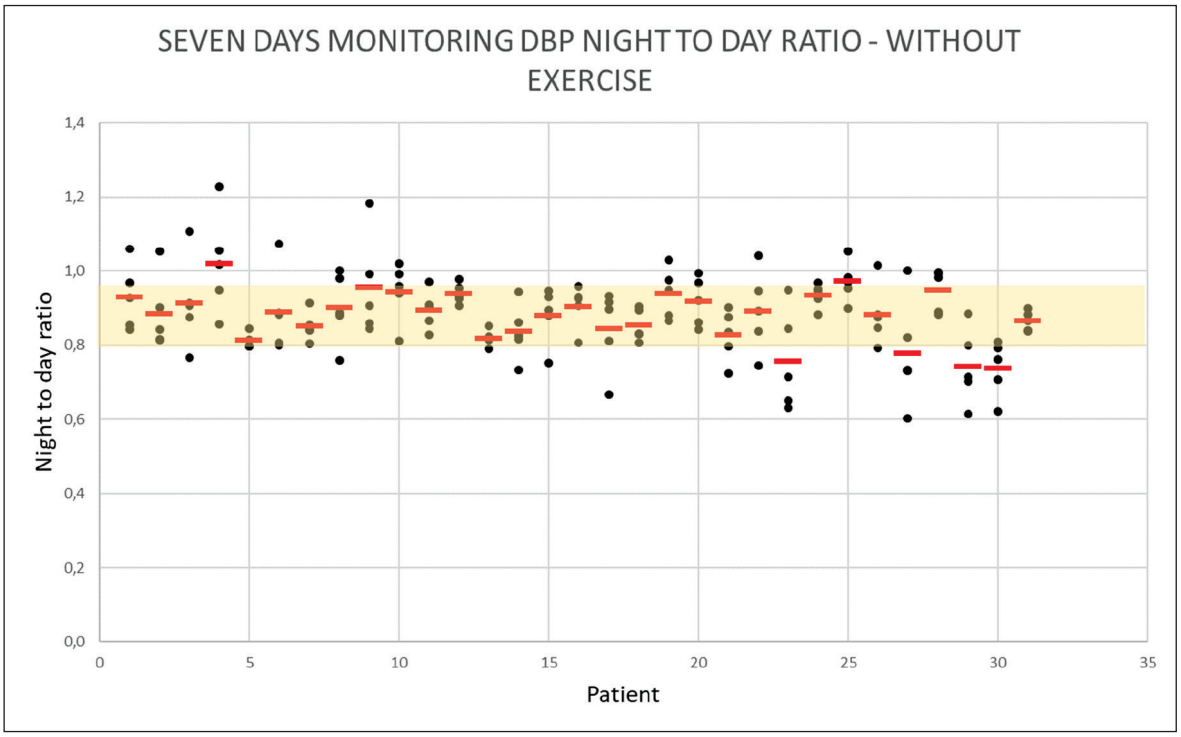

Figure13: *Seven-day ambulatory monitoring blood pressure monitoring in patients with ischemic heart disease: DBP night to day ratio in the days without exercise*

In the days without exercise, similarly no subject was 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.

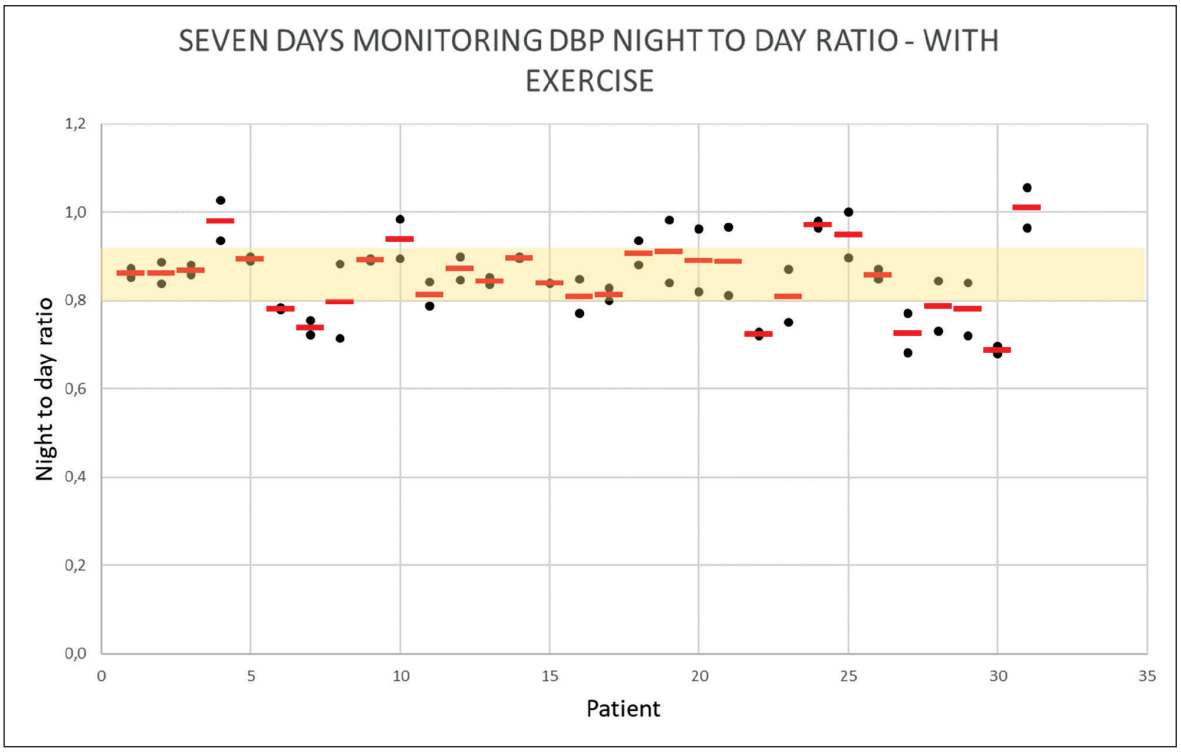

Figure14: *Seven-day ambulatory monitoring blood pressure monitoring in patients with ichemic heart disease: DBP night to day ratio in the days with exercise*

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.

Conclusion

Despite the low night-to-day ratio of blood pressure predicted increased risk for cardiovascular events in large studies, the determination during seven-day/24-h ambulatory blood pressure monitoring showed large variability in every patients in different consecutive days of monitorig.

The exercise program in cardiovascular rehabilitation does not influenced these night to day ration of blood pressure variability.

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Our Activity in Kenya

Takei Mitsuo, Iwane Miki

Medical Corporation Koshinkai in Japan,
(NGO) Kyoseinokai in Japan,
Grand Forest Japan Hospital in Kenya,
(NGO) Dream World Healthcare Programme in Kenya

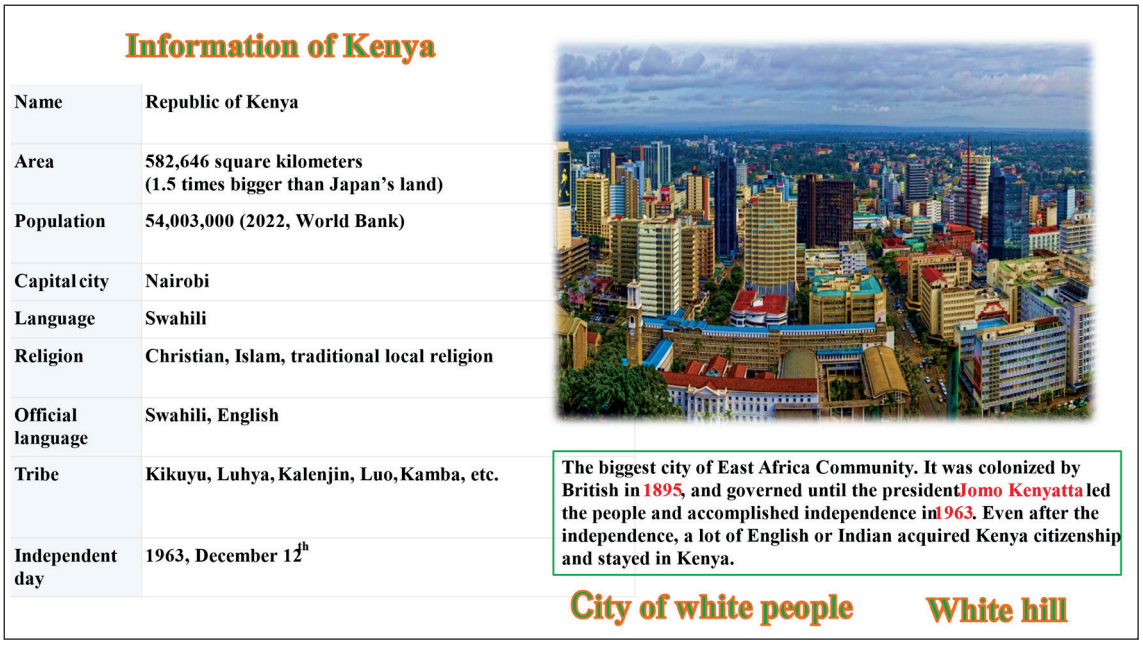
Introduction

How come we started the activity in Republic of Kenya?

A Kenyan friend of mine who used to live in Japan sent me a message of “HELP” and I decided to visit Kenya. That was a milestone of our activity in Kenya. Our activity in Republic of Kenya was started by “Human relationship”.

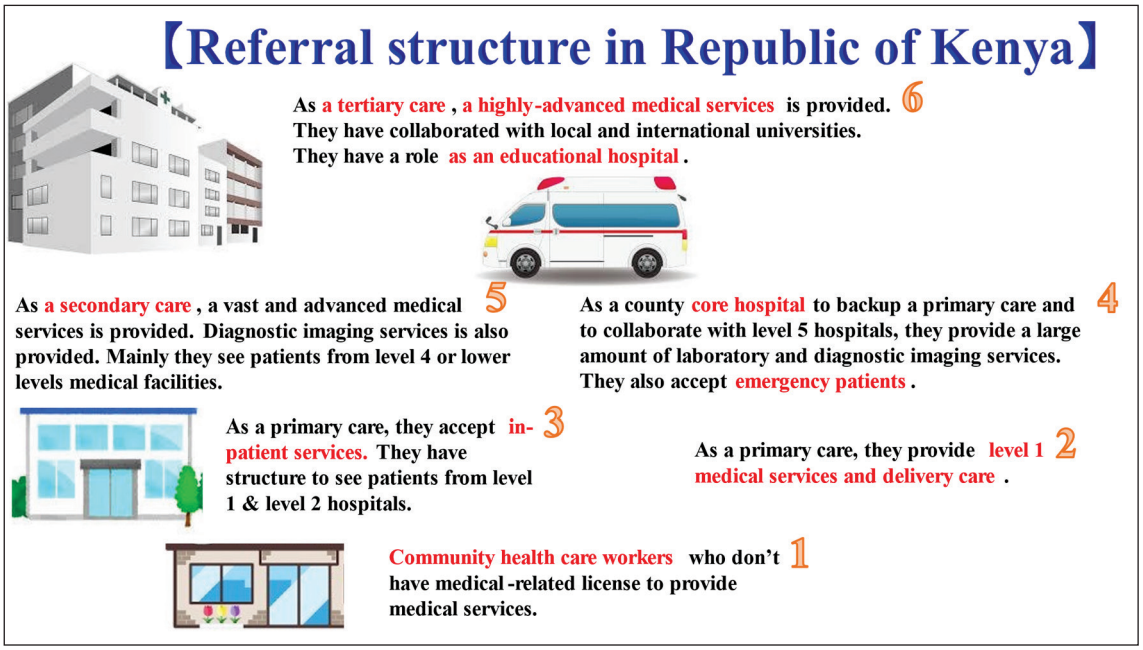
Information of Kenya

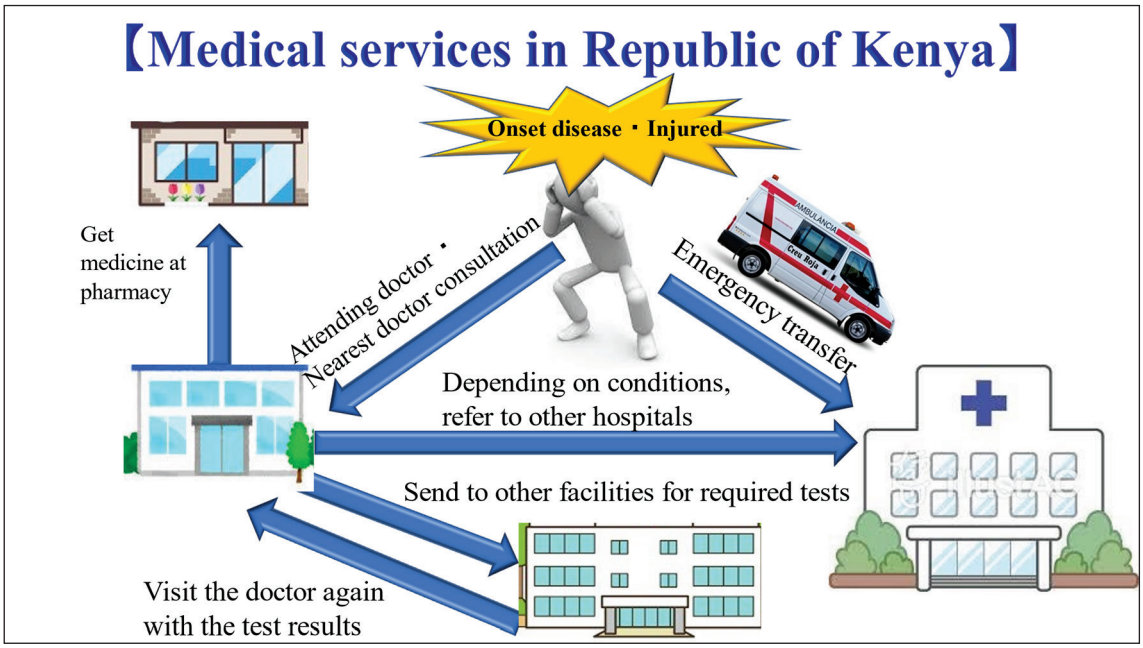
At first, I would like to introduce the situation of Republic of KENYA. Please look the 1st figure.



Referral structure in Republic of Kenya

This figure shows the medical service structure of KENYA. In Kenya there are 6 grade s of structure depended on the level of Hospital. Figure 3 shows the medical service system in Kenya. Please look the 2nd and 3rd figure.





Medical services in Republic of Kenya

There is no adequate universal health coverage (UHC) system in Kenya. In case of no insurance, a person has to pay 100% of medical service fee by himself.

There is no law or regulation to set a price of medical services. Each facility can decide a medical fee by themselves (asking price is accepted) freely.

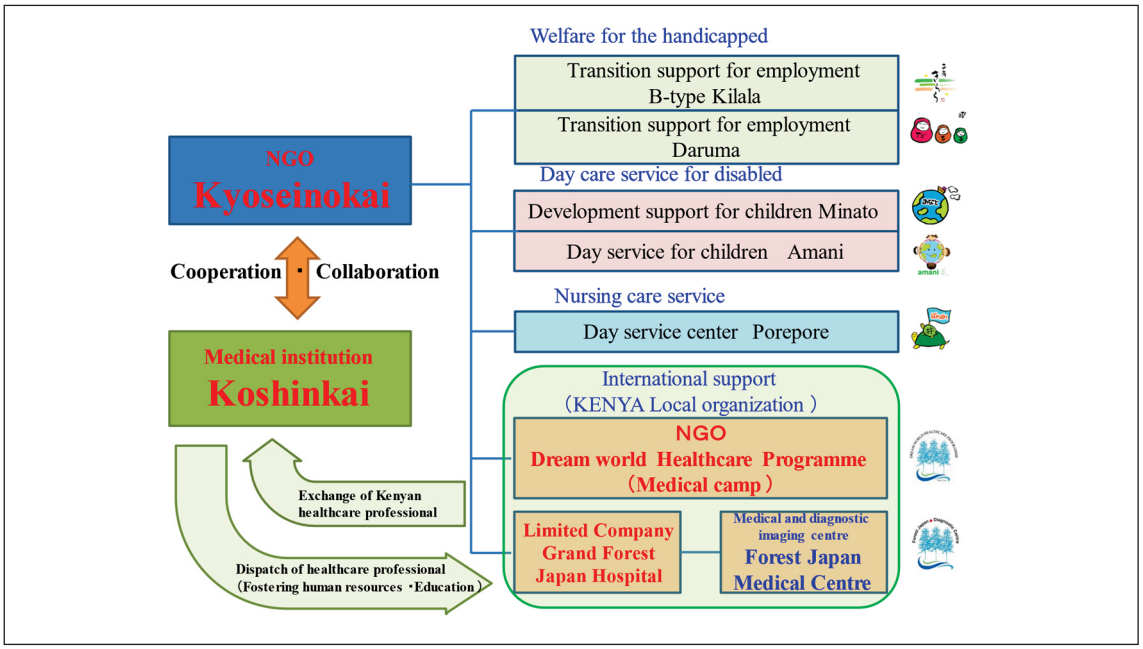
Our aim is to provide a high quality medical care and staff education thoughtful Japanese-style services.

Our fundamental motto

We preserve the dignity and precious lives of the Republic of Kenya and provide health care and welfare at the Japanese level that can contribute to sustaining and improving health, existing healthy life span and improving QOL.

We acquire the knowledge and skills necessary for the staff and make efforts to raise humanity on a daily basis and carry out their obligations with responsibility and awareness. We also collaborate with related facilities of Kenya and Japan, and will also contribute to society through activities such as friendship between Japan and Kenya that emphasizes public benefit, employment support for the Kenyan citizens.

Our Organization



Medical, Health and Welfare Improvement Project

From Oita, Hometown Japan to Medical Care and Welfare in the Republic of 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-intestine camera, colonic camera, blood, urine and stool testing analysis 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.

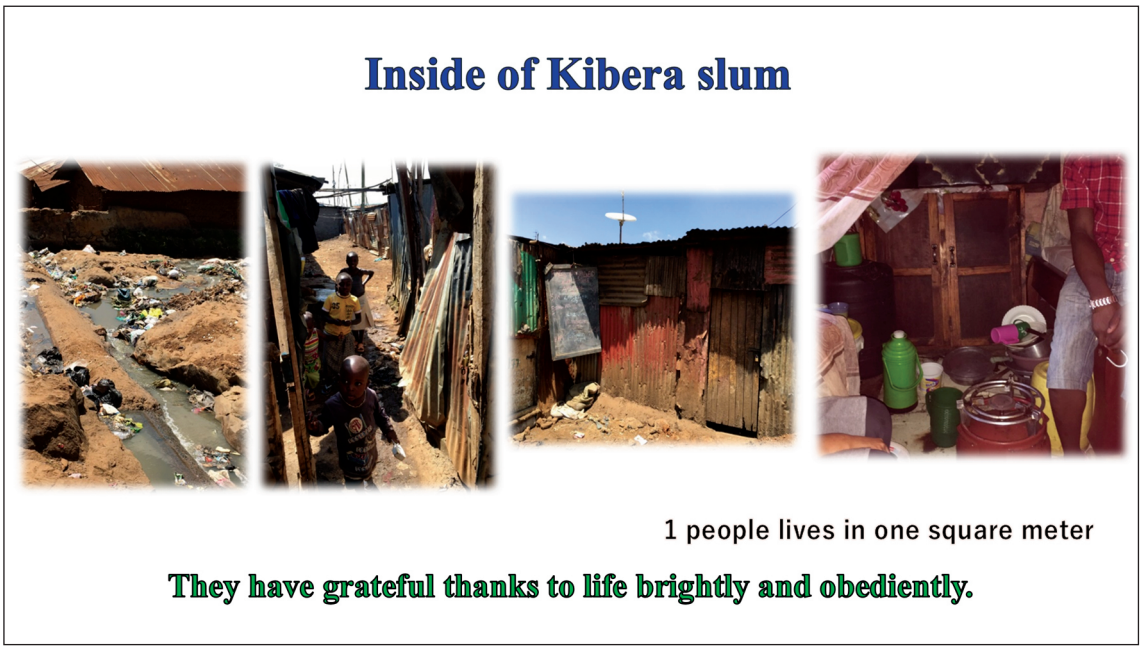
With economic growth in Kenya, the disease structure is changing and becoming more Westernized, especially in Nairobi City. As a result, lifestyle-related diseases are on the rise and the number of people with disabilities is increasing, as in Japan. In addition, there are few policies for children with disabilities. We are building a medical support system that takes these factors into account.

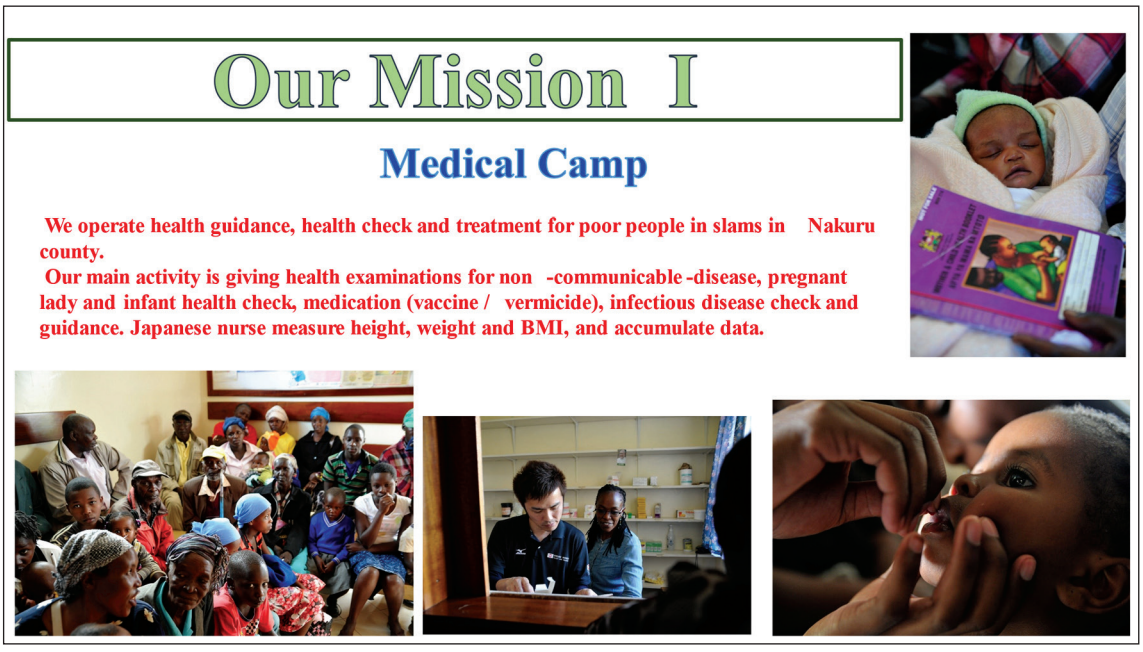
We are also focusing on human resource development. Good medical care, welfare, and healthcare require good human resources. Exchange between Japan and Kenya is mutually beneficial.

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.

Our Mission in KENYA

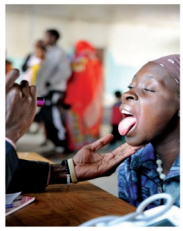
1. Medical Camp (Outreach to slum area)





Service content of medical camp

1. General treatment , medical examination
2. Gynecological check up
3. Pregnant HIV test and counselling
4. Family planning
5. Children health check, medical examination
   ① Vaccination
   ② Growth monitoring and Nutrient check
   ③ Administration of Vitamin A and vermicide
6. General examination（Blood, urine, infectious disease check :Malaria, etc. ）
7. HIV counselling（except 3）
8. Health education, sanitation education, health guidance, disease guidance



Medical Camp

Health check in school





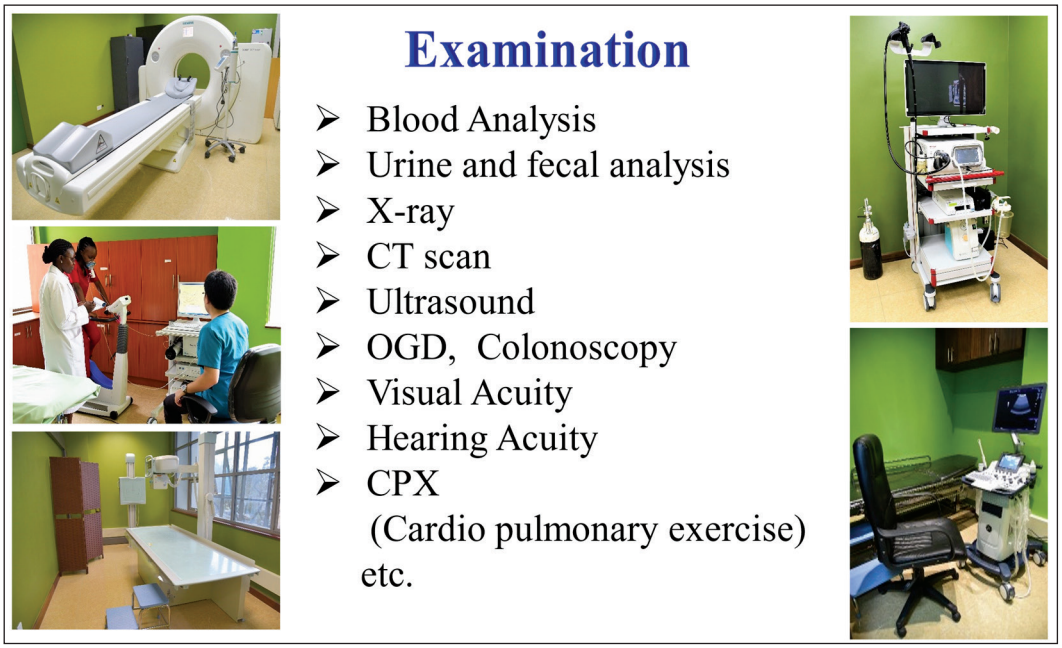
Summary of Medical camp data : from 1st ～160th

① Total number of patients: **72,222**
② General treatment : **26,555**（Some are overlapped)
③ Pregnancy women
Diagnosis : **620**, HIV related : **803**
Family planning: **1,435**, Vaccination, **353**
④ Children
Vaccination: **1,828**, nutrient check : **5,249**
Administration of Vitamin A and vermicide : **27,213**
⑤ Lab examination : **2,308**
⑥ HIV counselling : **2,531**


2. Medical Service to Kenyan

① Operates a Medical center

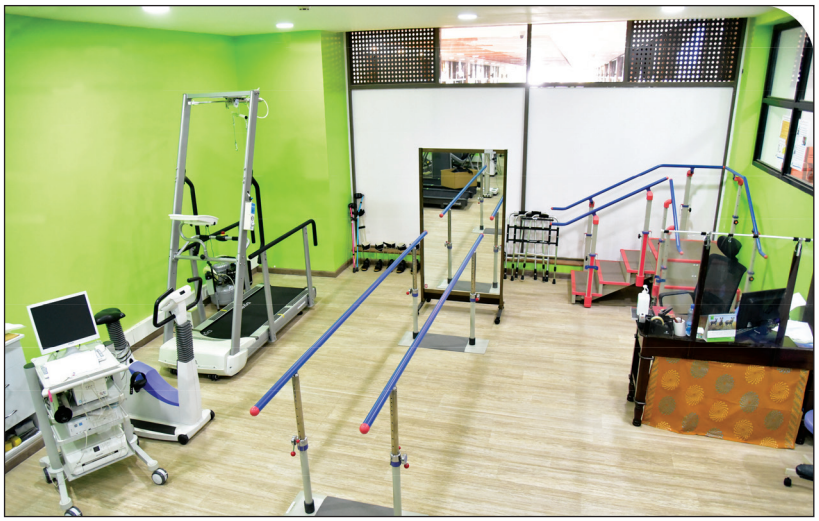
In 2013, we opened the Medical Centre in Nairobi.



A total of 26,199 people has been treated at Forest Japan Medical Center. We also conduct 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.

② Operate a Rehabilitation center



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.

③ Cooperation with Partner Countries

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.

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.

3. Education

Our Mission III

JICA and AOTS project：Training of human resources

Medical staff (Japanese and Kenyan) work together to share the skills and knowledge. It aims to sustain and improve healthcare for both citizens.

Moreover we promote a friendship each other and understand each culture and tradition which is a good opportunity for us.

EDUCATION FIRST !!

Education

【Target】 Kenyatta National Hospital, PT, OT, Students of University of Nairobi (PT、OT、NS、Orthotic specialist)
【Duration】 6th of August, 2019～28th of January, 2020
【Contents】
Lecture :①Fundamental movements ②Gait posture ③Rehabilitation evaluation（ROM,MMT,BRS）④FIM
Practice :①Fundamental movements ②Gait posture ③Rehabilitation evaluation（ROM,MMT,BRS）④FIM
Theme lecture :①Spinal cord injury ②About dysphasia ③About higher brain dysfunction
【Number of lectures & practices】Lecture:16 times, Practice:16 times, Theme lecture:13 times, Total **45 times**
【Number of attendants】**1,346 people ※ We collected questionnaire from the 1,241 attendants（92.2％）**

Africa Health and Wellbeing initiative by Secretary Cabinet of Japanese Government.

AfHWIN
Africa Health and Wellbeing Initiative

I am an official medical adviser for Secretary Cabinet of Japanese Government.

We will contribute to the formation of a multifaceted development system that combines public sector support with autonomous private sector industrial activities, based on regional characteristics, such as basic infrastructure, improved understanding of public health, and nutrition education.

We will work to enhance a wide range of health and medical services in the shape of “Mt. Fuji.”

Summary

The Limited Company „Grand Forest Japan Hospital“ was registered with the Government of the Republic of Kenya in 2013. 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. A total of 26.199 people has been treated at Forest Japan Medical Center. We also conduct health checks, which are rare in Kenya.

NONINVASIVE METHODS IN CARDIOLOGY 2024

Edited by: **Cornélissen G., Pohanka M., Siegelová J., Dobšák P.**

Published by Masaryk University Press,
Žerotínovo nám. 617/9, 601 77 Brno, CZ

First electronic edition, 2024

ISBN 978-80-280-0669-3

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