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NONINVASIVE METHODS IN CARDIOLOGY 2018

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Brno 2018

Under the auspices of

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ISBN 978-80-210-9109-2

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Biological Rhythms Described by Professor Franz Halberg and Johann Gregor Mendel Scientific Studies

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Prof. Dr. Franz Halberg (1919-2013) is a founder of modern chronobiology. Unlike other famous scientists devoting their activities mostly to presentation of honorary lectures at international scientific conferences Professor Halberg continued in scientific work until 2013. In the last 5 years we continue the chronobiological studies in Masaryk University together with Professor Dr. Germaine Cornélissen, Director of Halberg Chronobiology Center University of Minnesota, USA and we follow Professor Franz Halberg scientific legacy.

In 1990 Prof. Halberg and Cornelissen visited Masaryk University in Brno for the first time and presented chronobiological results in cardiovascular parameters in man at the Brno Symposium. Immediately, an intensive cooperation started between the Brno team, consisting of Prof. Bohumil Fiser, emeritus head of the Physiology Department, Czech Minister of Health and executive board member of WHO; Dr. Jiri Dusek, Prof. Jamila Siegelova, and Prof. Franz Halberg and Prof. Germaine Cornelissen from University of Minnesota, USA.

In Brno at that time we carried out the beat-to-beat noninvasive measurement of blood pressure, developed by Prof. Jan Penaz and young scientist Prof. Fiser, as well as measurements of baroreflex sensitivity and heart rate variability and Prof. Siegelova 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 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 in the University of Minnesota, USA.

Then for 30 years until now the chronobiological 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 1990 and 2008 the Brno team consisting of Prof. Fiser, Dr. Dusek and Prof. Jamila Siegelova 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 were made on newborn children's blood pressure, on blood pressure changes after the timed administration of low dose aspirin, on baroreflex sensitivity, and on groups of normotensive and hypertensive patients given antihypertensive therapy and without therapy. The cooperation resulted in many common publications.

From 1990 every year, sometimes twice a year, common meetings were organized in Masaryk University Brno, such as MEFA Congress or chronobiological congress presenting a lot of latest findings and scientific lectures, with the participation of Prof. Cornelissen and Prof. Halberg from Minnesota; Prof. Thomas Kenner, former president of the University of Graz, Austria; and Prof. J.P. Martineaud, Hopital Lariboisiere, Medical Faculty, Paris, France. Prof. Cornelissen prepared a lot of publications for congresses and symposia in Brno.

Prof. Franz Halberg appreciated scientific approaches of Johann Gregor Mendel (20.7.1822-6.1.1884). Johann Gregor Mendel was a natural scientist, founder of genetics and a discoverer of the basic laws of heredity. He worked as a monk and later abbot of the Augustinian monastery in Brno.

Based on his experiments, he formulated three rules that later became known as Mendel's inheritance laws. Later, his experimental data have been reviewed many times. Mendel was excellent mathematician and used the basic of statistics.

Prof. Franz Halberg also took part in symposium 1995 in Brno Mendel Forum, where Mendel work was presented.

In many lectures in Brno he cited Mendel´s findings and ideas and he admired the data that Mendel summarized from meteorology in the Central Europe.

Franz Halberg write a lot of articles about Mendel. Let me cited:

"Mendel, the meteorologist at heart, concomitantly mapped physical conditions and diseases, first with the head of a hospital in Brno, and continued recording them after the latter's death, implementing meteorology in relation to the epidemiology of disease. Mendel the meteorologist practicing chronomics was the topic of a lecture delivered at a symposium held at the Mendelianum in Brno, Czech Republic, here summarized with an update, and was also the topic of a keynote opening a symposium given in Nagoya, Japan, published in 1991.

The development of chronobiology under the guidance of Professor Franz Halberg, the science (logos) of life (bios) in time (chronos), and of chronomics, against the background of Mendel's contributions goes far beyond genetics. In keeping with Mendel the meteorologist, Professor Franz Halberg documented for chronobiological rhythms that light and food are not the only external switches. The "master switch", light, can be overridden more often and more critically than we visualize by feeding or by a magnetic storm.

Very important hypothalamic "oscillators" are not the only internal mechanism of biological rhythms. Time structures, chronomes, reside in every biological unit and in man.

Chronomes in us have a strong genetic component which, in turn, entered the genome in response to environmental chronomes, explored meteorologically by Mendel. The more remote environmental origin of rhythms and their less remote genetic aspect both qualify biological chronomes as the legacy of Mendel the meteorologist as well as the geneticist.

The need for coordinated physical and biological monitoring, the topic of a project on The BIOsphere and the COSmos, briefly BIOCOS, the project governed by Professor Germaine Cornelissen from Halberg Chronobilogy Ceneter, to complement genomics, can also be viewed as the legacy of Mendel the meteorologist/cartographer. Some of Mendel's meteorological data were meta-chrono-analyzed. Mendel himself published more often on meteorology than on what became genetics.

Prof. Franz Halberg, the father of chronobiology and excellent teacher, declares Johann Gregor Mendel as a chronobiologist.

In 1987 Prof. Cornelissen 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.

On November 22, 1994 BIOCOS was described for the first time. The BIOsphere and the COSmos, BIOCOS, as the task of building a novel transdisciplinary spectrum was pursued, and further periods of decades, centuries, and thousands and millions of years were documented. Much of the evidence was provided very successfully by Germaine Cornelissen, PhD, Professor of Integrative Biology and Physiology at the University of Minnesota.

Prof. Germaine Cornelissen has been the director of Halberg Chronobiology Center of University of Minnesota and of project BIOCOS until today.

We from Masaryk University continue together with Prof. Germaine Cornelissen, Halberg Chronobiology Center to participate on chronobiological studies in the footsteps of Professor Franz Halberg.

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Figure 1: *Mendel Forum 1995, in Moravian Museum in Ditrichstein Palast in Brno: Václav Adolf Kovanič from Hovorany by Čejč, author Mendel Medals of the Moravian Museum of the Earth and the Mendel Plaque of the Academy of Sciences, Dr. Jiřina Relichová MU, Dr. Anna Matalová, Director of Mendelianum, part of Moravian Museum, P. Tomáš Josef Martinec, OSA, abbot of the Augustinian monastery of Brno, Singo Nakazawa from Tokyo, from the Japan Mendel Society, which sponsored the conference, behind is Professor RNDr. Eduard Schmidt, CSc., Rector of Masaryk University, Petr Šuler, Director of the Ministry of Health, Dr. Pidra from MU, Brigitte Hoppe Heidelberg, Germany, Jan Janko Society for the History of Science and Technology from Prague, Dr. Z. Neubauer from University Giessen, Germany. Among them, Roger J. Wood from U. Manchester, Prof. Emil Paleček, Academy of Sciences, Dr. from Romania, Dr. Ludmila Marvanová, History Dept. in Brno, Ing. Pavel Osmer from VUT Brno, in second row from the right Prof. Siegelova, Dr. Al-Kubati, Prof. Fiser, in the niche of the door is Prof. Franz Halberg, USA.*

Figure 2: *Prof. Jarmila Siegelova, Prof. Franz Halberg, USA and Dinko Mintchev from the Bulgarian Academy of Sciences during presentation, 1995*

Figure 3: *Prof. Jarmila Siegelova, Prof. Emil Palecek, Prof. Eduard Schmidt, Prof. Franz Halberg, USA*

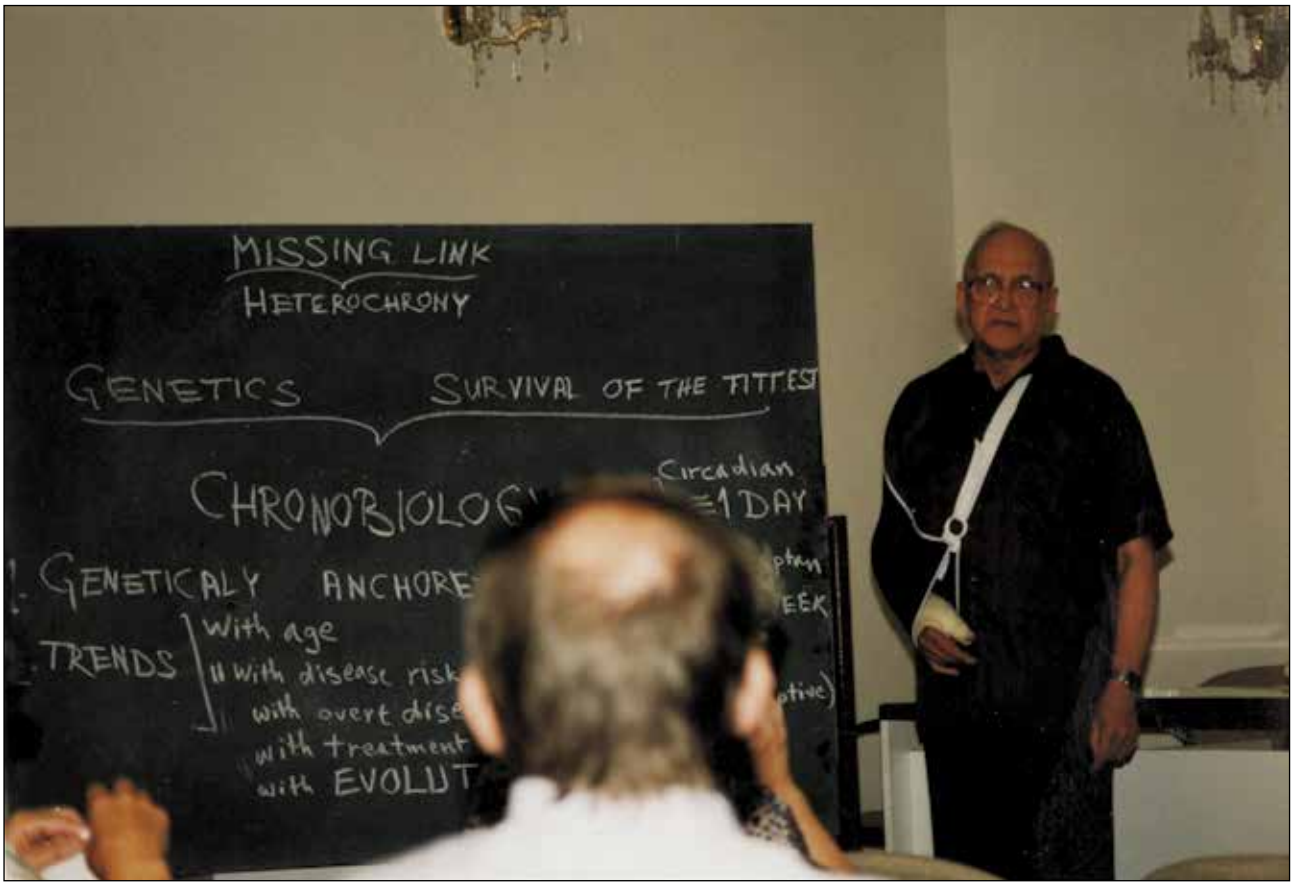

Figure 4: *Prof. Franz Halberg, USA during the lecture in Mendel Forum 1995*

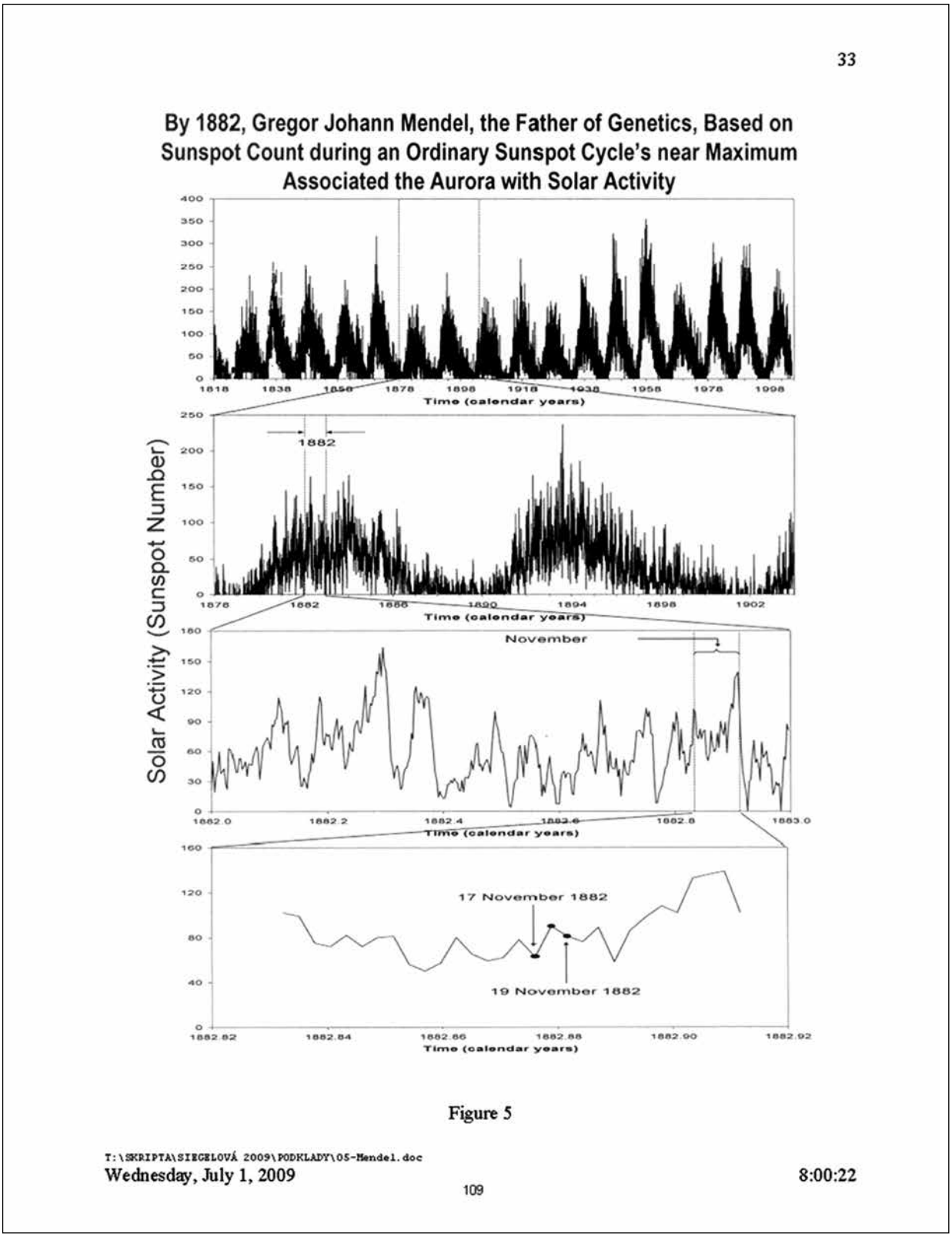

Figure 5: *Professor Franz Halberg publication: The original results of J.G. Mendel were analyzed by Halberg Chronobiology Center USA. On November 17, 1882, Mendel made the connection between sunspots and the aurora during a solar maximum that was not unusual whether it is viewed in the context of centuries (top), that of years (second row), of months (third row) or of days (bottom row). © Halberg.*

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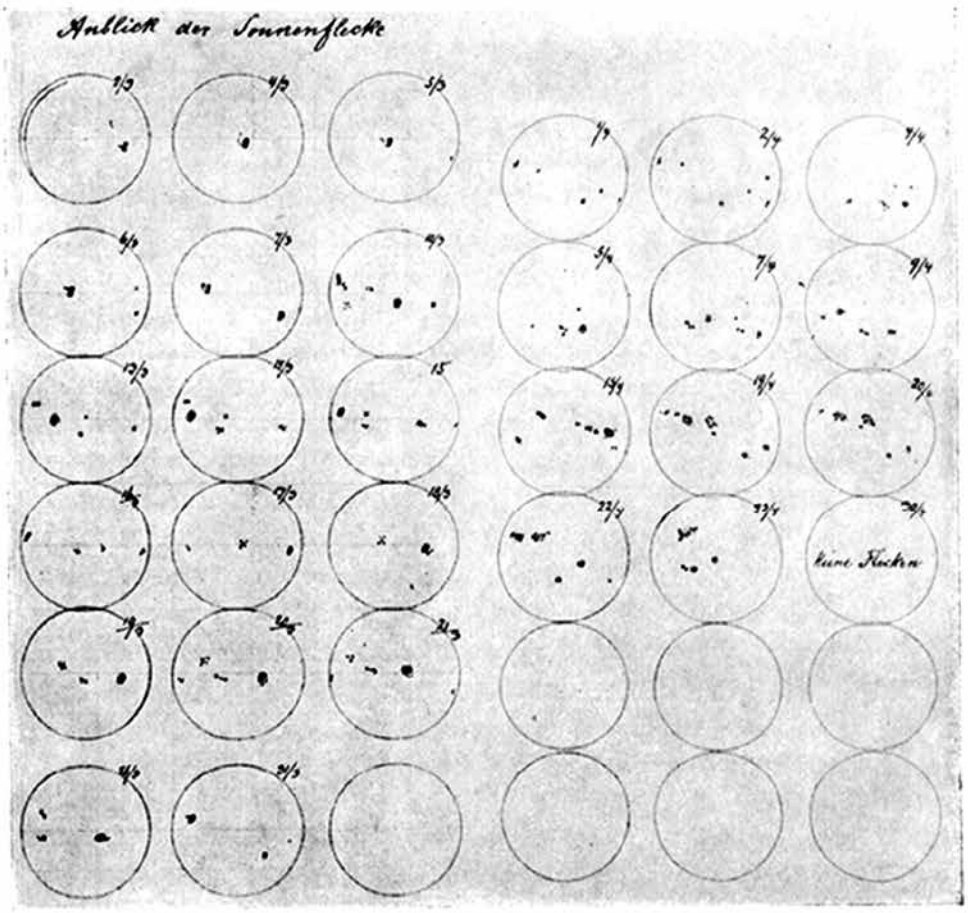
Mendel's notebook records date, number and location of sunspots, if any*



*View of sunspots *(Anblick der Sonnenflecke)* or of their lack (empty circles; *Keine Flecken)* in two pages with Mendel's sketches (from Iltis H. Life of Mendel. New York: Hafner, 1966 [originally published in English in 1932]. 336 p.)

Figure 6

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Wednesday, July 1, 2009 8:00:22

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Figure 6: *Prof. Franz Halberg publication: Mendel's drawings of sunspots show almost-daily changes in their appearance; sometimes the sun's disk is free of spots. These observations led him to postulate a connection between sunspots and the aurora.*

Figure 7: *Participants of the Mendel Forum 1995 at the statue of J.G. Mendel in Mendel Monastery, Brno*

Comments on the 2018 ESC/ESH and 2017 ACC/AHA Consensus Blood Pressure Guidelines Regarding the Use of Ambulatory Blood Pressure Monitoring (ABPM)

Germaine Cornelissen[1], Larry A Beaty[1], Jarmila Siegelova[2], Yoshihiko Watanabe[3], Kuniaki Otsuka[4], and Members of the Phoenix Study Group For the Investigators of the Project on the BIOsphere and the COSmos (BIOCOS)

[1]Halberg Chronobiology Center, University of Minnesota, Minneapolis, MN, USA; [2]Masaryk University, Brno, Czech Republic; [3]Women's Medical University, Tokyo, Japan; [4]Executive Medical Center, Totsuka Royal Clinic, Tokyo Women's Medical University, Tokyo, Japan

Dedicated to the memory of Earl Bakken and Franz Halberg.

Abstract

The new guidelines by the American College of Cardiology (ACC) and the American Heart Association (AHA) and those by the European Society of Cardiology (ESC) and the European Society of Hypertension (ESH) have summarized and evaluated available evidence with the aim to provide recommendations regarding the best management strategies for an individual patient with a given condition. Selected experts in the field provided a critical evaluation of diagnostic and therapeutic procedures, including an assessment of the risk/benefit ratio. Herein, we focus on recommendations specifically made in relation to the use of ambulatory blood pressure monitoring (ABPM). These recommendations are critically reviewed from a chronobiologic perspective. Evidence is provided to support the merit of a broader use of ABPM.

Introduction

In terms of diagnosis, the ESC/ESH guidelines from 2013 stated that "Office BP is recommended for screening and diagnosis of hypertension" [1]. In 2018, their recommendation is that "It is recommended to base the diagnosis of hypertension on:

- Repeated office BP measurements; or
- Out-of-office BP measurement with ABPM and/or HBPM if logistically and economically feasible" [1].

The new concept regarding blood pressure (BP) measurement consists of a "wider use of out-of-office BP measurement with ABPM and/or home BP monitoring (HBPM), especially HBPM, as an option to confirm the diagnosis of hypertension, detect white-coat and masked hypertension and monitor BP control" [1].

Noteworthy is the emphasis placed on HBPM, and on the detection of white-coat hypertension and masked hypertension, two conditions long known to underlie the limitation of clinic BP measurements. Herein, we provide evidence for the merit of extending the use of ABPM beyond these conditions. We also discuss the relative merits and limitations of HBPM as compared to ABPM.

Shift from Single to Multiple BP Measurements

The ESC/ESH guidelines recognize the usefulness of multiple unattended BP measurements: "Automated multiple BP readings in the doctor's office improve the reproducibility of BP measurement, and if the patient is seated alone and unobserved, the 'white-coat effect' can be substantially reduced or eliminated" [1]. It is noted that "the BP values are lower than those obtained by conventional office BP measurement and are similar to, or even less than, those provided by daytime ABPM or HBPM" [1].

By their nature, out-of-office measurements, obtained by means of ABPM and/or HBPM, generate multiple BP measurements. It is thus not surprising that the guidelines recognize their usefulness in that respect: "Out-of-office BP measurement … provide a larger number of BP measurements than conventional office BP in conditions that are more representative of daily life" [1].

One issue, however, is that out-of-office measurements are defined as "the use of either HBPM or ABPM, the latter usually over 24 hours". Restricting ABPM to 24 hours fails to consider:

- The large day-to-day variability in BP (Figure 1) [2]; and
- The novelty effect (Figure 2) [3].

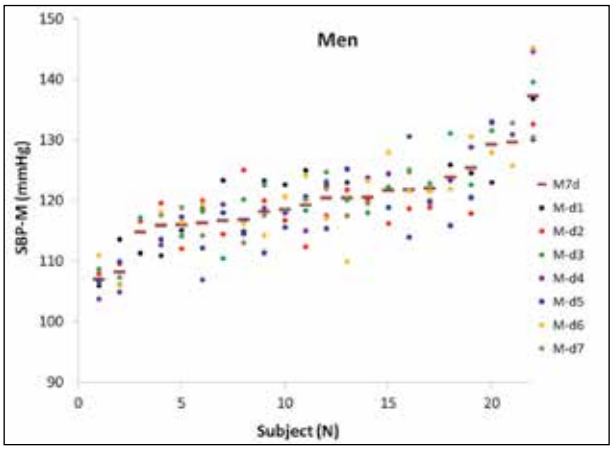

Figure 1: *Large day-to-day variability (of at least 7 mmHg from one day to another in the 24-hour MESOR (M) of systolic BP (SBP).*
© Halberg Chronobiology Center

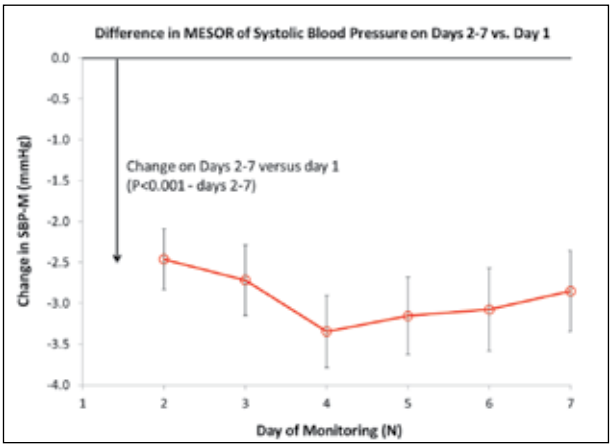

Figure 2: *Novelty effect: as compared to the first day of monitoring (horizontal line at 0.0), the 24-hour MESOR (M) of systolic BP (SBP) is on average more than 2.5 mmHg lower on the 6 subsequent days of monitoring.*
© Halberg Chronobiology Center

Home Blood Pressure Monitoring

The ESC/ESH guidelines provide the following information regarding HBPM: "Home BP is the average of all BP readings performed with a semiautomatic, validated BP monitor, for at least 3 days and preferably for 6–7 consecutive days before each clinic visit, with readings in the morning and the evening, taken in a quiet room after 5 min of rest, with the patient seated with their back and arm supported. Two measurements should be taken at each measurement session, performed 1–2 min apart" [1].

Note that more emphasis is placed on the standardization of measurements than on the length of monitoring, which is limited to just a few days prior to a clinic visit. Many patients in need of anti-hypertensive medication, however, routinely take morning and/or evening measurements every day. It is this longitudinal aspect of HBPM that is most attractive since it allows the visualization of any trend prompting to seek medical advice.

The ESC/ESH guidelines also note that "Recent meta-analyses of the few available prospective studies have further indicated that HBPM better predicts cardiovascular morbidity and mortality than office BP. There is also evidence that patient self-monitoring may have a beneficial effect on medication adherence and BP control" [1].

While HBPM certainly fills the above-noted merits, it should be considered that HBPM restricted to morning and evening measurements is not capable of providing a reliable assessment of the circadian variation in BP. As shown in Figure 3, BP measurements during the rest/sleep span are needed to estimate the circadian variation in BP [4].

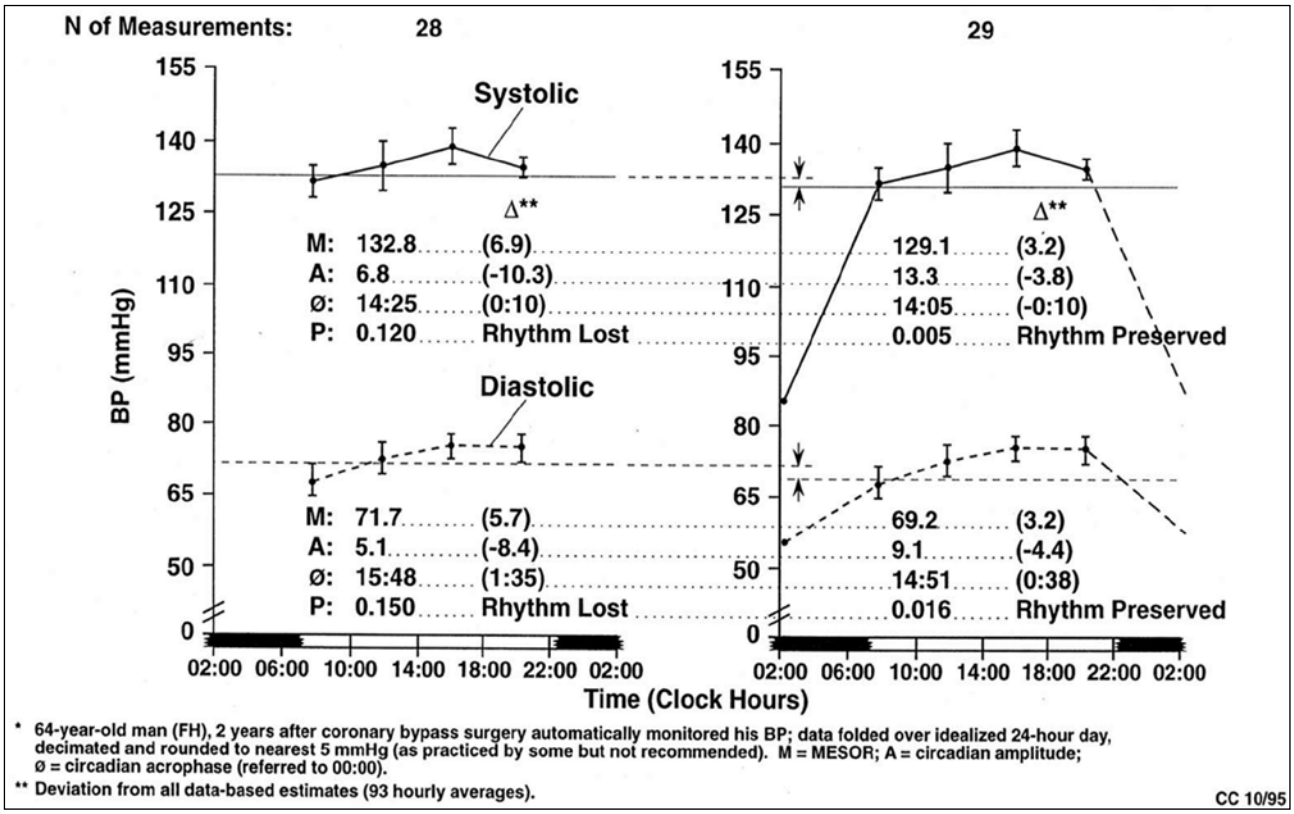

Figure 3: *Single nightly measurement added to 9 days of 4-hourly sampling during waking greatly improves circadian parameter estimation of BP. © Halberg Chronobiology Center*

Ambulatory Blood Pressure Monitoring

The ESC/ESH guidelines regard the use of ABPM as follows: "ABPM provides the average of BP readings over a defined period, usually 24 hours. The device is typically programmed to record BP at 15–30 min intervals, and average BP values are usually provided for daytime, nighttime, and 24 hours. ABPM values are, on average, lower than office BP values" [1]. They note that "ABPM is a better predictor of hypertension-mediated organ damage than office BP. 24-hour ABPM mean has been consistently shown to have a closer relationship with morbid or fatal events, and is a more sensitive risk predictor than office BP of cardiovascular outcomes such as coronary morbid or fatal events and stroke" [1].

Considering the large day-to-day variability in BP (Figure1) and the novelty effect (Figure 2), several consensus meetings of the BIOCOS (BIOsphere and the COSmos) Investigators have recommended that ABPM be carried out for at least 7 days at the outset, and that the data be interpreted chronobiologically [5]. This view differs from the guidelines in two major ways:

- First, a 24-hour profile is not enough; and
- Second, the circadian pattern of BP should be determined and evaluated in the light of time-specified reference values, and not limited to daytime, nighttime, and 24-hour mean values.

Circadian Variation in Blood Pressure

The circadian variation in BP is noted in the guidelines, notably the decrease during rest/sleep: "BP normally decreases during sleep. Although the degree of nighttime BP dipping has a normal

distribution in a population setting, an arbitrary cut-off has been proposed to define patients as 'dippers' if their nocturnal BP falls by more than 10% of the daytime average BP value; however, the 'dipping' status is often highly variable from day to day and thus is poorly reproducible" [1].

Note that experts responsible for the guidelines acknowledge both the arbitrary threshold of 10% used for a classification in terms of "dipping" and the poor reproducibility of the day-night ratio. Both issues have long been raised by us [6].

The guidelines list a number of conditions accounting for an insufficient nightly decrease in BP: "Recognized reasons for an absence of nocturnal BP dipping are sleep disturbance, obstructive sleep apnea, obesity, high salt intake in salt-sensitive subjects, orthostatic hypotension, autonomic dysfunction, chronic kidney disease, diabetic neuropathy, and old age" [1]. One argument for considering nocturnal BP cited by the guidelines is that "Studies that accounted for daytime and nighttime BP in the same statistical model found that nighttime BP is a stronger predictor of outcomes than daytime BP" [1].

It should be noted, however, that nighttime BP is best determined during undisturbed sleep. When assessed by means of ABPM, nightly values gain from being evaluated in the light of the entire circadian profile, which can then be interpreted chronobiologically. Doing so recognizes that both CHAT (Circadian Hyper-Amplitude-Tension, a 24-hour amplitude exceeding a threshold value) and ecphasia (acrophase occurring outside the anticipated interval, often related to a reversal of the circadian BP rhythm) are associated with a large increase in cardiovascular disease risk [7].

Should the Circadian Variation Be Described by the Day-Night Ratio?

The ESC/ESH guidelines state that a dampened circadian variation, assessed by the day-night ratio, is a predictor of risk, pointing to the fact that risk is primarily increased when BP is higher by night than by day: "The night-to-day ratio is also a significant predictor of outcome, and patients with a reduced nighttime dip in BP (i.e. <10% of the daytime average BP or a night-to-day ratio >0.9) have an increased cardiovascular risk. Moreover, in those in whom there is no nighttime dip in BP or a higher nighttime than daytime average BP, there is a substantial increase in risk" [1]. They also refer to "extreme dipping", but call the relation to risk as being paradoxical: "Paradoxically, there is also some evidence of increased risk in patients who have extreme dipping of their nighttime BP" [1]. Note that from a chronobiologic perspective, these findings are not paradoxical: they reflect abnormalities in circadian phase (ecphasia) and amplitude (CHAT).

In several outcome studies, reliance on the circadian amplitude and acrophase, determined by fitting a model (consisting of cosine curves with periods of 24 and 12 hours), has consistently been found to be superior to the use of the day-night ratio, as illustrated in Figure 4. In part, the difference can be accounted for by different factors:

- The estimation of amplitude and acrophase considers the entire BP profile instead of specific sub-spans. The circadian waveform of BP changes as a function of age. Particularly in the elderly, a post-prandial dip in early afternoon becomes accentuated, Figure 5. This decrease in BP in the middle of the day affects the computation of the day-night ratio more than it does for the estimation of the amplitude and acrophase.
- The definition of CHAT and ecphasia relies on reference values derived from ABPM records of clinically healthy peers that are qualified by gender and age, and eventually also by ethnicity. Accounting for gender differences and changes as a function of age contrasts with the arbitrary use of 10% for the day-night ratio applied across the board. Importantly, the chronobiologic reference

standards account for the nonlinear relation of cardiovascular disease risk as a function of the circadian amplitude, Figure 6. Doing so also reduces the extent of day-to-day variability in a classification in terms of "dipping" based on the day-night ratio illustrated in Figure 7 for the case of a 12-year ABPM record from a man, 74 years of age at start, treated for high BP [8].

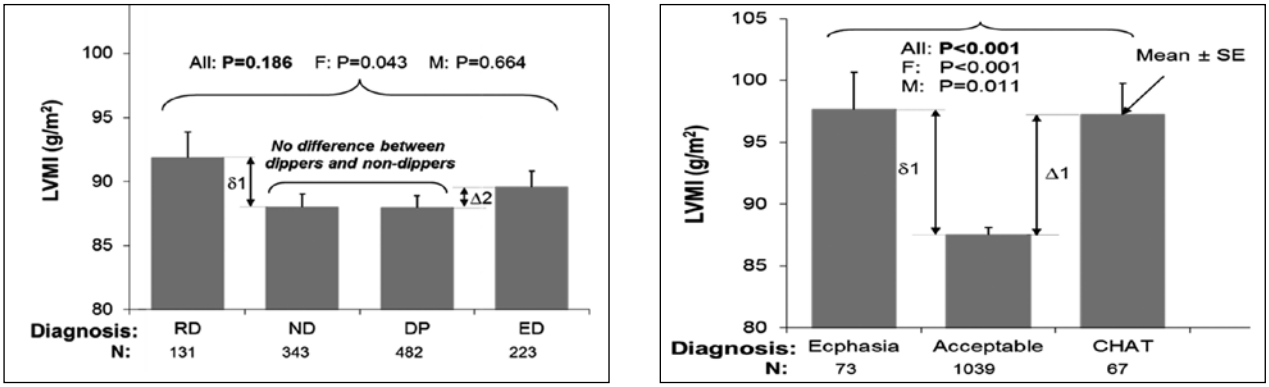

Figure 4: *Using left ventricular mass index as a surrogate outcome measure, a classification in terms of the day-night ratio only finds a small increase in cardiovascular disease risk associated with "reverse dipping" but not with "non-dipping" (left); by contrast, both ecphasia and CHAT are associated with much larger increases in cardiovascular disease risk (right). © Halberg Chronobiology Center*

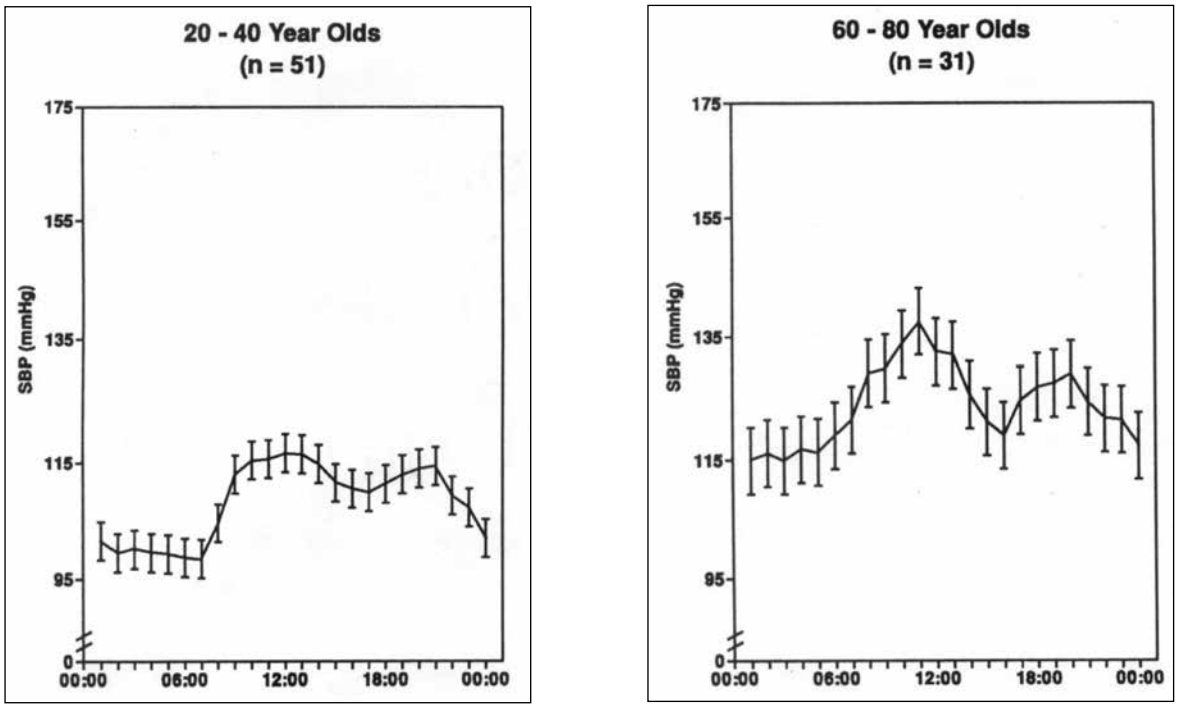

Figure 5: *Changes as a function of age in the circadian waveform of SBP in Caucasian women. Note the accentuated post-prandial dip in early afternoon in women 60-80 years of age (right) as compared to women 20-40 years of age (left). © Halberg Chronobiology Center*

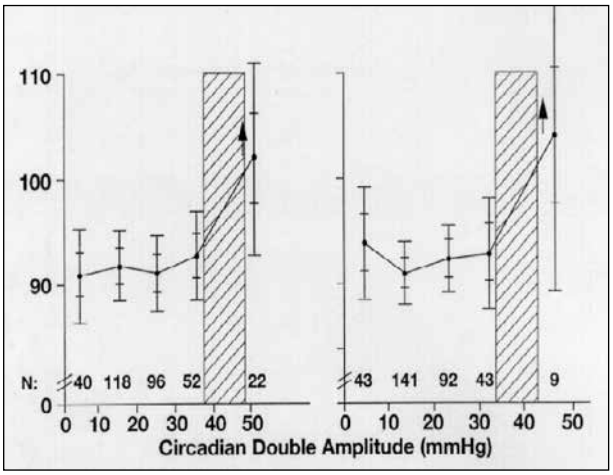

Figure 6: *Nonlinear relationship of cardiovascular disease risk as a function of the 24-hour amplitude of BP. Risk increases only after a threshold value is exceeded (CHAT). © Halberg Chronobiology Center*

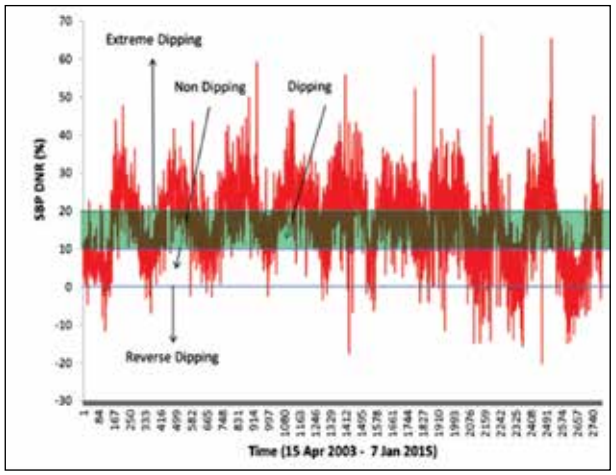

Figure 7: *Very poor reproducibility of the day-night ratio, determined in a 12-year record, account for in part by the circannual modulation of the circadian amplitude of BP. © Halberg Chronobiology Center*

Advantages and Disadvantages of ABPM and HBPM: ESC/ESH Perspective

The ESC/ESH guidelines define hypertension differently depending on whether BP was measured in the office, by ABPM or by HBPM. Thresholds for systolic and diastolic BP of 140 and/or 90 mmHg are recommended if BP is measured in the office. For HBPM, thresholds of 135 and/or 85 mmHg are recommended. In the case of ABPM, thresholds of 130 and/or 80 mmHg are recommended for the 24-hour mean. Additional cutoff values for daytime and nighttime means of 135 and/or 85 mmHg and of 120 and/or 70 mmHg, respectively, are also listed [1].

Advantages of ABPM viewed by the ESC/ESH are that it can identify white-coat and masked hypertension; it provides a stronger prognostic evidence; nighttime measurements can be obtained; measurements are obtained in real-life settings; additional prognostic value is obtained from BP phenotypes; and "abundant" information can be obtained from a single 24-hour session, including short-term BP variability. Disadvantages are that ABPM is expensive, not always available, and it can be uncomfortable.

By comparison, advantages of HBPM viewed by the ESC/ESH are that it can also identify white-coat and masked hypertension; it is inexpensive and widely available; that measurements can be taken in a home setting; that it can engage the patient; and that it can easily be repeated and used over long spans to assess day-to-day variability in BP. Disadvantages are that HBM only provides static BP measurements; that it may be prone to measurement error; and that it cannot measure BP during sleep.

The ESC/ESH guidelines also list clinical indications for HBPM or ABPM [1]: conditions in which white-coat hypertension or masked hypertension is more common; postural and post-prandial hypotension; evaluation of resistant hypertension; evaluation of BP control, notably in high-risk patients on anti-hypertensive medication; exaggerated BP response to exercise; presence of considerable BP variability in office measurements; and evaluation of symptoms consistent with hypotension during treatment. ABPM rather than HBPM is recommended specifically when nocturnal BP and the "dipping: status need to be assessed [1].

From a chronobiologic perspective, limiting the use of ABPM to 24 hours in special patient populations is short-sighted. Altered circadian patterns of BP variability have been shown to be associated with an increase in cardiovascular disease risk, even in normotensive individuals [5-7, 9-15], Figure 8. These results suggest that ABPM should be available for everybody, since these conditions cannot be diagnosed based on routine clinic measurements.

Community-wide 7-day/24-hour ABPM on 206 men and women 24-79 years of age indicated that:

- Outcomes after a 5-year follow-up differed with statistical significance between individuals diagnosed as normotensive or hypertensive (> 130/80 mmHg), but no such difference could be shown when the diagnosis was based on the first 24 hours of monitoring [15], and
- Outcomes also differed with statistical significance between individuals as high versus low risk, assessed by also considering BP variability and other "vascular variability disorders" (i.e., abnormal circadian patterns of BP and/or heart rate) [15].

The argument has been made that savings made by preventing the occurrence of more adverse events achieved by the across-the-board use of ABPM may very well cover the cost of ambulatory BP monitors and of the chronobiologic analysis and interpretation of the data thus obtained [16].

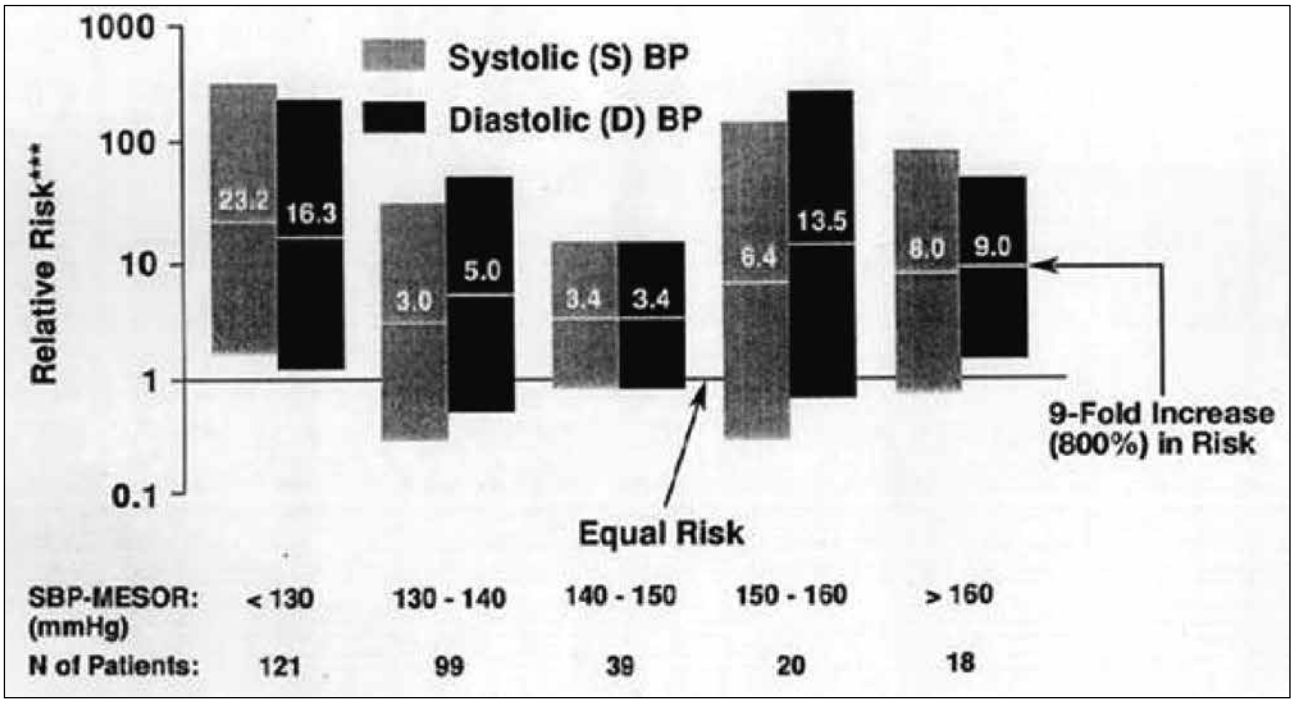

Figure 8: *Even in normotensive individuals, an excessive circadian amplitude of BP is associated with a large and statistically significant increase in the risk of cerebral ischemic events. Results from a 6-year prospective outcome study [15]. © Halberg Chronobiology Center*

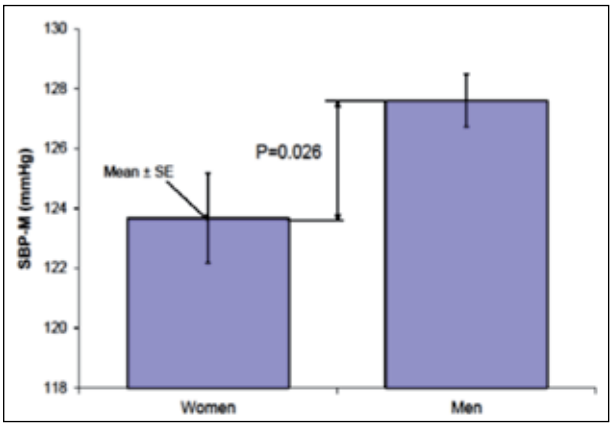

Figure 9: *Clinically healthy women have a lower MESOR (24-hour rhythm-adjusted mean) of systolic BP than men.*
© Halberg Chronobiology Center

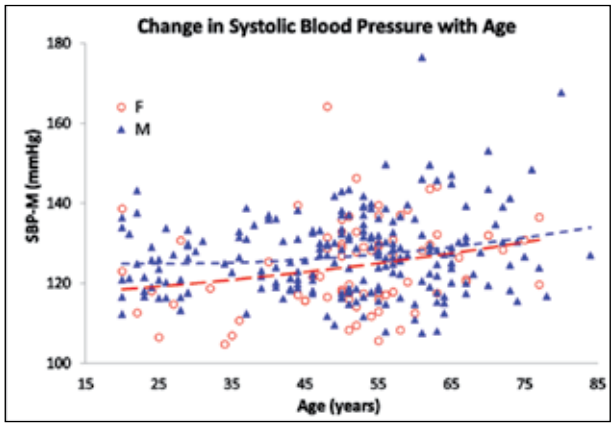

Figure 10: *In clinically healthy men and women, the MESOR of systolic BP increases with age*
© Halberg Chronobiology Center

Treatment of Hypertension

The ESC/ESH guidelines state that "No outcome-based randomized controlled trial has used ABPM or HBPM to guide the treatment of hypertension. Thus, ABPM and HBPM BP targets are based on extrapolation from observational data rather than on outcome trials". They note that "In population studies, the difference between office and out-of-office BP levels decreases as office BP decreases, to a point of around 115–120/70 mmHg, at which office and 24-hour ABPM mean BP values are usually similar" and that "This convergence has also been confirmed in treated patients" [1].

Such an interpretation, however, ignores BP variability and inter-individual differences. As noted above, chronobiologic trials indicate that an abnormal circadian pattern can be associated with an increased cardiovascular disease risk in the absence of an elevated BP average (Figure 8).

Hypertension in Older Patients

Referring to older patients (above 65 years of age), the ESC/ESH guidelines note the increased prevalence of hypertension as a function of age: "The prevalence of hypertension increases with age, with a prevalence of 60% over the age of 60 years and 75% over the age of 75 years" [1]. Accordingly, their recommendation consists of the following: "In very old patients, it may be appropriate to initiate treatment with monotherapy. In all older patients, when combination therapy is used, it is recommended that this is initiated at the lowest available doses. The possible occurrence of postural BP should be closely monitored and symptoms of possible hypotensive episodes checked by ABPM" [1].

From a chronobiologic perspective, several consensus meetings [5, 14] advocated to map age trends in clinical health as well as differences in relation to gender and ethnicity, so that acceptable limits account for such physiological effects. As repeatedly demonstrated, systolic BP increases at least until about 80 years of age, whereas diastolic BP reaches a maximum around 50 years of age. Women are also well known to have a lower BP but a higher heart rate than men. These differences, assessed in the Brno database [17], are illustrated in Figures 9 and 10.

Blood Pressure Measurement in Pregnancy

In agreement with the general recommendations discussed above, white-coat hypertension and conditions such as diabetes and/or kidney disease are the primary reasons to consider ABPM in the EAS/ESH guidelines: "ABPM is superior to office BP measurement for the prediction of pregnancy outcome. ABPM helps avoid unnecessary treatment of white-coat hypertension, and is useful in the management of high-risk pregnant women with hypertension and those with diabetic or hypertensive nephropathy" [1].

From a chronobiologic perspective, special reference values have been derived for each trimester of pregnancy [18]. As illustrated in Figure 11, these reference values account for the decrease in BP during the second trimester, and for the steady increase in heart rate [19, 20]. Such chronobiologic standards detected impending risk in one pregnant woman who presented with otherwise acceptable 24-hour BP means [21].

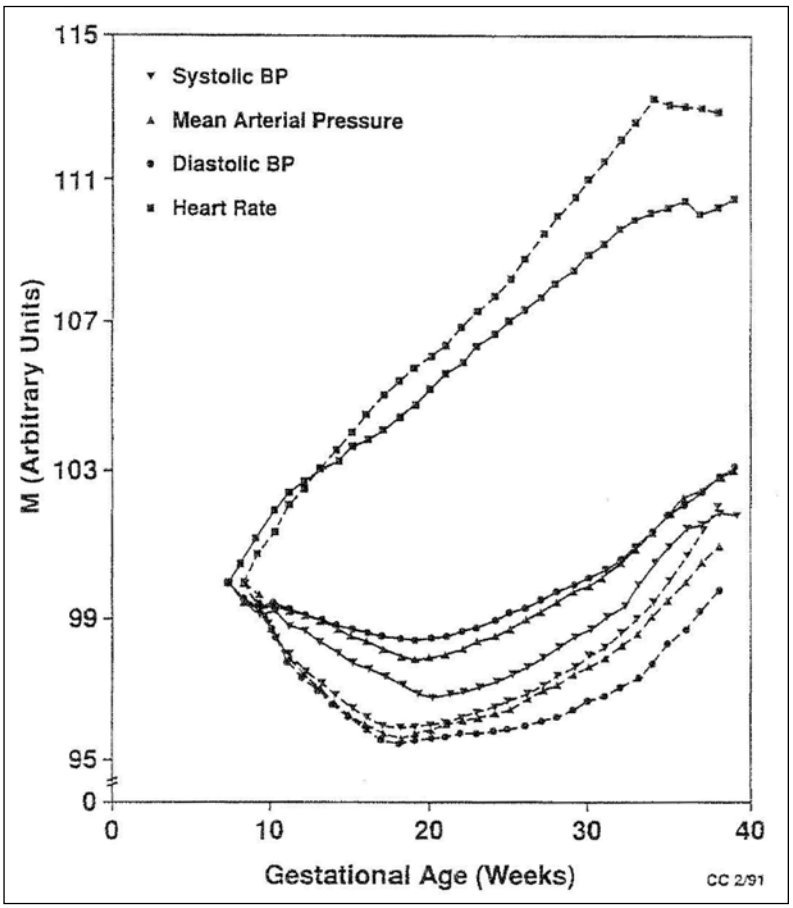

Figure 11*: Reconstructed time course of the MESOR (24-hour rhythm-adjusted mean) of BP and heart rate (HR) during pregnancy in clinical health (N=161; solid curves) or in the presence of gestational hypertension (N=25; dashed curves). © Halberg Chronobiology Center*

Hypertension in Diabetes Mellitus

The ESC/ESH guidelines state: "Recording 24-hour ABPM in apparently normotensive people with diabetes may be a useful diagnostic procedure, especially in those with hypertension-mediated organ damage" [1].

From a chronobiologic perspective, it has long been recognized that some patients with diabetes present with a reversed circadian BP variation, BP being higher by night than by day [22]. Such reversal of the circadian BP rhythm has been associated with the presence of autonomic nervous dysfunction [23]. But 7-day/24-hour ABPM may be able to predict pre-diabetes by detecting abnormal BP variability [24], thereby providing an opportunity to initiate countermeasures in a more timely fashion.

Blood Pressure Control in Hypertension: Drug Adherence

The usefulness of ABPM or HBPM in checking whether a patient is responding to treatment is also recognized in the ESC/ESH guidelines: "Directly observed treatment, followed by BP measurement over subsequent hours via HBPM or ABPM, can also be very useful to determine if BP really is poorly controlled despite witnessed consumption of medication in patients with apparent resistant hypertension" [1].

Need for Future Studies

The ESC/ESH guidelines mention as major gaps in the available evidence the need to determine "the incremental benefit for cardiovascular risk prediction of the addition of out-of-office BP (HBPM and ABPM) to office BP measurement" and "the optimal BP treatment targets according to HBPM and ABPM" [1].

From a chronobiologic viewpoint, however, the real benefits of ABPM will be fully appreciated only when repeated monitoring for spans longer than 24 hours guide personalized chronotherapy [25, 26]. It is not enough to lower an elevated BP, it is even more important to restore an acceptable circadian BP profile [27].

The 2017 ACC/AHA Guidelines

As compared to the 2014 guidelines, the scope of the 2017 ACC/AHA Guidelines for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults is more extensive, including the definitions of hypertension, diagnostic workup and evaluation, lifestyle management strategies for prevention and treatment, BP treatment thresholds and initial drug choices, and long-term monitoring [28]. Most recommendations support a more aggressive diagnostic and treatment approach, consistent with growing evidence from clinical trials and epidemiological studies [29]. The 2017 ACC/AHA guidelines, however, give only little consideration to ABPM, and consider HBPM to be equally meritorious in many situations: "Although ABPM is generally accepted as the best out-of-office measurement method, HBPM is often a more practical approach in clinical practice. … Both ABPM and HBPM typically provide BP estimates that are based on multiple measurements. A systematic review conducted by the US Preventive Services Task Force reported that ABPM provided a better method to predict long-term cardiovascular-disease outcomes than did office BPs. … A small body of evidence suggested, but did not confirm, that HBPM could serve as a similar predictor of outcomes" [28].

The 2017 ACC/AHA guidelines [28] enumerate the following tasks ahead in relation to ABPM use:

- ABPM and HBPM provide enhanced ability to both diagnose hypertension and monitor treatment. Although evidence is sufficient to recommend incorporating these tools into clinical practice, more knowledge about them is required.

- Areas of inquiry include closer mapping of the relationship of outcomes to ABPM and HBPM, so that definitions of hypertension and hypertension severity based on these measures can be developed, including the importance of masked hypertension, white-coat hypertension, and nocturnal hypertension.
- Reproducibility of ABPM and HBPM must be studied; cohorts should include a broader range of ethnicities.
- The practicality and cost of incorporating ABPM into Electronic Health Records (EHR) and routine care should be assessed.

Even though much evidence in chronobiology is already available to support the usefulness of HBPM and ABPM, it is our task to provide additional information to convince practitioners of the merit to routinely screen for abnormal BP variability, for Vascular Variability Disorders (VVDs) in particular [14]. White-coat hypertension and masked hypertension are obvious patient populations who can benefit from ABPM, but ABPM should also be considered for everyone, since cardiovascular disease risk can be associated with abnormal features of BP variability in the absence of an elevated BP per se. Practicality and cost have been invoked to limit the use of ABPM. New technologies, however, are emerging that may solve this issue [30], notably if most of the monitoring and data analysis can be performed by individuals themselves, who may seek medical advice only when needed.

Advances in technology are acknowledged in the ACC/AHA guidelines: "Technology for measurement of BP continues to evolve with the emergence of cuffless devices and other strategies that provide the opportunity for continuous noninvasive assessment of BP. The accuracy, cost, and usefulness of these new technologies will need to be assessed" [28].

These efforts are certainly worthwhile, although cuffless devices are not necessarily the only possible solution, at least in the short term. Whether wrist devices can be modified for accurate ambulatory automatic BP measurements, for instance, is being investigated by the Phoenix Study Group of volunteering members of the Twin Cities Section of the Institute of Electrical and Electronics Engineers (http://www.phoenix.tcieee.org) [31].

More surprising are other plans outlined in the ACC/AHA guidelines: "Further research on improving accuracy of office BP measurements, including number of measurements, training of personnel measuring BP, and device comparisons, will help standardize care and thus improve outcomes" [28].

Chronobiologic evidence accumulated thus far casts doubt on the likelihood of success of such measures, given the high variability in BP. Many factors in health affect BP, from genetics and lifestyle (nutrition, salt intake, alcohol consumption, smoking, activity and exercise) to the environment (altitude, meteorological conditions, space weather) and emotions [32-40]. Assessing BP variability, combined with reliance on longitudinal around-the-clock monitoring interpreted in the light of time-specified reference values qualified by gender, ethnicity and age, may prove to be a more fertile ground to improve outcomes.

Discussion and Conclusion

Both the European and the American guidelines agree on the merit of ABPM as a better predictor of adverse cardiovascular outcomes, as being better able to identify white-coat and masked hypertension, and as a valuable tool to assess nocturnal BP. Because of the cost and practicality of ABPM, the guidelines recommend its use only for 24 hours and in special patient populations. Even when ABPM is used, however, the data analysis is limited to the computation of daytime, nighttime, and 24-hour

mean values, and of the day-night ratio for a classification in terms of 'dipping", using an arbitrary limit of 10% applied across-the-board, even though the guidelines mention ethnic differences and changes as a function of age in the prevalence of hypertension.

Apart from cost, cuff inflation has indeed been a major hurdle that has limited the use of ABPM. It is thus understandable that much effort is being devoted to the development of cuffless devices, which will need to be fully validated before their use can be recommended. The use of wrist cuffs on the other hand has been increasing, as apparent from the growing interest in HBPM, although it requires the wrist to be positioned at heart's level to yield trustworthy measurements. The fact that HBPM readily allows longitudinal monitoring is a real advantage since it can reveal the presence of an untoward trend, prompting the patient to seek medical advice. Longitudinal monitoring, however, is not part of the ESC/ESH guidelines, which only recommend HBPM for 3 days prior to a clinic visit [1]. Only morning and/or evening measurements from HBPM are recommended in the guidelines, in stark contrast with self-measurements which have been practiced by chronobiologists since the early 1970s [41]. Self-measurements were advocated to be taken a few times a day, at intervals of about 3 to 4 hours from the time of awakening to bedtime, with nighttime measurements taken whenever waking up spontaneously during the night or preferably taken while asleep by a family member. Self-measurements are thus amenable to analysis for an assessment of the circadian variation, and specific reference values for them have been derived in clinical health [42].

The issue of cost associated with the use of ABPM needs to be revisited.

- First, the higher cost stems from its limited use. A larger demand is likely to bringing the cost considerably down.
- Second, part of the inflated cost of ABPM is related to its use by medical professionals. Making ABPM publicly available in libraries or community centers would also help lower the cost.
- Third, once ABPM is being performed, its implementation would gain from being reevaluated. Prolonging the monitoring from 24 hours to 7 days will barely increase the cost, and in return, much additional information can be obtained. In view of the large day-to-day variability in all circadian parameters, a more reliable BP profile will be available to guide the need and timing of treatment. Analyzing the data chronobiologically, abnormalities not only in MESOR, but also in circadian amplitude and acrophase can be detected when they are interpreted in the light of reference values from clinically healthy peers matched by gender and age. VVDs such as CHAT and ecphasia, which can be present in the absence of an elevated 24-hour BP mean, have been repeatedly shown to have superior predictive values than a classification in terms of "dipping" [6, 7, 14]. Moreover, only ABPM can assess a patient's response to treatment in terms of all VVDs. Not all anti-hypertensive medications have an effect on the circadian amplitude of BP [43]. Moreover, chronotherapy needs to account for the chronodiagnosis [44] since the optimal timing of treatment with a given anti-hypertensive drug is likely to differ between a patient with CHAT who has elevated BP values during the day and a patient with ecphasia who has elevated BP values during the night. Personalized chronotherapy [25] is estimated to help about two thirds of the patient population.
- Fourth, once the benefits of chronobiologically-interpreted ABPM are fully appreciated, both in terms of a more accurate diagnosis and as a guide to the optimization of treatment by timing, insurance companies will realize the merit of investing in an ounce of prevention rather in a pound of needed care [45, 46].

The ESC/ESH guidelines mention that no outcome-based randomized controlled trial has used ABPM or HBPM to guide the treatment of hypertension [1], but several chronobiologic studies have been conducted, which documented the merit of timed treatment [26, 30]. One important task that is urgently needed, however, is a rigorous comparison of outcomes between patients treated chronobiologically or conventionally. Can restoring a healthy pattern of BP variation help prevent adverse outcomes? Only limited indirect evidence is available thus far suggesting that it may be more important to restore acceptable circadian variation in BP than to lower BP more [27].

Finally, one topic apparently not covered by the guidelines relates to the detailed analysis of the BP waveform. Much work has already been done in this area in Brno and deserves further investigation.

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Support:
Halberg Chronobiology Fund
University of Minnesota Supercomputing Institute
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Changes with Kp in the Circadian Rhythm of Circulating Melatonin

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Introduction

Geomagnetic storms, generated by high-energy changes in the solar wind, which produces major shifts in the Earth's magnetosphere, are monitored and measured by the National Oceanic and Atmospheric Administration (NOAA) in the USA, and governmental organizations around the world because of their potential to impact systems on Earth. Solar coronal mass ejections (CME), high-speed solar wind streams (HSS), and solar flares are some of the solar activities associated with disruptive changes in radiation belts, atmospheric density, atmospheric heating, and magnetic currents, which in turn have impacts on satellites, power grids, pipelines, radio signals and navigation systems. Polar aurorae are a visible manifestation of these powerful storms, and can sometimes be seen 2/3 of the hemisphere away, they are so strong. Much of the destructive power of these storms is due to the disruptive influence that magnetic forces produce in electrical systems, by inducing powerful or unexpected electrical currents.

Global geomagnetic storm strength is quantified by the Kp index, which is derived from 3-hour measurements of local geomagnetic activity, known as K-indices, collected from a number of stations at different latitudes and longitudes around the world. Values of Kp range from 0 to 9, where 0 indicates quiet conditions and 9 indicates a major geomagnetic storm with strong aurorae visible (Bartels et al., 1939), Figure 1.

Kp	Aural Activity	Average Frequency
0	Quiet	
1	Quiet	
2	Quiet	
3	Unsettled	
4	Active	
5	Minor Storm	1700 per cycle (900 days per cycle)
6	Moderate Storm	600 per cycle (360 days per cycle)
7	Strong Storm	200 per cycle (130 days per cycle)
8	Severe Storm	100 per cycle (60 days per cycle)
9	Extreme Storm	4 per cycle (4 days per cycle)

Figure 1: *Relative activity represented by Kp-indices, and frequecy of occurrence in an 11-year solar activity cycle.*

Geomagnetic disturbances tend to be stronger and more frequent when solar activity is high. They have been shown to be associated with changes in health and welfare of living organisms on earth, as well as on electronic technologies. Biological systems are, after all, electrochemical in nature. Various studies have shown that periods of increased solar activity were associated with physiological changes. For instance, decreases in blood pressure have been reported (Dimitrova et al., 2004; Feigin et al., 2014; Ghione et al., 1998; Hrushesky et al., 2011). Changes in melatonin concentrations have

also been associated with high geomagnetic disturbances (Burch et al., 2008; Cornelissen et al., 2009; Tarquini et al., 1997; Weydahl et al., 2000). Heart rate variability (HRV) was found to be lower in 8 astronauts monitored during a magnetic storm, compared to 41 others monitored during quiet conditions (Baevsky et al., 1997). Higher heart rate and reduced HRV have also been documented longitudinally by 7-day/24-hour ECG (Otsuka et al., 2001), and results corroborated by others (McCraty et al., 2017). In a study in Minnesota, USA, the incidence of mortality due to myocardial infraction increased by 5% during years of maximum solar activity compared to years of minimum activity (Cornelissen et al., 2002). Magnetic storms are felt more strongly at latitudes closer to the poles, and melatonin concentrations have been found to decrease at higher latitudes (Cornelissen et al., 2009; Wetterberg et al., 1999; Weydahl et al., 2000). Depression and suicide rates are higher in spring and fall, which coincide with the times of maximal geomagnetic disturbance (Cornelissen et al., 2010; Halberg et al., 2005).

As to the question of the mechanism whereby these phenomena impact life forms, there is indeed evidence for the pineal, or possibly other parts of the brain, to be involved in the reception and mediation of the effect of electric, magnetic and electromagnetic field effects (Cherry, 2002; McCraty et al., 2017; Wilson et al., 1986). Brain waves (EEGs) and calcium ion fluxes have been altered by environmental electromagnetic fields in the same range as EEGs, which have been related to geomagnetic storms (Cherry, 2002). The effect is thought to be a resonant absorption of an oscillating signal (Adey, 1993; Bawin et al., 1996).

Melatonin is secreted principally by the pineal gland, in a rhythm determined, at least in part, by the suprachiasmatic nuclei, reflecting the circadian light/dark cycle (Claustrat et al., 1995; Wurtman, 2000). Melatonin and the suprachiasmatic nuclei are important in communications and coordination of the circadian system throughout the body. It is for this reason we look at melatonin and changes in melatonin related to global geomagnetic storms. If melatonin is impacted by geomagnetic storms, the entire body could be affected in a ripple of cascading changes downstream.

Predictable changes occur over the 24-hour day in many biological variables, and these periodicities must be accounted for in study designs to avoid confounding results. The age of personalized medicine, which factors in the effect of genetics and epigenetics into the diagnosing of human illness, is resulting in further refinements in our understanding and our diagnostic tools. Both of these advances have only recently been widely recognized as biological fundamentals. If space weather and geomagnetics are also a factor in human health, exposing the connections will further benefit the important task of improving human health.

Subjects and Methods

We analyzed melatonin data from two populations of 172 (S1: 40 males; 132 females) and 171 (S2: 61 males; 110 females) mostly healthy subjects in Florence, Italy. These data had previously been analyzed (Tarquini et al., 1997) by cosinor (Halberg, 1980; Cornelissen, 2014). Subjects were hospitalized under standardized conditions. Domestic lights were turned off from 22:00 to 06:30 in all seasons without correction for legal time, but natural light was not shielded. Venous blood samples for melatonin assay were taken every 4 hours for 24 hours, beginning at 08:00, and collected into chilled tubes. Nightly samples were obtained using a flashlight, mostly without awakening the subjects. Thus each subject provided data at 6 time points.

Analyses were carried out separately for each study, as data averages were too different between them to pool the data sets. At each circadian time point, linear regressions with Kp were carried out on the original melatonin data. Since melatonin has been found to change with age, changes in melatonin

were also linearly regressed as a function of both Kp and age, using Kp values taken from the day of sampling. Similar analyses were performed using Kp values taken from the day prior to blood sampling, since effects of magnetic storms are not necessarily immediate and may last for more than one day (Otsuka et al., 2001).

Data were $\log_{10}$-transformed (to satisfy assumptions underlying the use of the cosinor) and analyzed by single cosinor to estimate circadian rhythm characteristics (Tarquini et al., 1997). In order to test whether the circadian amplitude of melatonin is reduced in response to a magnetic storm, the anticipated decrease in the circadian amplitude as a function of age had to be accounted for first. Thus, the circadian amplitude of the $\log_{10}$-transformed data is regressed with age. Chi-square and Student's t-tests were applied to the residuals from this linear regression. If magnetic storms (gauged by daily average values of $Kp \geq 4$) were associated with a reduced circadian amplitude of melatonin, as previously found (Burch et al., 2008; Weydahl et al., 2000), one would expect Kp values corresponding to negative residuals from the regression model (i.e., amplitudes below the regression line) to be on average higher than those corresponding to positive residuals (i.e., amplitudes above the regression line). Likewise, one would expect to find the number of high Kp values (≥ 4) to be larger in association with negative than with positive residuals.

In Study 1 (S1), there were 21 of 172 circadian profiles recorded on days when $Kp \geq 4$, whereas in Study 2 (S2), there were only 5 of 171 records on days when $Kp \geq 4$. During the duration of our investigations, there were few moderate geomagnetic storms (general range: $4 \leq Kp < 7$) and no major storms (general range: $Kp \geq 7$) (Table 1).

Table 1: *Kp data summary. No major storms occurred during either study span**

Kp	N	N, Kp≥4	min	Max	Mean	SD
S1	172	21	0.500	5.410	2.523	1.174
S1 (day−1)	172	21	0.325	4.990	2.716	1.113
S2	171	5	0.500	4.510	2.102	0.881
S2 (day−1)	171	6	0.287	4.340	2.059	0.957

** S1: Study 1; S2: Study 2; N: Number of 24-hour records; N, Kp≥4: Number of 24-hour records on days when Kp assumed a daily average of at least 4; min: minimum daily average of Kp; Max: maximum daily average of Kp; Mean: average daily Kp on days of blood sampling; SD: standard deviation of daily Kp on days of blood sampling.*

Kp data, reflecting 3-hour spans, were obtained from ftp://ftp.ngdc.noaa.gov. Since they are reported in GMT time, which is one hour off from Florence, Italy, no adjustment for time zone was needed.

Results

Figure 2 shows the original melatonin data from Study 1 at each of six different circadian stages, 4 hours apart. The inset shows the circadian rhythm of melatonin averaged over all subjects.

Analysis of original melatonin data

Melatonin measurements at each of the 6 times (08:00, 12:00, 16:00, 20:00, 00:00, 04:00) were regressed against Kp values on the day of blood sampling. Because melatonin has been reported to decrease with age (at least during the night), age was also added to the regression model. In Study 1, higher Kp values were significantly associated with lower melatonin concentrations, for measurements

taken at midnight (P=0.043), Table 2. This result is consistent with previous studies showing that higher Kp values are associated with lower melatonin concentrations (Burch et al., 2008; Weydahl et al., 2000). A relationship between melatonin and either Kp or age was not found at any other time point.

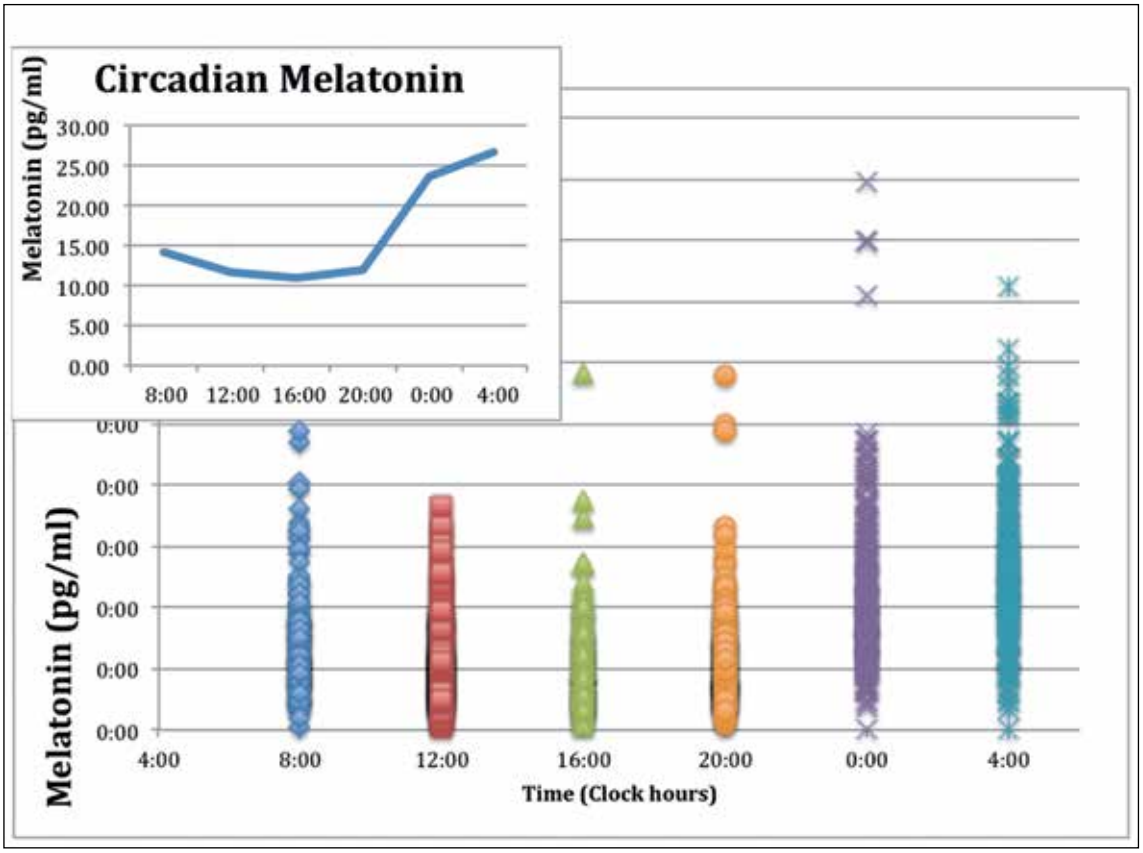

Figure 2: *Study 1: Raw melatonin data at 6 time points, 4 hours apart, covering 24 hours. Inset: Circadian melatonin rhythm averaged across all subjects.*

Table 2: *Study1: Regression with Kp and age of melatonin at 6 different circadian time points**

8:00	**R^2**	0.016	**overall P**	0.270
	Coef	*SE*	*t–test*	*P–value*
Age	0.058	0.039	1.493	0.137
Kp	−0.422	0.557	−0.758	0.449
12:00	**R^2**	0.021	**overall P**	0.168
	Coef	*SE*	*t–test*	*P–value*
Age	0.053	0.030	1.751	0.082
Kp	−0.374	0.431	−0.868	0.387
16:00	**R^2**	0.021	**overall P**	0.171
	Coef	*SE*	*t–test*	*P–value*
Age	0.052	0.032	1.629	0.105
Kp	−0.490	0.456	−1.075	0.284

20:00	**R^2**	0.008	**overall P**	0.501
	Coef	*SE*	*t–test*	*P–value*
Age	0.037	0.038	0.987	0.325
Kp	−0.384	0.535	−0.717	0.474
0:00	**R^2**	0.024	**overall P**	0.129
	Coef	*SE*	*t–test*	*P–value*
Age	0.008	0.063	0.132	0.895
Kp	−1.817	0.892	−2.036	0.043
4:00	**R^2**	0.004	**overall P**	0.743
	Coef	*SE*	*t–test*	*P–value*
Age	−0.032	0.061	−0.527	0.599
Kp	0.518	0.848	0.610	0.542

** Kp: Kp on day of sampling; SE: Standard Error; P-value from test of H_0: Coef = 0.*

Because there may be a delay in observing an effect, the regression was also done using daily Kp averages from the day before blood sampling (Table 3). Regression of melatonin with both Kp and age, using Kp averages from the day before blood sampling, was statistically significant at 4 of the 6 time points, showing that rising Kp are associated with decreasing melatonin concentrations. The association between melatonin and Kp is stronger when considering Kp on the day prior to blood sampling as compared to the same day as blood sampling, suggesting that the impact of geomagnetic disturbances is not immediate.

Table 3: *Study1: Regression with Kp and age of melatonin at 6 different circadian time points**

8:00	**R^2**	0.049	**overall P**	0.015
	Coef	*SE*	*t–test*	*P–value*
Age	0.050	0.038	1.308	0.193
Kp	−1.470	0.577	−2.549	0.012
12:00	**R^2**	0.030	**overall P**	0.078
	Coef	*SE*	*t–test*	*P–value*
Age	0.049	0.030	1.625	0.106
Kp	−0.685	0.452	−1.516	0.131
16:00	**R^2**	0.045	**overall P**	0.021
	Coef	*SE*	*t–test*	*P–value*
Age	0.046	0.032	1.461	0.146
Kp	−1.103	0.474	−2.327	0.021

20:00	**R^2**	0.016	**overall P**	0.247
	Coef	*SE*	*t–test*	*P–value*
Age	0.033	0.038	0.873	0.384
Kp	−0.781	0.561	−1.393	0.166
0:00	**R^2**	0.061	**overall P**	0.005
	Coef	*SE*	*t–test*	*P–value*
Age	−0.011	0.062	−0.176	0.860
Kp	−3.051	0.921	−3.311	0.001
4:00	**R^2**	0.038	**overall P**	0.040
	Coef	*SE*	*t–test*	*P–value*
Age	−0.034	0.059	−0.566	0.572
Kp	−2.194	0.873	−2.513	0.013

** Kp: Kp on day prior to blood sampling; SE: Standard Error; P-value from test of H_0: Coef = 0.*

Table 4: *Study 2: Regression with Kp and age of melatonin at 6 different circadian time points**

8:00	**R^2**	0.016	**overall P**	0.273
	Coef	*SE*	*t–test*	*P–value*
Age	−0.164	0.145	−1.133	0.259
Kp	2.878	2.714	1.061	0.290
12:00	**R^2**	0.022	**overall P**	0.152
	Coef	*SE*	*t–test*	*P–value*
Age	0.063	0.033	1.934	0.055
Kp	0.253	0.610	0.415	0.679
16:00	**R^2**	0.012	**overall P**	0.371
	Coef	*SE*	*t–test*	*P–value*
Age	0.023	0.017	1.334	0.184
Kp	0.186	0.328	0.568	0.571

20:00	**R^2**	0.015	**overall P**	0.287
	Coef	*SE*	*t–test*	*P–value*
Age	0.035	0.060	0.585	0.559
Kp	−1.585	1.108	−1.430	0.155
24:00	**R^2**	0.085	**overall P**	0.001
	Coef	*SE*	*t–test*	*P–value*
Age	−0.761	0.198	−3.835	<0.001
Kp	2.125	3.657	0.581	0.562
4:00	**R^2**	0.106	**overall P**	<0.001
	Coef	*SE*	*t–test*	*P–value*
Age	−0.863	0.222	−3.883	<0.001
Kp	7.632	4.082	1.870	0.063

** Kp: Kp from day of sampling; SE: Standard Error; P-value from test of H_0: Coef = 0.*

The strongest relationships between melatonin and Kp are found at midnight (Tables 2-4) and 4:00 (Tables 3 & 4). Melatonin is at its peak during the nighttime hours, and Kp also peaks around midnight.

In Study 2, no association was found between melatonin and Kp, either on the date of blood sampling, or one day earlier (Table 4). This is understandable in view of the lack of geomagnetic activity during the span of Study 2.

Single cosinor modeling of circadian rhythm in circulating melatonin

Cosinor analysis can be used to model the circadian rhythm of melatonin. Using a 24-hour cosinor model, a determination can be made whether circadian characteristics, such as the 24-hour amplitude, change in response to changing values of Kp. The data were $\log_{10}$-transformed to satisfy assumptions underlying the use of the cosinor method. Since the circadian amplitude of melatonin has been shown to decrease with increasing age (Cornelissen et al., 2000; Lee Gierke et al., 2016), any effect of Kp on the circadian amplitude of the $\log_{10}$-transformed melatonin data needs to take this result into account. Accordingly, the amplitude of melatonin was first regressed as a function of age. Residuals were then used to test whether magnetic storms (defined here as Kp ≥ 4) were associated with a further decrease in the circadian amplitude of melatonin.

As shown in Figure 3, the circadian amplitude of melatonin decreases with advancing age in subjects from Study 1 (P=0.029). The average daily value of Kp on days when residuals were negative (i.e., when the circadian amplitude of melatonin was below the regression line) was indeed higher (N=99, Kp=2.56) as compared to that on days when residuals were positive (i.e., when melatonin was above the regression line; N=73, Kp=2.48) (t =0.425; P=0.671). Using Kp from the day before blood sampling, Kp was again higher in relation to negative residuals (Kp=2.886) as compared to positive residuals (Kp=2.486) (t = 2.365; P=0.019).

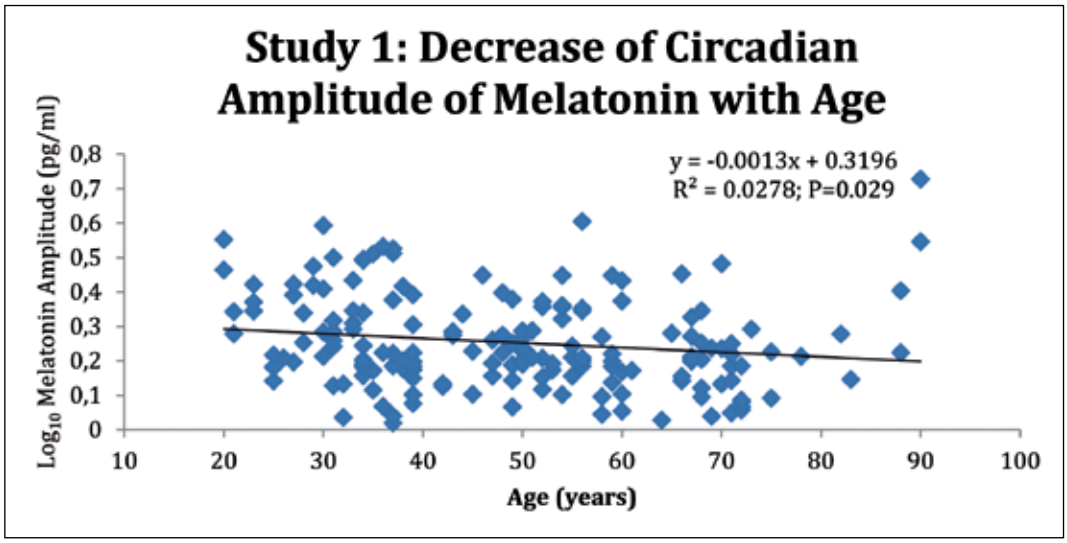

Figure 3: *Study 1: This model was used to determine whether a larger number of Kp values ≥4 is associated with negative residuals (amplitudes below regression line) as compared to positive residuals (amplitudes below regression line), and whether, on average, Kp is higher on days of blood sampling corresponding to negative versus positive residuals.*

Whereas in Study 1, negative residuals in the regression of the circadian amplitude of $\log_{10}$-melatonin as a function of age were more likely to be associated with a magnetic storm on the day prior to blood sampling (13.1%) as compared to positive residuals (9.6%), this difference was not statistically significant ($c^2 = 0.513$, P = 0.474).

A decrease in the circadian amplitude of $\log_{10}$-transformed melatonin data was also found in Study 2 (P <0.001), Figure 4. In this study, however, negative residuals are associated with a lower Kp

average as compared to positive residuals, whether considering Kp on the day of blood sampling (t = -2.255, P = 0.025) or on the preceding day (t = -1.189, P = 0.236). Such a result opposite to expectation can be accounted for by the fact that Study 2 took place during a solar minimum when there were hardly any magnetic storms.

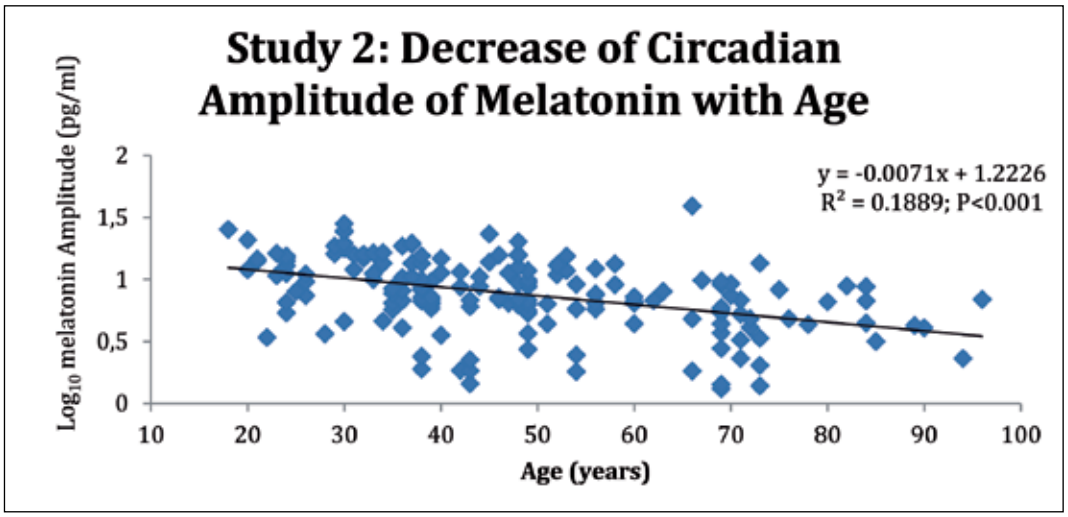

Figure 4: *Study 2: This model was used to determine whether a larger number of Kp values ≥4 is associated with negative residuals (amplitudes below regression line) as compared to positive residuals (amplitudes below regression line), and whether, on average, Kp is higher on days of blood sampling corresponding to negative versus positive residuals.*

Discussion and Conclusion

Results for Study 1 showed a relationship of smaller melatonin amplitudes when Kp is higher. They are consistent with other findings that magnetic storms are associated with a reduced circadian amplitude of melatonin (Burch et al., 2008; Cornelissen et al., 2009; Tarquini et al., 1997; Weydahl et al., 2000). Because melatonin, mainly secreted by the pineal gland, is so key to the circadian rhythm found in living things, it is important to understand the effects of geomagnetic disturbances.

Significantly, dampened circadian rhythms have been found to be associated with decreases in wellness. Heart rate variability is one variable commonly understood to decrease with age and illness, and to be associated with morbidity (Alabdulgader et al., 2018; Baevsky et al., 1997; Cornelissen et al., 2002; McCraty et al., 2017; Otsuka et al., 2001; Wetterberg et al., 1999). A decreased circadian amplitude of melatonin is found in patients with cancer (Halberg et al., 2006; Tarquini et al., 1999), and melatonin has been used to treat cancer (Li et al., 2018; Reiter et al., 2017). The circadian amplitude of blood pressure also deceases with age and infirmity (Cornelissen et al., 2016).

Considering melatonin determinations at different circadian stages, results indicated that melatonin was almost invariably negatively related to Kp, notably during the night, when using Kp on the day prior to blood sampling instead of on the day of study itself. These results suggest that the response to a magnetic storm is not immediate. A larger effect during the night can be accounted for by the higher nightly values of melatonin and the fact that Kp also peaks around midnight.

A decrease in melatonin during the night is in agreement with a reduced circadian amplitude of melatonin in response to higher geomagnetic activity, since it usually occurs as a result of lowered nighttime values, daytime values being usually quite low. When the data are $\log_{10}$-transformed, however, an increase in daytime values can also account for a decrease in circadian amplitude.

Results for Study 2 did not show a relationship between melatonin and Kp. But there were hardly any geomagnetic disturbances during Study 2, which corresponded to a minimum in solar activity, when magnetic storms are less frequent.

If magnetic storms are associated with changes in the amplitude of melatonin, there may be impacts to public health because melatonin is an important hormone with a strong circadian rhythm that is known to drive other bodily rhythms. Studies have already identified some health-related risks associated with geomagnetic storms and/or solar activity: lowered HRV (Alabdulgader et al., 2018; Baevsky et al., 1997, McCraty et al., 2017), increased incidence of myocardial infarctions (Cornelissen et al., 2002; Hrushesky et al., 2011), increased incidence of depression and suicide (Halberg et al., 2005). Further research into health-related impacts of geomagnetic storms is indicated.

Of interest in further understanding effects of space weather on human pathophysiology, it will be important to determine which specific aspects of the cosmic environment are responsible for various conditions related to human health. Increased radiation occurs during geomagnetic storms, environmental geomagnetics are disrupted, resulting in other environmental changes. Understanding the specific causes will aid in understanding health effects, and where to expect greater effects on health (such as at higher altitude or at higher latitude).

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Circadian Time Structure in Patients with Acute Hemispheral Cerebral Infarction Compared to Clinically Healthy Bedridden and Ambulatory Controls

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Dedicated to the memory of Erhard Haus, David Lakatua, and Jacqueline Swoyer

Abstract

Cerebral infarction is a major cause of neurologic dysfunction which can also lead to death. Many other systems in the body are affected by cerebrovascular events, while also affecting their risk or cause. The cardiovascular system has been closely associated with cerebral infarction (stroke), which can cause arrhythmias, other ECG abnormalities, and changes in the circadian pattern of blood pressure. This study was designed to examine the circadian rhythms of blood and urinary variables, and of clinical functions such as blood pressure in patients following a cerebral infarction. This article focuses on the cardiovascular time structure with the aims of:

1. Evaluating changes in the circadian time structure of patients following a stroke and establishing any role the rhythm disruption may have had on the deficits/dysfunction following the initial stroke;
2. Assessing disturbances in other known non-neurologic rhythms, such as cardiovascular changes that may complicate the patient's recovery;
3. Determining the extent of circadian disruption related to bed confinement by monitoring a group of otherwise clinically healthy individuals following the same protocol as the stroke patients and comparing their time structure to that of clinically healthy ambulatory controls.

Keywords

Bedridden & Ambulatory Controls, Blood Pressure, Cerebral Infarction, Circadian Rhythm, Stroke

Introduction

It is well known that strokes follow circadian, circaseptan, and circannual patterns in incidence (Cornelissen et al., 1993, Elliott, 1998, Johansson et al., 1989, Manfredini R et al., 2005, Ramirez-Lassepas et al., 1980, Smolensky et al., 2005, 2014). The cardiovascular system has been closely associated with cerebral infarction (stroke), which can cause arrhythmias, other ECG abnormalities,

and changes in the circadian pattern of blood pressure (Eguchi et al., 2002, Klingelhofer & Sander, 1997). Because of the relationship the central nervous system has with other systems in the body, the original goal of the study was to determine whether any circadian disruption follows the stroke event and/or whether pre-existing circadian disruption underlined its manifestation.

The original investigators had already reported on the effect of cerebral infarction on the circadian periodicity of plasma cortisol (Ramirez-Lassepas et al., 1975). The evaluation of the cardiovascular data is presented in this article.

Subjects and Methods

To evaluate the circadian time structure in patients following an acute hemispheral cerebral infarction (HCI), clinically healthy controls who followed the same protocol of bedrest and parenteral feeding were also studied. In order to assess any changes in circadian time structure related to continued bedrest in health, some of the healthy controls were also examined while ambulatory. The study thus consisted of three groups: stroke patients, bedridden controls, and ambulatory controls (Table 1). After receiving information about the study, all participants were asked to sign a consent form.

Table 1: *Population Information on Stroke Patients, and on Bedridden and Ambulatory Controls.*

Group	Variables	Number	Sex	Age Range (yrs)	Study Span (hrs)	Time Interval (hrs)
Stroke Patients:	Clinical Data	8	3 Women, 5 Men	54 - 72	48 - 96	1 - 4
	Blood & Urine	12	4 Women, 8 Men	54 - 72	48 - 72	4
Bedridden Controls:	Clinical Data	12	6 Women, 6 Men	45 - 65	48	4
	Blood & Urine	12	6 Women, 6 Men	45 - 65	48	4
Ambulatory Controls:	Clinical Data	5	1 Woman, 4 Men	45 - 65	48	4
	Blood & Urine	5	1 Woman, 4 Men	45 - 65	48	4

Twelve stroke patients (4 women and 8 men) presented at St. Paul Ramsey Hospital (now Regions Hospital) with an acute hemispheral cerebral infarction (HCI) within twelve hours after onset of neurological symptoms. This was the first HCI in all 12 patients. The patients were seen in the Emergency Department before entering the study protocol. None of these patients suffered any severe alteration of neurological function or level of consciousness. They did not require any antihypertensive medications, corticosteroids, or osmotic diuretics. All patients were put on bedrest and administered the basic metabolic requirements of water, calories, and electrolytes parenterally for the entire duration of the study. The intravenous solution was 5% dextrose in one-half strength saline with the addition of potassium chloride. The patients' fluid intake and output was also recorded. The patients were followed for at least 48 hours and up to 96 hours in the study protocol.

Twelve bedridden controls (6 women and 6 men) were enlisted in the study. These subjects followed the same environmental changes as the patients, including 48 hours of bedrest at the hospital and only parenteral feeding with the same formulation as the patients. Like the patients, the head of the

bed could not be elevated more than 30°. All controls had a thorough physical examination, including electrocardiogram and chest X-ray. None of the controls were on any medications.

Not all 12 bedridden controls were able to participate as ambulatory controls, however; only five did return as ambulatory controls. They were monitored for 48 hours and were allowed to follow their usual physical activity. They were allowed to leave the hospital between sampling times during the day, but stayed overnight at the hospital for two nights, going to bed by 00:00 and rising before 08:00. Their rooms had windows with natural lighting and they could control the light themselves. They were provided a regular hospital cafeteria diet, which included different choices of meals. There were no food restrictions, except that they were asked not to eat between meals. All controls were told to refrain from drinking (alcohol), excessive exercise, and sex during the study.

All three groups had clinical data recorded along with the collection of blood and urine samples. Clinical measurements in the stroke patients were obtained at 1- to 4-hour intervals, depending on the individual patient. In both sets of controls, the clinical measurements were taken at 4-hour intervals for 48 hours, but the blood pressure and heart rate of ambulatory controls were only taken for 28 hours. All three groups had systolic (S) and diastolic (D) blood pressure (BP), heart rate (HR), and oral temperature (OT) measured. Mean arterial pressure (MAP [(SBP + (2 x DBP))/3]), pulse pressure (PP [SBP-DBP]), and pulse pressure product (PPP [(HR x SBP)/100]) were calculated from the SBP, DBP and HR data. The majority of patients and bedridden controls, but not the ambulatory controls, also had central venous pressure (CVP) and respiratory rate (RR) measured. The collection of clinical data in the patients started depending on the time they were admitted into the hospital and into the study. The collection of samples in the controls, whether bedridden or ambulatory, started at 20:00 on the first day and went until 16:00 on the third day.

All clinical data were analyzed from each patient and control subject by single cosinor and then summarized by population-mean cosinor (Halberg, 1980) for each variable in each group. For each variable, parameter tests (Bingham et al., 1982) were performed, comparing all three groups and then the stroke patients to the ambulatory controls and to the bedridden ridden controls; the bedridden controls were also compared to the ambulatory controls. The circadian characteristics of the 5 subjects monitored as ambulatory or bedridden controls were also compared by the parameter tests and paired t test.

Results

The results of the population-mean cosinor and the parameter tests show statistically significant differences in the MESOR, circadian amplitude and/or acrophase among the three groups, as shown in Figures 1-5. On a population basis, the stroke patients have a statistically significant circadian rhythm only in HR ($P = 0.047$), and a circadian rhythm of borderline statistical significance in DBP ($P = 0.055$). The bedridden controls have statistically significant rhythms in SBP ($P = 0.044$) and in MAP ($P = 0.040$). The ambulatory controls, despite their small sample size of 5, showed statistically significant rhythms in HR ($P = 0.036$) and PPP ($P = 0.026$).

Comparison of Stroke Patients to Bedridden and Ambulatory Controls

Figures 1a-c show the differences in MESOR and circadian amplitude found between the stroke patients and the two groups of controls. Figure 1a illustrates the significant difference in MESOR of SBP, DBP, and OT among all three groups. The difference in the MESOR of HR did not reach statistical significance ($P > 0.05$). When comparing the stroke patients to the bedridden controls,

there is a statistically significant difference in the MESOR of SBP, DBP, and OT, and a borderline statistically significant difference in the MESOR of HR (P = 0.054). Stroke patients differ from ambulatory controls in the MESOR of SBP and OT, the difference in DBP bordering significance (P = 0.052). The circadian amplitude of HR of ambulatory controls differs statistically significantly from that of the stroke patients and the bedridden controls. The circadian amplitude of OT differs statistically significantly between the stroke patients and the ambulatory controls.

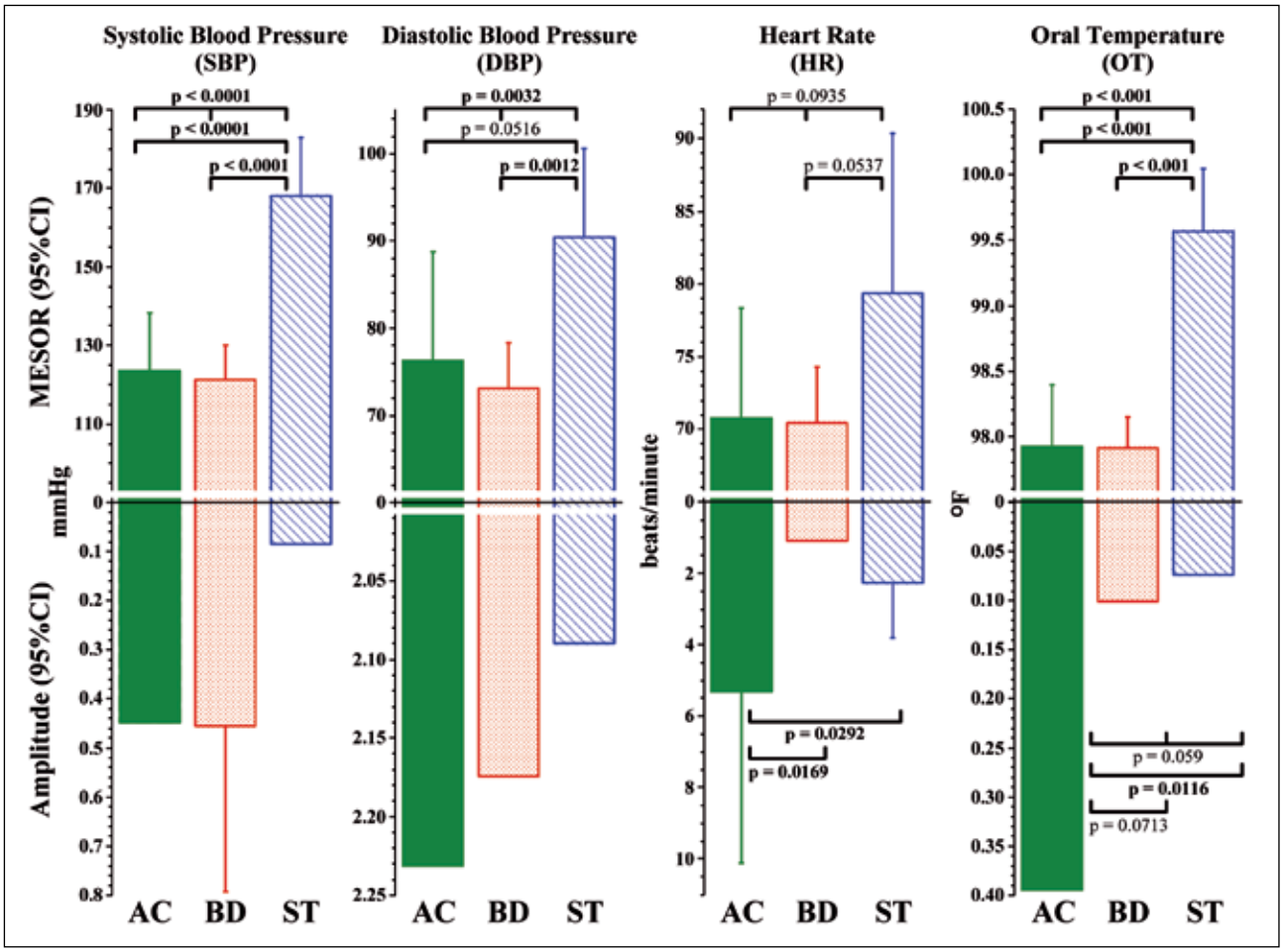

Figure 1a: *MESOR and circadian amplitude differences in SBP, DBP, HR, and OT between stroke patients (ST) in blue, bedridden controls (BD) in red, and ambulatory controls (AC) in green.*

The calculated variables, MAP, PP, and PPP, show statistically significant differences in MESOR among all three groups, as well as between stroke patients and either bedridden or ambulatory controls (Figure 1b). Differences in circadian amplitude were only statistically significant for PPP when comparing all three groups or ambulatory to bedridden controls.

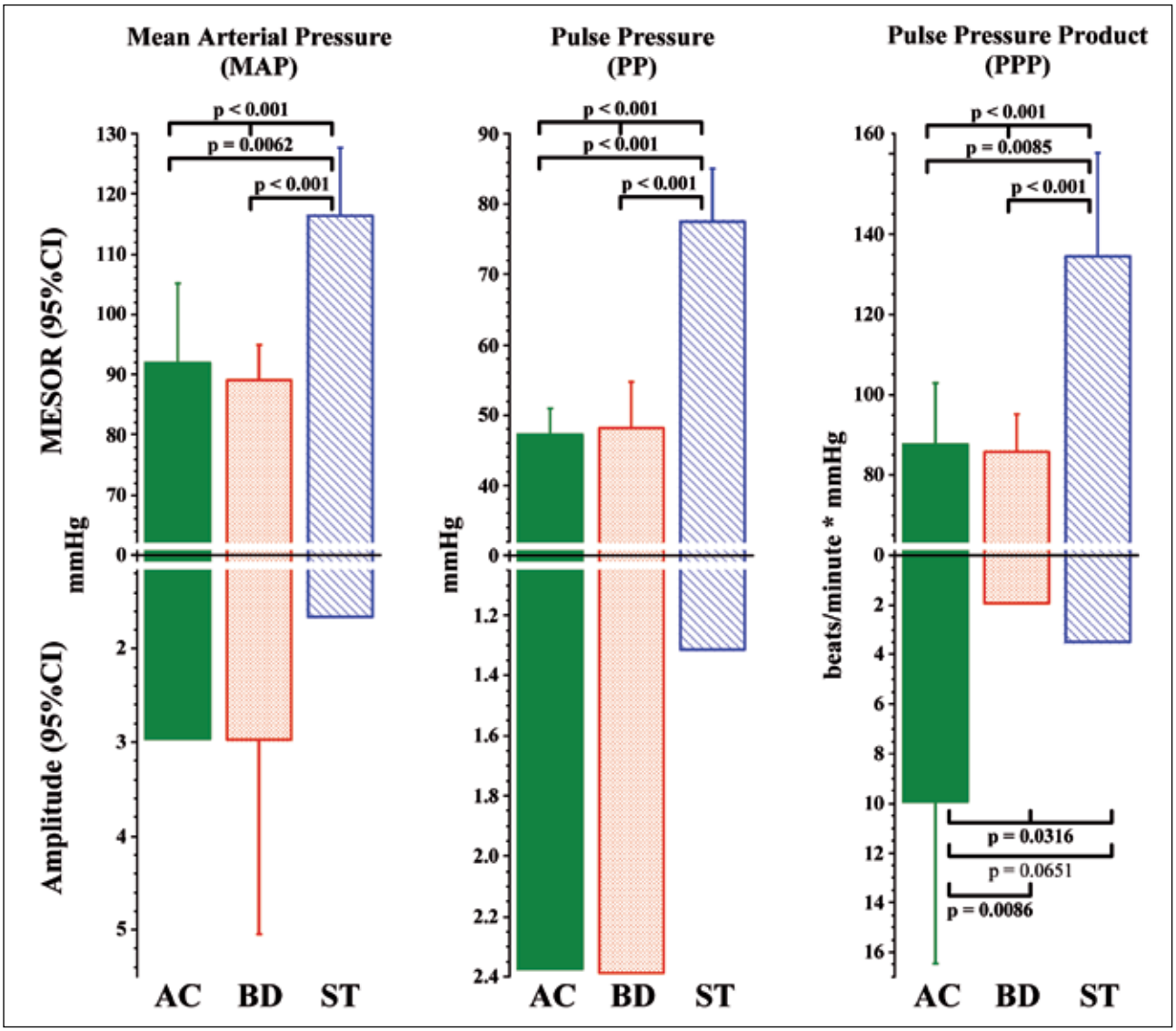

Figure 1b: *MESOR and circadian amplitude differences in MAP, PP, and PPP between ST, BD, and AC.*

There was only a statistically significant difference in the MESOR of RR (P = 0.012) between stroke patients and bedridden controls (Figure 1c), with no difference between those two groups in central venous pressure (CVP). These two variables did not show a statistically significant difference in circadian amplitude between the two groups.

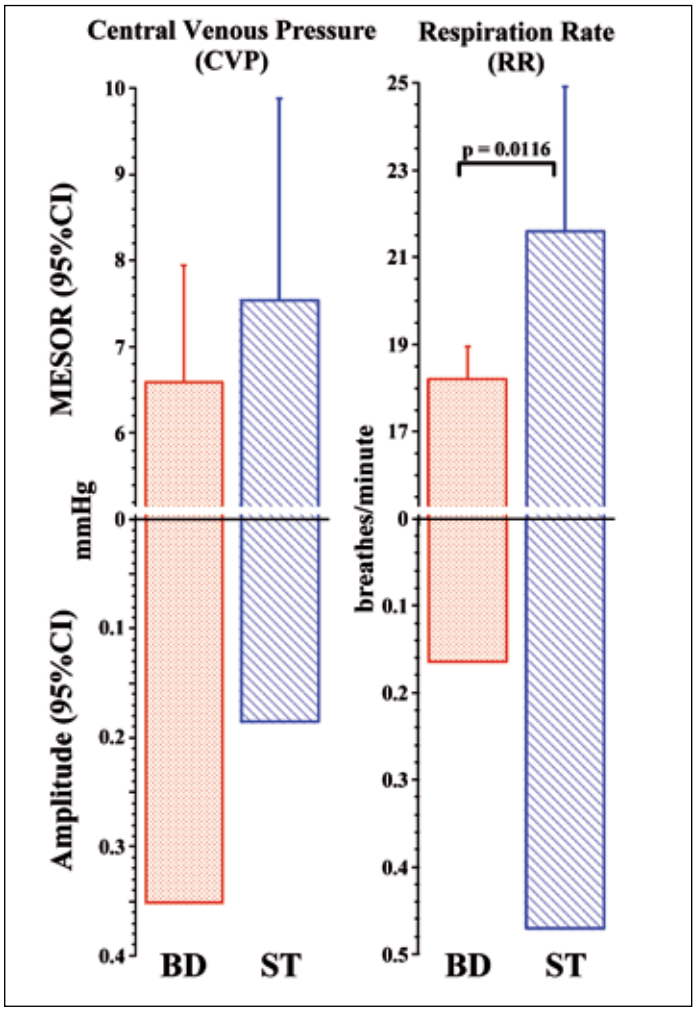

Figure 1c: *MESOR and circadian amplitude differences in CVP and RR between ST and BD.*

Figure 2 shows the large range of variability in the MESOR (top), circadian amplitude (middle) and acrophase (bottom) of HR (left) and OT (right) within each group. Population-mean cosinor estimates of the MESOR and circadian amplitude are shown as bars, within which individual estimates are displayed with a measure of their uncertainty. On the amplitude graphs, the solid horizontal line above the bar is the arithmetic mean (phase-unweighted average). As anticipated, it is larger than the phase-weighted average derived from the population-mean cosinor (height of bar). On the acrophase graphs, the top square in each section is the population estimate, followed by the individual acrophases for each participant shown as circles. All solid filled symbols (squares or circles) indicate statistical significance by single or population-mean cosinor; lightly colored ones indicate lack of statistical significance. The circadian acrophase of HR differs with statistical significance between the stroke patients and the ambulatory controls.

Figure 3 shows the population-mean cosinor results for HR and OT as polar plots. Ellipses represent 95% confidence regions for the joint estimation of the circadian amplitude and acrophase. They indicate the extent of inter-individual variation in each group. The confidence interval of the HR acrophase in both the stroke patients and the ambulatory controls is very large, covering 12 hrs 48 min in the stroke patients and 10 hrs 48 min in the ambulatory controls.

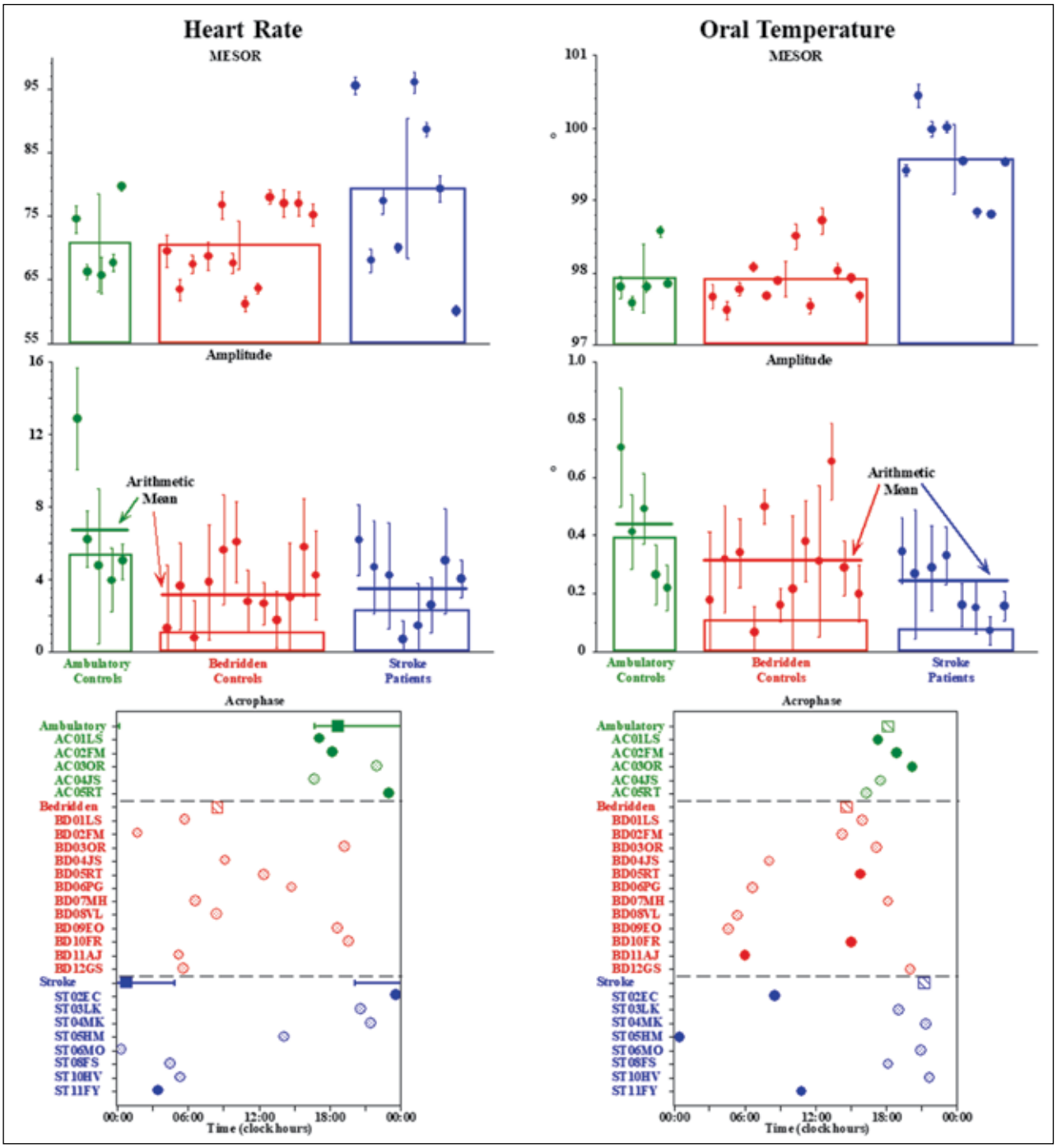

Figure 2: *Dispersion of individual estimates of MESOR, circadian amplitude and acrophase of HR and OT in ST, BD, and AC, shown with their standard error (MESOR, amplitude) or 95% confidence limits (acrophase), together with their respective population-mean cosinor estimates (bars). Note that population estimates of the amplitude are phase-weighted and are therefore smaller than the corresponding (phase-unweighted) arithmetic means shown as lines above the bars.*

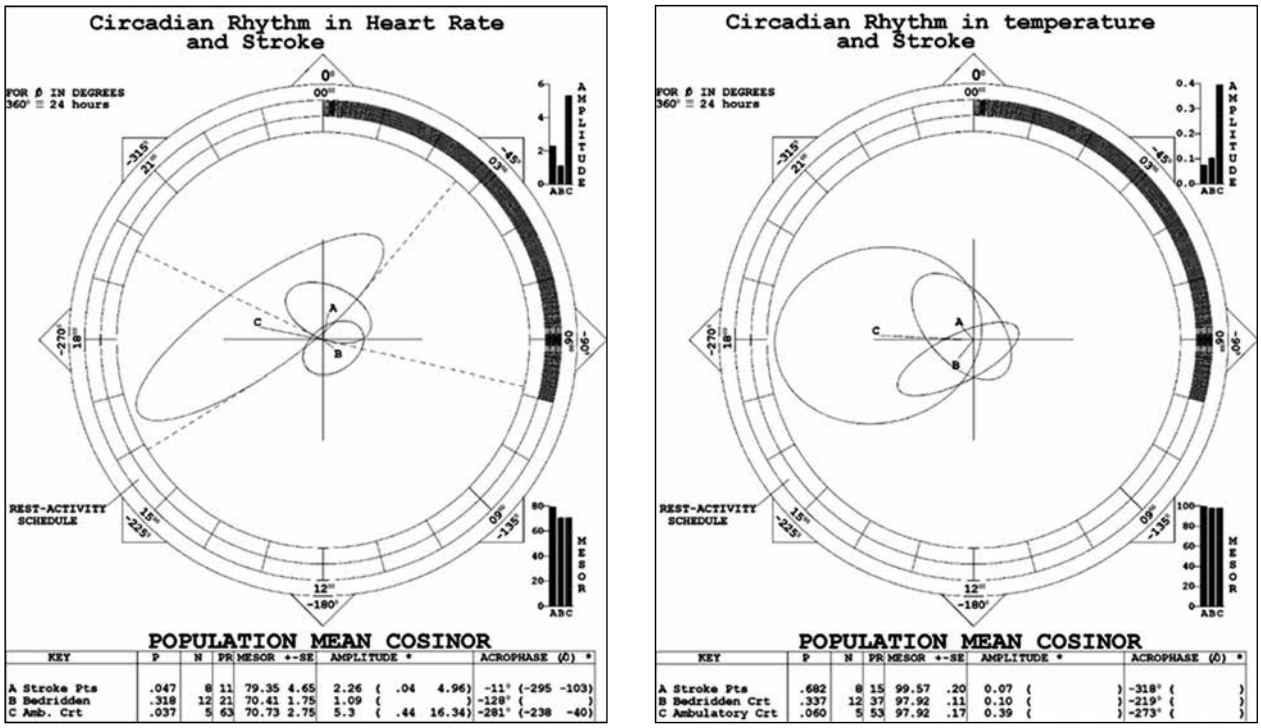

Figure 3: *Polar plots of HR (left) and OT (right) in ST, BD, and AC.*

Comparison of Stroke Patients to Bedridden Controls

To illustrate differences in the circadian time structure between the stroke patients (ST, blue) and the bedridden controls (BD, red), the respective 24-hour cosine models were displayed, using the parameter estimates from the population-mean cosinor (Figures 4a-c). In each graph, the ranges are kept the same on both vertical axes, but the scales were shifted since the MESORs may differ greatly between the two groups.

As seen in Figure 4a (left), stroke patients have a much higher SBP MESOR (168 vs. 121 mmHg) and a greatly dampened circadian variation (double amplitudes of 1.7 vs. 9.0 mmHg) as compared to the bedridden controls. Their DBP is also elevated (90.5 vs. 73.1 mmHg), but with a similar extent of daily change and an acrophase peaking 4 hrs and 44 min earlier than the bedridden controls (Figure 4a, right). SBP reached significance in the bedridden controls (P = 0.044) but not in the stroke patients (P = 0.906). Borderline statistical significance was reached for both stroke patients (P = 0.055) and bedridden controls (P = 0.061) in the case of DBP.

The circadian variation in HR and OT is almost in antiphase between the stroke patients and the bedridden controls (Figure 4b). The circadian acrophase of HR in the stroke patients is 7 hrs 48 min earlier than the bedridden controls, but their temperature acrophase occurs 6 hrs and 36 min later. Moreover, stroke patients have a higher MESOR of HR (79.3 vs. 70.4 beats/min) and OR (99.6 vs. 97.9 °F). No major difference in the circadian amplitude is noted between these two groups. The circadian rhythm of HR is statistically significant in the stroke patients (P = 0.047), but not in the bedridden controls (P = 0.315). On a population basis, a statistically significant rhythm in OT could not be demonstrated in either group.

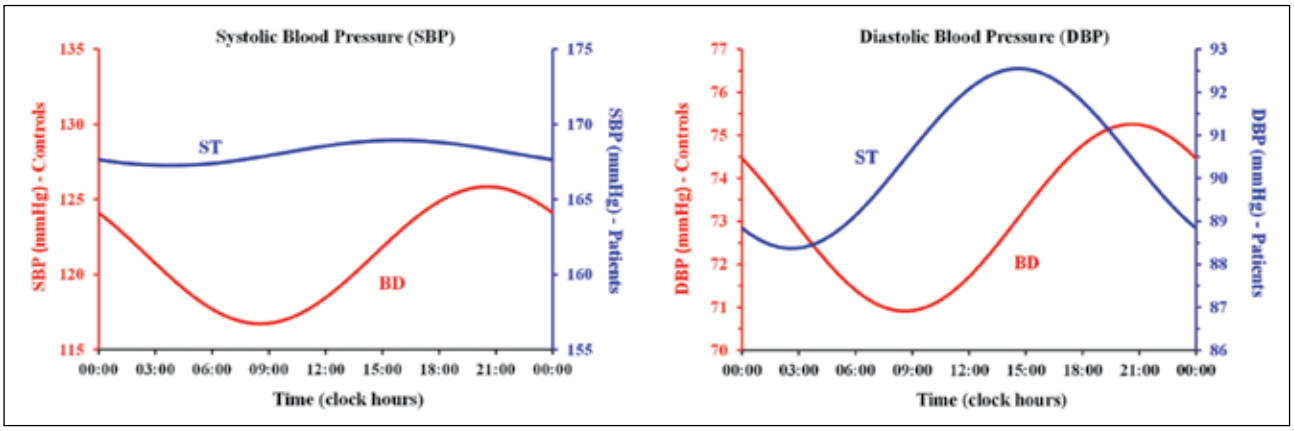

Figure 4a: *Differences in circadian profiles of SBP and DBP in ST and BD.*

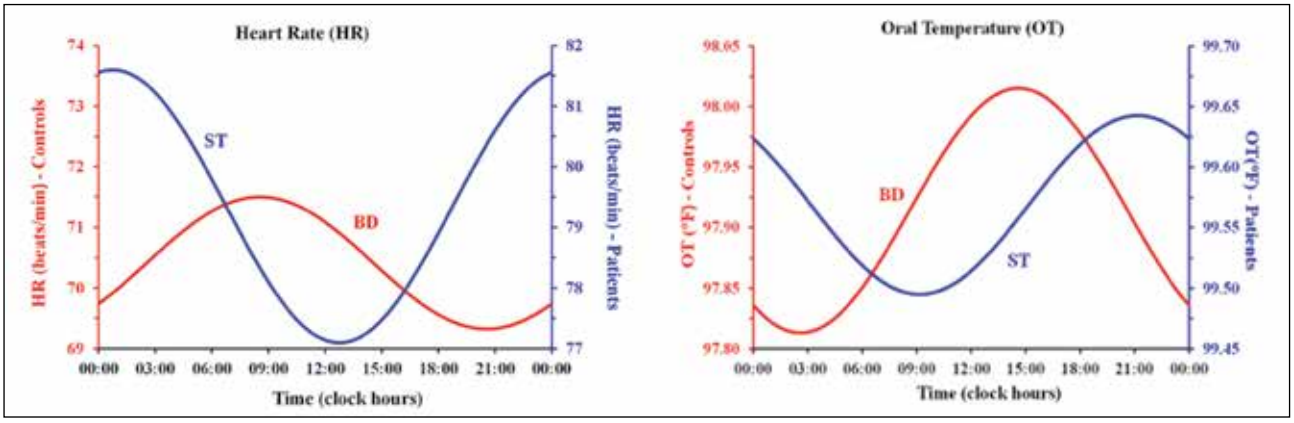

Figure 4b: *Differences in circadian profiles of HR and OT in ST and BD.*

In agreement with results for SBP, DBP, and HR, the MESOR of MAP, PP, and PPP is also higher in stroke patients as compared to bedridden controls (by 27 mmHg, 29 mmHg, and 49 mmHgxbeats/min%, respectively) (Figure 4c). The smaller circadian amplitude of MAP of the stroke patients as compared to the bedridden controls can be accounted for by their greatly dampened circadian variation in SBP. The larger circadian variation of HR in the stroke patients, combined with the almost opposite circadian variation of SBP and HR in the bedridden controls can account for the larger circadian variation of PPP in the stroke patients. As in the case of DBP, the circadian acrophase of MAP occurs earlier (by 5 hrs and 48 min) and that of PP occurs later (by 5 hrs 24 min) in the stroke patients as compared to the bedridden controls. A circadian rhythm could be demonstrated with statistical significance only for MAP in the bedridden controls ($P = 0.040$).

Similar to the other variables, the MESOR of CVP and RR is higher in the stroke patients as compared to the bedridden controls, Figure 1c. Stroke patients have only a 0.95 mmHg higher CVP MESOR than the bedridden controls, while their RR MESOR is 3.4 breaths/min higher. A circadian rhythm in these variables could not be detected with statistical significance.

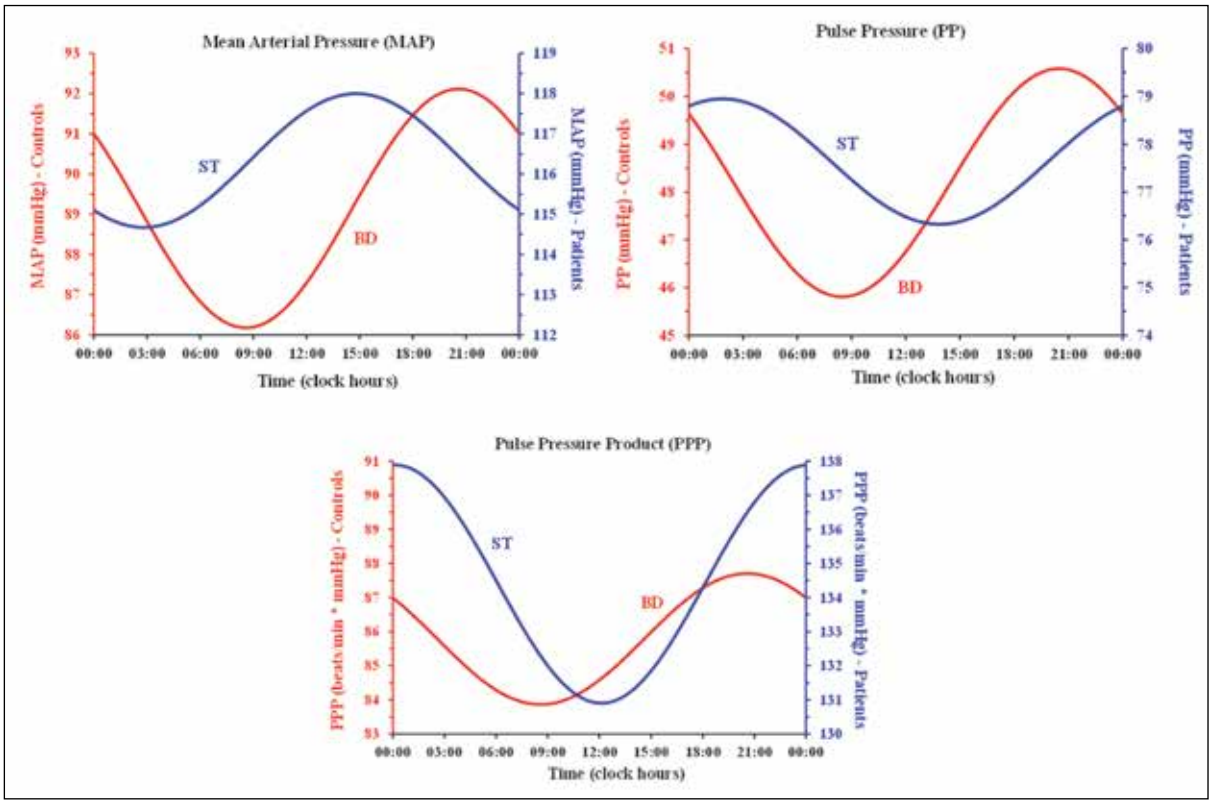

Figure 4c: *Differences in circadian profiles of MAP, PP, and PPP in ST and BD.*

Comparison of Bedridden and Ambulatory Controls

Figure 5a shows that ambulatory controls have a higher SBP MESOR than when they were bedridden, as could be anticipated. Similarly, their HR and PPP MESOR is also higher when they are ambulatory than when they are bedridden, Figure 5b. Moreover, the circadian amplitude of HR and PPP is also larger then, Figure 5b. Whereas the circadian acrophase of HR and PPP peaks in the afternoon, as expected, when ambulatory, they are greatly altered during bedrest, in part because a circadian rhythm cannot be detected with statistical significance in this case.

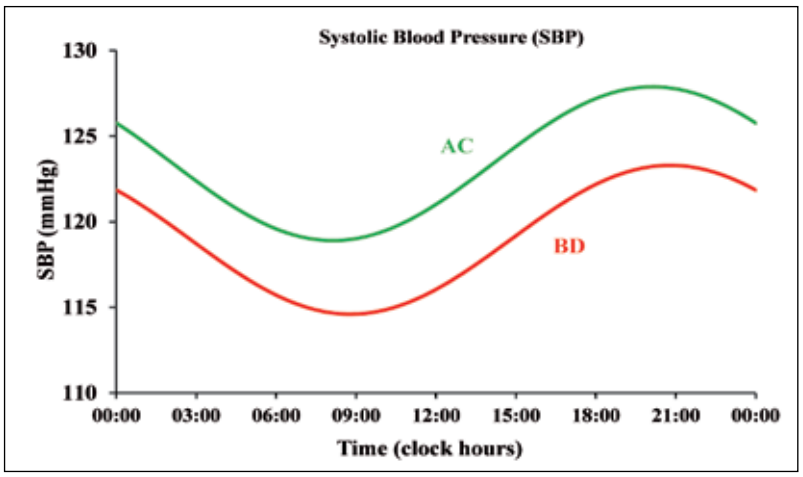

Figure 5a: *Differences in circadian profiles of SBP in BD and matched AC.*

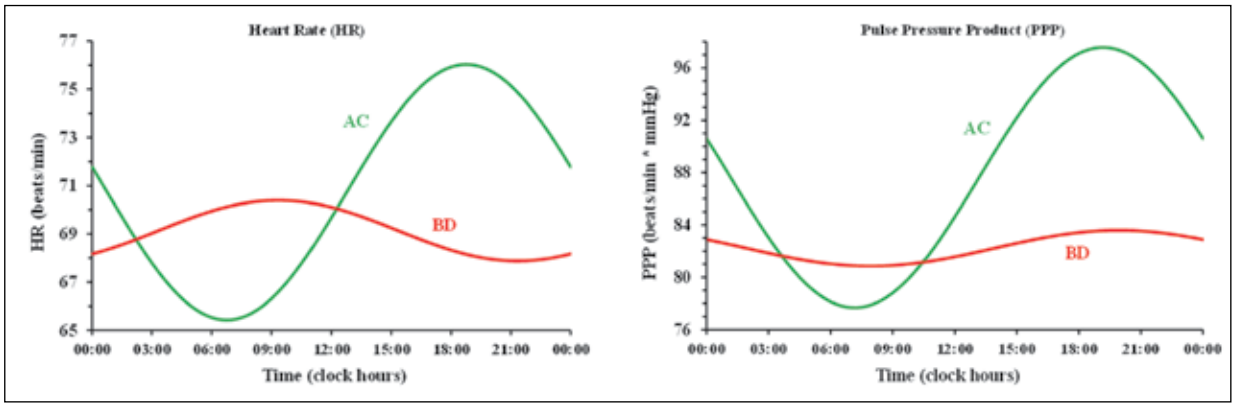

Figure 5b: *Differences in circadian profiles of HR (left) and PPP (right) in BD and matched AC.*

Discussion

It has been known that neurological changes occur after a cerebral infarction and other neurologic events, some causing neurologic dysfunction and even death. Even though not all non-neurologic alterations have been investigated, it is known that some of those changes occur in the cardiovascular system. This study aimed to go further to evaluate any changes/alterations in the circadian time structure of the cardiovascular system after a stroke. At the same time, there was the opportunity to also evaluate a group of clinically healthy bedridden controls of which a subgroup was willing to come back to be studied while ambulatory. Other investigators have studied the time structure in stroke patients, but without being able to study controls concomitantly.

A major shortcoming of this study was the lack of appropriate follow-up of the stroke patients. Long-term outcomes could have been associated with the extent of circadian rhythm alteration observed in almost all variables considered herein. It would have been interesting to learn how long it took for the circadian time structure to be restored in the stroke patients. Nevertheless, the study yielded some interesting results.

All stroke patients studied herein showed alterations in their circadian profiles as compared to clinically healthy subjects. The MESOR of their BP, HR, and OT was higher. Five of 8 stroke patients had temperatures up to 102 ˚F, with many over 100 ˚F occurring during the night time, a finding in need of further investigation since a review of the literature did not show any report of a reversed circadian temperature rhythm in stroke patients. On a population basis, a circadian acrophase of oral temperature occurring during the night is to be aligned with a circadian acrophase of heart rate also occurring during the night in stroke patients. An elevated heart rate has been associated with advanced white matter lesions in ischemic stroke patients (Kwon et al., 2014), but this study does not mention anything about the circadian timing of heart rate in these patients. A reversal or dampening of the circadian variation in heart rate was reported, however, post-stroke in a rat model (Tabuchi et al., 2001). Other differences in the circadian characteristics of stroke patients as compared to bedridden or ambulatory controls are difficult to interpret in view of the small number of study participants, the relatively short duration of monitoring done by staff rather than with automated devices, and the failure to invariably detect a statistically significant circadian rhythm in all variables considered herein. At the time of the study, ambulatory blood pressure monitors (ABPM) were not yet available.

Other alterations in the circadian characteristics observed in the stroke patients include an elevated blood pressure, in agreement with previous reports. High blood pressure in acute stroke is reported to

be elevated in up to 75% to 82% of cases (Chalmers, 2005; Willmot et al., 2004). Survivors of stroke, both hypertensive and non-hypertensive patients, also reportedly present a chronic disruption of their circadian blood pressure rhythm (Castilla-Guerra et al., 2009). Differences in the circadian amplitude and/or acrophase are compatible with the fact that the patients were bedridden and fed parenterally. The major alterations in the circadian time structure of these patients may relate primarily to the hemispheral cerebral infarction, as previously suggested (Klingelhöfer & Sander, 1997). The patients were not on any antihypertensive medication prior to the stroke and did not have a prior event.

Other studies have indicated that an altered circadian rhythm in blood pressure, notably an excessive circadian amplitude of blood pressure, is predictive of ischemic cerebral events (Otsuka et al., 1996, 1997). Patients with intra-cerebral hemorrhage were reported to have a higher incidence of abnormal circadian characteristics of blood pressure than patients with cerebral infarction, the major differences relating to a larger circadian amplitude of systolic blood pressure, a smaller standard deviation of heart rate, and a larger incidence of circadian acrophases of diastolic blood pressure occurring at times outside prediction limits in health (Jiang et al., 2010). Future studies could follow-up patients found to be at a higher risk of stroke, so that those who will suffer an adverse event could be monitored more thoroughly, preferably by ABPM immediately after a stroke event and at intervals thereafter, so that longitudinal changes in the circadian time structure of their clinical variables can be mapped. Information to be derived from such studies could then shed light on any additional treatment measures that may help their full recovery.

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Prof. MUDr. Bohumil Fiser, CSc. (22. 10. 1943 – 21. 3. 2011) Studied the Whole Live Baroreflex Sensitivity and Chronobiology

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In this year 2018 we remember 75 years from the birth of Prof. Bohumil Fiser. In the Department of Physiology as a young scientist he started the work together with Prof. Jan Penaz, who discovered the volume clamp methods of beat to beat measurement of blood pressure.

This measurement also gave Prof. Fiser the opportunity to study the role of baroreflex.

Many scientists thought that the role of hypertension is negligible despite the fact that baroreflex is the most important regulatory mechanism of blood pressure. This opinion was supported by the observation of baroreflex resetting. The resetting is in other words the shift of the curve of the relationship between carotid sinus pressure and systemic arterial pressure to the higher values of systemic arterial pressure. But this opinion was not shared by all scientists; the most prominent opponent Professor Slight claimed that it is clear that all forms of hypertension – whether primary or secondary to renal, hormonal, or environmental influences – have a neurogenic component. More recent evidence suggests that neural mechanisms, particularly impairment of arterial baroreflexes, play an important part.

In the recent years the long-term control of blood pressure was re-evaluated. The recent opinion is based on chronic electrical stimulation of carotid baroreceptor afferent fibers, on re-evaluation of time of chronic resetting lasting several days according to the more recent experiments. Furthermore decreased baroreflex gain appears to precede hypertension.

Years ago baroreflex sensitivity was regarded to correspond to the capability of the parasympathetic nervous system to react to a gross stimulus and thus concerns primarily vagal reflexes. Prof. Bohumil Fiser measured baroreflex heart rate sensitivity in ms/mmHg and it was the adequate method to study the blood pressure control function of baroreflex. The determination of baroreflex gain was necessary and Prof. Fiser used different methods of analysis of baroreflex in man.

The founder of modern chronobiology professor Franz Halberg demonstrated many years ago that the reliable diagnosis of blood pressure disorders can be performed on the basis of 24 hours of blood pressure monitoring at least. The recent Prof. Halberg studies suggest seven days monitoring to obtain a reliable estimates.

One of the study of Professor Fiser indicated the necessity to re-evaluate the role of the blood pressure decrease during the night.

Because the process of resetting lasts about 48 hours, the night decrease of blood pressure influences the baroreflex resetting. The normal chronobiology of blood pressure is therefore a factor protecting against hypertension.

This results of barorreflex sensitivity obtained by Prof. Fiser showed the necessity of studying chronobiology of autonomous nervous system using analysis of biological oscillation in man in health and disease, as was also presented in the 10th ESGCO (European Study Group on Cardiovasculation Oscillation, September 17th-19th 2018, Vienna, Austria), organized by Prof. Maximilian Moser,

University of Graz, Austria. In the future we will continue Bohumil Fiser studies and we will never forget him.

Figure 1: *Professor MUDr. Jan Penaz, CSc. and Professor MUDr. Bohumil Fiser, CSc. in Congress of Noninvasive Methods in Cardiology 1994, Brno*

Figure 2: *Professor MUDr. Bohumil Fiser, CSc., MUDr. Jiri Dusek, CSc., Professor MUDr. Jarmila Siegelova, DrSc. in Congress 7th European Meeting on Hypertension, Milan, Italy 1995*

Figure 3: *Baroreflex studies in Paris, Dept. of Physiology, Medical Faculty of Paris VII in 1995, from the right Professor Dr. Jean-Paul Martineaud, Paris, Professor MUDr. Jarmila Siegelova, DrSc., MUDr. Jiri Dusek, CSc., Professor Dr. Etienne Savin, Paris, Professor MUDr. Bohumil Fiser, CSc. and Dr. Philipe Bonnin*

Figure 4: *Chronobiological study of blood pressure in University of Minnesota, USA, 1995, From the right MUDr. Jiri Dusek, CSc., Professor MUDr. Jarmila Siegelova, DrSc., Professor Dr. Franz Halberg, USA, Professor Dr. Germaine Cornelissen, USA, Dr. Anna Portela, Spain and Professor MUDr. Bohumil Fiser, CSc.*

Figure 5: *Professor MUDr. Jarmila Siegelova, DrSc., Professor Thomas Kenner, M.D. dr.h.c. mult., University Graz, Austria and Professor MUDr. Bohumil Fiser, CSc., in Symposium in Graz, Austria, 2006*

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Influence of Compression Aids on Baroreflex in Patients after Cervical Spinal Cord Injury

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Key words

Cervical spinal cord injury, orthostatic hypotension, baroreflex, compression aids

Introduction

Patients after cervical spinal cord injury (SCI) suffer not only from senso-motoric deficit but also from autonomic dysfunction (Weaver and Polosa, 2005). These factors significantly influence cardiovascular system and blood pressure regulation resulting in resting as well as in orthostatic hypotension (OH) (Claydon et al., 2006). Verticalization as an important part of rehabilitation has positive effect on physical and psychical condition of patients and symptoms associated with OH negatively interfere with the rehabilitation of SCI patients.

Hemodynamics in cervical SCI is impaired on many levels. Although parasympathetic nerves regulating heart are anatomically intact, cervical spinal cord lesion interrupts sympathetic neural pathways. Loss of supraspinal control over the splanchnic and lower limbs significantly decreases total peripheral vascular resistance, which defines arterial BP (Weaver et al., 2012). The lacks of muscle pump activity in the lower limbs culminates in venous blood pooling in the legs with a risk of venous distension, venous valve insufficiency, blood stasis and increased risk of deep venous thrombosis (Popa et al., 2010). All these factors decrease venous return into the heart and consequently stroke volume (Hopman et al., 1998; Rimaud et al., 2012). Moreover lack of sympathetic chronotropic and inotropic effect cannot increase cardiac output in case of BP drop. Problem with maintenance of arterial BP during orthostasis influences cerebral blood flow, which is subjectively perceived as OH symptoms, like light-headedness, dizziness, blurred vision etc. in extreme ending as syncope (Chao and Cheing, 2008; Claydon et al., 2006).

Compression over-knee stockings are used as non-pharmacological prevention of deep venous thrombosis, venous insufficiency, orthostatic hypotension and edema formation in lower limbs not only in SCI patients (Ibegbuna et al., 1997; Popa et al., 2010; Rimaud et al., 2012, 2008).

Effect of compression aids to baroreflex function in SCI was never studied yet. Baroreflex is short-term regulatory mechanism of arterial BP regulation. BP is changed by heart rate (HR) and total peripheral vascular resistance (TPR) and it is very important during orthostatic challenge. Sympathetic vascular branch of baroreflex is clearly impaired by cervical spinal lesion. However cardiac baroreflex should be partially preserved due to intact vagal nerves (Krassioukov and Claydon, 2006; Weaver et al., 2012).

Cardiac baroreflex function can be estimated as an interaction between inter-beat intervals (IBI) and systolic blood pressure (SBP). Baroreflex sensitivity (BRS), defined as change of IBI caused by change of SBP by 1 mmHg, was the largely studied baroreflex function parameter in SCI (Phillips et al., 2012). Coherence is parameter of synchronicity between IBI and SBP mediated by baroreflex. In our previous paper we showed, during orthostasis cardiac baroreflex function parameters correlated with the spinal lesion level: the higher level of the spinal lesion, the lower coherence and BRS (Ondrusova et al., 2017).

This paper focused on effect of compression aids on cardiac baroreflex function in cervical SCI, because these patients usually suffer from OH. Because baroreflex control over blood pressure during orthostasis is impaired in cervical SCI, we hypothesize compression aids help to improve not only blood pressure but also causal coherence and BRS.

Methods

Subjects

The study was approved by Ethic committee of Faculty of Medicine, Masaryk University Brno. All subjects included in the study signed informed consent and were informed about the aims of this study and about used examination methods.

Patients with transversal spinal cord lesion (CSCI) in segments C5-C7 of trauma etiology were included in this study. All patients were classified as AIS A (Krishna et al., 2014). Total of 10 patients (9 men, 1 woman) were examined, aged 18 - 35 years. Time from spinal cord injury varied from 2 to 12 years. BMI: 22±5 kg/m2. All examined subjects were in chronic stage of SCI and they were stabilized, without acute health problems, without such kind of medication which might affect the results of measurement.

Experimental protocols

The study protocol consisted of four phases:

1) 10 minutes at rest in sitting position on a wheelchair without compression aids,
2) 8 – 10 minutes in the orthostatic phase without compression aids
3) 8 – 10 minutes in the orthostatic phase using compression aids.

Between phase 2 and 3, at least ten minutes resting phase in wheelchair was placed. Phase 2 and 3 were performed in random order and more times in consequent days, if it was necessary.

During each phase arterial blood pressure was measured continuously using the non-invasive volume-clamp plethysmography method (Finometer, FMS, Netherlands). Compression aids consisted of abdominal corset and elastic compression stockings (Loana Lonaris Cotton, Czech Republic, 19 - 21 mmHg). Upright position during orthostatic phases was ensured by verticalizer Balance Thera-trainer (Medica Medizintechnik GmbH, Germany). The patients reviewed their subjective feelings during orthostatic positions (presence of OH symptoms).

Data analysis

Sequences of systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse pressure (PP) and inter-beat intervals (IBI) were detected beat-to-beat from the continuous BP signal. Inter-beat interval was defined as a time interval between two neighbouring local BP minima corresponding to diastolic BP. For other analysis 300 samples long sequences were used.

IBI and SBP interact in closed-loop containing two directions of variability transfer: from SBP to IBI (baroreflex direction mediated by neural pathways) and from IBI to SBP (mechanically given non-baroreflex direction). Bivariate autoregressive model was used to mathematically open closed-loop IBI - SBP interaction and evaluate only causal baroreflex pathway (Faes and Nollo, 2010; Porta et al., 2002). Two important variables were computed: causal coherence Cohsbp ibi representing the strength of linear coupling from SBP to IBI and gain of transfer function from SBP to IBI containing causal coherence is an assessment of baroreflex sensitivity (BRS).

Because of the non-Gaussian data distribution and small number of patients, non-parametric analysis was performed. Median (lower quartile, upper quartile) of each analyzed parameter was calculated for each phase. Each combination of two phases was compared and difference between two phases was evaluated by pair Wilcoxon test.

Results

Compared to the rest, IBI significantly decreased during both orthostatic phases (Fig 1). SBP, DBP and PP significantly decreased only during orthostasis without compression aids. While Coh sbp ibi did not change, BRS decreased during both orthostatic phases as compared to the rest (Fig 2).

When patients used compression aids during orthostasis, SBP, PP and Coh sbp ibi were significantly higher than in orthostatic phase without using compression aids. Likewise BRS was higher when compression aids were used, but difference was borderline significant (p = 0.059). DBP and IBI were not significantly influenced by compression aids.

According to the subjective description of orthostatic symptoms, patients can be divided in two groups. Five patients did not suffer from OH symptoms regardless to using of compression aids. Other five patients felt better tolerance to OH (lowered intensity of OH symptoms) when compression aids were used.

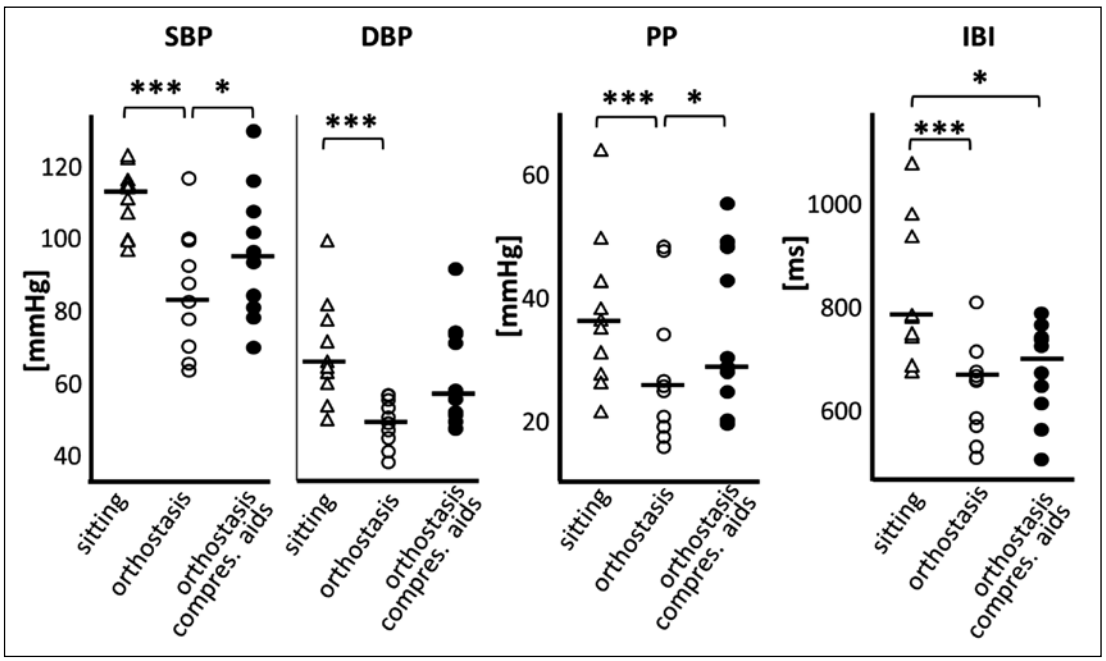

Figure 1: *Systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse pressure (PP) and inter-beat intervals (IBI) during sitting, during orthostasis without compression aids and during orthostasis, when*

compression aids were used. Short horizontal line represents median.Significance (Wilcoxon test): p < 0.05, p < 0.01**, p < 0.001***.*

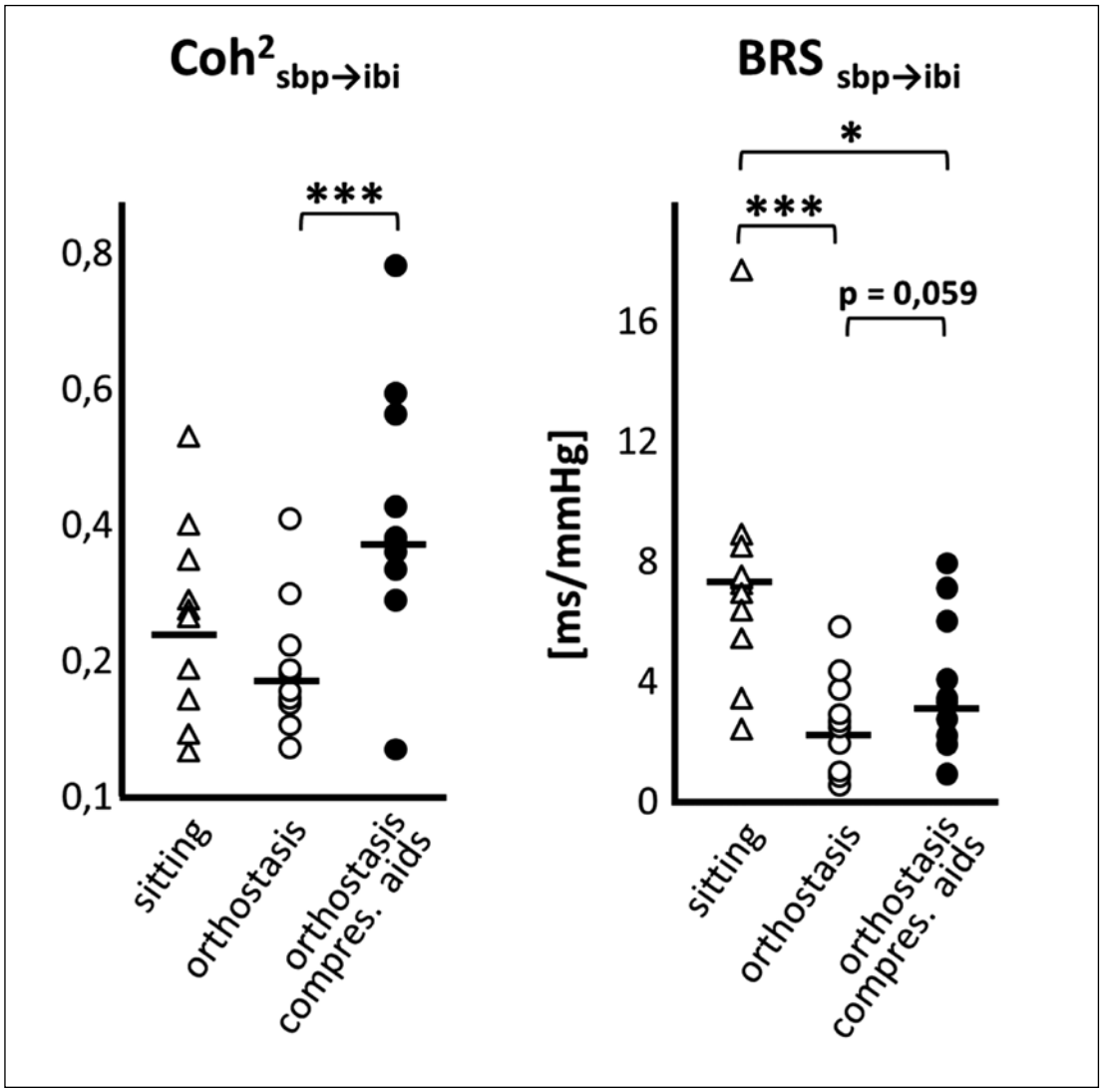

Figure 2: *Causal coherence (Coh2sbp→ibi) and baroreflex sensitivity (BRSsbp−ibi) during sitting, during orthostasis without compression aids and during orthostasis, when compression aids were used. Short horizontal line represents median. Significance (Wilcoxon test): p < 0.05*, p < 0.001***.*

Discussion

Blood pressure control changes during orthostatic challenge

Present study focused on effect of compression aids on basic cardiovascular parameters and baroreflex function during orthostatic challenge in patients afters cervical SCI. Arterial BP is defined by stroke volume, total peripheral resistance and heart rate. Regulation of all these variables is influenced by cervical SCI (Claydon et al., 2006; Krassioukov and Claydon, 2006). Loss of sympathetic supraspinal control over the most of vessel system led to the blood redistribution in arterial as well as in venous system during the verticalization of SCI patients (Weaver et al., 2012). Impaired mechanisms of venous return, decreased heart filling and therefore decreased stroke volume manifested as decreased PP in

CSCI. Decreased venous return accompanied by low peripheral resistance led to significant arterial BP decrease in upper part of body during orthostasis (Popa et al., 2010). Vagal branch of baroreflex was anatomically intact therefore suppression of cardiovagal activity via baroreflex increased heart rate (Phillips et al., 2012), but heart rate increase was insufficient to prevent BP drop.

Compression stockings are usually used to prevent blood stasis, deep venous thrombosis, venous distension (Chao and Cheing, 2008; West et al., 2012; Wieling and Groothuis, 2012). These effects of compression aids helped to increase venous return and in consequence stroke volume. Several authors have explored the options of blood-redistribution in SCI during exercise or body-position change during physiotherapy to improve performance or to limit post-exercise hypotension and/or OH, decrease venous capacitance in SCI patients who are not able to adjust their hemodynamics (Hopman et al., 1998; Houtman et al., 1999; Popa et al., 2010; Rimaud et al., 2008). In this study compression aids prevented to significant BP drop during orthostasis. Significantly higher SBP and PP during orthostasis with compression aids supported assumption of increased venous return and heart filling.

Changes in cardiovagal baroreflex function

Baroreflex is a most important short term-mechanism controlling BP during orthostatic challenge. Parameters of baroreflex function, Coh2sbp→ibi and BRS, suggested cardiac baroreflex impairment during orthostasis in CSCI. Previous studies in healthy able-bodied showed, that Coh2sbp ibi, and other parameters of causal SBP-IBI coupling mediated by baroreflex were low in resting supine or sitting position and it increased during orthostasis (Faes et al., 2013; Ondrusova et al., 2017; Porta et al., 2002, 2011). Unchanged Coh2sbp→ibi in CSCI during orthostasis was probably given by suppression of vagal control of the sinoatrial node in CSCI caused dysfunction of cardiac baroreflex information transfer from SBP to IBI.

Decrease of BRS can be explained on the graph in Fig 3, where the BRS is shown as curve slope of IBI in dependence on the SBP. Slope of IBI-SBP curve is relatively linear in physiological BP range, i.e. in baroreflex operating range. Slope of curve decreased in area of extremely decreased SBP. BP and BRS in CSCI were in physiological values during sitting. Verticalization caused significant BP decrease to a curve area with lower slope, i.e. lover BRS.

Improved BP during orthostasis with compression aids was accompanied by the increase of Coh2sbp→ibi and dampening of BRS decrease. Compression aids likely dampened suppression of vagal control over the heart which increased coupling between SBP and IBI and improve information transfer via cardiovagal baroreflex. However in case of BRS, probably slight improving of BP caused shift to the right in the IBI-SBP curve, i. e. to the interval with higher slope (Parlow et al., 1995). This shift was observed as a significant BRS increase, when compression aids were used during orthostasis in compare to the orthostasis without compression aids (Fig 3). In other words, function of BRS was probably unchanged in cervical SCI, but operation point in the function was shifted by BP drop from the physiological values to the area with low slope of curve.

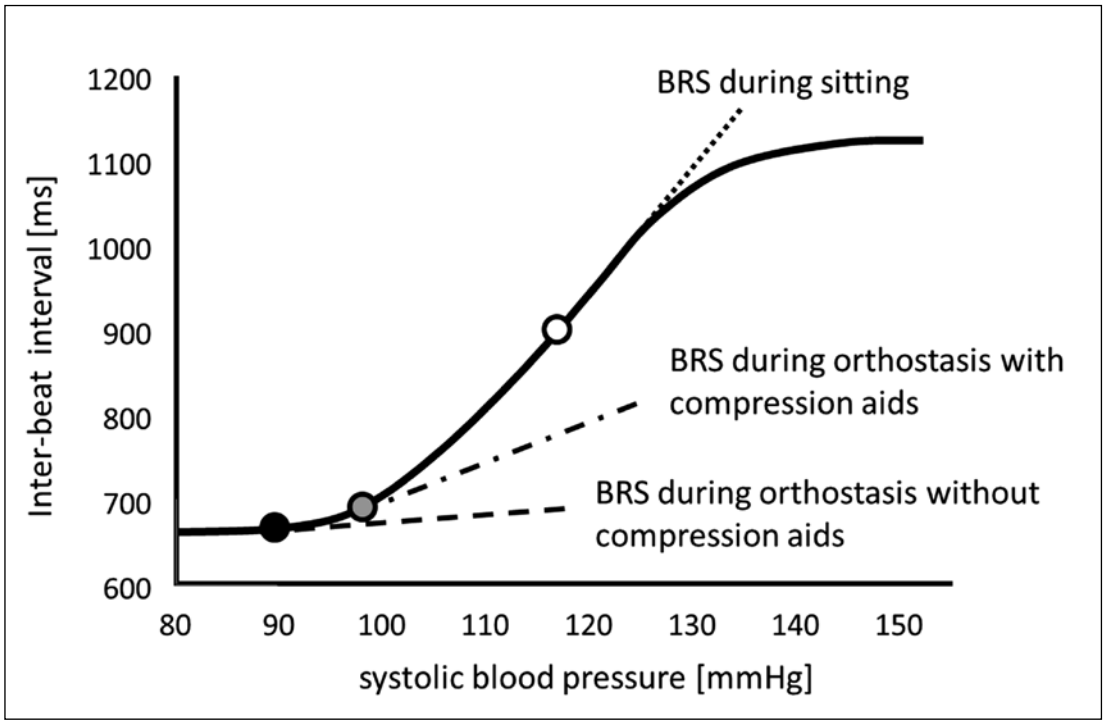

Figure 3: *Dependence of IBI on SBP. BRS is defined as a slope of this curve. Three phases of measurement of CSCI patients are marked as point on a curve. Graph modified from publications (Parlow et al., 1995).*

Subjective feeling of patients

Five SCI patients did not feel symptoms of OH regardless on compression aids. Another five patients felt significant improvement, when compression aids were used during orthostasis.

We suppose that resistance to the OH and its consequences is individual. Firstly spinal cord lesion of patients was transversally large but incomplete. Position of the lesion and its intervention to the autonomic neural pathways is therefore individual (Weaver and Polosa, 2005). Secondly, effectiveness of cerebral blood flow regulatory mechanisms influencing presence of OH symptoms could be variable (Weaver et al., 2012). Some author suggested that autoregulation of cerebral blood flow rather than systemic BP control plays a dominant role in the adaptation to OH in patients with SCI. (Bisharat et al., 2002; Claydon et al., 2006; Gonzalez et al., 1991).

Conclusion

Cervical SCI patients often suffer from OH given by loss of sympathetic supraspinal control. OH symptoms significantly interfere during physiotherapy and limit the patient‘s daily activities. Problem with BP regulation cannot be fully solve without the change of arterial peripheral resistance, but compression aids are able to prevent considerable BP drop during orthostasis and dampened baroreflex parameters decrease. However baroreflex function probably was not changed, only operation point of in SBP-IBI relationship was shifted by OH. Method of BRS and coherence evaluation respecting causality of SBP-IBI interaction showed sensitive enough to detect positive effect of compression aids to the cardiac baroreflex BP regulation.

Acknowledgment

MUNI/A/1157/2017, VEGA č.1/0117/17, APVV-0235-12 and ITMS project "BioMed Martin" no. ITMS 26220220187.

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Seven Day/24-h Ambulatory Blood Pressure Monitoring in Night Shift Workers

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Introduction

Franz Halberg and Germaine Cornelissen using ambulatory blood pressure monitoring showed the need to account day-to-day changes of blood pressure and heart rate and the necessity to circadian assessment of the hour-to- hour variability in cardiovascular parameters. Together with the Chronobiology Center of Minnesota we participate in the international project BIOCOS. The presentation in 2018 adds new results to this project BIOCOS (1,2,3,4,5,6).

Shift work schedule involving irregular or unusual hours, is becoming popular among people because of the high demand for flexibility and productivity in the workforce in modern society (7). It is reported that 15-30% of workers in America and Europe are engaged in different degrees of shift work, and the trend is increasing rapidly (8,9).

The purpose of the study

The aim of the study was to compare the 7-day/24-h blood pressure monitoring in healthy subjects and nurses working in day and night work shifts.

Methods

We examined 297 healthy subjects and 6 women (age 33 ± 12 years, body weight 70 ± 21 kg, mean height 165 ± 5 cm) and 4 men (age 28 ± 7 years, body weight 93 ± 11 kg, mean height 185 ± 5 cm).

The monitoring week in nurses was composed from the days with day work, days with night work and free days.

During the monitoring we evaluate the sleep time in different days in every nurse.

The subjects and nurses were recruited for seven-day ambulatory blood pressure monitoring.

Medical Instruments TM2431 (A&D, Japan) were used for ambulatory blood pressure monitoring (oscillation method). One-hour means of systolic and diastolic blood pressure were evaluated. We calculated mean systolic and diastolic blood pressure for seven days and every 24-hour profile.

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

Results

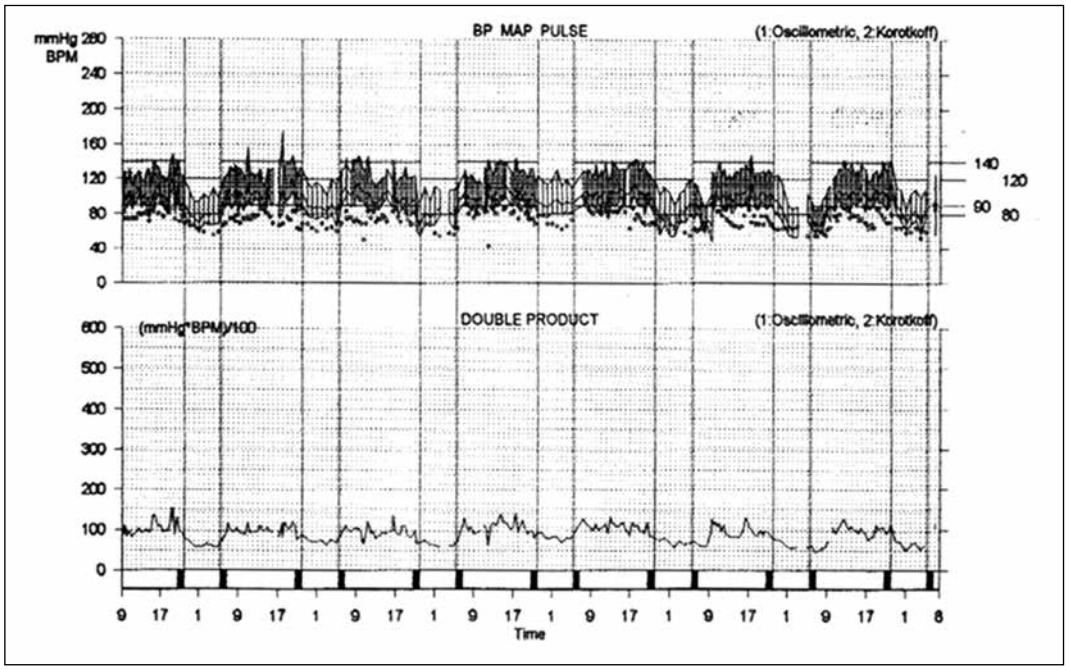

Figure 1: *Seven day /24-h blood pressure profile in healthy subject is shown in Fig. 1 and we can see circadian rhythm in blood pressure and double product*

In Fig. 1 is presented the record from seven day/24-h blood pressure monitoring in healthy subject with regular sleep. In the upper part we can see blood pressure (mmHg) and heart rate (b.p.m.), in the lower part double product (mmHg.bpm/100). In both parts of the record in one week (time in h) we can see the presence of circadian rhythm in cardiovascular parameters, increase during daytime and decrease at night.

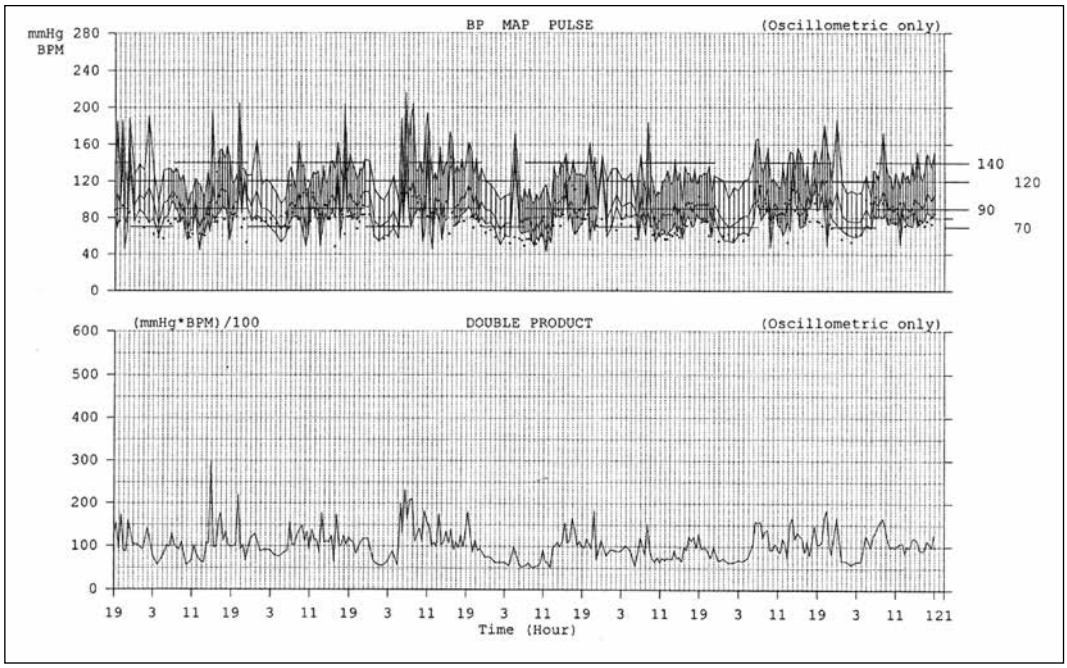

Figure 2: *Seven day /24-h blood pressure profile in nurse is shown in Fig. 2. We cannot see circadian rhythm in blood pressure and double product*

Fig.2 is showing record from seven day/24-h blood pressure monitoring in nurse (women) with shift work with irregular sleep. In the upper part we can see blood pressure (mmHg) and heart rate (b.p.m.), in the lower part double product (mmHg.bpm/100). In both parts of the record in one week (time in h) we can see the impairment of circadian rhythm in cardiovascular parameters.

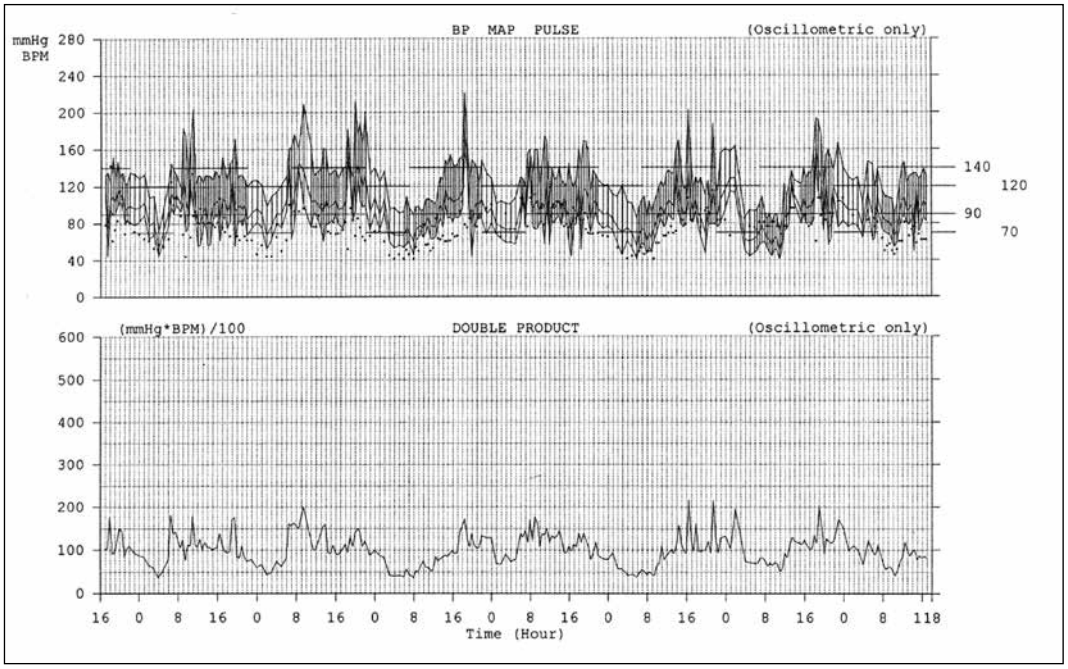

Figure 3: *Seven day /24-h blood pressure profile in nurse is shown in Fig. 3. We cannot see circadian rhythm in blood pressure and double product*

In Fig. 3 is presented the record from seven day/24-h blood pressure monitoring in nurse (man) with shift work with irregular sleep. In the upper part we can see blood pressure (mmHg) and heart rate (b.p.m.), in the lower part double product (mmHg.bpm/100). In both parts of the record in one week (time in h) we can see the impairment in circadian rhythm of cardiovascular parameters.

Tab. 1: *Working shifts in different days of 7 day/24-h blood pressure monitoring*

	DAY OF WEEK						
nurse No	1	2	3	4	5	6	7
1W	N	F	F	F	N	F	D
2W	D	N	F	F	D	N	F
3W	D	N	F	D	F	D	F
4W	N	F	D	D	N	F	D
5W	D	D	N	N	D	F	D
6W	F	F	D	F	F	D	D
1M	N	N	F	F	D	D	F
2M	F	D	F	D	F	N	F
3M	D	D	N	F	F	N	F
4M	N	F	D	N	F	F	D

W – woman, M – man, N – night shift, D – day shift, F – free day

Tab. 1 gives working days during the day time (D), working day with the work at night (N) and free day (F) that we can see in 6 women (W) and 4 men (M) during seven day/24-h blood pressure monitoring.

Tab. 2: *Sleep hours in different days of 7 day/24-h blood pressure monitoring*

DAY OF WEEK							
nurse No	1	2	3	4	5	6	7
1W		3 h	9.5 h	11.5 h		5.5 h	5 h
2W	11 h		5 h	7 h	8 h		3.5 h
3W	10 h	7 h	5 h	8 h	6.5 h	10 h	7.5 h
4W		9 h	6 h	12 h		11.5 h	5.5 h
5W	7 h	8 h	2.5 h	3.5 h	9 h	7 h	
6W	7.5 h	6.5. h	7 h	8.5 h	6.5 h	6.5 h	7 h
1M	4 h	3 h	8 h	6.5 h	5 h	7 h	8.5. h
2M	6 h	10 h	6 h	10 h	8.5 h		4 h
3M	7.5 h	9.5 h		4 h	8 h	4 h	
4M	2 h	8.5 h	11.5 h	2.5 h	13 h	7 h	9.5 h

W – woman, M – man, h – hours of sleep

In Tab. 2 there are presented sleep hours in different days in 10 nurses during seven day/24-h blood pressure monitoring.

Tab. 3: *Sleep hours per week of 7 day /24-h blood pressure monitoring*

nurse No	hours
1W	34.5
2W	34.5
3W	52.5
4W	39
5W	37
6W	43.5
1M	42
2M	44.5
3M	33
4M	53.5
mean	37,75
SD	2,75

W – woman, M – man, h – hours of sleep

In Tab. 3 there are presented sums of sleep hours in the week in 10 nurses during seven day/24-h blood pressure monitoring. The mean value of sleep per week in 10 nurses was 37.75 h per week.

In healthy subjects the sleep hours per day vary from seven to night-hours, per weeks from 49 to 63 hours. As it was shown in Table 3 our nurses have different decrease in sleep hours.

The sleeping in nurses is also shifted to different timing of the day, so that we can see the interruptions in circadian rhythm.

Tab. 4: *7 day/24-h blood pressure and heart rate MESOR*

nurse No	SBP (mmHg)	DBP (mmHg)	HR (bpm)
1W	134	79	82
2W	121	78	78
3W	129	70	72
4W	114	67	75
5W	110	70	78
6W	134	85	64
1M	122	75	73
2M	129	78	76
3M	130	76	78
4M	140	85	64
mean	126,3	76,3	74
SD	7,64	4,7	4,6

W – woman, M – man, h – hours of sleep

In Tab. 4 is presented MESOR of seven day/24-h ambulatory blood pressure monitoring. The Tab. 4 shows individual values of MESOR of systolic and diastolic blood pressure and MESOR of heart rate. The mean value from the week monitoring of MESOR of systolic blood pressure was 126±7.6 mmHg, of diastolic blood pressure 76±5 mmHg, of heart rate 74±5 bpm. These mean MESOR values are also presented in Fig. 4 for the whole group and week. We calculated from our seven day/24-h blood pressure monitoring mean values for every hour of all cardiovascular parameters and mean values for 24-h for every day and seven day mean values and we got the same results.

Tab. 5: *Seven day/24-h blood pressure and heart rate circadian amplitude*

nurse No	SBP (mmHg)	DBP (mmHg)	HR (bpm)
1W	9	6	7
2W	19	14	8
3W	14	8	13
4W	3	5	6
5W	5	6	3
6W	7	8	5
1M	9	9	4
2M	15	9	7
3M	6	5	6
4M	10	9	2
mean	9,7	7,9	6,1
SD	3,84	1,92	2,12

W – woman, M – man, h – hours of sleep

In Tab. 5 is presented circadian amplitude of seven day/24-h ambulatory blood pressure monitoring. The Tab. 5 shows individual values of circadian amplitude of systolic and diastolic blood pressure and circadian amplitude of heart rate. The mean value from the week monitoring of circadian amplitude of systolic blood pressure was 9.7±3.8 mmHg, of diastolic blood pressure 7.9±1.9 mmHg, of heart rate 6.1±2.1 bpm. The circadian amplitude for the whole week and the whole group is seen in Fig. 5.

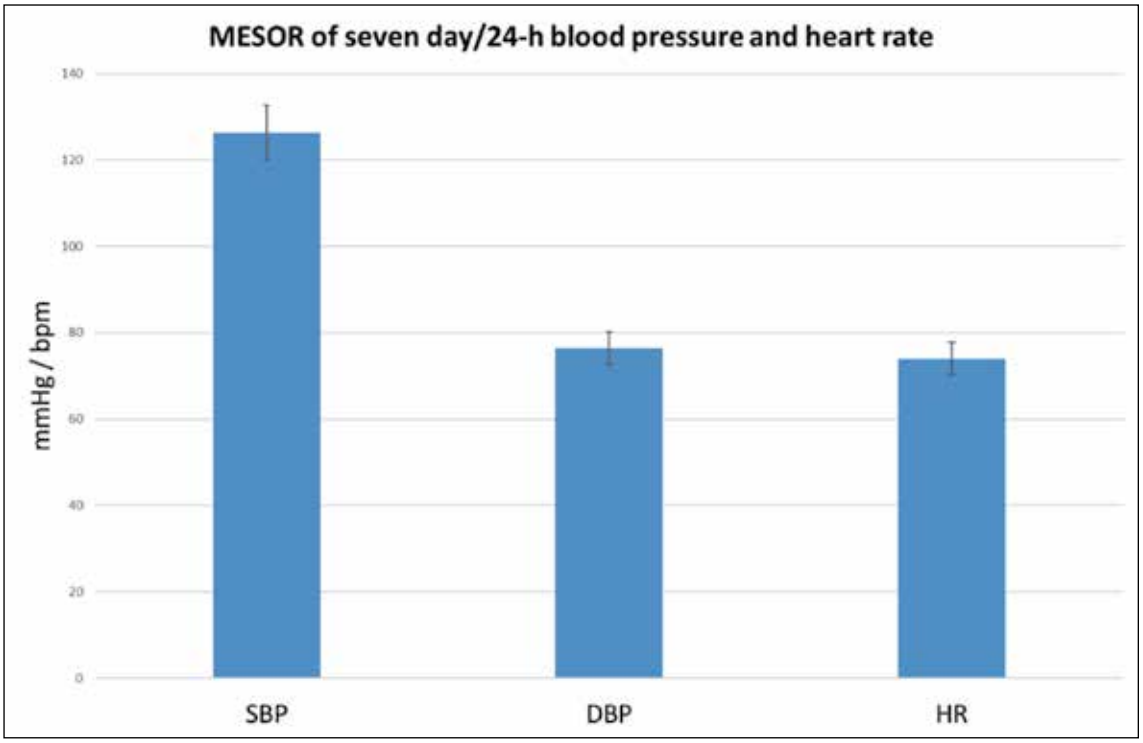

Figure 4: *Mean values of MESOR of 7 day/24-h blood pressure and heart rate*

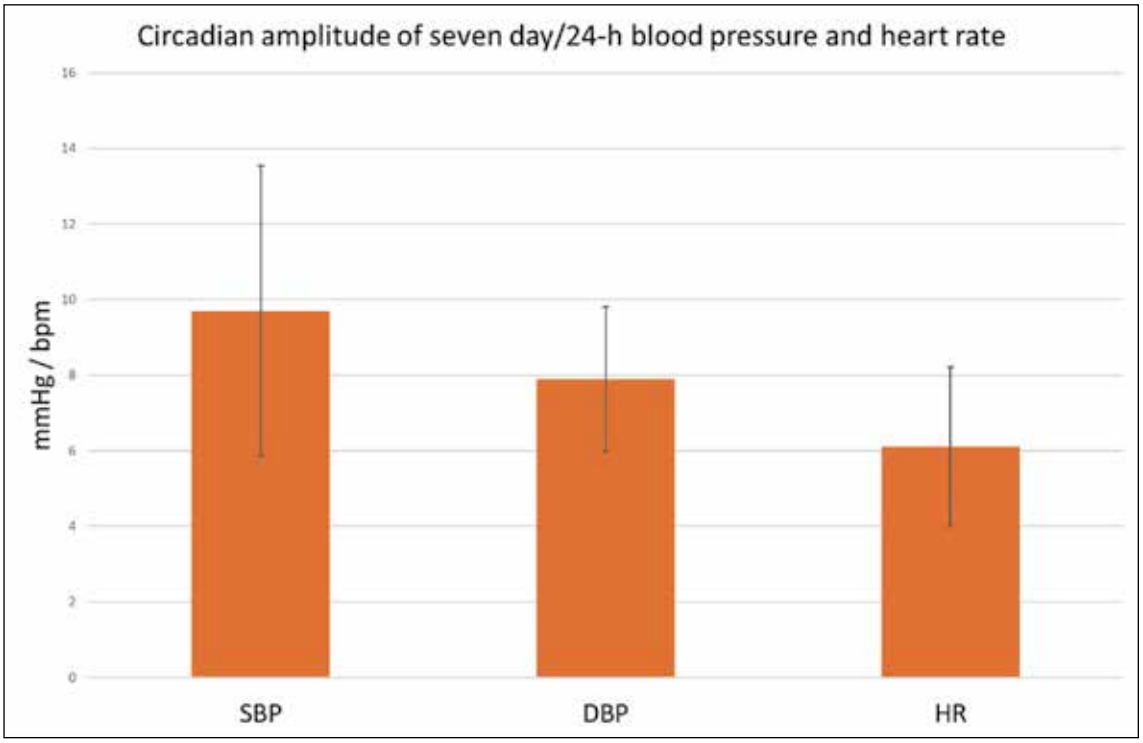

Figure 5: *Mean values of amplitude of 7 day/24-h blood pressure and heart rate*

Discussion

Shift work evokes circadian disruption, which disturbs the function of the intrinsic clocks in our body. Our body clocks tend to delay every day and require time to fully adjust after abrupt changes in any schedule that misaligns the external day length with the length of the bodily day. Work at night also means light at night (10, 11).

Shift work shows in Wang (7) study that each five years in shift work increases the risk of cardiovascular disease events by 5%. Each five years in shift work increases cardiovascular morbidity by 6% (13, 14).

Night-time workers are prone to cancer. Shift work is also know to present risk of insufficient sleep, insufficient physical activity, unhealthy diet, overweight, obesity, hypertension and diabetes mellitus type II. All risk factors in nurses aged 45 – 64 years increase the risk of ischemic heart disease (10, 12).

Conclusion

Seven day/24-h ambulatory blood pressure monitoring in night shift workers – nurses shows impairment of circadian rhythm depending on different working shifts.

The timing of working shifts in our study group is very irregular, in seven days are the days with day work shift, night work shift and free days.

In every individual nurse were different length of sleeping hours and the sleep was irregular to the relationship of day/night time.

In healthy subjects the sleep hours per day vary from seven to nine hours, per weeks from 48 to 63 hours and our nurses have different decrease in sleep hours per week.

The seven day/24-hour systolic blood pressure profiles vary from 110 to 140 mmHg and we can not use reference values for 24-h ambulatory blood pressure monitoring, while there is impairment in circadian rhythm because of irregular night work. The similar condition is valid for diastolic blood pressure.

The circadian amplitudes vary in every nurse according to the working conditions.

The study in our nurse group, using the 7-day/24-h blood pressure monitoring, showed great impairment of circadian rhythm in blood pressure and heart rate.

Further studies should show the necessity to improve the working conditions to lower the circadian rhythm impairment.

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Prof. MUDr. Pavel Braveny, CSc. (25.1.1931 – 31.7.2018) and International Congresses of Noninvasive Methods in Cardiology in Masaryk University, Brno

Jarmila Siegelova

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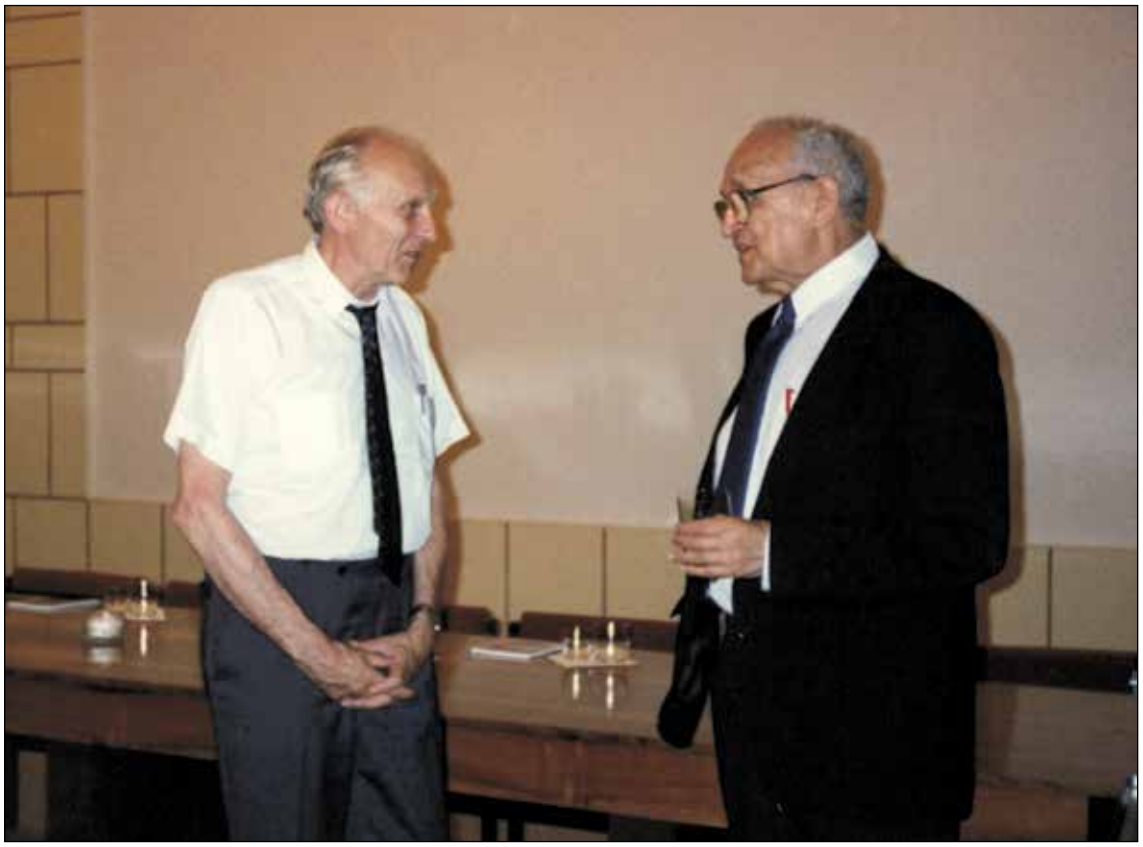
Prof. MUDr. Pavel Braveny, CSc. (was born in Brno, January 25 1931 and passed away on July 31, 2018 at the age of 87 years) graduated in 1951-1956 from the Faculty of Medicine of Brno University. In 1957 he became a lecturer at the Department of Physiology of the Faculty of Medicine J.E. Purkyně, now Masaryk University Brno, and in 1969 he achieved his habilitation.

From political reasons in the seventies of the last century he had to leave and moved to II. internal clinic of St. Anna Teaching Hospital as a researcher worker; with him moved also doc. MUDr. Josef Sumbera, CSc. and prof. MUDr. Jarmila Siegelova, DrSc. In 1990 he returned to the Department of Physiology and became Head of Department of Physiology (1990-1995). In 1990-1991 he was Dean of the Faculty of Medicine, in 1992-1998 the Vice-Rector of Masaryk University Brno for Science. Since 2000 he has been an Emeritus Professor at the Faculty of Medicine and he has been at the Department of Physiology his death. Professor Braveny participated also many times with us in the congresses and workshops of Noninvasive Methods in Cardiology, organized by Professor Siegelova since 1990 every year until now. Professor Braveny was an internationally recognized capacity in the field of normal and pathological physiology, especially cardiovascular physiology. He contributed scientifically and pedagogically significantly to the development of this field in the Czech Republic. We should never forget that the historical progress in science and medicine was achieved also due to the work of Professor Pavel Braveny.



Professor MUDr. Pavel Braveny, CSc. and Professor Franz Halberg, M.D., dr.h.mult. in Congress of Noninvasive Methods in Cardiology in Brno 1994

Professor MUDr. Pavel Braveny, CSc. and Professor MUDr. Jan Penaz, CSc. in Congress of Noninvasive Methods in Cardiology in Brno 1994

MUDr. Hana Svačinová, Ph.D., Professor MUDr. Jarmila Siegelová, DrSc., MUDr. Jiří Dušek, CSc.and Professor MUDr. Pavel Braveny, CSc. in Congress of Noninvasive Methods in Cardiology in Brno 2002

Professor MUDr. Pavel Braveny, CSc., PhDr. Karla Pochyla, Professor Dr. Helena Illnerová, DrSc., Professor MUDr. Jaroslav Blahos, DrSc., Professor RNDr. Eduard Schmidt, DrSc., Professor Bohumil Fiser, CSc. and Professor MUDr. Jan Zaloudik, CSc. in Congress of Noninvasive Methods in Cardiology in Brno 2003

Professor Dr. Germaine Cornelissen, Ph.D., PhDr. Karla Pochyla, Professor Dr. Helena Illnerová, DrSc., Professor MUDr. Jaroslav Blahos, DrSc., Professor RNDr. Eduard Schmidt, DrSc., Professor Bohumil Fiser, CSc., Professor MUDr. Jan Zaloudik, CSc. and Professor MUDr. Pavel Braveny, CSc., in Congress of Noninvasive Methods in Cardiology in Brno 2003

DrSc., Professor Bohumil Fiser, CSc., Professor MUDr. Pavel Braveny, CSc. and Professor MUDr. Jan Zaloudik, CSc. in Congress of Noninvasive Methods in Cardiology in Brno 2003

Professor Thomas Kenner, M.D., dr.h.c.mult., Brigite Kenner (from behind), Professor MUDr. Pavel Braveny, CSc., Doc. MUDr. Josef Sumbera, CSc., Professor Jarmila Siegelova, DrSc. in Congress of Noninvasive Methods in Cardiology in Brno 2013

Prof. MUDr. Petr Dobšák, CSc. 60 Years of Age

Jarmila Siegelova

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

Professor Dobšák, Head of the Department of Sports Medicine and Rehabilitation (2007 – until now), Head of the Department of Physiotherapy and Rehabilitation (2012 – until now), Faculty of Medicine, Masaryk University, Brno is a highly regarded scientist of worldwide renown in the field of normal and pathological physiology, internal medicine, sport medicine and a successful organizer in the field of physiotherapy.

On October 3, 2018 Petr Dobšák celebrated his sixtieth birthday, full of physical and intellectual energy.

During his studies at the Faculty of Medicine of Masaryk University he had been working in the Pathological Physiology where he extended his considerable knowledge of medicine; that became a basis for his further activities, mainly in the research of cardiovascular system in animal studies, and after his graduation in 1984.

Then he continued his scientific and teaching activities in the Department of Pathological Physiology as a lecturer. He was appointed a candidate for science (CSc.) in the field of Pathological Physiology1992. Let me give some personal memory. During the presentation of his scientific thesis on Microcirculation in animal studies, he also in the discussion showed his extraordinary knowledge of French language in the discussion with Professor Dr. E. Savin from Paris and showed the international range of his experimental work.

In the year 1994 he started as Assistant Professor of the Department of Pharmacology and Toxicology in University of Veterinary and Pharmaceutical Sciences Brno. From this University he obtained the study stay in University of Burgundy, Dijon, France. His international scientific work continued and resulted in a lot of scientific publications. In University of Burgundy he started also the first clinical studies in the Department of Cardiology, under Professor E. Wolf, together with Dr. Eicher on the low frequency electrical stimulation of skeletal muscles in patients with chronic heart failure.

In 1997 he moved back to Faculty of Medicine, Masaryk University in the Department of Functional Diagnostics and Rehabilitation (now Department of Sports Medicine and Rehabilitation) under the head of Prof. MUDr. Jarmila Siegelova, DrSc.

Since 1997 Prof. MUDr. Petr Dobšák, CSc. has been working at the Department of Functional Diagnostics and Rehabilitation and he continued his earlier co-operation with Professor Jean-Eric Wolf and dr. Jean-Christoph Eischer and co-operation with Japanese scientists. In the Department of Functional Diagnostics and Rehabilitation there were given lectures from Prof. Kou Imachi, Dipl. Eng., PhD, University of Tokyo, Prof. Masaki Anraku, MD, PhD, University of Tokyo, Prof. Yusuke Abe, MD, PhD, University of Tokyo, Prof. Atsushi Baba, MD, PhD, University of Tokyo, Associate Prof. Itsuro Saito, Dipl.Eng., PhD, University of Tokyo, Associate Prof. Takashi Isoyama, Dipl. Eng., PhD, University of Tokyo, Prof. Kozaburo Hayashi, Dipl. Eng., PhD, University of Osaka, Prof. Shin-Ichi Nitta, MD, PhD, Tohoku University Sendai, Prof. Makoto Tamai, MD, PhD, Tohoku University Sendai, Prof. Masahiro Kohzuki, MD, PhD, Tohoku University Sendai, Associate Prof. Yusuke Inoue, Dipl. Eng., PhD, Tohoku University Sendai, Prof. Kouji Shirai, MD, PhD, Toho University Chiba, Dr. Kazuhiro Shimizu, MD, PhD, Toho University Chiba, Msc. Akihiro Ogawa, PhD, Toho University Chiba, Japan, and this continued in the Department too.

Professor Dobšák also presented a lot of his scientific findings in international congresses and workshops in Japan every year, many times in France, in Hungary, in Austria, in Turkey, in Italy, in Canada.

He participated in international project with Japan (2000 - 2001 - visiting professor at the Research Center for Advanced Science and Technology, University of Tokyo, Japan. He was investigator of the research project: “Microcirculatory patterns in artificial heart recipients”, under the famous Prof. Kou Imachi and Prof. Yusuke Abe). The scientific cooperation with Japan continued in next project (2004 - 2007 - visiting researcher and researcher of the international grant project: “Investigation into the mechanism of muscle power improvement by low-frequency electrical stimulation and its clinical application for chronic heart failure patients”, Tohoku University Bioengineering Research Organization, Sendai, Japan) and from 2008 - co-investigator of the international clinical project: “CAVI (Cardio-Ankle Vascular Index) - New Global Arterial Stiffness Index”, evaluation of the prognostic significance of the CAVI parameter in healthy persons and patients with various types of so-called cognitive diseases within the Czech Republic of Development, Aging and Cancer, Tohoku University of Sendai, Japan, and Fukuda Denshi Co., Tokyo, Japan.

Professor Dobšák in the studies of Cardio-Ankle Vascular Index (CAVI) summarized a lot of data from the Czech population, in different pathological status, for example in patients with cardiac diseases, in patients with metabolic diseases in healthy population in middle Europe and also the effect of pharmacological and non-pharmacological therapy.

Professor Dobšák participated in European Project (OPVK, MŠMT CZ.1.07/2.2.00/28.0240) in the years 2012 - 2014 „Modification of the system of education in Physiotherapy” (Modifikace systému vzdělávání v oblasti fyzioterapie za účelem zvýšení konkurenceschopnosti absolventů) and the project was successfully defended.

Department of Sports Medicine and Rehabilitation and Department of Physiotherapy and Rehabilitation, Faculty of Medicine, Masaryk University, Brno continued in international cooperation also under leadership Professor Dobšák together with Professor Siegelová in cooperation with Medical Faculty, Lariboisiére Hospital (France), with Halberg Chronobiology Center of the University of Minnesota (USA), namely with Professor Franz Halberg and Professor Germaine Cornélissen, and with University in Graz (Austria), with Professor Thomas Kenner and Professor Nandu Goswami.

Scientific, medical, and organization capabilities of Professor Dobšák were appreciated by a number of awards, citations and memberships in scientific societies. Professor Dobšák has not only an extraordinary diligence, but also modesty and tolerance, almost permanent good mood and friendly relation to people. He is always ready to give advice and assistance to younger colleagues to whom he imparts his extensive scientific, research and pedagogical experience. His productive life is filled mainly with professional work and with work which is of benefit to the public.

Dear Professor Dobšák, I would like to wish you for myself and on behalf of all colleagues and friends and all those to whom you have been helping and who like you, many happy years, success in your work and first of all good health.

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5. Kenner T, Cornélissen G, Siegelová J, Dobšák P (eds): Noninvasive Methods in Cardiology 2016; Faculty of Medicine, Masaryk University, Brno, 145 p. ISBN 978-80-210-8391-2.

6. Cornélissen G, Siegelová J, Dobšák P (eds): Noninvasive Methods in Cardiology 2017; Faculty of Medicine, Masaryk University, Brno, 157 p. ISBN 978-80-210-8794-1.

Figure 1: *From the right MUDr. J. Dušek, CSc., Prof. MUDr. P. Dobšak, CSc., Prof. MUDr. B. Fišer, Masaryk University, St. Anna Teaching Hospital, Brno, CZ, Joint Meeting of Czech Physiology Society and english Physiological Society London in Prague, in 1998*

Figure 2: *From the right Prof. Jean-Eric Wolf, M.D. and Dr. Jean-Christophe Eicher, Center of Cardiology II, Hôpital du Bocage Dijon, France, Prof. Masahiro Kohzuki, Department of Internal Medicine and Rehabilitation Science, Tohoku University Graduate School of Medicine, Japan, standing Prof. MUDr. P. Dobšak, CSc., Prof. MUDr. J. Siegelová, Masaryk University, St. Anna Teaching Hospital, Brno, CZ in 2004*

Figure 3: *Prof. MUDr. P. Dobšak, CSc. in 21st Scientific Meetiong of the Interantional Society of Hypertension, Fukuoka, Japan in 2006*

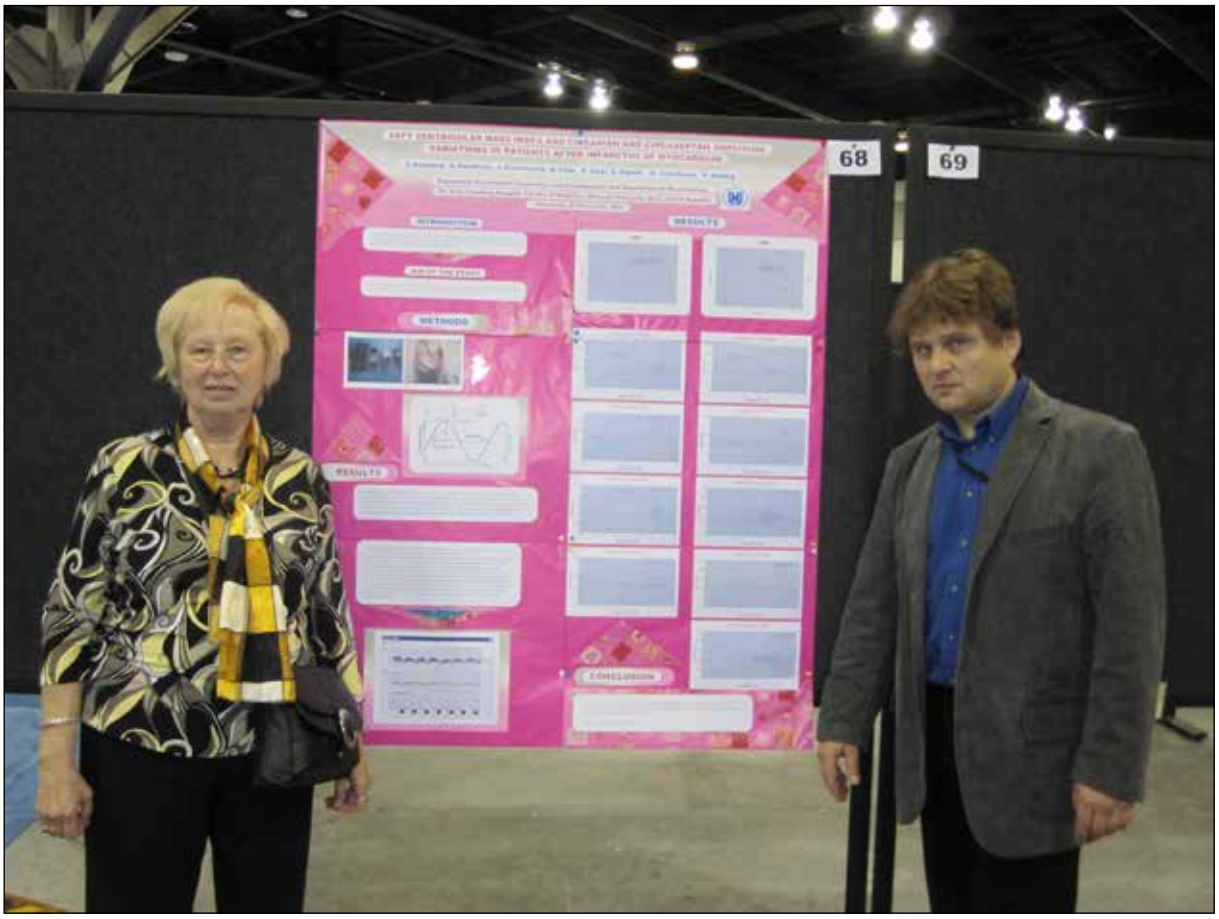


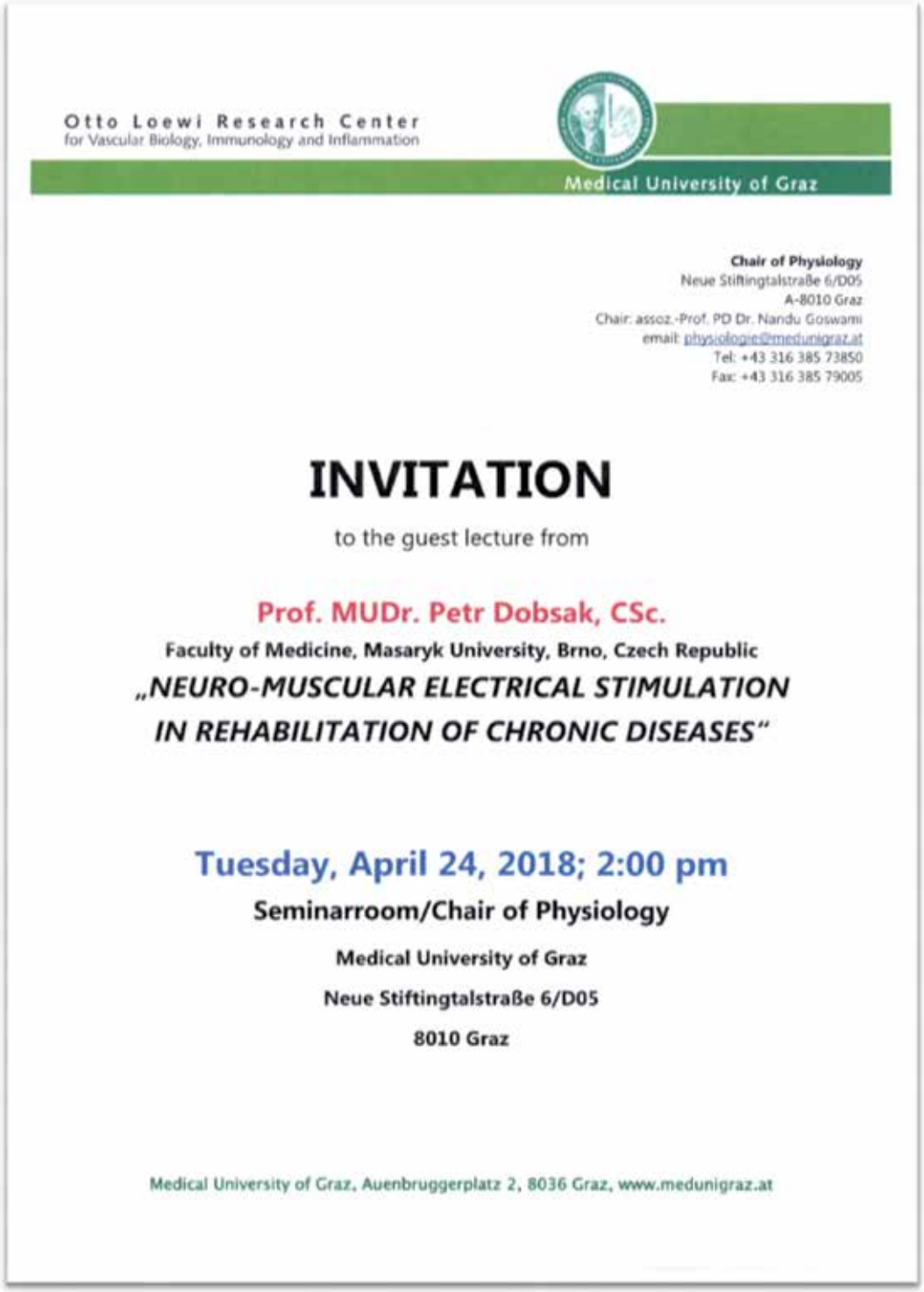
Figure 4: *Prof. MUDr. P. Dobšak, CSc. and Prof. MUDr. J. Siegelová, DrSc. in The 23st Scientific Meeting of the International Society of Hypertension, Vacouver, Canada 2010*

Figure 5: *Prof. MUDr. P. Dobšak, CSc. in Congress of European Society of Hypertension, Milan, Italy in 2011*

Neuro-muscular Electrical Stimulation (NMES) in Rehabilitation of Chronic Diseases

Petr Dobšák

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



Otto Loewi Research Center
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Medical University of Graz

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INVITATION

to the guest lecture from

Prof. MUDr. Petr Dobsak, CSc.

Faculty of Medicine, Masaryk University, Brno, Czech Republic

„NEURO-MUSCULAR ELECTRICAL STIMULATION IN REHABILITATION OF CHRONIC DISEASES"

Tuesday, April 24, 2018; 2:00 pm

Seminarroom/Chair of Physiology

Medical University of Graz

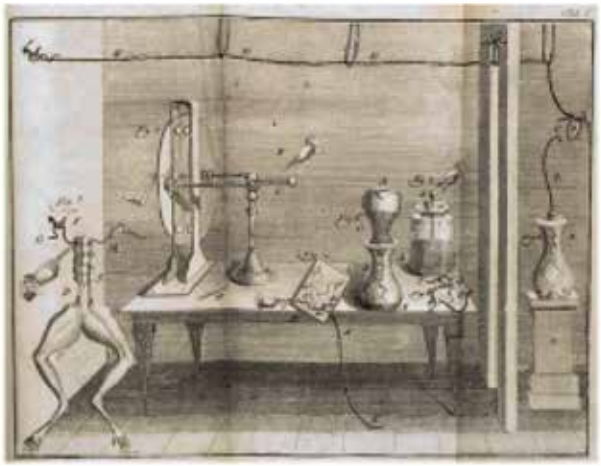
Neue Stiftingtalstraße 6/D05

8010 Graz

Medical University of Graz, Auenbruggerplatz 2, 8036 Graz, www.medunigraz.at

Luigi Galvani
(1737 – 1798)

Using electrical stimulation (ES) to trigger muscular activity is not a completely new methodology.



In 1790, Luigi Galvani first observed muscular contractions after connecting electrical wires to leg muscles severed from the body of frogs.

In 1831, Michael Faraday showed that electrical currents could stimulate nerves to create active movement.

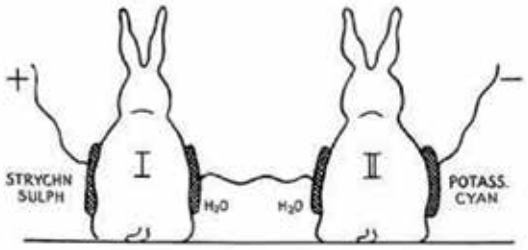
He developed the „faradization technique“ which was an effective treatment for motor paralysis.

Michael Faraday
(1791 – 1867)

Stèphane Leduc
(1853 – 1939)

In 1902, Stèphane Leduc designed an intermittent direct current unit, which became the basis for modern low-frequency electrostimulation therapy.

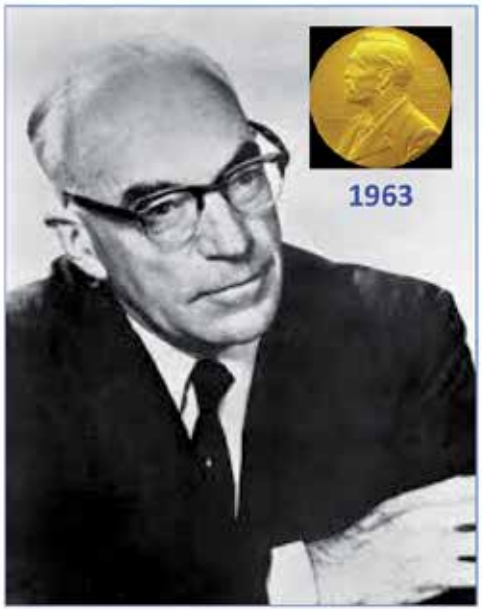
The use of Leduc´s stimulation unit became popular in the treatment of a variety of diseases during the period from 1920 to 1940.



Leduc's classic experiment showing that electricity was responsible for moving substances into the skin (iontophoresis)

In the period 1957-1961, *Sir* John C. Eccles, one of the pioneers in the research of the features of red and white muscles, defined rule that muscle function is determined by the type of innervation.

He implanted a nerve from cat red fiber into a white fiber. Consequently, the white fiber was completely transformed to red one („muscle plasticity").



Sir **John C. Eccles**
(1903 – 1997)

Pioneer work:

Buller AJ, Eccles JC et al. Interactions between motoneurones and muscles in respect of the characteristic speeds of their responses. J Physiol London 1960; 178: 326-42.

Dr. Yakov Kots
(1947)

Montréal 1976

Dr. Yakov Kots became famous for using electro stimulation in the training program of Russian athletes and his resulting studies were made public at the 1976 Montreal Olympics.

The electrical current (high frequencies 1.000 – 2.500 Hz) used for stimulating athletes was called „Russian Current" or „Kots current", and was soon also used by the athletes of other countries, thus becoming a widespread sports training method.

In the late 70s, **dr. Kots successfully applied his method** in the treatment in one of most famous ice hockey players,

Vyacheslav Fetisov

(multiple world champion and Olympic champion with the USSR national ice-hockey team).

Electrical stimulation

has made

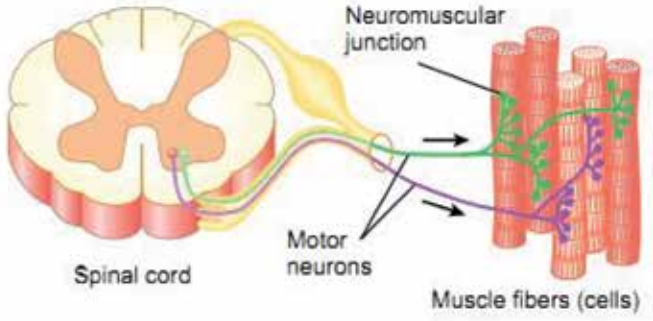
a fundamental contribution

to the understanding
of the influence of
motor neuron activity

on

muscle fiber phenotypes.

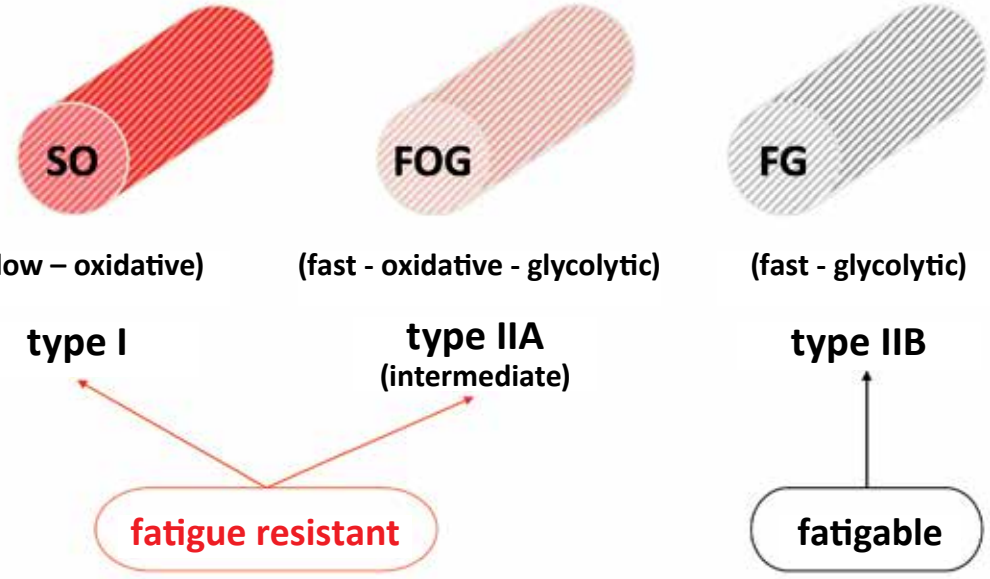
Fibre type is determined by the pattern of stimulation from the driving motor neuron which innervates the muscle.



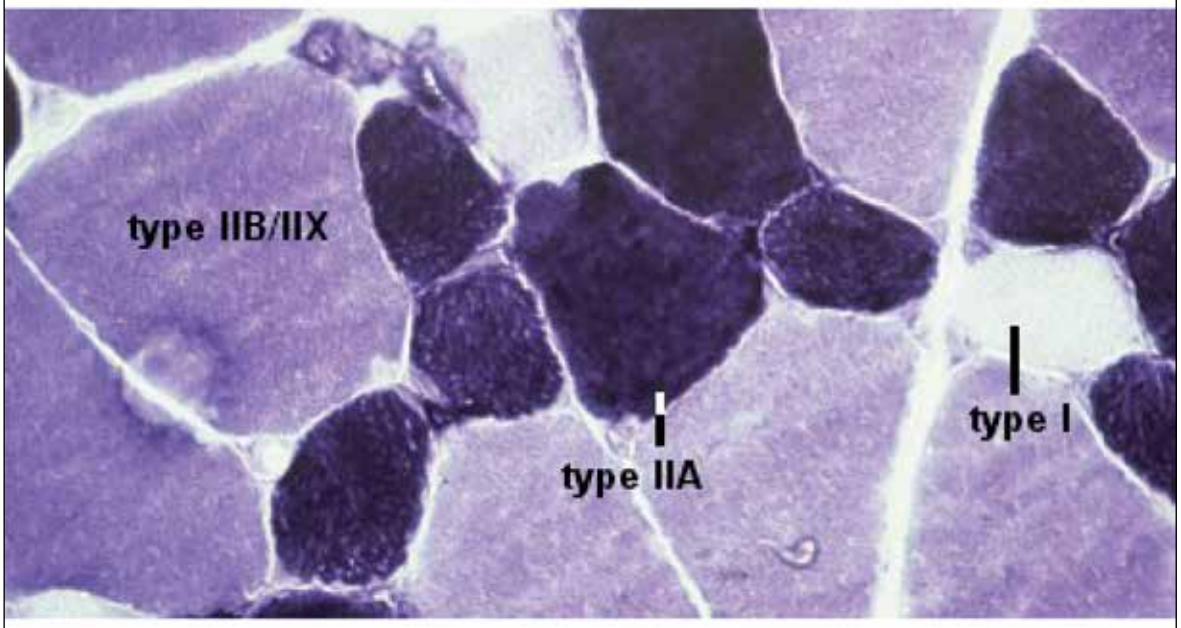
A years ago it was demonstrated, that slow („red"; oxidative; fatigue-resistent) fibers require continuous and permanent low-frequency ES, whereas the fast („whie"; glycolytic; fatigable) need intermittent high frequency ES.

Types of skeletal muscle fibers

(a routine classification)



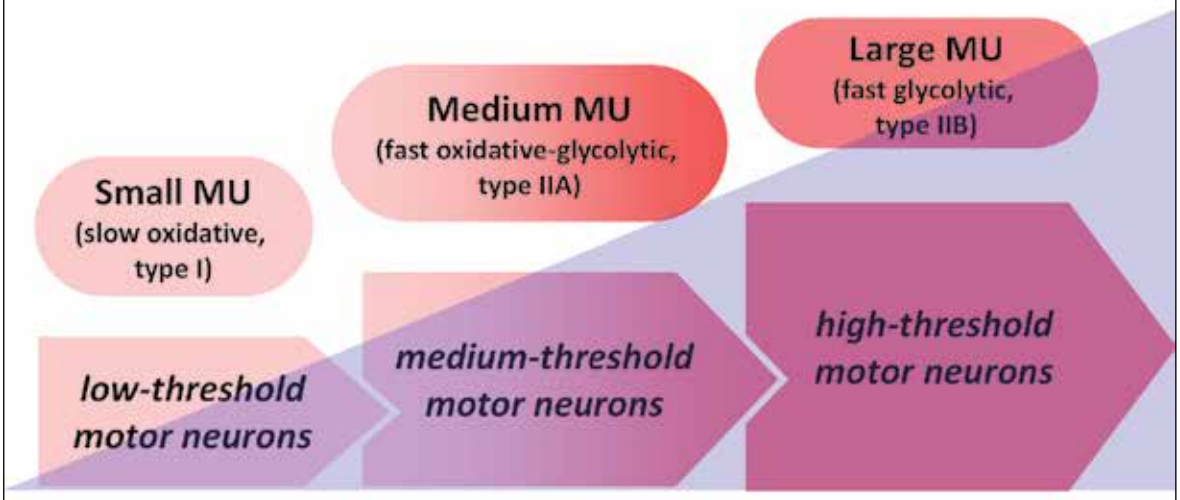
Cross-sectional view of muscle fiber types (m.soleus):



Skeletal muscle is - in fact - a mixture of type I, IIA and IIB muscle fibers and their different isoforms.

Courtesy: M. Müntener

Henneman's size principle states, that during gradually increased effort, motor units are recruited from smallest to largest:



▲

Henneman´s principle = hierarchical order of recruitment

Terminal diferentiation of the fibers is not completely constant

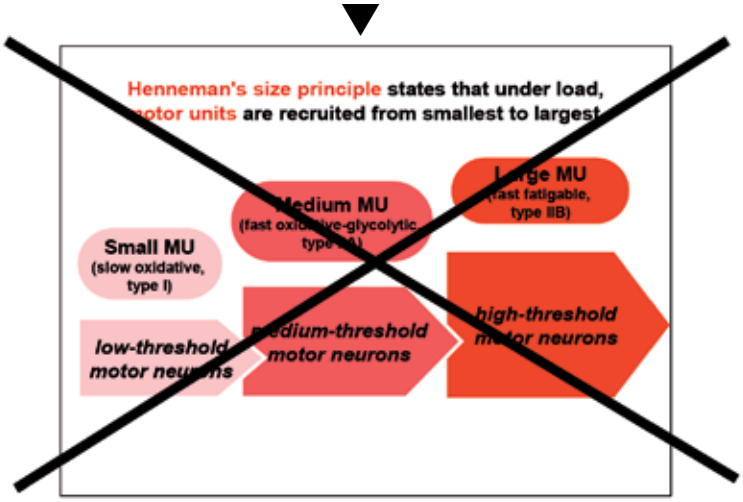
▼

muscle fibers are highly dynamic („plastic“ *) system ready for transformation

(The term „muscle plasticity“ was introduced by John C. Eccles in 1959.)*

This is of great clinical importance !

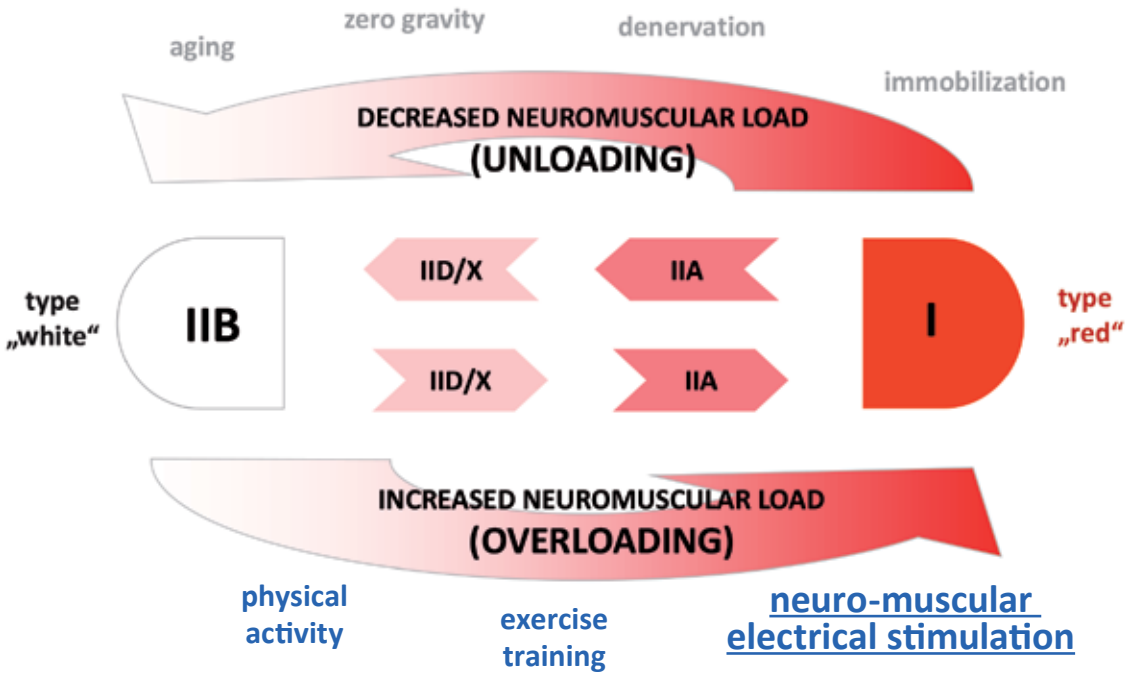
In ELECTRICALLY EVOKED CONTRACTIONS motor units are recruited in a "nonselective" or „random order" regardless of fiber type:



Electrical stimulation causes an immediate SYNCHRONIC DEPOLARIZATION of all motor units, including the largest ones !

Transformation of skeletal muscle fibers:

(By: *Pette D. Mammalian Skeletal Muscle Fiber Type Transitions.Int Review of Cytology 1997;170:143-197)*



In the RHB medicine the most used type of electrical current is the TENS (i.e. transcutaneous electrical neuro-stimulation), because it is usually well tolerated by most patients

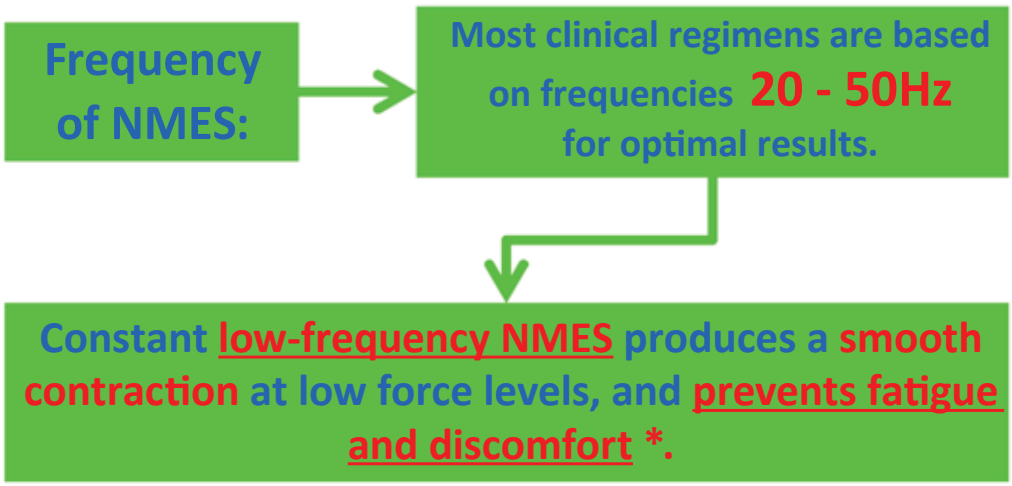
(Pette et al. 1999; Maffiuletti et al., 2011):

▼

Moreover, the muscle contractions triggered by electrical impulses (TENS) activate the sequence of metabolic and vascular processes very similar to those which accompany normal (voluntary) muscle activity.

Maffiuletti NA, Minetto MA, Farina D, Bottinelli R. Electrical stimulation for neuromuscular testing and training: State-of-the art and unresolved issues Eur J Appl Physiol 2011; 111(10): 2391–7.

Pette D, Vrbova G. What does chronic electrical stimulation teach us about muscle plasticity? Muscle Nerve 199; 22 (6): 666.

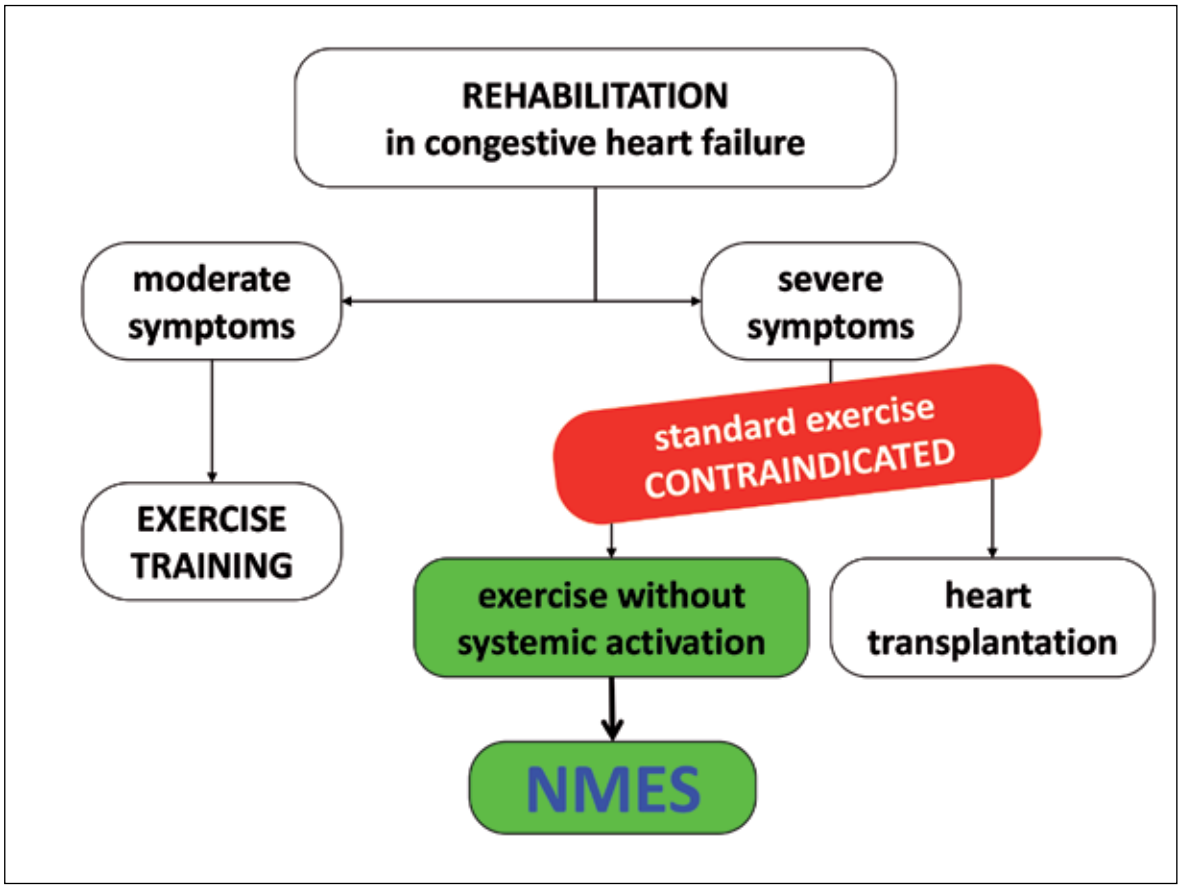


** Baker LL, Bowman BR, McNeal DR. Effects of waveform on comfort during neuromuscular electrical stimulation. Clin Orthop 1988;233:75–85.*

** Bhadra N, Peckham PH. Peripheral nerve stimulation for restoration of motor function. J Clin Neurophysiol 1997;14(5):378–393.*

** De Kroon JR, IJzerman MJ, Chae J, Lankhorst GJ, Zilvold G. Relation between stimulation characteristics and clinical outcome in studies using electrical stimulation to improve motor control of the upper extremity in stroke. J Rehabil Med 2005;37(2):65–74.*

NMES IN RHB OF PATIENTS WITH CHRONIC HEART FAILURE (CHF)



First pioneer work:

Maillefert JF, Eicher JC, Walker P et al.:

Effects of low-frequency electrical stimulation of quadriceps and calf muscles in patients with chronic heart failure.

J Cardiopulm Rehabil 1998; 18(4): 277-82.

Centre de Cardiologie II, Hôpital du Bocage, Dijon, France

Professor **Jean-François MAILLEFERT**

Doctor **Jean-Christophe EICHER**

Clinical trial (2001 – 2004):

Effects of low-frequency electrical stimulation on muscle power and blood supply in patients with chronic heart failure.

15 patients
(men, mean EF 20%,
mean age 56,5 yrs, NYHA III-IV,
all on waiting list for heart grafting)
underwent 6-week
RHB program based on
low-frequency NMES
of leg muscles.

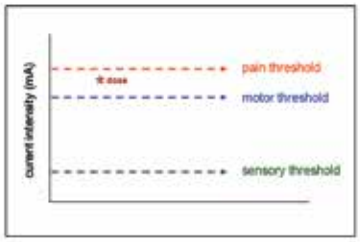
This was a first (official) clinical use of NMES in RHB of patients with CHF in the Czech Republic.

Methods:

stimulator
ELPHA 2000
(Danmeter®, Denmark)

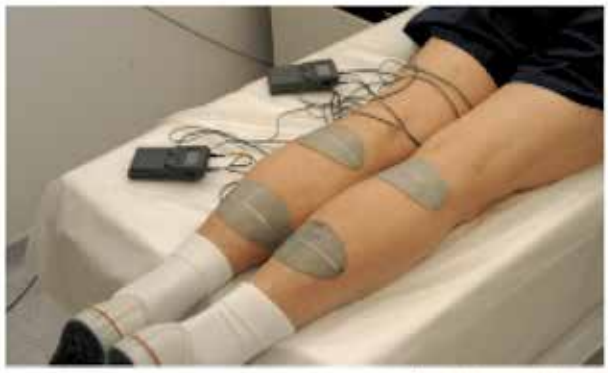
self-adhesive
electrodes 80 x 130 mm
PALS® Platinum
(Axelgaard, Denmark)

bi-phasic current



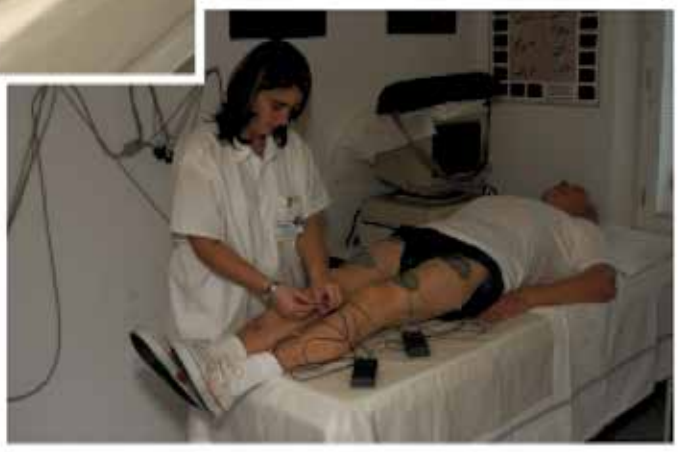
frequency	10 Hz
pulse width	200 µs
ramp-up & down	0.5 sec
work time	20 sec
rest time	20 sec
maximal amplitude	60 mA
power supply	9 V
total stimulation time	60 min

stimulation protocole design:



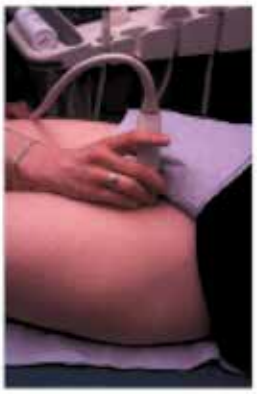
Patient R.L.,
55 yrs, NYHA III-IV
(on „waiting list“ for heart graft).

6 weeks of NMES applied to leg extensors in hospital.



Methods:

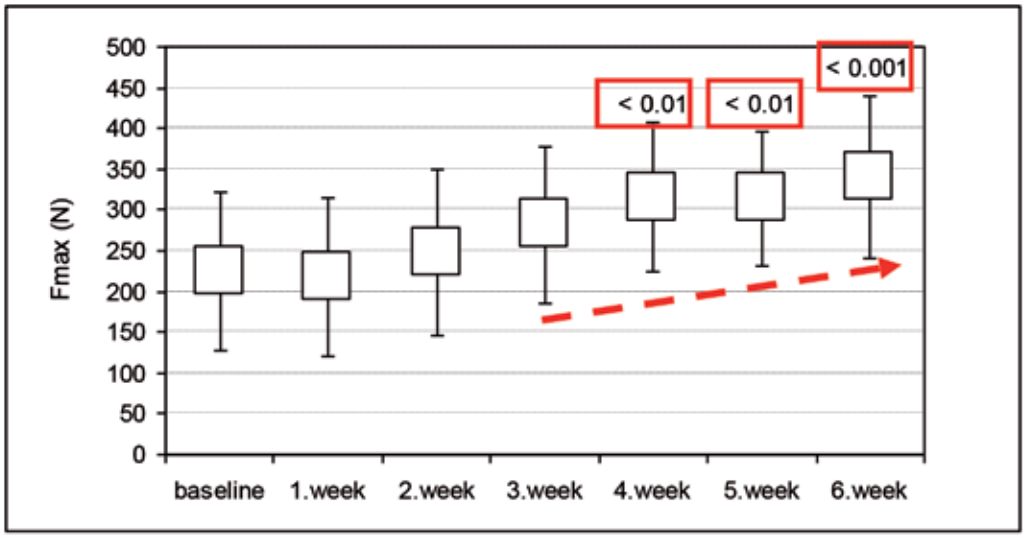
measurement of maximal muscle power (F_{max}) of leg extensors by isometric dynamometry



pulsed-wave Doppler velocimetry of femoral artery *(flow measurement in 15th, 30th, 45th and 60th minute of stimulation)*

Results:

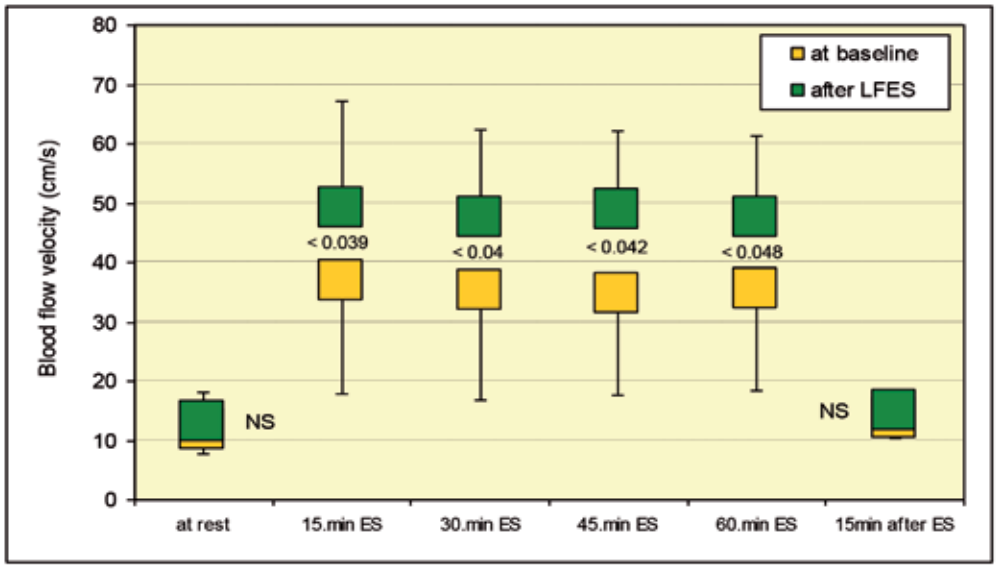
*** Changes of the maximal muscle power (F_{max}) of leg extensors during 6 weeks of LFES *(mean ± SD):***



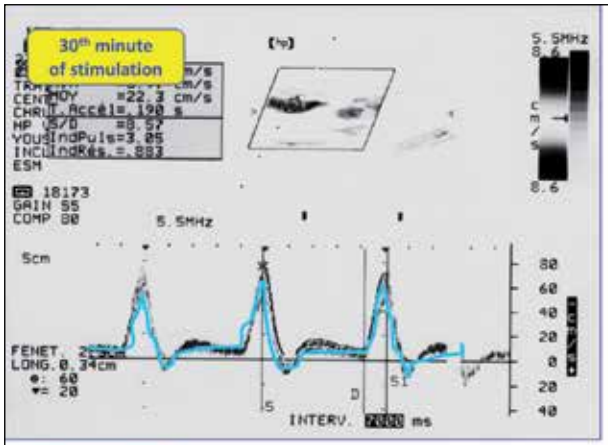
** Dobsak P. et al.: Low-frequency electrical stimulation increases muscle strength and improves blood supply in patients with chronic heart failure. Circ J 2006; 70: 75-82.*

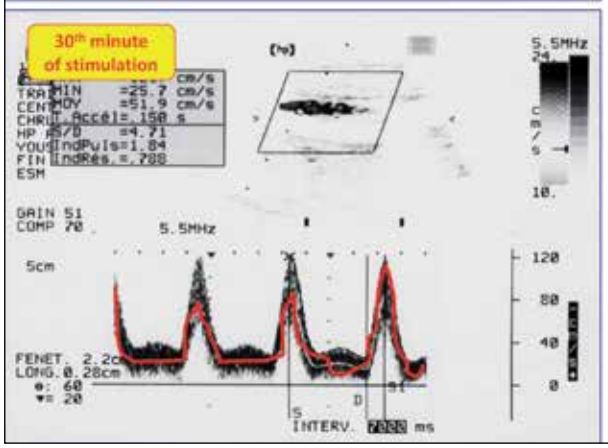
Results:

* Changes of blood flow during stimulation.



** Dobsak P. et al.: Low-frequency electrical stimulation increases muscle strength and improves blood supply in patients with chronic heart failure. Circ J 2006; 70: 75-82.*





at baseline
v_{max} = 22.3 [cm.s^{-1}]

after 6 weeks of NMES
v_{max} = 51.9 [cm.s^{-1}]

Patient V.M.,
57 yrs, NYHA III-IV

Conclusion:

1.
NMES may significantly improve skeletal muscle power and blood supply in patients with CHF.

2.
NMES can be recommended for the treatment of patients with severe grade of chronic heart failure.

Since 2004 *started an international cooperation with the* ***Department of Internal Medicine & Rehabilitation Sciences, Tohoku University of Sendai (Japan).***

Tohoku University Biomedical Engineering Research Organization

Tohoku University School of Medicine

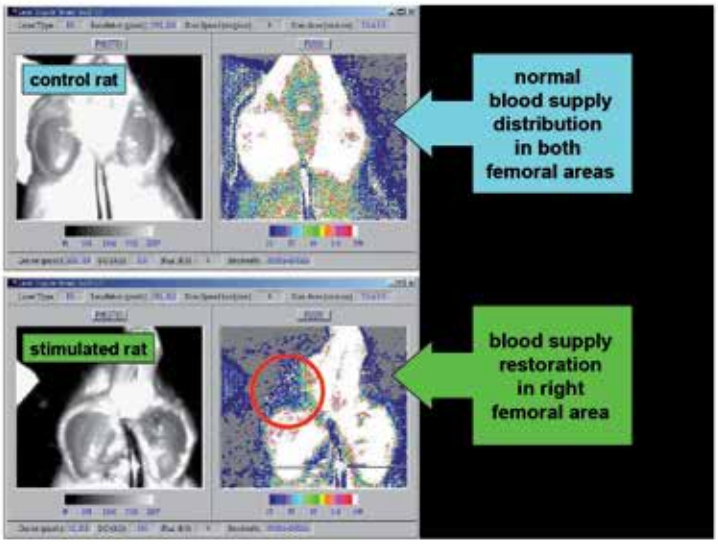
INVESTIGATION INTO THE MECHANISM ABOUT MUSCLE POWER IMPROVEMENT BY LOW-FREQUENCY ELECTRICAL STIMULATION AND ITS CLINICAL APPLICATION FOR CHRONIC HEART FAILURE PATIENTS

2004 - 2008

Nagasaka M., Kohzuki M., Fujii T. et al. :

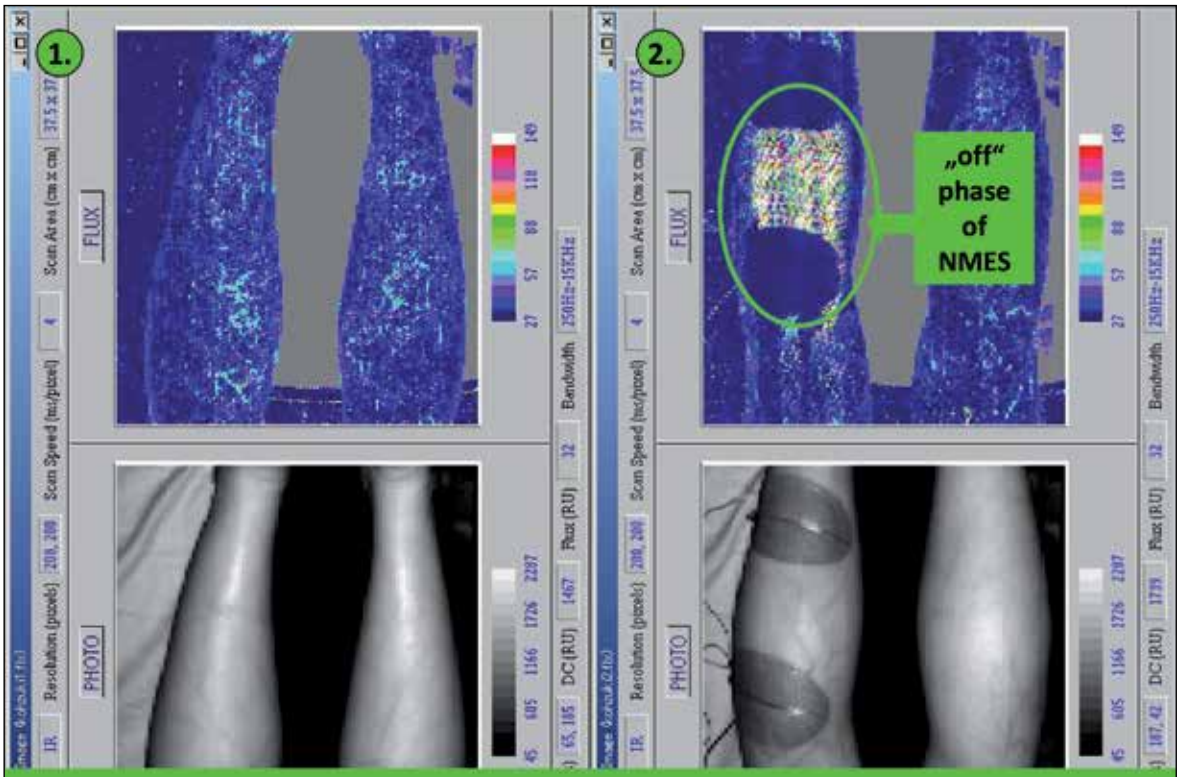
Effect of low-voltage electrical stimulation on angiogenic growth factors in ischaemic rat skeletal muscle.

Clin Exp Pharmacol Physiol. 2006; 33(7): 623-7.



1. chronic ES increases production of angiogenetic factors (VEGF, HGF)

2. chronic ES enhances regional blood flow in stimulated area



Example of blood flow intensity measurement assessed by laser-Doppler imager in a healthy subject (Dept.of Internal Medicine and Rehabilitation Sciences, Tohoku University of Sendai).

Czech Society for Cardiology

Working Group for Cardiovascular Rehabilitation

In 2006, at the 14th Annual Congress of Czech Society for Cardiology in Brno, the low-frequency NMES has been approved as a convenient method of rehabilitation, recommended for patients presenting contraindications for standard exercise training, including those with severe grade of chronic heart failure*.

**** From 2006 the RHB based on NMES is included in the official Guidelines of Cardiovascular Rehabilitation, edited by Czech Society for Cardiology.***

Clinical trial (2008 – 2010):

Effects of neuromuscular electrical stimulation and aerobic exercise training on arterial stiffness and autonomic functions in patients with chronic heart failure.

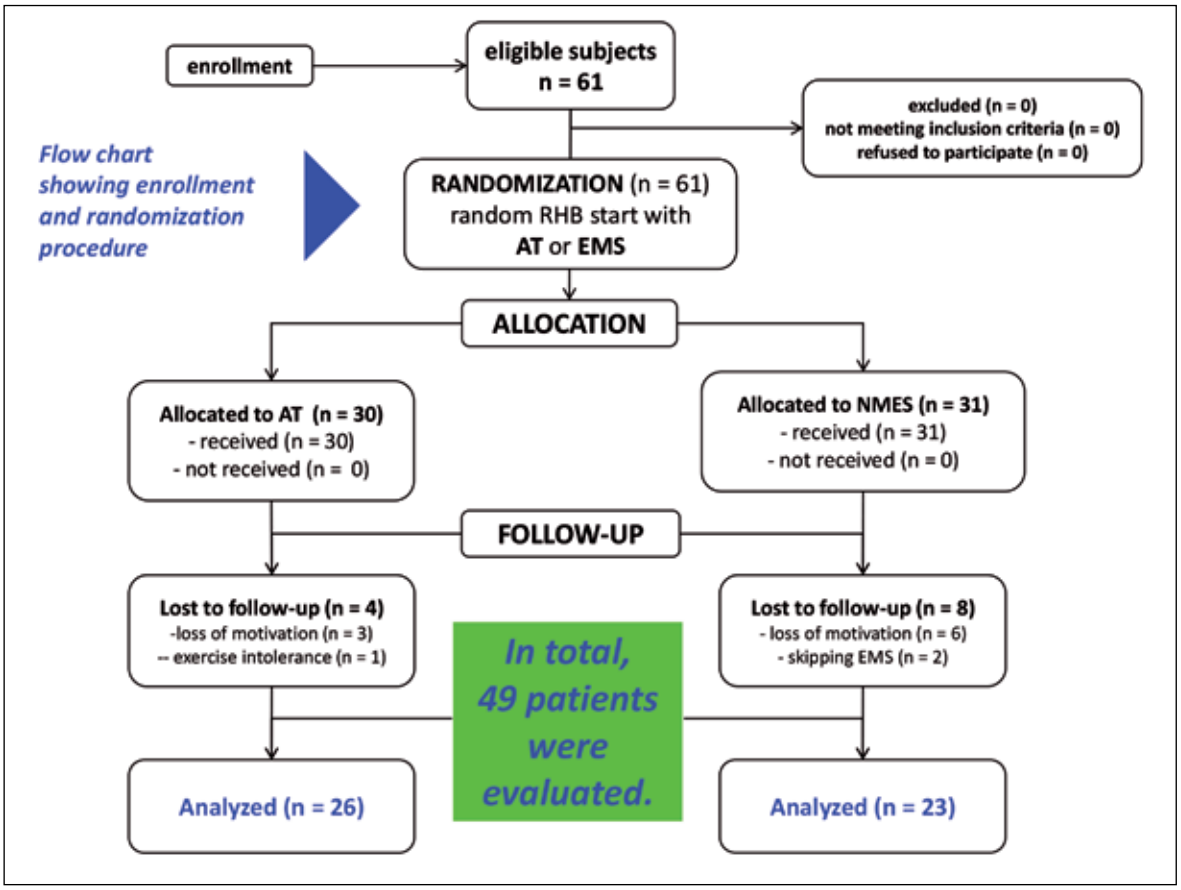
61 patients

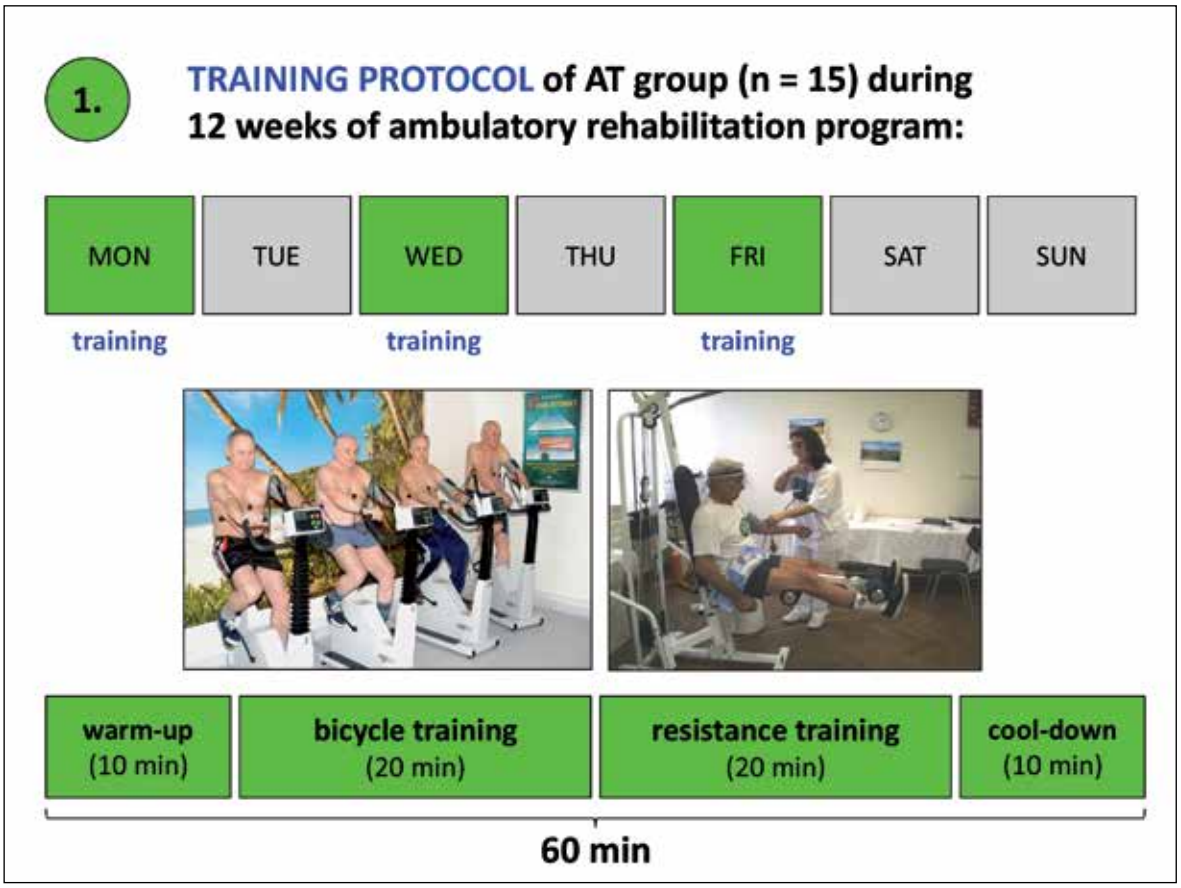
with stable CHF

[mean age 58.9(2.1) years; mean EF 31(4.2) %, NYHA II-III]

were randomly assigned into 2 groups:

a) aerobic training group (AT; n = 30)	b) stimulation group (NMES; n = 31)
▼	▼
12 weeks of supervised aerobic exercise training	12 weeks of NMES of leg extensors AT HOME


enrollment
eligible subjects
n = 61
excluded (n = 0)
not meeting inclusion criteria (n = 0)
refused to participate (n = 0)
Flow chart showing enrollment and randomization procedure
RANDOMIZATION (n = 61)
random RHB start with
AT or EMS
ALLOCATION
Allocated to AT (n = 30)
- received (n = 30)
- not received (n = 0)
Allocated to NMES (n = 31)
- received (n = 31)
- not received (n = 0)
FOLLOW-UP
Lost to follow-up (n = 4)
-loss of motivation (n = 3)
-- exercise intolerance (n = 1)
Lost to follow-up (n = 8)
- loss of motivation (n = 6)
- skipping EMS (n = 2)
In total, 49 patients were evaluated.
Analyzed (n = 26)
Analyzed (n = 23)


1.
TRAINING PROTOCOL of AT group (n = 15) during
12 weeks of ambulatory rehabilitation program:
MON
TUE
WED
THU
FRI
SAT
SUN
training
training
training
warm-up
(10 min)
bicycle training
(20 min)
resistance training
(20 min)
cool-down
(10 min)
60 min

2. **TRAINING PROTOCOL** of **group NMES (n = 23) during 12 weeks of rehabilitation program at home:**

MON	TUE	WED	THU	FRI	SAT	SUN
NMES	NMES	NMES	NMES	NMES	NMES	NMES

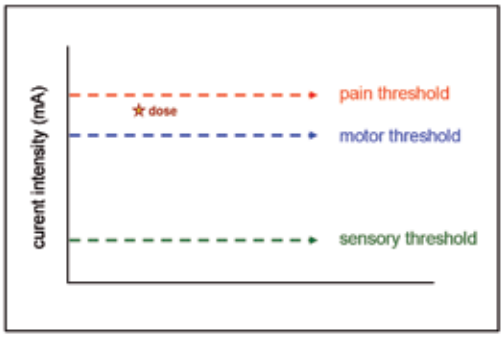
dual-channel, battery powered (2 x 1.5V stimulator

REHAB X-2

(CEFAR®, Malmö, Sweden)

NMES was applied to leg extensors of both legs (2 x 60min/day).

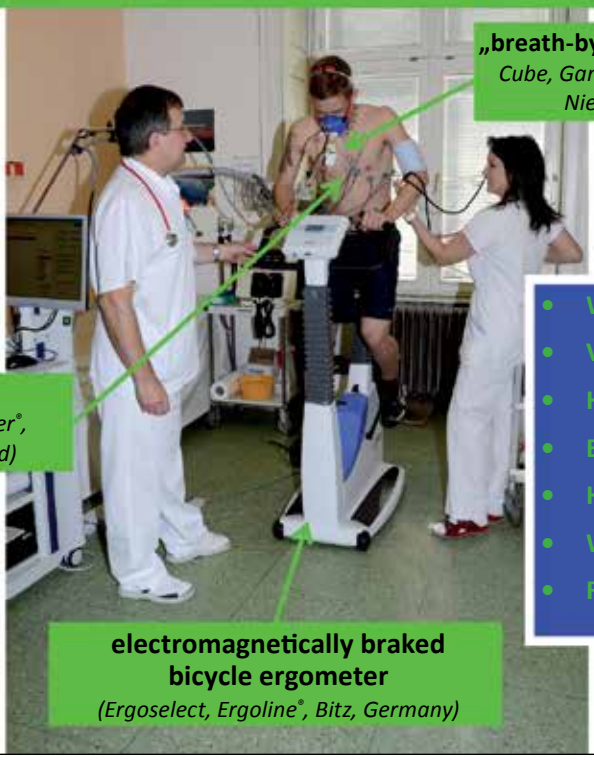
bi-phasic current



frequency	**10 Hz**
pulse width	**200 µs**
ramp-up & down	**0.5 sec**
work time	**20 sec**
rest time	**20 sec**
maximal amplitude	**60 mA**
power supply	**9 V**
total stimulation time	**60 min**

stimulation protocole design:

Spiroergometric testing for assessment of functional parameters and determination of training intensity:



„breath-by-breath" analyzer *(Power Cube, Ganshorn® Medizin Electronic, Niederlauer, Germany)*

12-lead ECG
(AT-104 PC, Schiller®, Baar, Switzerland)

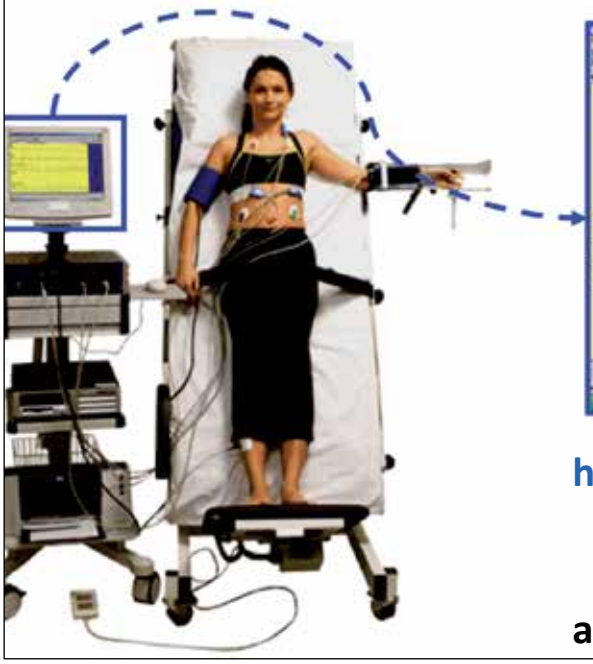
electromagnetically braked bicycle ergometer
(Ergoselect, Ergoline®, Bitz, Germany)

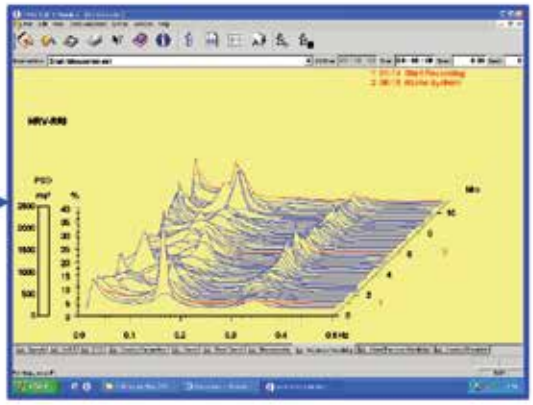
- W_{peak} . kg -1
- VO_{2peak} . kg -1
- HR_{peak}
- BP_{peak}
- HR_{VAT-1} = training
- W_{VAT-1} = training
- RPE_{VAT-1} = training

TASK FORCE® MONITOR
(Graz, Austria)

Methods:

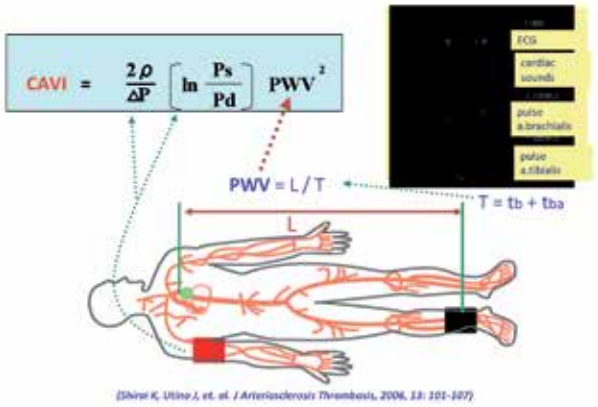
recording R-R intervals (RRI)
(5min duration and 300 RRI at least)





heart rate variability (HRV-RRI)
was obtained from the beat-to-beat data using an adaptive autoregressive model

Arterial stiffness was studied using recently introduced parameter called CAVI (Cardio-Ankle Vascular Index):



The equipment (VaSera® 1500) was provided by Fukuda Denshi Co. Tokyo, in cooperation with Institute of Development, Aging and Cancer (IDAC), Tohoku University of Sendai.

Both types of RHB reduced significantly CAVI:
in the group AT from 9.6(0.2) to 8.9(0.2), p<0.012;
in the group NMES from 9.3(0.2) to 8.7(0.2), p<0.013

		Results [1]		Differences [2]		
parameter [1]	group	baseline	12th week	value	% of values at baseline	p value [4]
CAVI [5]	AT	9.6 (0.2)	8.9 (0.2)	-0.7 (0.2)	-6.8%	0.012
	NMES	9.3 (0.2)	8.7 (0.2)	-0.6 (0.2)	-5.7%	0.013
	p value [3]	0.061				

[1] Arithmetic mean and standard error (SE)
[2] Pair-wise differences expressed as difference arithmetic mean (standard error) and as % of initial value
[3] Significance level of independent component in rmANOVA model
[4] Significance level of pair-wise (time-related) component in rmANOVA model
[5] rm ANOVA model computed using log-transformed data; trimmed mean used for parametric data description in these variables

* Both types of RHB led to significant increase of VO_{2peak} and also other key functional parameters:

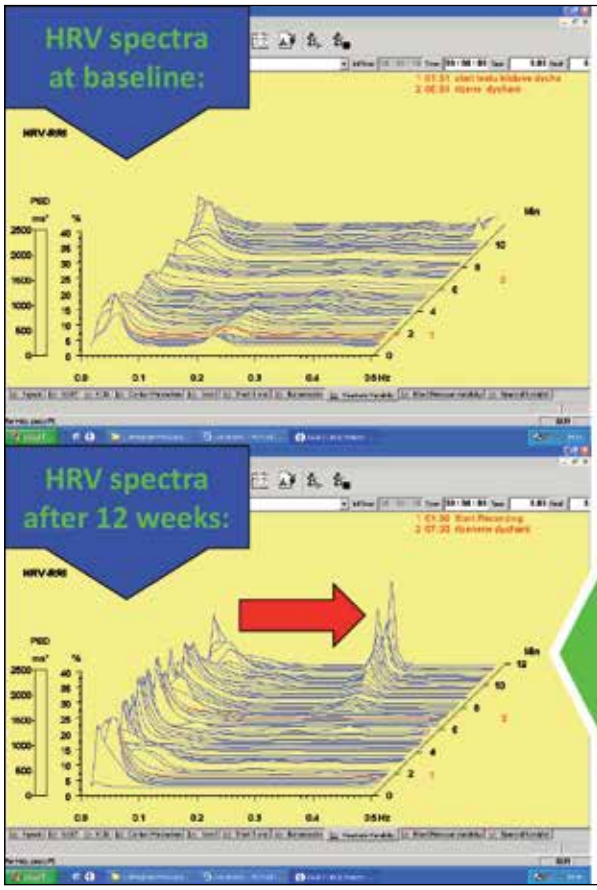
parameter	group	baseline	12th week	value	% of values at baseline	p value
VO_{2peak} (ml/kg/min)	AT	18.7 (0.7)	20.5 (0.7)	1.8 (0.6)	10.4%	0.004
	NMES	17.3 (0.7)	19.0 (0.7)	1.7 (0.3)	9.9%	<0.001
	p value [1]		*0.154*			
VO_{2AT} (ml/kg/min)	AT	11.3 (0.4)	12.7 (0.5)	1.4 (0.4)	12.2%	0.001
	NMES	10.5 (0.5)	11.4 (0.5)	1.0 (0.4)	9.4%	0.013
	p value [1]	*0.140*				
VE/VCO_2 slope	AT	31.5 (0.9)	29.8 (0.8)	-1.7 (0.9)	-5.4%	0.478
	NMES	33.1 (1.3)	31.1 (1.1)	-2.0 (1.1)	-6.1%	0.085
	p value [1]		*0.305*			
W_{peak} (watt/kg)	AT	1.2 (0.1)	1.4 (0.1)	0.2 (0.0)	18.9%	<0.001
	NMES	1.1 (0.1)	1.2 (0.1)	0.1 (0.0)	9.4%	0.004
	p value [1]		*0.302*			
HR_{peak} (bpm)	AT	126.0 (3.5)	136.9 (2.8)	10.9 (2.4)	8.7%	<0.001
	NMES	134.8 (5.2)	140.3 (5.0)	5.5 (2.1)	4.1%	0.014
	p value [1]		*0.163*			

[1] *Significance level of independent component in rm ANOVA model*

** Dobsak P. et al. Effects of neuromuscular electrical stimulation and aerobic exercise training on arterial stiffness and autonomic functions in patients with chronic heart failure. Artif Organs 2012; 36(10): 920-30.*

Group AT ► significant increase of HF parameter (+65.6%; p=0.001) and decrease of LF/HF ratio (-39.8%; p<0.001):

		Results:		Differences:		
Parameter	Group	baseline	12th week	value	% of initial value	p value
Total power	AT	348.2 (49.7)	492.2 (50.5)	144.0 (50.8)	41.4%	0.329
	NMES	351.1 (80.1)	578.3 (231.6)	227.2 (214.0)	64.7%	0.376
	p value		0.386			
LF	AT	65.6 (8.2)	42.7 (6.0)	-22.9 (8.4)	-34.9%	0.229
	NMES	62.1 (11.3)	44.8 (11.5)	-17.3 (14.9)	-27.8%	0.492
	p value		0.481			
HF	AT	56.8 (8.9)	94.1 (18.9)	37.3 (19.3)	65.6%	0.001
	NMES	50.3 (13.4)	73.1 (17.1)	22.9 (17.9)	45.5%	0.666
	p value		0.626			
LF/HF	AT	0.8 (0.1)	0.5 (0.1)	-0.3 (0.1)	-39.8%	<0.001
	NMES	0.7 (0.1)	0.6 (0.1)	-0.1 (0.1)	-11.7%	0.307
	p value		0.907			



Results:

Example:

patient M.N.
(F, 51 yrs.)

marked increase of High-Frequency Component of HRV (increased parasympathetic tone) after 12 weeks of NMES

Conclusion:

1.

AT or NMES RHB training has been shown to improve arterial stiffness, general autonomic balance and physical performance in patients with moderate grade of CHF.

2.

This study was one of the first clinical trials focusing on the effect of exercise training on vascular stiffness assessed by the new parameter CAVI in patients with chronic disease.

Clinical trial 2010 – 2012:

Exercise training combined with electromyostimulation in the rehabilitation of patients with chronic heart failure (a randomized trial).

Aim:

Evaluation of the effectiveness of the 12-weeks exercise training using combination of

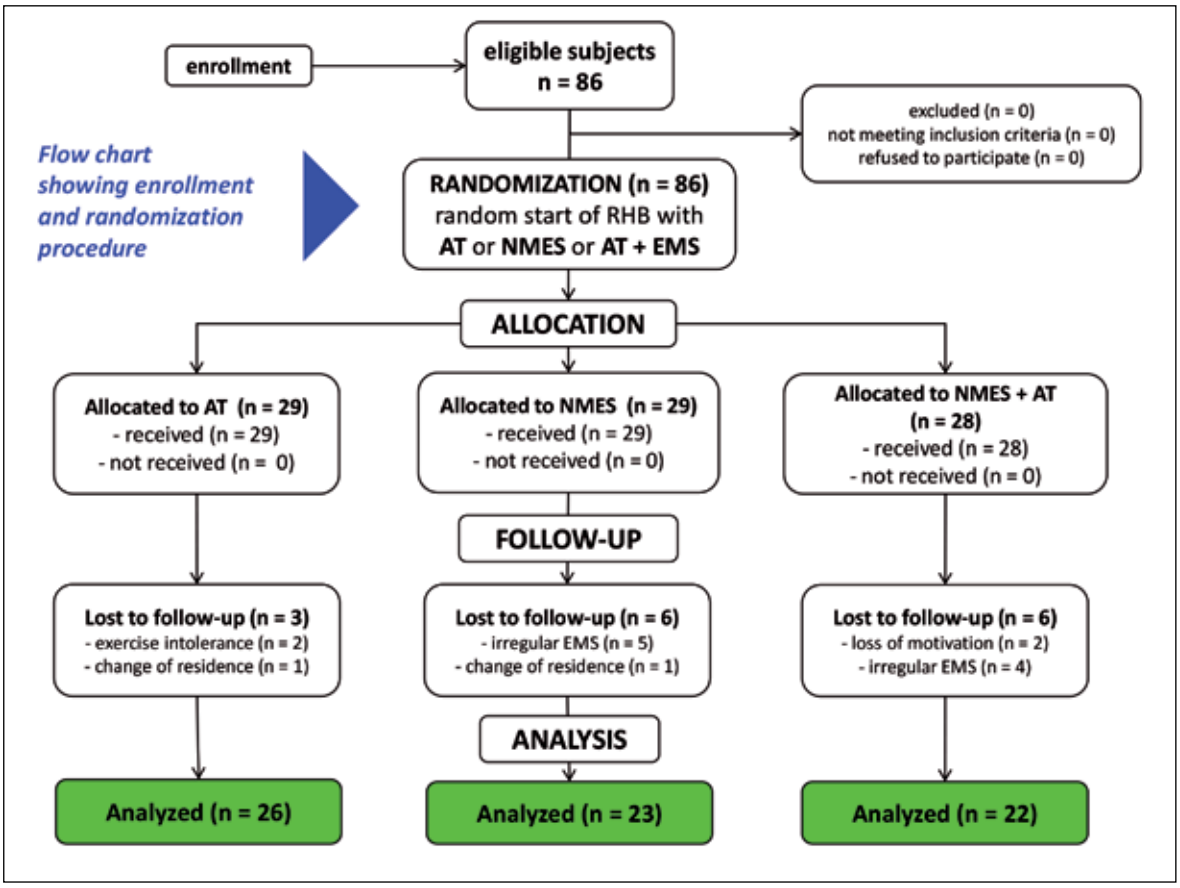
AT + NMES

in rehabilitation (RHB) program of patients with stable form of CHF.

It was speculated that combination of AT + NMES could have an additive effect.

Patients and methods:

Patients with CHF
(n = 71; age 59 ± 10.2 yrs,
NYHA II/III, EF 35 ± 9.1%)
were randomized into
3 groups:



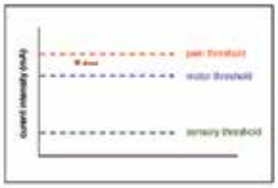
supervised aerobic training

on electromagnetically braked bicycle ergometers *(REHA E900, Ergoline®, Germany)* with **intensity at the level of individual VAT (VAT-1)**

NMES (at home)

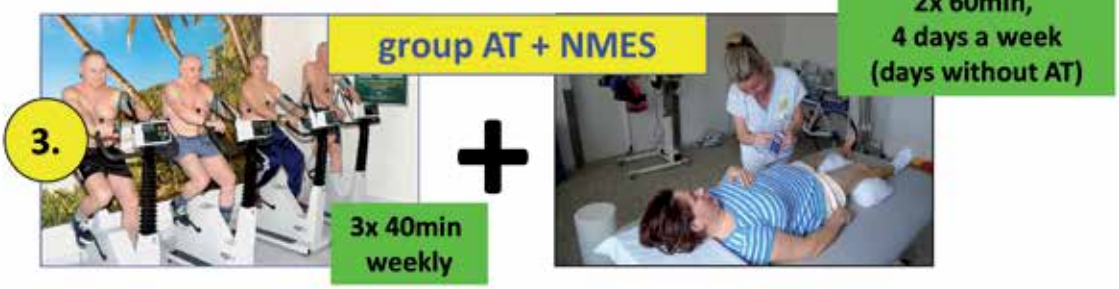
Rehab X-2,
Cefar-Compex®
(Malmö, Sweden)

bi-phasic current



frequency	10 Hz
pulse width	200 µs
ramp-up & down	0.5 sec
work time	20 sec
rest time	20 sec
maximal amplitude	60 mA
power supply	9 V
total stimulation time	60 min

stimulation protocole design:



Duration of given RHB training program = 12 weeks.

Methods:

VaSera® 1500 (Fukuda Denshi Co.)

(Department of Sports Medicine and Rehabilitation, St.Anna Faculty Hospital, Masaryk University of Brno, CZ)

Parameter	Results		Differences: T12 – T0		
	Baseline (T0)	12th week (T12)	Value	% of initial values	p
VO_{2peak} *(ml.kg^{-1}.min^{-1})*					
AT	17.8 (0.9)	20.6 (0.9)	2.7 (0.7)	15.2%	0.001
NMES	16.9 (1.0)	18.4 (0.9)	1.4 (0.3)	8.3%	0.001
AT + NMES	17.8 (0.9)	20.5 (1.0)	2.7 (0.5)	15.3%	0.001
p	0.405				
VO_2AT *(ml.kg^{-1}.min^{-1})*					
AT	11.4 (0.5)	12.5 (0.7)	1.1 (0.6)	9.6%	0.043
NMES	10.9 (0.6)	11.6 (0.5)	0.7 (0.3)	6.4%	0.030
AT + NMES	10.9 (0.5)	12.1 (0.5)	1.3 (0.3)	11.9%	0.001
p	0.568				
VE/VCO_2 slope					
AT	33.4 (1.2)	29.3 (0.9)	-4.1 (0.9)	-12.3%	0.013
NMES	33.2 (1.4)	30.2 (0.8)	-3.0 (1.1)	-9.0%	0.012
AT + NMES	31.4 (1.2)	28.5 (0.7)	-2.9 (1.1)	-9.2%	0.016
p		0.314			

* Results of CAVI measurement in group AT, AT + NMES and NMES:

Parameter[1]	AT (N = 26)	AT + NMES (N = 23)	NMES (N = 22)	p[2]
CAVI at baseline	9.31 (0.31)	9.17(0.24)	8.98 (0.23)	0.123
CAVI after 12 weeks	8.53 (0.21)[ab]	8.67 (0.28)[ab]	8.31 (0.23)[a]	0.041

[1] Statistical significance of differences evaluated using one way ANOVA

[a,b] the same letters denote homogeneous groups without statistically significant differences (Tukey post hoc test)

[2] Wilcoxon paired test

* *Soska V. et al. Exercise training combined with electromyostimulation in the rehabilitation of patients with chronic heart failure: A randomized trial. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub 2013;157(4):331-9.*

* Quality of life (MLHF score):

Parameter	Results		Differences: T12 – T0		
	Baseline (T0)	12th week (T12)	Value	% of initial values	p
MLHF score					
AT	34.3 (3.5)	24.7 (3.0)	-9.6 (2.1)	-27.9%	0.001
NMES	38.6 (4.9)	32.2 (4.9)	-6.4 (2.1)	-16.6%	0.008
AT + NMES	32.0 (4.0)	22.7 (3.5)	-9.3 (1.9)	-29.1%	0.002
p	0.021				

* *Soska V. et al. Exercise training combined with electromyostimulation in the rehabilitation of patients with chronic heart failure: A randomized trial. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub 2013;157(4):331-9.*

Comments to the results:

1. Studied exercise trainings **did not differ significantly between themselves** and this **study failed to objectively demonstrate the supposed greater benefit** from **AT + EMS** combination
(very likely due to complex pathophysiology of CHF, limited number of subjects analyzed, etc.).

2. These limitations, however, do not in any way decrease the clinical importance of NMES, which was shown as very effective method of cardiovascular rehabilitation.

NMES IN RHB OF PATIENTS WITH CHRONIC RENAL INSUFFICIENCY (CRI)

Study No. 1:

Intradialytic electrostimulation of leg extensors may improve exercise tolerance and quality of life in hemodialysis patients.

2009 - 2012

Since 2009,
the **Dept. of Sports Medicine & Rehabilitation,** St.Anne´s Faculty Hospital Brno,
developed and started a new

ID-RHB Exercise Program

(in cooperation with the IInd Department of Internal Medicine, St.Anne´s Faculty Hospital Brno)

1st supervised intradialytic exercise program in the Czech Republic !!!

22 patients

with CRI on chronic HD

(8M/12W; mean age 60.4 ± 9.7 yrs; mean duration of HD 4.8 ± 2.4 yrs):

a) aerobic exercise training group (AT; n = 11)

▼

20 weeks of intradialytic aerobic exercise training on bed-side ergometer

b) stimulation group (NMES; n = 11)

▼

20 weeks of intradialytic NMES training of of leg extensors

Patients:

a) aerobic training

(AT group; n = 11)

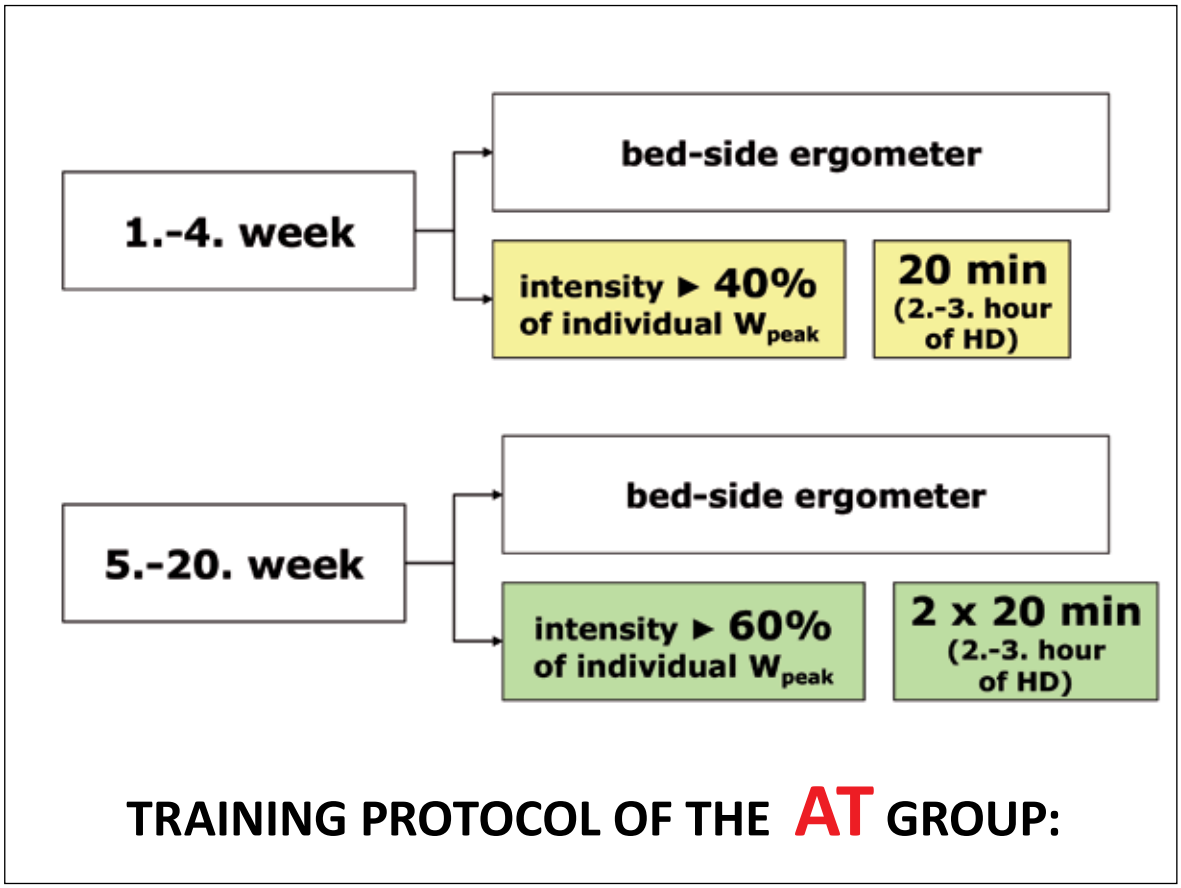
training intensity:

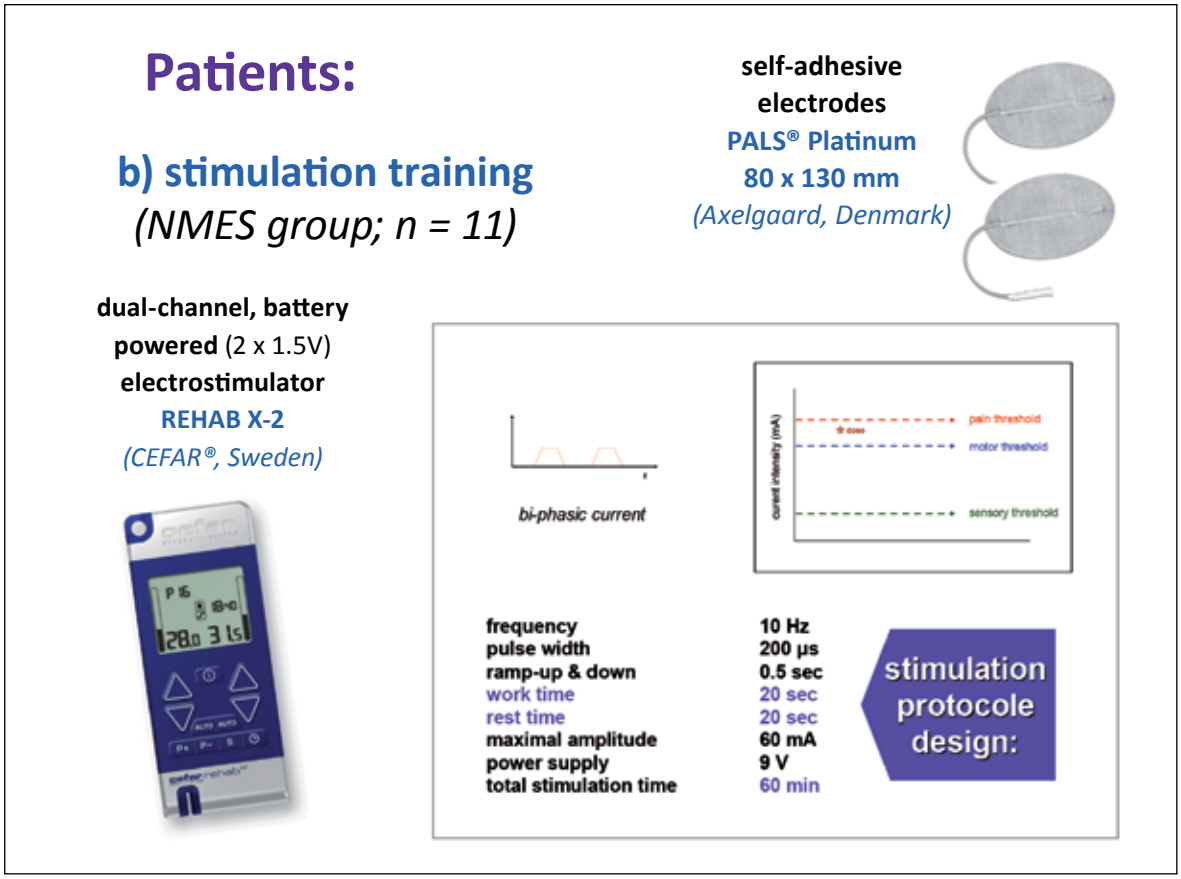
▼

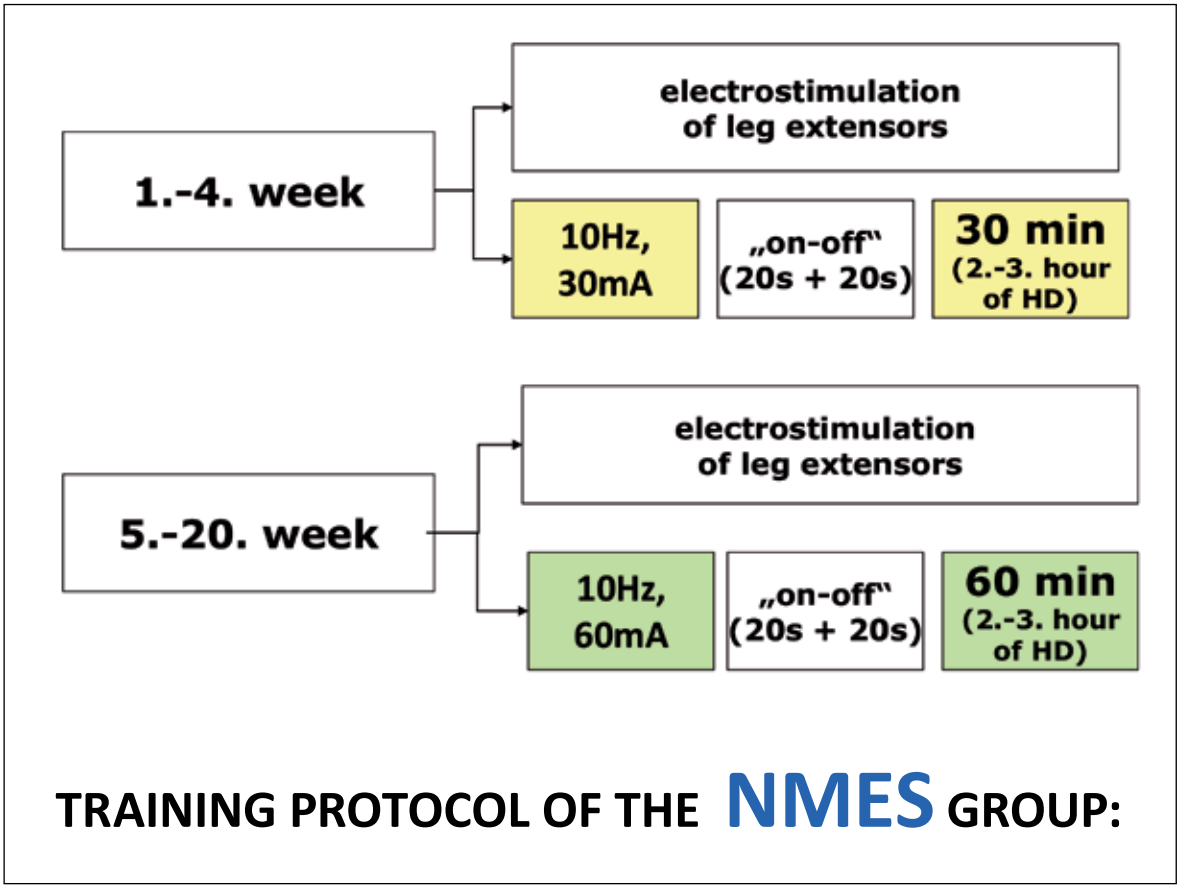
60%

of peak workload (W_{peak}) determined by ECG ergometric test at baseline

bed-side ergometer Monark 881E Rehab Trainer *(Vansbro, Sweden)*


1.-4. week
bed-side ergometer
intensity ▶ 40% of individual W_{peak}
20 min (2.-3. hour of HD)
5.-20. week
bed-side ergometer
intensity ▶ 60% of individual W_{peak}
2 x 20 min (2.-3. hour of HD)
TRAINING PROTOCOL OF THE AT GROUP:


Patients:
b) stimulation training
(NMES group; n = 11)
self-adhesive electrodes
PALS® Platinum
80 x 130 mm
(Axelgaard, Denmark)
dual-channel, battery powered (2 x 1.5V) electrostimulator
REHAB X-2
(CEFAR®, Sweden)
bi-phasic current
pain threshold
motor threshold
sensory threshold
frequency 10 Hz
pulse width 200 µs
ramp-up & down 0.5 sec
work time 20 sec
rest time 20 sec
maximal amplitude 60 mA
power supply 9 V
total stimulation time 60 min
stimulation protocole design:



Methods:

All tests were done at baseline and after 20 weeks of the given type of exercise:

isometric dynamometry *of leg extensors* (F_{max})

ECG ergometric test

(peak workload – W_{peak})

6-min „corridor walking-test"

(walked distance)

Simple questionnaire of QoL:

evaluation of the activities of daily living

(e.g. dressing, walking in a room, showering, climbing stairs up to the 1st floor without stops, etc.)

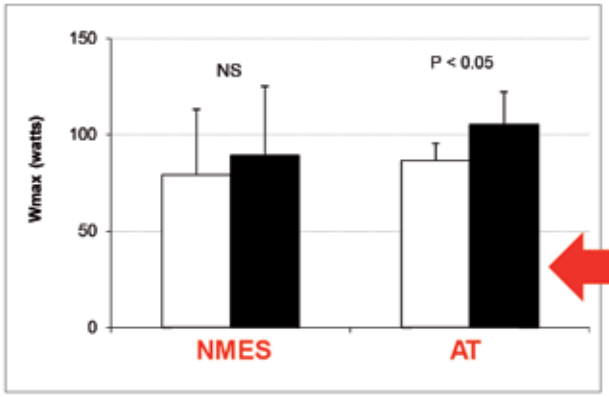
HD patients exercising on bed-side ergometer during hemodialysis procedure:

bed-side ergometer

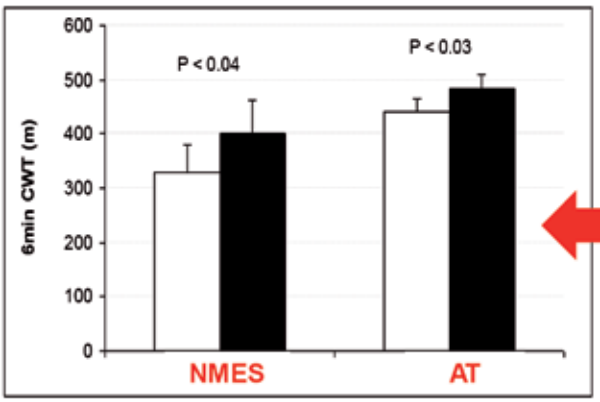
Monark 881E Rehab Trainer

(Vansbro, Sweden)

Results:



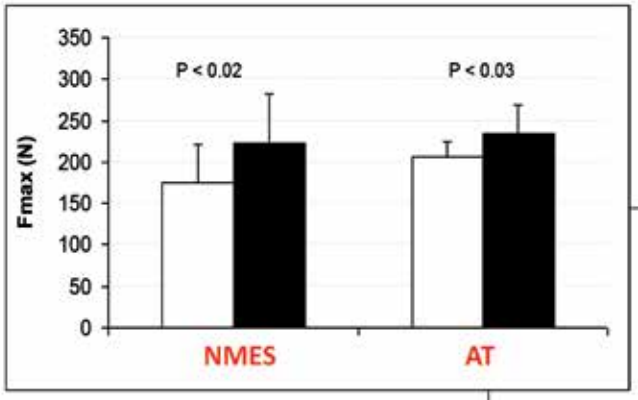
Significant increase of the peak workload (W_{peak}) assessed by ECG test in the group AT:



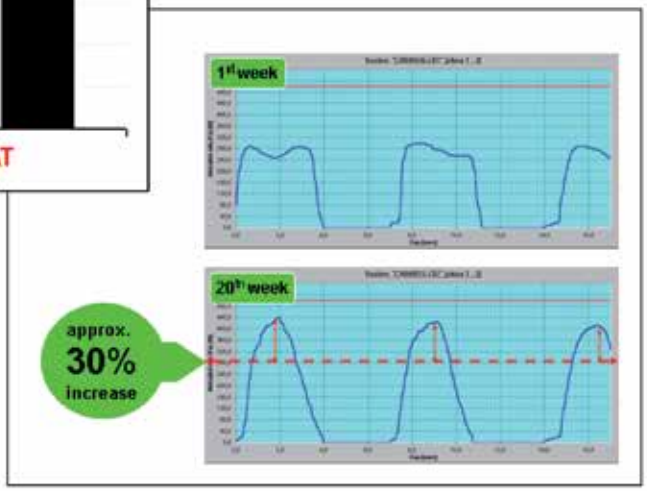
Significant increase of the distance walked (m) assessed by 6-min CWT in both groups:

Results:

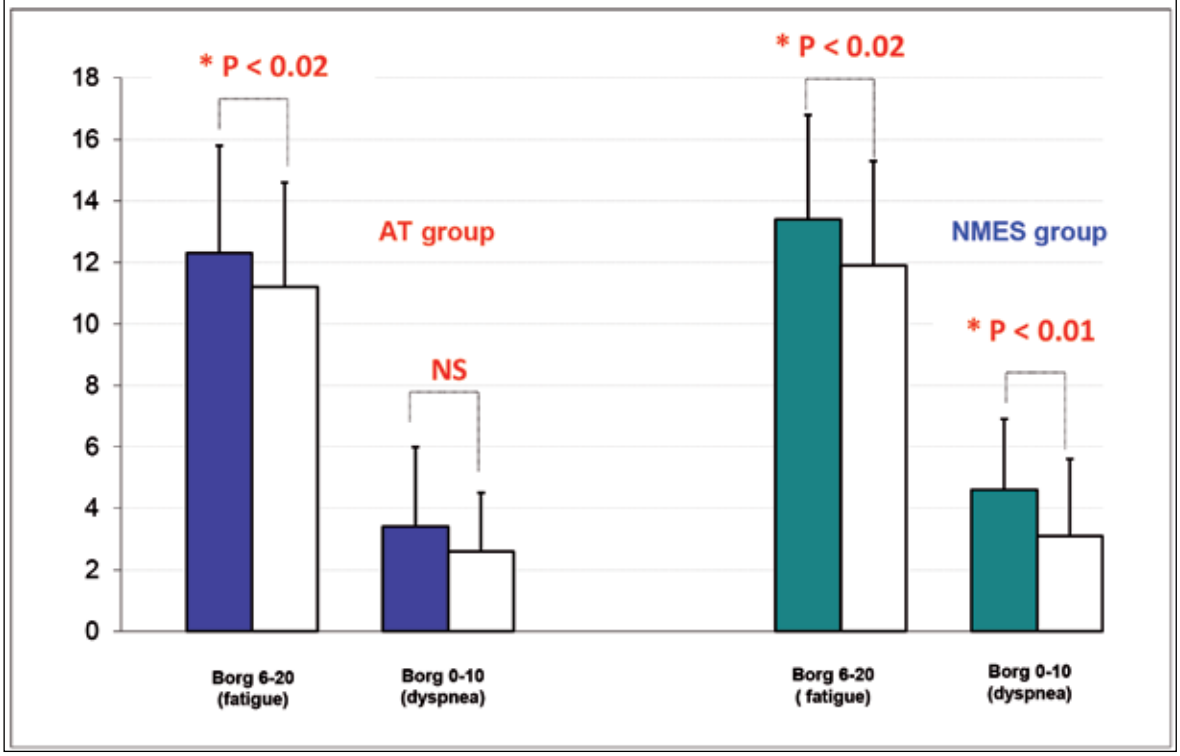
Significant increase of the muscle power (F_{max}) assessed by isometric dynamometry in both groups:



Example of the measurement of F_{max} at baseline and after 20 weeks of RHB *(original records)*:

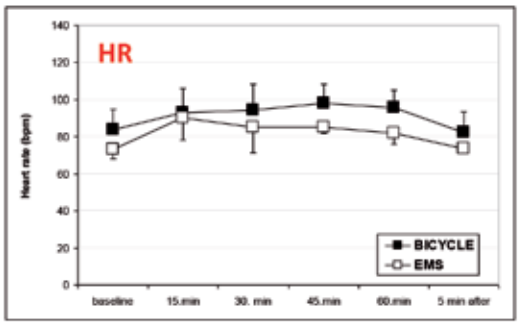


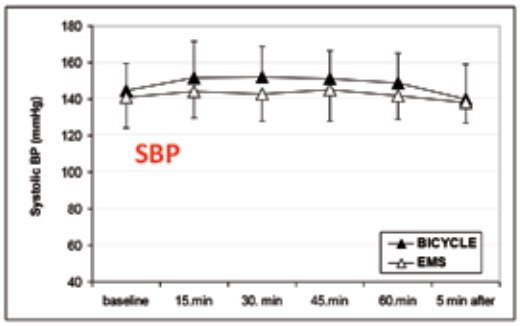
Quality of Life (daily/habitual activities assessed by Borg scales for fatigue and dyspnea)

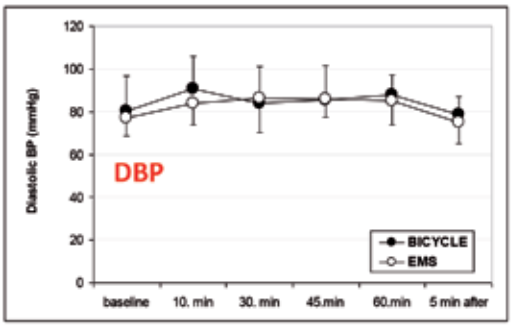


Results:

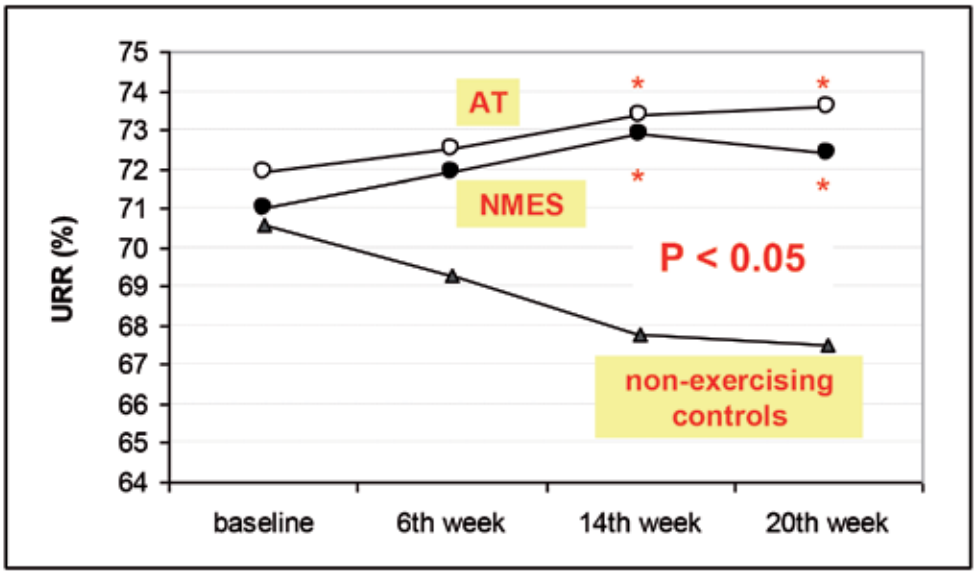
Mean values of HR, SBP and DBP registered during the intradialytic exercise period:







A significant improvement of urea removal ratio (URR) was observed throughout the ID rehabilitation period in both experimental groups *(compared to **10 non-exercising patients** who were used as **control** group)*:



Conclusion:

1.

*** 20 weeks of AT or NMES improved muscle power, peak workload, walked distance, urea removal ratio and QoL in HD patients.**

2.

NMES has been confirmed as a new and efficient RHB alternative in HD patients.

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

UNPUBLISHED RESULTS

Study No. 2

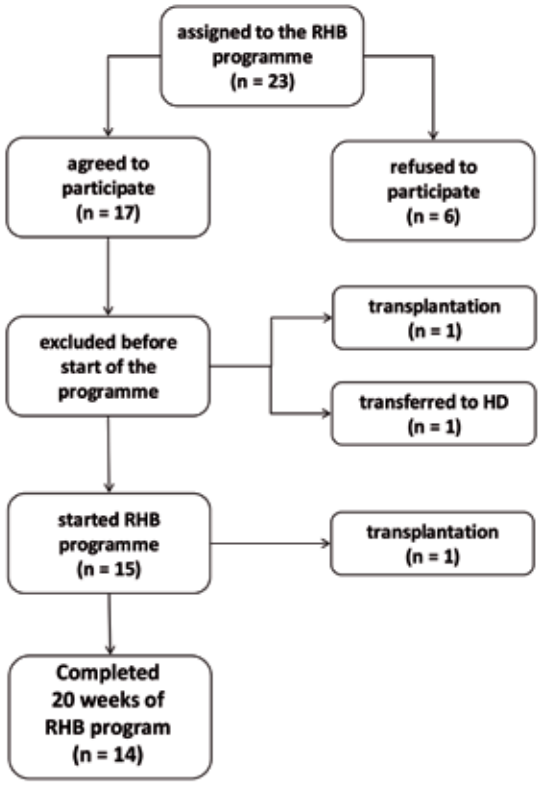
Home-based training using Neuro-muscular Electrical Stimulation (NMES) in Patients on Continuous Ambulatory Peritoneal Dialysis:

A pilot study.

2013 - 2015

Flow chart showing enrollment and randomization procedure

UNPUBLISHED RESULTS



Age	61.9 (13.7)
M / W	6 / 8

Patients:

All the subjects performed **CAPD at home 4-5x /day**. Exchange of dialysis solution through a CAPD catheter lasted **30 minutes**.

Patients:

Comorbidities:	Number (and %):
Hypertension	13 (92.9 %)
Dyslipidemia	10 (71.4 %)
Anemia	7 (50.0 %)
Diabetes mellitus type 2	7 (50.0 %)
Hyperuricemia	7 (50.0 %)
Hyperparathyroidism	6 (42.9 %)
Hyperphosphatemia	6 (42.9 %)
Obesity	5 (35.7 %)
Thrombosis	4 (28.6 %)
Cardiomyopathy	2 (14.3 %)
Asthma bronchiale	1 (7.1 %)
Hyperthyreosis	1 (7.1 %)
Vertebral algic syndrome	1 (7.1 %)

70 comorbidities in total.

REHAB *X-2 (CEFAR®, Sweden)*

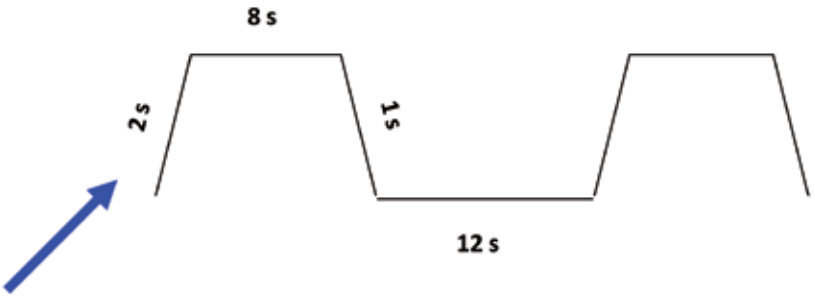
electrodes PALS® Platinum 80 x 130mm *(Denmark)*

First NMES application was done in all patients under staff supervision. After familiarization with the stimulation technique and the correct placement of electrodes, patients continued the NMES at home.

NMES was applied to quadriceps and calf muscles of both legs 2 x 30min/day.

A new type of NFES application protocole was designed:

intermittent biphasic current, frequency modulation 40-60Hz, working mode „on-off„, 2s ramp-up time, 8s period of contraction, 1s fall-down time, and 12s period of relaxation:



Based on our long experience, the slower rise time (2s) is subjectively perceived by the patients as more pleasant.

Methods:

To assess peak aerobic capacity (VO_{2peak}) and to ascertain the safety of exercise training, each participant completed a maximal incremental cardiopulmonary exercise test (spiroergometry) with 12-lead ECG, and blood pressure monitoring using standard methodology.

Methods:

Results:

Results of the initial interview showed that a large majority of the patients was **very sedentary; 89%** of them reported that the bulk of their activity consists of **brief walk** (about 20-30 minutes weekly at maximum) or other **lightweight activity**, eg. housework (cleaning, cooking, etc. about 40 min weekly at maximum).

All the patients said that they don´t perform any type of sport or leisure-time physical activity.

As the main reasons for the **low physical activity** they reported rapid onset of **premature fatigue** (especially of lower extremities), **dyspnea and pain of the locomotor apparatus.**

Changes in exercise performance at baseline and after end of rehabilitation program.

Characteristic[1] (N = 14)	Entry	End of study	Time change	p[2]
Duration of spiroergometric testing [sec]	397.5 (208.0; 660.0); 393.9 (129.5)	460.0 (237.0; 730.0); 469.6 (141.2)	62.5 (-90.0; 270.0); 75.8 (114.5)	0.041
HR_{peak}	116.0 (73.0; 134.0); 109.6 (20.6)	117.5 (84.0; 161.0); 116.9 (20.5)	5.0 (-16.0; 29.0); 7.4 (14.3)	0.078
W_{peak}/kg	0.7 (0.4; 1.4); 0.8 (0.3)	0.8 (0.6; 1.4); 0.9 (0.3)	0.1 (0.0; 0.4); 0.1 (0.1)	0.005
VO_{2peak}/kg [ml/kg/min]	10.1 (6.1; 17.3); 10.7 (3.0)	12.5 (9.6; 18.3); 12.9 (2.8)	2.4 (-0.6; 4.7); 2.2 (1.6)	0.002
RER	1.1 (0.9; 1.2); 1.0 (0.1)	1.1 (1.0; 1.2); 1.1 (0.1)	0.0 (0.0; 0.2); 0.1 (0.1)	0.023

[1] median supplemented by min; max and mean supplemented by standard deviation;
[2] Wilcoxon paired test

Changes in distance walked in 6 min (6-CWT) at baseline and after end of rehabilitation program.

Characteristic[1] (N = 14)	Entry	End of study	Time change	p[2]
HR mean (6min CWT)	104.3 (68.0; 124.5); 102.0 (17.6)	103.0 (72.0; 135.5); 103.3 (16.3)	-1.3 (-21.0; 22.2); 1.3 (12.1)	0.807
RPE (Borg scale 6 – 20)	11.8 (9.3; 15.0); 12.2 (1.7)	11.2 (7.8; 14.0); 10.9 (2.0)	-1.0 (-3.5; 1.0); -1.3 (1.2)	0.005
Distance - prediction	630.4 (448.5; 747.5); 600.8 (90.3)	620.7 (443.2; 754.5); 597.6 (91.1)	-2.7 (-33.0; 7.0); -3.3 (9.7)	0.346
Distance - reality	302.5 (105.0; 540.0); 316.7 (117.9)	351.0 (181.0; 554.0); 373.4 (114.1)	66.5 (-49.0; 144.0); 56.7 (58.4)	0.008

[1] median supplemented by min; max and mean supplemented by standard deviation
[2] Wilcoxon paired test

Changes in weight, BMI, arterial stiffness (CAVI) and muscle power (F_{max}) of the leg extensors at baseline and after end of rehabilitation program.

Characteristic[1] (N = 14)	Entry	End of study	Time change	p[2]
Weight [kg]	93.0 (64.0; 138.5); 91.5 (21.5)	91.0 (65.0; 131.5); 90.3 (20.0)	-1.0 (-7.0; 3.0); -1.2 (3.1)	**0.161**
BMI	31.1 (24.4; 41.0); 32.9 (5.4)	32.4 (25.2; 38.4); 32.0 (4.7)	-1.3 (-4.1; 1.5); -0.9 (1.9)	**0.074**
CAVI	**8.4** (5.6; 11.0); 8.3 (1.7)	**8.1** (6.0; 10.7); 8.0 (1.5)	-0.2 (-2.9; 1.5); -0.3 (1.2)	**0.432**
F_{max} (N)	**234.9** (92.9; 566.7); 243.6 (115.1)	**257.9** (106.9; 553.9); 269.9 (117.2)	14.7 (-40.5; 210.8); 26.4 (62.5)	**0.084**

[1] median supplemented by min; max and mean supplemented by standard deviation
[2] Wilcoxon paired test

Characteristic[1] (N = 14)	Entry	End of study	Time change	p[2]
Symptoms	80.2 (60.4; 93.8); 77.8 (9.4)	81.3 (70.8; 91.7); 82.0 (7.0)	6.3 (-20.8; 25.0); 4.2 (10.5)	0.074
Effects of kidney disease	57.8 (18.8; 92.9); 54.1 (23.5)	62.5 (9.4; 90.6); 58.9 (20.5)	1.8 (-21.9; 46.9); 4.8 (16.2)	0.307
Burden of kidney disease	**31.3 (0.0; 75.0); 32.6 (22.6)**	**50.0 (0.0; 68.8); 43.3 (19.7)**	**12.5 (-18.8; 37.5); 10.7 (14.4)**	0.022
Work status	0.0 (0.0; 100.0); 14.3 (30.6)	0.0 (0.0; 100.0); 17.9 (31.7)	0.0 (0.0; 50.0); 3.6 (13.4)	0.317
Cognitive function	90.0 (60.0; 100.0); 88.1 (11.1)	93.3 (73.3; 100.0); 91.9 (7.9)	0.0 (-13.3; 26.7); 3.8 (9.3)	0.248
Quality of social interaction	**76.7 (33.3; 100.0); 78.6 (18.0)**	**86.7 (73.3; 100.0); 87.6 (9.4)**	**0.0 (-13.3; 46.7); 9.0 (16.5)**	0.049
Sexual function	28.1 (0.0; 75.0); 27.4 (28.2)	28.1 (0.0; 75.0); 29.0 (26.7)	0.0 (0.0; 12.5); 1.6 (4.4)	0.317
Sleep	**67.5 (35.0; 80.0); 61.8 (13.5)**	**75.0 (35.0; 87.5); 68.9 (15.1)**	**7.5 (-37.5; 30.0); 7.1 (15.1)**	0.019
Social support	83.3 (50.0; 100.0); 81.0 (17.1)	83.3 (33.3; 100.0); 82.1 (21.1)	0.0 (-66.7; 50.0); 1.2 (29.6)	0.798
Dialysis staff encouragement	100.0 (0.0; 100.0); 91.1 (26.6)	100.0 (87.5; 100.0); 99.1 (3.3)	0.0 (0.0; 100.0); 8.0 (26.7)	0.180

Characteristic[1] (N = 14)	Entry	End of study	Time change	p[2]
Patients satisfaction	100.0 (66.7; 100.0); 91.7 (14.2)	100.0 (66.7; 100.0); 96.4 (9.7)	0.0 (-16.7; 33.3); 4.8 (13.8)	0.194
Physical functioning	**37.5 (0.0; 90.0); 38.8 (26.1)**	**55.0 (20.0; 80.0); 53.6 (19.3)**	**15.0 (-20.0; 55.0); 14.8 (21.0)**	**0.029**
Role-physical	**0.0 (0.0; 75.0); 14.3 (23.4)**	**25.0 (0.0; 100.0); 41.1 (43.4)**	**12.5 (-50.0; 100.0); 26.8 (42.1)**	**0.041**
Pain	**53.8 (22.5; 100.0); 53.6 (21.7)**	**67.5 (10.0; 100.0); 67.9 (21.8)**	**12.5 (-42.5; 47.5); 14.3 (24.3)**	**0.041**
General health	25.0 (0.0; 55.0); 24.3 (16.3)	37.5 (0.0; 65.0); 33.2 (19.1)	5.0 (-15.0; 50.0); 8.9 (17.0)	0.067
Well being	64.0 (40.0; 88.0); 66.3 (15.2)	74.0 (44.0; 88.0); 71.4 (12.8)	4.0 (-8.0; 24.0); 5.1 (10.1)	0.116
Role-emotional	**33.3 (0.0; 100.0); 45.2 (42.6)**	**100.0 (0.0; 100.0); 76.2 (38.0)**	**16.7 (0.0; 100.0); 31.0 (35.7)**	**0.016**
Social function	68.8 (0.0; 100.0); 63.4 (25.7)	75.0 (0.0; 100.0); 68.8 (27.2)	12.5 (-37.5; 37.5); 5.4 (23.9)	0.528
Energy	**47.5 (25.0; 65.0); 45.7 (12.5)**	**57.5 (35.0; 65.0); 53.9 (8.6)**	**5.0 (-10.0; 25.0); 8.2 (9.7)**	**0.012**

Limitations:

1. The main limitation of this pilot study was the small size of the tested group and also a lack of a control group.

2. It is necessary to take into account the specific conditions of the organization of provided dialysis care in the Czech Republic, especially the existence of massive superiority of hemodialysis over peritoneal dialysis.

3. This situation strongly influenced the availability of a sufficient number of subjects on PD for the eventual control group - in the period of implementation of the study, there were only 21 (!) patients on peritoneal dialysis in St. Anne´s Faculty Hospital Brno.

According to the latest information from
Institute of Health Information and Statistics (ÚZIS) there were **100 hemodialysis centers** with **1.272 dialysis beds**
in the **Czech Republic.**

*From the **7.155 treated** patients, **92% were on hemodialysis** and **8% on peritoneal dialysis.***

Citation:

http://www.uzis.cz/en/category/tematicke-rady/hemodialysis

Conclusion:

The results demonstrated that an improvement of exercise capacity and muscle power can be achieved by long-term lasting home-based NMES in PD patients.

This pilot study is the first clinical report dealing with the use of NMES in patients in CPD.

Conclusion:

Despite the mentioned limitations the results and conclusions of this study can be regarded as valid.

Our own and the international experiences clearly show that the functional parameters and quality of life in non-exercising patients on PD or HD progressively and permanently deteriorate.

Lo CY et al. Benefits of exercise training in patients on continuous ambulatory peritoneal dialysis. Am J Kidney Dis 1998; 32(6): 1011-18.

Molsted S et al. Five months of physical exercise in hemodialysis patients: effects on aerobic capacity, physical function and self-rated health. Nephron Clin Pract 2004; 96(3): 76-81.

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

Kosmadakis GC et al. Benefits of regular walking exercise in advanced pre-dialysis chronic kidney disease. Nephrol Dial Transplant 2012; 27(3): 997-1004. doi: 10.1093/ndt/gfr364.

Liu YM et al. Effects of Aerobic Exercise During Hemodialysis on Physical Functional Performance and Depression. Biol Res Nurs 2014 15.

Summary comments:

So far, in the **past 15 years,**
we succeeded to apply the
RHB program based on NMES
in **151 patients** with
chronic heart failure,
and to **25 patients** with
chronic renal insufficieny
(11 on HD and 14 on PD)
with **good results.**

self-adhesive
electrodes
PALS® Platinum
80 x 130 mm
(Axelgaard, Denmark)

Limitations of NMES:

1.

NMES = alteration of the normal recruitment order and the non-physiologic simultaneous activation of MU.

2.

NMES = non-physiologically induced muscle activation which could decrease efficiency of contraction and promote the development of neuromuscular fatigue.

Strategies must be designed as part of electrical stimulation regimens to offset the high degree of fatigue associated with NMES.

Recommended measures:

1. NMES application must be optimized to reduce fatigue and enhance power output by adjusting the associated stimulation parameters.

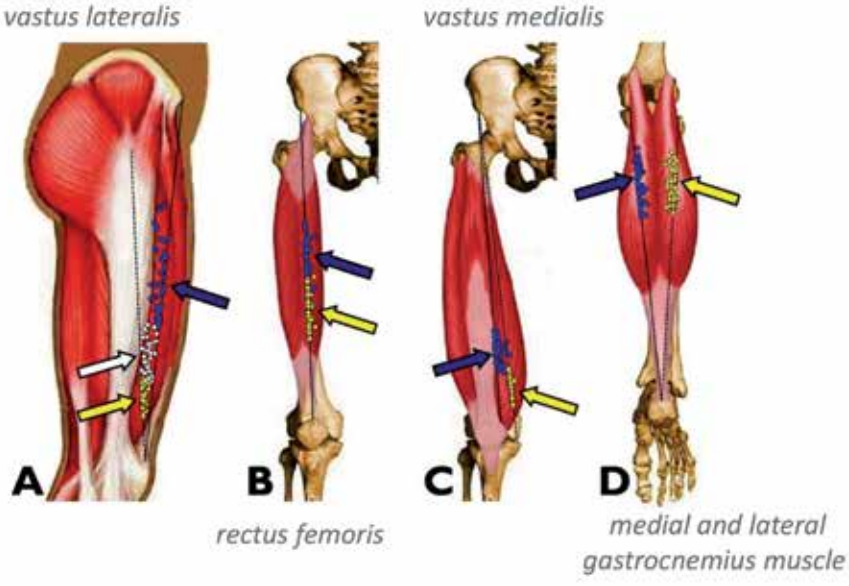
2. A full understanding of the settings that govern the stimulation is vital for the safety of the patient and the success of the intervention.

3. Consideration should be given to:

frequency, pulse width/duration, working mode, intensity (amplitude), ramp time, pulse pattern, program duration, program frequency

***and* targeted muscle group.**

Muscle motor point (MP) identification before the placement of electrodes is a simple strategy to improve NMES application in the context of clinical rehabilitation:



Position of the muscle motor points for the quadriceps and gastrocnemii in 53 healthy subjects *(From: Botter et al. Copyright © 2011 Springer).*

1.

Exercise training by NMES promotes neural and muscular adaptations that are complementary to the effects of voluntary resistance training.

2.

NMES increases physical performance and muscle power, reduce arterial stiffness, stabilize autonomic nervous system and improve quality of life in patients with severe chronic diseases

3.

NMES is non-expensive and safe method, does not require systemic activation and could be easily performed at home without medical supervision.

4.

We assume, that the therapeutic potential that NMES holds for rehabilitation medicine is immeasurable.

Photo documentation of Prof. MUDr. P. Dobšák, CSc. lecture 24.4.2018 in Graz

Figure 1: *Prof. N. Goswami, M.D. introduce the lecture before the team of the Institute of Physiology, University Graz, the lecture of Prof. MUDr. P. Dobšák, CSc., Masaryk University*

Figure 2: *The lecture of Prof. MUDr. P. Dobšák, CSc., Masaryk University*

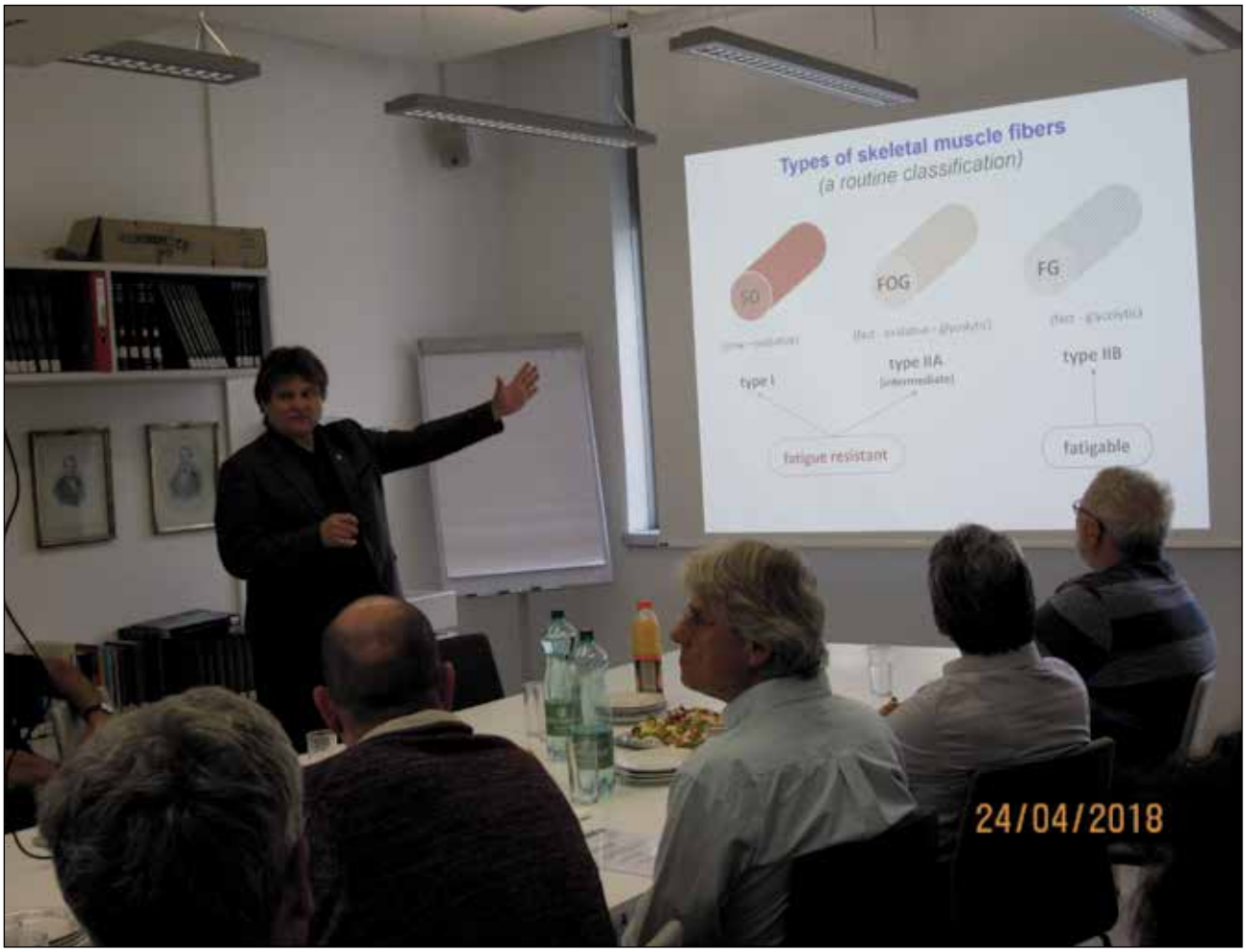


Figure 3: *The lecture of Prof. MUDr. P. Dobšák, CSc., Masaryk University*

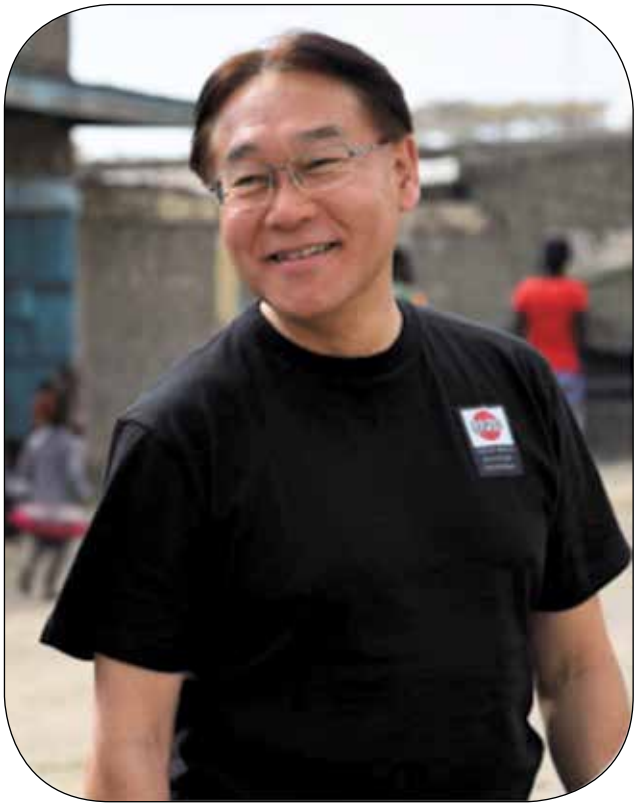
Figure 4: *Prof. Maximilian Moser, University Graz, discuss the lecture with Prof. MUDr. P. Dobšák, CSc., Masaryk University*

Figure 5: *Prof. N. Goswami, M.D., Graz, close the lecture of Prof. MUDr. P. Dobšák, CSc., Masaryk University*

Medical situation and our activities in Kenya

Mitsuo TAKEI, Miki IWANE

Medical Corporation KOSHINKAI, Japan,
Grand Forest Japan Hospital, Nairobi, Kenya



Dr. Mitsuo TAKEI, M.D., Ph.D. *CEO and Founder of Medical Corporation KOSHINKAI, Japan. CEO and Founder of "Grand Forest Japan Hospital", Nairobi, Kenya Chairman of "Dream World Healthcare Program", Nairobi, Kenya*

Introduction of Kenya

Population is 44.860.000 people (2014/World Bank). There are 47 tribes in Kenya (Kikuyu, Ruo, Masai, Somali and so on). Located on the east coast of the African continent of the equator, the area of Kenya is about 586.000 square kilometers (about 1.5 times larger as Japan). The capital, Nairobi, is the biggest city in the East Africa. Inner waters are approximately 10.700 square kilometers. Most of the waters originally come from Lake Turkana and Victoria. Kenya territory is characterized by diverse landscape, such as high alpine glaciers, large scale of volcanoes, ancient giant hills; flat deserts, coral reefs, small islands, etc. Kenya was colonized by Great Britain in 1895. Colonization continued for a long time, until the first president Jomo Kenyatta acquired the independence in 1963. Large number of English and Indian people stayed in Kenya and obtained Kenya citizenship.

National language:	Kiswahili
Official language:	English
Religion:	Christian, Islam, traditional religions, etc.
Rate of population change:	29.9%
Possible rate of change:	no data
Population density:	about 68 people/km^2
Birthrate:	12.4 (per 1.000 people)
Death rate:	4.3 (per 1.000 people)
Life expectancy:	54 years
Life expectancy (male):	53 years
Life expectancy (female):	56 years
Marriage rate:	no data
Divorce rate:	no data

History of our activities in Kenya.

The activities started when a Kenyan friend who used to stay in Japan asked us to visit Kenya. At that time, Kenya´s infrastructure or medical situation was worse and not well oriented. This situation was a real tragedy. For example, medical service in Kenya was just like the post-war-medical service in Japan. By seeing the medical circumstances, we were encouraged to do something (*"… and acting with a spirit of chivalry."*). That is the beginning of Kenya project. At first, we establish a local NGO and since 2013 we started first a Medical Camp in one slum, collaborating with Ministry of Health in Kenya. Our project tried to be the self-produced type, not depending on donation. The Medical Center was established in 2016. It is necessary to highlight that some type of Medical Corporation in Kenya does not exist, and for that reason, our project started as Limited Company.

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, aiming to help the society through activities, such as friendship between Japan and Kenya that emphasizes public benefit and employment support for the Kenyan citizens.

Project of Medical Camp

We operate health guidance, health check and treatment for poor people in slums in Nakuru County once a month (from May 2013). In order to help, improve and sustain the health of

Kenyan people, our main goal is giving health examinations for pregnant women, children and old adults (including non-communicable and infectious disease check, administration of medicaments, such as vaccination, vermicides, etc). Japanese nurses measure height, weight and BMI, and save data. We treat approximately 200 ～300 patients in each free Medical Camp. In total (until August 2018) we have already treated about 50.000 patients since 2013.

Services provided by the Medical Camp

1. general treatment, medical examination
2. gynecologic check-up
3. HIV test and counselling in pregnant women
4. family planning
5. children health check, medical examination:
   - ✦ vaccination
   - ✦ growth monitoring and nutrition check
   - ✦ administration of vitamin A and vermicide
6. general examination (blood, urine, infectious disease check: malaria, etc.)
7. HIV counselling (except 3)
8. health and sanitation education, health and disease guidance

Constitution of staff and numbers in medical camp

Number of Kenyan staff (the daily wage secured by the Kenya Ministry of Health):

- ✦ nurse (3),
- ✦ clinical officer (2),
- ✦ laboratory medical technologist (1),
- ✦ nutritionist (1),
- ✦ pharmacist (1),
- ✦ several medical students and volunteers, etc.

Number of Japanese staff (20 ~ 30 people in total):

- ✦ doctor,
- ✦ nurses,
- ✦ physiotherapists,
- ✦ occupational therapists,
- ✦ clinical engineers,
- ✦ medical technologists, etc.

Forest Japan Medical Centre

We opened Forest Japan Medical Centre in Nairobi on April 11th 2016 (Fig.1). We provided high quality medical equipment, mainly from Japan (CT scanner, ultrasonography, digital X-ray device, endoscopy, laboratory equipment, etc.). *"Quick diagnosis and treatment"* - this is the daily motto of our center, which we try to follow accurately. We can diagnose also from Japan (remote diagnosis) using an internet system.

Figure 1: *Opening ceremony (Medical Center in Nairobi, April 2016)*

Project of training of human resources

Medical staff (Japanese and Kenyan) work together to share the skills and knowledge, aiming to sustain and improve healthcare. Moreover, we promote a friendship and understanding between cultures and traditions. The project of training of human resources involves:

1. medical diagnostic service project at Kenya
2. target country : Republic of Kenya
3. duration: June of 2016 ~ May of 2019 (for 3 years)
4. target area: Nairobi city and Nakuru west sub-county
5. target group: Kenyan medical staff (doctors, nurses, radiographers, laboratory technicians, ultrasound technicians, pharmacists, etc.) in Nairobi city and Nakuru west sub-county.

Actual and future goals

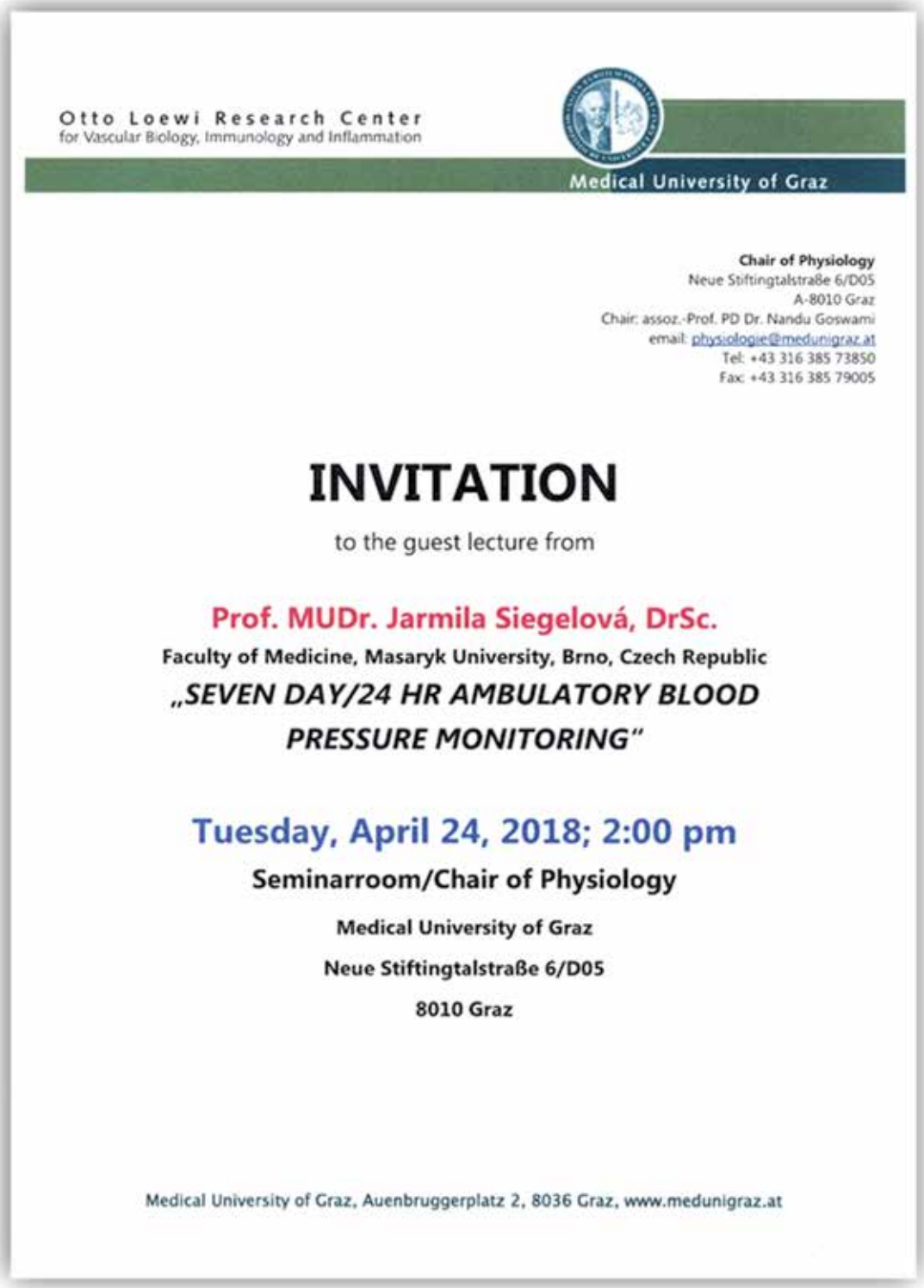
1. Dispatch Japanese medical staff to Kenya, and educate them (diagnosis, treatment skills, medical service, etc.).
2. Invite Kenyan medical staff to Japan and train them at Japanese medical facilities.

3. Spreading the information about our activities and educational program for community in Kenya.
4. A lecture and training program for Kenyan medical staff (mainly in Nairobi city), was already started.

Figures show health check in the Medical Facility at KAIZORA Institute (specialized in the treatment of children suffering from congenital cognitive disorders).

Seven Day /24 h Ambulatory Blood Pressure Monitoring

Prof. MUDr. Jarmila Siegelova, DrSc.
Faculty of Medicine, Masaryk University, Brno



Otto Loewi Research Center
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INVITATION

to the guest lecture from

Prof. MUDr. Jarmila Siegelová, DrSc.

Faculty of Medicine, Masaryk University, Brno, Czech Republic

„SEVEN DAY/24 HR AMBULATORY BLOOD PRESSURE MONITORING"

Tuesday, April 24, 2018; 2:00 pm

Seminarroom/Chair of Physiology

Medical University of Graz

Neue Stiftingtalstraße 6/D05

8010 Graz

Medical University of Graz, Auenbruggerplatz 2, 8036 Graz, www.medunigraz.at

Introduction

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

Figure 1: *Right sides Prof. MUDr. B. Fišer, CSc., Prof. Dr. T. Kenner, B. Kenner, Doc. MUDr. M. Pohanka, Ph.D., Dr. O. Schwartzkopff, Prof. Dr. F. Halberg, MUDr. J. Dušek, CSc., Prof. MUDr. J. Siegelová, DrSc. (Brno Consensus, 2008)*

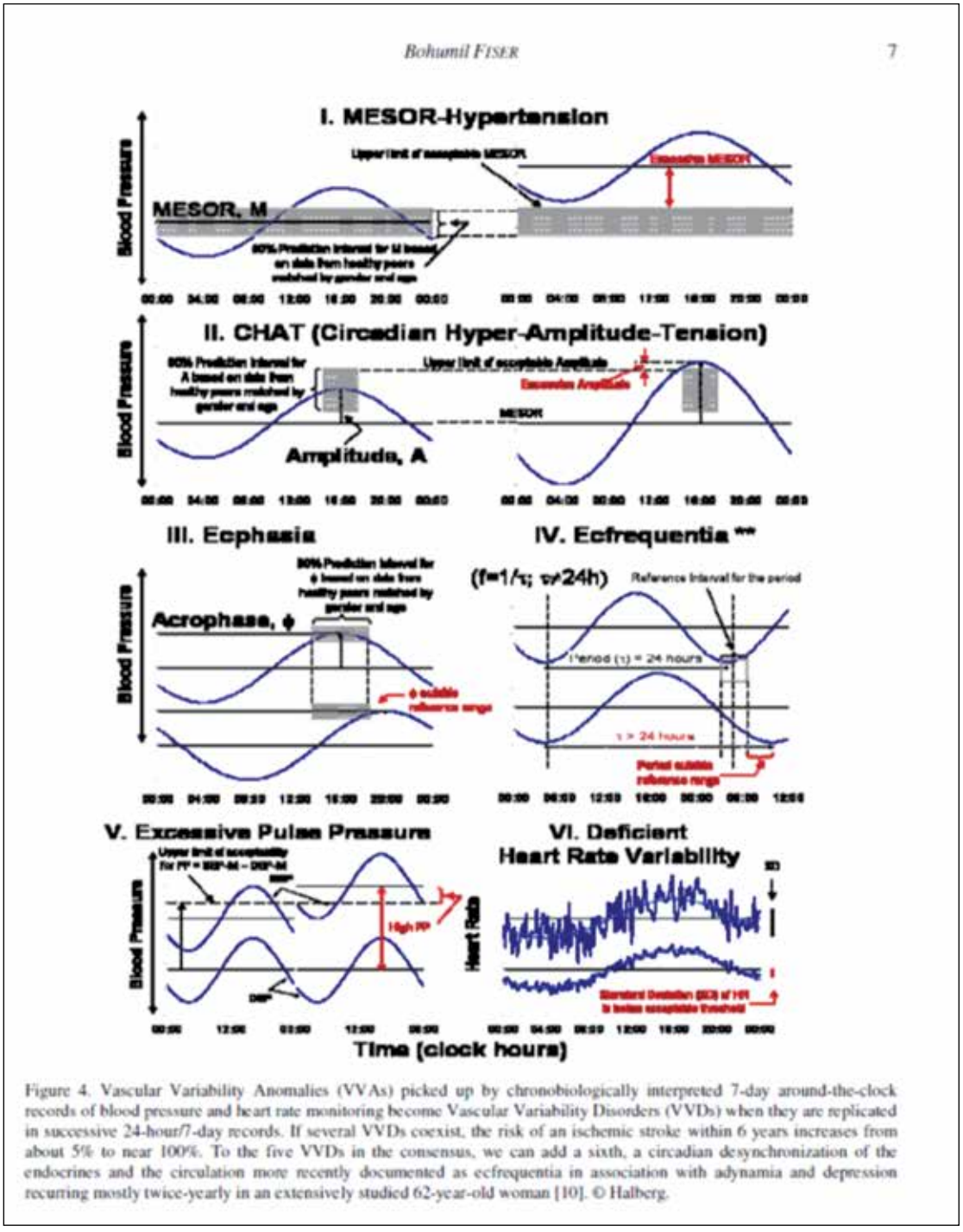

Figure 4. Vascular Variability Anomalies (VVAs) picked up by chronobiologically interpreted 7-day around-the-clock records of blood pressure and heart rate monitoring become Vascular Variability Disorders (VVDs) when they are replicated in successive 24-hour/7-day records. If several VVDs coexist, the 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

Many studies confirmed the prognostic significance of night-to-day blood pressure ratio for prediction of a higher rate of cardiovascular complications.

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.

The evaluation of night-to-day blood pressure variability during 7 days of ambulatory blood pressure measurement was the aim of our study.

Healthy subjects

Methods

Thirty subjects (18 males, 12 females), twenty one years to seventy three years old, were recruited for seven-day blood pressure monitoring. Medical Instruments TM2431 (A&D, Japan) were used for ambulatory blood pressure monitoring (oscillation method, 30-minute interval between measurements). One-hour means of systolic and diastolic blood pressure were evaluated, when night-time was considered from midnight to 0600 h and day time from 1000 to 2200 h, avoiding the transitional periods. Mean day-time and mean night-time systolic and diastolic pressures were evaluated every day.

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

Results

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

Variability of night-to-day ratio during 7-day monitoring is seen in figure.

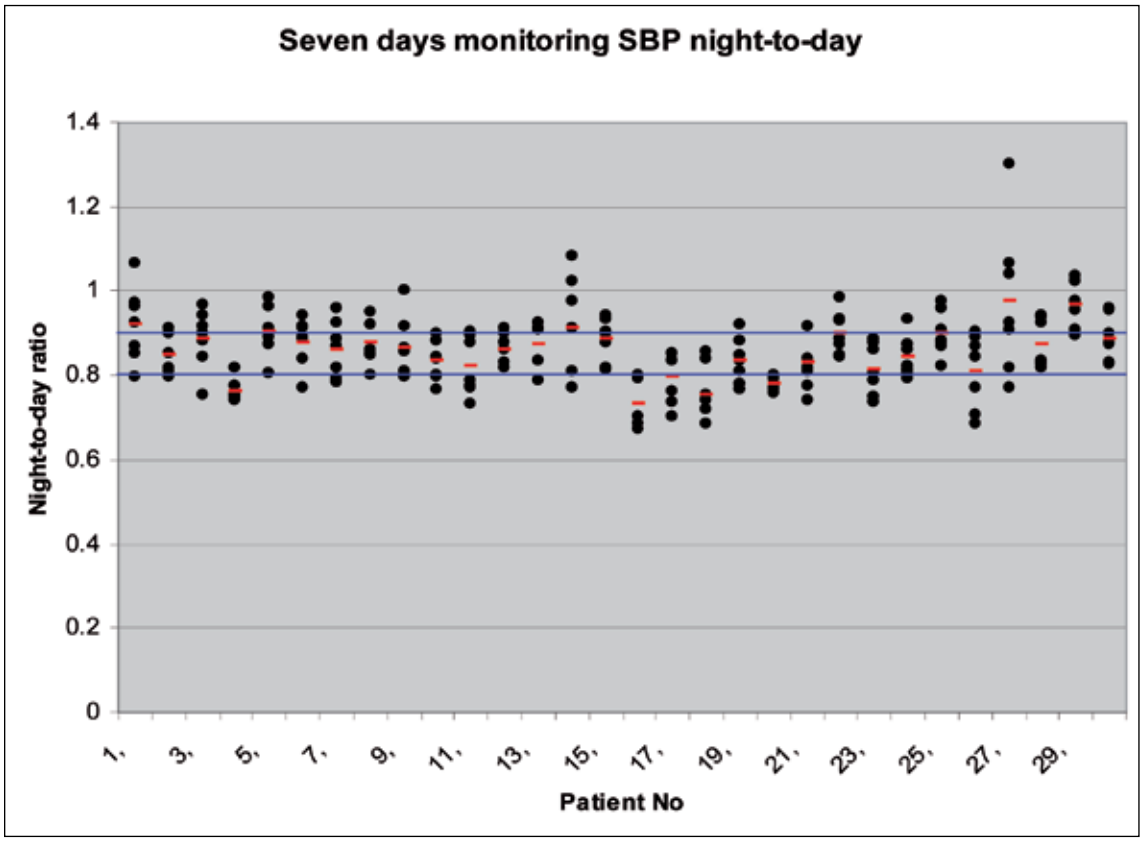

Figure 3

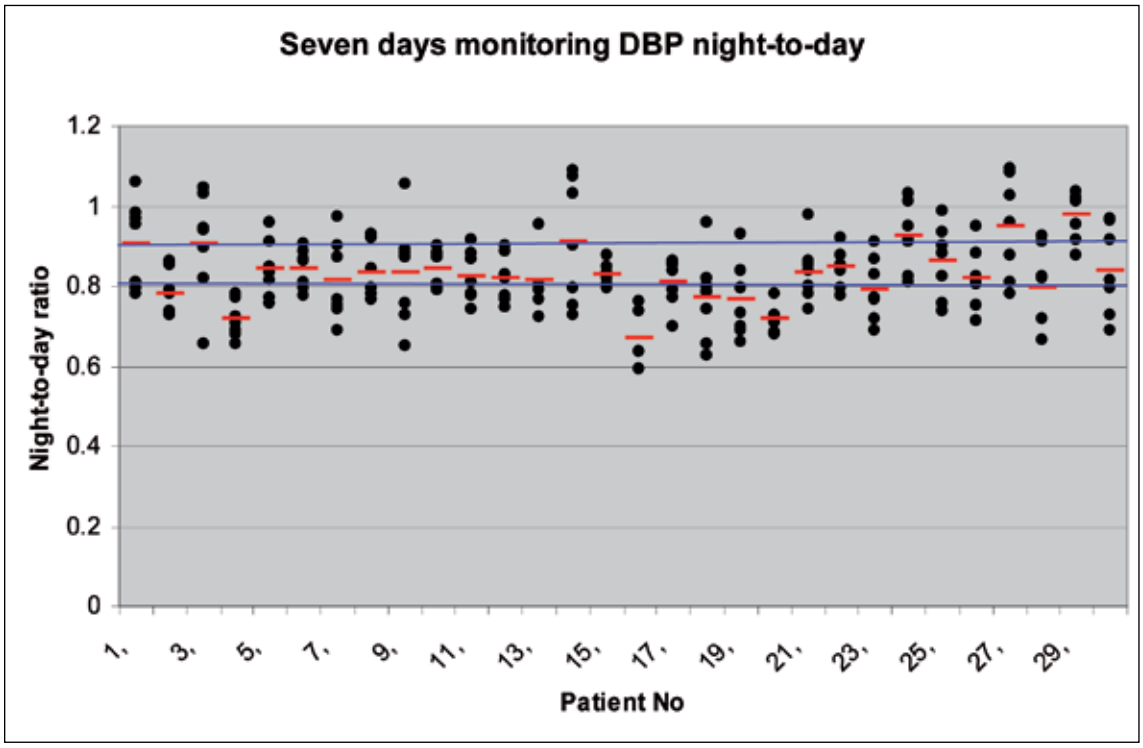

Figure 4

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 8 subjects (27 %) were one day classified as ultra-dippers and the other day as reverse-dippers.

Similarly no subject classified as DBP dipper or ultra-dipper every day was found. Four subjects (13 %) were one day classified as ultra-dippers and the other day as reverse-dippers.

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

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

Healthy subjects and exercise

Patients after infarctus of myocardium and exercise

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 – 2431 of the Japanese firm A&D 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.

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 pictures.

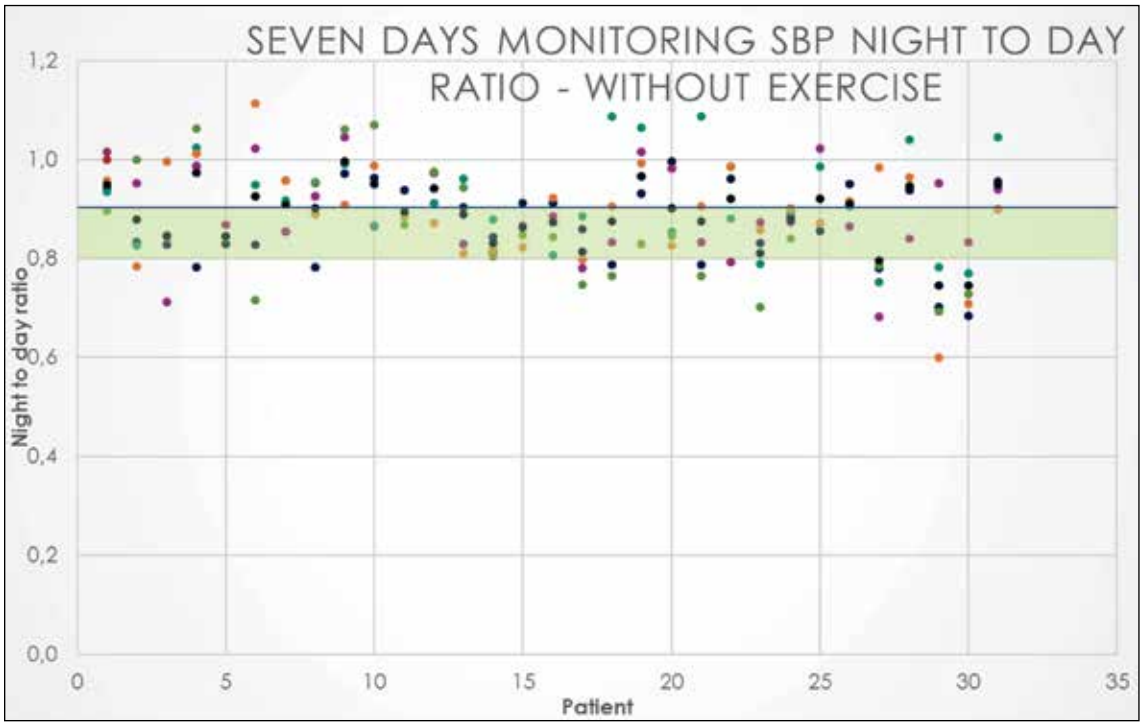

Figure 1: *Seven-day ambulatory monitoring blood pressure monitoring in patients with ichemic heart disease: SBP night to day ratio in the days without exercise*

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.

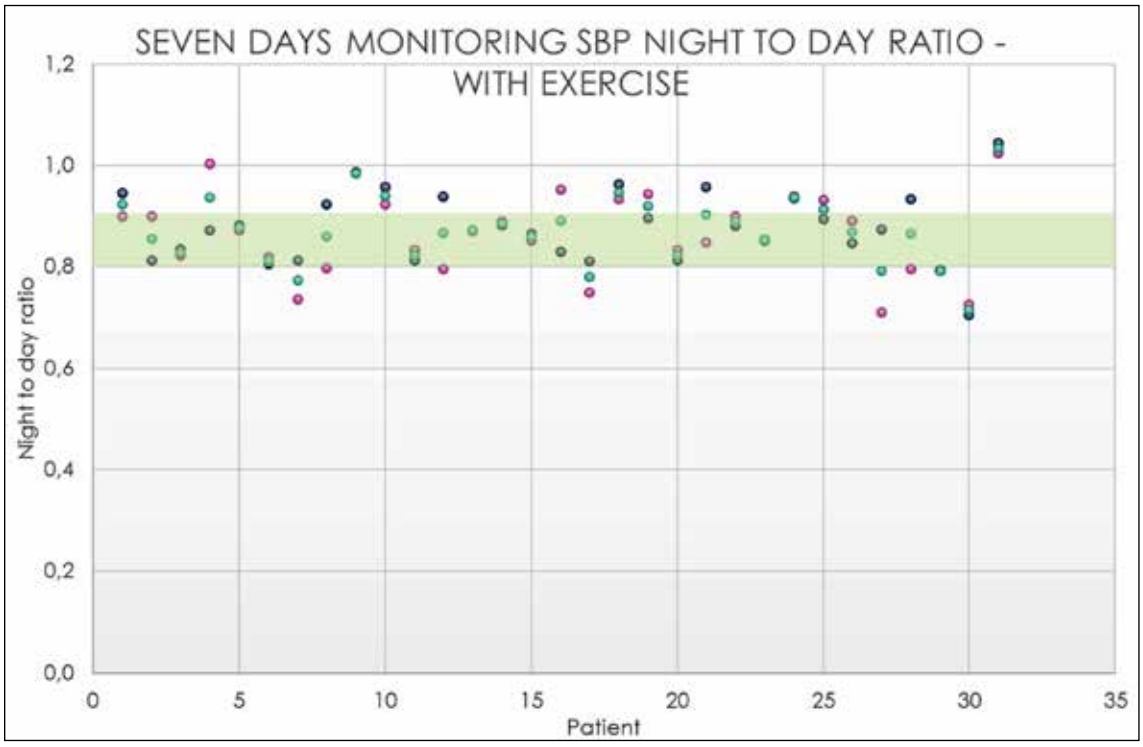

Figure 2: *Seven-day ambulatory monitoring blood pressure monitoring in patients with ichemic heart disease: SBP night to day ratio in the days with exercise*

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.

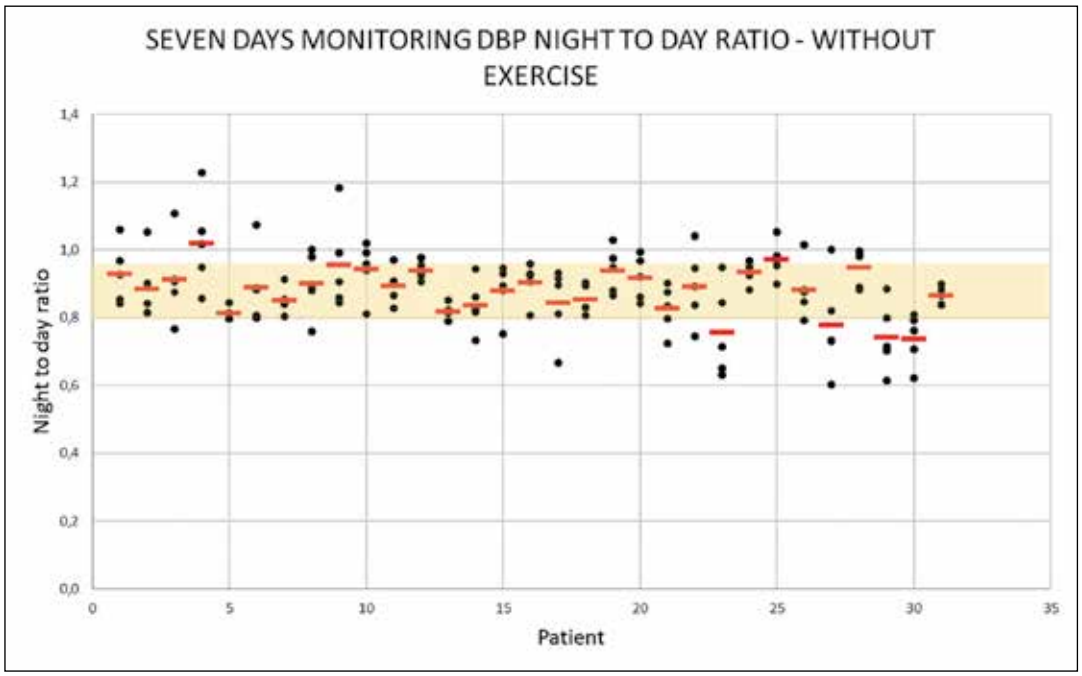

Figure 3: *Seven-day ambulatory monitoring blood pressure monitoring in patients with ichemic heart disease: DBP night to day ratio in the days without exercise*

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

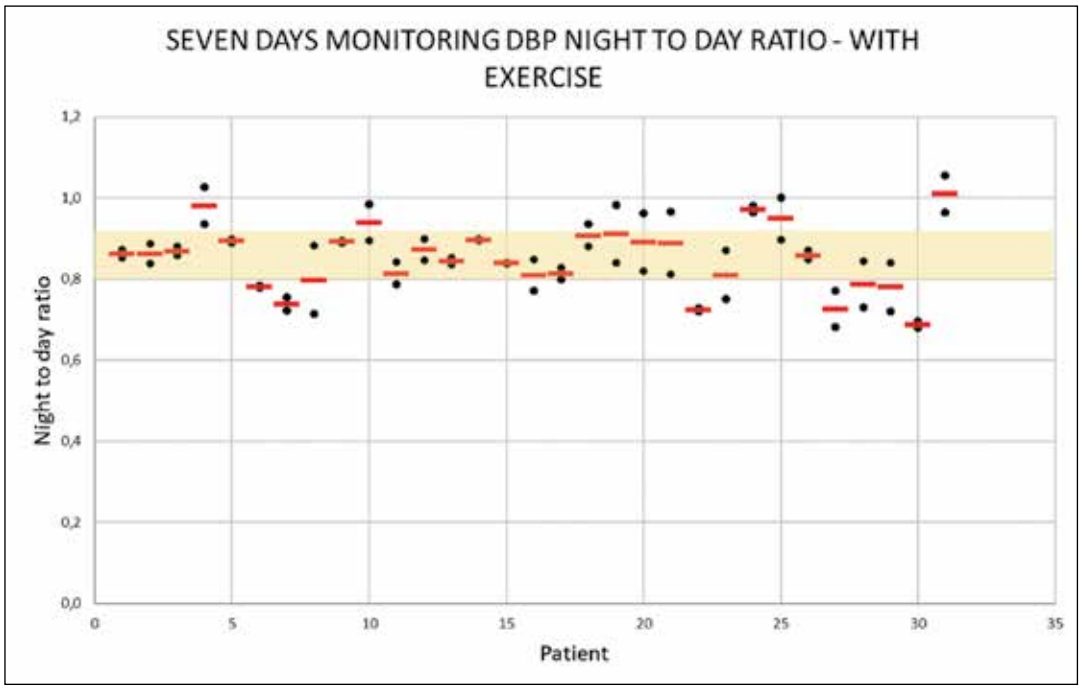

Figure 4: *Seven-day ambulatory monitoring blood pressure monitoring in patients with ichemic heart disease: DBP night to day ratio in the days with exercise*

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 ambulatory blood pressure monitoring.

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

Photo documentation of Prof. MUDr. J. Siegelová, DrSc. lecture 24.4.2018 in Graz

Figure 5: *Prof. N. Goswami, M.D. began the lecture before the team of the Institute of Physiology, first Prof. Maximilian Moser, 24.4.2018 in Graz*

Figure 6: *Prof. MUDr. J. Siegelová, DrSc. started the lecture, Graz 2018*

Figure 7: *Prof. MUDr. J. Siegelová, DrSc., Graz 2018*

Figure 8: *Prof. N. Goswami, M.D. discussed the lecture, Graz 2018*

Figure9: *Prof. N. Goswami, M.D. in discussion with Prof. MUDr. J. Siegelová, DrSc., Graz 2018*

Figure 10: *Univ. Prof. Anna Gries, Univ. Prof. Dr. Dieter Platzer, Univ. Prof. N. Goswami, M.D., PD Dipl. Ing. Dr. Hermut Lackner, Prof. MUDr. J. Siegelová, DrSc., Prof. MUDr. P. Dobšák, CSc., Prof. Dr. Andreas Rössler, Univ. Prof. Dr. Eugen Gallasch, Univ. Prof. Dr. Daniel Schneditz, Dr. Bianca Brix, Dr. Zdenko Kasac, Dr. Thomas Lehner, Anita Ertl, Institute of Physiology, Graz 2018*

In memoriam Clara Maria Kenner, Dr. in Phil. Mag. A Phil. (1967 - 2018)

It is with great sadness that we have learned that Clara Maria Kenner died on Tuesday, October 16, 2018, at the age of 51 peacefully in the circle of her family.

The last visited in family of Prof. Kenner was at the occasion of invited lectures of Prof. MUDr. P. Dobšák, CSc. and Prof. MUDr. Jarmila Siegelová, DrSc. in Dept. of Physiology Medical University of Graz, Austria in April 24, 2018.

The visit of family of Univ. Prof. Thomas Kenner. On the picture is Prof. MUDr. Jarmila Siegelová, DrSc., Dr. Clara Kenner, Univ. Prof. Thomas Kenner, Brigitte Kenner and Prof. MUDr. P. Dobšák, CSc.

Univ. Prof. Dr. Thomas Kenner, M.D. dr. H. mult. cooperated with us the last 28 years in the Masaryk University, Brno.

Our thoughts are with Professor Kenner´s family at this difficult time.

Prof. MUDr. Jarmila Siegelová, DrSc. and Prof. MUDr. Petr Dobšák, CSc.

How Life in Space Can Benefit Older Persons on Earth!

Nandu Goswami[1,2] ✉

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Introduction

Physiological deconditioning similar to that seen in spaceflight also occurs on Earth, especially as a consequence of the aging process and also due to bedrest or bed confinement and/ or immobilization. Illness or injury in older persons frequently requires hospitalized based care. However, the immobilization that occurs during hospitalization is itself a major factor in physiological deconditioning and functional decline and in older persons can further contribute to a downward spiral of increasing frailty, dizziness upon standing up (orthostatic intolerance) and increased risk and incidence of falls.

Bedrest is used as a ground-based analog for studying the effects of weightlessness on physiological systems as seen during space flight (Jost, 2008; Pavy Le Traon et al., 2007). Bedrest immobilization is used routinely by space agencies to simulate effects of physiological deconditioning induced by spaceflight (Arzeno et al., 2013; Cvirn *et al*., 2015; Oshea *et al.,* 2015). As older persons spend up to 80% of their time in hospital bed-confined, bedrest studies can also help in furthering our understanding of the deconditioning process during hospitalization in older persons.

Astronauts in space spend substantial time doing physical training to counteract the deconditioning due to the effects of microgravity and to alleviate orthostatic intolerance on return to Earth. Could such physical activity programs carried out by astronauts in space be used during bedrest immobilization in older persons to counteract deconditioning as well? This is important as early interventions are known to be associated with decrease incidence of orthostatic intolerance, falls and falls related injuries (Singh *et al*., 2008).

Recent data generated from bedrest studies related to space research suggest that resistance exercise, together with proper nutrition, is effective in maintaining physiological functionality in astronauts during spaceflights of up to six months duration. Similarly, some studies have suggested that nutritional therapy (for example, high protein diet), along with resistance training, improves lean muscle mass and muscle strength in older persons. This could a long way in decreasing the incidence of orthostatic intolerance, falls and falls related injuries, especially upon standing up following long term bedrest confinement (Goswami et al., 2018).

Therefore, knowledge obtained from space research can provide guidance towards optimizing health care strategies to tackle bed-confined deconditioning, especially in older persons (Goswami et al, 2017).

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NONINVASIVE METHODS IN CARDIOLOGY 2018

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

Published by Masaryk University in 2018
First edition, 2018
Print run: 60 copies

Printed by Tiskárna Knopp s.r.o., U Lípy 926, 549 01 Nové Město nad Metují

ISBN 978-80-210-9109-2

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ISBN 978-80-210-9109-2