

**Report of activities of the Halberg Chronobiology Center (HCC): 2018** 31 December 2018

As 2018 comes to a close, it is time to reflect on activities this past year and to thank all our colleagues here and abroad for the continued success of the Center.

The HCC was as productive as ever, thanks to cooperation with colleagues locally, nationally and internationally. Progress was primarily made in the context of blood pressure and heart rate monitoring, as this is an interesting time when rapid technological advances are changing how data can be collected, analyzed, and transmitted. The importance of assessing blood pressure and heart rate variability, notably in terms of their circadian characteristics, and of screening for circadian rhythm alterations is becoming more widely recognized. These were topics we studied in relation to a number of circumstances. In so doing, we learned about adaptation to the space environment, and about how to restore healthy circadian patterns for health maintenance and risk assessment. Selected highlights are detailed below.

Interesting new information was obtained from the ECG monitoring of astronauts during long-term missions on the International Space Station with Kuniaki Otsuka, Professor at Tokyo Totsuka Royal Clinic, Women's Medical University's Executive Medical Center, Japan, in cooperation with members of the Japanese Space Agency. Our manuscript on adaptive processes of the autonomic system in healthy astronauts, gauged by changes in heart rate variability, has been published in Scientific Reports. Its topic focuses on associations with structures and functions of neural networks in the brain in an attempt to determine how the autonomic regulatory system may adapt to environmental conditions in space. Different astronauts seem to adapt using complementary mechanisms involving the circadian system. Ongoing studies now explore the effect of magnetic activity on these adaptive processes by analyzing ECG records covering 48 instead of just 24 hours.

We are happy that our long-term association with Yoshihiko Watanabe, Professor of Internal Medicine at Tokyo Women's Medical University, Japan, will continue after his recent retirement, and we look forward to seeing him in Minnesota for weeklong visits in the winter and in the summer for many years to come. As Yoshihiko was invited to deliver a lecture at the end of his tenure, it gave us an opportunity to review the results from our long-term cooperation. Among his major contributions to chronobiology are (1) the lessons we learned from longitudinal around-the-clock monitoring of blood pressure and heart rate on himself, his son and several of his patients, some spanning 10 years or longer; (2) novel approaches to the chronotherapy of blood pressure disorders; and (3) evidence supporting the influence of space weather on blood pressure and heart rate. We documented for the first time the presence of an about 11-year periodicity in heart rate and heart rate variability, a finding later extended to other long-term time series and to other solar signatures, such as the about 1.3-year transyear. From the effect of autogenic training to the test of different anti-hypertensive agents on the circadian rhythm of blood pressure and his unique personalized chronotherapeutic approach based on weeklong ABPM profiles following treatment at 6 different circadian stages of each patient, we learned about the importance to restore a healthy circadian profile in addition to lowering blood pressure itself.

Thanks to support from the A&D Company (Tokyo, Japan), weeklong records of blood pressure and heart rate continue to accumulate, not only from Japan and Minnesota, but also from Belgium, the Czech Republic, and Kazakhstan, as part of our BIOCOS project. These activities earned the invitation by Wop J Rietveld, Professor at Leiden University in The Netherlands, and Luiz Menna-Barreto, Professor at the University of Sao Paulo, Brazil, to contribute a review to a special issue of

Biological Rhythm Research dedicated to the perspectives of chronobiology around the world. It was an opportunity to review the history of blood pressure measurement, the methodology available for its chronobiologic assessment, and how current advances in technology and wireless communication may bring a sea change to healthcare. From this perspective, our comments on the recommendations related to the use of ambulatory blood pressure monitoring in the new guidelines by the American College of Cardiology and the American Heart Association and in those by the European Society of Cardiology and the European Society of Hypertension included the need for a greater emphasis on longitudinal around-the-clock measurements interpreted chronobiologically. The evidence provided in support of our views was presented and discussed at the yearly meeting on Noninvasive Methods in Cardiology organized by Jarmila Siegelova, Professor at Brno's Masaryk University, Czech Republic. With Jarmila and her team, we are currently investigating the effect of shift work on blood pressure and heart rate.

As co-investigator on a 3-year grant awarded to Lyazzat Gumarova, Associate Professor at Al-Farabi Kazakh National University, Almaty, Kazakhstan, to study the chrono-physiological mechanisms of the adaptation of the cardiovascular system in humans to environmental and socio-ecological factors, we are currently examining how body mass index correlates with various indicators of circadian hemodynamics in Kazakh university students. Obese or overweight young men have abnormal circadian patterns of blood pressure and heart rate. An overall effect of body mass index on the blood pressure of young men is not found in young women, suggesting that estrogens, which are highest at the age of the study participants, may offer cardio-protection.

Alterations of the circadian rhythm in body temperature were demonstrated by around-the-clock monitoring of patients with advanced primary open-angle glaucoma by Denis Gubin, Professor at Tyumen's Medical University, Siberia, and his team. The fact that the condition is characterized by progressive retinal ganglion cell complex damage may account for our observation that the body clock still works in these patients, but its synchronization to the 24-hour environment is compromised, evidenced by delayed bedtime and shortened sleep duration as the condition worsens. This year, Denis has been invited by his University to become Editor-in-Chief of the Tyumen Medical Journal, which he plans to develop into a Journal of Chronomedicine. I was pleased to accept his invitation to serve on the journal's editorial board.

With renewed interest in timed restricted feeding to strengthen the circadian system as a means to address the obesity epidemic, we analyzed data from a small randomized, single blind, crossover trial comparing morning versus evening feeding. The study, inspired by results first reported by Franz Halberg in the 1970s, was conducted in a secondary care center by Ram B Singh, Professor at the Halberg Hospital and Research Institute in Moradabad, India. As anticipated, feeding in the evening was associated with a significant increase in body weight, body mass index, and waist circumference, whereas feeding the same amount of energy in the morning was not. Fasting blood glucose was lower on morning than on evening feeding and glycosylated hemoglobin increased in association with evening feeding but decreased in association with morning feeding. Consuming most calories earlier rather than later in the day may thus offer protection against the metabolic syndrome. The topic of timed restricted feeding was also reviewed in a book on the role of functional food security in global health, co-edited by RB Singh. With him, we continue to serve as editors-in-chief of the World Heart Journal.

Effects of gender, age, diet and smoking status on the circadian rhythm characteristics of circulating plasma lipid peroxides and antioxidant enzymes were investigated further in data on clinically

healthy Indians obtained by Ranjana Singh, Associate Professor of Biochemistry at King George's Medical University, Lucknow, India, and her father, RK Singh, Professor of Biochemistry at the Shri Guru Ram Rai Institute of Medical & Health Sciences, Patel Nagar, Dehradun, India. As many other physiologic variables, advancing age was associated with a decreased circadian amplitude of catalase; in the case of superoxide dismutase, glutathione peroxidase, and glutathione reductase, the circadian amplitude started decreasing around 40 years of age. Malondialdehyde was lowest among vegetarians who do not smoke. A vegetarian diet was also associated with lower glutathione peroxidase in both males and females. Catalase was lower among smokers, who also tended to have a smaller 24-hour amplitude, notably in 20- to 60-year olds. These results have just been accepted for publication in *Biological Rhythm Research*.

A new cooperation was initiated this year with Julie Sletten, who recently defended her doctoral thesis on circadian rhythms of the fetal heart rate and heart rate variation in low-risk and pre-gestational diabetic pregnancies at the University of Bergen, Norway. It started as a simple question regarding the use of the cosinor suite of programs in CATkit (Chronomics Analysis Toolkit), and it developed into lively discussions of some interesting methodological aspects of data analysis related to the challenges of analyzing short and dense time series with her and her mentor, Dr. Jørg Kessler. Results on her data extend our reference values on the circadian rhythm of heart rate from birth to old age and in pregnancy to fetal life, when they already served to detect differences in the presence of pre-gestational diabetes.

Locally, we are indebted to El Nolley and Chris Adams, volunteering IEEE engineers of the Phoenix Project with whom we continue to explore alternative noninvasive techniques to measure blood pressure. New technological advances were briefly reviewed in our invited *Biological Rhythm Research* paper, from attempts to rely on photo-plethysmography to noninvasively measure blood pressure on the wrist, to new devices for home blood pressure capable of automatically collecting data during the night, and devices based on the analysis of the blood pressure waveform. Such recent advances in technology represent a unique occasion to integrate chronobiological methods and concepts into these evolving systems to make sure that massive data collection does not happen at the expense of quality data analyses.

We are particularly indebted to Software Engineer Larry Beaty for continued cooperation on several fronts. The development of an ambulatory blood pressure monitor on the wrist that would automatically correct for position relative to heart level may be revived with help from members of the Institute for Engineering in Medicine. Such a device could then serve to diagnose the different VVDs (Vascular Variability Disorders, i.e., abnormalities in the circadian variation in blood pressure and heart rate) more easily than by ABPM, for a refined assessment of cardiovascular disease risk. As a complementary approach, we became interested in analyzing the blood pressure waveform recorded over very short spans following an invitation to cooperate with Daniel Duprez, Professor of Cardiology, and David Jacobs, Professor of Epidemiology, both at the University of Minnesota.

In preparation for an online course in chronobiology, we also started devising simulations to illustrate key concepts of chronobiology and time series analysis. While our application for funding scored well, it was not funded, and we are currently exploring new opportunities. Preliminary steps in the design of dynamic mathematical simulations were achieved with help from Software Engineer A. Chase Turner, using Mathematica. Chase's interest in the Apple's ResearchKit led us to learn how to retrieve data from the Apple watch. It also served as part of the physiology research project of Philip Mic, an undergraduate student from our department.

At the HCC, Mary Sampson helps editing manuscripts. Her and Linda Sackett-Lundeen's endeavor to making available the entire collection of Franz Halberg's 3600 published works electronically in a fully searchable form is steadily proceeding. Linda has also been instrumental in several projects, including the analysis of data from stroke patients, compared to bedridden and ambulatory controls, and literature searches related to time restricted feeding. We both spoke to a group of seniors about circadian rhythms at the York Cooperative in Edina, where we were pleasantly surprised to reconnect with one of the volunteers in the Minnesota-Japan breast cancer study originated by Franz Halberg, Erhard Haus and Teru Kawasaki. Cathy Lee Gierke added several new features to her CATkit program. The program now has the capability to run the population-mean cosinor and corresponding parameter tests. The program has also been extended to run more than a single record at a time. The software and its documentation are regularly updated and uploaded to CRAN. Cathy's researched the effect of geomagnetic disturbances on the circadian rhythm of circulating melatonin. As anticipated, magnetic activity was associated with decreased circadian amplitude of melatonin, which was primarily contributed by a decrease during the night. With her, we also turned back to our project on the Atlas of chronomes (time structures) when Medhi Horri, a former student of Franz Halberg and Jim Holte, returned from his home country and expressed interest in contributing to the activities of the HCC.

Work at the HCC attracted several invitations to lecture at various meetings this year. In April, a video on chrono-cardio-metabolic diseases was presented at the inaugural meeting of the new Lebanese Society for Chronobiology in Beirut, Lebanon. In May, a video entitled "Franz Halberg: a maverick ahead of his time" was presented by invitation from Walter Kofler, President of the International Academy of Science, at the International Symposium dedicated to the 25th anniversary of the Russian Section of the International Academy of Sciences (Health and Ecology). The accompanying paper was published in the Russian section of the Herald of the International Academy of Sciences. In October, a Power Point entitled "Factors influencing human blood pressure and heart rate in clinical health" was presented by co-author Vincenzo Valenzi, Professor of Biophysics at the University of Rome "La Sapienza", Italy, at the XIII International Conference on the Applied Biophysics, Bionics and Biocybernetics in Kiev, Ukraine. Also in October, we all contributed remotely by computer to Jarmila's annual workshop on Noninvasive Methods in Cardiology held in Brno, the Czech Republic.

More projects are ongoing, including the mapping of circadian rhythms of patients with normal-weight obesity under the leadership of Dr. Pavel Homolka, Physician at Masaryk University in Brno, Czech Republic, and of patients in the ICU with Elizabeth Luszczek, Assistant Professor of Surgery at the University of Minnesota. With Pavel and Manlio Vinciguerra, Principal Investigator at the International Clinical Research Center, Brno, Czech Republic, we analyzed blood pressure data from their Kardiovize Brno 2030 project, a prospective cardiovascular health study in Central Europe.

In addition to Philip Mic, two other undergraduate students from our department did a research project with us. Fatimatou Saka analyzed the blood pressure data from the NIH DASH (Dietary Approaches to Stop Hypertension) study from a chronobiologic viewpoint. The effect of the DASH diet on blood pressure was circadian stage-dependent and differed between men and women. She presented her results in a poster at the department's annual CardioPalooza event. Yen Nguyen analyzed circadian parameters from 7-day/24-hour ABPM records obtained from residents in Tosa, Japan, a long-term project started with Kuniaki. As anticipated, women had a lower blood pressure than men, but, contrary to expectation, such a difference was no longer found in subjects treated for

high blood pressure, suggesting that current practice does not account for gender differences in determining targets to treat. A similar finding was made by another student, Shahrukh Rizvi, who had worked on the Brno, Czech Republic, database, also consisting of 7-day/24-hour ABPM records.

We had the pleasure to meet in person Katarina Borer, Professor in the School of Kinesiology at the University of Michigan, with whom we had studied the effect of exercise on post-menopausal women several years ago. We were also pleased to reconnect with David Blask, Professor and Head of the Laboratory of Chrono-Neuroendocrine Oncology in the Department of Structural and Cellular Biology at Tulane University, when he came to lecture on “Circadian time-of-day-dependent ocular light exposure: bad and good consequences for cancer metabolism, progression and therapeutic responsiveness”.

With great sadness, we mourn the loss of several friends and colleagues. Miguel Angel Revilla Ramos, Professor of Applied Mathematics at the University of Valladolid, Spain, passed away on April 2, 2018. His long-term support of our activities and his lasting friendship will be dearly missed. On October 21, 2018, Earl E. Bakken, co-founder of Medtronic, passed away. While he will be primarily remembered for his development of the first external, battery-operated, transistorized, wearable artificial pacemaker in 1957, we shall always be indebted to him for his staunch support of chronobiology. The regular meetings we enjoyed over the years with him and Franz Halberg remain vivid in my mind and are a lasting inspiration in everything I do. Thomas Kenner, Professor of Physiology and former President of the University of Graz, Austria, died just before Christmas, on December 22, 2018. We shall treasure his legacy and continue to learn from his always inspiring lectures at the Brno meetings, where we had the privilege to meet him and his wife Brigitte on several occasions. We also recently learned about the passing on September 17, 2017, of BD Gupta, Emeritus Professor at the Post-Graduate Institute of Medical Education and Research in Chandigarh, India, with whom Franz Halberg conducted the first chrono-radiotherapy trial of cancer patients, which led to the doubling of the two-year disease-free survival of patients treated at the time of their peak tumor temperature.

The HCC continues to benefit from cooperation with many more colleagues locally, nationally, and internationally. In particular, we are grateful to Drs. Francine and Julia Halberg who serve as advisors to the HCC. Their continued support of activities at the HCC is much appreciated.

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