Report of activities of the Halberg Chronobiology Center (HCC): 2024 24 December 2024

As we celebrate the end of 2024 and prepare for the arrival of 2025, we thank our colleagues here and abroad for the opportunity of continued cooperation.

Our book "Chronobiology and Chronomedicine: From Molecular and Cellular Mechanisms to Whole Body Interdigitating Networks", invited by the Royal Society of Chemistry was published in February. It covers all physiological systems and their role in several biological processes and disease conditions, with contributions from experts around the world. It was an ambitious project that was highly rewarding to bring to fruition as it greatly enriched our understanding of the diverse ways by which circadian (and other) rhythms shape our physiology.

With Kuniaki Otsuka, Professor emeritus at Women's Medical University (Tokyo, Japan), we summarized results obtained on the International Space Station. We documented the role played by circadian rhythms in endpoints of heart rate variability (HRV) and magnetic fluctuations on the astronauts' adaptation to the space environment, and showed how HRV changes in different frequency ranges can provide insight regarding the involvement of different brain mechanisms. Interest in both circadian rhythms and non-ionizing radiation is growing now that we are at the verge of space commercialization and space agencies are planning missions into deep space where radiation, microgravity, confinement and isolation, distance from earth, and closed or hostile environments will be even greater challenges than they have been thus far. With Kuniaki, we also continued to explore the role played by the 12-hour clock, which is thought to have a molecular mechanism even more ancient than that underlying the circadian system. A reinforced 12-hour component helped astronauts adapt to space. It also helped residents of a rural Japanese town adapt to irregular schedules in their everyday life.

With Denis Gubin, Professor at Tyumen State Medical University, Russia, we expanded our investigation of light in physiology. Light signaling to the suprachiasmatic nuclei being the primary synchronizer of circadian rhythms, awareness has increased of the importance of keeping a regular schedule of light exposure during the daytime and its avoidance at night. Monitoring residents of the far-north in Siberia offers a unique opportunity to study the effect of light of different wavelengths on physiology in view of the drastic seasonal variation in day length. During the spring equinox, Arctic residents with excessive exposure to blue light at night had a higher body mass index (BMI), a relation mostly characterizing those carrying the G allele in the melatonin receptor 1B gene, which is associated with altered melatonin signaling and secretion. As compared to the spring equinox, during the winter and summer solstices, the phase of the circadian melatonin rhythm was delayed and its normalized amplitude was reduced. While similar in extent and direction, the phase delay related to a deficit in morning exposure to blue light in the summer, compared to an excess evening exposure to blue light in the winter. Delayed phases of blue light exposure and melatonin during winter and summer solstices compared to spring equinox were associated with disadvantageous changes in markers of metabolic health. The importance of light was further discussed in a review of circadian disruption associated with glaucoma, while another forthcoming publication reviews methodological aspects of circadian light hygiene, the practice of adjusting the 24-hour dynamic range of light exposure to support the natural sleep-wake cycle and circadian rhythms. As actigraphy data largely contributed to the above findings, an invited review of wearables in chronomedicine is currently in press and available as a preprint ahead of publication.

Our close cooperation with Masaryk University continued. There, Jarmila Siegelova, Professor, and Alena Havelkova, Associate Professor, participated in our project on the BIOsphere and the COSmos (BIOCOS), with support from the A&D Company (Tokyo, Japan). Several results were presented at the meeting in Brno, Czech Republic, organized this year by Associate Professor Michal Pohanka. Notably, the reliability of the Ambulatory Arterial Stiffness Index, computed from ambulatory blood pressure monitoring (ABPM) records, was found to accurately reflect arterial stiffness in population studies, but the large uncertainty associated with its determination may limit its use for the management of individual patients. Yoshihiko Watanabe, Professor in the Department of Medicine, Nippon Dental University Hospital, Tokyo, Japan, contributed new results on the chronotherapy of blood pressure using nutraceuticals such as eggplant and Kalahari watermelon. These results and those on the analysis of actigraphy data, where a challenge is the detection and management of non-wear data, will be published in the forthcoming issue of Noninvasive Methods in Cardiology. The Brno Proceedings will also include results from Pavel Homolka and his team, with whom we cooperate on a study of normal-weight obesity. We look forward to his visit to Minnesota with Michal Pohanka and Dr. Mariana Omelková Kárová.

In August, the HCC hosted Dr. Fernanda Gaspar do Amaral, Adjunct Professor, Federal University of São Paulo, São Paulo, Brazil. She came to familiarize herself with our computer programs to analyze the time structure of actigraphy records from patients who had their pineal gland removed, usually the result of surgery or treatment of a brain tumor. The patients were primarily adolescents who were monitored prior to treatment and who were followed-up for one year on treatment consisting of personalized melatonin supplementation. It was a great occasion to have the whole team working together in person at the HCC. A. Chase Turner (software engineer) helped extract and format the data. Cathy made sure that her R program, CATkit, worked properly and made some needed adjustments before showing Fernanda how to use it. HCC in-house programs ran by Germaine checked Cathy's CATkit results. Visualization of the results indicated the need to identify non-wear episodes, so that corresponding spurious data could be deleted prior to analysis. This work was presented by Chase on behalf of the team at the meeting in Brno and the corresponding manuscript is now in press in the Proceedings of the meeting.

With Christian Schubert, Professor at the Medical University of Innsbruck, Austria, Dr. Lennart Seizer, University Hospital of Tübingen, Germany, and Joschua Geuter, University College London, London, United Kingdom, we documented about-weekly or about-half-weekly variations in biomarkers assessed longitudinally in single case studies. We also published a methodological review on sampling in the context of studies in psychology.

This year marked the renewed cooperation with Dr. Rollin McCraty, Director of Research, HeartMath Institute, Boulder Creek, California. We analyzed HRV endpoints determined from synchronous around-the-clock ECG records spanning about 15 days from groups of about 20 participants in five different countries and found synchronized about weekly variations in two of the five locations that coincided with groups where Rollin's team observed significant long-term correlations across participants using a completely different methodological approach. These results were published in Scientific Reports. In the middle of the study, participants performed a 15-minute meditation session, which was associated with increased HRV documented for several endpoints. These data were shared with an honor student we mentored. Her thesis on the physiological effects of meditation on cardiovascular system variables earned her to graduate *summa cum laude*.

The cooperation with David Jacobs, Professor of Epidemiology, and Daniel Duprez, Professor of Cardiology, both at the University of Minnesota, continues, as results on subclavian calcification and its association with future cardiovascular events are currently being summarized for publication. With Larry A Beaty (software engineer), we are also processing additional tonometry records obtained by Mary Whipple, Assistant Professor with the University of Minnesota School of Nursing, who is examining sex differences in the effects of breaking up sedentary behavior on vascular function among older adults with type 2 diabetes.

At the HCC, Larry added new features to our "sphygmochron" program that analyzes ABPM records to identify VVDs (vascular variability disorders, i.e., alterations in the variability of blood pressure and heart rate) that outcome studies found to increase markedly the risk of cardiovascular disease. We prepared a video to illustrate the program: what it does, why it does it, and how it does it. The video, posted on the revamped HCC website, also documents how to run the program using a real ABPM record as illustrative example. Cathy Lee Gierke was instrumental in rebuilding our website, which now has the capability of posting educational videos. Chase made progress in coding a suite of cosinor-based procedures in Mathematica, finding the right infrastructure to make his programs easily usable across platforms. Chase attended the Wolfram Summer School (https://community.wolfram.com/groups/-/m/t/3208866?p_p_auth=fIFHqpy4 and https://education.wolfram.com/summer-school/). It was held June 23 – July 11 at Bentley University in Waltham, MA, where he benefitted from advice from the founder of Mathematica and his associates. He also helped with different projects, as apparent from our publications. Linda Sackett-Lundeen continues work on the bibliography of Franz Halberg, now handling papers published during the last 10 years of his life.

As in prior years, several students came to work on research projects at the HCC, while other students came to us to write their capstone. The HCC presented at several international meetings. We all attended virtually the meeting in Brno, held on October 30. Germaine also made a presentation on chrononutrition and metabolic health at the 27th World Congress of Clinical Nutrition held in Sofia, Bulgaria, November 1-3. Jarmila and Germaine were also invited to present their work at the 13th International Congress of Cardiology& Diabetes, held in New Delhi, India, November 9-10. Jarmila presented results from 7-day/24-hour ABPM records in the context of cardiac rehabilitation after cardiac disease, while Germaine talked about the morning surge and the circadian-circasemidian (24h-12h) coupling in blood pressure. The University of Minnesota Foundation invited Larry and Germaine to highlight their work on the chronobiology of blood pressure at their annual Heritage Dinner event.

The HCC continues to benefit from cooperation by 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 greatly appreciated.

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