Report of activities of the Halberg Chronobiology Center (HCC): 2022 24 December 2022

As another year is coming to an end, we thank our colleagues here and abroad for the opportunity of continued cooperation. Some highlights below illustrate activities at the Halberg Chronobiology Center during 2021.

Focus remained centered on the monitoring of blood pressure in health and disease and on changes in the time structure of heart rate variability in astronauts during long missions on the International Space Station (ISS).

Work with Kuniaki Otsuka, Professor emeritus at Women's Medical University (Tokyo, Japan), in cooperation with members of the Japanese Space Agency, focused on 24-hour ECG monitoring of astronauts during long-term missions in space. Monitoring during repeated missions and repeated monitoring during a 1-year spaceflight revealed how human physiology adapts to the space environment. The role played by the 12-hour component in this adaptation process was found to be important to strengthen the circadian rhythm. Our results are reported in Scientific Reports. Previous results published in this journal were selected to be included in the 2019 and 2022 Annual Reports of NASA.

Our project on the BIOsphere and the COSmos (BIOCOS) continues in several countries, notably in Brno, Czech Republic, and in Tokyo, Japan, with support from the A&D Company (Tokyo, Japan). With growing interest in cuff-less blood pressure monitors, acknowledged by a consensus article from the European Society of Hypertension, we started the testing of the YHE (China and U.S.) wrist-worn blood pressure monitor. Its accuracy, as is the case for most other similar devices, however, is still not sufficient for clinical use, as reviewed in an article published in this year's Noninvasive Methods in Cardiology. Cuff-less blood pressure devices spark much interest for automated longitudinal monitoring, as performed in chronobiologic studies, and warrant further testing in cooperation with El Nolley, Chris Adams, A Chase Turner and Larry A Beaty, volunteering IEEE engineers of the Phoenix Project.

Within the MESA (Multi-Ethnic Study of Atherosclerosis) project, our analysis with Larry Beaty of beat-to-beat blood pressure waveforms recorded for a few minutes over the radial artery is also proceeding, as a complementary approach to ambulatory blood pressure monitoring. Now that several features characterizing the blood pressure waveform have been estimated, their merit in predicting adverse cardiovascular events is being investigated by David Jacobs, Professor of Epidemiology, and Daniel Duprez, Professor of Cardiology, both at the University of Minnesota. The R code we developed to analyze the data will now be applied to identify markings corresponding to specific events occurring within a cardiac cycle from similar records obtained over the femoral and carotid arteries from a subset of the study participants. Results discussed in monthly meetings with Matthew Allison, Professor of Public Health, University of California, and his team, are being summarized in poster presentations and planned forthcoming publications.

Work with Denis Gubin, Professor at Tyumen State Medical University, Russia, continued. On patients with primary open-angle glaucoma, we showed that loss of retinal ganglion cells is associated with depression scores, suggesting that it may affect non-visual photic transduction and lead to mood disturbances. We also found that increased damage to retinal ganglion cells in glaucoma altered lipid metabolism that is linked to a specific polymorphic clock gene variant. We are also in the process of analyzing data from workers of Yamburg's Settlement in the far north of

Siberia, who are engaged in month-long stays in Yamburg, alternating with month-long stays in their home cities.

The annual Workshop on Noninvasive Methods in Cardiology, organized by Jarmila Siegelova, Professor at Masaryk University, Brno, Czech Republic, was held on October 12. As she became Professor Emerita, Jarmila was honored with a Lifetime Achievement Award delivered by her department head, Professor Petr Dobsak. The HCC delivered three presentations, including work with A. Chase Turner, retired Software Engineer who demonstrated rhythmometric analyses in Mathematica. In honor of the late Professor Pavel Prikryl, we also presented the results of his latest study on the effect of Telmisartan on cardiovascular markers in cardiac patients. We showed that blood pressure, heart rate, cardiac output, ejection fraction and brain natriuretic peptide, as well as angiotensin II, plasma renin activity and bradykinin are circadian periodic, and that Telmisartan and Lisinopril both have positive effects on cardiovascular health.

At the HCC, Mary Sampson and Linda Sackett-Lundeen continued their work on the bibliography of Franz Halberg by listing a number of keywords associated with each publication, and preparing an updated version of the bibliography to include links to each entry whenever one is available. Since titles listed date as far back as 1946, sometimes this task almost resembles detective work! Mary is also keeping us abreast with newly published articles in chronobiology. She also helps with the English editing of papers for the World Heart Journal. Cathy Lee Gierke, now retired, remains part of our team, as we are discussing her expanding her CATkit program to include polar displays of cosinor results, which may require a restructuring of the entire program so that it can be uploaded to CRAN, the Comprehensive R Archive Network that stores code and documentation for R.

Our weekly lab meetings are still being held on Zoom. Chase made considerable progress in converting a number of our in-house software for chronobiologic analyses in Mathematica, including a nonlinear algorithm to estimate periods with their confidence limits and generating polar displays of cosinor results. In relation to all ongoing projects, the expertise of advice from Larry are greatly appreciated. In addition to work related to the MESA project, the automatic non-invasive, cuff-less monitoring of blood pressure remains one of several topics of interest.

Several students came to work on research projects with us. Aisha Omar learned about gender differences and changes as a function of age in several endpoints of heart rate variability derived from 7-day/24-hour ECG records. Gaosheng Lo confirmed the higher reproducibility of rhythm characteristics over the day-night ratio of blood pressure in ambulatory records from Indian women monitored during pregnancy. Jennifer Lawal learned about the morning peak incidence in myocardial infarctions. Next semester, she will examine corresponding circadian patterns of several biomarkers of cardiovascular diseases. Kiley Holen Flanigan assessed the effect of morning treatment with long-acting Carteolol on the circadian rhythm of blood pressure. While effective overall, a decrease in blood pressure could not be documented for 27% of the patients. It was found to be effective primarily during the daytime but not during sleep at night. The data she analyzed are from Yoshihiko Watanabe, Professor Emeritus of Internal Medicine at Tokyo Women's Medical University, Japan. Several students also came to the HCC to write their capstone.

Germaine took advantage of the possibility to lecture remotely to accept multiple invitations to participate at international meetings. Among others, she lectured on blood pressure variability in health and disease at the 11th International Congress of Cardiology and Diabetes, held in

Alexandria, Egypt on 21-22 October 2022. She also reviewed some results on clinical nutrition obtained with international cooperation at the 25th World Congress on Clinical Nutrition, held at Era University, Lucknow, India, on 26-27 November 2022. Finally, at a special session devoted to the memory of Franz Halberg, part of the 8th World Congress on Chronomedicine, held in Varanasi, India, on 14-16 December 2022, she delivered the opening lecture “In Franz Halberg's footsteps”, highlighting key findings in the last decade obtained with colleagues worldwide, many of them disciples of Franz. Kuniaki presented joint work at the 68th Annual Meeting of the Japanese Society of Aerospace and Environmental Medicine, held on 24-25 November 2022 in Tokyo, Japan.

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 much appreciated.

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