

Season's appreciations

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Abstract

To follow the tradition set by the late Franz Halberg, highlights of research performed over the last year from his Minnesota Center are summarized. They illustrate the broad international cooperation enjoyed by his center and the diversity of applications of the discipline he founded. The results briefly summarized herein in the form of an annotated bibliography are a testimony that his legacy continues to live on and constitutes a tribute to his memory. *Clin Ter* 2015; 166(2):55-58. doi: 10.7417/CT.2015.1814

Key words: *abnormal circadian patterns, atlas of chronomes, cancer, circadian disruption, day-to-day blood pressure variability, environmental influences, feeding time, individualized chronotherapy, locomotor activity, sleep*

As a new year starts, there is much we can be thankful for. The Halberg Chronobiology Center remains as active and productive as ever, thanks to our team in Minnesota and to the collaboration of many colleagues in the USA and abroad, as illustrated in some of our interesting findings from 2014.

The data from ambulatory blood pressure monitors obtained within the scope of our project on the BIOSphere and the COSmos (BIOCOS) continue to accumulate, over long periods of time in some of us, as well as in communities and clinical settings. The results reinforce the need to monitor for longer than 24 hours and to assess abnormalities in the variability of blood pressure and heart rate (1-5), as documented earlier with Pietro Cugini in this journal (6). Our chronobiologic approach has shown merit in terms of both prognosis and treatment.

With Kuniaki Otsuka, special focus on age trends has revealed an increased incidence of circadian disruption in the elderly (7, 8). With Elena V. Syutkina and Anatoly Masalov, screening a pediatric population for abnormal circadian patterns in blood pressure and heart rate found their presence to be associated with a higher body mass

index (9). With Krassimira Hristova and R.B. Singh, using myocardial deformation imaging to quantify the contractility of the left ventricle in health, we showed the circadian stage-dependence of regional deformation, an important result pertaining to ventricular function (10).

With R.B. Singh and Fabien De Meester, a new milk formulation was tested in under-nourished infants (11). As compared to dairy milk, it was associated with a larger weight gain and a decline in postprandial blood glucose. A more pronounced effect of evening versus morning feeding is yet another new application of Franz Halberg's demonstration that a calorie is not just a calorie: it is different if ingested at dinner versus breakfast.

As in previous years, we participated in the Noninvasive Methods in Cardiology meeting organized by Jarmila Siegelova in Brno, Czech Republic. Data collected by her doctoral fellow and analyzed by Cathy Lee Gierke, who recently joined our laboratory, served as material for one of the presentations, investigating the day-to-day variability in circadian characteristics of blood pressure in relation to exercise (12). Cathy also presented her results at the Cardio Palooza (13, 14) organized jointly between the department of Integrative Biology and Physiology and the Lillehei Institute (Cardiology) with which our center is now affiliated.

With Cathy and Larry Beaty, we started an ambitious project, preparing an "atlas of chronomes" (15). It is conceived as an electronic encyclopedia compiling information on multi-frequency rhythms mapped in our laboratory since its foundation by Franz Halberg in the mid-1950s. In addition to focusing on circadian and circannual rhythms, the atlas will include periodicities shared with the broader environment, with the aim to gain a better understanding of external influences on human physiology, psychology, and pathology (16, 17). Complementing the atlas, Mary Sampson is scanning works published by Franz Halberg, so that his legacy can be made available through the University library.

The Halberg Chronobiology Center keeps attracting visitors. Continuing a 25-year tradition, Yoshihiko Watanabe came to work with us to optimize the administration of several anti-hypertensive drug combinations by timing (18).

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His important results emphasize the need for individualizing treatment timing, Figure 1.

Lyazzat Gumarova won a CRDF travel award, granting her the ability to work at the Halberg Chronobiology Center as a visiting scholar for several months. She worked on analyzing the time structure of locomotor activity, which we are now evaluating along with that of blood pressure and heart rate, Figure 2. Our joint work has implications for health maintenance as more people monitor their own locomotor activity.

Jinyi Wu and his son Bing are working with us to develop a system to incorporate chronobiologic concepts into telemedicine. The goal is to design a miniaturized noninvasive cuffless blood pressure monitor for broad use. This does dovetail in with ongoing work by the Phoenix Study Group, which is composed of volunteers from the Twin Cities chapter of the Institute of Electrical and Electronics Engineers.

Pavel Homolka and Robert Prosecky came to discuss possible cooperation on blood pressure monitoring of patients with usual weight obesity (normal weight, high body fat). With Pavel Homolka and Kristian Brat, we analyzed blood pressure records from members of Czech Antarctic Scientific Expeditions obtained in Antarctica and in the Czech Republic and determined that there is a physiological load associated with working in a cold environment (19).

Many more cooperative studies are underway. With Zhengrong Wang, we found that space weather influences the incidence of cardiovascular disease (20). With RK Singh and his daughter Ranjana, we found differences in the circadian rhythms of vitamin D and calcium in diabetic patients versus healthy controls (21). With Weihong Pan, we are again involved in sleep research, looking at activity and ECG records for the presence of an about 90-minute cycle related to the alternation between REM and NREM sleep. With Mikhail and Olga Blank and Daria Denisova, we assessed the relative prominence of the circadian and half-weekly variation in temperature and pulse and found that it predicted cancer recurrence in their population of patients. The list is far from being exhaustive, but it gives a glimpse of ongoing activities at the Halberg Chronobiology Center (22-37).

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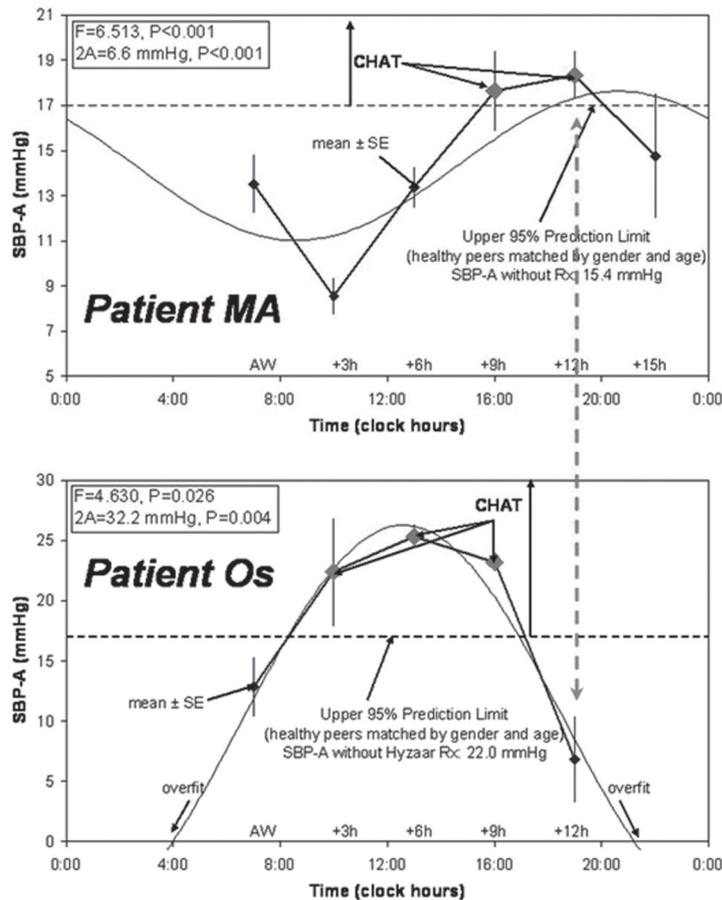


Fig. 1. Optimization of treatment by timing. A combination treatment of losartan/hydrochlorothiazide was taken once daily, the time of its administration remaining the same for at least one month before it was changed to another circadian stage. Each of the 30 patients in this study received the treatment at 6 different times (either upon awakening for at least one month, then, 3, 6, 9, 12 hours after awakening for another month each, and finally for another month at bedtime). At the end of each stage corresponding to a different circadian treatment time, 7-day/24-hour ambulatory blood pressure monitoring was carried out to yield estimates of the circadian rhythm characteristics. Results for the 24-hour amplitude of systolic blood pressure are shown for two of the 30 patients. Each dot represents a weeklong ABPM profile. Treatment time is shown on the abscissa. The effect of the same dose of the same drug combination on the same patient differs predictably depending on the time of its administration. The fact that the circadian acrophase of the response rhythm differs from one patient (MA) to another (Os) points to the merit of individualizing the optimization of treatment by timing (chronotherapy). Data from: Y. Watanabe (18). © Halberg Chronobiology Center.

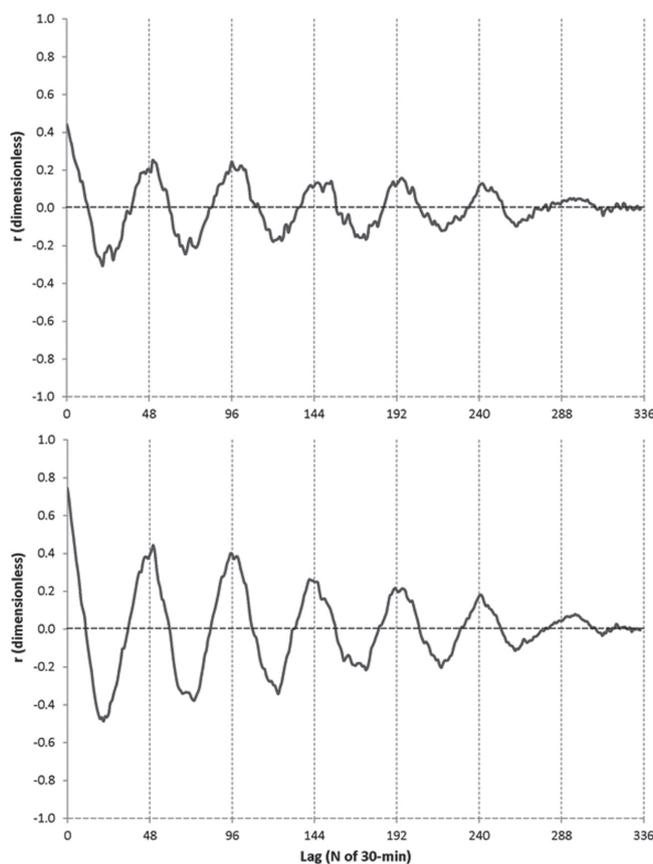


Fig. 2. Cross-correlation of systolic blood pressure (top) and heart rate (bottom) versus activity of a clinically healthy woman. Blood pressure and heart rate data collected at 30-minute intervals with an ambulatory monitor (TM-2430) from A&D (Tokyo, Japan). Activity data collected every minute with the MicroMotion Logger of Ambulatory Monitoring Inc. (Ardsley, NY, USA) and averaged over consecutive 30-minute intervals. Whereas the circadian rhythms of both HR and SBP are synchronized with that of locomotor activity (peaks at integer numbers of days; dashed vertical lines), HR is more closely associated with activity than SBP (cross-correlation coefficients remain higher in the case of HR as compared to SBP). Data from: L. Gumarova (unpublished). © Halberg Chronobiology Center.

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