Prediction and prevention

Chronobiologist **Professor Germaine Cornelissen** is exploring circadian and other rhythms in blood pressure under different environmental circumstances through large-scale data collection and analyses. Here, she discusses her research journey to date

How did you become involved in research on circadian blood pressure rhythms, and what have been your inspirations?

My doctoral thesis on time series analysis caught the attention of Dr Franz Halberg, who invited me to join his laboratory. Known as the Father of Chronobiology, he was a legendary, pioneering and inspiring scientist. My inspiration lies in the application of our chronobiological approach to reduce the number of people who die of preventable heart attacks and strokes.

What was the significance of your Womb-to-Tomb study in establishing definitions of clinical health for different ages? Why is this important in the management of vascular abnormalities?

Our Womb-to-Tomb study provided critical information about blood pressure variations in health. Chronobiology defines health positively rather than as the absence of disease. Ranges of variability in circadian blood pressure characteristics are narrower for individuals than for populations. Any deviation from an individual's 'normal range' means that problems can be detected earlier; before there is deviation from the conventional population-based norms. Differences in circadian blood pressure characteristics, well within the traditionally accepted normal range, were detected between clinically healthy subjects with a positive versus negative family history of high blood pressure and/or cardiovascular disease, suggesting that rhythm alteration may precede the onset of overt disease. It is important since high blood pressure is asymptomatic; symptoms occur only after organ damage. The study laid the foundation for defining different vascular variability abnormalities.

Can you explain the clinical applications derived from being able to predict how blood pressure in a patient will change throughout the day in response to different stimuli?

The most important clinical application of response rhythms is individualised chronotherapy. Patients treated once a day benefit from knowing their best time to take their anti-hypertensive medication in order to maximise efficacy and minimise undesired effects. The same dose of the same drug taken by the same patient can have predictably different effects on the daily blood pressure average and on the circadian profile depending on what time of day it is taken. This is important because a deviant circadian amplitude or phase can carry a cardiovascular disease risk greater than that of high blood pressure itself. As with the timing of anti-hypertensive medications, the timing of other stimuli, such as exercise, can affect the circadian blood pressure rhythm. Understanding how blood pressure varies in response to stimuli in everyday life helps health maintenance.

What issues stand in the way of implementing around-the-clock monitoring of hypertensive patients as a standard in the clinic?

Some issues should be addressed. We need to spread awareness to clinicians of the merits of a chronobiological approach versus single clinic measurements. In addition, the cost of monitoring will come down considerably once this method is more widely implemented. The perceived burden associated with longer-term monitoring (over several days) should be refuted. Newer monitoring devices are addressing issues of comfort and convenience, which have been deterrents to longer-term monitoring.

Why is self-monitoring of blood pressure particularly critical in your research?

So much can be learned from data collected automatically as a function of time. Such longer-term monitoring of blood pressure can:

- Indicate whether there is a change in health well before there is abnormality in relation to conventional thresholds
- Indicate whether there is a change while on treatment, prompting adjustment in medication, dosage and/or timing
- Aid diagnostic accuracy
- Distinguish changes that are part of healthy ageing versus the development of blood pressure disorders

Have any particularly significant findings emerged from your research into the effects of environmental phenomena, including solar cycles and changes in the Earth's radiation environment, on blood pressure?

Circadian rhythms, the relationship between physiologic variability and the 24-hour day, are accepted and well understood. At the Halberg Chronobiology Center, we are now researching other environmental cycles, such as solar cycles and periodic changes in the radiation environment, and their effects on physiology and pathology. What triggered our curiosity was our finding of a 7 per cent increase in myocardial infarctions after a solar magnetic storm and an associated decrease in heart rate variability. The long-term monitoring of blood pressure and heart rate illustrates how cycles with periods of about 154 days (cis-half-years), 1.3 years (transyears) and 11 years (solar cycles) reflect solar signatures. These cycles may impact physiology and health and have potential implications for long-term missions in space.

Understanding blood pressure

Blood pressure is a universally used metric for cardiovascular health. Researchers at the Halberg Chronobiology Center, **University of Minnesota**, USA, are using chronobiology for a more accurate diagnosis and personalised treatment

IT IS ESTIMATED that undiagnosed blood pressure abnormalities account for about 1,000 deaths per day in the US, representing a significant yet preventable cause of death. Blood pressure is an extremely useful indicator and monitor of various cardiovascular diseases (CVDs) and is a tool commonly used by healthcare practitioners worldwide.

One of the biggest challenges facing the improvement of blood pressure monitoring and the development of chronotherapies is convincing physicians that single office measurement and single-day ambulatory monitoring are insufficient

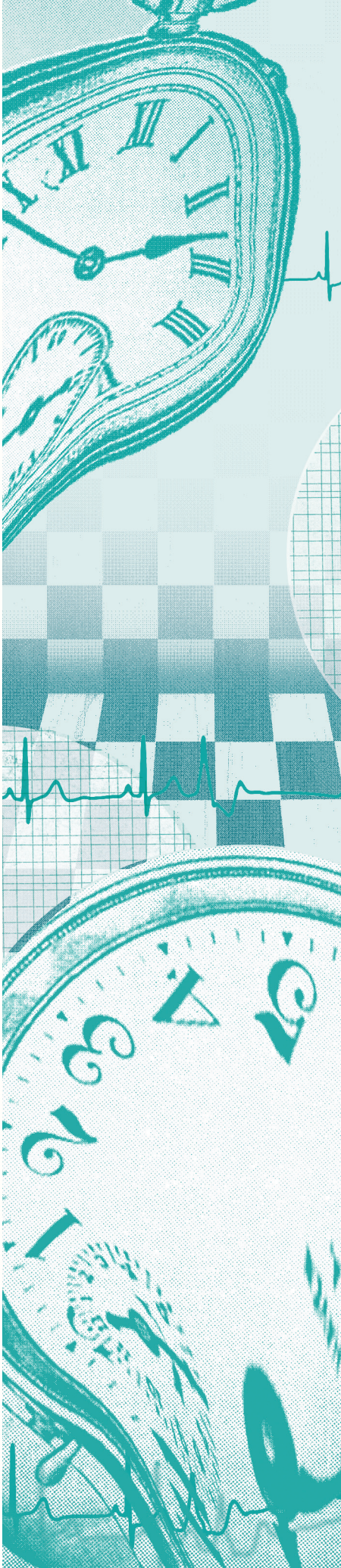
Blood pressure is measured through the use of a sphygmomanometer. The most common context for a measurement remains a visit to the doctor's office. This provides a snapshot of blood pressure at a given point in the daily fluctuations of the human body – the circadian cycle. Research conducted by Dr Franz Halberg during the 1990s showed that these snapshots are insufficient to accurately diagnose hypertension and other abnormal circadian blood pressure patterns assessing CVD risk. Blood pressure varies throughout the 24-hour day and is affected by other factors, such as exercise and emotional states. However, office measurement remains widely used in the medical community. Monitoring blood pressure automatically around the clock provides more complete information by accounting for the circadian variation. Doing so for more than a single 24-hour day further accounts for day-to-day variability in the circadian profile, which can be related to events in everyday life.

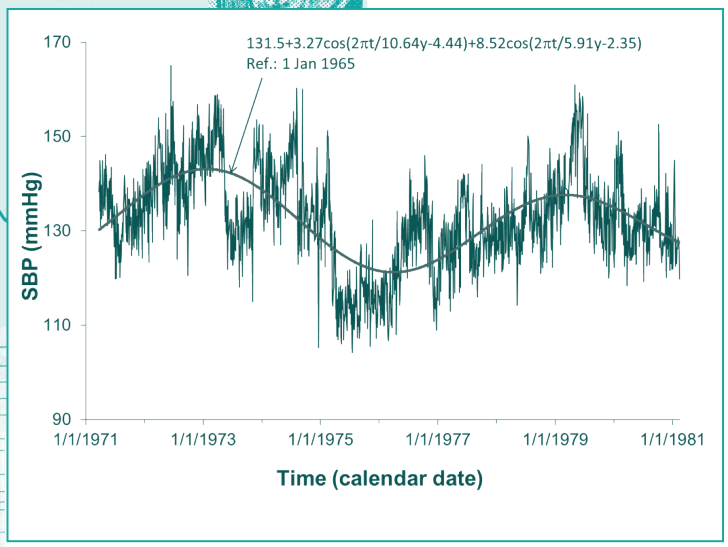
The circadian rhythm accounts for predictable changes during the day, with lower values during rest and higher values during the active daily span. Its characteristics (average, extent and timing of change) in health are determined by genetics, epigenetics and responses to a variety of environmental stimuli. More importantly, it is affected by CVD. As such, the circadian profile of blood pressure varies from one person to another and from day to day in any given person. Additional environmental (weekly, monthly, yearly) cycles modulate the circadian rhythm. The fields of chronobiology and chronomics are dedicated to using this information towards prevention, better diagnosis and treatment, and for understanding how we interact with our environment.

It is the interplay between physics and biology that interests Professor Germaine Cornelissen and her team at the Halberg Chronobiology Center, University of Minnesota. Cornelissen is one of the leaders in chronobiology and is focused on blood pressure monitoring in everyday life for clinical applications such as developing personalised chronotherapy. She has undertaken two large-scale projects aimed at optimising health through blood pressure monitoring and mapping long-term cycles in relation to their environmental counterparts.

IN A HEARTBEAT

The Womb-to-Tomb project established circadian reference standards in health. Deviations therefrom, referred to as vascular abnormalities, were found to occur before the onset of disease. These findings led directly into the ongoing Biosphere and Cosmos (BIOCOS) Project, which has already documented that abnormal circadian patterns of blood pressure – which can be treated – raise CVD risk. By collecting and analysing data from across the globe, BIOCOS revealed the need to monitor





Long-term monitoring of blood pressure and heart rate revealed the presence of cycles also found in the Sun, such as the around 11-year cycle in solar activity. This is illustrated by the 20-year record of one subject.

blood pressure around the clock for more than 24 hours, and to interpret the data in terms of circadian rhythm characteristics compared to chronobiologic reference limits. BIOCOS projects are ongoing in clinical settings, in private practice, and in two Japanese communities where comprehensive community health screening is focused on the health of the elderly. They are carried out by investigators interested in exercise physiology and rehabilitation, and by researchers interested in nutrition and cardiovascular health. They are conducted in schools and by dedicated individuals who have monitored themselves for decades.

While these discoveries are the stand-out successes of BIOCOS so far, the latest work provides tantalising results concerning the effect of the environment on blood pressure and CVDs. The environment in this case includes both terrestrial and extraterrestrial weather, particularly solar cycles and the Earth's radiation environment. Not only should this work provide vital information concerning the prevention and treatment of CVDs, it could provide valuable information in preparation for human space exploration. "Mapping long-period cycles is amazing and opens a new view of life intrinsically interwoven with the environment in which it evolved," explains Cornelissen.

One of the biggest challenges facing the improvement of blood pressure monitoring and the development of chronotherapies is convincing physicians that single office measurement and single-day ambulatory monitoring are insufficient. This is an issue of efficiency of diagnosis versus cost. Cornelissen is working on both issues and has a set of case studies written specifically for physicians in the pipeline. She argues why better blood pressure monitoring is worthwhile pursuing: "Monitoring can be performed outside the physician's office; reductions in false positive and false negative diagnoses and in the incidence of morbid events will likely lower, not increase healthcare costs".

TIME WILL TELL

The BIOCOS project is continuing to collect blood pressure data from around the world. These data will be used to further optimise measures of health, serving as health surveillance, a means to optimise community health, a marker rhythm to personalise the optimal timing of treatment, a gauge of the efficacy of treatment and a check for possible undesired effects, and also a tool for self-evaluation. Effects of exercise in health and for the purpose of rehabilitation are also being studied.

The information from BIOCOS is being collated with earlier chronobiological discoveries at the Halberg Chronobiology Center to create an 'atlas of chronomes'. This will map the dynamic characteristics of multi-frequency cycles. This compilation will take the form of a searchable encyclopaedia and contain charts and syntheses of results from different publications. These data will include decades of research, which when compared, might well yield new discoveries and avenues for exploration. Equally, this should provide an excellent resource from which chronobiology can be taught both to academics and physicians.

New technology promises to expand the field even further. As wireless communication becomes cheaper and faster, more and more individuals are expected to participate in studies and the scale of projects such as BIOCOS are likely to increase. Cornelissen envisages a bright future for blood pressure chronotherapy as a result of these advances: "This is an exciting time when smart devices with sensors are being developed for widespread use. This will make it possible to record and chronobiologically analyse huge volumes of data in real time. The possibilities for monitoring vital signs toward health and performance optimisation are almost endless".

BEYOND CIRCADIAN RHYTHMS IN BLOOD PRESSURE

OBJECTIVES

- To establish definitions of clinical health, in terms of blood pressure variation, for a variety of ages
- To provide fundamental knowledge on chronobiology to inform individualised chronotherapy, such as for hypertensive treatment
- To investigate the influence of solar and cosmic radiation on human physiology and pathology

KEY COLLABORATORS

Professor Kuniaki Otsuka, MD, PhD, Chronomics and Gerontology; **Associate Professor Yoshihiko Watanabe, MD, PhD**, Medicine, Tokyo Women's Medical University, Medical Center East, Tokyo, Japan • **Professor Jarmila Siegelova, MD**, Physiotherapy and Rehabilitation, St Anna Teaching Hospital, Masaryk University, Brno, Czech Republic • **Associate Professor Lyazzat Gumarova, PhD**, Al-Farabi Kazakh National University, Almaty, Kazakhstan • **Dr Ram B Singh, MD**, Halberg Hospital and Research Institute, Centre of Nutrition and Heart Research, Moradabad, India • **Members of the International Project on The BIOsphere and the COSmos – BIOCOS** (coordinated at the Halberg Chronobiology Center) • **Members of the IEEE Twin Cities Phoenix Project** • **Dr Francine Halberg** and **Dr Julia Halberg** serve as advisors to the Halberg Chronobiology Center

FUNDING

Halberg Chronobiology Fund • University of Minnesota Supercomputing Institute • A&D Company

CONTACT

Professor Germaine Cornelissen
Director of the Halberg Chronobiology Center

University of Minnesota
Room 715 Mayo
420 Delaware St SE
Minneapolis
Minnesota, 55455, USA

T +1 612 624 6976
E corne001@umn.edu

http://z.umn.edu/HalbergChronobiologyCtr
http://bit.ly/GermaineUoMinnesota

http://bit.ly/RGCornelissen

GERMAINE CORNELISSEN received her BSc and MSc in Physics and MEd from the University of Brussels, Belgium, before being awarded her PhD, also in Physics, at the University of Brussels in 1976. She later joined the lab of Dr Franz Halberg, chronobiology expert. She has received a number of awards and honours including the Hoechst Foundation Chronobiology Award in 1983. She is a foreign member of the Russian Academy of Medical Sciences, a fellow of the International College of Cardiology, and an elected member of the Leibniz Society and of the International Academy of Science.