

## STROKE AND OTHER VASCULAR DISEASE PREVENTION BY CHRONOMICS

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### Abstract

To reduce the need for rehabilitation, BIOCOS, coordinated from the Halberg Chronobiology Center in Minnesota, has been collecting international reference values, notably of blood pressure (BP) and heart rate (HR), specified as a function of time, gender and age, to identify abnormality within the physiological range, so that prophylactic intervention instituted in a timely fashion may reduce the incidence of adverse outcomes, while also serving basic transdisciplinary science. BIOCOS, a project aimed at studying BIOlogical systems in their COSmos, has obtained a great deal of expertise in the fields of blood pressure (BP) and heart rate (HR) monitoring and of marker rhythmometry for the purposes of screening, diagnosis, treatment, and prognosis.

### INTRODUCTION

Chronobiology is the study of the mechanisms of biologic diversity in time, complementing the study of biologic diversity in space, genetics. Most if not all components of variation found in biota are also found in the environment, and vice versa (1). Genomics is complemented by chronomics, the cartography of chronomes (structures in time). Chronomics are the basis of a functional genomics, ideally based on continuous surveillance by monitoring, which should, sooner or later, replace reliance on time-unqualified spot-checks. The study of human chronomes can

serve the derivation of refined reference values to better define health and to identify pre-disease, so that prophylactic interventions can be instituted as early as possible, preferably before disease sets in (5-7). The focus is thus put on pre-habilitation, in the hope that the need for re-habilitation will thereby be reduced (8-10). As a start, the 7-day/24-hour monitoring now implemented in several centers worldwide sets an example for the establishment of refined reference values and the assessment of vascular disease risk associated with abnormalities in the variability of BP and HR that may occur within the physiological range. With instrumentation from the A&D company (Tokyo, Japan), if not (yet) with implantable miniaturized instrumentation now being developed, the project on the BIOSphere and the COSmos (BIOCOS) is ongoing in Brno, in Tokyo and the city of Urausu in Hokkaido as a whole, in private practice in Brussels, and in special nutritional, fitness and immigrant population projects in Moradabad, Michigan and California, and with shorter series in the elderly in Jinan, in patients with non-insulin dependent diabetes in Mexico City, in pregnant women in Yerevan, and in gastrointestinal medicine in Florence, as well as in Minnesota, where a relation between the circadian amplitude of BP and vascular disease risk was first uncovered (9,10). To reduce the need for rehabilitation, BIOCOS, coordinated from the Halberg Chronobiology Center in Minnesota, has been collecting international reference values, notably of blood pressure (BP) and heart rate (HR), specified as a function of time, gender and age, to identify abnormality within the physiological range, so that prophylactic intervention instituted in a timely fashion may reduce the incidence of adverse outcomes, while also serving basic transdisciplinary science.

## METHODS

Each BP/HR record is analysed by sphygmochron, consisting of a combined parametric and non-parametric approach. Parametrically, the data are fitted with a model consisting of cosine curves with periods of 24 and 12 hours by cosinor. Non-parametrically, the data are compared with time-specified 90% prediction limits derived from similar records obtained from clinically healthy subjects matched by gender and age. The percent time elevation and the area of excess are determined respectively by the duration and area under the curve delineated by the data when they are excessive and the upper 95% prediction limit. The timing of overall excess is estimated as the center of gravity of the area of excess. The diagnoses of MESOR hypertension and CHAT (circadian hyper-amplitude-tension) are made when the MESOR and/or the circadian amplitude of BP is above the upper 95% prediction limit for the MESOR and/or the 24-hour amplitude of clinically healthy peers matched by gender and age.

## RESULTS

CHAT is associated with a large increase in vascular disease risk, notably cerebral ischemic events and nephropathy. Together with a decreased heart rate variability and an elevated pulse pressure (above 60 mmHg), CHAT accounts for the difference in morbidity within 6 years between <4% and 100%. *Figure 1* shows an example of CHAT in a woman, TS, 27 years of age, who had intermittent MESOR-hypertension

and intermittent overswinging (CHAT). On two office visits by two university physicians, she was described as healthy, even though she showed the record of her ambulatory monitoring. CHAT is more likely to occur among patients with borderline hypertension and in patients with glucose intolerance. Treatment schedules that are associated with a decrease in the circadian BP amplitude are found in large clinical trials to be associated with lesser morbidity/mortality from stroke than treatment schedules that are associated with an increase in the circadian BP amplitude. Women who will develop gestational hypertension and/or preeclampsia have a larger circadian BP amplitude during the second and third trimester of pregnancy than women with uncomplicated pregnancies.

Among the 166 profiles collected in Brno, MESOR hypertension was found in 35 records (21.1 %), CHAT was diagnosed in 15 records (9.0 %), and an excessive pulse pressure occurred in 9 records (5.4 %) (2 or 1.2% with CHAT). Among the 217 profiles collected in Urausu, MESOR hypertension was found in 51 records (23.5 %), CHAT was diagnosed in 34 records (15.7 %), and an excessive pulse pressure occurred in 33 records (15.2 %) (4 or 1.8% with CHAT). Among the 147 profiles obtained in Brussels, MESOR hypertension was found in 40 records (27.2 %), CHAT was diagnosed in 23 records (15.6 %), and an excessive pulse pressure occurred in 31 records (21.1 %) (3 or 2.0% with CHAT). Differences in the prevalence of MESOR hypertension, CHAT, excessive pulse pressure (and/or decreased heart rate variability) may stem not only from differences among populations in different geographic locations, but also from differences in the subject/patient populations (e.g., in terms of gender, age, economic status, general health status) and from differences in the choice of treatment administered, if any (kind, dose and timing of medication).

## DISCUSSION

CHAT is a condition encountered worldwide as documented by BIOCOS. Reference values for blood pressure parameters have led to the identification of new disease risk syndromes, such as CHAT (circadian hyper-amplitude tension, a condition characterized by a circadian amplitude exceeding the upper 95 % prediction limit), BP-ecphasia (a condition characterized by a deviant circadian acrophase of blood pressure), and DHRV (decreased heart rate variability, defined as a below-threshold standard deviation of heart rate measurements collected around the clock). Together with an excessive pulse pressure (above 60 mmHg), CHAT and DHRV can make the difference between <4 % and 100 % morbidity in a 6-year prospective study (11, 12).

Accordingly, CHAT needs consideration for health promotion everywhere. Even when based on less desirable manual measurements, it is associated with a reduction of lifespan in a 28-year European perspective. Outcomes in BIOCOS will be critical to find out what are optimal therapeutic modalities for patients with CHAT,

which can be diagnosed in the absence of MESOR hypertension (12, 13). The modification of the circadian patterns of BP and HR by the treatment should be taken into consideration, so that the beneficial effects of BP lowering drugs are not hindered by less desirable changes in the variability of BP and/or HR brought about by the treatment. Broadening the scope of monitoring is likely to be associated with a reduction in the cost of instrumentation, once a system of education at all ages is in place.

BIOCOS, the project aimed at studying BIOlogical systems in their COSmos, has obtained a great deal of expertise in the fields of blood pressure (BP) and heart rate (HR) monitoring and of marker rhythmometry for the purposes of screening, diagnosis, treatment, and prognosis. Information gained from this work suggests a close link between mental health and cardiovascular health (13, 14, 15, 16). Too often the argument is presented that a chronobiological approach relying on longitudinal monitoring of vital signs and on a computer-assisted analysis for an inferential statistically guided interpretation of the results is too complex and too expensive and hence cannot be generally introduced to developing countries where a cost-effective health care system is needed the most. In the following, these misconceptions are dispelled and the case is made for cardiovascular health that chronobiology offers the most promising approach to improving the quality of care at a reduced cost.

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## PREVENCE CÉVNÍ MOZKOVÉ PŘÍHODY A OSTATNÍCH CÉVNÍCH ONEMOCNĚNÍ POMOCÍ CHRONOMIKY

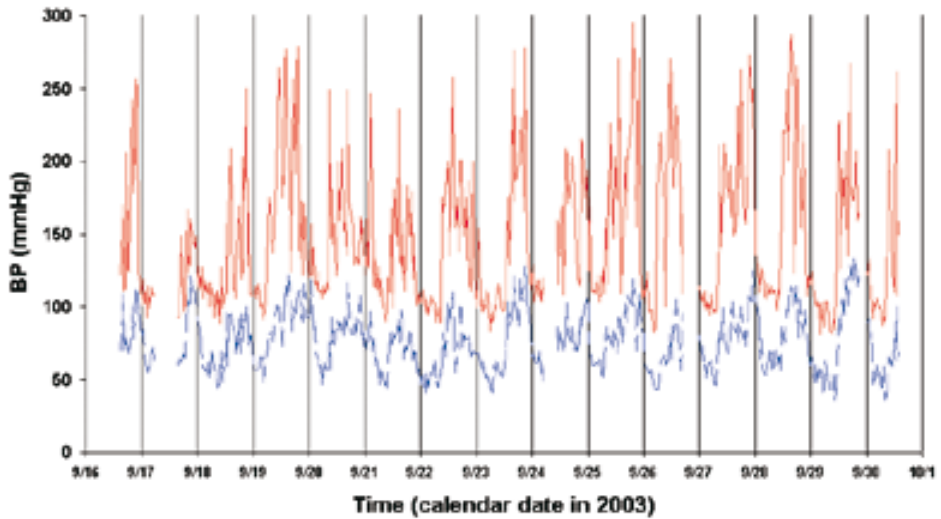
### S o u h r n

S cílem snížit potřebu rehabilitace shromažďuje mezinárodní projekt BIOCOS, koordinovaný z Halbergova chronobiologického centra v Minnesotě, v mezinárodním měřítku referenční hodnoty, zejména krevního tlaku a srdeční frekvence, vyjádřené jako funkce času, pohlaví a věku, kvůli identifikaci odchylek v rozsahu fyziologického rozmezí tak, aby včasná profylaktická intervence mohla redukovat výskyt nepříznivých následků a přitom sloužit základnímu transdisciplinárnímu výzkumu. V rámci projektu BIOCOS zaměřeného na studium biologických systémů (BIO) v jejich prostoru (COS - kosmos), byly získány značné znalosti v oblasti monitorování krevního tlaku a srdeční frekvence a v rytmetrii ukazatelů pro potřeby vyhledávání, diagnózy, terapie a prognózy.

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**Time Course of Systolic and Diastolic Blood Pressure (BP)  
of 27-year old woman (TS)**



*Fig. 1*

Woman, TS, with intermittent MESOR-hypertension and intermittent overswinging (CHAT). Large moment to moment and day to day variability in systolic and diastolic blood pressure of an untreated asymptomatic 27-year old woman (TS). The high values are not likely to be outliers or erroneous readings since they occur repeatedly over several consecutive hours, and do so not only during this span but also during other spans when TS was wearing a different cuff and/or a different TM-2421 monitor from the A&D company (Tokyo, Japan).