Franz Halberg memorial lecture: Extended Consensus on Blood Pressure Variability

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Aim. To review evidence for around-the-clock monitoring of blood pressure (BP) serving several purposes: surveillance for health maintenance, refined diagnosis and prognosis, personalized optimization of treatment by timing (chronotherapy), and as a tool to gain a better understanding of environmental influences on human physiology and pathology.

Background. Circadian rhythms prominently characterize BP, heart rate (HR), and a host of other physiological variables. Their characteristics differ as a function of gender and age, as well as ethnicity and health status. The mapping of circadian rhythms in BPand HR in healthy from neonates to centenarians led to the derivation of time-specified reference standards qualified by gender and age.

Subjects and Methods. Within the scope of our Project on the BIOsphere and the COSmos (BIOCOS), subjects around the world have been monitored around the clock for 7 days or longer in cooperating centers. Typically, data are analyzed by "sphygmochron", a two-pronged approach consisting of a parametric and non-parametric evaluation of the data. Parametrically, a 2-component model consisting of cosine curves with periods of 24 and 12 hours is fitted by least squares to the data by cosinor, yielding estimates of the MESOR (Midline Estimating Statistic Of Rhythm, a rhythm-adjusted mean, usually more precise and more accurate than the arithmetic mean), and of amplitude (measure of half the extent of predictable change within a cycle) and acrophase (measure of the timing of overall high values recurring in each cycle) of each component, for comparison with reference norms (90% prediction limits from healthy peers matched by gender and age). Non-parametrically data stacked over an idealized 24-hour day are compared to the reference time-specified 90% prediction limits in health to obtain the percentage time elevation, extent of blood pressure excess, and timing when most excess occurs. Deviations from norms are known as Vascular Variability Anomalies (VVAs), or Disorders (VVDs) when they persist upon repeating the monitoring.

Results. ***Definitions***: VVAs include an elevated MESOR of BP (MESOR-hypertension), an elevated pulse pressure (PP), an excessive circadian amplitude of BP (CHAT, brief for Circadian Hyper-Amplitude-Tension), an odd phase of the circadian rhythm of BP, but not HR (ecphasia), too low a standard deviation of HR (DHRV, brief for Deficient Heart Rate Variability), and too high a systolic BP x HR product. ***Health surveillance***: The transient occurrence of VVAs such as CHAT has been related to loads in everyday life, as documented from longitudinal records interpreted in the light of a diary in several individuals. Routine monitoring may help us know ourselves better and improve our lifestyle. ***Diagnosis and prognosis***: Whereas the relationship of the BP MESOR with cardiovascular disease risk is linear, that of the circadian amplitude of BP and the standard deviation of HR is nonlinear: a threshold needs to be exceeded for risk to increase. Except for the BP x HR product, VVAs are mostly independent and additive. In one outcome study, an adverse event occurred within 6 years of the monitoring in only 8.7% of the subjects diagnosed with uncomplicated MESOR-hypertension, but it occurred in 29.1% and in 53.3% of the subjects with one or two additional VVAs complicating MESOR-hypertension; all 3 subjects with 3 additional VVAs suffered an adverse event. Uncomplicated MESOR-hypertension was found in 34.7% of the subjects, with 18.5%, 5.1% and 1.0% having 1, 2 or 3 additional VVAs in addition to MESOR-hypertension. Subjects diagnosed only with CHAT or DHRV, accounting for 2.4% and 1.7% of the population, would not be treated under current standard care. In several outcome studies based on actual adverse events or on biomarkers such as the left ventricular mass index, the circadian amplitude and acrophase interpreted in the light of reference values qualified by gender and age, are better predictive of cardiovascular disease risk than the day-night ratio used for a classification in terms of "dipping". ***VVAs and other biomarkers***: PP correlates positively with body mass index (BMI) and with indices of inflammation (CRP, TNF-α). The standard deviation of HR decreases with increasing BMI. Ecphasia is more prevalent among patients with type-2 diabetes and autonomic nervous dysfunction. ***Chronotherapy***: Treatment can be optimized by timing, using non-pharmacologic agents such as coQ10 or anti-hypertensive medication that do not all have an effect on the circadian amplitude. Several protocols have been designed. One lesson learned is the need to adjust treatment timing in the light of the diagnosis, as patients with the same average BP may differ greatly in terms of their BP variability that places them at different cardiovascular disease risk. Personalized chronotherapy was shown to benefit more than 2/3 of patients. Treating VVAs as well as an elevated BP can cut in half the number of strokes and overall cardiovascular events. ***Environmental influences***: Longitudinal records spanning a decade or longer have shown the presence of cycles with periods characterizing solar activity. Magnetic storms are associated with a marked decrease in HR variability.

Discussion and conclusion. Awareness of the merits of a chronobiological approach versus single clinic measurements should be spread more widely, notably now that newer monitoring devices are addressing issues of comfort and convenience, which have been deterrents to longer-term monitoring. Data collected automatically as a function of time can: a) indicate whether there is a change in health well before there is abnormality in relation to conventional thresholds; b) indicate whether there is a change while on treatment, prompting adjustment in medication, dosage and/or timing; c) aid diagnostic accuracy; and d) distinguish changes that are part of healthy ageing versus the development of blood pressure disorders.