Heart Rate Variability: How to Assess Effects of Mild Therapies on Autonomic Control in Small Groups of Mild and Borderline Hypertensives?

To the Editor:

In their recent retrospective study, Singh et al. could demonstrate on the basis of the impressively huge data set of the Framingham Heart Study that, first, short-term heart rate variability (HRV) is reduced in men and women with systemic hypertension and, second, among normotensive men, lower HRV was associated with a greater risk for developing hypertension. The authors concluded that autonomic dysregulation is present in the early stage of hypertension. Their findings are important but were not very surprising because the reported HRV reduction was generally in accordance with findings of earlier studies. However, what they inevitably left out of consideration was the analysis of the diurnal variation of blood pressure, heart rate, and their respective variabilities. Particularly, the asleep/awake ratios of blood pressure are probably more specific and sensitive than temporary daytime parameters. From the methodical point of view, the study was characterized by the strong and uncompromising use of statistics, but unfortunately without showing any raw data, eg, by using scatter or box plots of the blood pressure and HRV data. Moreover, one important question remained unanswered: How did the HRV parameters and the covariates change during 4 years of follow-up?

Independently and without knowledge of the results from the above study, we also studied the differences of linear and nonlinear HRV parameters in (only) 25 essential nontreated hypertensive subjects with respect to their status of hypertension. The study was carried out from Spring to Fall 1998, and the results are not yet published. The purpose of our study was to gain experience in the collection and interpretation of HRV data from hypertensives for further studies. When comparing our HRV mean values with the values from the Singh study, we were very surprised: After log transformation, the mean values of LF, HF, and LF/HF were approximately identical with those of Singh and colleagues in Table 2 of their paper. As a result of the small N, our SEM (standard error of the mean) values were up to 10 times higher than those of the huge Framingham group. Consequently, significant differences between subgroups could not be demonstrated, and both specificity and sensitivity of all HRV parameters were extremely poor. The separation of subgroups was much better for the nocturnal BP fall, which could not be observed by Singh et al because of the Framingham study design. And we achieved better results using nonlinear HRV parameters instead of the linear spectral HRV markers LF and HF. The most prominent correlation, for example, could be observed between the relative nocturnal blood pressure fall and the approximate entropy (ApEn) of daytime heart period dynamics. As the clinical relevance of our observations remains to be proven, it makes sense if, in future, results like ours could be taken into consideration when analyzing large clinical databases of heart beat and blood pressure data. Particularly, it would seem to be very promising to analyze the time course of 24-hour BP level, if available, and to also include nonlinear measures in 24-hour HRV analyses.

Another problem is how to make use of subtle group differences of huge cross-sectional studies, like those of Singh and colleagues, when dealing with only a few but very individual subjects. And what does adjustment of measures for clinical covariates (eg, age, gender, body mass index, alcohol consumption, and cigarette smoking) mean in the clinical practice?

These problems and others, occurring in clinical practice as well as in many clinical research settings, are not new, but most studies, eg, in hypertension, have not adequately taken the constraints of daily clinical routine into consideration.

In the future, we therefore propose to design preferentially longitudinal sectional or single case HRV studies rather than cross-sectional clinical HRV studies. These studies could address the question: How do HRV parameters change in individuals over longer periods of time with respect to the change of their status of hypertension and with respect to clinical covariates? These studies would not provide odds ratios or similar epidemiological parameters, but clinicians would be enabled to judge an increase or decrease of HRV parameters in individuals, eg, during therapy, which may be more informative than one single starting value. It is a well-known phenomenon that on the one hand sensitivity and specificity of 24-hour HRV measures are generally poor, but, on the other hand, reproducibility in individuals is excellent. Thus, small changes of autonomic control, eg, as an effect of a mild antihypertensive intervention, may be well demonstrated in individuals but may be smeared in large populations.

We suppose that, when following the above recommendations, HRV methods may help to gain further insight into subtle rhythmic and individually different regulatory processes in the human organism. All HRV parameters are per se mirrors of the whole human time organism, reflecting a multitude of internally and externally triggered physiological rhythms that influence each other. Mild therapies, like sports activities or psychosomatic therapies, are often individually conceptualized to stimulate rhythmic processes in the human organism and to enforce self-regulatory processes. Their therapeutic effects are naturally difficult to recognize because they are masked by various clinical or daily life activities that spontaneously influence many clinical parameters more than the therapy itself. The analysis of HRV in individuals, including methods from nonlinear dynamics and taking the 24-hour heart rate and BP variations into consideration, altogether could well have the power to become a useful diagnostic tool, particularly in mild and long-term antihypertensive treatments.

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**Response**

We thank Bettermann et al for their comments and their interest in our work.1 We were unable to assess the diurnal variation of heart rate variability (HRV) because our study was based on daytime ambulatory ECG recordings. It is reassuring, however, to know that the mean values of the LF, HF and LF/HF ratio (after log transformation) from our population-based study (931 men and 1111 women) was nearly identical to values in their study of 25 patients. This was despite the intermediate duration (2 hour) of our recordings compared with their 24-hour recordings.

Bettermann et al raise an interesting point concerning the change in HRV variables over time. Unfortunately, we did not have follow-up HRV data to include in our report. Such data are being acquired now and will allow us to address longitudinal changes in HRV in future studies. We agree that it would be interesting to analyze the time course of 24-hour blood pressure levels and nonlinear measures of HRV.

Power spectral measures of HRV are characterized by large inter- and intra-subject variations,2 which probably reflect the dynamics of physiological control mechanisms over time and even during steady-state conditions.2,3 This complicates the extrapolation of results from a population study to an individual patient in clinical practice. As mentioned in our paper, in theory, HRV, as a surrogate measure for autonomic tone, may aid in the management of hypertension4 by guiding the selection of an appropriate drug. An extension of this concept by Bettermann et al, suggesting the use of longitudinal/single case studies evaluating changes in the autonomic profile of an individual patient over time and the effects of antihypertensive therapy on the HRV parameters, deserves evaluation. This is reinforced by recent data suggesting that postural changes in spectral profiles can be recognized and forecast within individuals.4

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