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## **Chronobiology Predicts Actual and Proxy Outcomes when Dipping Fails**

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# Letter to the Editor

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## Chronobiology Predicts Actual and Proxy Outcomes when Dipping Fails

To the Editor:

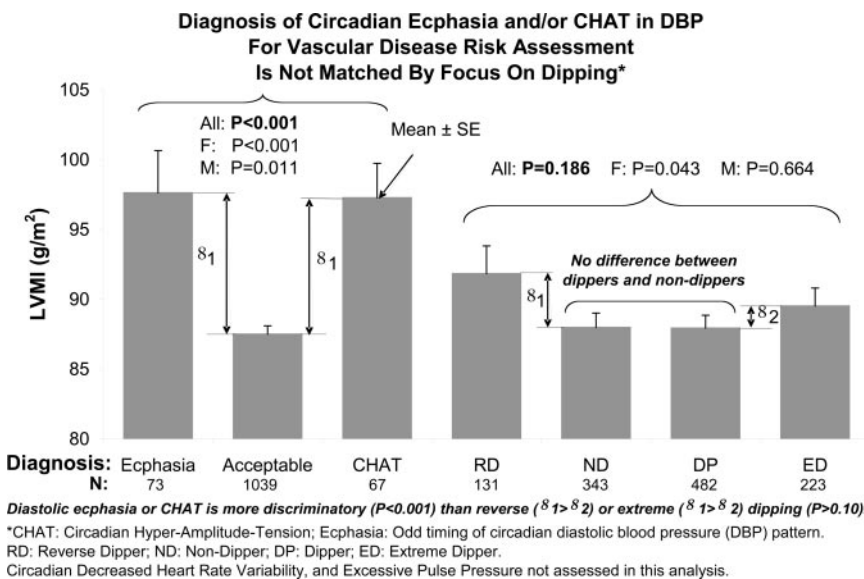
As a gauge of variability, dipping, based on day-night ratios of blood pressure, is much discussed,<sup>1</sup> with 2194 hits in a search of the literature on the Internet. But, as compared with dipping, a classification based on chronobiological end points (such as the circadian amplitude and phase) interpreted in the light of reference values specified by gender and age offers superior discrimination in our data. Abnormality in the normal range can occur as (1) a (circadian) blood pressure overswing or circadian hyper-amplitude-tension (CHAT) gauged by a circadian amplitude exceeding the upper prediction limit of presumably clinically healthy peers of the same gender, age group, and ethnicity; (2) an excessive pulse pressure gauged by a persisting excessive difference between systolic pressure, when the heart contracts, and diastolic pressure, when the heart relaxes, measured around-the-clock; (3) circadian ecphasia, an odd timing of the daily blood pressure swing in the absence of an oddly timed daily heart rate pattern to rule out effects of work and sleep schedule shifts that may affect the timing of both blood pressure and heart rate rhythms; or (4) too little heart rate jitter, gauged by a reduced around-the-clock standard deviation of heart rate.

In a 6-year prospective study of 297 patients with no initial history of morbid cardiovascular event undergoing 48-hour ambulatory blood pressure monitoring,<sup>2</sup> a circadian amplitude above the upper 95% prediction limit of clinically healthy peers matched by gender and age had a relative risk of 4.27 (95% CI: 2.43, 7.51;  $P < 0.001$ ), whereas nondipping was not discriminatory (RR = 1.37; 95% CI: 0.75, 2.51;  $P > 0.05$ ). Analyses of 1179 untreated patients<sup>3</sup>

indicate that the concomitantly assessed left ventricular mass index (LVMI) of patients with an abnormal circadian pattern of diastolic blood pressure (DBP) is greatly elevated (Fisher statistic from 1-way ANOVA:  $F = 15.959$ ,  $P < 0.001$ ), contrasting with the LVMI of reverse dippers, nondippers, dippers, or extreme dippers ( $F = 1.605$ ,  $P = 0.186$ ) (Figure).

Much larger LVMI values, considered as a surrogate outcome measure available from all 1179 patients, are observed in the presence of abnormal circadian patterns of DBP, whether the phase occurs at an odd time (ecphasia) or whether the amplitude is excessive (CHAT). Comparable elevations in LVMI are not seen for patients with an abnormal day-night ratio. A similar comparison based on systolic blood pressure (not shown) also favors a classification based on cosinor-derived circadian characteristics, whether considering all patients (All) or only women (F) or men (M), as does broader evidence in the Table. In populations of presumably healthy subjects and untreated or treated hypertensive patients, usually with no prior cardiovascular morbidity, a classification in terms of dipping based on the day-night ratio, routinely assessed in our analyses, has not contributed risk information beyond prediction achieved by means of chronobiological end points.

To detect variability disorders, we need to replace the single office measurement of blood pressure by a 7-day profile of 3-hourly (self-) or denser (eg, half-hourly) automatic measurements analyzed chronobiologically, because there can be large day-to-day variability in circadian characteristics.<sup>4,5</sup> We may find a midline estimating statistic of rhythm (MESOR)-hypertensive patient, whose overall blood pressure is seemingly well treated by drugs, with acceptable measurements during office hours, but who may still have much too high or much too



LVMI, used as a surrogate outcome measure available from all 1179 participants, is compared among patients classified in terms of circadian characteristics assessed by cosinor (3 columns on left) or in terms of dipping gauged by the day-night ratio (4 columns on right). Comparison by 1-way ANOVA overall (All) and separately for women (F) and men (M). LVMI values are greatly elevated when diastolic ecphasia or CHAT is diagnosed (corresponding to abnormal circadian patterns of diastolic blood pressure) but not when the day-night ratio is negative (reverse dippers), too small (nondippers), or too large (extreme dippers). Ambulatory blood pressure monitoring may serve the broader derivation of normative values in health for circadian parameters.

**Outcomes of Chronobiological Screens of Blood Pressure and Heart Rate\***

No. of Patients	No. at Follow-Up	Sampling	No. Measurements: Total (Outcomes)	Finding
10	10 (up to 5 years)	5/day daily	Up to 9125 (only partially analyzed)	Among P. Scarpelli's patients, the 4 who died with malignant hypertension had a larger circadian BP amplitude than the 6 who were still alive (SBP: $t=1.84$ ; $P=0.103$ ; DBP: $t=2.99$ ; $P=0.017$ ) <sup>7</sup>
63	21 after 28 years	every 4 hours for 2 days	756 (252)	9 of 10 subjects without CHAT are alive whereas 7 of 11 subjects with CHAT are dead 28 years later ( $\chi^2=6.390$ ; $P<0.01$ ) <sup>8</sup>
56	56 (Concomitant LVMI)	every 15 minutes for 24 hours	5376 (5376)	Classification by Y. Kumagai of patients by LVMI (<100; 100–130; >130 g/m <sup>2</sup> ) reveals elevation of circadian BP amplitude at LVMI in 100–130 range whereas BP MESOR elevation occurs only at LVMI >130 <sup>9</sup>
221	221 (time of delivery)	every 1 hour for 48 hours in each trimester of pregnancy (336 profiles)	16 128 (16 128)	In addition to an 8 mm Hg difference in mean value between women who will or will not develop complications (gestational hypertension, preeclampsia) already observed during the first trimester of pregnancy, the occurrence of complications is also associated with BP profiles characterized by an elevated circadian BP amplitude. In particular, one case (JK) of CHAT where warning was not heeded was followed 8 weeks later by severe preeclampsia, premature delivery, and 26 months of hospitalization of offspring at a cost of about \$1 million <sup>10</sup>
297	297 after 6 years	every 15 minutes for 48 hours	57 024 (57 024)	CHAT, a reduced circadian standard deviation of HR, an excessive pulse pressure (>60 mm Hg) are large risk factors (larger than hypertension) for cerebral ischemic events, nephropathy and coronary artery disease, even when BP is within acceptable limits <sup>2</sup>
2039	2039 (Concomitant LVMI)	Hourly averages for 24 hours	48 936 (48 936)	In C.H. Chen's subjects, LVMI is increased in patients with CHAT, a reduced circadian standard deviation of HR, or an elevated pulse pressure. The relation between LVMI and the circadian end points is nonlinear in data summarized in the Figure
23	12 after 7 years	every 15 minutes for 9 days	19 872 (10 368)	10 of 20 patients with no consistent BP abnormality are alive and well; 2 of 3 patients with consistent BP abnormality reported an adverse vascular event ( $P=0.015$ by Fisher exact test) <sup>11</sup>
80	80 (Response to treatment administered 2 hours before daily BP peak vs control group treated 3 times a day)	every 4 hours for 24 hours before and on treatment	960 (960)	With smaller doses of medications, BP was lowered by R. Zaslavskaya to a larger extent and treatment was accompanied by fewer complications. Treatment: propranolol, clonidine, or $\alpha$ -methylodopa ( $P<0.05$ for each effect) <sup>12</sup>
18	18 (12 weeks)	every 30 minutes for at least 24 hours on each of 3 regimens	$\geq 2592$ ( $\geq 2592$ )	Treating CHAT may prevent adverse vascular events: As compared to placebo, nifedipine (1 mg BID at 08 and 20) increases and benidipine (4 mg/d at 08) decreases the 24-hour BP amplitude. The resulting increase vs decrease in CHAT incidence may account for the corresponding difference between the No. of stroke events of 7.6 vs 3.5 and the total No. of cardiovascular events of 20.4 vs 8.8 per 1000 person-years on nifedipine vs benidipine <sup>6</sup>
Totals:				
2807	2754		160 769 (>141 636)	

SBP, systolic blood pressure; HR, heart rate.

\*By comparison with several classical studies, the number of measurements in chronobiological work completed thus far is likely to be larger, and confounding by intersubject variability is likely to be smaller.

low values during the night: high DBP around 120 mm Hg values each night because the medication no longer works (patient DJ), or low DBP values <30 mm Hg because it works too well (patient BLB). In both cases, such nightly readings present a danger in themselves and because they are associated with the

occurrence of CHAT that can also happen when most or all values are within the acceptable range.

In MESOR-normotensive patients, the single blood pressure measurement in the provider's office may be acceptable, but if CHAT is present, their risk of stroke and other severe vascular

diseases may be greater than that associated with MESOR-hypertension (high blood pressure), all chronobiological diagnoses relying on a reference database preferably adjusted for gender, age, and ethnicity for all variability disorders. Whereas, on the average, blood pressure may not be too high or too low, variability in blood pressure, heart rate, or both may be abnormal. CHAT can thus be traded for a seemingly acceptable average, an undesirable outcome. Treatment of variability disorders can reduce the risk of severe morbid events,<sup>6</sup> even among seemingly normotensive patients who, rather than relying on office spotchecks, monitor for 1 week for a chronome (time structure) analysis.

The long-proposed assessment of circadian rhythmicity<sup>4,5</sup> as part of a much broader time structure can now be obtained cost effectively, with automatic monitors available with an 80% price reduction and free chronobiologic analysis (come001@umn.edu) until a Phoenix Project (<http://www.phoenix.tc-ieee.org/>) will enable all users to analyze their data themselves by cosinor. With actual outcomes based on sample sizes larger than the 297 cases in Reference<sup>2</sup> or other studies listed in the Table, it seems desirable to compare in other already available databases the relative merits of a classification based on dipping (which in the study herein had no statistically significant predictive value) with one based on a chronobiological assessment of the data, and to apply chronobiological principles to individually optimize the timed prophylactic or palliative treatment of patients diagnosed with prehypertension or MESOR-hypertension, respectively.<sup>4–6</sup> Fixed demarcations used for the day–night ratio do not account for the fact that the circadian blood pressure pattern is influenced by more than sleep–wake and activity and that it also changes with age. To further compare the relative merits of the circadian parameters and of dipping in all populations, cosinor analyses of ABPM data from existing outcome studies are offered at the Halberg Chronobiology Center.

Human monitoring around-the-clock for decades has also proved its heuristic value and provides a vast perspective beyond dipping classification.<sup>4,5</sup> It awaits clinical scrutiny as a mechanism of inhibitions and exacerbations of disease, including sudden cardiac death, quite apart from an attempt at tighter control of blood pressure disorders akin to benefits of dense glucose monitoring already documented for the treatment of diabetes.

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