

Chronobiology Impacts Response to Antihypertensive Drug Regimen in Type 2 Diabetes

Chronobiology is the term applied to the study of how body rhythms are governed by our environment, starting with the solar system, which cycles night and day and changes one season into another (1). Bodily responses encompassed by chronobiology determine both everyday behavior and expression of illness (2). Key rhythms modulating health and disease states may be circadian (lasting about 24 h and defining sleep-awake patterns) or infradian (lasting longer than 24 h, as in monthly menstruation). Adjusting timing of medical treatment to its differing effects depending on the patient's circadian state as currently applied in nocturnal asthma (3) and arthritis (4) is called chronotherapy. Hermida et al. (5) report a prospective, randomized, open-label, blinded end point trial of how varying the time of day during which antihypertensive drugs are taken may affect cardiovascular risk in hypertensive patients with type 2 diabetes.

That chronotherapy might assist in management of hypertension was appreciated by Barter et al. (6) in a retrospective 24-h study of a single patient with systolic and diastolic hypertension treated with hydrochlorothiazide in 1976. Availability of continuous 24-h blood pressure monitoring devices prompted a French study in 1985 suggesting that each hypertensive patient be evaluated over a full day with subsequent antihypertensive drug treatment scheduled to fit daily periods of highest pressure (7). Noting that "many cardiovascular disorders occur with greatest frequency between 06:00 and 12:00 AM," Cooke and Lynch (8), in 1994, proposed that a chronotherapeutic approach to therapy might proffer advantage in thromboembolism, hypertension, angina, and acute myocardial infarction by facilitating improved patient outcomes. Predicting that chronotherapy for ischemic heart disease would be forthcoming, the University of Texas established a chronobiology department in 1996 (9). As newer classes of antihypertensive drugs have been introduced, focused attention on blood pressure during sleep increased

with growing hope that cardiovascular complications might be reduced in frequency and intensity (10).

The study by Hermida et al. of 448 hypertensive patients with type 2 diabetes who had ambulatory blood pressure measured initially for 48 h and then annually over a mean of 5.4 years found that administering antihypertensive medications at bedtime produced a significantly lower cardiovascular risk (adjusted by sex and age) than that in a randomly selected cohort given their antihypertensive drugs upon awakening. Taking antihypertensive drugs at bedtime significantly decreased the adjusted risk of cardiovascular death, myocardial infarction, and stroke (0.25; $P = 0.003$). Bedtime treatment significantly reduced both sleep-time blood pressure mean with a 12% cardiovascular risk reduction per 5 mmHg decrease in asleep systolic pressure during follow-up.

It is well known that shift workers have increased diabetes and obesity, worse glucose control, and higher rates of cardiovascular disease and mortality (11). Changing the clocks back in spring is associated with increased myocardial infarctions. Supporting these observations are short-term experimental studies showing that misalignment of behavioral and circadian cycles results in adverse cardiometabolic end points including higher arterial blood pressure, glucose, insulin, ghrelin, cortisol, and catecholamines (12). Genetic studies point to molecular mechanisms based in highly conserved controllers of periodicity or *Zeitgeber* (13,14). These molecular clocks are located in the central nervous system and in peripheral tissue, communicating with each other and responding to a great number of inputs presumably designed to maintain homeostasis of the entire organism relative to changing environments.

An article by Hermida et al. (15) demonstrating that treatment synchronized to the biology of hypertension is highly effective in diabetes and nondiabetes gives support to the concept that treatment

synchronized to the biology of metabolism might also be effective especially as glycemia is particularly difficult to management. There is some use of chronotherapy in current glycemia treatment; however, it is not a major focus. For example, bedtime insulin is used to lower the tendency of the blood glucose to rise in the morning. The conventional explanation is that insulin counters the tendency to increase hepatic glucose production by the normal nocturnal surge in growth hormone and cortisol. However, newer data suggest a greater complexity—liver cells themselves have molecular clocks that govern hepatic glucose production and fat storage suggesting regulation of hepatic steatosis (16). Meal-associated insulin treatment targets the expected postprandial rise in blood glucose. Indeed, molecular genetic studies identify a clock gene for β -cell mitochondrial function that in part governs insulin secretion. The new technology of 24-h continuous glucose monitoring promises insights into how we might better define normalcy and tailor glycemic treatment. Another example is the use of statin therapy at bedtime to lower LDL cholesterol because lipid metabolism is nocturnal. The study by Hermida et al. (5) prompts us to reexamine the basis for management of glycemia through the lens of chronobiology.

A key strength of the report by Hermida et al. (5) is that it confirms the well known J curve for adverse outcomes in systolic blood pressure as measured in a clinic but shows no such effect for systolic blood pressure while asleep, for which the lowest blood pressure is associated with the lowest hazard ratio. The recently published Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial failed to show a difference in major cardiovascular outcomes between intensive and nonintensive systolic blood pressure targets of <120 and <140 mmHg, respectively (17). Had the investigators considered the pragmatic reality of drug effect possibly being altered by chronobiology, their results might have differed, as the timing of dosing of blood pressure medications was not standardized. Other

possible variables that may have altered the effect of antihypertensive treatment during the study include differences in lifestyle and behavior practices including meditations, exercise, diet, stress reduction, and sleep hygiene policies.

At the least, Hermida et al. proffer a strong argument for establishing each newly managed hypertensive diabetic patient's circadian pattern of time-related blood pressure elevation as a potential correctable variable when designing an individualized antihypertensive regimen. In a larger perspective, we should be alert to ignoring inherent cycles of nature that contribute to establishing blood pressure responses as well as, according to some investigators, the basis of our growing obesity pandemic. Awareness and response to ticking biological clocks must be kept in mind when constructing pertinent therapies, as evidence now supports the thesis that knowledge of chronobiology is a concern when building a chronotherapy for hypertension (18).

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