Chronotherapy of cardiovascular pathologies: a hopeful strategy

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To the Editor:

The number of poorly controlled hypertensive patients worldwide is alarmingly high, and the introduction of antihypertensive drugs with principally novel mechanisms of action is not anticipated.[1] Instead, better adherence to treatment, fixed antihypertensive drug combinations and careful self-monitoring are recommended. However, the chronotherapeutic approach, that is, considering daily rhythms in physiological functions and pathological alterations, may offer a novel insight into hypertension treatment with emerging perspectives. Chronotherapy means the optimization of therapeutic strategies respecting the body's circadian rhythms. The circadian rhythms of various physiological functions are determined by mutual interactions of activating and hypnogenic neurohumoural systems. Under physiological conditions, blood pressure (BP) is characterized by prominent circadian variations with a steep increase in the morning and a deeper descent during nocturnal rest.[2] Subjects with attenuated BP decline at night, that is, non-dippers (less than 10% decline of the daily value) or individuals with nocturnal hypertension, show increased risk of adverse cardiovascular events or death. Of note, the asleep BP mean was recognized as the best predictor of cardiovascular outcomes.[3] Moreover, severe cardiovascular events occur predominantly during the morning BP surge, which predisposes atherosclerotic plaques to rupture.[2] Thus, there is an effort focused on adopting treatment schedules that target these haemodynamic alterations.

The MAPEC (Ambulatory Blood Pressure Monitoring for Prediction of Cardiovascular Events) study, with a median follow-up of 5.6 years and 2156 patients, was the first prospective trial indicating that shifting one or more antihypertensive drugs from the morning cocktail to bedtime significantly improved ambulatory BP control, lowered the asleep BP mean, improved the sleep-time relative BP decline and reduced the prevalence of non-dippers as shown by 48 h ambulatory BP monitoring (ABPM). Most importantly, both total and major cardiovascular events were significantly reduced, irrespective of the type of antihypertensive medications. However, extrapolation of the results to the general population was limited due to the single-centre study design.[4]

Recently, the Hygia Chronotherapy Trial has been published in *European Heart Journal*. This study confirmed the previous success of hypertension chronotherapy achieved in the MAPEC study. The 6.3-year median patient follow-up Hygia study involved 40 primary care centres and investigated 19,084 hypertensive patients. According to the results of the trial, ingesting the entire daily dose of hypertension medications at bedtime compared with all drugs being administered upon awakening remarkably reduced the primary cardiovascular disease (CVD) outcome as well as the risk of each of its single components. Lowering asleep BP mean and reducing non-dipping prevalence appear to be principal factors underlying the CVD risk attenuation.[3]

The exciting chronotherapeutic approach by Hermida *et al.* raises a number of considerations. First, the 45% reduction of cardiovascular events is substantially larger than the benefit achieved in recent cardiovascular studies. This implies that respecting the pathophysiological principle of circadian BP variations represents a highly effective approach overwhelming the principle of BP smoothness maintenance. Moreover,

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chronotherapy may find its application in several other cardiovascular pathologies, such as resistant hypertension,[5] elevated heart rate (HR) in hypertension,[6] type 2 diabetes[7] and heart failure.[8] Importantly, this strategy is easy to introduce without an additional burden to the health care system. In fact, a subanalysis has indicated that ABPM was substantially more effective and less costly than daytime office BP measurements due to decreased expenditures for medical examinations and reduced costs of elevated BP-associated vascular pathologies. Thus, the annual monetary benefit of the ABPM model seems to be much higher than the direct ABPM-associated costs.[9] In line with this, chronotherapy might become a hopeful strategy of cost reduction for health care providers and payors.

Second, a question emerges: What pathomechanism makes the bedtime drug application to be of such an importance? Attenuation of the renin–angiotensin–aldosterone system (RAAS) or the sympathetic nervous system may result in reduced cardiac output, attenuated peripheral resistance and increased peripheral blood flow associated with a more physiologic pattern of haemodynamics, with adequate nighttime BP decline.[10] However, mechanisms beyond BP reduction that may contribute to the prominent cardiovascular benefits of the Hygia and MAPEC studies should also be considered. A relation between circadian rhythms and homeostatic processes governing cellular apoptosis and necrosis was described.[11] Dyssynchrony of gene expression and concomitant molecular rhythms may result in adverse tissue growth and pathologic remodelling of the heart and vasculature.[12] Thus, preserving natural variations of cardiovascular gene expression *via* the tissue-local effect of RAAS inhibition may potentially result in more physiological vascular and myocardial remodelling, kidney damage attenuation or energetic metabolism improvement.[7,13] Moreover, chronotherapy may interfere with specific pharmacodynamic and pharmacokinetic characteristics of a particular substance facilitating haemodynamic and structural protection and reducing the adverse effects.[14] Hypothetically, some yet unknown mechanism of increased vascular wall and target organ sensitivity to inappropriate shear stress during the resting period could also participate. These matters should motivate cardiovascular scientists to consider the application of potential cardiovascular protectives predominantly in the resting period of experimental animals, when greater benefit might be expected.

Third, the circadian variations and the bedtime treatment of other principal risk factors such as reduced insulin sensitivity, lipoprotein and triglyceride concentrations or platelet aggregability should be investigated to optimize the therapeutical benefit. The plasma glucose level seems to undergo circadian changes relatively independent of external factors such as eating habits or medicines;[15] indeed, the chronotherapeutic approach in terms of increased sleep quality improved metabolic parameters in type 2 diabetic patients.[7] A systematic review of 25 studies revealed that circadian rhythmicity generates a pro-thrombotic state reflected by hypofibrinolysis and hypercolagulation in the morning hours potentially contributing to higher cardiovascular risk in the early period of the day.[16] On the contrary, although cholesterol biosynthesis undergoes circadian variations with the principal production in the night/morning hours, clinical trials did not show any benefit of chronotherapy *versus* conventional statin therapy for the treatment of hyperlipidaemia.[17]

Finally, HR and non-dipping HR are neglected cardiovascular risk factors. They could also be better controlled by an evening schedule of antihypertensive drugs with HR-reducing potential, such as betablockers or some calcium channel blockers, or by other HR-reducing substances, such as ivabradine and melatonin, potentially yielding additional protection in hypertensive patients with increased HR.[6]

Taken together, the chronotherapeutic approach to the treatment of hypertension and other cardiovascular pathologies has a potential to become a regular part of the therapeutic strategy if confirmed in ongoing chronotherapeutic trials with cardiovascular population.

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Tomas Baka: Investigation; Validation; Writing – review & editing.

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