Optimizing Pharmacotherapy for Limiting Cardiovascular Remodeling
A Matter of Timing
Therapy to Match Biology*
Bodh I. Jugdutt, MD, DM
Edmonton, Alberta, Canada

Cardiovascular remodeling is a major mechanism leading to adverse outcome. The renin-angiotensin-aldosterone system (RAAS), with angiotensin II as its primary effector peptide, plays an important regulatory role in cardiovascular remodeling. Most angiotensin II is formed via the angiotensin-converting enzyme (ACE) pathway, providing rationale for use of ACE inhibitors. Hypertension and myocardial infarction are the top 2 causes of adverse cardiovascular remodeling. Although hypertension results in hypertrophic remodeling, myocardial infarction results in predominantly dilative remodeling. A major goal of pharmacotherapy is to limit cardiovascular remodeling and improve outcome. Evidence from randomized trials has established ACE inhibitors as first-line therapy for hypertension and post-infarction heart failure. Many studies have shown that ACE inhibitors produce benefits beyond blood pressure lowering and act at the tissue level to limit remodeling. However, despite the wide use of ACE inhibitors, many patients continue to suffer from complications of adverse remodeling.

How can we optimize benefits of pharmacotherapy? One approach is the timing of therapy to match biological need through chronotherapeutics, with attention to chronobiology (the body’s biological time structure), circadian (24-h) rhythms, and wake–sleep patterns (1,2). In this issue of the Journal, Martino et al. (3) underscore the importance of chronotherapy and diurnal timing in hypertrophic pressure-overload remodeling; they show that remodeling occurs mainly during sleep time and propose administration of ACE inhibitors such as captopril during sleep time for optimal limitation of remodeling.

Homeostatic or chronobiological therapy? Until recently, homeostatic therapy has been the dominant approach to pharmacotherapy. It is based on the theory of constancy of the milieu intérieur or internal environment advanced by French Physiologist Claude Bernard (1813 to 1878) and the underlying principle of homeostasis proposed by the American Physiologist Walter Bradford Cannon (1871 to 1945). In this construct, deviation from set levels of biological variables activate inherited homeostatic mechanisms that provide moment-by-moment regulation and restore constancy of the internal milieu. Homeostatic therapy is aimed at maintaining constant drug blood/tissue levels over 24 h to achieve sustained therapeutic benefit.

Advances in chronobiology since the 1960s suggest that biological functions and processes are precisely organized in time and space; inherited biological clocks and rhythms regulate physiological and biochemical variables, pathophysiology and disease progression, manifestation, sympotmatology, and response to therapy (1,2). Circadian rhythms are controlled by a master clock residing in the suprachiasmatic nuclei of the anterior hypothalamus and the pineal gland. Timekeeping is determined by clock genes (per1, per2, per3, bmal, clock, CRV) and melatonin. Circadian clocks are adjusted through environmental cues such as light–dark patterns that entrain the peaks and troughs in synchrony with wake–sleep patterns. The human circadian time structure shows typical peak times for several variables (1,2) that are important for cardiovascular remodeling. These include: 1) atrial natriuretic peptide, calcitonin, cholesterol, and triglycerides during early sleep time; 2) growth hormone and melatonin during late sleep time; and 3) cortisol, renin, angiotensin, aldosterone, catecholamines, arterial compliance, blood pressure, platelet aggregation, and blood viscosity in early wake time. Studies suggest that circadian rhythms in peak severity of cardiovascular diseases match these peaks; for example, angina, myocardial infarction, sudden cardiac death, ventricular arrhythmias, thrombotic stroke, and hypertensive crises in early wake time and Prinzmetal angina and hemorrhagic stroke during sleep time. Disruption of circadian rhythms in night-shift workers results in increased cardiovascular risk. Studies have shown that inappropriately timed therapy can be harmful.

Chronotherapy aims at synchronizing peak drug levels with peaks of disease markers associated with adverse events and avoiding adverse side effects during troughs. Chronotherapy has already been applied in the treatment of several conditions, including essential hypertension. Whereas blood pressure peaks during wake time and dips during sleep time in essential hypertension, the sleep–time dip is reduced, absent, or reversed in secondary hypertension. Because nondippers in essential

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hypertension are susceptible to target organ damage, and too small a decline in blood pressure during sleep increases the risk of left ventricular hypertrophy, therapy during sleep time might be beneficial in such patients. Although ACE inhibitors and other antihypertensive therapies at night time have been shown to restore diurnal dipping patterns in nondippers (4,5), the effect of this approach on hypertrophy was never assessed.

**Optimal timing of therapy for optimal benefit.** Martino et al. (3) addressed the important question of whether the therapeutic benefit of ACE inhibitors on pressure-overload hypertrophy exhibits significant diurnal variation. They compared the effect of the short-acting ACE inhibitor captopril, given intraperitoneally during sleep time (lights on at 7 AM) or wake time (lights off at 7 PM) for 8 weeks, beginning 1 week after surgical constriction of the descending aorta in young mice. Previous studies already showed that chronic pressure overload, induced by constriction of the ascending aorta in rats, results in severe left ventricular hypertrophy associated with normal renin and elevated ACE, and ACE inhibitors decreased hypertrophy and mortality. Martino et al. (3) demonstrated that only sleep-time captopril limits cardiovascular remodeling and improved systolic function. As expected, these anti remodeling effects of captopril were correlated with attenuation of tissue ACE mRNA levels that peaked at sleep time. These benefits were independent of blood pressure lowering because the decrease in blood pressure (on 24-h monitoring) was similar with sleep- or day-time captopril, and the effect of wake-time captopril on remodeling was identical to that of placebo.

Several points arising from the study of Martino et al. (3) deserve emphasis. First, the finding that the heart and its vessels remodel during sleep time endorses diurnal timing of pharmacotherapy for hypertrophic pressure-overload remodeling. Second, the finding that the efficacy of captopril therapy on remodeling is critically dependent on timing during sleep time is clinically highly relevant for optimal benefit in pressure-overload conditions such as aortic stenosis and aortic coarctation, and possibly hypertension. Third, the overall findings support chronotherapy as an effective approach for optimizing limitation of remodeling, with the clear message that diurnal considerations may be important for optimal therapeutic benefit.

A fourth point relates to the remodeling benefit observed with a short-acting ACE inhibitor such as captopril. Other ACE inhibitors such as enalapril, fosinopril, lisinopril, perindopril, and ramipril are longer acting. An early study in rats showed that short-term elevation of blood pressure during sleep time, induced by repeated injections of angiotensin II over 4 h, resulted in a similar degree of hypertrophy as sustained blood pressure elevation produced by continuous angiotensin II infusion (6), suggesting that the acute load is sufficient to trigger chronic hypertrophy. Therapy with short-acting agents may be a more effective therapeutic approach and avoid adverse effects. The practice of using multiple doses, slow-release, and long-acting drugs to cover both wake and sleep times may need re-evaluation.

There are several points in the study of Martino et al. (3) that need verification. 1) Although molecular clocks that orchestrate biological functions may be altered by disease and therapy, the circadian clock genes *mper2* and *mbmal1* did not change with the interventions. 2) Other molecules of the RAAS besides ACE (such as angiotensin II, aldosterone, ACE-2, and angiotensin 1–8) that are pertinent for cardiovascular remodeling may show diurnal variation. 3) Non-ACE pathways that can generate significant amounts of angiotensin II under certain conditions including ACE inhibition may show diurnal variation. 4) Reversal of sleep/wake times in mice compared with humans may result in different short-term and long-term effects on diurnal molecular changes and remodeling. 5) Most experimental studies demonstrating beneficial effects of ACE inhibitors on remodeling gave the drug in drinking water, which would have been ingested during wake time rather than sleep time. 6) The benefits in young mice may differ in older mice because age may affect circadian rhythms; this is especially pertinent because the disease addressed is more common in adult and elderly humans, as is the burden of stroke and heart failure. 7) Although the mouse model has its merits, confirmation in higher pre-clinical models (e.g., pig and dog) and humans might be desirable, especially because human plasma renin, aldosterone, and angiotensin have been reported to peak in early wake time (1,2).

In summary, timing of therapy on the basis of biology makes sense, and chronotherapy is a potentially effective approach for treating pressure-overload hypertrophic remodeling. Whether post–myocardial infarction remodeling shows diurnal variations and benefits from chronotherapy deserves study.

**Reprint requests and correspondence:** Dr. Bodh I. Jugdutt, 2C2 Walter MacKenzie Health Sciences Centre, Division of Cardiology, University of Alberta Hospital, Edmonton, Alberta T6G 2R7, Canada. E-mail: bjjugdutt@ualberta.ca.

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