

Myocardial Repair Around-The-Clock

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As an intern in 1952, we admitted patients with acute myocardial infarction wherever a bed was available on the medical service, but always as far from the nurses' station as possible, so that they would not be disturbed by the commotion, especially the frequent telephone ringing.

—Eugene Braunwald¹

Significant advances in the diagnosis and management of patients with ischemic myocardial syndromes^{1,2} have occurred since Herrick's classic description of acute myocardial infarction (MI) 102 years ago (1912). With progress in technology, it became clear that lethal ventricular arrhythmias were a common cause of death that could be prevented by immediate electric defibrillation of the heart. This led to the development of the modern coronary care units (CCU). These units facilitated continuous monitoring and defibrillation for life-threatening arrhythmias, the rapid treatment of recurrent myocardial ischemia, and early recognition and initiation of various therapies for pump failure and cardiogenic shock.

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A consequence of the modern CCU environment (and critical care units in general) was the loss of the normal sleep-wake cycle for patients admitted to the busy critical care environment. Sleep is a restorative process, leading to important circadian variations in protein synthesis and cellular repair³ that affect many organs including the heart.⁴ Inadequate sleep induces a state of catabolism and impaired immunity, which may lead to delayed wound healing^{5,6} and altered myocardial energetics.⁷ With continued progress, the emphasis of CCU care has shifted to improving outcomes by reducing infarct size with early reperfusion frequently implemented with primary percutaneous coronary intervention during the initial hours of infarction. With this, time spent in the CCU is frequently <24 hours, with discharge to home within 72 hours. Thus, for contemporary patients, the synchrony between endogenous biological clocks and the external circadian rhythm is re-established more rapidly than in the past. Nevertheless, those with clinical courses complicated by shock or heart

failure can remain in the CCU for days where disruption of sleep-wake cycles may have important long-term functional consequences.

In this issue of *Circulation Research*, Alibhai et al⁸ report the effects of disrupted circadian rhythm on the reparative response after an acute MI. Mice with a nonreperfused anterior infarct and a usual 12-hour sleep-wake cycle were compared with those where the normal biorhythm was disrupted by initiating a 10-hour sleep-wake cycle for 5 days to simulate hospitalization in a critical care environment. Despite only mild short-term, diurnal disruption, the postinfarction left ventricular (LV) remodeling at 8 weeks was markedly accentuated, resulting in greater LV dilatation, a fall in LV ejection fraction (45% versus 60%), and greater LV hypertrophy (8.19 versus 6.70 mg/g body weight). These changes were secondary to accentuated infarct thinning and circumferential infarct expansion in the disrupted mice.

Experiments to understand the mechanism for deleterious infarct expansion and adverse remodeling point to altered inflammatory responses with impairment of the healing process when the circadian clock is disrupted. Myocardial necrosis triggers a complex temporally orchestrated inflammatory response that is designed to clear the wound of dead cells and matrix debris while at the same time activating reparative pathways necessary for fibrosis and scar formation.^{9,10} Mild disruption of sleep-wake cycles reduced early myocardial neutrophil infiltration and tissue myeloperoxidase. At the same time, myocardial expression of monocyte chemoattractant proteins (monocyte chemoattractant protein-1 and monocyte chemoattractant protein-3) increased and was accompanied by increased early macrophage infiltration (Figure 1). Greater LV dilatation was apparent in disrupted mice as early as 1 week after infarction and progressed in the late phase (8 weeks), despite comparable infarct volumes.

At first glance, deleterious remodeling in sleep-disrupted animals may seem paradoxical because a reduction in neutrophils should attenuate inflammation-mediated LV remodeling. Scar composition may be fundamentally altered via time-dependent dynamics in matrix metalloproteinases in a fashion that leads to infarct thinning and expansion.¹¹ In addition, there is a complex interplay among innate immune responses and various white blood cell subtypes (neutrophils, macrophages, and lymphocytes) in infarct healing. As a result, alterations in the time course, macrophage subtypes (eg, M1 to M2 subtype transition), and temporal cytokine release profile may importantly contribute to deleterious remodeling in this situation.⁹ Despite promise in preclinical animal models (where the acute inflammatory response may be accentuated), clinical trials to modulate inflammation with a variety of agents have thus far been unsuccessful.¹⁰ The study by Alibhai et al⁸ suggests that maintaining the normal circadian clock may accomplish this in a nonpharmacological fashion.

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

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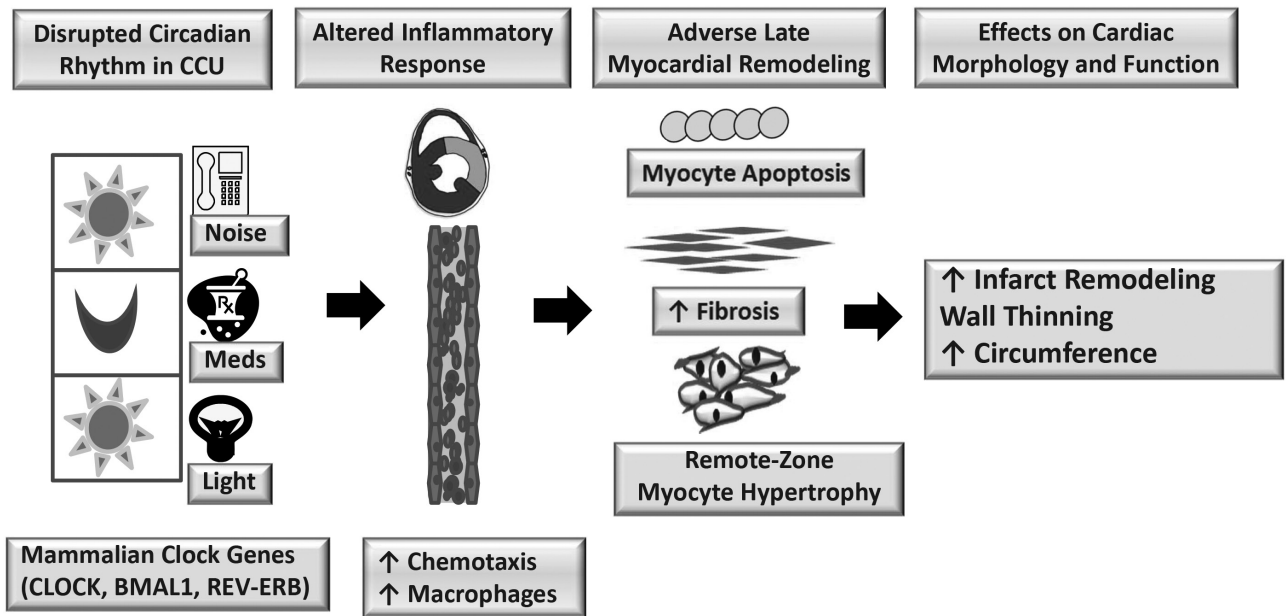


Figure. Schematic diagram to show the detrimental effects of loss of circadian rhythm after acute myocardial infarction (MI). Circadian rhythm is finely regulated by several mammalian clock genes including CLOCK, BMAL1, and REV-ERB. Loss of circadian rhythm because of noise, lights, and medications during intensive monitoring in a coronary care units (CCU) setting after acute MI can activate innate immunity, alter the inflammatory cellular response, and induce the expression of chemotactic cytokines. This may accentuate deleterious left ventricular remodeling by altering extracellular matrix turnover, cellular apoptosis, remote-zone cardiomyocyte hypertrophy, and interstitial fibrosis to ultimately depress cardiac function.

Alterations in selected constituents of the myocyte cellular circadian clock were examined in remote and infarcted myocardium. The normal diurnal variations in clock, *per2*, *nfil3*, and *revorb* were globally attenuated in the myocardium of disrupted mice. To further link myocyte circadian variations and inflammation, circadian locomotor output cycles *kaput* (CLOCK) mutant mice⁸ were studied. The lack of this crucial gene was associated with excess local influx of macrophages and neutrophils after infarction. Although supportive of a role of CLOCK genes on the postinfarction inflammatory response, the key physiological experiment demonstrating adverse LV remodeling in CLOCK knockout mice subjected to coronary occlusion (like the disrupted sleep–wake cycle mice) was not performed. Cardiac-specific CLOCK knockout mice do not exhibit a circadian variation in infarct size and actually demonstrate a smaller infarct size than wild-type mice, suggesting that they are suspended at the wake-to-sleep interface that is cardioprotective.¹² This observation is difficult to reconcile with increased neutrophil infiltration, but it is plausible that the effects in the whole animal reflect disruption of central circadian variations in the systemic inflammatory response rather than tissue-specific circadian variations. As a result, testing the role of CLOCK on postinfarction remodeling may require complex genetic manipulations that can conditionally knock out CLOCK in a tissue-specific as well as systemic fashion immediately after an infarct is established.

Although previous studies have focused on the role of neutrophil-mediated injury at the time of reperfusion, a growing body of evidence suggests that accentuation or prolongation of the postinfarction inflammatory response may have greater importance in contributing to adverse LV remodeling and dysfunction after MI.^{9,13} The cellular effects include the focal loss

of cardiomyocytes, increased myocardial fibrosis, and cardiomyocyte hypertrophy in the remote zone (Figure). Despite the detrimental effects of neutrophils and the inflammatory surge immediately after infarction, studies that have either depleted or inhibited macrophages from the inflamed myocardium have shown opposite results in both preclinical and clinical studies. Certain subpopulations of macrophages are critical for the repair of acute MI, and a shift to a proinflammatory M1 subtype may underlie the deleterious effects of circadian clock disruption on postinfarction remodeling. Because of this complexity, demonstrating an effect of inhibiting inflammation on clinical outcome may be problematic as recently demonstrated in a large randomized trial of the proinflammatory complement inhibitor pexelizumab in patients with MI, which showed no effect on mortality.¹⁴ Unfortunately, the promise shown in small initial studies of new therapies is too often not borne out in appropriately powered multicenter randomized trials.^{10,15}

What are the potential effects of an altered sleep cycle on postinfarct remodeling today? As the authors carefully point out, the present findings have important limitations. The nonreperfused mouse infarct model with 5 days of sleep–wake cycle disruption does not really represent contemporary cardiac care in the reperfusion era. Timely reperfusion leads to reduced infarct size, with average ejection fraction in unselected patients with ST-segment–elevation MI being 50% after primary percutaneous coronary intervention.¹⁶ An acute hospitalization for uncomplicated MI is frequently no more than 2 to 3 days, with the average time spent in the CCU disrupting the circadian rhythm <24 hours. In addition, medical therapy including statins with their pleiotropic effects on myocardial repair and regeneration and pharmacological agents that reduce postinfarction remodeling (β -blockers, angiotensin-converting enzyme inhibitors, and

aldosterone antagonists) have all improved clinical outcomes and reduced postinfarction LV remodeling. Nevertheless, these findings are relevant to the high-risk subset of patients with complicated infarct. This should prompt us to reconsider how we maintain biorhythms and these beneficial repair mechanisms in the acute critical care setting, in general.¹⁷ A simple low-cost strategy to keep lights off and noise down may provide high-value care that favorably affects LV function and outcome.

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Disclosures

None.

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