On Circadian Variation of Myocardial Reperfusion Injury

Eugene Braunwald

I
n 1729, Jean Jacques d’Ortous de Marian, a French scientist, made the fascinating observation that plants that unfolded their leaves when exposed to sunlight (presumably to increase photosynthesis, a process that had not yet been discovered) continued to rhythmically unfold their leaves in the morning and fold them in the evening even when they were maintained in constant darkness.1 d’Ortous had discovered an innate regulatory mechanism that allowed the plants to anticipate when daylight would be expected to begin and to wane. It is now widely appreciated that since fluctuations of the environment occur in the 24 hours required by the earth to rotate once on its axis, it would be useful if organisms could be prepared suitably for these fluctuations. Indeed, circadian “clocks” have been identified in all eukaryotic cells and even in some prokaryocytes.2 It has been suggested that circadian clocks were present in the earth’s earliest life forms. The uniform presence of circadian rhythmicity suggests that the ability to anticipate changes in the environment and to prepare for them provides an evolutionary advantage, otherwise it would probably not have persisted.

All mammals studied to date have developed 2 major classes of circadian clocks. The first to be recognized, the central “master” clock, is controlled by light, converted in the retina into neural impulses that are transmitted via the retinohypothalamic tract to the suprachiasmatic nucleus within the hypothalamus. This clock is responsible for circadian variations in the activity of the autonomic nervous system, resulting in changes in physiological parameters, including vascular resistance, arterial pressure, cardiac output, and heart rate as well as in the secretion of a variety of hormones, including cortisol and catecholamines.3

The master clock also exerts some control on the second, and more recently discovered peripheral circadian clocks, which have been found in every type of mammalian cell studied thus far.2 However, these clocks can and do also function independently. Indeed, it is likely that it was these peripheral innate clocks that were responsible for the folding and unfolding of plant leaves described by d’Ortous. Most studies of these clocks have been carried out in the fungus Neurospora, in Drosophila and in a variety of rodents, but they have also been found in human cardiac tissue.4 These peripheral circadian clocks are controlled by so-called “CLOCK” genes that have been found to control approximately 10% of all genes expressed in the mouse heart, which exhibit circadian rhythmicity.5 This results in cyclic variations in mRNA and protein synthesis and thereby influence cardiac contractile function as well as oxidative and nonoxidative metabolism of carbohydrates and lipids. For example, the increase in the capacity to metabolize carbohydrates before awakening prepares the heart for the expected increased activity.

Innate circadian variations in gene expression have been observed not only in cells obtained from intact hearts but also from cardiomyocytes studied in cell culture.2 The latter observations prove that they are truly innate, and although they may be influenced by the master clock in the intact organism, they are certainly capable of autonomous function. Cardiomyocyte-specific circadian clock mutant (CCM) mice, in which the circadian clock has been selectively disrupted, have provided important information on the function of these genes.6

In 1985, in an analysis of the Multicenter Analysis of the Limitations of Infarct Size, Muller et al7 observed a marked circadian periodicity in the time of onset of the clinical manifestations of acute myocardial infarction, with a peak incidence between 6 AM and noon. This increased morning incidence has been confirmed repeatedly in individual populations and in a meta-analysis of more than 60,000 patients.8 We observed that it was abolished in patients receiving β-blockers, suggesting that it is related to adrenergic activity,7 whereas Ridker et al9 showed that it was abolished by aspirin, pointing to an involvement of activated platelets in the process. We also found an increased incidence during early morning hours in unstable angina,10 which also has been reported by others for sudden death,11 stroke, ventricular arrhythmias, cardiogenic shock, aortic aneurysm rupture, stent thrombosis,12 and transient myocardial ischemia. Obviously, something is going on during these morning hours. It could be related to the morning increases in adrenergic activity13 as well as to circadian variation in thrombogenicity, such as a reduction of fibrinolytic activity. Indeed, in recent studies, Takeda et al14 have shown that the thrombomodulin gene, a clock-controlled gene, is responsible for circadian oscillation of thrombomodulin mRNA and protein. Other studies have shown that the CLOCK genes regulate the expression of both plasminogen activator inhibitor-1 as well as the morning increase of platelet aggregability.15 Thus, temporal changes in thrombogenicity can help to explain the circadian variation of the onset of cardiovascular events.

In this issue of Circulation Research, Reiter et al16 describe circadian variation of another important component of acute coronary events, infarct size. They report that in patients with ST-segment elevation myocardial infarction treated with primary percutaneous coronary intervention, infarct size peaked at 1 AM. This is about 8 hours earlier than the reported 6 AM to noon peak of the onset of infarction.7,8 Because the area of myocardium at risk and the ischemic time (the interval between the onset of pain and the first inflation of the angioplasty balloon) in the study by Reiter et al16 did not vary during the 24-hour cycle,
the observed circadian variation in infarct size probably is related to differences in reperfusion injury; hence, reperfusion injury was greatest at 1 AM. Because there is increasing evidence that reperfusion injury results from opening of the permeability transition pore of the inner mitochondrial membrane, resulting in mitochondrial damage and thereby myocyte death, it could be hypothesized that in some manner, not yet determined, there is circadian fluctuation of the opening of this pore.

These results by Reiter et al. build on and add to previous preclinical and clinical observations. Durgan et al. recently reported in mice that there was a >3-fold increase in infarct size when infarction/reperfusion was carried out at the sleep-wake transition than at the wake-to-sleep transition. They also provided evidence that the diurnal variation of 2 kinases, Akt and glycogen synthase kinase 3, may explain the differences in infarct size after ischemia/reperfusion. This circadian difference in reperfusion injury was not observed in CMM mice.

The findings of Reiter et al. are also consonant with 3 sets of observations on patients with acute myocardial infarction. Mukamal et al. reported that the highest peak creatine kinase levels occurred in patients with myocardial infarction whose symptoms commenced between midnight and 6 AM, and the highest incidence of heart failure was seen in patients whose symptoms began around midnight. In patients with acute ST-segment elevation myocardial infarction, Suarez-Barrientes showed that infarct sizes were larger in patients with ST-segment elevation myocardial infarction whose symptoms began between midnight and noon than those occurring between noon and midnight.

Reiter et al. should be commended for conducting this challenging translational research. Given the previous robust preclinical observations described by Durgan et al. and the above-mentioned clinical observations, Reiter et al.’s observations of circadian variation of infarct size in patients with acute myocardial infarction who are treated with reperfusion represent a useful independent confirmation.

In many hospitals, patients whose infarcts develop between midnight and 6 AM have longer prehospital delays and longer door-to-balloon times, with worse clinical outcomes, than those whose infarcts occur during daytime hours. When these procedural challenges are taken together with the increase in infarct size and greater myocardial damage in infarcts that begin at night, it becomes especially important for hospitals and their cardiologists to ensure that the quality of care that is rendered to patients with acute myocardial infarction does not also exhibit circadian variability.

References
On Circadian Variation of Myocardial Reperfusion Injury
Eugene Braunwald

doi: 10.1161/CIRCRESAHA.111.260265

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/110/1/6

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation Research can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation Research is online at:
http://circres.ahajournals.org/subscriptions/