Is There a Better Time of Day to Have a Heart Attack?

David J. Lefer

It is widely accepted that time influences cardiovascular health and disease, including the time of the day, day of the week, or season of the year. For example, myocardial infarctions occur with greatest incidence early on a Monday morning, in fall/winter. Peak incidence in adverse cardiovascular events, such as acute myocardial infarction, arrhythmias, and sudden cardiac death, has classically been ascribed to temporal changes in extracardiac factors. These factors include fluctuations in posture, physical exertion, food consumption, and body temperature over the course of the day contributing toward changes in sympathetic and autonomic activity, numerous endocrine and paracrine factors, as well as thrombolytic factors, ultimately influencing cardiovascular function and/or precipitating an adverse cardiovascular event. Recently, what has become increasingly evident is a significant contribution of intrinsic mechanisms mediating temporal dependence of cardiovascular physiology and pathophysiology. For instance, travelers retain time-of-day oscillations in sudden cardiac death, in such a way that the peak incidence is equivalent to the early hours of the morning in the time zone of origin.

What might be the nature of an intrinsic mechanism that influences cardiovascular function in a temporal manner? Over the last several decades, multiple laboratories have highlighted the existence of circadian clocks within virtually all mammalian cells, including critical components of the cardiovascular system. Circadian clocks are molecular mechanisms residing within individual cells that directly modulate cellular function during the course of the day. This is largely a transcriptionally based mechanism, composed of a series of positive and negative feedback loops made up of more than 13 transcription factors. Scientists studying genetically modified mouse models of altered circadian clock function have recently demonstrated that circadian clock genes contribute very significantly to time-of-day-dependent changes in both heart rate and blood pressure. This same clock mechanism has also been shown to directly regulate multiple thrombolytic factors, such as PAI-1 and thrombomodulin, raising the possibility that it might also contribute toward temporal oscillations in adverse cardiovascular events.

In this issue of Circulation Research, Durgan et al sought to test the hypothesis that the time of day at which the heart is subjected to ischemia/reperfusion injury influences subsequent tissue damage and left ventricular contractile function. The study revealed a 3.5-fold oscillation in infarct size, depending on the time-of-day at which the ischemic episode occurred, with the greatest infarct size observed at the sleep-to-wake transition. Interestingly, this is the same time of the day when the incidence of myocardial infarction peaks in humans. The investigators also report that this temporal dependence in ischemia/reperfusion tolerance is absent in a mouse model in which the circadian clock is specifically disrupted in the cardiomyocyte (CCM mouse [cardiomyocyte-specific circadian clock mutant]). The authors performed very elegant studies, both early (ie, 24 hours) and late (ie, 30 days) after reperfusion following ischemia. The effects of the circadian clock were evident in terms of early infarct size at 24 hours of reperfusion as well as adverse remodeling, fibrosis, and contractile function at 30 days postreperfusion. The investigators therefore conclude that the cardiomyocyte circadian clock mediates time-of-day-dependent oscillations in myocardial ischemia/reperfusion injury tolerance. Additional experiments provide initial insights into the mechanism of how the cardiomyocyte circadian clock genes modulate myocardial cell injury. Specifically, Durgan et al show that oscillations in the phosphorylation status of glycogen synthase kinase-3β are associated with the extent of myocardial cell injury in wild-type animals and that serine 9 is chronically phosphorylated in the CCM mouse.

The circadian clock within the heart has previously been shown to be altered by multiple cardiovascular risk factors, as well as during various disease states. Obesity, diabetes mellitus, hypertension, simulated shift work, aging, and ischemia/reperfusion have all been shown to influence this molecular mechanism. Coupled with the findings by Durgan et al, the possibility arises that alterations in the clock mechanism during disease states contribute to greater tissue damage and contractile dysfunction following myocardial infarction. It remains to be seen if the human myocardium displays a similar response to the circadian clock. Studies defining a role for the circadian clock within the human heart are likely to be difficult and would require intensive follow up on a large number of patients that experience acute myocardial infarction at various times during the day. Measurement of circulating biomarkers of myocardial injury and left ventricular function would be necessary to assess the extent of myocardial cell injury. Furthermore, additional studies are required to define the precise cellular and molecular signals within the cardiac myocyte that are modulated by the circadian clock at the sleep-to-wake transition (ie, zeitgeber time [ZT]12). It is likely that various cardioprotective signaling cascades are significantly downregulated at this time.
time resulting in an enhanced susceptibility to ischemia and reperfusion. Insights into how the circadian clock modifies myocardial reperfusion injury may help develop new therapies for the treatment of acute myocardial infarction. From a methodological standpoint, it is also important for investigators to consider the time of day when myocardial infarction is induced in animal models when comparing various gene-targeted mice or potential cardioprotective therapies; the time at which the experiments are performed should probably be kept constant. Future research efforts might also be focused on identifying ways to reset the heart clock as a means to improve ischemia/reperfusion tolerance.

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None.

**References**


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