Clinical Consequences of Circadian Mismatch

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Published online April 20, 2017; Updated June 14, 2021

Although often it seems like we live and die by the clocks on our smart phones, our hearts haven't caught up to our digital schedules. Within each of us beats the heart of a primitive hunter/gatherer, finely tuned to the rhythms of the natural world. Critical aspects of cardiac metabolism are still governed by intrinsic cellular clocks that are fixed to ancient schedules of sleep and wake, fasting and eating. However, in our modern world of artificial lights and late-night snacks, we're constantly pushing our bodies off of those fundamental circadian rhythms, causing a jarring mismatch between our hearts' metabolic cycles and workload. The clinical effects could be devastating.

According to Martin Young, D.Phil., of the University of Alabama at Birmingham, broadening our understanding of cardiac circadian clocks could help unravel some of the mysteries of the failing heart. For instance, circadian rhythms could help explain why shift workers double their risk of cardiovascular disease, why people are more likely to have arrhythmias or heart attacks in the morning than at night, and how synchronizing treatments with cardiomyocyte clocks could save lives.

TICK TOCK, TOCK TOCK

To find these answers, we must first look inside the heart's muscle cells (cardiomyocytes). In a review article in the *Methodist DeBakey Cardiovascular Journal,* Young explores how cardiomyocytes sync metabolism with circadian rhythms. Essentially, each of these cells has a circadian clock that coordinates activities based on 24-hour sleep/wake and feeding/fasting cycles. These clocks partition high-energy, adenosine triphosphate (ATP)-consuming tasks so that the body is primed for action while the organism is awake, leaving maintenance activities for sleep. During the day, when we're expected to be awake and active, cardiomyocytes rev up glycolysis and glucose oxidation, using daytime meals to power the heart through our most energetic period. In the middle and end of the awake phase, glycogen and triglyceride synthesis peak, Young explains, likely stocking up nutrient stores in response to a successful hunt/forage/trip to McDonald's. When we go to sleep, the heart's maintenance crew takes over to replace old or damaged proteins and lipids; this process is powered by energy reserves now free from the day's higher contractile demands.

Of course, the heart isn't the only organ adhering to a strict intracellular schedule—nearly every cell in the body has some kind of internal clock. Interestingly, the cellular clocks in the brain and the heart respond to different time-of-day-dependent signals. Neural cell clocks cycle according to light exposure, whereas cardiac cell clocks depend on chemical signals in the blood when we eat.

THE AMERICAN HEART ASSOCIATION'S "INTENTIONAL APPROACH TO EATING"

The latest AHA Scientific Statement on Meal Timing and Frequency advises physicians to counsel patients in an intentional eating approach to lower risks of cardiovascular disease. Notably, many of the recommendations underscore the importance of timing food intake to circadian rhythms (emphasis added):

- "Understand the patient's frame of reference in how he or she may define meals and snacks
- Recommend distributing calories over a defined portion of the day
- Recommend eating a greater share of the total calorie intake earlier in the day to have positive effects on risk factors for heart disease and diabetes mellitus
- Promote consistent overnight fast periods
- Link eating episodes to influence subsequent energy intake (e.g., place snacks strategically before meals that might be associated with overeating)
- Include intermittent fasting approaches as an option to help lower calorie intake and to reduce body weight
- Use added eating episodes to introduce a wider variety of healthful food options and to displace less healthful food
- Use planned meals and snacks timed throughout the day to help manage hunger and to achieve portion control"

Source: St-Onge MP, Ard J, Baskin ML. Meal Timing and Frequency: Implications for Cardiovascular Disease

Importantly, even though cardiomyocytes will adjust metabolism in response to a rush of glucose from a meal, there also appears to be a fixed aspect to these clocks. Laboratory experiments show that even if you remove all environmental and chemical stimuli—in ex vivo rodent hearts, for instance—the aforementioned metabolic rhythms persist. All circadian clocks, cardiomyocyte or otherwise, synchronize with the environment through a process called entrainment. Thus, circadian clocks aren't just reactionary; they've evolved to anticipate our daily energy needs, directing cellular activity in a continuous 24-hour loop—whether we stick to the schedule or not.

MODERN MISMATCH

So what does this mean for the modern human? On a fundamental level, we're often out of sync with our bodies' natural rhythms. Every time we stay up staring at blue-lit screens when we're supposed to be sleeping or eat a late-night meal, we send the heart conflicting signals, pushing it off the carefully-calibrated schedule perfected over millions of years. It's a recipe for disaster.

Young likens the heart to an engine pumping the blood around the body. Just like a mechanical engine, the heart only works if all the parts are firing at the correct time. If the timing isn't right, the engine won't function. Preventative maintenance, he points out, is also key, and circadian rhythms keep that maintenance moving on schedule.

"When you're awake, you damage proteins and other components in many tissues, including the heart. So when you're asleep, you have to get rid of those damaged parts and replace them. It's like changing the oil," Young says. "If you disrupt sleep, you lose that period of repair. Over time, if you're not continuously replacing damaged components, the damage builds up. That can lead to cardiovascular disease."

This mismatch between circadian rhythms and lifestyle pressures can also cause the heart to enlarge. Young explains that when nature says we ought to be sleeping, cardiomycoctes anticipate lower blood pressure and heart rate, so they begin protein synthesis. However, if someone starts walking around, increasing blood pressure and possibly adding food to the mix, that protein synthesis machinery goes into overdrive. The cells build and build (but not necessarily repair), creating an enlarged heart primed for failure.

SLIGHTLY SHIFTED

Of course, the classic example of the mismatch is in shift workers. Young compares their lifestyle to a state of eternal jet lag. "Their body thinks they're supposed to be sleeping, but they're awake and causing stress. Then when they go to sleep in the afternoon, their body doesn't think they should be sleeping. They're completely out of sync because the clocks reset relatively slowly to changes in environment and behavior," he says. "A shift worker might work for two days on, then two days off. Their internal clocks are constantly trying to catch up, but there's just not enough time. So these shift workers are constantly in a jet-lag state. That leads to obesity, diabetes, cardiovascular diseases, and cancer, and it all links to circadian disruption."

But what about those afternoon naps—can't we catch up there? Unfortunately, it doesn't look like it. Young says, "In terms of cardiovascular disease, I don't think there's any evidence for naps. If you take a nap in the afternoon, the internal timekeeping mechanism still knows it's the afternoon, so it's not revving up the repair mechanisms at that time. It leads to a mismatch."

TIMING IS EVERYTHING

That's not to say that circadian research is only useful for those of us burning the midnight oil. Even assuming "normal" sleep-wake patterns (that is, getting the recommended 7 to 8 hours of sleep at night), the heart experiences predictable cycles of vulnerability. For instance, physicians may have observed that their patients are more likely to experience cardiovascular events—including heart attacks, arrhythmias, sudden cardiac death, and stroke—right after waking up.

"Not only does the incidence of heart attacks increase in the early morning hours," Young says, "but tolerance to heart attacks seems to be lower, too. If someone has a heart attack in the morning and is taken the hospital and reperfused, you find that they have more damage to the heart than people who have similar heart attacks and reperfusion in the evenings."

Young hopes that circadian rhythm research might allow physicians to take advantage of natural cardiac metabolism cycles to make mornings a little safer, perhaps by adjusting the time of day when certain medications are taken. Consider aspirin, commonly recommended to prevent clot formation and heart attacks. According to Young, platelet activation and aggregation rises in the early morning, which raises the risk for heart attacks. Many people take aspirin at breakfast, which may be toward the end of the high-risk period.

"We find that when someone wakes up, they can have a heart attack instantly. By taking their medication at breakfast, they've actually missed the vulnerable window, "he explains. "Although there hasn't been a full clinical trial yet, some studies in humans show that people who take aspirin in the evening had less platelet activation in the morning compared to those who take their medication at breakfast." This plays into the concept of chronopharmacology, the idea that certain medications might have varying impact depending on when they're taken during the day.

Similarly, patients at high risk for cardiovascular events might consider shifting their cardiovascular workout to the afternoon when the heart is less stressed. In most healthy individuals,

evidence suggests that scheduling a run in the morning and strength training in the afternoon would optimize cardiovascular and muscular gains, respectively. However, Young cautions, that schedule could be more dangerous for a person at high risk of cardiovascular incidents. An early morning cardio workout would stress their heart right at its most vulnerable time of day, potentially "tipping them right over the edge and inducing an adverse event."

DISEASE AND DYSSYNCHRONY

Mounting evidence suggests that certain disease states are somehow related to circadian dysfunction. However, researchers haven't yet figured out exactly how disease states disrupt circadian clock mechanisms. According to Young, studies reveal a mismatch in circadian rhythm mechanisms in both humans and animals who have metabolic diseases such as diabetes and obesity. But scientists have yet to prove whether the mismatch causes the disease or vice versa or whether it's a self-perpetuating loop.

Pharmaceutical companies have taken note. They are looking into drugs that could target circadian mechanisms to put diseased patients back into sync with their environments to help with disease recovery. In animal experiments, Young notes, there is already evidence to suggest circadian rhythm-restoring drugs could work. "There are mice studies showing that when researchers give the animals compounds that specifically affect the circadian clock, the animals lose weight and have lower risks of diabetes and atherosclerosis," he says. Whether similar drugs could work in humans has not yet been tested.

Although pharmaceutical interventions are realistically years away, lifestyle changes could make a huge difference in getting back on our hearts' natural schedule. Young's studies indicate that the most powerful change would simply be tapering off the number of calories consumed over the course of the day. Similarly, intermittent fasting, with periods of at least 12 hours without eating (ideally overnight) can help reset those cardiomyocyte clocks. It's the "reset," whether that be eating a big breakfast after fasting or simply waking up to morning light, that Young cites as key to restoring circadian rhythms.

Hospital administrators might also take note of the importance of circadian rhythms for patients recovering from cardiovascular incidents. Young points out that critical care units (CCU) are one of the most disruptive environments from a circadian perspective: "Even when the lights are dimmed, there is some light. Patients are exposed to constant noise. When someone has an IV in, they're getting constant nutrition." The adverse effects can be demonstrated in animals; for instance, when caged animals have their circadian rhythms disrupted after a heart attack, outcomes worsen. "So do we really have the ideal settings in the CCU and ER?" Young asks. It's a question certainly worth policy consideration.

There's still a lot of research to be done before scientists to fully work out the secrets of the heart's inner clock. But it's already clear that many of our lifestyles are not ideal for heart health. "Whenever our circadian rhythms are disrupted, it always seems to be bad. It always seems to lead to pathology. It just goes to show you how important circadian biology really is," Young says. "The light-dark cycle has been on Earth since life began. We've evolved to be in rhythm with this natural cycle. But now we have artificial light at all hours, we can eat whenever we want, we work 24/7, and we have all these electronic devices giving us light exposure. We are completely destroying the normal circadian environment and it's contributing to the diseases we're seeing."

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Conflict of Interest Disclosure:
Laura Gerik is assistant managing editor at the *Methodist DeBakey Cardiovascular Journal.*

Keywords:
circadian clock, glucose, heart, metabolism, transcription, shift work