The circadian clock in heart failure

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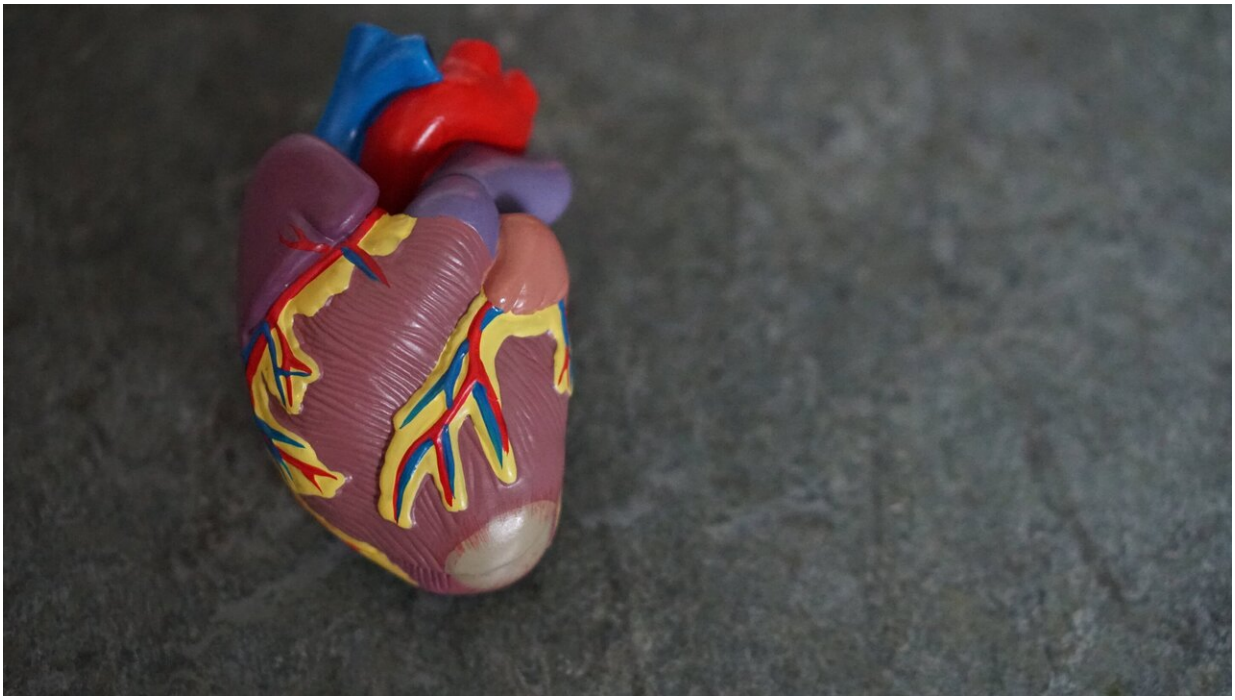

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Disrupting circadian rhythms, which change naturally on a 24-hour cycle, has been implicated in heart disease, but it is unclear how it leads to the condition. A research team at Baylor College of Medicine and collaborating institutions investigated the function of the protein Rev-erbα/β, a key component of the circadian clock, on heart disease development in animal models and human patients.

The team reports in the journal *Circulation* that Rev-erbα/β in cardiomyocytes mediates a normal metabolic rhythm that enables the cells to prefer lipids as a source of energy during the animal's resting time, daytime for mice. Removing Rev-erbα/β disrupts this rhythm, reduces the cardiomyocytes' ability to use lipids in the resting time and leads to progressive dilated cardiomyopathy and lethal heart failure.

"We studied how the Rev-erbα/β gene influenced the metabolism of the heart by knocking it out specifically in mouse cardiomyocytes," said co-corresponding author Dr. Zheng Sun, associate professor of medicine, section of endocrinology, diabetes and metabolism and of molecular and cellular biology at Baylor. "Lacking the gene resulted in progressive heart damage that led to heart failure."

To learn how Rev-erbα/β mediated its effects, the team analyzed gene and protein expression and a comprehensive panel of metabolites and lipids, during both the awake and sleep hours. They found that the Rev-erbα/β gene is highly expressed only during the sleep hours, and its activity is associated with fat and sugar metabolisms.

"The heart responds differently to different sources of energy, depending on the time of the day," explains co-corresponding author Dr. Lilei Zhang, assistant professor of molecular and human genetics and of molecular physiology and biophysics at Baylor. "In the resting phase, which for humans is at night and for mice in the day, the heart uses fatty acids that are released from fats as the main source of energy. In the active phase, which is during the day for people and at night for mice, the heart has some resistance to dietary carbohydrates. We found that without Rev-erbα/β, hearts have metabolic defects that limit the use of fatty acids when resting, and there is overuse of sugar in the active phase."

"We suspected that when Rev-erbα/β knockout hearts cannot burn fatty

acids efficiently in the resting phase, then they don't have enough energy to beat. That energy deficiency would probably lead to changes in the heart that resulted in progressive dilated cardiomyopathy," said Sun, a member of Dan L Duncan Comprehensive Cancer Center.

To test this hypothesis, the researchers determined whether restoring the defect in fatty acid use would improve the condition.

"We know that fatty acid use can be controlled by lipid-sensing metabolic pathways. We hypothesized that if we fed the Rev-erbα/β knockout mice more lipids, maybe the lipid-sensing pathways would be activated, override the defect and consequently the heart would be able to derive energy from lipids," Sun explained.

The researchers fed Rev-erbα/β knockout mice one of two high-fat diets . One diet was mostly high-fat. The other was a high-fat/high-sucrose diet, resembling human diets that promote obesity and insulin resistance. "The high-fat/high-sucrose diet partially alleviated the cardiac defects, but the high-fat diet did not," Sun said.

"These findings support that the metabolic defect that prevents the heart cells from using fatty acids as fuel is causing the majority of the cardiac dysfunction we see in the Rev-erbα/β knockout mice. Importantly, we also show that correcting the metabolic defect can help improve the condition," Zhang said.

Clinical implications in obesity paradox and chronotherapy

"There are three clinical implications from this work," Sun said. "First, we analyzed the molecular clock function in heart tissues of patients with dilated cardiomyopathy who had received heart transplants to explore

whether the clock function was associated with the severity of cardiac dilation in humans. Tissue samples were taken at different times of the day and the ratio of the gene expression of the circadian genes Rev-erbα/β and Bmal1 was calculated providing a chronotype. We found that the heart chronotype correlates with the severity of cardiac dilation."

"The second implication is that obesity and insulin resistance, long-known clinical risk factors for heart failure, can be paradoxically protective against heart failure, within a certain time window, probably by providing fatty acids in the resting phase," Sun said.

Finally, the researchers explored the possibility of pharmacologically manipulating fatty acid and sugar metabolism to improve the condition. They found that while medications can help restore the altered metabolic pathways, it was important to give the drugs aligned with the internal circadian rhythm of the corresponding metabolic pathways. If the drugs were given out-of-sync with the pathway they were intended to restore, the treatment did not improve the cardiac condition."

These findings highlight the importance of chronotherapy, the scheduling of medications according to the circadian rhythm, not just in this study, but for many other medications.

"Of the top 100 most prescribed drugs in the U.S., at least half of them have a target that is connected to a circadian rhythm," Zhang said. "This indicates that for these drugs to be effective, they need to be taken in a time-specific way. Unfortunately, they are not. We want to emphasize the importance of taking the circadian rhythm into consideration when scheduling medications."

More information: Chronotype Myocardial Rev-erb-mediated diurnal metabolic rhythm and obesity paradox, *Circulation* (2022). DOI: 10.1161/CIRCULATIONAHA.121.056076

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