Cellular 'power grid' failure triggers abnormal heart rhythms after a heart attack

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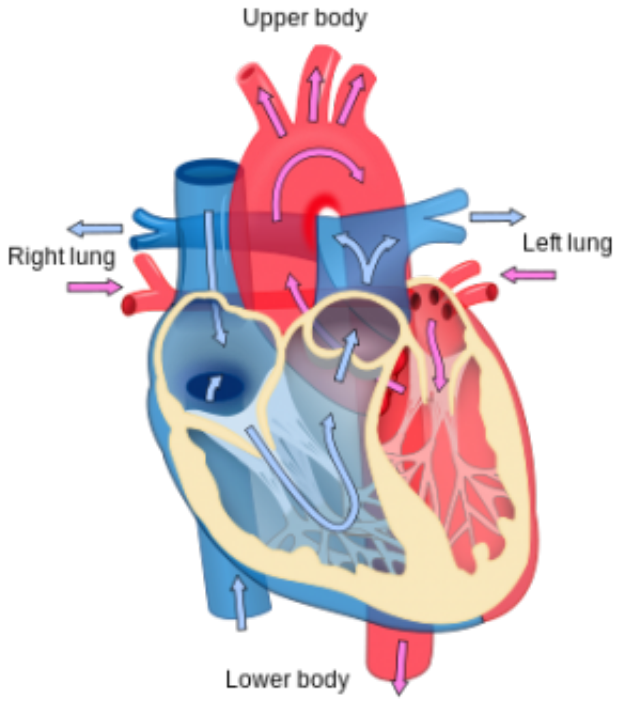

Heart diagram. Credit: Wikipedia

Heart attack survivors often experience dangerous heart rhythm disturbances during treatment designed to restore blood flow to the injured heart muscle, a common and confounding complication of an otherwise lifesaving intervention.

Now a duo of Johns Hopkins researchers working with rat heart cells

have shown that such post-heart attack arrhythmias are likely triggered by something akin to a power grid failure inside the injured cardiac cells. This power failure, the team found, is caused by disruption to the cells' mitochondria—the tiny powerhouses that fuel all cell life—when they become destabilized during the "resuscitation" period after a heart attack and trigger chaotic cell-to-cell signaling that interferes with the heart's entire electrical network.

The experiments, described ahead of print in the *Journal of Molecular and Cellular Cardiology*, offer what scientists believe is a first-of-a-kind detailed glimpse into the chain of events that occur inside the cells of the heart muscle during and after a heart attack. The findings, the research team says, can advance efforts to make heart attack treatment safer.

"Prompt treatment with stents or a balloon angioplasty to open up blocked arteries and restore blood flow to injured areas of the heart muscle is life-saving, yet paradoxically it can also increase the risk for potentially fatal arrhythmias," says Soroosh Solhjoo, Ph.D., a cardiology postdoctoral fellow at the Johns Hopkins University School of Medicine. "We believe our findings not only provide insights into the genesis of these electrical anomalies, but also illuminate a possible way to prevent them."

The experiments reveal that the sudden loss of energy supply to the heart cells and the subsequent rapid "reboot" during treatment causes mitochondria to falter and trigger a whirlwind of aberrant electrical signals. These chaotic signals quickly ripple throughout the entire heart, wreaking havoc in the cell-to-cell electrical signaling needed to keep the heart beating normally.

To mimic the energy starvation of heart muscle during a heart attack, the researchers created a "heart attack in a dish" by covering a thin layer of rat heart cells with glass to cut off the supply of oxygen and nutrients.

Then, using a powerful microscope that magnifies and lights up the electrical circuitry of the cells, they watched the chain of events that unfolded inside them. Like a rolling blackout observed from a space satellite, the mitochondria—the cells' energy generators—began flickering out. As mitochondria ceased their energy production, heart cells gradually went motionless.

When the researchers lifted the glass, allowing oxygen and nutrients to flow back in—much as would be the case during reperfusion treatment with stents for example—the mitochondria flickered back to life. But instead of lighting up all at once, they resumed energy production haltingly—a process the researchers described as oscillation. Like sub-optimally fueled engines, these wavering mitochondria produce energy intermittently. As a result, the underpowered heart cells fire weakly and chaotically, forming a tiny cluster of misfiring muscle tissue, which creates a roadblock in the heart's circuitry. When an electric signal hits such a roadblock, it gets rerouted.

"The disrupted electric impulse gets diverted to neighboring cells, causing them to misfire as well," says Brian O'Rourke, Ph.D., professor of cardiology at the Johns Hopkins University School of Medicine. "Then, the aberrant signal can propagate in abnormal circuitous routes within the heart muscle, eventually leading to full-blown fibrillation." Fibrillation is a life-threatening arrhythmia in which the heart squirms and quivers instead of pumping rhythmically.

When the researchers pretreated the heart cells with a derivative of the sedative drug benzodiazepine before subjecting them to conditions that mimic a heart attack, the cells' mitochondria managed to regain normal function quickly, in effect restoring a steady supply of energy that prevented the cells from misfiring. Developing drugs that stabilize mitochondrial energy production, the team says, could help preserve cardiac function following a heart attack.

In their experiments, the researchers noted that the mitochondria of heart cells that lost oxygen and nutrient supply for a half-hour recovered smoothly. However, cells that were deprived of oxygen and nutrients for an hour had a bumpier recovery, marked by mitochondrial flickering and chaotic electrical signaling. Although the parallels in timing may be merely coincidental, the investigators say, the finding echoes the "golden hour" standard for heart attack treatment established by clinicians. Patients who undergo treatment within that window have much better recovery.

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