New therapy could preserve vessel function after heart attack

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Scientists have identified the process that causes blood vessels to constrict during and after a heart attack. They've also demonstrated that delivering a vital molecule that is depleted during this process directly to those blood vessels can reverse damage and help restore blood flow.

The Ohio State University medical researchers say these findings have the potential to improve outcomes for patients with acute coronary episodes related to ischemia, and to ameliorate the restriction of blood supply to the heart.

The study is published online this week in the journal *Proceedings of the National Academy of Sciences.*

“This is a useful therapeutic approach and should be easy to translate,” said Jay L. Zweier, director of the Davis Heart and Lung Research Institute at Ohio State University Medical Center and senior author of the study. “This should enable improved treatment of patients with unstable coronary syndromes and heart attacks, allowing enhanced restoration of blood flow and preservation of heart muscle at risk.”

Scientists have known that following a heart attack blood vessels around the heart do not properly dilate and may constrict because of problems in the cells that line the vessel walls. But until now, they did not precisely understand why. Zweier and colleagues set out to determine the cascade of events that leads to the loss of vessel vasodilatory function and, in the process, identified a potential solution that would dilate

and reopen vessels, improving blood flow.

In examining isolated hearts, the research team observed that in hearts subjected to a lack of blood flow, or the ischemia that occurs during a heart attack, the ability of the vessels to remain dilated is impaired because production of the nitric oxide molecule that dilates the vessel stops. This stoppage can be traced to depletion during ischemia of a molecule that is a critical cofactor required to activate the enzyme nitric oxide synthase (NOS), which produces the potent vasodilator nitric oxide. This critical cofactor is a molecule called tetrahydrobiopterin, or BH4.

In fact, the loss of BH4 during ischemia not only prevents production of nitric oxide and the dilation it causes, but actually causes the enzyme NOS to completely reverse course and instead produce an oxidant called superoxide that leads to constriction of the vessels.

Zweier noted that the longer that blood flow is stopped during a cardiac event, the more severe the loss of BH4 – meaning the chances of restoring blood flow are increasingly reduced. The study showed a marked loss of BH4 after 30 minutes without blood flow, and more than 90 percent depletion after 45 minutes.

“What wasn't known before was that as the time of ischemia progresses, the function of the enzyme is impaired and subsequent coronary flow is reduced. There is loss of enzyme function plus the switch from dilation to constriction,” said Zweier, also a professor of internal medicine. “Following a heart attack, vessels tend to constrict and mircovascular occlusion occurs, but what you need is a patent circulation with dilated vessels for restoration of coronary flow, or the muscle will die.”

Because depletion of BH4 during ischemia is irreversible, the heart and coronary vessels cannot generate their own repair – which has important

consequences for efforts to restore blood flow. So the scientists also developed a way to package the molecule and deliver it directly to the vessels. They discovered that the treatment was effective in partially restoring the process that opens and dilates the vessels with improved coronary flow.

Zweier said that because this approach controls blood vessel function at the cellular level, BH4 infusion could be used not just for acute heart attack treatment, but also to help prevent new blockages of coronary arteries after procedures such as angioplasty or bypass surgery.

He said the depletion of BH4 likely results from the burst of free radicals associated with both ischemia and the shock of the reintroduction of flow. This work is part of Ohio State medical scientists' ongoing search for ways to control the reintroduction of oxygen and other nutrients to the heart following a heart attack or other conditions with compromised coronary flow in a way that will prevent any further damage to the cardiac muscle. The key is striking a delicate balance between reducing the burst of free radicals that accompanies the reintroduced blood, which can damage tissue, and the need for enough free radicals to generate a stress response that will improve heart function and healing.

Source: Ohio State University