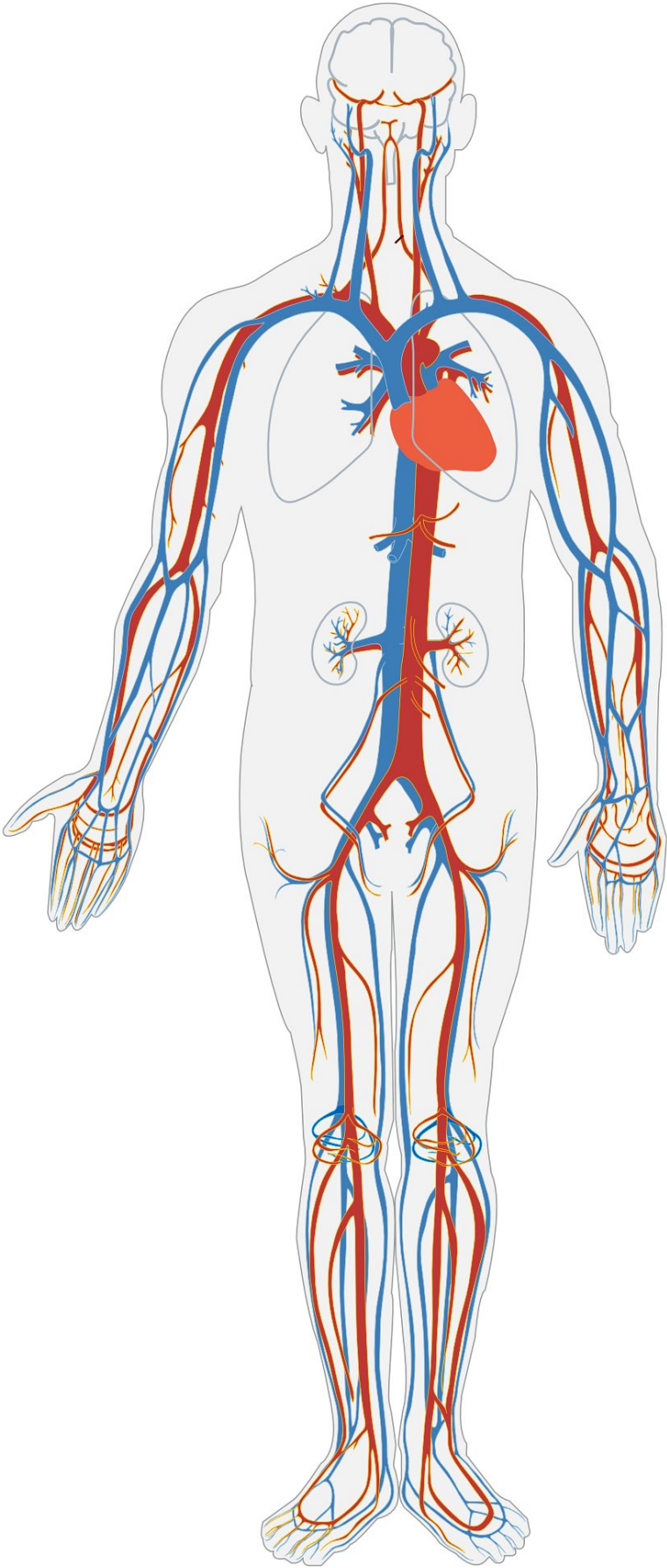


Researchers identify important new signaling molecule involved in vascular health

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In the 25 years since the Nobel Prize was awarded for discovering the role that nitric oxide (NO) plays in the cardiovascular system, researchers have been racing to learn more about how this mysterious signaling molecule works to repair blood vessels damaged by a heart attack, stroke or other cardiovascular event. University of Maryland School of Medicine (UMSOM) researchers and their Wake Forest University (WFU) colleagues today announced an important missing piece of the puzzle.

Their new study published in [*Nature Chemical Biology*](#) found that heme, an iron-containing compound abundant in circulation and in our cells, binds to NO and ferries it around the vascular system. This enables NO to regulate blood flow, [blood pressure](#), blood clot formation, and likely other signaling processes involved in healing damaged [blood vessels](#).

While the signaling roles of NO have been studied extensively over the past three decades, researchers have yet to understand how this short-lived molecule travels from blood to signaling targets in the blood vessel wall.

To address this gap, the team led by UMSOM and WFU researchers characterized the formation of a stable NO intermediary called NO-ferroheme. The team demonstrated in animal studies that, after injection, NO-ferroheme is transported in blood, often bound to albumin, and travels to the blood vessels and causes them to dilate, lowering blood pressure.

"We know that [nitric oxide](#)—with its extremely short half-life of less than a second in blood—must have a way of moving through the bloodstream and into blood vessels via a stable mechanism," said study lead author Anthony DeMartino, Ph.D., Assistant Professor of Medicine at UMSOM.

"We worked out the chemistry and the kinetics of how NO-ferroheme is physiologically generated in the [test tube](#), and then demonstrated how it works in an animal model, which provides strong evidence of our hypothesis."

To conduct their studies, the research team decided to investigate heme, best known for its role in oxygen delivery (via hemoglobin) in the blood, but also a common signaling target for NO. They mixed ferric heme (an oxidized form of the compound that can cause cellular damage) with NO and the antioxidant glutathione (found in high levels in most cells) to see how they would react in a laboratory setting.

They found that in the presence of glutathione, NO rapidly reacts by binding rapidly to the heme, forming a stable, reduced heme compound called NO-ferroheme. The team then decided to test the effects of this compound on two hallmark properties of NO: as a vasodilator and as a regulator of blood platelet aggregation (which causes the formation of blood clots).

When mice were infused with NO-ferroheme, the compound had vasodilation effects, increasing blood flow in the arteries and lowering blood pressure. Further, NO-ferroheme inhibited platelet aggregation in human blood platelet samples.

"My laboratory has worked for more than two decades trying to understand how NO can diffuse in blood and in cells without being destroyed by reactions with other radicals and heme bound proteins like

hemoglobin and myoglobin," said study lead and corresponding author Mark T. Gladwin, MD, UMSOM Dean and Vice President for Medical Affairs, University of Maryland, Baltimore, and the John Z. and Akiko K. Bowers Distinguished Professor.

"The stabilization of NO by forming NO-ferroheme allows it to diffuse across distances, almost like a chemical flying saucer, to directly bind to and activate target enzymes that control blood flow."

"The NO-ferroheme can also bind to albumin, which is the most abundant protein in our blood. We hypothesize that NO-ferroheme-albumin can be developed as a drug to target different disease states where NO is impaired such as pulmonary hypertension, diabetes, and obesity."

Dr. Gladwin and his longtime collaborator and co-senior author Dany Kim-Shapiro, Ph.D., Professor and Chair of the Department of Physics at WFU, have worked together for more than two decades to understand how NO is transported in red blood cells and regulates blood flow.

"One of the most surprising things that came out of our study was the role of the glutathione; both in the novel chemistry in forming the NO ferroheme and in its effects in vivo," said Dr. Kim-Shapiro. "We still have a lot more work to do to fully understand this."

There are many complicated facets to NO that researchers have yet to unravel. They know it has Jekyll and Hyde characteristics with beneficial effects in the vasculature to improve blood flow to arteries and tissues as well as in immune defense, where NO is used by macrophages to kill invading bacteria. At the same time, NO is poisonous at high doses and can be utilized by cancer cells to increase blood flow, causing tumors to quickly grow or to help cancer cells spread.

Uncovering NO-ferroheme as a biological "middleman" represents an important step towards understanding the nuanced signaling mechanisms of NO both under healthy conditions and in myriad disease states.

The research team next want to explore the mechanism of how NO-ferroheme is imported into vascular cells needed to trigger the observed signaling.

They also want to further investigate the use of NO-ferroheme as a potential therapeutic. A pressing need is for new therapeutics to treat damage to blood vessels called ischemia-reperfusion injuries. These injuries—triggered by the loss of oxygen to arteries after, say, a stroke or cardiac arrest—often lead to permanent tissue damage. Having a safe drug to quickly restore [blood flow](#) to effected tissues could potentially help mitigate the devastating effects of these cardiovascular events.

Qinzi Xu, MD, Assistant Professor of Medicine at UMSOM, and Jason Rose, MD, MBA, Associate Professor of Medicine and Associate Dean, Innovation & Physician Science Development at UMSOM, were co-authors of this study.

More information: Thiol-catalyzed formation of NO-ferroheme regulates intravascular NO signaling, *Nature Chemical Biology* (2023). [DOI: 10.1038/s41589-023-01413-3](https://doi.org/10.1038/s41589-023-01413-3) , www.nature.com/articles/s41589-023-01413-3

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