Medical Xpress

Blood platelets trigger events that cause organ damage after heart surgery

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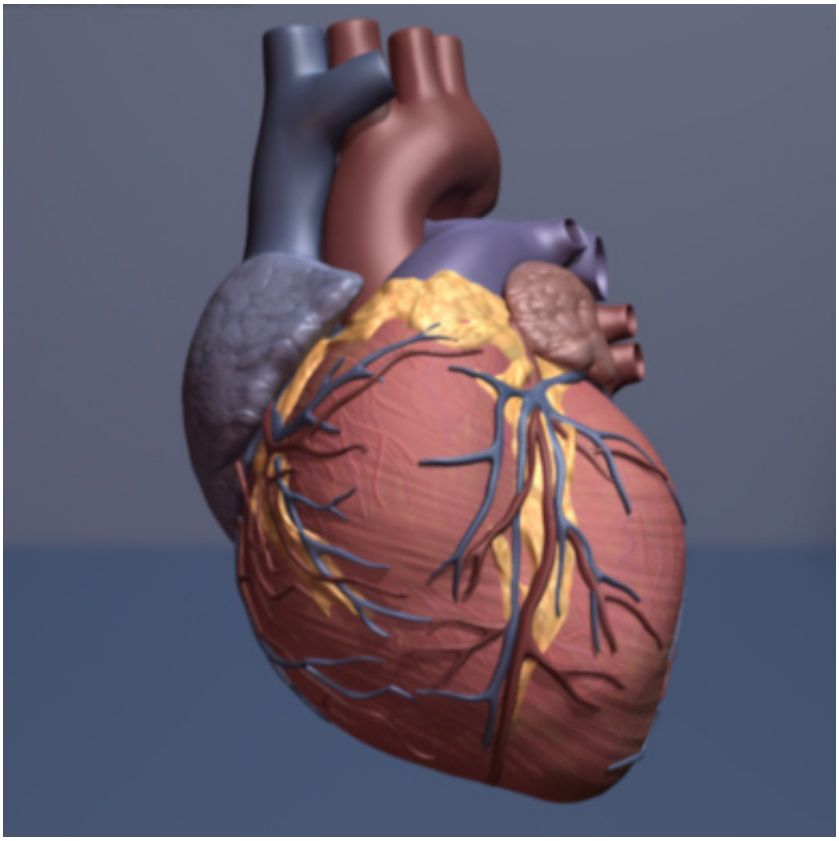

Human heart. Credit: copyright American Heart Association

Even as surgeons have become more highly skilled at performing lifesaving heart surgeries, the overall outcome of the procedure continues to be threatened by complications such as acute kidney or lung injury and neuro-cognitive decline.

For example, measurable damage to the kidney is seen in about 54 percent of patients after coronary artery bypass grafting surgery.

Damage to kidneys and other organs is not so much triggered by the surgical repair of the heart itself but rather by the massive inflammatory response, which arises from multiple factors: the machinery used to keep blood and oxygen flowing, changes of blood flow during the surgery, and tissue responses to the surgical trauma.

How this inflammatory response develops and how it might be avoided are described in a study publishing online March 18 in *Science Advances* by a team of researchers led by Jörn Karhausen, M.D., assistant professor in the Department of Anesthesiology at Duke University School of Medicine.

"We're running into a problem where the heart can be fixed, but we might create a different injury to the patient that can be dangerous and totally change their long term-prognosis," Karhausen said. "If we can understand this phenomenon, hopefully, we can prevent it or at least minimize it."

In the current paper, Karhausen and colleagues—testing in mouse and rat models, in human cell lines and analyzing patient samples—described a little-understood interplay between platelets in the blood and mast cells, which are tissue-immune cells typically located close to blood vessels.

The work builds on a series of earlier studies by Karhausen and others that had demonstrated a link between platelet responses during cardiac surgery and organ injury. Platelets are mostly appreciated for their role in bleeding and blood clotting, but it was unclear what role they played in the development of tissue damage.

In the current study, Karhausen and colleagues discovered that activated

platelets attach to the vessel wall and come into close contact with mast cells. Because mast cells can launch extremely powerful inflammatory responses, including life-threatening allergic reactions such as anaphylactic shock, the group further investigated the communication between these 2 cell types.

The researchers observed rats undergoing a procedure that mimics many aspects of cardiac surgery in humans. They found that in this setting, platelets become activated and aggregate in small vessels in certain susceptible tissues, where they trigger mast cells and cause the release of inflammatory compounds typically aimed at fighting pathogens.

In addition to launching a powerful generalized inflammatory response, widespread mast cell activation could also be the source of a variety of common problems in cardiac surgery, including extended periods of low blood pressure through release of blood vessel-dilating mediators and direct organ damage through release of tissue-digestive enzymes.

The researchers confirmed their findings by manipulating both platelet activation and mast cell activation using genetically altered animals. Both manipulations changed the course of inflammatory events, demonstrating that platelet activation was sufficient to launch mast cell-dependent inflammatory responses. Indeed, inhibiting platelet activation during surgery in the rats curbed the life-threatening inflammatory cascade.

"Evidence from our rat cardiac surgery model showed that the platelet antagonist clopidogrel stopped microvascular platelet deposition, prevented the associated drop in platelet count, and reduced mast cell-mediated inflammatory and tissue injuries," Karhausen said. "This is in line with many clinical observations we have recently made both in cardiac surgery and in critically ill patients, for example during sepsis, and suggests an important mechanism that could be controlled with

known drugs."

Karhausen noted, however, that platelet inhibition also poses a considerable bleeding risk in this setting, potentially requiring a more targeted approach to inhibit mast cell activation.

More information: "Platelets trigger perivascular mast cell degranulation to cause inflammatory responses and tissue injury" *Science Advances* (2020). advances.sciencemag.org/content/6/12/eaay6314

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