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NIBIB-supported bioengineers work to reduce platelet activation and clotting in patients with VADs

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A team of NIBIB-supported bioengineers, aerospace scientists, and cardiovascular clinicians are improving the function of the thousands of life-saving ventricular assist devices (VADs) implanted in advanced heart failure patients each year. VADs are mechanical pumps with a small rotor that spins at high speeds to circulate the blood. However, these life-saving pumps can create pockets of turbulence that increase the risk of platelet activation, which results in unwanted, dangerous blood clots and stroke.

Previously, the team re-engineered the VADs to remove these pockets of turbulence, which reduced more than 90% of platelet activation and clotting. In the current study, to further reduce risk, the team examined the role of platelet stiffness in the activation of clotting with the goal of developing treatments that would increase platelet pliability and further reduce platelet activation and clotting.

Heart failure happens when the heart cannot pump enough blood and oxygen to support the organs of the body. According to the American Heart Association, about 5.1 million people in the United States have heart failure. It is estimated that there are from 75,000 to 150,000 patients in the U.S. with end-stage heart failure, where VADs are used as a bridge while awaiting a heart transplant. More recently, VADs are providing an alternative to transplant, allowing a near normal quality of life.

The double-edged sword of platelet activation

Although they are a life-saving technology, VADs have been compared to jet engines -- with blood propelled by a rotor at up to 12,000 rpm. The high speed creates shear stress --the force pressing against the wall of the device as the blood rushes past it. Blood platelets, whose normal function is to form clots to repair vascular damage, can become activated by shear stress in VADs. Such activation can result in unwanted clotting, arterial blockages, and stroke.

In previous work, the approach of redesigning VADs to reduce unwanted clotting was a huge improvement. However, the reengineered state-of-the-art VADs continue to carry an approximately 1-10% risk of initiating dangerous clotting events. Says Marvin J. Slepian, M.D., Professor of Medicine and Biomedical Engineering, University of Arizona, Tucson, a senior member of the research group, "As we reach the physical limitations of optimizing VAD design, we are now turning to the study of the biomechanical properties of platelet activation to further reduce dangerous clotting. We are moving from the engineering domain, where we altered the device, to the biological, where we try to alter the platelets so they become more flexible and therefore, less reactive as they flow through the VAD."

Designing a delicate measurement technique

Ongoing work has identified intracellular elements that govern platelet stiffness, including actin filaments and microtubules. The goal is to test what Slepian has deemed "mechanoceuticals" that may act on these cellular components to reduce stiffness and increase flexibility. However, determining what agents make a platelet mechanically more pliable relies on developing a method to measure platelet stiffness.

There are a number of standard ways that the stiffness of different cell types is measured. Unfortunately, they almost exclusively rely on anchoring the cell to a substrate and pulling it to see how much it stretches. If this were done to a platelet it would instantly fragment and activate. Therefore, a method had to be developed that employed minimal interaction to obtain a precise measurement without activating the platelet.

To achieve this delicate balance, the researchers combined two techniques. Dielectrophoresis (DEP) is a technique in which an electrical field gently moves the platelets into position on an electromechanical measurement chip. With the second technique, called electro-deformation (EDF), platelets are gently stretched by oscillating (alternating) electrical fields, which deform the platelet and provide a measure of its stiffness without inducing activation. With this combination, the researchers obtained reliable measurements of platelet stiffness; now the method can be used for testing compounds that make platelets more pliable and less reactive to shear forces in VADs.

The group sees the design and testing of this measurement tool as the first installment of their shift in focus to changing the physical responsiveness of cells with mechanoceuticals. In addition, based on preliminary work, the researchers believe the electromechanical measurement chip has potential as a diagnostic and research tool. Potential future applications include examining the relationship of disease progression to increasing cell stiffness found in tissues during aging. Another area of interest is cancer, given that tumor cells can become less stiff and more pliable, which may be a critical step enabling tumor cells to metastasize to other tissues.

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