Clotting protein hardens aging hearts: Researchers link von Willebrand factor to heart-valve calcium deposits

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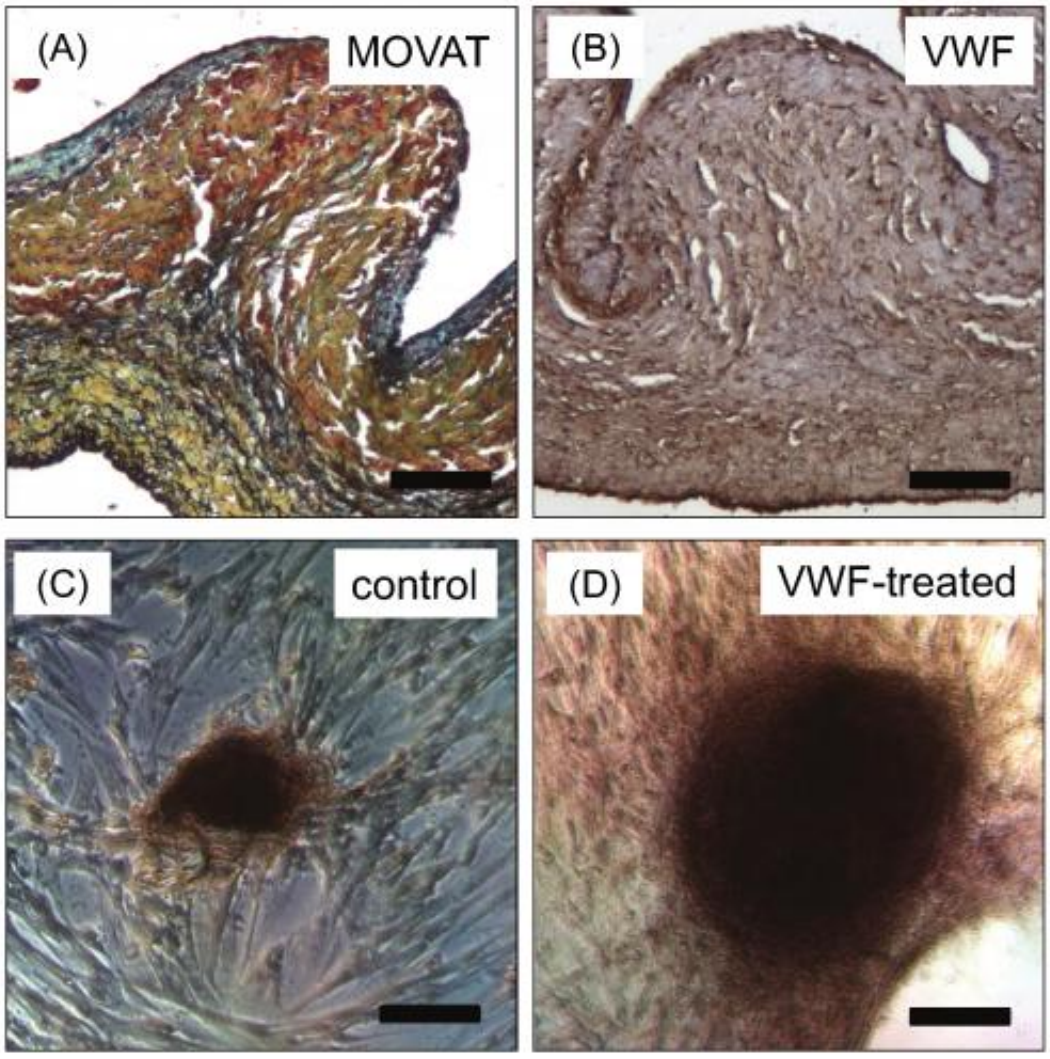


A new study by Rice University researchers shows how the extracellular matrix in heart valve tissues changes with age, including the accumulation of von

Willebrand factor (VWF), a blood-clotting protein. At top left is a sample of an elderly pig valve; at right, staining reveals the accumulation of VWF throughout the tissue. At bottom are porcine aortic valve interstitial cells not treated with endothelial cell VWF (left) and treated with endothelial cell VWF (right). The VWF appears to prompt formation of larger calcific nodules. Credit: Integrative Matrix Mechanics Lab/Rice University

Heart valves calcify over time, and Rice University scientists are beginning to understand why.

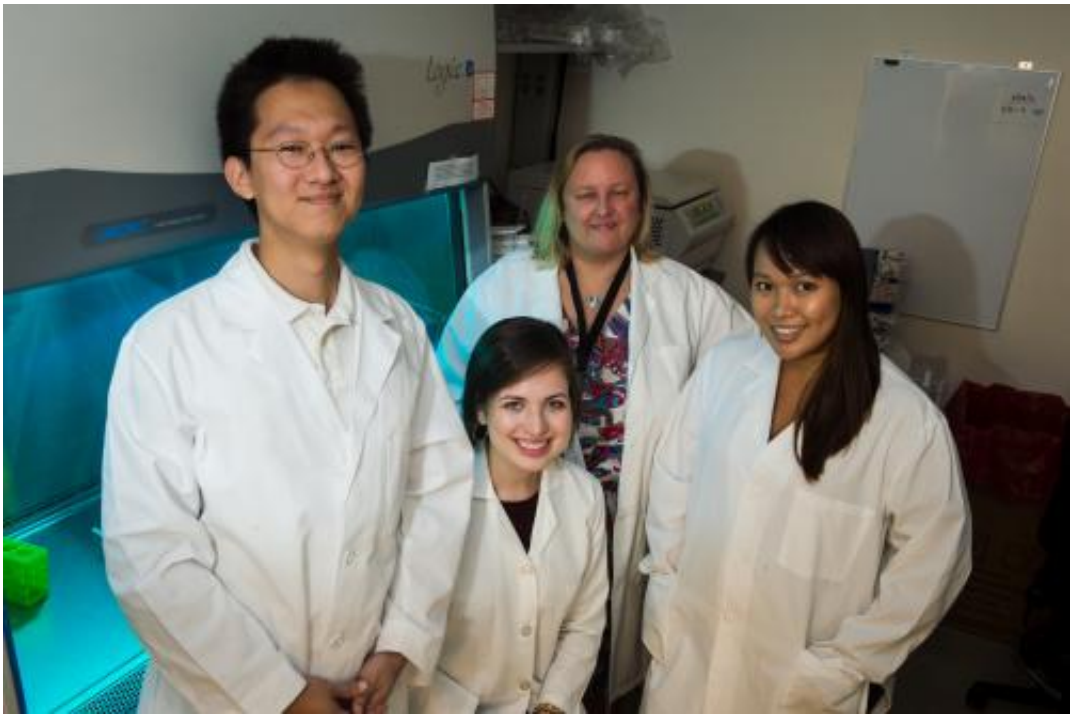
The Rice lab of bioengineer Jane Grande-Allen found through studies of pigs' heart valves that age plays a critical role in the valves' progressive hardening, and the problem may be due to the infiltration of a protein known as von Willebrand factor (VWF). Tissues from pig valves are commonly used to make human heart-valve replacements.

VWF helps regulate blood clotting in both pigs and humans but, as the Rice team discovered, it finds its way over time into the collagen-rich interior of the valve tissues. Because clotting is not an issue in collagen, there is no apparent need for VWF to be present. The researchers went looking for a connection to the calcium nodules that form in the tissues and make the valves' leaflets less flexible, which decreases blood flow to the heart.

The new work, detailed in the American Heart Association journal *Arteriosclerosis, Thrombosis and Vascular Biology*, "opens up a huge line of investigation," Grande-Allen said.

The paper's lead author, Liezl Balaoing, a graduate student of Grande-Allen and Rice research scientist Joel Moake, studied valves from pigs of three ages: 6 weeks, 6 months and 2 years (as stand-ins for young,

middle-aged and old human hearts). Through staining, Balaoing traced the migration of a number of clotting-related proteins common to pigs and humans from the surface endothelial cells to the inner interstitial cells.



Rice University researchers have determined that von Willebrand factor, a blood-clotting protein, plays a critical role in the progressive hardening of heart valves in pigs as they age. The researchers believe the same process is occurring in human heart valves. Clockwise from left are Rice senior Kyung Taeck Minn, Professor Jane Grande-Allen, Liezl Balaoing and Rice alumna Allison Post. Credit: Jeff Fitlow/Rice University

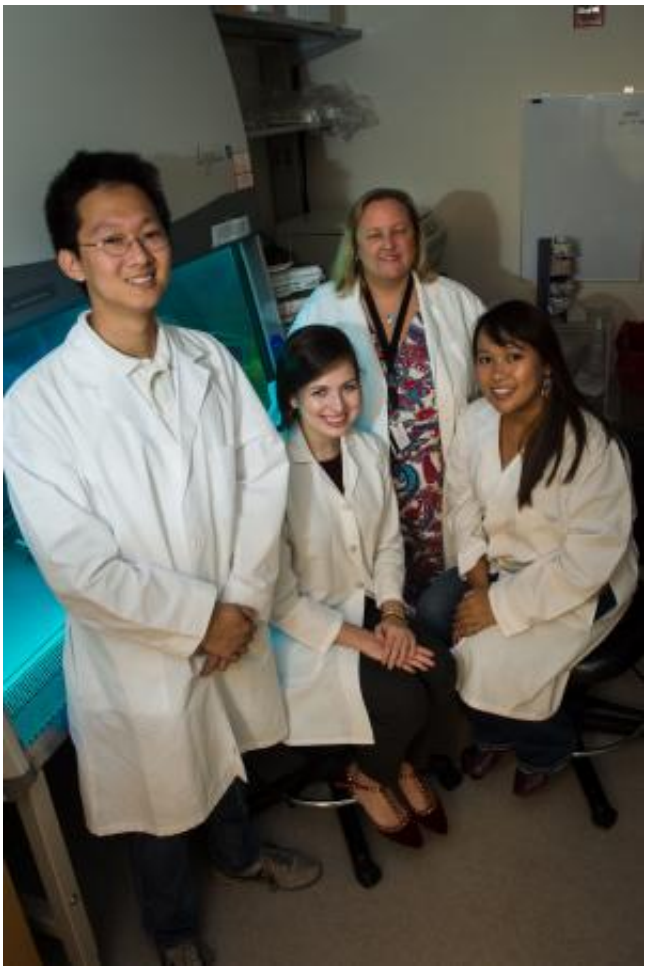
The tests showed that as a valve ages, VWF and other proteins gather in the valve tissue's interior. They then tested how valve interstitial cells that produce calcium nodules in diseased valves respond to VWF. When interstitial cells were intentionally exposed to VWF, "there was a

dramatic increase in the size of the nodules at every age," Balaoing said.

"Endothelial cells on the outside of the valve are making most of these (clotting-related) proteins," Grande-Allen said. "We found they don't just float away into the blood or stay on the valve surface. Some of them penetrate down into the tissue."

What remains to be seen is why. Heart valves are in motion from birth to death and are perhaps the most active connective tissue in the body. The researchers suspect the breakdown of collagen over time, as well as the constant stretching of the valve, opens gaps through which the proteins can travel.

"As you get older, collagen becomes less organized," Balaoing said. "Because the distinct arrangement of extracellular matrix disappears, I think proteins like VWF permeate inside the valve more than what you would see in young, healthy adults."



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"We clearly know that our bodies and our whole physiology change with age," Grande-Allen said. "Biologically, characteristics like blood-clotting change with age too. The remarkable finding here is that aspects of changes in blood clotting are very strongly linked to the propensity to form calcified heart valves."

Grande-Allen said she saw signs of VWF invasion into the valves' interiors in earlier work, but it took a systematic effort by Balaoing to get to the truth. Now they hope to find the binding mechanism that keeps the proteins in place, as that discovery could lead to treatment. "We want to know if VWF and other clotting-related proteins are doing things to the valve interstitial cells and extracellular matrix that may contribute to calcification and other valve diseases," Grande-Allen said.

More information: atvb.ahajournals.org/content/e … .113.301936.abstract

Provided by Rice University