 BY KATIE BUNKER

Places in the Heart

Pinpointing the cause of cardiovascular complications

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Insulin is most widely known for its ability to move glucose into cells, and also for what happens when it doesn't do its job well enough. But it has other functions, too. In a paper published in the *American Journal of Physiology, Endocrinology, and Metabolism* in September, Zhenqi Liu, MD, assistant professor of medicine at the University of Virginia in Charlottesville, and his team of researchers confirmed that insulin increases blood flow in the capillaries inside the heart muscle of healthy humans as well.

Here's how, according to Liu: Insulin binds to receptors in the endothelium (the layer of cells on the inside of the blood vessel wall) and activates a signal pathway that produces nitric oxide. Nitric oxide dilates or widens the blood vessels. In people with type 2 diabetes, this process of nitric oxide production and widening of the blood vessels is inhibited by a lack of or decreased response to insulin.

Now Liu and his team want to look more closely at two specific factors that are known to cause insulin resistance in people with type 2 diabetes—free fatty acids and a hormone called angiotensin II—to determine if these two factors inhibit insulin-mediated blood flow in the heart muscle. "The vast majority of patients with diabetes die from cardiovascular complications, but the mechanism is not clear as to how these people get heart problems," Liu says. His research, funded by a grant from the American Diabetes Association, could help explain why 60 to 70 percent of people with diabetes eventually die from cardiovascular diseases.

Bubbles and Waves

Liu will be using a state-of-the-art technique called myocardial contrast echocardiography (MCE) to measure the effect of free fatty acids and angiotensin II on insulin-mediated blood circulation in the small blood vessels inside the heart muscle. The noninvasive technique allows researchers to measure how well blood is pumping through the small blood vessels in the human heart. It uses gas-containing microbubbles as contrast agents to help highlight certain areas. After the microbubbles enter the veins, they join the path of blood circulation, following the same route as red blood cells do through the vessels. When exposed to ultrasound, waves are produced that are subsequently reflected by the microbubbles, sending reflective signals back to the ultrasound machine.

Because researchers know that microbubbles share space with red blood cells, they can estimate the amount and speed of blood flow in that area of the body by monitoring the intensity of the signals produced by the microbubbles. This information helps researchers determine the level of blood flow in the small blood vessels where the microbubbles are located—if the signal isn't as strong, then fewer microbubbles have made it to the small blood vessels, suggesting that something is impeding that process.

Finding a Solution

"I'm hoping in the future to use [MCE] to find out, first, what intervention can increase or decrease blood flow to the heart muscle," says Liu, "and second, in patients with diabetic cardiovascular complications, if we can use this technique to make an early diagnosis and targeted treatment for complications in the heart." If his hypothesis about the role of angiotensin II and free fatty acids in insulin resistance in the small blood vessels of the heart is confirmed, it could produce new options for treatment. For example, if the action of angiotensin II and free fatty acids could be inactivated or at least warded off, two major sources of insulin resistance would be taken out of the picture.

Liu's first task is to determine the effects of these two factors in test subjects who do not have diabetes, obesity, or insulin resistance. This will require a very complex experimental design, which is still evolving. But it is likely he will use six separate test groups of 15 to 20 subjects each for both the free fatty acid and the angiotensin II legs of his experiment. All subjects in this phase will come from this "healthy" population.

The six-group fatty acid study will be divided into a control group that will receive

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a saline (salt and water) solution; a group that will receive saline plus insulin; a group that will receive an intralipid (fat) suspension; a group that will receive intralipid solution plus insulin; a group that will receive aspirin and the intralipids; and a group that receives aspirin, intralipids, and insulin.

According to Liu the first, third, and fifth groups will serve as controls for the second, fourth, and sixth groups, respectively.

Why this complex mix? It is known that a specific enzyme is involved in fatty acids–induced insulin resistance, and that aspirin inhibits the action of that enzyme and improves insulin sensitivity in patients with insulin resistance. Liu wants to know if aspirin will exert this same effect on insulin resistance in the small blood vessels of the heart.

The groups examining angiotensin II will be set up much the same way, but with angiotensin II infusions instead of intralipid, and an angiotensin II receptor blocker called Candesartan instead of aspirin. Candesartan binds to a specific receptor where angiotensin II usually binds, preventing angiotensin II from exerting anti-insulin effects.

After these studies on healthy individuals, Liu's team will then study patients with diabetes, with and without microvascular complications. The specific setup of those studies will depend on the results of the tests on healthy subjects. Ultimately, Liu anticipates that the study will shed some light on the link between diabetes and cardiovascular complications and heart disease.

"If you give patients optimal diabetes control, you can dramatically decrease cardiovascular events in those patients," Liu says. "It's lifesaving for those folks—that's the motivation behind me looking in this direction."