Medical News & Perspectives

Could a New Method to Detect Coronary Inflammation Prevent Heart Attacks?

Jennifer Abbasi

A team led by scientists at the University of Oxford has developed the first method to detect inflammation in the heart's blood vessels using a standard clinical imaging procedure, computed tomographic (CT) angiography.

Inflammation contributes to both the formation of arterial plaques and their destabilization, which leaves them vulnerable to heart attack–causing ruptures, said principal investigator Charalambos Antoniades, MD, PhD, an associate professor of cardiovascular medicine at the University of Oxford. If the new method is further validated, it could be used to predict the formation of plaques before it occurs for primary prevention of atherosclerosis and to identify vulnerable coronary plaques that are set to rupture, a long-sought goal in cardiac medicine.

Antoniades' team developed the method based on a recent biological discovery. The accepted wisdom is that perivascular fat sends inflammatory signals to the arteries. Building on findings first published in 2013, the researchers have now confirmed that inflamed coronary arteries also "talk" to the fat that surrounds them, sending signals that change its lipid composition and water content.

In a new article in *Science Translational Medicine*, the researchers also described how these changes—a shift toward more watery fat closest to inflamed arteries—can be measured by a new metric called the perivascular fat attenuation index (FAI) using standard noninvasive heart scans. The FAI, a measure of fat cell lipid content and size, is the integral of fat attenuation obtained from reconstructed CT of adipose tissue.

A Narrow View

According to Keith Channon, MD, a coauthor on the study and a professor of cardiovascular medicine at the University of Oxford, a key problem with the risk stratification that currently directs management of coronary artery disease is this: The focus for decades has been on narrowing or blockages. But "plaque biology and plaque behavior is more important than merely the degree of narrowing caused by the plaque," Channon explained.

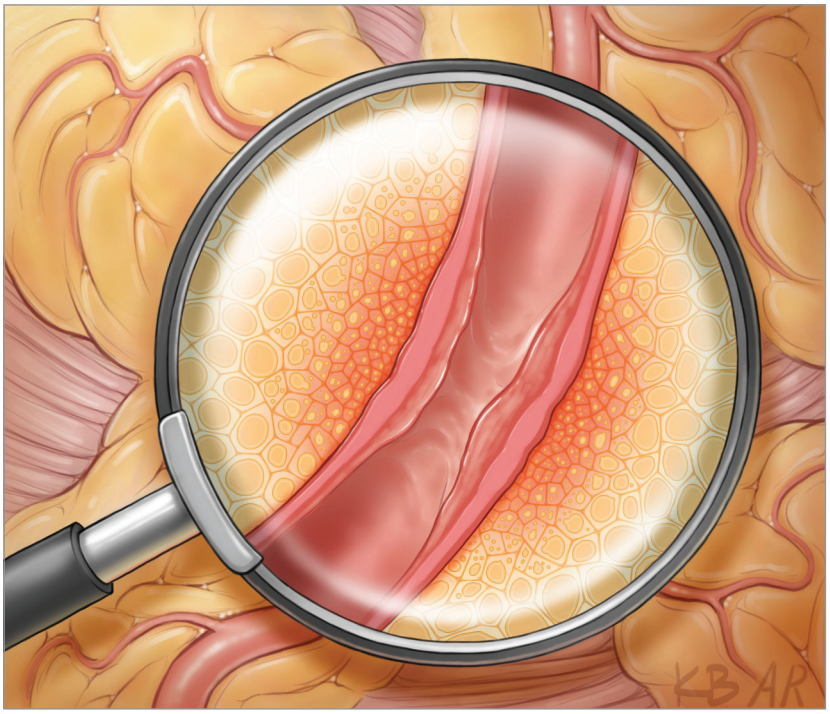
In fact, "about half of the heart attacks that occur [are] in arteries that weren't seriously or significantly narrowed the day before the heart attack," said Mayo Clinic cardiologist Stephen Kopecky, MD, who was not involved with the new research. The opposite is also true: Many patients with large, hardened plaques don't go on to have heart attacks.

The result? "We just don't have a test that predicts the future for when a plaque's going to rupture and a heart attack's going to occur," Kopecky said.

Unstable plaques are driven by inflammation and tend to be chock full of white blood cells like macrophages, Channon said, so it stands to reason that measuring coronary inflammation could be a crystal ball into future heart attacks. But there's no practical way yet to image inflamed blood vessels in the clinic. The common laboratory biomarker for inflammation, C-reactive protein, can indicate that the process is under way somewhere in the body, but it's not location specific and isn't a strong predictor of heart attack in individual patients.

Enter Channon and Antoniades' new study. First they set out to confirm their recent discovery that inflamed human arteries send signals to the fat tissue surrounding them, which senses these signals and changes its composition. To do so, they obtained pieces of aortic tissue from patients undergoing cardiac surgery, and at the same time isolated immature fat cells from adipose tissue deposits surrounding coronary arteries of patients. The fat cells were then cocultured with human aortic tissue pretreated with a proinflammatory agent.

"When we induced inflammation in these aortic tissue samples, then the fat cells growing around these samples lost



nearly completely their ability to accumulate fat," leaving them more "watery," Antoniades said.

Based on these findings, the researchers hypothesized that lipid accumulation in fat cells could be evaluated in patients by studying spatial changes in fat tissue attenuation with CT. In CT scans of fat tissue biopsies from patients undergoing cardiac surgery, the fat content in the samples was indeed associated with the degree of CT attenuation.

Using algorithms that they developed to obtain the FAI, the researchers then analyzed scans from patients with atherosclerosis who had diagnostic CT angiography. Compared with healthy individuals, the presence of disease in the coronary arteries of patients with atherosclerosis generated a strikingly different FAI in the area surrounding the artery.

"We were able to tell whether there is disease in the coronaries only by looking into the attenuation of the perivascular space," Antoniades said.

Next, patients admitted with a heart attack were scanned first during the acute phase and then again 5 weeks later. Applying their perivascular FAI to scans of culprit and nonculprit lesions in these patients as well as stable patients, the researchers were able to discriminate areas of ruptured plaques that caused the heart attack from stable plaques and could even observe changes around culprit lesions after a heart attack.

"This means that by studying perivascular FAI, you can detect the vulnerable plaques, and you can track changes of plaque inflammation happening weeks after the heart attack," Antoniades said.

All the scans were performed on routine clinical CT scanners, but the analysis—which requires 45 minutes of skilled-operator time on high-power computers—needs to be streamlined to make it widely applicable. "We are now developing new tools that enable us to get the results within 5 minutes," Antoniades, said.

The Missing Piece?

The big question mark that now hovers over the research is the predictive value of the FAI and whether it improves on current risk stratification.

Douglas L. Mann, MD, chief of cardiology at the Washington University School of Medicine, called the study "very provocative and interesting" but said it falls short of showing that the new method will be an added value. "Obviously you can't do everything in one article," he said.

Kopecky agreed: "It's very interesting and hypothesis generating, but it's not quite ready to supplant the other more standard methods we have for assessing risk. We need to show correlation with hard end points, things like heart attack, strokes, death."

To that end, the researchers are currently analyzing a cohort of around 2000 individuals who had a CT angiogram up to 10 years ago at Germany's Erlangen University Hospital and have been followed up for cardiac and all-cause mortality since then.

"We are now analyzing the CT angiogram scans to see if perivascular FAI analysis can predict cardiac death," Antoniades said.

The results of this study could be published as soon as early next year. If the findings are positive, Antoniades said the FAI could be integrated into cardiovascular risk scores alongside standard tools like coronary calcium and other information from CT angiography. These scans reveal hardened calcified plaques and narrowings, but as used today do not reveal inflammation in the arteries.

"Currently the CT angiogram gives you one result: stenosis and where," Antoniades said. "Now with the new biomarker, each CT angiogram will have an additional readout and that will be inflammation."

Ideally, that readout will indicate that plaques will start forming soon or that existing plaques are either stable or vulnerable to rupture. Physicians may use this additional knowledge to help decide how aggressively to recommend behavioral changes, whether to start statins to prevent atherosclerosis, or to advise patients with existing disease to try expensive new drugs like lipid-lowering proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors or anti-inflammatory agents like canakinumab.

"It's about understanding the disease process in people so that we are able to give the right treatment to the right patient at the right time rather than just sort of trying to make sure everyone gets everything all of the time," Channon said.

The metric could be most useful for restratifying patients who are considered at medium risk of developing heart disease or having a heart attack into high- or low-risk categories.

"I think where this could be of additive value is in those people who are somewhere in an intermediate range, and if the fat attenuation score was very high, then you might be inclined to move in earlier," Mann said.

Because the FAI changes with local inflammatory shifts, it could also be used to track whether treatments are working. The researchers believe the metric could be used as a new primary end point in drug trials, shortening the wait-time to results. They also hope this new method to detect blood vessel inflammation could be applied elsewhere in the body to help prevent stroke, aortic aneurysm, and peripheral arterial disease, for example.

"There is lots of potential applicability," Mann said. "I think it's premature to claim victory, in terms of where it will fit in, but I do think it's a step forward." ■

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