Evaluating Patients With ANOCA (Angina With Nonobstructive Coronary Arteries)

CLD talks with Jennifer A. Tremmel, MD, MS, FSCAI.

Dr. Tremmel discusses identifying and treating patients with ANOCA (also referred to as ischemia with nonobstructive coronary arteries [INOCA]), and her role as Co-Director of the Microvascular Network along with Dr. Tim Henry.

Who are the patients with ANOCA?

The majority of these patients are women, but up to a third are men. They have chronic angina, for at least three months, but I would say most of them have had symptoms for years. Generally, these patients experience typical angina, meaning it comes on with physical exertion and/or emotional stress and goes away with rest. It can sometimes have atypical features like coming on out of the blue. These patients have usually had one or more quite thorough cardiac evaluations with stress testing, echo, and sometimes coronary angiography, but nothing has been found and they continue to have their symptoms. ANOCA patients often have multiple emergency department visits, have undergone several tests, and are frequently going from one doctor to the other because they just keep being told nothing is wrong. We all see these patients. The problem is that a traditional cardiac workup is insufficient for identifying an underlying cause of ANOCA, and by reassuring patients based on traditional cardiac testing, we may be incorrect in telling them they do not have a coronary issue. In addition, such reassurance does nothing for a patient's symptoms, so they simply move on to the next physician in hopes of finding someone who can help them.

Is ANOCA a microvascular dysfunction problem?

Not necessarily. This is a frequently held misconception. There are actually several possible etiologies of ANOCA including endothelial dysfunction, epicardial vasospasm, and myocardial bridging, in addition to microvascular dysfunction, which can be structural (due to capillary plugging and/or rarefaction) or functional (due to spasm). People can also have some combination of these abnormalities. ANOCA is not a diagnosis in and of itself, but instead requires a thoughtful and thorough evaluation to identify the underlying etiology/etiologies.

Could ANOCA also be categorized under a broader term like "refractory angina"?

Yes, that's one way to look at it. Angina is incredibly common, and this is refractory angina in the sense that no one is figuring it out or fixing it. I liken ANOCA patients to our patients with chronic total occlusions (CTOs), and I care for both. I do the patients with the worst obstructive coronary disease and the patients with no obstructive coronary disease. They are both populations with angina who are currently underserved, but as an interventional community, we have the opportunity to make a big difference. Regardless of where it comes from, I want to help people with angina to not have angina anymore and improve their quality of life.

Is there a role for noninvasive evaluation of ANOCA?

As an interventional cardiologist, I focus on the invasive evaluation, but there are useful modalities, with positron emission tomography (PET) and magnetic resonance imaging (MRI) being the top two. Their main limitation is that they only investigate structural microvascular dysfunction. If you only do a noninvasive evaluation, these modalities won't provide a comprehensive evaluation of your patient. If it turns out your patient has microvascular dysfunction, then this type of noninvasive imaging can be helpful, but if your patient doesn't have microvascular dysfunction, or has other etiologies in addition to microvascular dysfunction, they still might require invasive testing. Likewise, a cardiac computed tomography angiography (CCTA) can diagnose the presence of a bridge, but does not tell you if the bridge is causing the patient's symptoms or is simply an incidental finding.

At what point might you see these patients?

I see a lot of these patients and they can come from various places. They often find me, and more and more because there are discussions on social media, these patients now find each other and then figure out who can help them. Increasingly, as there is greater awareness, I get a lot more referrals from providers, which is good. That means that physicians are understanding there is something wrong and there is something we can do about it. One of the things I stress that I don't think clinicians always understand is that a typical stress test isn't going to necessarily find any abnormality in these patients. Getting a stress test and having it be normal simply rules out obstructive coronary disease, but it doesn't necessarily rule out one of these occult coronary abnormalities that we are talking about here.

In evaluating these patients, the three main things we are looking for are microvascular dysfunction (structural/functional), endothelial dysfunction/spasm, and myocardial bridging. I test for all of these things in every patient I take to the cath lab for ANOCA testing. Our comprehensive invasive evaluation of these patients involves 1) testing for spasm at the epicardial and microvascular level by giving acetylcholine in the coronary artery; 2) performing intravascular ultrasound to evaluate for diffuse plaque that might be limiting fractional flow reserve (FFR) even though the vessel doesn't look obstructed, and myocardial bridging, which often cannot be seen on angiography alone and requires intravascular ultrasound imaging; and 3) we then put in a coronary pressure wire where we can measure pressure and flow. We assess the microvasculature again, this time with adenosine, measuring coronary flow reserve (CFR) and the index of microvascular resistance (IMR). If the patient has a bridge, we test that with dobutamine and diastolic FFR or resting full-cycle ratio (RFR) with the same pressure wire.

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What are the different therapies that can be used to help ANOCA patients?

If you can figure out the cause(s) of ANOCA, it can help guide therapy. Studying treatments in this area has been challenging because there are so many different endotypes, as they are called, particularly if people have a combination of them. You could have structural microvascular dysfunction or epicardial spasm or a myocardial bridge, or you could have all three at once. I have developed my own algorithm for treatment, and other people who regularly care for these people tend to have their own algorithm as well. The CorMicA trial[1] also used an algorithm dictating therapy based on what endotype(s) a patient had. At this point, we have a rough suggestion of what medications to start with based on the physiology of the abnormality itself. We do the treatment based on what we find, which is at least better than shooting in the dark when somebody comes in with chest pain and you're like, "Oh, let's just try this med; let's try that med." If you at least know what's wrong, you can try to pick something that makes sense given the pathophysiology you are seeing. Ultimately, more research is definitely needed.

What do you recommend if someone wants to learn more about how to diagnose and treat ANOCA patients?

I am co-directing the Microvascular Network (MVN) with Tim Henry. We have been bringing together interventionalists and other providers from around the U.S. and Canada for nearly 2 years. The MVN is a physician-led group aimed at identifying North American providers in this space, standardizing diagnostic and treatment modalities in a way that works with our healthcare system, and creating a pathway for patients as well as physicians and hospitals to streamline taking care of and studying these patients. There are currently over 70 members and it is growing. One of the benefits is that we have now identified many of the centers in the country focused on helping these patients, and one of our goals is to train providers who want to start doing this at their institution. We recommend people get proctored on at least a few cases to start. Proctoring involves having somebody come to your hospital to teach you or you going to their hospital to learn. The MVN can help get that learning started and answer any questions as you begin to understand how to interpret the data, what you might do for treatment, and even how to start a whole program. The MVN will be a great support as more and more people are expressing interest in starting these programs. If you are at a center that is not interested in doing this testing or doesn't have the bandwidth to do it, at least you can know where the other centers are located. Like CTOs, not every facility is going to be able to treat these patients, but we can always get patients to institutions that do. Recognizing that a patient could benefit and then getting them to a place that can do the testing is a great start.

I have been treating chest pain for over 25 years, including both refractory angina as well as microvascular angina. At the Lindner Center's Women's Heart program, we have one of the busiest clinics in the country.

The importance of the microvasculature has been becoming increasingly clear and treatment of microvascular angina remains a major unmet need. Patients' quality of life is significantly impaired and they are at risk for major adverse cardiac events. It is now an exciting time for microvascular disease because we are testing some unique treatment strategies including novel therapeutics, cell therapy, gene therapy, and the coronary sinus reducer. We not only have better techniques to identify the source of the problem and for making an accurate diagnosis, but unique and novel therapies that will potentially make a difference in people's lives.

Involvement in the Microvascular Network has been an extremely positive experience. It has allowed us to expand the number of centers across the United States that understand and are taking care of people with microvascular dysfunction. Over the last year we have made tremendous progress and are excited about the next steps.

Timothy D. Henry, MD, FACC, MSCAI
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If you are located in the eastern half of the United States and are interested in learning more about the Microvascular Network, contact Dr. Henry via CLD's manging editor Rebecca Kapur at rkapur@hmpglobal.com. If you are located the western half of the U.S., please contact Dr. Tremmel at jtremmel@stanford.edu.

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Are there pathways that you would recommend people avoid or certain types of imaging that you find are less useful because they are not going to help answer your questions?

Yes. I see a lot of repeated stress testing and even repeated angiography when you can tell that this person is not going to have obstructive disease. Patients have had 5 stress tests and 2 angiograms, for example. I would say if you are at the point where you think you need to do an angiogram and are quite certain the patient doesn't have obstructive disease, it is time to do the angiogram at a center that can do invasive vascular function testing. Don't just do an angiogram. That is a waste of everyone's time and money. If you think it is spasm, then the patient needs to go to the lab with the plan of putting in acetylcholine to test. I want to emphasize that it is also not appropriate to do an angiogram, see no obstructive disease, and then tell the patient: "You have microvascular dysfunction," or "You have spasm." You could say, "You might have [X]," but until that testing is done, you have no idea what they have. The most common result we see is patients being told, "You must have microvascular dysfunction because I don't see anything on your angiogram." But we have a way to test that, and we should test and confirm before saying that to our patients. Of course, I am glad that people are at least thinking about microvascular dysfunction because even 10 years ago, they wouldn't have even said that. They would just tell patients, "You're fine," and that would be it. So, we have made progress.

As a reminder, ANOCA is a working diagnosis. It is not an end diagnosis in and of itself. It requires a thorough and thoughtful evaluation to actually

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figure out what these patients have. MINOCA is the same thing: the patient had a myocardial infarction (MI) but has normal coronaries. Like with ANOCA (or INOCA), now we have to figure out what is wrong.

Let's talk about the language. INOCA is ischemia related.

Yes, INOCA is ischemia and nonobstructive coronary arteries. ANOCA is angina and nonobstructive coronary arteries. The reason I don't like to use INOCA is that it implies that you need to demonstrate ischemia, which often can't be done by our traditional stress tests. At Stanford and the Mayo Clinic, we have shown that traditional stress testing (SPECT, stress echo, and exercise treadmill) are insufficient for identifying an occult coronary abnormality in patients with angina and nonobstructive coronary arteries. Perhaps PET and MRI can better detect subendocardial ischemia, but those aren't routinely done. The misconception that traditional stress testing is valuable in these patients has negative implications for how we treat these patients and for guidelines we write regarding the treatment pathway for chest pain, so being clear is important. I think the term INOCA and involvement of ischemia confuses things. I prefer to use ANOCA because all these patients have angina and nonobstructive coronaries, but they don't all have demonstrable ischemia and nonobstructive coronaries (until we do our invasive testing).

Any final thoughts?

If people are interested in being a member of the Microvascular Network or want to learn more about ANOCA, invasive functional testing, and/or the treatment of these patients, I would encourage them to reach out by email. We would love to have them involved. ■

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CLINICAL NEWS

When Fibromuscular Dysplasia Hits a Family, Abdominal Aortic Aneurysms May Too

One disease is more common in people assigned female at birth, while the other is more common in people assigned male at birth. But a new publication details a "shared complex genetic architecture" between the cardiovascular conditions that could explain why, when one member of a family develops fibromuscular dysplasia (FMD), another may develop an abdominal aortic aneurysm (AAA).

"We used complementary genetic approaches to validate the relationship between these two highly sex-biased conditions, raising some interesting questions regarding sex differences relating to a common, shared genetic risk profile," said senior author Santhi K. Ganesh, MD, an associate professor of internal medicine and human genetics, and a cardiologist at the University of Michigan Health Frankel Cardiovascular Center.

Ganesh and colleagues analyzed family histories from 73 people with FMD and 463 of their first-degree relatives who volunteered to participate in clinical research. They discovered that, in a family where one person had FMD, the risk of a male member of that family developing an AAA was significantly higher. For example, the father of a person with FMD was twice as likely to experience AAA.

The research team then compared a new polygenic risk score for FMD and established polygenic risk scores for AAA to verify a shared genetic basis for both diseases, Ganesh says. The results point to specific genes that may underlie both diseases, providing new biological understanding of vascular diseases. The findings also support that screening for abdominal aortic aneurysm in male relatives of patients with FMD may be useful, along with currently established AAA screening guidelines.

Reference

1. Katz AE, Yang ML, Levin MG, et al; VA Million Veteran Program. Fibromuscular dysplasia and abdominal aortic aneurysms are dimorphic sex-specific diseases with shared complex genetic architecture. *Circ Genom Precis Med*. 2022 Nov 14: e003496. doi: 10.1161/CIRCGEN.121.003496

What is Fibromuscular Dysplasia?

Fibromuscular dysplasia (FMD) is a non-atherosclerotic, noninflammatory arterial disease that primarily affects women. It most commonly affects the renal, extra-cranial carotid, and vertebral arteries, but has been reported in almost every arterial bed. FMD may cause stenosis, aneurysm, dissection and/or occlusion in affected vascular bed(s). Asymptomatic patients with FMD may be asymptomatic and have disease discovered incidentally during imaging for other reasons. Treatment consists of lifestyle modification, antiplatelet and antihypertensive therapy, and percutaneous or surgical revascularization and/or repair when indicated.

—Learn more about FMD: *Rainer K, Devireddy C, Wells BJ. Renal artery fibromuscular dysplasia. Cath Lab Digest. 2019 Oct; 27(10):1,17.*