Vasoreactivity Testing and Chest Pain Guidelines: Is the IIa Recommendation Warranted? *INOCA Part II*

Dr. Morton J. Kern, Long Beach, California, with Drs. Colin Berry, Glasgow, Scotland; Sam Butman, Cottonwood, Arizona; Peter Block, Atlanta, Georgia; Bernard DeBruyne, Aalst, Belgium; Gregory Dehmer, Roanoke, Virginia; Tim Henry, Cincinnati, Ohio; Spencer King, Atlanta, Georgia; Lloyd Klein, Sonoma, California; Michael Kutcher, Winston-Salem, North Carolina; Amir Lerman, Rochester, Minnesota; Kreton Mavromatis, Atlanta, Georgia; David Moliterno, Lexington, Kentucky; Srihari S. Naidu, Westchester, New York; August Pichard, Washington, DC; Jon Tobis, Los Angeles, California; Olga Toleva, Atlanta, Georgia; Bonnie Weiner, Worchester, Massachusetts.

The July 2022 *CLD Editor's Corner* was devoted to INOCA (ischemia with no coronary artery disease) and how to test and treat it.[1] INOCA and MINOCA (myocardial infarction with normal coronary arteries) are now widely known and gathering attention regarding their diagnosis and treatment. Many labs now have sensor guidewires and software to make this possible. Specialized centers are setting the protocols for provocative coronary vasoreactivity testing in INOCA patients.

Recently, Dr. Lloyd Klein of Sonoma, California, raised concern about the 2021 chest pain guidelines,[2] where INOCA testing was given a IIa recommendation, the same as fractional flow reserve (FFR). Dr. Klein commented, "I'm not enamored of the new chest pain guidelines. I'm amazed that the ISCHEMIA trial was simply ignored. But I'm especially surprised that provocative acetylcholine (ACh) testing is given a IIa rating in normal coronaries if INOCA is suspected. This is based on one randomized controlled trial comprised of 76 patients treated this way. I'm wondering what others think of provocative testing routinely."

To recap, guidelines and consensus statements contribute to patient care, help clinicians choose appropriate procedures, and serve as a common foundation for decision-making in many common scenarios and some complex settings. Guidelines are written by committees that require membership with an unbiased approach. Unfortunately, the committee selections often exclude membership by some experts with perceived conflicts with industry or specific research. While never a perfect document, a guideline or consensus statement remains useful, while understanding the exceptions for specific clinical patient circumstances.

Is Vasoreactivity Testing Common?

Mort Kern, Long Beach, California: Lloyd, if the basis for this recommendation comes from just a couple of studies, then I agree it seems premature to give such a strong recommendation since, as I hear, not many centers are proactively testing (for INOCA, see July 2022 *CLD Editor's Corner*[1]). Since INOCA now has wide visibility for cath labs, more patients will be evaluated. However, coronary vasoreactivity testing requires special preparations, including withholding vasoactive drugs (radial spasm cocktail) before testing and experience with coronary flow measurements. Most testing centers will often forego ad hoc testing and schedule a second procedure since radial drugs are given routinely. I'm having trouble going back to femoral access for this now.

Bonnie Weiner, Worchester, Massachusetts: It seems to me after the diagnosis of angiographically "normal coronaries," a thorough search for other diagnoses and therapy is appropriate. After that and with con-

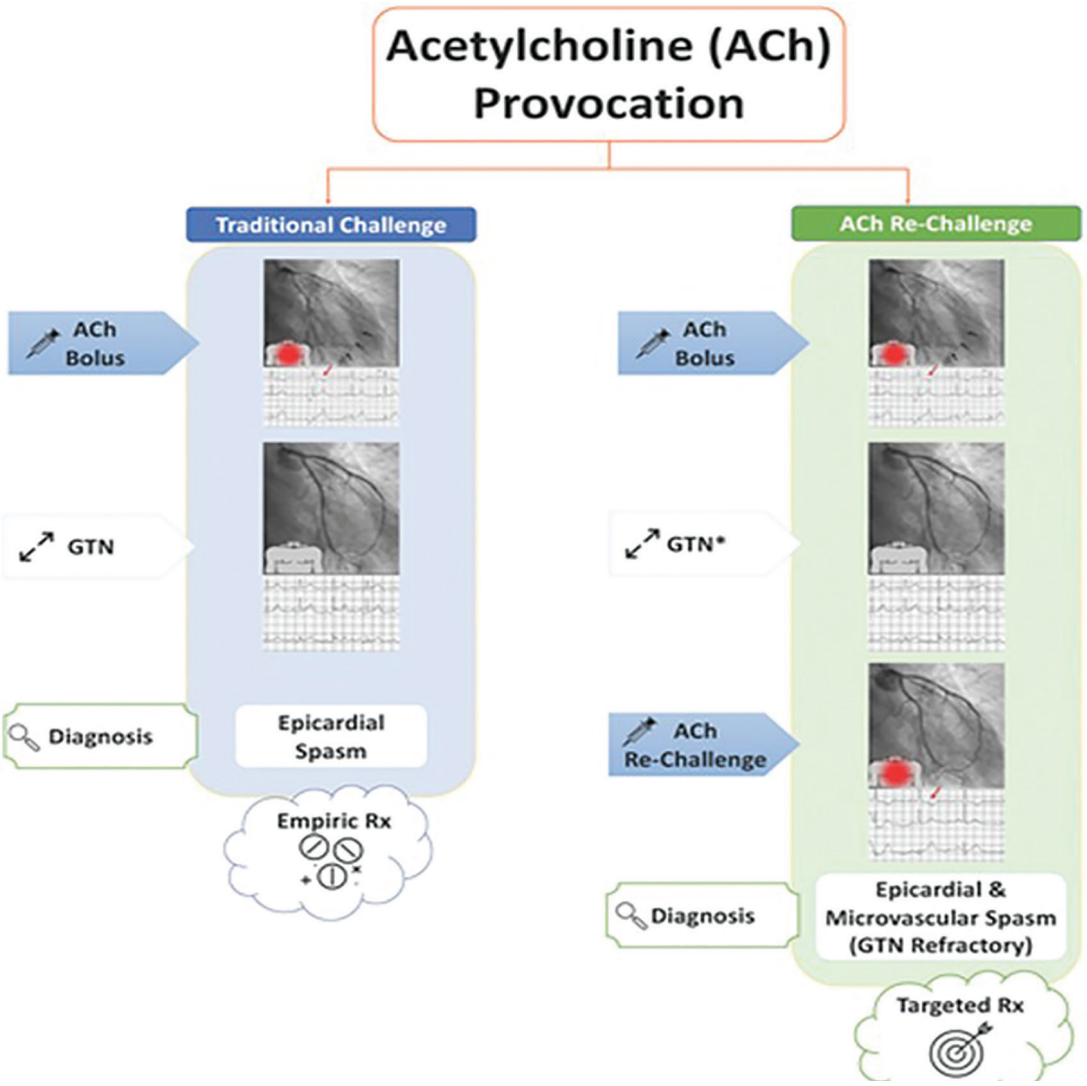

Figure 1. The traditional approach (left) to provocative acetylcholine testing allows diagnosis of epicardial coronary spasm or microvascular spasm without differentiation of endotypes. Acetylcholine (ACh) rechallenge (right) after administration of glyceryl trinitrate (GTN) might help target therapy by differentiating between GTN-responsive and GTN-nonresponsive epicardial spasm as well as diagnosing mixed epicardial and microvascular coronary spasm. The same patient with vasospastic angina in the figure (adapted with permission from Seitz et al†) has epicardial spasm during the challenge, but also coexistent microvascular spasm during rechallenge with ACh despite GTN. Further rechallenges after administration of alternative vasodilatory medications may further help direct therapy.

†Seitz A, Feenstra R, Konst R, et al. Acetylcholine rechallenge: a first step toward tailored treatment in patients with coronary artery spasm. J Am Coll Cardiol Intv 2022; doi: 10.1016/j.jcin.2021.10.003

Figure reprinted with permission from Ford TJ, Mikhail P. Acetylcholine (re)challenge from diagnosis to targeted therapy. JACC Intervention 2022; https://doi.org/10.1016/j.jcin.2021.11.022*

tinued limiting symptoms, a planned procedure for [vasoreactivity and INOCA] testing would be appropriate. I would add these (Jurassic period) references that are also relevant.[3,4] [*MK*: Ergonovine is no longer used, but ACh is.]

Kreton Mavromatis, Atlanta, Georgia: I think with meticulous history taking (often not done) and a thorough non-invasive evaluation (often including coronary computed tomography angiography [CCTA] as well as ischemia testing), if your patient is left with a diagnosis of angina + ischemia, then INOCA testing is reasonable. Of course, this combination is often not achieved prior to cath, but the guideline writers assumed it would be and always should be. I wouldn't let a femoral approach dissuade me in this situation [need for INOCA testing].

Smoking and Vasoreactivity

August Pichard, Washington, D.C.: I would be in favor of advanced testing when a patient is "suffering" from chest pain (CP) syndrome and there is no diagnosis. As we know, chronic pain may lead to significant alterations of life, including severe psychological issues. I also learned to always test for thoracic outlet syndrome (costoclavicular syndrome) in these cases. It can cause chest pain that simulates angina, and it can be effectively treated with rehab exercises, and rarely with surgery. I did get to find a lot of them!

In addition, recall that smoking and cold test (hand into ice water) alter coronary flow. Atilio Maseri and we at Mount Sinai in New York City demonstrated this [vasoreactivity] by measuring coronary vasodilatory reserve. (Lloyd, were you a fellow with us then?).

Lloyd Klein, Sonoma, California: Gus, I was your fellow on this project. Smoking causes both diffuse vasoconstriction and spasm at coronary stenoses and in susceptible patients.

Spencer King, Atlanta, Georgia: Somewhere I may have the angiograms of an 18-year-old smoker who got Dr. Woody Cobbs on that kick [checking for spasm]. I cathed this patient after an anterior myocardial infarction (MI). The arteries looked normal. Woody asked me to cath him again while he was smoking. This time there was a bulky thrombus in the left anterior descending (LAD). He stopped smoking and was anticoagulated until he had a motorcycle accident. While in the hospital for his broken leg, he started smoking again. He had an MI and died. The autopsy showed layers of laminar thrombus and a fresh occlusion at the LAD site. I don't think Woody ever wrote it up. [*MK*: So many observations of importance never come to the surface for a call to action.]

Michael Kutcher, Winston-Salem, North Carolina: Back in the late 1970s and early 80s when I was a cardiology fellow at Emory, one of our non invasive attendings was Dr. Woody Cobbs. He would ask us do a "cigarette smoking test" on patients who were smokers with normal coronary arteries. We would do a before-and-after smoking cigarettes coronary angiogram. Initially, I thought this was a dubious request, but the findings of reduction of coronary diameter and even some spasm after smoking were striking. Dr. Cobbs was ahead of his time.

Peter Block, Atlanta, Georgia: There are no easy answers to this question of provocative testing, especially if most diagnostic angiograms are done via the wrist. Practically speaking agreeing with (or not) the guidelines does not help much. Ergonovine is out of style but would bypass the drug issues of testing during radial caths. The vasodilatory cocktail could be avoided but have intracoronary (IC) nitroglycerin (TNG) ready.

Here is another cute tip: if your patient is a smoker, ask them to light up a cigarette. Do an angiogram after 2 deep inhales. It amuses the lab folks and patients completely but comparing a before and after angio frequently surprised me with the change in coronary diameter. The snickers disappear, diagnosis is made, and you become a folk hero. [*MK*: Peter, do you know how much trouble we would get in if we did this in today's labs? Early retirement would be the least of my worries…]

Gregory Dehmer, Roanoke, Virginia: There are a series of articles involving the effects of smoking where patients were tested before and while smoking during their procedure. These were mostly in patients with coronary artery disease (CAD). You can find these by doing a PubMed [pubmed.gov] search: "Hillis LD and smoking". According to Dave Hillis, several patients, when shown their data, were moved to quit.

David Moliterno, Lexington, Kentucky: One of the papers from a lifetime ago. Cigarettes are easier to administer in the cath lab than cocaine.[5] "As compared with baseline measurements, the diameters of nondiseased coronary arterial segments decreased on average by 7%±1% after cocaine use (P<0.001), by 7%±1% after smoking (P<0.001), and by 6%±2% after cocaine use and smoking (P<0.001)."

Growth in INOCA Testing?

Tim Henry, Cincinnati, Ohio: There are lots of interesting anecdotes, but the question about testing for INOCA-ANOCA and MINOCA is not trivial. For many reasons, testing is a critically important unmet need and we should work to make care better! The new guidelines were not based on one randomized trial with <80 patients. Here are some key points worth remembering:

1) 20%-40% of cardiac cath patients have no significant CAD (depends on your use of CTA) with a higher percentage in women.
2) 17% of ISCHEMIA study patients had no obstructive disease on CTA with most women, patients with chest pain, and ischemia.
3) 25%-35% of patients in ISCHEMIA and COURAGE studies still had angina despite revascularization. Also, 40-60% of the medically treated group still had angina.
4) The WISE study and many others show increased major adverse cardiac events (MACE) in patients with coronary microvascular disease (CMD).
5) We presented data that 5% of ST-elevation MI (STEMI) patients had MINOCA with a lower event rate in hospital but equal or higher events at one year, because they are ignored and do not get a real diagnosis.
6) The microvasculature is incredibly important and a major unmet need for diagnosis and treatment. Consider the patients with:
   a) CMD;
   b) Heart failure with preserved ejection fraction (HFpEF) (75% have abnormal coronary flow reserve [CFR]);
   c) POST MI: highest risk patients have microvascular obstruction;
   d) Post percutaneous coronary intervention (PCI) and chronic total occlusion (CTO) chest pain.

There are a host of novel treatments. Stop ignoring these patients and make a proper diagnosis. Put them in a clinical trial. There are lots of data showing noninvasive imagining is a suboptimal method with a poor correlation to CFR/ACh testing. The CORMICA study showed that invasive testing was superior to clinical/noninvasive testing

I did my first CFR in 1987 with Bob Wilson at the University of Minnesota with his homemade Doppler flow catheter. We had a series of 20-25 patients (mostly women) that had stents placed for mild mod CAD (60%-70%), but still had CP and had abnormal CFR, something that still happens every day in the United States.

For the record, I did 3 coronary reactivity tests today. We only do patients that have failed empiric therapy with class 3 or 4 angina. I hired one of my Cedars fellows who is shockingly busy, because there are so many patients out there that have been ignored. I'm guessing 250+ coronary reactivity tests

were done in the last 2 years by both Doppler and thermodilution. We have 3 ongoing clinical trials and 2-4 to start in the next 6 months, including cell therapy, coronary sinus reducer, gene therapy, and novel therapeutic strategies (WARRIOR study). These patients deserve our attention and should be tested. If you cannot test, then at least refer them to a center that understands and is working with INOCA and MINOCA.

Bernard DeBruyne, Aalst, Belgium: I cannot agree more with Tim. CMD is indeed critically important for many patients whom we see daily. However, CMD remains hopelessly the "black box" of the coronary circulation for at least three reasons: It is invisible to the eye, it is not reproducible in animals nor on the bench, and — most importantly — its precise measurement remains elusive.

In Aalst (Belgium) and in Eindhoven (Netherlands) we have developed and have been applying for a couple of years routine continuous coronary thermodilution, which allows us to obtain measurements of absolute flow (in mL/min), absolute microvascular resistance (in WU), and to calculate microvascular resistance reserve (MRR) (which should become for the microcirculation what FFR is for the epicardial circulation). It takes 5 minutes and necessitates a dedicated catheter (RayFlow), software (Coroventis), and controlled saline infusion at room temperature. Not rocket science, but devilishly accurate. The term "precision medicine" is used and abused +++. Continuous thermodilution is a step towards true precision measurements.

Amir Lerman, Rochester, Minnesota: Assessment of microvascular function with the assessment of endothelial function should be a part of the comprehensive assessment of our patients in the cath lab with nonobstructive CAD. At Mayo, it is a part of our routine clinical practice since 1995, using the Doppler wire and using adenosine and acetylcholine with an extremely low complication rate (3 coronary dissections in over 2500 patients at the early stage). The assessment helps to determine the mechanism of symptoms and ischemia, helps guide medical therapy, increases patient satisfaction, and reduces cost at follow-up. The ischemia is undetected by noninvasive tests.

Bonnie Weiner, Worchester, Massachusetts: Although I agree with the importance of INOCA and that evaluating it is important, particularly in women, we must recognize that most diagnostic studies do not occur in centers with the kind of interest and resources we would like. Furthermore, until there are effective therapies, the interest in these settings is likely to be minimal. We are not likely to see an increase in referrals to research centers until technologies are widely (inexpensively and/or valued) available. I would also reinforce the message that patients coming to the cath lab with "chest pain" and without a full workup should be discouraged [from ad hoc testing]. That alone would enrich the population suitable for further evaluation for INOCA.

Sam Butman, Scottsdale, Arizona: A strong yes to the age-old idea of good history taking and re-evaluation of any noninvasive testing results prior to angiography. For instance, too many patients undergo invasive studies based on an abnormal stress nuclear or echo study in the face of an accompanying normal stress electrocardiogram (ECG), too often simply representing a false positive study. Add in, what in retrospect are many patients with nonischemic chest pain and other diagnoses, and the time and cost of INOCA testing will be of little value. INOCA testing is here to stay and it is definitely another frontier for us. Its origin goes back to the days of even simpler testing in the cath lab, like the Cold-Pressor Test (Google it if interested) which was useful in detecting coronary spasm and often used in lieu of intracoronary ergonovine provocation. Keep a dry towel nearby.

Jon Tobis, Los Angeles, California: At UCLA, in patients suspected of having coronary artery spasm, we do acetylcholine and adenosine testing from the femoral approach. In addition, I've seen six patients who had intermittent nonexercise-induced chest pain and a history of migraine. These patients all had a patent foramen ovale (PFO) with right to left shunting. Angiography demonstrated coronary spasm. When we closed the PFO, the migraines and the chest pain were relieved. I did not bring them back for repeat acetylcholine testing because I assumed that the insurance companies would not pay for it. I believe there are some vasoactive substances that pass through the PFO to trigger migraine and or chest pain. When the PFO is closed, the vasoactive substances are metabolized as they pass through the pulmonary capillary circulation. [*MK:* Unique observation, worth a study.]

Srihari S. Naidu, Westchester, New York: One of the challenges with recent guidelines is that they are endeavoring to construct them with broader representation, which somewhat takes away from scientific expertise on the panel. In addition, there's been more consensus-based elevation of recommendations than evidentiary-based recommendations, something that is lost in the translation. A IIa with Level of Evidence C should be very different than a IIa with Level of Evidence A. The evidence base for FFR versus that for INOCA testing reflects this tension.

Olga Toleva, Atlanta, Georgia: I echo what is said by Tim Henry, Bernard De Bruyne, and Amir Lerman, all very experienced with a deep understanding of coronary physiology.

We all struggle to make an accurate diagnosis and agree on techniques, knowing that some methods we rely on are not perfect. There is a strong effort in the community toward working together and agreeing on endotypes, approaches to diagnosis, and finally, targeted therapy.

I have worked at Emory for a year now and do both thermodilution boluses with CoroFlow and Doppler studies following the ACh and adenosine protocols that Cedars-Sinai, Mayo Clinic, Christ Hospital, and others are doing (Figure 1 shows a proposed challenge and rechallenge for ACh provocation studies.[6]). Out of 100 studies, I've only had two patients that had noncardiac chest pain, and all the others had positive studies without complications. ACh is safe. I use three ACh concentrations infused via a microcatheter. The referrals are carefully selected and have had at least one prior cath with unobstructed coronaries. The yield is high. It is not difficult to find these patients and I, like Tim, have become very busy, very fast.

However, the continuous thermodilution [absolute flow] is something different. I went to see it in Aalst, and it offers an additional high-fidelity interpretation worthy of our attention. It is easy to use and if you're already using a microcatheter to infuse ACh, the RayFlow catheter is the same (no extra steps or extra cost). No need for adenosine [*MK:* Saline infusion at 20 mL/min produces hyperemia like adenosine] and a total of 5 min of automated saline infusion to obtain flow, resistance, and MRR.

There is so much we need to work on, from accurate diagnosis to therapies to help patients that often have a very poor quality of life and are devastated because they have no clear answers for their chest pain.

Colin Berry, Glasgow, Scotland: I have learned from the expertise and endeavors of many colleagues in this email chain, and I am very grateful for it. The European Society of Cardiology (ESC) gave a IIb recommendation for acetylcholine testing (led by Javier Escanad and colleagues[7]). CorMicA was a registry-based trial involving 391 patients and 151 randomized in a blinded, sham (placebo)-controlled trial with follow-up to one year.[8,9] Note that 7 in 10 people of the randomized population were women. This result contrasts with the preponderance of men in CAD/congenital heart disease (CHD) trials. This difference reflects the natural history of ischemic heart disease where small-vessel disease predominates in women with angina. However, angina trials and healthcare interventions focusing on CHD will preferentially engage men. The CorMicA trial also included a prespecified health economic analysis.[10] It is not easy to randomize patients into an acetylcholine protocol

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— Amir Lerman, Rochester, Minnesota

when the diagnosis involves a patient response and blinding; hence, all patients received acetylcholine. iCorMicA is currently assessing the external validity of our results and whether patient benefits can be achieved without the need for acetylcholine, ie, guidewire testing only with linked therapy, with a double-blind design, and vasospastic angina can still be diagnosed based on clinical judgment, regardless of the randomized group (https://clinicaltrials.gov/ct2/show/NCT04674449). Look out for our CorCTCA trial,[11] hopefully to be reported at the American Heart Association Scientific Sessions.

The Bottom Line

"Conversations in Cardiology" in these pages on guidelines regarding specific practices and syndromes like INOCA stimulate our understanding of current practices, what the future may need, and what it looks like. While the decisions of guideline committees often result from a consensus and not necessarily the current state of opinion, they form a framework for good practice, and set the stage for future research to support or refute our clinical approach to our patients. ■

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Morton J. Kern, MD, MSCAI, FACC, FAHA
Clinical Editor; Chief of Cardiology, Long Beach VA Medical Center, Long Beach, California; Professor of Medicine, University of California, Irvine Medical Center, Orange, California

Disclosures: Dr. Morton Kern reports he is a consultant for Abiomed, Abbott Vascular, Philips Volcano, ACIST Medical, and Opsens Inc.

Dr. Kern can be contacted at mortonkern2007@gmail.com
On Twitter @drmortkern

Don't miss the letter from Christopher Buller, MD, Medical Director at Teleflex, regarding the company's **Langston® Dual Lumen Catheter Reintroduction**, *with commentary from Morton Kern, MD.*
See page 41.