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Refining Nuclear Scintigraphy for ATTR-CM Diagnosis

Announcer:

You're listening to *On the Frontlines of ATTR-CM* on ReachMD. Here's your host, Dr. Mary Leuchars.

Dr. Leuchars:

Welcome to *On the Frontlines of ATTR-CM* on ReachMD. I'm Dr. Mary Leuchars, and joining me to discuss how we can improve nuclear scintigraphy for transthyretin amyloid cardiomyopathy, or ATTR-CM, diagnosis is Dr. Saurabh Malhotra. He's the Director of Advanced Cardiac Imaging at Cook County Health and a Professor of Medicine at Rush Medical College in Chicago. Dr. Malhotra, thanks so much for being here today.

Dr. Malhotra:

It's my pleasure. Thank you, Mary.

Dr. Leuchars:

To start with some context, Dr. Malhotra, what role does nuclear scintigraphy play in diagnosing ATTR-CM, and what has to be ruled out before a positive scan can be considered diagnostic?

Dr. Malhotra:

Nuclear scintigraphy actually has changed the way we think about ATTR-CM now. One of the major advances, so to speak, that happened that has made our understanding of ATTR-CM so much better and has allowed folks across the world to diagnose this disease more efficiently is the recognition that nuclear scintigraphy is a highly specific test for diagnosis of ATTR-CM.

So this is performed using certain tracers that, previously, were being used for bone imaging. But over several years, actually, we realized that these do tend to light up the heart in patients who have ATTR-CM, as well. This was actually confirmed to a large extent in the seminal work by Gilmour and colleagues, published in 2016, wherein, amongst patients who had biopsy-proven ATTR-CM, nuclear scintigraphy was 100 percent specific in diagnosing ATTR-CM.

So at least we understand that it plays a very critical role in diagnosing ATTR-CM. But to your second question, this specificity is only available when the other—although less common—form of amyloidosis is ruled out, which is light-chain amyloidosis. And that can be ruled out by simple serological tests. And this high diagnostic accuracy and specificity of nuclear scintigraphy is only conferred in the setting of lack of light-chain disease.

Dr. Leuchars:

So when a patient reaches a nuclear lab, what acquisition choices, like tracer selection, imaging time point, and use of SPECT have the biggest impact on whether we get a reliable result?

Dr. Malhotra:

I think, of the choices that you provided, the biggest impact is the use of SPECT. And that was highlighted in the quality metrics published by the American Society of Nuclear Cardiology, wherein a lab performing quality imaging for cardiac amyloidosis has to use SPECT 100 percent of the time. So every patient who is being imaged for ATTR-CM has to undergo SPECT imaging. The other choices are important, not crucial or critical. The use of SPECT is absolutely critical.

So when a patient comes to the nuclear lab, we have three tracers worldwide that can be used. In the US, we use a pyrophosphate, or PYP, or HDP, also called oxidronate. We do not have DPD available in the US, but that's available in Europe. These tracers were studied interchangeably, and that is one thing that folks don't recognize—that, even though all three of them are bone tracers, their

pharmacokinetics, how they are removed from the cavity of the heart, and how they are taken up by the bones—which is what the intention of these tracers were when they were originally discovered and developed—are not the same.

For example, if a lab is using HDP because now there is a shortage of PYP—we have been using HDP preferentially for three years now—HDP washes out very quickly, quicker than PYP. We have always been a lab that does one-hour imaging instead of the three-hour imaging time point, because we think that allows for faster scanning, the patient experience is better, and studies have shown that there is really no diagnostic differences if you image patients at one hour or three hours after tracer injection. However, when it comes to tracer selection, if a lab has been doing three-hour imaging, and they're now using HDP instead of PYP, because of that faster washout from tissue, there have been occasions where studies have been called as falsely negative at three hours when using HDP as the tracer, when those patients were truly positive and abnormal if they were to be imaged at one hour.

So I think those nuances, when it comes to tracers, have to be understood. Nuclear cardiology labs and nuclear cardiologists have not worked with bone-avid tracers in the past. That is not something that is under the purview of a cardiologist. But we have been using these tracers to diagnose a cardiac condition, so our awareness about how these tracers work, just like other tracers that we use for perfusion imaging, also needs to be improved, so we can select the imaging time point based on the tracer that we are using, and also are aware of the challenges that we may see when we use a particular tracer versus other.

Dr. Leuchars:

So once we have those images, how do you confirm that the tracer uptake is truly myocardial rather than residual blood pool?

Dr. Malhotra:

That's a very important question Mary. And this is going back to your second question, your previous question, which is about what has the biggest impact in getting a reliable result. And SPECT—the answer is SPECT. Everybody has to use SPECT 100 percent of the time to confirm myocardial tracer uptake and differentiate that from residual blood pool activity. And we've been using SPECT from the get-go, actually. Ten years now, we've been using SPECT, even before there was recognition that SPECT is the gold standard to confirm myocardial tracer uptake. And when you have SPECT imaging, there is very little doubt, when you review these images that have been imaged as a SPECT acquisition, that the tracer activity indeed is coming from the myocardium and not from the residual blood pool. The residual blood pool is the biggest reason for a falsely positive scan. So the confirmation of myocardial tracer activity only comes if SPECT has been performed, because if one is only using planar imaging, the planar image, because of its low resolution and spatial resolution, cannot differentiate whether the tracer activity is in the blood pool or in the myocardium.

And another important thing to remember here is that we should not interchangeably use the presence of tracer activity on planar images and SPECT images. You can have planar images that may look markedly abnormal because of blood pool, and you may have SPECT images that look completely negative, wherein there is absolutely no tracer uptake in the heart. So, in those situations—actually, in every situation—one has to rely on the tracer activity on SPECT and not on planar images. And that's why there's 100 percent utilization of SPECT across the board in every patient who's getting imaged for ATTR-CM.

Dr. Leuchars:

For those just joining us, this is *On the Frontlines of ATTR-CM* on ReachMD. I'm Dr. Mary Leuchars, and I'm speaking with Dr. Saurabh Malhotra about refining nuclear scintigraphy approaches for ATTR-CM diagnosis.

So some of the greatest diagnostic challenges come with studies that don't match the clinical picture. If you're looking at a negative or equivocal scan in a patient with a strong clinical suspicion of ATTR-CM, which pitfalls do you consider first, and what's your next step?

Dr. Malhotra:

If the test is negative, I have to stick my neck out and say here that we haven't called tests equivocal now—at least in our lab—for several years, because we are using SPECT. So either it's abnormal, wherein there is tracer uptake in the myocardium, or it is negative, and we can differentiate the blood pool from the myocardium. So there are no equivocal scans, but they can be negative scans.

Let's talk about the pitfalls first. Is there something that we did wrong that resulted in negative scan? And yes, that can happen, and that's going back to the tracer selections. If you're using a tracer like HDP—or DPD in Europe—then those tracers wash out of soft tissue, including the myocardium, much faster than PYP does. And then they wash out, they're taken up by the bone, and the myocardial activity at three hours could look suppressed, so much so that it may be called negative in these patients.

The other pitfall is, of course, relying purely on planar images, which is absolutely wrong. The visual scoring grade one, two, and three should only be done on SPECT and not on planar. Again, that can cause equivocal scans. If your planar is odd but your SPECT is not, then that's probably the most common reason why folks tend to call these scans equivocal.

Now, if your scan indeed is negative and you did it the correct way, there can be circumstances when it can be, indeed, negative.

Maybe it is early disease. Maybe this is a gene-positive patient in whom you're performing a first scan to assess whether they have any disease in the heart or not. That is definitely a possibility. It could also be that, if this is early disease, maybe the uptake in the myocardium is not diffuse, which is what we tend to see in complications, and is more patchy, which becomes tedious to delineate with plain SPECT. And the use of SPECT CT in those circumstances really adds that much more incremental diagnostic value in early disease states.

Now, going a little more beyond that into advanced topics in amyloidosis, patients can have amyloid fibrils that are not avid to these tracers, and those are called type B amyloid fibrils. And that has been reported in certain situations in the literature and especially in folks with certain mutations. And if folks have certain mutations that result in a negative study, one has to be aware of those. In those circumstances, a tissue biopsy is actually required. If your clinical suspicion is high and the patient's clinical picture fits that of ATTR-CM, then going the next step would be either performing an MRI if you have the capabilities to do so, and/or doing a tissue biopsy or endomyocardial biopsy to confirm whether there is indeed ATTR-CM in the heart or not.

Dr. Leuchars:

Finally, Dr. Malhotra, how can we translate these principles into more consistent practice, from the way studies are reported to the way specialists work together?

Dr. Malhotra:

I think one of the things that we have to accomplish is that there is a need for guidelines. The publications that we have thus far are consensus statements and not guidelines specific to how nuclear scintigraphy should be performed for ATTR-CM. I think that is the need of the hour, and folks are looking for something to guide them into practicing the right way. A lot of the practices are based on somewhat outdated information, and there is always a hesitancy to change. And I think such a guideline would not only allow for consistent application of the technique as to how to perform the study and the type of tracers, but also the way we would want to report our findings.

And also, to clarify on those findings would be the fact that grade one uptake is not equivocal, because, again, as I mentioned before, these are bone tracers and heart doesn't have a bone in it. So if you have any tracer activity within the heart, what do you do with mild uptake patterns in the heart? I think those have to be clarified further so these patients are identified accurately and, hopefully, at an earlier stage than what we are doing right now.

Dr. Leuchars:

So with that in mind, I want to thank my guest, Dr. Saurabh Malhotra, for joining me to discuss how we can enhance diagnostic accuracy in ATTR-CM with nuclear scintigraphy. Dr. Malhotra, it was really great having you on the program.

Dr. Malhotra:

Likewise, Mary. Thank you so much.

Announcer:

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