

## Transcript: IV Agents to Improve Echo Images, Value and Safe Administration

Dr. Kyle Klarich: Hello everybody, this is Kyle Klarich coming to you from Mayo Clinic in Rochester, Minnesota. I'm here today to talk about the use of ultrasound enhancing agents in clinical practice and in the research setting. And today we have two world's experts in this area. I'll introduce Dr. Mays Ali first from Mayo Clinic Florida. Dr. Ali is a non-invasive cardiologist with interest in diagnosing and treating structural heart disease as well as hypertrophic cardiomyopathy and valvular heart disease. We're pretty proud of her because she's a recent, relatively recent graduate of our cardiovascular fellowship program. After completing her medical school and residency at Hopkins University, she was, I should say, we were lucky enough to recruit, recruit her into our fellowship training program. While she was phenomenal enough that we definitely wanted to keep her on staff, her research interests do include the safety of ultrasound and ultrasound enhancing agents. So I think it's really appropriate that we have her here to speak to us about that. And as an aside, we both teach together in the Mayo Medical School where she's very passionate about medical education. Our other expert, many of you have already heard the same program as Dr. Jeremy Thaden. He's an associate professor of cardiology and practices in the division of cardiac ultrasound where he is the clinical practice chair and also chair of quality in our practice. So I think it's obviously very appropriate for him to be here on this topic. Additionally, I think all of you know he's a phenomenal expert in structural heart disease as well as three dimensional imaging. So I think we're in for a really interesting conversation today about ultrasound enhancing agents. I think I'll start with a question, really general question to Dr. Thaden to start out, what are the indications for ultrasound enhancing agents and how are you using them in your clinical practice today?

Dr. Jeremy Thaden: Yeah, thank you Dr. Klarich for the, for the kind introduction and for the question. So we, we use ultrasound enhancement agent or echo contrast in a fairly conventional way. I would say the most common indication that we use it for is for endocardial border definition. So, and I think, I think most labs would say that. So when we can't visualize two or more segments of the endocardium, we'll use ultrasound enhancement agent to better visualize. And I would say we use it in close to half of our stress echocardiograms. So probably a little bit more in the dobutamine group than in the exercise group. But overall probably close to half. And then my estimate would be probably 10, 10 to 15%, maybe a little bit more of our resting transthoracic studies. So again, most of those are for endocardial border definition, but it's also very useful for differentiation of, of masses. So we use it to look for, for vascular supply to masses, so, so helping to differentiate a tumor. I see smiling Dr. Dr. Klarich 'cause you can probably tell us a lot about that to differentiate tumor from thrombus, which would be nonvascular and then we use it or increasingly using it in TE as well. And the, when we see a left atrial appendage that has thick sludge, that can kinda help us differentiate from smoke or sludge from a true thrombus. So if we see that, if we see that enhancement agent reach the tip of the appendage, we know it's most likely sludge and not an organized thrombus. And that can help us differentiate which patients it's safe to cardiovert. But those would be the main indications I think that we use it for.

Dr. Kyle Klarich: Well that's great. So basically what you're telling me is you're using it really heavily in the stress echo lab for endocardial border definition to help with identification of regional wall motion abnormalities. But it's also pretty handy in that, for that same indication in the transthoracic practice.

Dr. Jeremy Thaden: Correct.

Dr. Kyle Klarch: Yeah. And then in addition to that, one of my passions, cardiac masses and tumors, looking for contrast enhancement of tumors to see if they have a vascular supply which can point us in one direction or the other as a clue to whether they are malignant or thrombus. And then, or or maybe even some, not too many of the papillary fibroblasts. So I'm sorry for that divergence there. I diverge. But the left atrial appendage, I think I just wanted to query you a little bit more, as we do use that not infrequently in the lab to see if the whole left atrial appendage fills in. I think it can be difficult to know how long to wait because with these patients, they have a really slow flow through the left atrial appendage. Do you have any answer, either you or Dr. Ali on that?

Dr. Jeremy Thaden: You know, when we first started doing this, we didn't have a contrast preset on our TE imaging. So, so I think one, one thing when you start is, is to meet with your team or meet with your representative to figure out a, a contrast preset for the TEE, which is helpful. But, but I would say generally you want to, you know, to start off you wanna turn your MI down generally to about 0.2 or so, and then basically you, you wanna turn the gains down and essentially I'm, you know, image the appendage and have the appendage in view before the contrast comes. 'cause I can say it is a little, can be a little bit challenging to reorient yourself if you don't have that view once the contrast goes in. So I think, you know, having your presets, having the view that you want before the contrast goes in. And then generally we give a slightly smaller dose of contrast depending on which agent you're using. We often give about half dose initially and then redose if we need to. 'cause sometimes you need a little bit less, but then as you point out, it can take a while for it to actually fill the tip. So you actually have to wait. I mean sometimes it's multiple, multiple beats and, and several clips to see it finally fill into the appendage. But if you do see it eventually fill, even if it's delayed, to me that suggests that it's not organized thrombus, that it's probably still sludge.

Dr. Mays Ali: I've waited upwards of a minute or two for the appendage to completely fill, just to confirm to myself that I can actually see the tip of the appendage. And the same thing with masses. I mean you won't see a mass and hands initially, but with vascularity, depending on the amount of vascularity, it can certainly enhance over a period of several seconds to upwards of, of a minute. And I would agree with the point about making sure your mechanical index is turned down and without having a preset on the machine, knowing ahead of time at least where your MI button is and optimizing your image before you start injecting the ultrasound enhancing agent. So that really sets you up for success.

Dr. Jeremy Thaden: Yeah, I think one of the things that I've heard from our sonographer experts who, who do a lot of contrast is your image, you know, your settings should be optimized to image the contrast, not the soft tissue. So if you, you know, if you're, if you're, if you're doing the imaging and you know the mass that you want to image is already bright, then it's gonna be harder to differentiate, you know, the bright contrast from the bright mass. So really when you start, that mass should be dark and your image setting should be optimized for the contrast and not for the soft tissues.

Dr. Kyle Klarich: I think that's extremely important point there that you really need to optimize images for contrast. And having that preset button is really helpful because some of these, some of these settings on different machines, they're all over the place and it's hard for those of us that don't use 'em every day to kind of remember where they are. At least that's my problem. But maybe not for those of you that are more technically advanced. But I think the bottom line is here that we use it a lot mostly in our stress practice, but we certainly use it in transthoracic practices, well for masses in wall motion as well as in our new, new, more newly, I would say in our TEE practice, probably in the last five to 10 years, really gotten comfortable with it, especially since we now have the myocardial index or MI settings that we can adjust for TEE appropriate imaging. So those are very helpful. Maybe I'll come back to you, Dr. Thaden, who in the lab will administer the ultrasound enhancing agent or echo contrast. And I, I'll maybe just pause here and also make the distinction I, which I read to do in the beginning is that ultrasound enhancing agents, or echo contrast is that we're talking about today is different from the saline that we use to identify patent foramen ovale. So agitated saline is a great contrast agent, but it doesn't pass through the pulmonary vascular bed. And so today we're really focusing on those, those commercially available agents that we actually can need to open a bottle and handle differently, which you might get into in a few minutes. But, so that comes back to the question then, who is the administrator of the echo contrast agent?

Dr. Jeremy Thaden: So in our practice, you know, for, for many, many years now, and certainly before I was involved in the Echo lab, we've had really a sonographer driven protocol. So we found that with, with appropriate protocols that sonographers can decide, really decide who should get contrast, kind of based on the indications that we discussed. And, and we've found with, with, with adequate training that they do an excellent job both determining who needs it but then administering. So in our practice, I would say the sonographers give the majority of contrast, our ultrasound and enhancement agent in our stress practice. There are some, some of our exercise physiologists who are involved in the stress tests who also give it, and then our nurses also give some, so we have kind of those three roles giving contrast. But, but in our practice it is mostly sonographer driven process. As far as the decision and then administration of, of contrast,

Dr. Kyle Klarich: Is that something that would be kind of uniform across the United States do you think and in other countries or do you think it tends to be given by different providers in different areas?

Dr. Jeremy Thaden: When we, I guess at least when I've talked to other, other, other institutions, it's been mixed. I mean I think, I think that there are a good number of institutions that, that do it the way we do it, but I think it's, it's somewhat mixed from what I understand.

Dr. Kyle Klarich: Yeah, I think one of the barriers has been, you know, historically has been reimbursement, but more recently just who does it and how do you get that IV start that you need. That's not as an, you know, in the stress lab we often have IVs because we're giving, you know, especially in the dobutamine practice, it's, it's part of the protocol. But anyway, I think those are certainly very, very important clinical practice issues that each practice has to consider. How they would fit into the workflow of starting an IV and then having a someone who's really expert in administrating the contrast. Dr. Ali, do you have anything else to add to that?

Dr. Mays Ali: Yeah, I would just add that I think appropriate training is really important and then recalling that depending on the ultrasound enhancing agent that's being used, appropriate storage. So some require refrigeration, some require mixing prior to administration. And so certainly goes beyond just being able to inject the agent. It's appropriate handling and mixing of the agent to ensure that it's done safely and that we can truly get all the images that we need

Dr. Kyle Klarich: As long as we're on the topic of safety and you know, training and making sure that things are done correctly. Are there any potential side effects from these contrast agents, these ultrasound enhancing contrast agents that are audience should be aware of?

Dr. Mays Ali: Yeah, so these ultrasound enhancing agents are not without potential side effects, but I think it's important to note that the majority of patients that receive these ultrasound enhancing agents do very well and they're very safe. We have seen in our retrospective review kind of more commonly seen side effects such as back pain and headache, roughly one in 200, I would say a little less than half a percent. And then patients can experience other things like flushing. We've seen things like rashes or a feeling of unsteadiness or, or this non-specific sensation of, I just don't feel right. Those tend to be very self-limiting side effects and patients will do well after 30 minutes or so of discontinuation of the ultrasound enhancing agent, there have been unfortunately some much more rare, severe and critical adverse reactions to ultrasound enhancing agents. Luckily these have been but less than one in 10,000. But we have seen patients who had loss of consciousness, loss of pulse or ST segment elevation. And then important to note that, you know, we categorize these, sometimes when we think of anaphylaxis we think, oh, someone can't breathe, they, their airway gets swollen. But we've seen things like changes in heart rhythm, heart

rate that really do qualify as very severe reactions. The good news is that they are very, very infrequent, less than one in 10,000, but everyone needs to be aware of them.

Dr. Kyle Klarich: Great. Well that, I think that was a really nice and comprehensive summary Dr. Thaden. Anything else to add to that?

Dr. Jeremy Thaden: No, that, I think that's great. I mean, you know, speaking of the, the back pain issue is, is interesting 'cause that's one that is not serious, not life-threatening and typically self-limiting but can be very uncomfortable for patients and it happens to be one of the more common ones. So there is some emerging data and on our, in our publication that we, we showed this as well that it may actually have to do with the, the essentially giving some contrast agents as a bolus. So what we've found was that in patients who received a bolus of contrast, they were more likely to get back pain versus patients who received an a steady state infusion actually got more contrast but they didn't give the bolus, they had a steady state infusion, we're actually much less likely to have back pain. So that, that is one thing that's kinda interesting that we're exploring and other publications have looked at this as well. There's some data to suggest that the steady state infusion may reduce the risk of back pain and some of these other, some self-limiting side effects.

Dr. Kyle Klarich: Well that's a really, that's a really pertinent hint that you wanna look, you know, if you can and use the steady state infusion, which I would imagine is primarily limited to those stress studies that we do as opposed to like looking at left atrial appendage contrast, we would possibly do more of a bolus sort of a situation there, but that way we can at least mitigate in some of our patients the vast majority by giving them the infusion as opposed to a bolus. I think that's a great hint. And then the other thing that you both mentioned, I think Dr. Ali may wanna expand upon this a little bit is the anaphylaxis. I think I heard you say that the anaphylaxis heart rate problems, you know, not the typical I can't breathe. Can you just expand upon that or maybe reinforce some of the concepts so people will have a sense of what to do in those situations?

Dr. Mays Ali: Yep, absolutely. So I've seen, you know, issues particularly, I'll use one example of bradycardia. So patients experiencing bradycardia and having really dangerously low heart rates with receiving these ultrasound enhancing agents. And so what's really important in that particular case is ensuring that you have an appropriately trained team and that you have medications on hand, things like epinephrine, things like atropine, essentially, you know, if you have to run a code on a patient because they are profoundly bradycardic or you've had loss of pulse, we don't think of these in the traditional sense of anaphylaxis perhaps, but these are very severe reactions that patients have had. And this is in my viewpoint honestly a, a contraindication to patient receiving any of that similar ultrasound enhancing agent moving forward.

Dr. Kyle Klarich: So would you start out obviously with the atropine to try to bring their pulse rate up possibly, you know, if it's very severe, you might be in a code situation as you alluded to, but are there other tools that you would use? You know, I think about anaphylaxis, you know, would you use solumedrol, prednisone, whether it be Benadryl, those types of things that you'd throw into the mix there?

Dr. Mays Ali: Yeah, I think that the most critical thing, I mean certainly it might be a little bit of like a mass cell activation where there's a big histamine overdrive, but I think of this as really being an effect on the electrical system of the heart. And so really using agents like epinephrine I think is probably would be one of my first go-tos. And I don't know if Dr. Thaden if you have additional thoughts.

Dr. Jeremy Thaden: So we, we have kind of protocolized the, the response, so we have this the for anaphylax anaphylaxis or anaphylactoid type reactions. And so with any anaphylactic reaction, epi, epinephrine, antihistamines and steroids are all considered important for some of the reactions that we've seen more, more recently in particular have not really involved, you know, typical either they have patients haven't had, you know, urticaria, they haven't had hives, they haven't had bronchospasm, you know, they haven't had the typical anaphylactic type reactions, anaphylactic type type signs or symptoms. And so if a patient has primarily, bradycardia for instance, we've seen patients with symptomatic bradycardia soon after contrast administration. In a case like that, I think it's reasonable to, to give an atropine if you have it. But then understandably having a a very short uh low threshold I should say, to give epi epinephrine and kind of all of these other medications if the patient remains severely symptomatic. So I think it's, it's, it's a mixed bag I think potentially depending on what the patient presents with as far as symptoms, but definitely would have a very low threshold to treat with epinephrine, antihistamines and steroids for anaphylaxis.

Dr. Kyle Klarich: Although the ultrasound contrast agents ultrasound enhancing agents are relatively safe. I mean one in 10,000 serious in, you know, reactions maybe one in what you say 200

Dr. Mays Ali: Roughly

Dr. Kyle Klarich: Have a, you know, significant back ache or headache or maybe just some unusual symptoms kind of non-specific that, so we could feel pretty assured that not only can we use them with great safety, but we have pretty effective therapies to treat the reactions that they would have. And we should withhold contrast if we think it would enhance the study. However, once someone does have a reaction then we should write it down as a, as a allergy to that specific agent is what I think I heard you said Dr. Ali, if, would you say you could use another contrast agent potentially a different, 'cause we know there's several available.

Dr. Mays Ali: Yeah we've seen, you know, our patients have had a severe reaction to one agent but then tolerated another agent. Well, so I think you need to be cautious using additional agents, but as long as you're appropriately monitoring the patient, I would say, you know, they all have different gases and microsphere and and shells and so whether there's some cross reactivity is maybe a little bit unclear. We don't have as much data so I would be more cautious but I wouldn't let a reaction to one agent preclude me from using a another one in the future. I dont know, Dr. Thaden if you feel similarly.

Dr. Jeremy Thaden: Yeah, and this is, yeah, so this is a a and also an area that's a little bit unknown and this is kind of where our allergy colleagues can, can kind of aid. So I think these patients ideally should be referred to allergy for additional evaluation. Now there's some workup that can be done acutely to see whether it's an anaphylactic reaction, but then the follow-up because one of the things that has gotten a lot of attention is polyethylene glycol. So the available agents that to today for ex except for one, so two of the three have polyethylene glycol. And so there's some, you know, some of these patients perhaps not all, but some of these patients could be reacting to the polyethylene glycol in the, you know, in the agent. So two outta three of the agents have it, it's incorporated into the contrast agent in a slightly different way for each. But this is where allergy can help us. Is it, you know, is there a specific component of the ultrasound enhancement agent that's that, that the patient is reacting to or because if it's the polyethylene glycol, then there's an alternative agent for that particular one would we would choose optison. So optison is the one agent on the market that doesn't have polyethylene glycol in it. And so as it would be a good option for those types of patients.

Dr. Kyle Klarich: That's very interesting and it sort of talks to this, the fact that we sort of lump contrast reactions into all contrast agents, but there may be some variation amongst contrast agents rather than just saying that they're all good or they're all bad in a certain patient because they had a, a secondary effect. And then one of the other questions that comes up is if a person does have, you know, the back ache headache, one of the more sort of non-specific kind of mild symptoms, would that patient then go on to possibly develop more serious symptoms with, you know, with further administration of those contrast agents?

Dr. Jeremy Thaden: So

Dr. Kyle Klarich: Or do we even know that?

Dr. Jeremy Thaden: Yeah, so we think that the, those reactions are unrelated. So we think that the, that the back ache headache, the back ache in particular we think is from a potentially

accumulation of the contrast agent, the bubbles within the renal, within the renal vasculature. And so we, we think that that those are essentially completely unrelated. So, so we don't think that patients who have back pain are likely to develop serious adverse reactions. And I, I think of per, personally I think of the back pain as a relative contraindication here 'cause don't think of it as a dangerous reaction, but I think this also speaks to having the option for more than one, you know, having the expertise to, to administer more than one contrast agent in your own lab is helpful for when this comes up. So that's another thing I I think I would advocate for, for most labs, you know, even if you have a primary agent that your lab likes to have a second agent available as another option for those patients who've reacted to a, a contra a contrast agent in the past.

Dr. Kyle Klarich: Well that's, that's fascinating. Dr. Ali, do you have anything else to add?

Dr. Mays Ali: No, I think that Dr. Thaden summarized that well.

Dr. Kyle Klarich: Well this has been a really fascinating conversation about echo enhancing agents, primarily the IV administered i, well I guess to cut all the even agitated saline IVs administered. But the commercial agents that we use for primarily endocardial border definition currently in our own practice, half of our patients are getting that in general for stress testing and another 10 to 15% for routine transthoracic. And then we have the sort of kind of niche things looking for thrombus in the left atrial appendage when you're in the presence of sludge. And then the last thing would be tumors. The side effects are by and large quite rare, but we could choose a different agent even for mild side effects if we have that capability within our lab. And lastly, the serious adverse side effects or serious adverse reactions would be treated like an anaphylaxis treating first the rhythm issues, which usually are bradycardia but then escalating that to steroids and, and, and antihistamines in order to, and then at that point in time we tell that patient that particular contrast agent and maybe if it was the per floral glycols, what could you say that again?

Dr. Mays Ali: Polyethylene glycols.

Dr. Kyle Klarich: Yeah, thank you polyethylene glycols. Then we would probably steer, steer clear of those if we needed contrast down the road. Yeah. So I think this has been a really very deep and very helpful conversation to an area that's evolving. And thank you both for your active research and leadership in this field. Thank you for taking time outta your very busy clinical practices to join us and appreciate the multidisciplinary approach here today too.