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TRANSCRIPT - GR 09 30 22 ***"Coronary Microvascular Function in Health and Disease"*** – John Lindner, MD from the University of Virginia

UVA IMR

00:19:34Well welcome everyone, Thank you, uh, who came here in person. And, thanks to those uh on Zoom as well Today I have the honor of introducing Dr. Jonathan Lindner. Dr. Lindner is currently the Vice Chair of Research in the division of Cardiology,

- 00:19:49the Director of the Translational Imaging and Research Center and the Francis Myers Ball, Professor of Medicine.
- 00:19:55He completed his Medical school training at the University of Texas, Southwestern, and Residency there as well, he went on to do his fellowship and cardiology here at Uva, where he was awarded the Dean's award for excellence in clinical teaching, and the young investigators award for the American Society of Echo Harriet.
- 00:20:14These awards, however, were just the beginning of a very productive career in cardiovascular medicine, one that would include, among many other honors, serving as the President of the American Society of Echo Cardiography, and the Chair of Clinical and Translational Science at the National Institute of health.
- 00:20:30Dr. Nalinder took his first academic appointment here at Uva for a suit where he served for eight years before moving out west to Oregon and Health and Science University,
- 00:20:40where he would go on to excel, both as a clinician educator and a researcher serving there as our cardiology fellowship Program Director, the Director of cardiovascular imaging research, and that primate multimodality imaging center at Ohsu.
- 00:20:55He has now returned back to Uva only very recently, which were very excited, as his research career has truly Ah, pioneered! Very interesting research in the realm of contrasted ultrasound for non-invasive molecular imaging in the evaluation of microvascular function and dysfunction
- 00:21:13of course we all know what makes a true academic rate is the number of patents that they hold. So Dr. Linder has two patents, you know. I think That's good. It's not great. One of them is in Australia. So you get some points for creativity. Maybe he can get up to five by the end of his tenure.
- 00:21:32So enough jokes for me is Dr. Jonathan Lindner?

Unknown Speaker

00:21:37Thank you very much.

UVA IMR

00:21:43Oh, thanks, It's uh! It's a great to be here.

- 00:21:46I will actually counter that uh, that uh,
- 00:21:50the number of patents, the impact as a as a researcher, as a translational researcher is not the number of patents. It's the impact that you have on patient care. That's what this talk is going to be

about, which is There's a lot of knowledge gaps in microvascular function and dysfunction. And there's a lot that I think that we can do at Uba to kind of address some of those gaps. It is great to be back here at University of Virginia after being gone for about sixty years. I've been keeping close tabs with my fur ends here. And There's so many people that I've I've

- 00:22:19encountered already in the two months that I've been back
- 00:22:22uh that I've known from way back, when which kind of tells you something with people who stick around for that amount of time. So uh great to be back and talking to you guys uh in person. Here's my research support. Um! Just about all the Uh Niagara one Grants and the grant from Nasa involved microvascular dysfunction. So we'll be talking about some of that stuff, and none of the stuff that has to do with industry has anything to do with my best of dysfunction.
- 00:22:45Um! So here's the outline the outline up at the top. Bad things come in small packages. We're going to be talking about the pointering micro-sirculation, and how it works, and how it goes bad. So we're going to start with coronary, microvascular anatomy and physiology. Get the foundations in through there. Talk about what's called primary microvaster dysfunction and secondary obstructive microvascular syndromes, and then finish up with just one slide on my thoughts of where we can play a role at Eva Nickel
- 00:23:13i'll put a laser pointer on there. How's that?
- 00:23:16That's right. I can use this all right. So let's start with microvascular physiology. So on the right-hand side here is an arterial. This is a technique that we use in our laboratory a lot to understand. Contrast agent vascular functions.
- 00:23:30It's in your vital microscopy, and this happens to be in a mouse and mouse muscle bed, and this mouse has a little bit of unstable blood pressure. And what do you notice about this?
- 00:23:38You see how it's twinkling. It's get bigger and small. This is Second-by-second adjustment of arterial or tone, and this is essentially what's needed. This muscle. Has a certain amount of blood flow that it wants, and this second-by-second adjustment arterial atoned is what ensures that it's getting the right amount of profusion, and the reason why that's important is from this graph. This is from Rafael Rubio and Bob Byrne as in the Burn Cardiovascular Research Center. Okay. So all of this work was done here at Uva, and really set the tone for understanding microbes
- 00:24:08for all the blood flow. And what I like to say this is Bobburn Actually, Raphael Rubio did most of this work, but they essentially showed this as if they take a dog in this case, and they increase the oxygen demand and decrease the oxygen man, or all these different physiologic interventions that the blood flow goes up and down accordingly. In other words,
- 00:24:27any increases or decrease in the oxygen demand have to be met
- 00:24:31by increases in decreases in the micro-circulation. And the reason for that is that oxygen extraction of one really doesn't change that much changes a little bit, but it doesn't change that much. So you have to essentially increase the decrease of what your demand is, and it is actually the microcirculation that determines what that flow is. So just a review of the circulation. As you guys know, the arteries and veins. The arteries is where we as cardiologists spend a lot of our time with extense, but it's the least interesting vessels in my mind, so they resign on the surface of the
- 00:25:01where they are unperturbed by contract all forces. But then you've got the microcirculation which resides in the muscle, and there's so much blood volume. This is such a dense vascular supply that at rest. As you're sitting here, about five percent of your heart, mass
- 00:25:16is the blood vessels in the microcirculation. It can go up to as high as fifteen percent of the mess during hypermia, when blood vessels kind of open up, really astounding.
- 00:25:25And this is essentially what it looks like. This is from a a rat heart. Now most of the gatekeeper in terms of resistance. So whenever you want to increase or decrease, flow, you have that increase or decrease, conductance or resistance, which is the inverse, and that mostly happens in arterials, and to some degree capillaries as well.

- 00:25:44So when we start talking about dysfunction of this microvascular. Ah! These microvascular units people have come up with the schema of classification. This is one of them from one of the most prominent microvascular groups which is in your Palokamichi. Um, I don't find this to be helpful at all, you know essentially, they say, microvascular disease, and the absence or presence of coronary disease or intrinsic mycardial disease, or I atrogenic
- 00:26:09microvascular dysfunction, like, when we go in the balloons and knock stuff downstream into the micro circulation I don't find this to be that helpful instead. What I find to be helpful is to kind of talk about what is the mechanism? Because if you're going to choose a therapy to treat microvascular dysfunction. You got to know the mechanism right? And so that's how I prefer to classify things. So let's talk a little bit about the classification, and how microvascular this structure happens.
- 00:26:31So here's a micro-circulation. So here is the big artery which goes into and in blue. Here is the macro-circulation. Red green is the microcirculation. And so inside the muscle here we have large arterial small arterials where a lot of the resistance is controlled. Okay. And then the capillaries. Now, a lot of how arterials kind of react, whether they dilate or constrict has to do with the pressure within them, whereas more distal microcirculation responds to metabolic
- 00:27:00forces. Hypoxemia need for substrate. Now, here are all the things that can essentially go wrong with the vessels that are in the scheme here. So big vessels. You guys already kind of know about
- 00:27:14coronary artery. Disease is the Biggie, but we can also have vasculitis that affects them, spasms,
- 00:27:19vascular spasm, and myicardial bridging in the small vessels. Here's what we got so in the arterial or circuit where a lot of the resistance is regulated by squeezy relaxy. You can have vasomotor abnormalities, but you can also have obstruction in both the arterial as well as the capillaries. And we'll talk about that.
- 00:27:38You can also have issues with external forces. Okay, things that are essentially on the outside of the vessels pressing in, and we'll talk a little bit about that. And then there's this thing called riology, and I'll. I'll describe to you what reality is. But down here is essentially where there is, you can see where the resistance is offered at rest, and during Hyperemia, so that at rest most of the resistance that's essentially controlling the low amount of blood. So the heartbeats arrest A kind of medium amount is from the arteriol or tone, and then, during exercise, everything dilates, and most of the resistance shifts

Unknown Speaker

00:28:07to the capillary bed.

UVA IMR

00:28:10All right. So now let's start talking about things categorized in terms of the mechanisms for microbes or dysfunction that we may see in our patients the first thing that most of you guys probably think about when you, because most of you have heard about microvascular dysfunction. Right?

- 00:28:23Yes,
- 00:28:24yes, just even if it's no just give me a Yeah, that's good. So most of what we kind of think about our bases of motor abnormalities too much squeezy. Okay. So what do we mean? You know, how do we kind of define this in terms of hemodynamics? So here's what we mean. So I've shown you this already. This is um endogenous um uh vasodilation that I show you that the auto regulation would be uh with uh,

- 00:28:50come out of that
- 00:28:50um endogenous auto-regulation of an arterial And what that's doing is it's trying to keep your blood flow where it needs to be So This is the auto-regulatory curve at rest, which says
- 00:29:01A normal heart means about one Ml. Per minute program of tissue. And if your blood pressure goes up where your blood pressure goes down, or you have a little bit of a pressure loss because of a stenosis, it still keeps it at one Ml. Per minute program of tissue, because you have all of this adjustment.
- 00:29:15Now, if we give a vasodilator, essentially, what happens is this. So you're going to see an arterial running up and down here on the screen. I'm dripping adenosine onto this prep. And look what happens. This is not sped up. That is real time of what happens with adenosine. We do, and you like in the stress lab.
- 00:29:31What that does is it opens up all the vessels so that your resistance is fixed at a low level.
- 00:29:38If resistance is fixed at a low level, then your blood flow is essentially just, dependent upon your profusion pressure. So normally we can increase blood flow by about five-fold.
- 00:29:48All right. So that is essentially what we call flow reserve, and that's what's normal
- 00:29:53Now when we think about microvascular dysfunction we're thinking. Most people think about this, which is instead of during maximal hyperemia. This curve is tilted a little bit. So you, just for whatever the pressure is, you don't get as much flow. Okay, because the micro vessels are not responding in a way that they should,
- 00:30:09and that can even happen at rest. So people don't talk about that as much, but this can actually happen at rest.
- 00:30:14So that's what we consider to be abnormal vasomotion. However, there's another way
- 00:30:19that abnormal flow reserve can happen. And I want you guys to remember this because it's really important for understanding what it means when you actually get a number of spit out at you from a pet scan. It says, Flow, reserve, so flow! Reserve is just the ratio of this flow of this flow. So if you're resting, blood flow is higher and classically. That's because you're tachycardic or your hypertensive or your anemic, Then, essentially, even if you're even if your hypothesis is completely normal.
- 00:30:47You'll have less flow reserve right now. Interestingly, a lot of people who have microbasket or dysfunction have increased resting flow without any reason for it, and we're starting to investigate that and figure out why it is. It's obviously a metabolic problem and a problem with substrate use. But that's ah just something for you guys to kind of keep in mind.
- 00:31:05So what does this abnormal kind of vascular response look like? Well, again, here's the normal. Up at the top is a normal auto-regulating bed
- 00:31:16here's at the bottom. This is what Microsoft looks like. This is from a model that we we actually observed in our laboratory. Do you guys see that it looks like that arterial has has a girdle on it? Okay, you guys who are twentieth century, Do I need to explain what the girdle is.
- 00:31:32Yeah, yeah, no, we're not going to do that. So you can see that this vessel is essentially just spasm all over the place. And here's what's interesting, which is, everybody loves to say. Oh, microvaster, dysfunction only occurs because of spasm and arterial, as it turns out, capillaries also have some contractile elements in them. So this is a capillary with individual red cells just struggling to try to get through this kind of spasm.
- 00:31:57Ah, ah, capillary. And the reason for this is the capillaries actually have mias and an optimism. Okay, And that's really important when we start trying to figure out who's going to respond to what drug? Because inhibiting Mycen and an actin may be a way to to essentially rescue capillary microvascular dysfunction. But I just wanted you guys to put eyes on kind of what this looks like. It's pretty drastic as well.

- 00:32:19So if anybody ever comes up to you and says, well, I know the mechanism for microbes or dysfunction of why the you've got this this kind of spasmy stuff going on. Forget it, they don't. And the reason is that every single patient is different. It is complex, or the regulation of arterial or tone into some degree capillary of,
- 00:32:37is a balance between bases of dilators and basic constrictors. Here's all the vasodilators I can think of, and these are constrictors. The Edvs are the end of feudal derived Pasadena, and it's even more complex in that which is, they come from all different cell types. They come from not only the end ofelium, but they can't come through muscle cells that can be circulating the myocytes. Even your erythrocytes and platelets have things that are basic constrictors, and these are dilators to affect their own regional local environment. And so really micro vascular dysfunction can happen from
- 00:33:06almost any cell type that's gone awry, but also any imbalance between vasodilators and days of constrictors.
- 00:33:13So if we just take one of the cynicquinons of microvascular dysfunction, which is that that which is associated with hyperlipidemia. So just take a look at dyslipidemia the mechanism for essentially abnormal base evaluators is incredibly, very
- 00:33:30dyslipidemia's cause Ras activation. It causes decrease, endivial nitric oxide bioavailability nitro oxide is a a pretty powerful base of dilator, and it's from a lot of you know, in this subsection there's a ton of different mechanisms decreased. Substrate that a large name decrease production increase in inhibitors like Atma uh scavenging of N. O. From the oxygen species. And then there's Thrombo inflammatory processes from this epidemia. But also this lividemia causes all of your blood vessels to be
- 00:34:00way more sensitive way more sensible. So I’m not using. I'm the only person seeing my laser pointer here. Sorry this lipidemia has caused a tremendous amount of sensitivity to any basic constrictors that happen to be there.
- 00:34:12So the bottom line that I’m trying to get across to you is any one disease State is not just one thing that's causing microbes or this function like this with the data, it's really complex. And if I just take something like the reactive oxygen species.
- 00:34:25Reactive oxygen species can happen from all of these different things that can go back and essentially create microbasket dysfunction like diabetes hyperplycemia, hypertension, smoking, hyper epidemia. And then this increased reactive oxygen species downstream from it is a bunch of abnormal daze of motor patterns
- 00:34:43so the lesson that I'm trying to give you is this is really a complex process. A patient can have multiple different disease states that feed into microvascular dysfunction and downstream from that are a bunch of different pathways that can be activated, and because of that really one of our best things to do, besides giving a bunch of
- 00:35:00vasoactive agents is to try to treat the underlying causes. Right. Quit the smoking, treat the hyper lipidemia, et cetera. So that's going to be one of the lessons.
- 00:35:11How do we find people clinically who have microvascular dysfunction?
- 00:35:15This is the most common pathway which is Somebody comes in with symptoms, and we send them for non-invasive testing stress. Ecgs tricycle stress fusion imaging with nuclear or even mri in this institution, and they're found to have something positive Now, if they do have a positive scan. There are some patients who you say this can't be coronary artery disease, either because they're not in the right category, or they've had a prior angiogram, or Ct or an Antio.
- 00:35:41In that case you have a presumed diagnosis. But in order to really make the diagnosis, you have to rule out the destruct of coronary order disease. Okay? And then essentially, you have the diagnosis. You say, Okay, this is what I think is going on. You have symptoms. You have an abnormal stress test. You have no cardio disease. Now, some patients actually get some, but not all. Get um sent for advanced diagnostics,

- 00:36:03and we're going to talk about those advanced diagnostics here in a second. They can be either non-invasive or invasive,
- 00:36:09but the importance of essentially nailing down this diagnosis is for the following reasons: When I have patients who are who are sent to me. For you know, microbes or dysfunction, this is often what they look like at the beginning of the visit.
- 00:36:22There's probably some smart Alex in the zoom room who are looking at this saying, Actually, that's what the patient looks like at the end of your visit. Jonathan.
- 00:36:29Yeah, I'm done there. So number one. Patients do not like this diagnosis mostly because of how they are treated by the health care. Environment, number one. Often the symptoms that they have are not mild, even though we don't think about it as being a serious disease. It is a serious disease, and it can cause significant symptoms.
- 00:36:48Symptomatic patients are really dissatisfied with being told. Well, you Don't, have any blockages and not having an explanation.
- 00:36:55The prognosis for microvascular dysfunctions, i'll show you, is not the nine, and there are currently available therapies that work. There are new therapies that are being evaluated. And if you don't make the diagnosis, you're not going to go through therapy. So that's why it's important to make the diagnosis. And Here's just the prognosis thing. So this is males and females with cornary flow reserves that are normal down here and abnormal, and this is May's major address cardiac events.
- 00:37:20The prognosis for microvascular dysfunction for maze is every bit as high as if your positive stress test was from coronary artery disease.
- 00:37:27Okay, So let's get on the therapy bandwagon and see what we can do for some of these patients.
- 00:37:33All right. How do we work this up? So you got a patient who, you say? Ooh! Well, this person may have microbes or dysfunction, but kind of a classic patient. Not that old more common in women, a lot of stress, some hydrolyidemia, maybe some type, two diabetes. So how do we actually do the advanced diagnostics? Well,
- 00:37:50you can do a couple of things. If you're looking for arterial spasm, you can actually look at the diameter of big vessels, and that essentially requires coronary and geography. While you're giving a bunch of basic violators. You can also measure, just flow reserve with certain vasodilators, and that essentially looks at the capacity for the entire network.
- 00:38:09Or you can do things that are actually a little bit more nuanced, like measuring microvascular resistance, microvascular resistance.
- 00:38:17But the issue also comes up. What vasodilator am I going to give somebody. So here's all the different basal dilators that we have used to essentially test microbascular functions, and you can see some of them are more geared to It's bigger vessels or medium vessels, or there are more distal circulation.
- 00:38:33And so you know often what we do Is we use a couple of different base or dilators to pretty much knock down the location of where the the problem is, but also whether it's endophilial, dependent or not, which helps us define how a patient is going to respond to therapies.
- 00:38:50Now. Word of warning, which is, i'm talking about microvascular dysfunction. Then you've heard me mention arterial spasm they're not necessarily distinct at an entities. These are, I won't go into detail of these studies, but the bottom line is, There is a lot of overlap
- 00:39:05kind of makes sense right? If the small vessels are having some problem with their day's emotion, why wouldn't the bigger vessels as well, Right? That's also why people who have microvascular dysfunction sometimes will have rhinos, and they often have migraine headaches and all kinds of other things like this. So So just be aware that you never really necessarily have pure disease.
- 00:39:24So how do we work on Microsoft's function? If you think somebody's got it, They've already had a positive stress test. They don't have a a small vessel's disease. Well, here's the thing that you can

do. Number one. As I said, you can do profusion imaging during base of dilator stress, and it has to. It requires a a profusion imaging quantitative technique, and that means quantitative pet quantitative. Mri, although very often on Mri, you'll see this subject of cardio defect and contrast echo, which is a technique that I helped develop here at UVA, back in the nineties with the

- 00:39:54other folks where we can actually do within seconds bedside for fusion imaging. And this is just an example here in the distal septum of a blood flow abnormality right there. From Microsoft dysfunction
- 00:40:04You can also send these people to the Cath lab for a three hour affair, where we put a bunch of different wires flow wires and pressure wires for the coronary arteries. We measure their blood vessel diameters during basal virus stress we measure the flow, reserve, and we can even measure microvascular resistance by measuring the corner a flow and pressure relationship. Right?
- 00:40:25So it's not important to know for internal medicine folk it's not important to know all of these techniques. What's important to know is there are techniques that are out there that are invasive and non-invasive for really walking down this diagnosis. You just have to use them correctly.
- 00:40:41Now in terms of the work up for these things. The Us. Does not have guidelines on this, but the Europeans do, and the European guidelines really are kind of funny. They essentially have two different figures saying how you can go about this, and the first one is what I just told you, which is a patient, has symptoms that get some sort of a stress test, and then you prove that they don't have any coronary artery disease, and you're done. You just make the presumptive diagnosis The other way of doing it is what I just showed you, which is, you do some other techniques
- 00:41:08that can essentially use different laser dilators, such as squirting and adenosine, and then squirting in some acetylcholine and figuring out whether or not. Something is a big vessel or a small vessel, and if you are dependent or independent, so that you can get what's called your inoka endotypes, What's going on. Inoka is Ischemia with no obstructive coronary disease.
- 00:41:29Now, here's the problem which is, you can do all of that work.
- 00:41:33Does it really matter in terms of how we give you therapy. And right now the answer to that is no,
- 00:41:39there is no precision. Medicine
- 00:41:42approach to sit there and say you're going to respond to this drug or that drug, or this approach or that approach based on you know whether you respond poorly to acetal calling versus adenosine, which work in different parts of the the micro circulation and through different pathways.
- 00:41:57So what are those therapies? Well,
- 00:41:59here are all the therapies that have been tried, and we use in clinical practice, So nvd is people who have vasomotor micromasco Dysfunction. This is a big Vessel dysfunction with spasm and this is from essentially disordinomia disease, mostly of the diabetics that can essentially cause abnormal fluorescent.
- 00:42:16So here's all the things from microbasket, dysfunction nitrates calcium channel antagonists ah combined out inergic, Agnes all the things that you think about in terms of vasodilators, other things that you may not have thought about, certain medications that are kind of specifically targeted to Ischemia as well as other things. Here's a very interesting category, which is Rokkinis, and it's a
- 00:42:39is a kinase that phosphorylates mice and light chain. And so it essentially makes your actin myas and more squeezy if you will. So if you inhibit that you essentially get not only arterial or vasodilation, but also possibly capillary dilation as well.
- 00:42:53So those are all the drugs that can be tried. The problem is, we can't predict which patient is going to respond to any of these.
- 00:43:00So essentially it's a trial and error type of a thing, and I think we can do much better on that, and that's one of the main gaps that we've got right now.

- 00:43:08Now, here's the other thing that you guys have to do and have to know about for microbes, for dysfunction, which is, besides the drugs you have to tell people to do, the stops. And here's all the things that you need to tell them to stop smoking getting stressed out. Stop using illicit drugs, stop taking over the counter and energy supplements that are essentially things that are stricter.
- 00:43:26Stop your light. Is it lousy? Diet me right. Stop sitting on the couch. Stop screwing with your Circadian rhythm. It's a long story. But yes, or Kadian actually has a role in all this. Stop paying the doctor who tells you It's all in your head, and stop obsessing over national politics, good luck with that one.
- 00:43:42So those are all the things that you can do in terms of medical therapy and counseling patients who have microbascular dysfunction. Now from vasomotor dysfunction. Remember, we're still in the vasomotor category.
- 00:43:55Now, the other thing that I told you about is treat the underlying disease
- 00:43:59treat the underlying disease that's causing it as well, right,
- 00:44:03and it actually works. So here's just an example. This is an extreme example. This is from our laboratory, where we use contrast to the measure, myocardial profusion and patients with severe hyperlipidemia. Okay. And so on. One day we measured their microvascular blood flow and their myocardi which was abnormal because their cholesterols were sky high, and these people got sent that same day for, like a protein apheresis, where we essentially suck all the like proteins out of the bloodstream, and that same day we measured the my Cardio blood flow, and what we have
- 00:44:32into it went up,
- 00:44:34and if we actually take the plasma from Pre in the post, and we do these what's called coronary Ring tension essays in response to acetylcholine. You can just see that as we've taken
- 00:44:43the the plasma, the Ldl out of the plasma. We've actually made these vessels much more likely to respond to physiologic phase of dilators.
- 00:44:55So I won't Go into the mechanism of that. It's just a good demonstration of treating the underlying condition. This is another study of Hyperlidemia also to some degree. It's not strong, but to some to be treating Diabetes melodies. And this is actually something that actually has great relevance here at Uva. Um Gene Barrett and I back in the <unknown>unknown<unknown>s and early
- 00:45:13we're studying this other people who have essentially taken over this, that there is a lot of very interesting vascular signaling from insulin that you can actually make better in insulin-resistant states.
- 00:45:24Um
- 00:45:26The way that you can essentially treat microvascular dysfunction is prevent it from happening.
- 00:45:30At all. And this is where actually the Nasa's story. So the net. This is where the Nasa Grant comes in, which is really kind of fine. There's a tremendous amount of stuff that you guys don't know that's going on at Nasa to try to protect astronaut health.
- 00:45:42It makes sense, because you know the worst pr disaster in the world, for Nasa would be like an astronaut dying on our way to Mars or back. That's really bad, plus you lose a crew member skill level, which actually puts the whole crew in jeopardy. And so Nasa is extremely interested in this and they've engaged. Ah! My services, together with my co-investigators to understand what happens in with space, an exposure of of the heart to the blood vessels that could be dangerous. And so essentially what we're doing right now. We're studying astronauts of,
- 00:46:11for during and after long duration missions on the International Space Station, where I have to go down. Monday, Tuesday. I was down in Johnson space that are doing some of these studies. So in low Earth orbit we're studying microgravity stress of confinement in a little tin can with a bunch of people. You may not like microbiome changes with the diet that they have, but also a little bit of radiation. There's extra radiation up in orbit.

- 00:46:36Now we're actually funded for like twelve more years, so that we can measure uh changes that happen. Assist Lunar Mission. Some of the missions around the moon with the Artemis program, which is having some problems for anybody who's been watching the news. Um! And in those studies we're going to actually be studying galactic radiation and solar radiation, which are big players. Radiation is a huge issue with causing dysfunction of many organs in your body, and the reason why we want to do this is, we want to develop mitigation strategies that are going to protect
- 00:47:04the big vessels and the small vessels from having injury from the microgravity to the stress, and especially radiation. So what is this radiation, by the way? So we live here on earth and we're protected? We're protected on earth from radiation because of something called the ban. All,
- 00:47:18then, Allen belts are the ionosphere, and it essentially blocks most of the solar radiation. Ah! And galactic radiation, however, in deep space beyond, about the one thousand miles or so you get exposed to some. Really, I I won't. Go into what these elements are, but they're toxic and they're nasty, and they're nasty to a lot of things with the blood dust. They cause oxidative stress. They cause endopelial dysfunction. They cause inflammation. They cause coagulation, and they decrease your ability to repair
- 00:47:47causes. All of these things, including micro vesco dysfunction and early coronary artery. Disease Most of the Apollo Mission that astronauts died of early coronary artery disease.
- 00:47:56So with my two co-investigators, we're part of what's called the cipher project we're actually figuring out how radiation, especially with space radiation, essentially triggers, microbascular and macrovascular dysfunction and atherospheres so interesting side out there.
- 00:48:12So that's vasomotor funniness. Okay, So Now, let's talk about realologic abnormalities. So anybody here know what riology means?
- 00:48:22No, no former biomedical engineers or anything. Riology is essentially the study of how things kind of slip through the vessels right. It talks about, you know. It takes into account essentially um viscosity and branch point function of blood vessels like that. So let me explain to you kind of what riology is is kind of all about. So here's a graph showing you arteries, arterials, capillaries, vaniels, veins. And this is the intermicardial component

Unknown Speaker

00:48:49as blood is flowing through the

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00:48:52this is on a log scale of blood velocity. Blood has to slow down as it's going through the capillaries in order for it to do its thing to essentially release oxygen, gather up carbon dioxide and give you nutrients to your tissues that they need.

- 00:49:08So it has to slow down, and yet you don't want slowness in your big vessels. Otherwise you'll never get anything into your your organs. And so a lot of the slowing down happens to be from the increased relative cross-sectional area from capillaries. If you add up all those capillaries, it's a much bigger cross-sectional area than your heart is right, but that's only part of the story. The other part of the story is riology, biology, meaning that when blood goes into capillaries
- 00:49:34it's no longer a fluid
- 00:49:36for those of you who are nerds it's called, and a non-newtonian fluid right it's no longer uniform. Essentially you have particles like red cells that actually have to deform because they're bigger than the size of the capillary. So they have to be formed. They interact with the Glycolics. If you guys remember what that is, and you have plasma skinning on the outside. And so there's all these

things that essentially determine realology, and a lot of work has been done over the last forty, fifty years on this, so that once you get down to the small

- 00:50:06vessels like the capillaries, the relative apparent viscosity of blood. Because of this non-neutonian nature becomes very high. In other words, blood becomes more viscous at the capillary levels because of this
- 00:50:19and that's a problem That's a problem for certain disease states, because in order for you to become hyperimic, you need to be able to have red cells slip through the capillaries really quick. So this is a muscle bed. I've got fluorescently labeled Microbes as a marker of kind of red cell velocity. Here this is at rest
- 00:50:37down here is during Hyperemia.
- 00:50:40You can barely see those guys, can you? I mean, there really is zipping through there. Imagine if you had essentially sludging at the capillary level that wasn't allowing that to happen. Well, the sludging happened. The answer to that is, yes, and here's my good example of this. This is a patient of mine that I saw in clinic.
- 00:50:56She came in. She had P. And H. You guys know what P. And H is per-axis or nocturnal in an area. It's a disease where you have too much complement attacking your red cells and your red cells become very unhappy. They lice. They're bigger than they're supposed to be. They're abnormal deformability.
- 00:51:11And she came in with a cardiomyopathy that was not from coronary artery disease. And these people do develop coronary thrombosis. But that was a it.
- 00:51:19I did a vasodilator of contrast, echo, study on her. And this is what the data kind of looked like you guys, don't know what this means. All I can say is this blood by the rate constant of this curve is about five times too slow during hybrid it was striking. It's just like
- 00:51:35whoa that is sludgy. So she actually got put on anti-c five therapy with the equilibrium
- 00:51:43Her ef came up to forty seven percent. And I said, Whoa! Wait a second. Maybe she was like diffusely ischemic, because of all the sludiness. And so I re-measured her vasodilator capacity, and sure enough, her red cells were essentially slipping through much faster.
- 00:51:58So this is a great example of essentially a real logic cardiomyopathy. Somebody who is chronically ischemic because of sludge. Does this happen in other disease? States? Of course it does sickle cell. So
- 00:52:10I had a grant on Nih Grandon's sickle cell for many years, where you're actually studying this and for sickle cell it's not just because the sickled cells are stiffer and Don't go through capillaries Whenever you have homolysis of red cells, you release free heat,
- 00:52:24and whenever you release free heat, that's what preheme does. It sucks up all your nitric oxide, and you do not flow really well, right. And so, because of that, you know, studies that we've done, and hard and skeletal muscles all have shown that if you've got sickle cell disease, your blood is not moving through your small vessels quite as well, and that can be contributing to ischemic syndromes. And interestingly, if you give sickle cell patients in this case it says Hc. Here this hydroxyeria therapy for sickle cell disease converts. Essentially it makes the red cells
- 00:52:54plus more Hebrew and F is the mechanism, but essentially it made cells, you know, Zip through a little bit faster. So these are examples of real logic abnormalities. Now, the other thing that you guys do on a weekly basis or a monthly basis is, you give blood products to people who are anemic. But guess What
- 00:53:12if you give fresh blood versus old blood? The old blood looks different. The red cells, the red cells aren't real deformable so they can't squeeze through those capillaries, and old blood has more free. Heme release just like a sickle cell.
- 00:53:26And because of that, when you transfuse people with old blood rather than new blood. You actually get

- 00:53:32a slower blood flow through the microcirculation to just remember that next time you give somebody a massive transfusion or something, and somebody who may have severe hyperlimidemia and a little bit of other things react to oxygen species.
- 00:53:45And the reason why it's important is, is, I'm not going to go into all of these, but there are actually therapies for what we like to call erythrocytopathies. Okay, things that essentially cause the red cells to be kind of abnormal, and I won't go into all of them. But the bottom line is, some of them are directly active against the the red cell processes themselves.
- 00:54:04I want to finish up with kind of one last concept
- 00:54:08for micro vascular dysfunction, which is the last classification which is obstructive or compressive disease.
- 00:54:19So we've talked about vasor motor abnormalities. We've talked about reology, which is sludging, and this is kind of like sledging. But this is more obstructive from the inside or compressive from the outside. Now we're not going to talk about post-mi microvascular. No reflow that's a whole lecture in and of itself. But you guys know that
- 00:54:36any organ that undergoes is schema. If you allow reflow to happen, a lot of the vessels don't be open, and it's from a lot of stuff. It's from edema and frombosis. That is a form of microvascular dysfunction. But, um! We don't kind of classify it as that just because it's just kind of has its own, its own deal. So what disease states are we talking about? We'll talk about really, first of all, anything that can cause a micro vascular obstruction. Okay, And here's a good example that's pregnant right now. Covid
- 00:55:06Covid: nineteen. So you guys probably have had plenty of lectures on Covid and know the path of biology.
- 00:55:14But my guess is, you, Haven't necessarily thought deeply about what happens to the small vessels of the heart or other organs. When you have severe Kovat infection.
- 00:55:30The most common reason for it is Rv. Dysfunction for stuff that's going on in the lungs. But you can have Lv dysfunction as well, especially in in the Icu. Now that can happen from a traditional Myo site of infection, essentially a myochromatitis, or it can be from inflammatory. Myorities from the cytokine store. Okay, you essentially cause a.
- 00:55:51You can also have the takasubo or stress cardiomyopathy from being so sick. Ah, but there's also these disease states that are essentially from an endotheliopathy. Centrally the virus getting into the endothelial cells, or the cytokines affecting the end of real cells and smooth muscle which essentially cause constriction and promos.
- 00:56:12And I've got a grant going on right now where we actually studied Kovat nineteen, and it would be the predominance of this mechanism.
- 00:56:20This is just a patient who is coming in with a Covid. So this is a patient, you see, St. Elevation. So she had been in for two days with a Covid infection started healthy chest pain, besty elevations.
- 00:56:31Ah, Angi Graham looks okay in the big vessels, but there tends to be some of this distal funniness going on through here a little bit of pruning, and when I did contrast echo at the bedside on her, I could actually find a perfusion, defect highlighted by the arrows there, and a ped fusion defect over here, and a couple at the tips of each papillary muscle. So this is essentially spotiness,
- 00:56:54profusion, abnormalities.
- 00:56:56And And this is what I'm talking about with Uva having a role in this, which is, you know, there's very few centers that essentially can go in and do bedside profusion, imaging to be able to diagnose these things right? You tell me what can you know? Go into to a critically ill, patient, and measure their microvascular fusion of the bedside. And so this is an example of a brombotic engeiopathy
- 00:57:16brought on by a viral infection Covid in this case that essentially triggered an obstructive micro vascular dysfunction. And there's other things that can do this as well like the primary ones. Ttp:

- 00:57:29the I see h us right, all right. Other things that can cause things like this. Um. Drugs, adverse reactions to drugs. So this is Punat Nip anybody from hemong here.
- 00:57:44Oh, all right for for it Has anybody heard of that nip?
- 00:57:50Yeah, Excellent. So Pennsylvania is a third-generation tyrosine kinase another
- 00:57:54and um everybody wants to use it because it's effective against drug resistance. Cml: It's a some degree aml as well, so everybody wants to use panet, and the problem is, if you use penet and them at pretty high doses that are pretty effective. Uh twenty percent of people get stroke or heart attack.
- 00:58:10Okay, now, nobody goes to the Kathleen, because generally they're all in like some sort of crisis or something. But who wants to raise your hand here if you want to use a drug that causes a twenty percent of a rate of stroke or heart attack
- 00:58:23first year, a year and a half. It ain't going to happen. And so people are not using it, and it turns out that that is a third generation. That also is very broad spectrum. So this was an interesting story because the people who are studying this, some of the world's most famous cardi oncologists. They came to me and said, Hey, you got the way of essentially figuring out what's causing this, And in some of your techniques that you develop what is causing this, and what can we do about this?
- 00:58:48So, um
- 00:58:51next slide. There we go. So we essentially use some of the techniques that we developed that you have just seen, which is for fusion imaging, but also molecular imaging from wrong will a brand factor and platelets to essentially come up with what is going on and what is going on. I won't, perseverate on this is, you get tiny little blood clots in the small vessels of your heart. That's what's causing this in it all because you've got too much font willibrant factor on your blood vessels that are creating platelets. And this is what's creating things like this, which is a big wall motion abnormality in this
- 00:59:21mouse. Yeah, we can do, Mouse echo. So this is a big wall-mush in atomality, and you can see that the blood vessels of this mouse are just fine. It's the small vessels that are affected.
- 00:59:29So we kind of came up with that. And why is that important? Well, it's kind of important, because we can now apply this information to to humans to be able to treat them if we can have the techniques for diagnosing this form of microvascular dysfunction. So This is a patient who's admitted. This is when I was at Ohsu, and
- 00:59:46I came in with chest pain, St. Elevation. You can see there now. This person was a Cml patient on panet, and they were in blast crisis, and they had plate with a count of ten. Do you think that I could talk a Cath lab doctor, into taking this person into a cath lab for a pci.
- 01:00:02You ain't going to take them. So they said, you we ain't doing that, you know. Treat them conservatively, Work better, whatever you can. I took one look at this patient's echo that was done at the bedside right around the time that that first Tkg was done. You see this, Walmart? And you guys see this Walmart in.
- 01:00:17Does anybody see anything interesting about that that heart? What it's interesting about that heart. The Walmart's. Now that that area is thick, it's not thin, classically in a schema. Everything becomes thinner, not thicker.
- 01:00:30That's weird. So we did profusion, imaging what you're seeing, and on the uh upper right here, and what you can see here is these: You see those tiny little black holes in there. A tiny little folk looks like a leopard pattern. That's essentially the hallmark of a microvascular antiopic roboticantiography. So what we did was we essentially took the the drugs in this case in a single system that worked in our mice. And we said, Well, if you're not, then take them to the Catholic. We're going to give you something that I think may work against, that. We're against this process. And sure enough, we made his sts come down. We need to.

- 01:01:00His proponents go down, and he died about two weeks later from some other thing from a bowel rupture, and we got his heart, and we actually found the remnants of a thrombotic Antioch in his heart. So that's a great story of how you can think
- 01:01:13you're aware of these disorders as an internal medicine doctor who's treating patients in the Icu with sickle cell
- 01:01:22with Ttp. Who are receiving tyrosine kind of you can essentially think a little bit more freely if you're aware of these microvascular syndromes, and you know there are people around can help you make the diagnosis and help guide your therapy. Um one last form of microvascular dysfunction. That's obstructive that I want to talk about.
- 01:01:41Be compressive. Okay? And people don't talk about this enough.
- 01:01:46And here's one of the disease states. That is kind of the cynical known of obstructive microvascular dysfunction, which is hypertropic part of my office. So people have known for years that flow. Reserve is really abnormal and hypertropic pretty well, and maybe one of those things that actually causes the heart to become a little bit fired when you get these microphy processes in the heart that trigger erythmias in hypertroves.
- 01:02:07If you look at the blood vessels on the hypertros on histology, they look at normal they're bigger and they've got medial hyperplasia. And when I do contrast, echo, do you see these little and diastically Here you see those little rhymes in the muscle, the right lines. These are really big,
- 01:02:23dilated, huge, intromicardial arteries, and the reason why they exist is because of this abnormality that happens in hypertropic cardiomy and hypertrophic cardiom in in normal hearts. Here's what happens when your heart squeezes when your heart squeezes
- 01:02:39blood in some of the big arterials gets shoved backwards, Okay, Squeeze goes backwards into the big vessels that take the blood that's coming forward and backwards, and they act as capacitors and then discharge it right. Well, guess what. If you've got hypertrophic cardiomyopathy, and you are not relaxing properly,
- 01:02:56you don't get the discharge, and so these vessels tend to become bigger and bigger and bigger, and you tend to get less flow into the heart, especially less flow reserve. And that's why people have been able to show a relationship between lower blood flow, reserve, and more likely to have scar in the heart from
- 01:03:13ah on delayed enhanced gap. Here's what it looks like. So here's an apical four chamber View somebody with hypertropic cardiomyopathy. What do you notice about the septum compared to this area? You don't have to be a contrast eco- expert it's darker isn't it, it's less blood flow. These are the uses, the kinetics I won't go into all this. The bottom line is, it's incredibly common
- 01:03:33to have abnormal microvascular blood flow in the absence of coronary artery, disease, and hyperotropic cardiomy. And it can be transmeral. It can be diffuse some endocardial patchy. Okay, very few people actually have completely normal blood flow.
- 01:03:48I will go into this. This. I will tell you that if you do something to resolve the gradient, these three patients. Just look at these two patients. These are two patients who had low blood flow.
- 01:04:00They got myectomy.
- 01:04:02They got on myectomy. That's it. They hacked off a little portion of the septum. They relieved the gradient on these patients, and after leaving the gradient on these patients, they actually got in both the high perturbed and non-hypertrophy regions their flow reserve recovered
- 01:04:18meaning that you don't get that, you don't have those really high intromyocardial pressures if you don't have an systolic systolic blood pressures of two hundred and eighty Right?
- 01:04:28All right. Does that make sense to you guys?
- 01:04:31Yeah. So um, it's not just hypertrophic. You have to think about other disease processes. Where this happens. Auretic regurgitation in aerodynamic agitation. What happens in diastaly when they're supposed to be for blood flow into the myocardial micro-sticulation.

- 01:04:44There's blood flow coming back into the Lv cavity it distends the heart; it increases, pressures in the heart, and it essentially compresses those poor little microbath vessels, especially in the end of Cardiac Desynchrony left on the ranch park.
- 01:04:56People have always said, Why do we? Why do we get chest pain with left bungle branch block?
- 01:05:02Why is that happening? And why do we see profusion defects in some of these people? Well, some of the reasons is because when one part of the heart is squeezing, the other is trying to relax, and that part that's squeezing is preventing the part that's trying to relax from having his blood vessel something.
- 01:05:16And then there's myasite Edemia ah edema, for example, from the Skeeva Reef fusion and trace of just a demoscentric compression. So these are all three things that are treatable. Right? We leave gradients from hypotrophic cardiography fix aortic reggitation, re-synchronize Patients these are All things that can actually prove microbascular. Ah! Problems from compressive forces.
- 01:05:38So second to the last slide here, what are we doing here in? Ohsu? Well, one of the things that I've been tasked with when I was recruited back here was to essentially start a microvascular health unit, both clinical and research. Every patient that goes into. This is going to be a research subject in my mind,
- 01:05:53and the reason that why this is the right place to do it is, we have tremendous skill in cardiovascular imaging that is needed for this. Both Ct. Mri, contrast echo, but also, you know, people in the Cath Lab
- 01:06:06who are, you know, extremely interested in microvascular diseases. Okay, uh, you know, starting with Rogasa many years ago. And now, Angela Taylor um Microvascular physiology is something that is extremely strong here, starting with Bobburn and Brian dooling and continuing to this day. But we also have data scientists. You know we have this whole school of data science that's going up. We need people to essentially help us with massive amounts of data that are going to come from the Ehr Radiomics, imaging data to be able to
- 01:06:36essentially come up with a personalized, You know, program personalized medicine program for microvascular dysfunction. We can't do it without everybody's involvement, though there's so many different
- 01:06:46um Ah! Fields and areas of specialty that need to fill in. Ah need to. Ah put into this whole process because microvascular dysfunction is not a disease of cardiologist's disease, and just about every ah some specialty,

Unknown Speaker

01:07:01What? I

UVA IMR

01:07:02and I hope that I've been able to convince you of that today. So here's our summary for today.

- 01:07:09Hopefully, we've learned a couple of things um besides just vascular physiology. So number one abnormalities at the microbastro level are important in the path of biology of both acute and chronic cardiovascular diseases. We have new methods for interrogating for microvascular dysfunction.
- 01:07:27We should use these, and we should use this more often uh therapy is directed at the micro circulation, whether it's from these or motor abnormalities or oppressive forces or obstruction. Um. They've been slow to develop just because of the complexity of the underlying path of biology.

However, they are being diverse. They are being developed. They're diverse in their actions, and I think we have to have ways of being able to predict response, using some of the tools that we have. Uh. And then, Lastly, I think your Uva we really are poised uh to essentially, really play on a major role

- 01:07:57and refining these pathways.
- 01:07:59So that is it for me. Thank you so much for your attention. Thank you. People on Zoom who have ah, who have engaged in in all of this. I'm happy to take any. Ah, any questions

Unknown Speaker

01:08:22you might just

UVA IMR

01:08:24whoops.

- 01:08:25Excuse me
- 01:08:30the the of kidney disease and cardiac microvascular issues, Any merit in studying the change after kidney transplant
- 01:08:43in the
- 01:08:43Oh, what a great question! Who did that come from? That? Came from Swaki Row?
- 01:08:48Yeah. What a great question! Yeah. So the answer to that is that that field absolutely is something that is just right for study. If you think about all of the things that actually happen,
- 01:09:00and with you know, with end-stage, renal disease, and with dialysis, you have these huge cataclyamine surges every time you go on dialysis. You've got the you know markedly increased Ah, cytokine levels that that play a role in Thrombo information and microbes or dysfunction, and some of the things that actually, maybe you know, there are some people who believe that microvest or dysfunction in the kidney itself, as things start, worsening is one of those things that essentially increased the trajectory of renal dysfunction
- 01:09:28The problem is that it is almost untouched as a as a
- 01:09:33Uh, as a mechanism. We do see a lot of patients who develop chest pain, and sometimes some of the Kg. Changes and some little proponent leaks, and you know we often write these up to Oh, well, this is, you know they don't have court. They may not have obstructive corner yard agencies, and we just sit there and say, Oh, this is hypertension from dialysis, or this is from a uh, you know, a thick heart without the hypertension responses. The bottom line is, I think there's something there, and I think we need to study it.
- 01:10:08How are you, Dr. Loa? Good to see you again?
- 01:10:11It's only been eighteen years.
- 01:10:13Thanks for the talk, Dr. Lynn there when we're talking about how we fix the cardio coronary disease either with stenting or with bypass. Is there a big difference in what happens in the microvasculature when you do one versus the other.
- 01:10:27Yeah. So stenting generally, unless you're causing things to go downstream. And you've got iitrogenic microvascular dysfunction stenting will essentially not affect microvascular flow, with two exceptions. So number one:
- 01:10:42If If stenosis is severe enough that it's actually a limiting forward flow, remember there are endotherial, dependent days of dilator mechanisms. And if you've got essentially a tight enough stimulus upstream that you never really get to hypermic. So whenever you are maximally vasodilated and hybrid from exercise

- 01:11:00a lot of the vessel. Dilation happens because you have a metabolic dilation downstream, but you have to have flow-mediated-based vibrations. So the vessels slightly upstream dilate and Don't become part of a problem. If you don't have the increase in the vasoderation downstream, You're never, you know, because of stenosis you're never going to get the secondary phase of dilation and a few of the pendant dilation. Not only that,
- 01:11:21but those mechanisms tend to be a little bit down regulated so number one. Just by opening up the blood vessels you may get better microvascular function. The second thing is, is, any time that you have microbes or dysfunction in addition to epicardial coronary artery disease. That is, you know that's essentially a double whammy, and because there's actually an ongoing study right now to actually look at the prevalence of microvascular dysfunction after pci in patients, and whether or not they respond to, to, for example,
- 01:11:50a facet of a ro kinase in the other.
- 01:11:53Thanks. Sure,
- 01:11:57Jonathan, I really enjoyed your presentations. It's all. It's something new to me.
- 01:12:02The two things that came to my mind was, and the patients with diabetes. Okay, Who?
- 01:12:10We can obviously looking at the eyes. See that you've got a lot of micro vessel disease, Because and what is puzzled me is that when we, even though we open their large vessels, they it does nothing to
- 01:12:28to you know, to the scheme that that's going on in their toes, they still lose their pros. The second point, which is more common, are the patients who have caught just
- 01:12:39hypertension,
- 01:12:41and they have arterial, or with a constriction. So in that situation again, you would have disorders in micro-vascular circulation. Okay, And are the current therapies that we are using improve the microscope circulation.
- 01:12:59Yeah, so it's A. It's a nuanced question. It's going to be a bit of a nuanced answer. So I'll start with the easy one, which is the hypertension, which is a lot of the drugs that we use to treat hypertension actually from the pathways that they go after
- 01:13:14by definition, are treating certain forms of bas on motor abnormalities. Right? If if if increase in ras is actually part of microbes and dysfunction, or cheap people ace inhibitors, or a r B. It works if we're treating patients with beta blockers from the sympathetic uh tone, it works. And so a lot of the calcium Channel antagon. So all these things that we use for hypertension essentially are helping you. You are absolutely correct at things that actually, once you get essentially a stiffness of the blood vessels. So you know hypertension over time. The
- 01:13:44it increases your elastic modulus, your elasticity of your blood vessels. Once those vessels become stiff you get stiffness all along the whole arterial or tree. And what happens is you just don't. You essentially have a decrease in the conductance even before you get to the microcirculation. So it's kind of additive to the micromas of this function in terms of the diabetes spot on any time that you see kind of microvascular abnormalities, whether it's from protein or the kidney, or from a retinal examination,
- 01:14:13you can pretty much be sure that there is some abnormalities in the micro circulation. The only problem is, the studies that have been done today have not really been that strong in showing a great connection with severity of these micro vascular uh complications of diabetes and the severity of the functional abnormalities from um. You know, there's a whole other line of research that people like Ben Horton, you know are studying trying to study with, uh, you know, responses to insulin. So in insulin is a big bases dilator. If you guys don't have, you know, through any of
- 01:14:44another question here in the chat from Dr. Abate, I believe. Great job. Can you comment on sex differences in hormone?

- 01:14:52Oh, yes, so. Uh, so Antonio probably noticed that estrogens were essentially something that we consider using, and people who have severe microvest and dysfunction. So it is much more common in the pre menopausal uh a female population, microbesque or dysfunction. People are trying to figure out why that is a a lot of it does have to do with the we, you know,
- 01:15:14because it can respond to hormones. The exact pathways are not known. However, you can actually take
- 01:15:20a um, you know, ever since Sex, as a biologic variable became something that was important in funding grants. But a lot of people now kind of studying these things, and you can essentially find, with every pathway that I show you, whether it is ah, you know, increased sensitivity to basic constrictors like end upeline or decrease nitric oxide or ah impaired smooth muscle, you know response to adenosine.
- 01:15:46You can find papers that essentially say that there are sex differences based on hormonal levels, so which of them is most important? I don't know,
- 01:15:55and I'm not sure anybody can answer that. But he's spot on that that the kind of middle-aged female population is a much more common population to have this this disorder, and it tends to, as they tend to go post Menopausal, and get older. It tends to essentially lessen over time.
- 01:16:19A little answer. But in the maybe a younger population who has microbastier disease from perhaps like a problem not thromb himbolic, but micro-thromb by a process you talked about.
- 01:16:32Do they? Have you ever seen them get worse ischemic pain with better blood pressure control because they're taking away that profusion pressure.
- 01:16:42Yeah, it's a it. So there's somebody who's kind of thinking about physiology right? So
- 01:16:49higher blood pressures essentially will increase my Cardio oxygen demand by increase in wall stress. But at the same time, maybe you need that higher pressure to overcome as robotic Tangiopathy. As it turns out if you've got to thrombotic and geography, What you've done is you've obstructed a microvascular unit. Okay, And if you've obstructed the smallest microvascular unit it's feeding eight capillaries. If it's further up into the fifty microns you're obstructing about sixty to eighty cap rates, so the bottom line is, if you are destructed, it doesn't matter where your pressures are.
- 01:17:17You ain't going to get past the obstruction now in other forms like daes of motor. Yeah, maybe you do need just an increased profusion pressure in order to kind of get through there. The problem is any time that the blood pressure is higher. Probably your vaser motor tone in your microcirculation is also high,
- 01:17:34so the there is such a thing as actually going too low on the blood pressure. Then you are hypo brief. So essentially. What we try to aim for is normal attention.
- 01:17:44Big surprise there, eh?
- 01:17:49All right. Well, this was fun. These were good questions. Um attentive audience. Thank you so much for coming, And if anybody has any other questions, text me email me. Come, find me. I'm around Now,