BAIREY MERZ: So I was asked to talk about coronary microvascular dysfunction and diastolic heart failure. I hope to convince you that these are two epidemics, and that they may help us understand some of the disparities that we're seeing where female cardiovascular disease outcomes are not as good as men. So let me see if I can convince you of that.

These are my disclosures. Of course, we always disclose these days. I don't think any of this represents conflict of interest, but you can decide.

OK. So here's kind of our setup. We're going to talk about coronary microvascular function as well as diastolic heart failure. We'll talk about CMD, which is now what it's being called in both the American journals as well as the *European Heart Journal.* It's actually in the guidelines, in the European ischemic heart disease guidelines. Diastolic heart failure, which is probably a term that you know better as HFpEF, heart failure with preserved ejection fraction. And then we'll talk about these two and whether or not they're related.

So you've seen this in many journals. Non-obstructive CAD rates are high. They always have been relatively high, but they've been climbing, and there's a lot of hypothetical reasons why. Maybe the aging epidemic, maybe because we now include in study women. Might be the statin epidemic. Some epidemiologists think that our population is turned into cholesterol fed rabbits. We don't smoke, so we don't have these big obstructive plaques anymore, but we have plenty of fatty atherosclerosis because diet hasn't really changed.

That said, this slide shows that women are much more likely to have no or non-obstructive coronary disease when they have an ACS and they get an angiogram. And it's pretty consistent.

We were asked by National Heart Lung and Blood 20 years ago, in response to a program announcement to study this phenomenon, we now call it coronary microvascular dysfunction.

Here's a case example published in circulation a number of years ago. The representative panel A is an abnormal exercise stress test. It looks like there's a proximal or mid LAD lesion. Panel B, of course, shows that there's no obstructive coronary disease when they go up to the angiogram. Panel C is where we take it a step further. Instead of doing an FFR, as you would do for an obstructive lesion that you were trying to decide about how to handle, you do a CFR, coronary flow reserve.

And what we were able to show in the WISE is that these women very often had microvascular dysfunction, meaning their coronary flow reserve in their small arterioles was-- the dilation was insufficient. So when they exercise, when they are under emotional stress, they have genuine angina and the ischemia due to a low coronary flow reserve.

They also often have elevated left ventricular and diastolic filling pressure-- 15, 20, even 25. This is, of course, in the absence of a reduction in ejection fraction. There's no valve disease. There's no cardiomyopathy or myocarditis. So it's an unexplained elevated filling pressure.

And then we also did intravascular ultrasound early on in the WISE, and demonstrated that well over 90% of these women had atherosclerotic plaque, despite having quite normal appearing angiograms. Suggesting that these women, including some men, are able to have a lot of atherosclerosis without really showing us the obstruction or luminal irregularities.

When we look at other data sets, as we have with the NCDR, as others have done in Europe with their large registries, this phenomenon appears to be about 80% women, so it is female dominated. With our outcome data, we've also estimated that we have over three million women in the US, and the outcome data suggests that this is a higher morbidity and mortality than a female specific disease like breast cancer. So this really is something we should all be paying attention to.

Here's data, again, from systematic reviews published initially with Bugiardini and JAMA. And then here's a more extensive one demonstrating one year clinical event rates in patients-- and these now are women and men, not exclusively women, with non-obstructive CAD. And basically, you see that the event rate is not benign.

Anything that you read in an older textbook-- or even some of the contemporary textbooks now-- still call it cardiac syndrome X. Signs and symptoms of ischemia, but no obstructive coronary disease. And that old prognostic studies suggested that this was benign, that this did not have adverse event rates, including myocardial infarction, death, stroke, and the development of heart failure. So we need to re-learn, we need to rethink that, and we need to change those textbooks.

We've also demonstrated in additional data sets-- I had a Canadian fellow who then went back and is working on those big Canadian registries that are as rich in phenotype being as the Europeans and the Scandinavians. And she was able to demonstrate with Karen Humphries, an epidemiologist in Vancouver, that it is the women with non-obstructive CAD that appear to have the elevated risk compared to men.

And we're now linking this with their pharmacologic data as well as they'll be exploring pharmacologic genetic to see-- well, number one, to ask is it because the men get treated. And a lot of our registry data suggests that men that have angiograms end up on statins and women don't. And so it may be just a real simple treatment issue. Versus whether or not there are true hard-wired genetic and epigenetic, women are XX and men are XY. And there may be hard-wired differences that account for some of this prognostic difference.

So working together with an international group, we have tried to sort of redefine myocardial ischemia. And again, if you look at our US journals and our US RFAs, and our US guidelines, we don't call it CAD anymore, coronary artery disease. We call it ischemic heart disease, IHD. And it's either stable ischemic heart disease, SIHD, or IHD that is unstable in acute coronary syndrome.

So what you can see in this diagram that we published in the*European Heart Journal* is there's lots of ways that you can have ischemia. And when you think about this, you already know this. You know that there's this ischemia in HOCM. You know that there's ischemia in left ventricular hypertrophy-- we used to call it LVH with strain.

So it's not that big of a cognitive shift if you actually think about what you learned in the textbooks. But basically, you have that epicardial coronaries, which have been the last 35 years of our interest and turned cardiovascular disease mostly into plumbing. And we have atherosclerotic disease, stable and vulnerable plaque. We have vasospastic disease. Some people will still call this Prinzmetal's angina, and that can be in the setting of obstructive coronary disease or not.

And what we really have not paid a lot of attention to, but we have modalities now that will tell us about it, including pat, including invasive coronary flow reserve, is our micro vasculature.

Now again, if you go back, and especially if you're an interventional cardiologist, the code word for this, sometimes to get some recognition on the radar screen, is collateral flow. And then the lights will come on, and they will say, oh, yes, I know about collaterals.

But all of these are mechanistic pathways for ischemic heart disease. And indeed, they can overlap. So as you might imagine, ischemic heart disease is complicated and multi-factorial.

All right. So let's talk a little bit of more about the micro vasculature. Again, a diagram, a picture sometimes saves us a thousand words. It's very clear in other areas where you have issues dealing with the myopathies, that you will have adverse coronary arterial remodeling leading to ischemia, leading to evidence of ischemia even in simple testing like exercise stress testing.

We also know from these cardiomyopathic problems that myocardial fibrosis as well as adverse remodeling can then be evident and contribute to these downstream consequences. And these downstream consequences have been observed in our coronary microvascular dysfunction patients.

So now we're starting to interrogate these mechanistic pathways. A, to understand CMD, and if and how and when we might want to consider treating it. But even more importantly, because we have this other epidemic, called heart failure with preserved ejection fraction, and there may be some commonality in these mechanistic pathways that we have described in these myopathies.

All right. And then one more pictorial diagram. This is something that we worked hard on early on in the WISE, trying to understand why-- and at the time, we were only studying women-- why women, in the setting of risk factor conditions, which are pretty standard traditional risk factors, could develop so much plaque without any obstruction.

And looked at issues of reproductive hormones, because again, this is one of the big differences between women and men, certainly worth a look. Doesn't always explain everything about heart disease. Sometimes doesn't explain anything, but it's always worth a look. And you always get asked about it, so you have to study it.

And then looking at inflammatory pro oxidative stress and other things that are different. Women have different autoimmune disease across a lifetime. And Haynes' data shows us that when women enter menarche, they pop up their CRP, where men stay the same. So it makes a lot of sense that there probably are pathogenetic mechanisms in terms of how women and men deal with different insults to a better or less well degree, and that this might not fully protect women, but just might make them look different, or it might make their atherosclerotic burden look different.

We also did a lot of work with testing the micro vasculature and who and how is controlling the micro vasculature. Because again, it is dominantly free of atherosclerosis. And these are the resistance arterioles, they are very much controlled by the autonomic nervous system, as well as its own local control, endothelial function and non-endothelial.

We've spent a lot of time with our MRI, looking at diastolic function, and validating these tissue tagging. As well as other newer software packages to sort of try to get away from this echo controversy of is it real, is it not real. We're interested in Takotsubo cardiomyopathy, because this may actually be the most intense expression of coronary microvascular dysfunction. No one has proven that yet, but it's certainly a leading hypothesis.

So we're pretty interested in all of these areas. It's very interdisciplinary, and it involves not only physiologists, physicists who work the magnets, but psychologists and sociologists who are looking at things like stress and environmental factors that contribute to sympathetic nervous system activation. So it's pretty fun. It's pretty holistic, and these are the areas that we're looking.

OK. This is just one example of something that we've now been funded to get started on. Magnetic resonance imaging, like ultrasound, has no ionizing radiation, in addition to being our best estimate of LV mass, LV volumes, valvular disease, aortic stiffness. Increasingly, it is used in, for example, in the UK, it's dominantly used now for myocardial perfusion, rather than SPECT. So we're behind Europe in that regard in using a modality that is pretty good for perfusion.

For obstructive disease, we are working very hard with different imaging. This is a postdoc in DB Ali's lab demonstrating that these rim artifacts-- if any of you are MRI folks, MR perfusion for subendocardium has been marred by this Gibb's ringing artifact. And we are working hard and have good preliminary data, now funded to go forward with this, to demonstrate that we really can consistently see the subendocardium compared to the subepicardium.

And again, if you think about anything that you already know, like a HOCM, or a left ventricular hypertrophy, or an aortic stenosis ventricle, the subendocardium is going to get hit first. And so being able to see a different kind of regional ischemia, not epicardial coronary disease, I think will be increasingly important as we go forward with our aging epidemic and the different forms of ischemic heart disease.

We published this in *Circ CV Imaging* last year, demonstrating that we now can detect coronary microvascular dysfunction. These were exclusively on our wise women with a sensitivity and specificity that rivals SPECT for epicardial obstructive coronary disease. So we do have a tool now that is noninvasive, and we hope to continue to translate this into something that is guidelines-based and increasingly available in our US population.

We've also demonstrated that perfusion in these patients portends an adverse prognosis. So previously, our prognostic data was cath lab-based, either just demonstrating non-obstructive disease, or demonstrating a limited flow reserve. And we do flow reserve invasive testing when needed to help with disease management, to try to decide what to do with a young reproductive aged woman, whether or not to load them up with cardiac drugs, but it still is an invasive test. And so to have a non-invasive test that actually can help you understand who should and who should not possibly be treated is important.

We've also been able to document the natural history of coronary microvascular dysfunction. This is an abstract one of my fellow presented last year at the ACC in San Diego. And when we look at all comers that qualify having symptoms and signs of ischemia but no obstructive coronary disease, if you look carefully, about 10% have had a prior MI, either by history, positive troponins, or by late gadolinium enhancement.

And as you know, MR is really our gold standard for seeing relatively small infarcts. Echo, of course, SPECT, can see big infarcts, or clinically significant infarcts, as they would tell us.

But as it turns out, about 10% of these patients have evidence by LGE. And then we were able in a one year follow up study of a little over 200 patients to be able to demonstrate about a 2% annual new infarct rate. Again, this rivals obstructive coronary disease, although the infarcts are relatively smaller, as you might imagine, because they are in microvascular territories, compared to more segmental infarcts that you would see in obstructive coronary disease.

We see all sorts of different patterns, as you might imagine, because again, this is not in an LAD left circ diagonal obtuse marginal territory. And these used to be called myocarditis, but when the magnet doesn't see any evidence of myocarditis, it's unlikely to be myocarditis.

And when you're presenting with patients that have symptoms and signs of ischemic heart disease, they have evidence of ischemia on some kind of stress testing, then it looks like, smells like, it feels like ischemic heart disease, it's just a different phenotype. And we're increasingly calling this female pattern, although probably about 15% of these patients are men, so it's not exclusively women.

Again, here are just examples of these infarcts. And some are small, some are large. They are definite infarcts, no doubt about it. And they're also not diffuse fibrosis. This isn't a Fabry's. This is not some other unusual. This is ischemic heart disease. And these patients often have traditional risk factors. And as I showed you in the IBIS data, they've got atherosclerotic plaque. So this isn't sort of a completely different disease. Again, we think it's just a different pattern of presentation.

Again, just a couple of case examples. I just always like to show this, because in cardiology seeing is believing. And I can show you spectroscopy numbers, but people tend not to believe it.

So again, you know, here's a 56-year-old woman. She's diabetic, she's dyslipidemic, hypertensive, persistent angina history of NSTEMI. And here's scar. And it's not in a traditional pattern.

Similar 26-year-old with recurrent MIs thought to be due to recent ramus artery spasm. She had a history of multiple miscarriages. And again, if you take careful histories, many of these women either have autoimmune disease or have gestational complications of pregnancy-- preeclampsia, eclampsia, gestational diabetes.

She had a mid myocardial scar basal Sept. So lots of scar. She had an integral MI, meaning she had positive troponins. But at our one year follow up, we didn't detect any more scar. So it was either in the same territory or it is conceivable there are false positive troponins, or that our LGE protocol, it was so small we didn't pick it up. We didn't give her enough.

All right. And then is there any relationship to this stress induced or otherwise known as Takotsubo cardiomyopathy. And again, you've all heard the story about why it's called Takotsubo. It was not described by Dr. Takotsubo in Japan. It was described by Dr. Teraoka. But Takotsubo is these Japanese fishing jars-- and I still don't really understand why the octopus can't get out, but they say that it can't. I've seen octopuses in aquariums, and they look like they get out of anything.

But the classic is that it is after some type of typical psychological mental stress, it is in this setting of intense sympathetic stimulation, and investigation has documented that sort of a catecholamine storm. It's characterized by the cardiologist doing the angiogram or the echo as apical ballooning of the left ventricle, a pretty standard-- looks like the octopus fishing jar.

Recovery-- and I've seen recovery in hours-- but days to weeks. And we and others have demonstrated persistent abnormal coronary microvascular dysfunction slash endothelial dysfunction Amir Lerman has showed at Mayo after recovery. So these women are not normal, despite not having any obstructive coronary disease.

And that's the question, again, is this related? This is another epidemic that seems to be female dominant. It's hard to know how much of it is a true new epidemic, and how much of it is now that we actually study and look at women, and we take people to the cath lab and we pretty consistently do echoes in anyone who looks like they're having an ACS. It could be that we're just doing discovery of something that's been there all along.

All right. And then, again, back to asking, are aspects of coronary microvascular dysfunction perfusion sort of the background? There's a lot of silent ischemia, for those of us that did that research in the '80s. And so would there be silent microvascular ischemia, and then it just presents one day after an intense catecholamine storm into Takotsubo. So again, research is ongoing.

We are moving now to try to understand diastolic dysfunction, diastolic function, and whether or not any of these are related. Again, mostly because of this female phenotype that HFpEF appears to be mostly women.

All right. So we're going to move on to diastolic heart failure. WISE women with or without documented ischemia have elevated MACE. This was one of the first aims of the WISE National Heart Lung and Blood said, cardiac syndrome X in small data sets, typically no more than 100 or 200, mostly women, mostly young women, followed for two to three years have an excellent prognosis.

Is that true? Study enough women-- we studied 1,000 women in the original WISE cohort-- and we followed them initially for five years, and now we have ten year death rates. These are seven year MACE rates. The MACE non-fatal MI, hospitalization for heart failure, stroke, cardiovascular death, as well as all-cause cardiovascular event, a combined event rate.

And what you can see, of course, is that we have fairly high rates compared to a reference control group of Women Take Heart, which is 10,000 women who underwent exercise stress testing and risk factor evaluation. They all had to be asymptomatic. It was a community asymptomatic reference control group.

And what you can see is a fivefold increase in events. So these women with open arteries, but signs and symptoms of ischemia, are at increased risk. And you know, this was sort of one of the first deliverables to National Heart Lung and Blood.

Notably, the most frequent event was hospitalization for heart failure. And with a case selection, we have validated this. And it is heart failure. [DING] It's not something else-- that's just telling me I should start this lecture. And so we had a tenfold combined heart rate-- well, it still thinks I'm on California time, I think.

And this was a surprise to us, because we saw the atherosclerotic burden, we saw the traditional risk factors. I mean, if you have a diabetic dyslipidemic and hypertensive midlife woman and she has a heart attack, who's surprised? She has a stroke, I'm not surprised.

But she develops heart failure within seven years with a normal ejection fraction-- often a supernormal ejection fraction. I think our mean initially was in the mid 60s in the WISE. So that didn't completely make sense to us. And again, when you see something that doesn't make sense, then you're curious and you want to try to figure it out.

So we did validate this. And in fact, it genuinely is heart failure. The heart attacks really are heart attacks, and the heart failure really is heart failure. And clearly what we saw was at seven years, a relatively higher development of heart failure compared to myocardial infarction.

And as you see, subsequent a WISE study has shown that these infarcts are fairly small. So these aren't LAD infarcts where ejection fraction drops to 35%. So the suspicion was these heart failure hospitalizations likely were heart failure with preserved ejection fraction.

OK. So let's look a little bit more about this. This is non-WISE data, but this is stuff you can look up pretty much anywhere. Prevalence of and mortality from heart failure by gender. We have an equal heart failure prevalence, so women and men in the US today have the same amount of heart failure, but women have a higher mortality. And this is despite adjustment for age, because if you look at any kind of registry data, women on average are older, in part because they live longer than men.

But this is a total mortality that is more adverse for women. Indeed, women represent a minority of women in heart failure trials, and this is very similar to our ischemic heart disease trials. And women comprise 6% to 38% of heart failure trial participants.

So then is it that surprising that women have a higher mortality? All of the things that we've tested have probably been inadequately tested in women, and perhaps inadequately deployed in women. That's certainly something we see pretty regularly in the ischemic heart disease field.

And yet what you're going to see is that there's probably a pretty good reason why there weren't very many women in these heart failure trials. They didn't meet entry criteria. And why is that? Because they don't have reduced ejection fraction. And all of those heart failure trials were HFREF trials, right? That's the heart failure we know. That's the heart failure that we've tested. And actually, we have pretty good therapies for heart failure.

All right. So again, back to national demographics. Distribution of ejection fraction among men and women with heart failure, most heart failure in women is HFpEF So number one, they're ineligible for those previous trials. And number two, what therapies do we have for HFpEF? So under-treated, but there is no good treatment yet that we think we know about.

Here's a summary of the clinical trials of HFpEF, and these are directed at what we think are mechanistic pathways. We of course have tested left ventricular performance and wall stress with dig and diuretics. Those were early trials. Those were negative.

We also looked at activation of the RAS and sympathetic RAS initially, first, ACE ARB, as well as most recently, aldosterone blockade. And we can debate the [INAUDIBLE] trial, whether it was positive or negative, but it couldn't have been real positive to have two sites mess them up so badly.

How about the sympathetic nervous system? Well, actually these are the two positive trials. Relatively small, but they were outcome trials looking at beta blockers. Hmm. Starting to sound like maybe ischemia is involved.

And so the question is, is coronary microvascular ischemia-- again, thinking back to our myopathic problem, because these are people that have heart failure with preserved ejection fraction, so that to me tells me that there's something wrong. It's a myopathy. And is this a mechanistic pathway for HFpEF.

All right. So let's summarize and then I'll show you some new data. CMD is more prevalent in women. CMD, again, coronary microvascular dysfunction. It's a mechanistic pathway of ischemic heart disease. 20 years of WISE as well as other investigators, again, in Europe, in Japan, in Canada solidify this bulk of evidence.

Heart failure with preserved ejection fraction is also more prevalent in women. It's also a mechanistic pathway for heart failure, heart failure hospitalization as well as adverse outcomes. No doubt about it.

So now let's ask the question, and this is our new data, is CMD related to HFpEF? And if yes, by what mechanistic pathways? And again, why are we bothering to do this? Because if we can figure out mechanistic pathways, we can start testing either traditional drugs that we know go after something like ischemia, or novel pathways, novel drug pathways.

All right. So let's move on. So magnetic resonance imaging made a big leap forward with this tissue tagging. And this is a very reproducible, very valid, less susceptible to loading conditions, less susceptible to operator and angulation and all of the things that you need a really good echo core lab to consistently be able to measure diastolic function.

And this is the work of Mike Nelson, a postdoc that has been with us for a number of years and on his way to UT, University of Texas, for a faculty job. This is an example of how we look at this. And again, the grids that are taken as we slice the heart and get a complete package, where not only do you get asystole and diastole, but you get tau, which is pretty important to trying to figure out what the ventricle's doing in diastole.

So here's initial study that Mike and I published, again,*Circ Imaging.* We had 22 cases, which were WISE women. And these were WISE women with coronary microvascular dysfunction, so they were presenting with ischemia. They were not presenting with heart failure.

And what you can see is they're pretty well matched to our reference control group. We have a magnet reference control group of midlife women that are age, hormonally matched, as well as body surface area or BMI matched. They just don't have risk factors and they don't have ischemic heart disease. They have to pass a stress test.

Our global MPRI stands for myocardial perfusion reserve index. This is an index. This is not absolute blood flow yet, although we're working on that in the magnet. And what you can see is that our cases have a reduced flow index. Again, this is a non-invasive coronary flow reserve, where our controls have a normal perfusion index.

Our WISE patients are most often middle aged, overweight. They have preserved ejection fraction. Traditional risk factors, while they are most frequently present, do not explain much of the variance in coronary microvascular disease flow reserve. So while risk factors appear to be part of the deal, they are permissive, they are not determinative, and clearly something else is going on.

All right. I have too many circles. So here's just an example of our circumferential strain rates as well as our tau. And you can see that there are differences even in this relatively small case matched set in terms of diastolic function.

And again, you know, this could be related to ischemia. This could be related to hypertension. It wasn't related to LV remodeling. It was not related to ejection fraction, simple things that we can measure.

So already WISE patients have diastolic dysfunction. Probably not a big surprise, but this now starts to explain why their filling pressures are elevated simply at rest when we put the pigtail catheter down.

Well, another thing that we've been able to do with the magnet is MR spectroscopy. This time for myocardial fat infiltration. This is not pericardial fat. This is not epicardial fat. This is not even visceral fat, in the sense that it's not the same as fatty liver. But it's sort of-- it's going in that direction. It's actual triglyceride infiltration of the myocardium itself.

And what we were able to demonstrate is our WISE subjects, again, in red, compared to our reference control subjects, again, had much worse circumferential strain, much worse diastolic dysfunction, but they had elevated intra myocardial triglyceride.

And you can see a nice correlation here between the extent and magnitude of triglyceride and their diastolic dysfunction, suggesting that this may be either causal, or-- well, it's clearly associated. So hard to know exactly the cart and the horse, but the idea came around by animal models where hearts that are ischemic resort to fetal fuel utilization. And then you can have fatty buildup in the actual muscle itself. And could this be contributing to the stiffening?

And this would certainly be a novel hypothesis that links diastolic dysfunction with ischemia, and also a mechanistic pathway, meaning you could go after the triglyceride infiltration if ischemia therapy did not work. So greater myocardial triglyceride infiltration, an inverse relationship between myocardial triglycerides and diastolic dysfunction.

This is not our work, but something as we go forward with this new project we will also be looking at, the magnet is very good for looking at issues of aortic compliance. And women and men differ in terms of aortic stiffening, and they have a differing relationship. This is color coded similar to a lot of other things, where the women are in red and the men are in blue. And you can see that the women have much more linear relationships between diastolic function of the left ventricle and aortic compliance or aortic stiffness, where the men don't.

And this, again, is likely a contributor to this HFpEF epidemic that, again, is mostly women. And this is something also that the magnet can study pretty easily. You don't need to do yet another measurement like [INAUDIBLE] or a pull back when you're in the cath lab.

So this is what we're actually testing in this new project, and we call it the microvascular ischemia heart failure with preserved ejection fraction hypothesis. We think we've shown this in early WISE studies. We think we have also contributed to the knowledge here. So now we have two knowledge gaps, one is that repeated ischemia reperfusion episodes, similar to what I showed you on that LGE, those recurrent-- that 10% that have existing MIs when they're studied, and then that 2% per year of new MIs. Small MIs, repeated ischemia reperfusion episodes facilitate preconditioning and preservation of cardiomyocite contractile and microvascular function against ischemic injury. These women are not dropping dead as much as obstructive epicardial coronary disease, and yet they are ill.

Ischemia reperfusion, then knowledge gap number four, and preconditioning lead to cardiomyocite fat accumulation, relaxation impairment resulting in diastolic dysfunction and heart failure with preserved ejection fraction.

And this is the protocol. We have an invasive arm as well as a non-invasive arm. The invasive arm is basically to nail these concepts down. We'll be using the Millar catheters, which are old-fashioned but back, because we're pretty interested in diastology and pressure volume loops, and a bunch of provocative stressors.

Again, people like ischemic heart disease. They look pretty good at rest in your clinic, and then they go out and do something and have a heart attack or develop heart failure. So like we learned 50 years ago with obstructive coronary disease, you gotta do stress testing to see that their reserve is limited and to identify disease before they get sick.

And then we're working, again, to maximize the magnet for pretty much one-stop shopping for ischemic heart disease as well as heart failure and myopathy. We also will be doing some coronary magnetic resonance angiography, again, working with DB Ali, who's been able to demonstrate quite well in China that he can see epicardial coronaries.

So again, trying to catch up with the CT angiography and offer a modality that could look at for obstructive coronary disease without radiation.

All right. And then this is our fairly complicated protocol, but we're just getting started. We've been able to do it in a couple of microvascular ischemic patients and one HFpEF patient. They were able to get through it lying flat. We're going for stage one, stage two and three, not four, because they have to lie flat in the magnet and get through this protocol.

And this is just an example of some of the things that we're collecting, so you can see magnetic resonance angiography on the top. And hopefully, in our somewhat beefier Americans, including our women, bigger than the traditional Chinese subjects, we're hoping we'll be able to make pictures as good as this.

And then we also, of course, can do T1 mapping for fibrosis, for edema when people are acutely ill for things like myocarditis should any of this turn out to be that. And these are just some pictorial examples of the kinds of things that we can see.

For example, we have a cohort of lupus patients who, again, have signs and symptoms of heart disease, no obstructive coronary disease by CT angiography. And we're showing that their T1 is quite different from our reference controls.

No big surprise, but it is telling us that lupus impacts the myocardium, which has historically been hypothesized. There's case reports when patients go into heart failure, and then they get a gallop, and then it goes away. But no one's really been able to document this. And so this is something, again, with new technology, you make new discovery about these diffuse systemic diseases and cardiac involvement.

So in summary, coronary microvascular dysfunction is more prevalent in women. It contributes to this female phenotype. It often is giving us the same kinds of signals, adverse events, but often these women are not included in clinical trials because they don't have obstructive coronary disease, which previously has been sort of the sine qua non of ischemic heart disease.

Diastolic heart failure, heart failure with preserved ejection fraction, is also more prevalent in women, again, contributing to the lack of women in a lot of our clinical trials and the lack of knowledge about how to treat this.

Are these two related? Initial data support this via a mechanism of ischemia leading to myocardial fat accumulation. If this is true, anti-ischemic therapy should be tested. And again, this will be providing a platform in human beings, and helping us understand what next trials we should be doing in HFpEF. Because currently, it's pretty much of a wasteland.

So I will close with that, and I'm happy to take questions. Thank you.