WILLIAM G HUNDLEY, MD: My name is Greg Hundley. I'm a cardiologist and more recently and have become interested in this field of cardio-oncology. And the aspect that we bring to it is trying to-- so what is cardio-oncology? Let's just back drop a little bit. What we think is occurring is patients that are now treated for chemotherapy for many cancers-- breast cancer, leukemia, lymphoma-- those that survive beyond four years, their primary cause now of morbidity and mortality is a cardiovascular event. So this talk is going to be sort of centered toward that.

And then my angle as a cardiologist-- I'm a noninvasive, imaging cardiologist. And we've been using this technology, magnetic resonance imaging, to help us identify and understand who might be getting into difficulty with their chemotherapy. So that is where we're going to walk through.

So these are my disclosures here, some companies that we work with that help build equipment to detect this problem. And then we will be talking about the off-label use of magnetic resonance imaging and the administration of gadolinium-- we'll go through that-- contrast use for cardiac studies.

So we'll start with a case. This is a 45-year-old Hispanic woman with newly-diagnosed breast cancer. And she was begun on Epirubicin and cyclophosphamide. So Epirubicin is an anthracycline-type chemotherapeutic agent. And then cyclophosphamide is another chemotherapeutic agent. And after 150 milligrams per meter squared-- the way this medication is dosed is based on body surface area, and that's a very low dose of the anthrocycline therapy-- she developed dyspnea on exertion at 20 yards, so very active in the community and now can't walk from here to this table right up here without becoming short of breath. In addition, she developed an inability to lie flat at night and had lower extremity swelling.

Prior to the initiation of the chemotherapy, she had some mild hypertension. She was taking an anti-hypertensive medicine. Her blood pressure was 155 over 85, but otherwise no risk factors for coronary arteriosclerosis. Pre-chemotherapy, what happens is when you're going to receive chemotherapy now, you undergo an assessment of cardiac function. And so they measure your left ventricular ejection fraction. And hers was 55% by echo. And she had delayed relaxation was noted from the mitral inflow velocities.

So when she's seen, her chest x-ray has new pulmonary edema. Her left ventricular ejection fraction had fallen to 40%. And so she was admitted to the hospital for diuresis and initiation of ACE inhibitors.

So what we're going to work through in this talk, how frequently does this occur? Is this condition, this drop in EF and the dyspnea, is that related to her chemotherapy? And then how will we manage it? And can we reverse it?

So the outline of the talk, we're going to examine some data refuting as well as supporting the conjecture that cardiovascular disease is associated with cancer treatments. It's kind of an interesting story. Then we'll briefly review the mechanisms of anthracycline-related cardiovascular injury after cancer treatment. We'll present some new research utilizing the MRI to detect subclinical cardiovascular injury-- so injury to the heart of the vascular system before the EF drops-- after cancer treatment. And then we'll discuss therapeutic options. What do we do for these patients once we have this condition?

So currently, let's just walk through what are the recommendations for managing patients that are going to receive potentially cardiotoxic chemotherapy? So at first, we obtain the baseline EKG with an assessment of LVEF. That can be done with a MUGA scan, an echocardiogram, or an MRI, and then also, a cardiovascular risk assessment. If the patient has a low EF-- that's an EF below 50%-- then they are referred to, basically, a cardiologist.

If the EF above 50%, then we go ahead and administer the anthracyclines. And currently, what we do is if someone is scheduled to receive a very high dose-- so 400 to 450 milligrams per meter squared-- they'll go into a surveillance program, where their EF will be measured sequentially. If not, if they're not going to receive that high dose, then the only thing that we do is we check on them if they become symptomatic. We check on them if they become symptomatic. So that's kind of the existing state of where we are today and how we follow these patients.

And the question is going to be, is that right? So there was some data presented that suggested that that was the correct thing to do. And where did that come from? So these are three studies not published too long ago, in 2001, in 2004, and in 2008, that studied the administration of anthracycline. So that's one of the most toxic forms of the chemotherapy for the cardiovascular system. And we're going to walk through. And one of these, all of these concluded that we do not need to monitor these patients more aggressively.

And so how did they come to that conclusion? And to walk through that, we're just going to look at this one study over here, the one published in 2008 by Ganz. And so what they did is they recruited from the cancer sort of a collaborative group. 1,176 patients were going to enter their study, so a very large number. And they were going to follow their left ventricular ejection fraction after they received the chemotherapy.

But interestingly, of the 1,176, only 180 participated in the study. So the 180 were those that responded to the contact. 59% never responded when they tried to catch them. 13%, some of the data were lost. 7%, people refused. 3% were ineligible. So they end up with 180 subjects.

163 of the subjects, they were going to look at them over a five to eight-year period, and 17 over a 10 to 13-year period. So from our 1,176, we're dealing with 180. And then we're going to follow 163 and 17. And we're going to look at their left ventricular ejection fractions.

And what did we find? Well, at five to eight years, patients that received anthracyclines, they ended up with a pretty good EF, 63%. In a person-- most of us in the room, unless we have a cardiac condition, our ejection infraction is 60% to 65%. And in the patients that did not receive the cardiotoxic chemotherapy, their EF was a little bit higher, maybe 65%. And then at the 10 to 13-year period, looks almost the same. The EFs are all in the 60-some percent.

So although many of the institutions chose not to participate, in this selected sample with up to 13 years of follow up, this was the conclusion of the paper. Exposure to doxorubicin did not increase the likelihood of adverse cardiac events. And this was published in a journal, *The Journal of Clinical Oncology*, which is the most widely-read oncology journal after the *New England Journal of Medicine*. In medicine, we rank these journals. We call them impact factors. And the *New England Journal* has an impact factor of around 28. This is very important. And this journal has an impact factor of almost 20.

So here's the study that's published. And this is what we were basing this on. With these potentially cardiotoxic chemotherapies, we really don't need to follow them, because there's actually no problem.

Now, here's another study. This study was also used to support the idea that we don't have an issue with administering chemotherapy to patients. And this was published in the *New England Journal of Medicine.* And this is 3,222 women. And they have a form of aggressive breast cancer. And they're going to be randomized to one of three treatment arms, one of three treatment arms. And this is up here. And they're following them for their morbidity and mortality.

One of the regimens, or two of the regimens, have the anthracycline chemotherapy in them, this ACT one, and the ACT plus trastuzumab. And then this TCH one, this does not have the anthracycline included. So here is the disease-free survival on the y-axis. And this is time on the x-axis in months. And so 60 months is five years. And what they saw and what was interesting here is that the disease-free survival for cancer was relatively the same across all the studies. And so that's suggesting that the anthracycline regimens and the non-anthracycline regimens are relatively equivalent.

In this study, they also looked at cardiac function. And that's on this slide. And so they assessed down here in this gold, dark gold, bar, the incidence of congestive heart failure. And what you see, the three regimens, the ACT, the ACT plus trastuzumab, and the TCH, the incidence, or the percentage, here 0.72% and 0.4%. And so the conclusion from the paper was that, gosh, these anthracycline-containing regimens, they really don't cause heart failure, because we only saw it in 0.7%, 0.4%-- you know, a very small segment of the population.

But on the same graft, which is not commented on, we look down here in this dark brown. How many patients had a drop in their left ventricular ejection fraction of 10% or more? So they started at 60. And they fell to 50. How many did that? And what was striking is you have 11%, 19%, 9%. So a relatively high percentage of individuals actually drop their ejection fraction a substantial amount. In fact, if our left ventricular ejection fraction is below 50%, we end seeing a cardiologist, or an internist, or someone. And we're initiated on therapy.

And so a paper was written about this. And one thing to just go back to, when they defined heart failure-- we just had Dr. Pisani-- when they defined heart failure, the definition that they used was class four, class class, New York Heart Association class heart failure. They didn't report the New York Heart Association class one or two heart failure. So an editorial was then written about these two studies and why they may be incorrect. The Slamon study-- so that's the *New England Journal*-- may under-emphasize the incidence of heart failure, because it did not include class one or two. And there was a relatively high rate of patients dropping their ejection fraction by greater than 10%.

The retrospective study, the one I talked to you about before, the Ganz study, those design studies likely underestimate the true incidence of cardiac events, because important data points on patients who relapsed and/or died are missing. Remember, they started with 1,176 patients. And they only followed 180. What happened to the 900? They could have experienced the condition, and they were left out.

And what's surprising is in a study like that that's going to make such a strong conclusion, it got published in a high-profile place. And so the current thinking is, a-ha, maybe this is not correct. So as these papers were coming out, there was a whole other line of manuscripts coming out that suggested, wait a minute. Do we have a problem? So let's walk through those.

So the first of those studies is looking at the development of congestive heart failure in breast cancer survivors. And these data come from the Surveillance Epidemiology and End Results, or SEER, database. So these are Medicare women that are on Medicare. So they're over the age of 65. And they are treated for adjuvant breast cancer and followed over seven years. And so there are three regimens here that are listed. There's radiation treatment, which is in the blue one. There is chemotherapy that does not have the aggressive forms of anthracyclines, the yellow line. And then there's the aggressive anthracycline chemotherapy in the green line.

And over here, these are the proportion of individuals that do not have congestive heart failure. And what you see is you follow out five, six, seven years, that in the green line, 40% of the people now have heart failure. So they're collecting billing codes that are coded in hospital medical records. And what they're showing in this study is whoa, wait a minute. We're actually getting quite a large number of heart failure diagnosis codes.

So that was Medicare patients, older ones. What about younger patients? So this was a study that was published in the *Journal of the National Cancer Institute.* This was 12,5000 women. The average age is 60. So half are below and half are above, all with stage one to three breast cancer, followed from 1999 to 2007 at eight cancer research network not-for-profit HMOs. And let's just focus over here on this side of this table.

This column here is the hazard ratio. So that means what's your risk above the normal population for developing the condition of heart failure? And what you see is if they receive an anthracycline, there's an increased risk. If you receive a non-anthracycline regimen, there's an increased risk. If you receive combination chemotherapy, there's a very high risk. And then, again, other regimens that do not have these potentially cardiotoxic, there's also an increased risk. So now we have data with billing codes from HMOs that are also indicating heart failure diagnoses, so starting to refute some of that other information.

What about diagnoses related to cardiovascular conditions that are not heart failure, heart attacks, strokes things of that nature? Well, that was also looked at in this SEER database, so again, following billing codes. This particular study has 63,566 breast cancer patients. And what they found is that cardiovascular disease was the leading cause of death, followed by breast cancer recurrence in these various disease states-- stage one, stage two, stage three, and four breast cancer. Cardiovascular disease is the leading cause of morbidity and mortality.

So stage one is listed over here. And the white bar are those that are dying from cardiovascular-related events. The black are those that are dying from a breast cancer-related event. Stage two-- again, breast cancer, cardiovascular disease-- over here with metastatic disease, the patients more often die of the cancer. So again, another study suggesting that not only is it heart failure, but also heart attacks and strokes are being experienced by these women. Of those women that died as a result of cardiovascular disease, only 25% had any cardiovascular co-morbidity at the time they started their chemotherapy, implying that something related to the treatment is the cause for the cardiovascular event.

Exertional fatigue and quality of life-- not only do breast cancer patients experience cardiovascular events after adjuvant chemotherapy, but they also experience exertional fatigue and reduced quality of life. In fact, 33% of breast cancer survivors experience persistent, progressive fatigue of an unknown origin. And this form of disability reduces one's ability to return to work and function on a daily basis.

This is a study that just supports that. This is a survey that's administered to breast cancer survivors, and it's asking the question, if you can't go back to work or what are the difficulties that you're having? Why can you not get back to work? What are the most important issues there? And that's highlighted over here in this last column of this table. And when you have a negative mark over here, that's a barrier for returning to work.

And what do you see that is identified is an important problem? Fatigability reduced energy and drive, some changes in temperament, having difficulties driving, having difficulties performing housework-- all of these activities of daily living, they're experienced by these individuals. And so what we have were two pieces of science moving forward, one saying, ah, we don't have a problem, and another one with large number of patients saying, yes, we do have an issue. And I think when we look at the data from no, we don't have a problem, there are flaws in that. One, we didn't characterize the patients necessarily the correct way in the New England paper. And the other one excluded a large segment of the population.

In the other data sets that are followed, where we have all this billing code and registered data, it looks very supportive that we have a problem. Moreover, the women are actually reporting that in their activities of daily living. Is this an important concern? And the answer is yes. Why? Because we have a large number of cancer survivors now in the United States.

This is a plot of 1971 through 2005 showing this increase in the cancer survivorship. And now, out in 2014, this number exceeds 14 million individuals in the US alone. So it's an important problem affecting many individuals in our communities.

Now, this is just a mechanistic slide. And the reason I'm going to show it just briefly is it's interesting to me in science how these anthracyclines are causing the problem. They kind of hijack, they hijack a normal process that we have. And just quickly, interestingly, what occurs is our bodies produce this substance called nitric oxide. You've probably heard about it. As you start to exercise, nitric oxide is released and helps the blood vessels dilate.

So in general, it's a good thing. It's over here in green, does many good things. It lowers your blood pressure, anti-anginal, prevents your blood from clotting, all these wonderful things. So nitric oxide is good.

What happens in the administration of some of the chemotherapies is they rev up the production of nitric oxide to super high levels. And in addition, they rev up the production of these other superoxide free radicals. These are things that our cells produce to fight infections. And so they rev both of those systems up, producing tons of both of those things. And what happens when you have lots of nitric oxide and lots of superoxide, there is a preferential movement in the pathway down this bad pathway to produce this thing called peroxynitrite, which hurts the heart cells and damages them, damages the cells in the blood vessels and causes all of the issues and problems.

So it's interesting that this is-- we've understood a lot of the science here. We'll talk about this, how we're going to prevent some of this injury later with therapies that can block all of this. But it's kind of hijacked a pathway that normally helps us.

So this slide is how are we going to understand if patients are experiencing cardiac dysfunction related to the administration of these drugs? And so first, we want to provide sort of like a little mechanism of what's going on and how we get the drop in EF and the development of heart failure. So if we're exposed to the anthracycline, we have the nitric oxide problems and the superoxide problems. And what that causes is the mitochondria, the little energy producers in our cells, to become dysfunctional.

And we see that, if we were able to go in and take a biopsy and look at some microscope slides, what happens is the heart cells swell. And they become inflamed and damaged. Then what's manifest next is we have impairment of regional function partly of the heart to contract and relax. Some things we don't see very well, but again, we have impaired regional heart contraction and relaxation. We call that LV function.

Then what happens? If it keeps on going, heart cells start to die. And when heart cells start to die, they're replaced. Just like if we cut our skin, they're replaced by fibrous tissue. So we have collagen deposition and what we call remodeling. And then, and then the EF drops. So the EF is dropping way out here, but all these other things have happened.

We're monitoring the EF, all right. And then if the EF continues low, we get heart failure. So today, in the gray, what we do is monitor the EF. And then we monitor exercise capacity, because we get to do exercise stress tests. But we're not picking up all these problems. So our thought process was can we go back earlier and use this MRI technology to image these aspects of the disease? Because if we could do that, we could catch this much earlier and prevent the EF from dropping and prevent heart failure.

So how are we going to do that? Now, I may need some help from the guy back there. Click-- there it goes. OK, great. So we're going to use this magnetic resonance imaging technology, all right? And I just want to explain to you a little bit about how it works. Number one, it can measure EF really, really well. And I'm going to kind of walk out here and show you how we do that. I'm going to borrow-- can I borrow your cup of water here?

SPEAKER: Yes.

WILLIAM G HUNDLEY, MD: So how does it measure EF relative to other technologies? And so to illustrate that, EF, we've got to calculate volumes. So how much volume is in this cup of water? Well, what we're going to do is we're going to get a series of slices. We're going to lay the heart out, and we're going to make slices just like this from the tip and keep going incrementally all the way up. And in each slice, we're going to trace the area, and we're going to know the thickness of that slice. And so if we then sum all those up, regardless of the shape of that cup, I can tell you exactly how much water is in there.

So let's translate that to this image that we have up here. These are slices of the heart, starting at the base in the top left and marching all the way out to the apex. On these images, the heart muscle is gray and the blood pool is white. Because the blood is moving, it provides its own contrast. So we don't have to give any contrast. The other thing that's happened with this technology is that whole series of images, crisp and clear, it's like high definition TV, is all acquired in about 20 seconds, all those slices. So it's very efficient and very accurate. And we can calculate the volumes and then the ejection fraction very well. The volumes is end diastolic volume minus end systolic volume after the heart is squeezed divided by the end diastolic volume. That's what EF is.

Over here, also with the MRI, we can do this technique. It looks like a little checkerboard that we applied to the heart. And when we put that checkerboard on there, what happens is it allows computers to go around and quantify and measure how the heart is contracting and relaxing very accurately, better than you and I can do it with our eyes. So what we first started to do is let's take some patients that are going to receive chemotherapy that might be cardiotoxic and follow these MRI exams on them. The US government gave us some money to do that. And let's look at the results.

So our study is going to be women, or women and men that are going to receive anthracycline. So some are going to be breast cancer, and some are going to be leukemia, lymphoma. The average age is 52, 63% women, 76% white, 24% black. They have hypertension, hyperlipidemia, diabetes, coronary disease, and smoking, about what we see in the general population.

They're going to go on to receive chemotherapy. And let's look at what happened to the results of the MRI as they receive their chemotherapy. So to understand that, we're going to walk through this graph. On the x-axis, the bottom here, we're going to get a measurement at baseline before they start their chemotherapy, then one month after their chemotherapy, three months after, and six months after.

Now, the six month point is interesting, because they finished the chemotherapy at three months. They finished it at three months. Over here on the y-axis, we have the end diastolic volume, so that's when the heart is big like this. And then we, on the right y-axis, we have the end systolic volume after it squeezed down.

So what do we notice? So here, we start with end diastolic volume and end systemic volume. And after one month of receiving chemotherapy, they get one dose, not the 450 milligrams per meter squared. All of a sudden, the end systolic volume increases. So what that means is the heart was here, and it squeezes down to have a good EF. Well, now it's here. And it doesn't squeeze as far. That's increased. And it happened one month after receiving chemotherapy.

So consequently, we go over here and look at this graph. And that tells us what happens to the ejection fraction. So the ejection fraction is plotted on this y-axis. And then before chemotherapy baseline, the one month, the three month, and the six months. And we see the EF drop just like that, after one month. And then it stays low. And interestingly, after we've stopped the chemotherapy, it stays low at the six month point.

On this little graph here, this is the analysis of the checkerboard data. And that's called strain. And the more negative your strain value is, the better you are. It's kind of a weird way of doing it, but that's the way it's measured. And so you start down here with a nice, normal value. And you see this drift to be less negative. And so there's more impact here out here at the six month time point. And all these, these p-values, all mean that these are all significant. So the EF drops in the folks receiving the anthracyclines after the first dose. That was a new finding. And it remains reduced after the chemotherapy is stopped.

It didn't-- and what happens is sometimes when you're doing a study like this, you want to know, well, is there something else going on in the background? So we do statistical analyses. And those results persist after it doesn't matter how old you were-- if you're young or old. Didn't matter if you're a man or woman. Didn't matter if you were white or black. Didn't matter if it was leukemia or breast cancer. Didn't matter if you had hypertension or didn't. And it didn't matter how much chemotherapy you received. And that's what's shown in this graph over here. The drop in EF occurred whether your dose of chemotherapy was low or whether it was high.

So now, what we want to do, we can use this MRI technology to measure EF really well-- a little bit more precisely than the other methods. And we show that it's declining. That's bad. Now what we want to do, though, is we want to go back. And can we catch an abnormality that occurs before the EF drops? Because that's what we want to know. We want to stop things before the drops.

So now what we're going to do is use a different aspect of the MRI scan to achieve that. And to do that, we're going to give a contrast agent. We're going to give a contrast agent. And this contrast agent is called gadolinium. Those of you that manage patients that go for MRIs, you're going to have heard of gadolinium.

Now, gadolinium is kind of unique. It's not like an ultrasound contrast agent or a cath lab contrast agent or anything like that, where we've got the contrast agent in the body and we pass x-rays through, say with ionic contrast, and we look at the diffraction. Or with ultrasound contrast, the micro bubbles where we passed the ultrasound in and it reflects off the bubbles, and we can see some. It's not like that.

What gadolinium does, goes into the body, and it helps to see water better. It helps us see water better. So what this is a cartoon, of all these little gold circles here, these are water molecules, and actually the hydrogen on the water molecules. And what the gadolinium does is it helps those show up better. And so we use that today-- this side is kind of hard to look at-- but we use that today for those of you that are at centers that are doing cardiac stress testing-- we use this property of gadolinium to do cardiac stress tests, all right?

And what we do is we administer the gadolinium. It comes in. You can see the water in the center of the left ventricle. You see it get brighter. And then areas in the heart muscle-- it's hard to see from back here-- but up here at the tip, you can find perfusion defects due to blockages in the coronary arteries. So the areas that have normal myocardium, normal perfusion, have higher signal intensity. And areas that are subtended by a stenosis, they have perfusion defects. And we use that to diagnosis ischemia So it's useful.

The other thing we can do with gadolinium is wait. We can wait after we've administered it and take another picture. And that's the property of it that we're going to talk about. So if we wait five or 10 minutes and we take another picture, what happens-- this is called a four-chamber view of the heart. And the gadolinium clears out of areas that don't have damage. And it stays in areas that do have damage.

So this is a person that's had a heart attack. And this is what's called a four-chamber view. So over here, it's called a four-chamber, because this is the right atrium, the right ventricle, the left atrium, the left ventricle. And this black here, the black, is the myocardium of the heart muscle. And black is normal. So if we have black, that's good.

What you notice up here at the tip of the heart, we call the apex-- see all the white-- that's where the heart attack was. That's the part of the heart muscle that died. So it shows up infarcts very well. And this is just more imaging. You can see this is a profusion defect here, a little bit easier to see in the first part. And then we can also look at wall motion.

And we use this-- just as a little side note for you, those of you that are kind of working in this area-- this is another four-chamber view up here at the top right. So here is the right atrium, right ventricle, left atrium, left ventricle. Here's the black from normal heart muscle. And here's all the white along the lateral wall. And that's a very large heart attack involving the lateral wall.

You see that the white concentrates on the inside wall first. In patients with heart attacks, that's the furthest point away from where the blockage would occur. Because remember, the heart arteries, the epicardial arteries, run on the surface. And then they dive down into the heart muscle. And so when you have a heart attack where the blockage is out here, the point furthest away is along the endocardial surface. So we can use patterns of the white in people that come in with chest pain syndromes or heart failure. And now, we can tell you why the EF is low. And this is a pattern that's consistent with a heart attack or a myocardial infarct.

Over here, this is a pattern. Look at this one's a little different. See, the white is on the outside of the heart? It's not on the inside of the heart muscle wall. It's on the outside. And that's consistent with myocarditis. So people that get the flu or something like that and have an infection in their heart, that shows up on this very well. And we make the diagnosis now.

This is another patient over here with a different pattern of white that you may have heard that from Dr. Pisani. But this is someone with amyloid, where you have this ring of white that occurs. And so now, we diagnose amyloid. And you don't have to go for biopsies. We do that now with MR.

So we have this technique that can show up injury. But all of the injuries I'm showing you here are focal injuries, right? They're congregated, right? There's an infarct. You know, it's very dense right there. It's very dense myocarditis right here.

Now, we're going to switch to trying to identify an injury that is diffuse throughout the heart. And I'm going to just show you that here. So over here, just to compare the two, this is a short axis view. So let's go back. It's a delayed enhancement image. This is the left ventricular myocardium, all here. Here's the blood in the cavity right here. Here's the dark black, which is healthy and normal. And the arrows are showing you evidence of a heart attack. And this is what the histopathology looks like. These pink things, that's the heart muscle cells. And the very light pink-- so dark pink, heart muscle-- light pink is the fibrous tissue from the scar from the heart attack.

Now, here's somebody over here. Look at that short axis view. I told you that the black was normal. So you look at that and you say, oh, wait a minute. That looks pretty normal, right? But look on the histopathology. Look at all the white pink in there. That's all fibrosis and injury from a diffuse process, a diffuse process throughout the heart. So can we use this technology to identify a diffuse process? Doesn't look like it, because if we look at the pictures, we don't see it, just like we did with the heart attack. It's not as clear.

So we had to come up with a new technology. So that's one of the advantages, I think, of being at Wake Forest. They help develop new technologies, develop new products, and then put them out on the market and things like that so that they can be useful worldwide. And so the problem was, how do we come up with-- this is meant to be the left ventricle here. And these are the short axis slices. So these are rings of heart muscle. And there's the cavity there.

And all these little splotches, we've got to find and detect a process that's diffuse throughout the heart. And so that's kind of what we developed and came up with. And the way we did it is divided the heart into these little blocks. You call them voxels. On a TV screen up here, we call them pixels, because they have two dimensions. And we know their x, y, and z-coordinates in space. So we have a point here. We give it a number, and a point here and a number. It's just like on a map.

And then we also measure the signal intensity in that. So each one of those voxels has four unique numbers, an x, y, and z-coordinate, and a number for its signal intensity. We administer the gadolinium. These are short axis views. It's very hard to see here, because we have a lot of lights in the room. But there's a yellow line here and a red line. And down here is the cartoon. So we measure the x, y, and z. We know the signal intensity of all the little blocks. And we plot that on a graph. We plot those signal intensities on the graph.

And we can see in someone that's normal, it's relatively healthy. We have a nice, homogeneous, low signal intensity graph. But now, let's look at a series of experiments where there is exposure to anthracyclines. And we're going to look at some of the subjects that are going to be healthy and not exposed. So that's going to be on the left, normal. We're going to have those that are exposed to doxorubicin but do not drop their ejection fraction and those that get the anthracyclines and do drop the ejection fraction.

Down here is the histopathology. And so here is normal. Heart muscle cells, when you lay them out, they're all striated and long. You know, they're wrapping and contracting, Over here, very similar, and then here, the ones that are getting the injury-- look. There is that heart muscle injury. Remember the slide earlier? See all this white things that are? Those are the vacuoles, and the swelling, and the injury that's occurring.

Well, what happened with our graphs? Well, here we can see in the normal ones a very low number, low mean, two. Here, the mean is down even around zero, so it's normal. And look here-- our graph over here indicating injury, right there, a very high number. So now we have a technology, very interesting here. We have a technology that's almost like doing a biopsy on someone without having to do the biopsy. It's an imaging biopsy. And it identifies the injury early.

So one of the things we do-- we'll talk about it a little later-- is we use magnetic resonance imaging. And we've got a technology now that we've published on. And we've used it in people. And it identifies the injury before the EF drops. So that would help us to identify those at risk for heart failure.

But I told you that these women also experience cardiovascular events. That's heart attacks and strokes. That doesn't come from heart muscle injury. That means there is a blood vessel injury. So another thing we've been using the MRI technique to do is to assess blood vessel function. Well, anyway, that should be a cineloop. And what this is, here is the heart here in the center. And there's the aorta going all around like that. And this is sort of the main vessel that's carrying blood throughout your body.

Here are the carotids up here. And here are the renal arteries. And then these are the iliac arteries going off to your legs. And what we can do with the MRI technology, again in a short period of time, is we can measure the speed at which the blood flows through the system. And what happens is when you develop injury to the blood vessels, they get stiff. And when they get stiff, the blood moves faster. So speed of blood means stiffer arteries. And it's much more work for the heart to perform.

We call that pulse wave velocity. And it's a very useful measurement. And it predicts risk of heart attacks and strokes in many different populations. So this is a table looking at different individuals, hypertension, diabetes, kidney dysfunction, even healthy individuals, large numbers of subjects. And it's an independent predictor of adverse cardiac events.

So just quickly, we lay out the aorta. We measure two different points. And we look at how quickly the blood goes between the two points. And that helps us calculate the pulse wave velocity.

So we did another study. And we said, are the patients that are receiving the anthracycline therapy, are they experiencing stiffening in their arteries relative to those that wouldn't, that are not receiving chemotherapy? So here is the study population. We have a control group of 13. And we have patients receiving the anthracyclines. There's 40 of them. And they're pretty similarly matched for age. There are a few more cardiovascular comorbidities in the individuals that are treated for chemotherapy.

So let's look at the bottom graph first. This is the individuals that are the control population. They're not being treated for cancer. We get a baseline measurement over here. And we get a measurement four months later in everyone. So each line is a person. What we see as a nice low pulse wave velocity, low speed, 4.5. And if we repeat the measure, it doesn't really change very much.

Now, let's look at the patients treated for cancer with anthracyclines. Number one, if we average all the pulse wave velocities at baseline, it's 6.9. And we would expect that, because they have more of those cardiovascular comorbidities. What happens after the chemotherapy? All of them increase the pulse wave velocity. It goes from 6.9 to 13.5. Every single participant, it increased at four months. That magnitude of increase-- we do statistical analyses-- not only was it statistically significant, but it was clinically important. That increase is consistent with aging the cardiovascular system by 20 years.

So if you were 40, your heart and blood vessel system is now age 60. If you're 60, it's 80. That's the significance of that. Why? How did that happen so quickly? What was going on? And to that, we had to turn back to a series of other experiments looking at blood vessels. So this is a blood vessel in the heart muscle, embedded in it. So these are called microvessels. These are the little, tiny blood vessels that supply different areas. We've looked at them in the walls of the aorta. We've looked at them in the heart, et cetera.

And what you see here in this subject receiving saline is that we have a nice, thin wall, a very compliant vessel. This is the anchoring tissue, this blue. It's fibrous tissue all around. It's very healthy. And along the inner lining of this wall, the cells are very thin. They're not really sticking out or anything like that.

Now, look over here. This is a similar small blood vessel after receipt of anthracycline. Number one, see all these black dots on the inside wall? That means those cells are injured or dead. Those are the endothelial cells. Look how angry it looks with the thickening, abnormal thickening, of the wall. And look at all the inflammation that's occurring around. And so that's what's going on with the blood vessels.

You know, many of these treatments that we're now using for cancer, just as a side light, what are we trying to do? We're trying to disrupt the cancer's blood supply. Remember, they kind of grow their own blood supply. So we're attacking that. Well, a lot of these agents also attack our native vessels. And so this is some of the mechanism that we believe is responsible now for the development of heart attacks and strokes, the non-heart muscle related injuries.

So what do we do about this? Are there therapies that we can use to prevent some of this? And so individuals around the world in studies with small patient numbers have started to use different agents. One of the common ones are ACE inhibitors. You're going to see that in all these, ACE inhibitors like this, or carvedilol, common therapies that we use to manage patients that have heart failure, administered to these particular patients help improve the left ventricular ejection fraction uniformly. Now, what we don't have are studies in large numbers of patients.

And also, it's a little bit difficult to administer some of those agents as you're receiving chemotherapy. Because as you know, as you receive the chemotherapy, you get very hypotensive. So taking another medicine that lowers your blood pressure can lower your blood pressure so much that you can pass out and fall. So looks effective, but we haven't implemented these therapies widely due to that problem.

So what else could we do? One of the current thinking-- very interesting here-- is to exercise, is to exercise during receipt of cancer treatment. What happens is that stimulates some of the processes in your body that go around and scavenge that extra superoxide and nitric oxide. So exercise is currently being tested.

And then something that we're interested in doing and have a study ongoing now at Wake Forest is the administration of statins, the cholesterol-lowering drugs. Now, why in the world would we give cholesterol-lowering drugs to patients that are being treated for chemotherapy? Well, it has to do with other benefits of the statins, the antioxidant and anti-inflammatory aspects of the status. And what are those?

So remember our friend here? Here is our nitric oxide, which is a good thing. It was being over-produced. And this superoxide was being over-produced. And they were making lots of this very bad thing, the peroxynitrite. When we administer the statins, it cuts down on the overproduction of nitric oxide. And number two, it stimulates processes that go around and scavenge and pick up and take these guys out of production. So the statins could have a real benefit.

And in observational studies, statins have shown to be associated with lower cardiovascular morbidity and mortality, lower cardiovascular morbidity and mortality, in women that happen to be taking statins for secondary heart prevention that also happened to get chemotherapy. So in observational studies, this is, again, looking at survival probability over here. And what we see is that the women that happen to be taking statins do much better and have less heart failure than those that don't that are treated for chemotherapy. And then we have several other studies that are marking on the same thing.

This one here, study population of 154,000, of which 7,400 were selected with breast cancer, and just showing that breast cancer recurrence was lower in statin users. This one here, simvastatin, this particular slide is just addressing if we happen to be taking a statin, does that affect the cancer treatment? The answer is no. Some of the preliminary data in these large observational studies with thousands and thousands of patients suggests that it may even, in fact, be beneficial for the treatment of cancer.

So at Wake Forest, we have a trial going on. For those of you that are in the community, you would have seen it in the paper. It's carried on at Wake Forest at Forsyth, at many of our surrounding hospitals. And so the participants can be recruited into either of those. And the women with stage one to three breast cancer that are going to be scheduled to receive anthracyclines are randomized to receive atorvastatin or a placebo. And they're followed for 24 months. They have serial examinations with MRI.

We are also looking at cognitive function, exercise capacity, and the like. And all of that's provided and funded by the study. And there's also some incentive for participation. With the MRI. We're looking at vascular issues that I've talked about. And we're also looking for cardiac function, and also this voxel stuff I talked about for early cardiovascular injury.

So in summary, I think that the population-based data indicates improved cancer related survival for several childhood and adult malignancies. However, the billing code data suggests this reduction in mortality and morbidity is being offset by an increase in cardiovascular events, including heart failure. I think some of those-- remember the Ganz study and that New England study-- I think they kind of missed it. I think we do have heart failure. And we do have cardiovascular events, because that's what the large population-based studies are showing. And that is impacting our ability to treat cancer successfully. We're trading one disease process for another.

Recent studies suggest a variety of injuries to the cardiovascular system may initiate early upon receipt of the cancer treatment. We showed it after one dose. Advancement in imaging and biomarker technology may identify those at risk for cardiovascular injury in cancer treatment, not only the imaging with the MR, but the MRI, but also with serum biomarkers, troponins, and things like that. We may be able to pick up this injury earlier. And there are studies ongoing across the country for that.

And then finally, preliminary observational and animal study results suggest that concurrent receipt of statins may have attenuate the development of cardiovascular dysfunction during receipt of anthracycline-based chemotherapy. And whether they do, in fact, reduce morbidity and mortality, that awaits the result of a randomized trial. And we're performing that here now in the community.

So that is the conclusion of what I have to present. I'd be happy to answer questions. I also want to thank the organizers of the meeting for allowing me to speak. But all of the individuals at Wake Forest that helped carry out this work over the years, the Department of Engineering, biomedical engineering, public health sciences, the Department of Internal Medicine, the Department of Radiology, all of these have been instrumental, not only with faculty level but also the staff level, which you all are keenly aware help get all the research done. So that's what I have. Be happy to answer questions.