Melanie Cole (Host): Welcome to the podcast series from the specialists at Penn Medicine. I'm Melanie Cole, and today we're exploring heart failure with preserved ejection fraction or HFpEF.

Joining me is Dr. Stuart Prenner. He's a Cardiologist and an Assistant Professor of Clinical Medicine at Penn Medicine. Dr. Prenner, it's a pleasure to have you with us today. And while the incidence of heart failure with reduced ejection fraction has decreased, the incidence of heart failure with preserved ejection fraction or HFpEF continues to rise.

I'd like you to briefly explain the role of ejection fraction in heart failure diagnostics, the difference between preserved and reduced ejection fraction. Do patients with these conditions have a similar disease course? Are they treated the same way? Give us a little bit of background and an update on what's going on with this.

Stuart Prenner, MD (Guest): Sure happy to do so, and thanks for having me. So the first thing to recognize before we get into the actual types of heart failure is just to remind our listeners that heart failure is a clinical condition. And so, it's the patient telling a story of certain signs and symptoms that they have. Usually shortness of breath, fatigue, signs of fluid buildup, and the physician is thinking that the heart is the likely explanation for this. Heart failure really is a clinical condition first and foremost. It turns out that when we image the heart, one of the biggest branch points in terms of how we label these conditions is whether or not the heart is squeezing normally. And so, that's where the concept of ejection fraction comes in.

And in general, we've set a cutoff of about 50%, meaning that if somebody's got symptoms of congestive heart failure, but the heart is squeezing normally, meaning the ejection fraction is greater than 50%, we label that as HFpEF or heart failure with preserved ejection fraction. Whereas if the heart is not squeezing normally, or the ejection fraction is under 50%, we label it as heart failure with reduced ejection fraction.

That's an important distinction. We recognize, though, that there's some gray area. Patients with ejection fractions of between 40 and 50 are labeled as heart failure with mid-range ejection fraction. Although we know from lots of clinical studies that these patients tend to behave more like reduced ejection fraction heart failure.

In terms of why this matters, this distinction is important because these different patient populations behave very differently, both in terms of their response to

medical therapy and also just who these patients are in general. Patients with reduced ejection fraction heart failure tend to be younger. They may also have genetic causes for their heart failure that run in their family. Whereas people with heart failure with preserved ejection fraction tend to be in their late sixties and seventies. And in general, they have one or multiple common comorbidities that include obesity, diabetes, and hypertension.

Whether patients have preserved or reduced ejection fraction, all forms of heart failure tend to progress over time. And so, it's important that people with these conditions are seeing physicians and getting medical care. But to your question, they're treated very differently. Whereas reduced ejection fraction heart failure has something like 20 plus guideline-directed class I indications for treatments and devices, heart failure with preserved ejection fraction up until recently has had very little in the way of interventions that were shown to have significant benefit.

Host: That's so interesting, Dr. Prenner. So then along that line, HFpEF is a challenging condition to recognize and even diagnose. Are there some clinical indicators or tools for referring providers, including primary care providers, that they should be aware of when considering HFpEF? And tell us some of the diagnostic strategies that your team at Penn Medicine employs.

Dr. Prenner: So, one of the biggest challenges about heart failure with preserved ejection fraction is that it really requires a high index of suspicion because the echocardiogram can otherwise look very normal. Unlike HFrEF, where the ejection fraction is by definition normal, it will be normal in HFpEF. So, you have to look a little more deeply at the echo and also think about what the patient's telling you when you're trying to consider whether the patient has this diagnosis. We know from some studies that unlike in reduced EF heart failure, where the BNP, or the natriuretic peptide levels are generally positive, particularly when people have symptoms, we know that in HFpEF, the BNP can be normal in at least a third of patients, partly because many of them are obese. And also because the hearts are normal size. And so, they're not sort of stretched the same way and these patients will not secrete BNP. The other thing that can be challenging is that upwards of 30% of people will not have too much structural abnormality on their echo.

So we're used to thinking that people with HFpEF always have left ventricular hypertrophy. That's often not the case. And so again, it requires a very high index of suspicion when your patients are coming to you with unexplained shortness of breath, and for example, they have never smoked. With that in

mind, there are some scoring systems that are worth mentioning that can help us to recognize this condition a little more early.

And one of them that I wanted to mention is called the H2FPEF score. H2FPEF. It should sound a little bit like the CHA2DS2-VASc score that helps us determine what to anticoagulate patients for non-valvular AFib in the sense that you get points for that criteria. And when you add them up, if you can get to a certain score, it tells you whether somebody with unexplained shortness of breath is likely to have HFpEF.

And so, you get points for high blood pressure. You get points for age over 60, you get points for atrial fibrillation and a couple of parameters that come from a routine comprehensive resting echocardiogram. If the H2FPEF score is over six, really, even five to six, the patient has a very high likelihood of having HFpEF if you sent them to the cath lab. Whereas patients with scores of one or two are very unlikely to have HFpEF. What we know in general, though, is if the score is sort of in the intermediate range or high—but you want with more certainty to rule this in—most patients should be referred for exercise right heart cath.

So, it's important to recognize that we now have some scoring systems in place to help us recognize this condition a little earlier before people are requiring lots of diuretics. And so, that's the treatment strategy that we use at Penn Medicine. I apply that template. I look very critically at the echo, not just for left ventricular hypertrophy, but also for the left atrial size. Whether there are features of pulmonary hypertension that are present and whether the diastolic dysfunction is significantly abnormal. Then, I apply the scoring system and I go from there, and I tailor the workup to each patient individually. I also am always making sure that there are not features that are consistent with what I call kind of zebras or things that mimic HFpEF, but are treated much differently.

And there I'm thinking about things like hypertrophic cardiomyopathy, cardiac amyloid, and sarcoid.

Host: I'm glad you made that point. So, as you've been saying, historically, there've been limited therapeutic options for HFpEF, but this is really changing dramatically. Can you discuss the specific interventions recently approved, including SGLT2 inhibitors? And on the horizon, what makes this so exciting? And what is Penn Medicine's experience with these treatments and others? What technologies besides medicine are available for this condition?

Dr. Prenner: That's why I think being in this space is so exciting, because unlike for HFrEF or reduced, where like I mentioned, we've got a dozen

medications, devices, and all of these have had robust clinical trial data, up until last fall, we really had no pharmacologic intervention that met a primary endpoint in a large scale clinical trial. And that was changed by the EMPEROR-Preserved study that looked at SGLT2 inhibitors in both diabetics and non-diabetics who either had a heart failure hospitalization or had an elevated BNP level. And I was very excited about this because this is the first clinical trial that met its primary endpoint.

And for me has really elevated SGLT2 inhibitors to one of the main tools that I'm using in this patient population. It also turns out that SGLT2 inhibitors are good medications for diabetics and for people with chronic kidney disease. And this is probably at least half of people with HFpEF anyway. The other sort of exciting areas are a relook at Entresto. As many will recall, Entresto is one of the most powerful medications for HFrEF, but sort of missed the mark in the primary end point for efficacy in HFpEF in the PARAGON-HF study. But more recently, there's been some post hoc analysis looking at the outcomes, particularly in women and particularly in people who, even though their ejection fraction is technically normal because it's over 50, are kind of in the lower end of things under 57 in the study seemed to benefit.

And what's really exciting is that we're seeing a change in the heart failure guidelines literally, as we speak. The 2022 heart failure guidelines that just came out now have recognized both Entresto and SGLT2 inhibitors in the pharmacologic management of HFpEF. So, this is super exciting and is literally changing sort of, as we are speaking. In terms of what we can offer patients beyond these medications, one of the technologies that I think has had a good evidence-base and is very promising in this patient population are these implantable PA sensors. The brand name is CardioMEMS, but there are others, in which we implant through a right heart catheterization a small sensor that stays in the pulmonary artery and gives us basically longitudinal information about these patients filling pressures. And what's really cool is that in the CHAMPION study, we saw that this markedly reduced rehospitalization in a well-selected patient cohort. And so again, you have to select the right patient. Someone who's got really terrible dietary indiscretion or medication noncompliance may not be benefited, but for the right patient, these sensors have really enabled us to partner with patients and keep very high risk patients out of the hospital. And so, I think the future is bright for HFpEF for all of these reasons.

Host: I agree with you. So I'd like you, Doctor, to talk about the HFpEF Program at Penn Medicine and its ability to care for these patients. As you've mentioned many different aspects of the approach to caring for these patients,

what differentiates the program and how important is that multidisciplinary approach? I imagine there are many providers involved.

Dr. Prenner: I think the first step is to make sure that you are actually treating the right diagnosis. We do as much testing as is necessary to ensure that we are truly dealing with HFpEF. And also that we're not missing something like cardiac amyloidosis, we're not missing hypertrophic cardiomyopathy. And so it's really important to both have a template when you approach these patients so you don't miss things, but then also to do the adequate amount of testing so that, you know, confidently that you're dealing with this.

And I am routinely referring patients for exercise right-heart cath so that I know what I'm dealing with and that I know for example that I'm not dealing with something like pulmonary hypertension. Once we have the diagnosis correct, you're absolutely right, that this really requires a multidisciplinary intervention for a couple reasons.

One is that the comorbidities that these patients have often drive the heart failure. So, you have to kind of put your money down on addressing these patient's comorbidities, whether it's sleep apnea, whether it's diabetes, whether it's weight loss. So, we rely heavily on our colleagues in sleep medicine and endocrinology, in bariatrics, and obesity related medicine to really try to address these comorbidities.

AFib plays a huge role in these patients' symptom burden. And so, we rely very heavily on our electrophysiology colleagues to weigh in on sort of rate and rhythm control for these patients. And then the other thing that we offer is really a tailored approach to the medical management, including the diuretic management, both to get these patients feeling better, but then in general, to try to reduce the amount of diuretics they need in the long term.

In that respect, we rely heavily on our nursing partners and on our nurse practitioners and our colleagues in renal, to try to work to keep these patients out of the hospital. The last thing I always try to do is to figure out sort of what is making each patient's heart failure syndrome tick because many of these patients, even though they have a common diagnosis, are coming to that for various reasons.

And so that's where I sort of discuss phenotyping where we better understand what's driving the patient's heart failure so that we can better care for them. And lastly, and I think we can't underemphasize this, like any condition where the prognosis is more poor than we'd like and where there's a paucity of drug and

device interventions, we strongly encourage our patients to participate in clinical trials. And so, that's another area where at Penn Medicine we can offer our patients something they can't get everywhere. And whether it's an exercise intervention, a drug intervention or other, we really have over a dozen NIH and investigator initiated clinical trials to offer our patients.

And many of them take advantage of these and enjoy what that offers them in addition to the clinical management. So, that's how we approach these patients. They're all different. They all require a different workup and management. But then ultimately we try to offer them what clinical trials make sense for them.

Host: Finally, Dr. Prenner, what would you like referring physicians to know if they have a patient with suspected HFpEF and when you would like them to refer to the specialists at Penn Medicine?

Dr. Prenner: So, as I mentioned before, heart failure with preserved ejection fraction is very common. Two to 3% of the American population has congestive heart failure. And nowadays, upwards of 50 to 60% of it is preserved ejection fraction, as we're getting better at treating a lot of the things that lead to people developing a left ventricular dysfunction.

And so, this is a common form of heart failure that's only becoming more common as you mentioned in the beginning of our discussion. And so, the first thing to mention again is that people have to have a very sort of high index of suspicion for this. If you have a patient in their sixties and seventies who has unexplained shortness of breath, you should very quickly think about this diagnosis.

And part of it is taking a history. The other as I mentioned is that again, with the scoring system, telling us that the common risk factors for HFpEF are diabetes, high blood pressure and obesity, if you see somebody who's short of breath with those comorbidities, you should definitely be thinking about HFpEF.

In terms of when people should be referring, I think it's really, for two reasons. One is if after you've applied the scoring templates and checked some blood work and gotten an echocardiogram, you're sort of not having enough evidence to convince you that this is, or is not the case, you know, you're in sort of this intermediate risk. That's definitely a reason to refer because we can do a little bit of a deeper dive and recommend the appropriate next test, which may or may not be catheterization, but may be a stress echo or a cardiopulmonary exercise test or an MRI. So that's one reason to refer is if you have a patient

with unexplained shortness of breath, and you've applied these risk scores and you're getting sort of an intermediate result. That's a good reason to refer.

The other is the patient who may be carrying around this diagnosis. And it wasn't always labeled as HFpEF, it was called diastolic heart failure, or it went by other things or just chronic volume overload and the patient is a frequent flyer in the hospital or they're really symptomatic. And yet when you look at them, their EF is normal and you're not sure why. These are people who are also very important patients to refer because once heart failure patients start getting hospitalized for heart failure, and particularly more than once, their prognosis and the natural history of the disease is very poor.

And so these are people who should definitely be referred sooner than later. We can make sure that they have been appropriately worked up and then consider things like PA sensors to work with them and keep them out of the hospital. So those are two common groups that should be referred.

Host: What an informative podcast this was Dr. Prenner. Thank you so much for joining us and sharing your incredible expertise and telling us about the program for HFpEF at Penn Medicine. To refer your patient to Dr. Prenner at Penn Medicine, please call our 24/7 provider only line at 877-937-7366, or you can submit your referral via our secure online referral form by visiting our website at pennmedicine.org/referyourpatient. That concludes this episode from the specialists at Penn Medicine. For updates on the latest medical advancements, breakthroughs and research, please follow us on your social channels. I'm Melanie Cole.