

Robert Fraser:

[00:15](#)

(music). Good morning. Welcome to the AHA HCM podcast titled hypertrophic cardiomyopathy, diagnosis and clinical implications of structural phenotypes. This is one of a series of podcasts from the American Heart Association HCM initiative, sponsored by Bristol Myers Squibb. I am Rob Fraser, cardiologist with the Minneapolis Heart Institute hypertrophic cardiomyopathy clinic. Today I am joined by three special guests with expertise in the field of hypertrophic cardiomyopathy. We have two physicians and one patient representative.

The first, Michelle Kittleson is director of education and heart failure and transplantation, director of heart failure research, and professor of medicine at the Smidt Heart Institute, Cedar Sinai. She has clinical expertise in the management of hypertrophic cardiomyopathy, particularly in the management of advanced heart failure and was a member of the writing committee for the 2020 ACC AHA hypertrophic cardiomyopathy guidelines.

Our second guest, Dr. Michael Burke is an assistant professor of medicine at Emory University in Atlanta. He runs a research laboratory that focuses on understanding the biologic mechanisms and cause of abnormal heart function in genetic cardiomyopathy. He has clinical expertise in the management of hypertrophic cardiomyopathy, advanced heart failure, and cardiovascular genetics with an emphasis on cardiomyopathy genetics. He was a member of the writing committee for the 2020 ACC AHA hypertrophic cardiomyopathy guidelines just like Dr. Kittleson.

And our third guest, Kathryn Redmond is a hypertrophic cardiomyopathy patient who was diagnosed around 2008 after many years of symptoms. She has tremendous insight into the challenges of living with the condition and we're very happy to have her with us today. Over the next 30 minutes or so, we'll discuss the similarities and differences of obstructive and non-obstructive hypertrophic cardiomyopathy, including the diagnosis and management of these two phenotypes or variations of the same disease. So with that being said, I'd like to jump into this conversation. Dr. Burke, to frame our discussion today, can you remind us what is the definition of hypertrophic cardiomyopathy?

Michael Burke:

[02:32](#)

Sure. So hypertrophic cardiomyopathy is left ventricular hypertrophy of greater than or equal to 15 millimeters in any LV segment when there's no clear alternate diagnosis such as hypertension, aortic stenosis, some kind of infiltrative process,

and if the individual has a known pathogenic mutation, then the criteria is greater than or equal to 13 millimeters for diagnosis.

- Robert Fraser: [02:57](#) Thank you for framing things, and Dr. Kittleson, what do we mean when we say obstructive and nonobstructive hypertrophic cardiomyopathy?
- Michelle Kittle...: [03:06](#) Sure. So obstructive versus nonobstructive hypertrophic cardiomyopathy is based on the pathophysiology of the condition. So you have septal hypertrophy, thickening most commonly in the septum, which leads to narrowing of the left ventricular outflow tract, which then leads to abnormal blood flow that dynamically displaces the mitral valve leaflets, ultimately leading to this pressure gradient or a dynamic outflow tract obstruction. So obstructive hypertrophic cardiomyopathy will have evidence of dynamic outflow tract obstruction on echocardiogram. Contrast that with nonobstructive cardiomyopathy where this outflow tract gradient will not be seen on echocardiogram.
- Robert Fraser: [03:51](#) Thank you for clarifying. Dr. Burke, how does the mitral valve and its leaflets as well as the subvalvular structures contribute to what Dr. Kittleson described as the obstructive phenotype or the obstructive version of hypertrophic cardiomyopathy?
- Michael Burke: [04:05](#) There's really two main mechanisms. First with classic asymmetric septal hypertrophy or ASH, which is the majority of HCM cases, the flow vector of blood going out the LVOT is actually changed. And the second is that there are, as you mentioned, a range of subtle anatomic abnormalities of the mitral valve and the sub mitral apparatus that predisposed to systolic anterior motion or SAM. So these are things like elongated mitral valve leaflets and anterior displacement of the papillary muscles or the chords. I think to understand this, you need to kind of imagine things three dimensionally.
- First, remember that the LV myocardium is arranged in overlapping sheets of cells that effectively cause the LV to contract in a spiral fashion that generates a flow of blood up the LVOT and out the aortic valve sort of like wringing out a wet towel. Now imagine that you're looking at the LVOT and the aortic valve from the apex. So you've got the mitral valve on the right and the septum on the left. With ASH, that septum is now largely blocking the direct line of flow out the LVOT and it forces the blood to go around the septum, and then it becomes really directed at the mitral valve, particularly at the anterior mitral leaflet.

So as the blood flows around this bulging septum, the AMVL essentially gets caught, if you will, by this abnormal blood flow and it gets pulled towards the septum, and that is SAM. Mind you recall, these leaflets are also anatomically predisposed to being more in the way really by being either anteriorly displaced or longer than normal and as systole progresses, the septum comes further into the LV all of a sudden. In late systole, the anterior leaflet comes so far over and actually classically touches the septum, at which point you get this surge in LV pressure because blood flow going out is blocked.

And that's why on echo, you'll see this classic late peaking, dagger shaped Doppler wave form, and as a note for fellows that are listening, seeing SAM in real-time on 2D echo can actually be challenging when you're learning how to read echo, but you can see it really well on M-mode, probably one of the best uses of M-mode. You'll see that in the parasternal long axis view when the tracer goes through the septum and the mitral valve.

- Robert Fraser: [06:20](#) Thank you very much. That was a very thorough and helpful answer. So Kathryn, I want to jump to you and get your input. We've now heard very nicely about how obstructive and nonobstructive variations are really the same disease, but patients can have one or the other. Are you clear on what phenotype or which variation of hypertrophic cardiomyopathy you have? Has that been explained to you by your physicians?
- Kathryn Redmond: [06:46](#) Hey, hi guys. Yeah. I've been very lucky with my heart team that they're very honest and straight forward with me. So I do have obstructive. So it's been diagnosed back in 2008.
- Robert Fraser: [06:58](#) All right. And we're going to come back to you and talk a little bit about your diagnosis and treatment a little bit later. Thank you very much. Dr. Burke. I want to come back to you one more time. Can you talk a little bit about how we diagnose obstructive versus nonobstructive HCM? Are there any particular protocols or cutoffs that Dr. Kittleson might've hinted at earlier when we talk about pressure gradients and such?
- Michael Burke: [07:19](#) Sure. So the pressure gradients that we're looking at are greater than 30 millimeters of mercury is considered obstructive and generally, greater than 50 is considered pretty severe obstruction. To figure this out, I think to start, there are several physical exam maneuvers that can actually help you in the clinic and the maneuvers are actually all based on changes in LV load and contractility, and if you understand that concept of LV load and contractility, you can understand obstruction very well in

HCM. The one that's most commonly mentioned is Valsalva, but other ones are squat to stand, hand grip, passive leg raising, walking even, although that's a little impractical, I think in clinic.

So if you want to start with, let's start with Valsalva since that's at least to me, anecdotally the commonest one that people use. So Valsalva actually induces a very complex and temporal set of physiologic changes, but for the purposes of this discussion, a properly performed Valsalva will ultimately impede venous return, makes the LV chamber size a little smaller, increases the sound of the murmur as the gradient goes higher. Now the problem is not everyone performs a Valsalva properly. So this is one of these things that if it changes, it's informative, but if not, it doesn't actually help you because it could just be that the patient didn't perform an effective Valsalva maneuver for you.

It's why when you're sending someone for an echo, you can't stop with the Valsalva if the gradient doesn't change that much. You still need to exercise them. So I'd actually like to put in a plug for my favorite, which is actually the squat to stand. So first off, what you do is you have the patient stand up in the exam room. Then with the stethoscope on the chest, you have them squat. This quickly increases venous return and SVR so you're increasing both preload and afterload, and the net effect is usually a decrease in the sound of the murmur. Then, again while you're still listening to them, you have them stand up ideally quickly, and that reverses these changes and causes the murmur to get louder.

In my experience, it's actually the standing phase which gives the most noticeable change on auscultation, and I think that's just because people tend to go down very slowly and carefully so they don't fall on their backside, but they tend to stand up much quicker, but I don't have much evidence to prove that. That's just my experience. Now, there's going to be some patients that can't do this, someone with really horrendous arthritis, someone that's very debilitated, but with the profile of patients that have HCM, in my experience, the vast majority of these patients can actually do this maneuver. Sometimes you need the MA to come in and hold onto the other arm to balance them properly, but it can usually be done and to me, it's the most reliable physical exam maneuver.

And another one that some people like, particularly for debilitated patients, I'll use this is just a simple passive leg raise with the patient supine on the exam table. That increases venous return and will reduce the murmur. The last physical maneuver I'd mentioned is one to avoid, which is hand grip. So

this is where you do this forceful hand grip for about 30 seconds and theoretically, it increases the SVR and the LV volume, which would reduce the murmur, but it's a pretty unreliable method because the physiologic response is actually more complex than that and it's very variable person to person. I also personally have found that when you try to do this, some people will Valsalva really hard and that messes things up too. So I actually recommend against that.

You've got plenty of other maneuvers. Well, actually the last thing to mention on physical exam is to just keep your ear open for ectopy. So if someone has a PVC while you're listening to them, then the post PVC beat where the LV contractility is increased, aortic pulse pressure is decreased, they're going to have a louder murmur. It's the auscultatory version of the classic Brockenbrough-Braunwald-Morrow sign. So that's the physical exam. Now, if you're in the cath lab doing a hemodynamic study, there are several options. First off and classically used is amyl nitrate. It's an inhaled agent, it's got a rapid effect. It's an arterial vasodilator so it's going to drop afterload and increase your gradient. I should note though, that's actually technically an off-label use.

I had to actually look that up while we were doing the guidelines because I wasn't aware, and as we're aware, actually many cath labs these days are not doing a lot of human dynamics study so I find that amyl nitrate is really restricted to really big HCM centers that are doing lots and lots of hemodynamic studies, but you can also look for the Brockenbrough-Braunwald-Morrow sign by trying to induce a PVC and if your lab's equipped for it, you can also do supine exercise with the catheters in place. Now really the most important tool and certainly the most widely used is echo. Of course at rest, you still do these provocative maneuvers, particularly the Valsalva is the one that I see used all the time, and actually, many echo techs will know to do that on their own, at least in the centers that I've been at.

If the gradient goes sky high with that, you actually don't need to exercise them again. If it goes up to a hundred or something like that, you actually might be putting them at risk by doing exercise, but the exercise stress echo is likely to be the most definitive test so long as there are reasonable windows. Actually, a better way to say that would be at least of the provocative maneuvers, it's been the one that's shown to have the highest pickup rate for detecting provokable elevation of the gradient, and this is established enough that it's actually several separate recommendations in our guidelines.

So there's a Class 1 recommendation to do TTE with provocation maneuvers for resting gradient less than 50. It's a Class 1 recommendation to do an exercise echo with Doppler for symptomatic patients where the resting gradient is less than 50 and cannot be provoked, and it's a Class 2a to do an exercise stress Doppler, even in asymptomatic patients where the resting and provoked gradient is less than 50. So in summary, you've got physical exam maneuvers. The commonest is Valsalva. I'd advocate for squat to stand. You can provoke the gradient in the cath lab and then for most patients, the best test is really the exercise stress echo with Doppler.

- Robert Fraser: [13:02](#) Thank you, Dr. Burke. Dr. Kittleson, anything you'd like to add?
- Michelle Kittle...: [13:05](#) I mean, that was so amazing. I feel like I should be taking notes of all the wisdom that Dr. Burke just provided. I think it's just such a beautiful reflection of the pathophysiology in action when it comes to the physical exam and echo findings of hypertrophic cardiomyopathy, and the cath lab maneuvers are historically interesting and provide a lot of insight into the pathophysiology, but generally in this day and age of beautiful echocardiograms are not usually used clinically, but what a fantastic overview. Thank you, Mike. I love that.
- Michael Burke: [13:39](#) Thanks.
- Robert Fraser: [13:40](#) Yeah, I would emphasize that was very nice. Dr. Kittleson, we've previously talked on podcasts about the epidemiology of HCM and how it occurs in somewhere between, we think one in 200 or one in 500 Americans as best as we can tell. Do we know anything about the epidemiology of the various phenotypes, the percentage of patients that either have the obstructive or the nonobstructive variant?
- Michelle Kittle...: [14:05](#) Yes. Fortunately for all of us, it's pretty easy to remember that generally, it's a third, a third, a third. So a third of patients will have a nonobstructive phenotype and two thirds will be like our patient guest Kathryn and have an obstructive phenotype, and of those two thirds, it's pretty much roughly split. Half will have it at rest and half will have it on provocation. So a third, a third, a third, and the most important take home message there is, if you do not see it at rest, don't forget to do a provocative maneuver because half of the patients who have obstruction, which will impact management, you might not see it at rest.
- Robert Fraser: [14:43](#) Thank you. Now Dr. Burke, we're going to start to talk a little bit about the symptoms for both the variations. Can you tell a little

bit about how each phenotype causes heart failure symptoms and what those heart failure symptoms are?

Michael Burke:

[14:57](#)

Sure. So LV outflow tract obstruction typically produces a significant degree of dyspnea. So if you recall a few minutes ago, I mentioned how this is a late systolic phenomenon. Again, that's because it takes time for the LV cavity to narrow and the anterior leaflet to come over to the septum, and as a result, the gradient and therefore the symptoms produced are oftentimes highly dynamic, which is a classic feature of hypertrophic cardiomyopathy. Specifically again, this is the gradient is load and contractility dependent. So the easiest example I can give of that is that with a more hyperdynamic ventricle like you get with exercise, the symptoms that the patient reports can be effort dependent, and it's important to take a good history and pick that up from the patient.

I'd be curious to hear what Kathryn's take on that was around the time of her diagnosis, but another important thing to keep in mind is the increased LV pressure of course contributes to worsening LVH and diastolic dysfunction. Both of those things probably also cause significant dyspnea, and the outflow tract obstruction definitely can lead to transient myocardial ischemia. When that blood pressure inside the ventricle is well into the hundreds, that's going to impede that blood flow of the small coronary vessels and that causes another common symptom in HCM patients, which we don't think about as much, which is chest pain that actually can be hard to distinguish from garden variety angina and the guidelines have a lot of recs in how you can work up coronary disease in these patients.

The last thing I would also point out with the obstructive patients is that there isn't really a great correlation between symptoms and gradient. I've definitely had patients with very elevated gradients who were surprisingly asymptomatic and others with more mild elevations that were very limited. So it is a complex disease. You can't pin your hat on any one feature causing X degree of symptoms so people just need to be aware of that, but the classic LVOT obstruction is dyspnea and also chest pain. Now the symptoms in nonobstructive HCM are more likely to be due to progressing heart failure. To me, this is a more ominous phenotypic profile. Of course, I'm a heart failure, heart transplant physician, as is Dr. Kittleson so we see the end stage of this quite frequently.

Now it usually starts out as diastolic dysfunction, but at least 5% of the overall HCM population is going to progress to significant systolic dysfunction. You have to remember that this is a

disease that at the molecular level, is caused by aberrantly strong sarcomere contractility, and that translates to a baseline high-ish EF, and what we know now is that when the EF "falls" in an HCM patient, a dip down to below 50% is a really significantly reduced EF and connotes a much higher risk profile.

There's no way to really equate the two, but to me, an HCM patient with an EF less than 50 is sort of similar to a DCM patient with an EF less than 35, at least as far as my concern level goes. Now, a big caveat to that is that the HCM patients who have an EF less than 50 progress slower than do DCM patients so that's important to keep in mind. They really are different diseases, but at least it marks a higher degree of risk. Now, the distinction between these obstructive and nonobstructive diseases are important therapeutically as well.

Robert Fraser: [18:27](#) So that was a nice segue there to mention therapeutics because Dr. Kittleson, I'd like to hear a little bit about how we treat patients who have the obstructive version of hypertrophic cardiomyopathy, both from a medication perspective and then what are our options when we can't seem to get symptoms under control with medications alone?

Michelle Kittle...: [18:47](#) Yes. Perfect. I love this question. So just as Dr. Burke mentioned, the cardinal symptoms of outflow tract obstruction, obstructive hypertrophic cardiomyopathy are exertional chest discomfort and shortness of breath, and there's little correlation between symptoms and the degree of the gradient. So that's important for two reasons. Number one, you will titrate your therapy to symptom control. You're going to try to make the exertional chest discomfort and shortness of breath go away, and two, you will not follow the gradients on the echo to tell you how you're doing because the gradient is by definition dynamic and it doesn't correlate with symptoms. So you titrate your treatment to symptoms alone. That's very important.

So what are you going to give? Well, back in the olden days before anyone knew anything about exactly what was happening in these hearts, the giants of the day, the clinical giants of hypertrophic cardiomyopathy knew that making the ventricle relax a little more was a good thing. So beta blockers were first line and still are first-line medical therapy to treat the exertional chest discomfort and shortness of breath of obstructive hypertrophic cardiomyopathy. Beta blockers are preferred over verapamil, diltiazem, our nondihydropyridine calcium channel blockers because they're less likely to cause peripheral vasodilation, and let's keep in mind, verapamil and diltiazem are different animals than amlodipine and its dihydropyridine cousins, which should not be



used because we don't want to vasodilate these patients. They do not tolerate vasodilation well as Dr. Burke, very elegantly explained when he talked about the physical maneuvers of afterload reduction.

So beta blockers, first line over verapamil, diltiazem, titrate to symptoms. Titrate up until their heart rate's limiting, their blood pressure's limiting, and/or their symptoms go away. If their symptoms go away, fantastic. If their symptoms don't go away, then you think about other options. So what are your other options? There's other medical therapy, disopyramide, a very powerful negative inotrope, but now in this newest iteration of the guidelines, the 2020 guidelines, we've placed septal reduction therapy on par with disopyramide as the next step for patients who fail beta blocker, calcium channel blocker therapy for management of symptomatic obstructive hypertrophic cardiomyopathy. So when you're thinking about septal reduction therapy, it's patients who are severely symptomatic despite medical care, and then you have two options.

You can shave off the septum surgically, open up the chest and deal with that septum, or there's an ablation where you have a controlled myocardial infarction to that septal perforator that controls the proximal septum and makes it thinner, in both cases, trying to shrink down the septum to remove the outflow tract obstruction. Which one do you choose? Well, myectomy tends to be more durable and ablation tends to have about a 10% risk of complete heart block. Anywhere from seven to 20% of patients in trials and observational registries may need repeat ablation. So it really depends on is the patient a surgical candidate? How old is the patient? How frail is the patient and what are the patient's preferences? It's a great area for shared decision-making, going through the risks, the benefits, and the patient's goals and preferences. So that's where we stand today from an approved medication standpoint or approved therapy standpoint, beta blockers, calcium channel blockers, disopyramide, then septal reduction therapy on even par.

Mavacamten, which is not yet approved, but is a very, very exciting advance, which I'll touch on briefly since there's no current clinical application for it. So it's really exciting in a way because this is finally disease directed therapy. Instead of randomly targeting the fact that this heart is just too strong for its own good with beta blockers or calcium channel blockers, now there is a myosin inhibitor that specifically reduces that excessive cross-bridging with actin that's the major problem in hypertrophic cardiomyopathy. So pathophysiologically directed therapy that has now been shown in a Phase III trial EXPLORE-

**Commented [PSL1]:** Dr. Kittleson misspoke. She should have said "myectomy" instead of myomectomy. Myomectomy is removal of uterine fibroids. Can you cut out the "om" part so it sounds like myectomy?

**Commented [SS2R1]:** I will have her re-record this sentence.

HCM, patients with obstructive symptomatic hypertrophic cardiomyopathy, that there was better exercise capacity as measured by maximal oxygen consumption and symptoms. So I think this is a very exciting advance, and it remains to be seen where mavacamten is added to the current clinical algorithm.

Robert Fraser:

[23:32](#)

Thank you, Dr. Kittleson. That was a very nice, very thorough discussion on medical therapy for obstructive HCM. I want to point out that in the future, we'll have dedicated podcast to address the ins and outs of septal reduction therapy and likely to also address the new novel therapies that are coming up the pipeline for patients who have hypertrophic cardiomyopathy. Dr. Burke, let's hear about the other half. What do we have for medications and interventions for patients who have the nonobstructive version of hypertrophic cardiomyopathy?

Michael Burke:

[24:03](#)

So first of course, there's asymptomatic and symptomatic patients. So for asymptomatic nonobstructive HCM, there's really not a clear drug treatment option at this point. I'm only mentioning this because I want people to stay tuned because this could change drastically in the coming years. There are a couple of studies ongoing to see whether certain drugs are actually disease modifying, and these are some people are looking at ACEs and ARBs and of course, mavacamten with their other Phase II trial showed, and certainly, the excellent work from MyoKardia by Eric Green that was published in science a few years ago, shows that in the animal models, mavacamten actually looks to be disease modifying, meaning that it can actually reduce the amount of hypertrophy in established HCM models.

So that could change the entire field. That would probably be one of the biggest advances in HCM since the definition that it's of monogenic disease, but we don't have the data yet. So for asymptomatic patients, there's nothing that we do right now other than our serial screening. Now for symptomatic nonobstructive HCM, of course, the story is different. As I mentioned before, this is kind of more consistent with evolving heart failure, and I should note that there really is not good data in this population, but our current recommendation in general is to treat this like it's heart failure. So if their EF is still 60%, but they have heart failure symptoms, a lot of times, these people are going to have some volume overload. So considering diuretics as appropriate.

Of course, you've got to be judicious because if you over-diuresis these people, you may actually produce a gradient in someone that's got significant septal hypertrophy, but once

their EF starts to dip, which again, for an HCM patient is less than 50, again also without terrific data, we recommend typical neuro humoral blocking drugs, but the reason we say this is that the remodeling process, once the EF starts to drop, whether you're looking at serum levels of norepinephrine, or if you're looking at animal models and looking at genetic or transcriptomic profiling, you see very similar processes going on in failing hearts, whether the primary insult was HCM or DCM. So we believe that this is reasonable. We don't have cause to think that neuro hormonal blocking drugs would not work in HCM patients.

Robert Fraser: [26:25](#) All right. Thank you. Kathryn, we've had a really nice discussion about so far, both the diagnosis as well as the different medical therapies for patients who have either obstructive or nonobstructive hypertrophic cardiomyopathy. Now tell us a little bit about your course. What were symptoms? How were they treated? Was it straightforward or have there been twists and turns?

Kathryn Redmond: [26:49](#) There's been a whole journey. There's a lot of symptoms. Try to make me comfortable. I mean, I went to the doctor because I was having severe chest pain all the time. It felt like I was having a heart attack. Also, I was shortness of breath. I was passing out. My blood pressure kept dropping. My heart was racing through the roof. I mean, I felt very weird and this is very abnormal for somebody that's in their twenties and stuff. So finally, I was screened back in 2008 and they started me on beta blockers, which I've noticed it does help, but the problem is that didn't totally help. So I had to have open heart surgery to trim the septum, even though that's growing back now, which is sad and scary at the same time.

I've also been put on a pacemaker defibrillator since I kept going in cardiac arrest. So it's to balance out with that, with now, with the fluid in the lungs because I'm on eight diuretics a morning and also my kidneys are failing. So I mean, it's exhausting trying to balance out all the symptoms. I mean, the electrical part, I have patients A-Fib, tachycardia, and now I told my team and they checked it out. My heart does stall in the different parts so they're trying to do therapy so it doesn't feel like it's stalling because you could just be walking around or sitting and you just feel a small pause and it starts beating. So it's scary, but I'm glad I'm still here.

Robert Fraser: [28:10](#) Yeah. Kathryn, thank you so much for your willingness to share your story with us. Having seen many patients with hypertrophic cardiomyopathy, unfortunately your case is

somewhat classic in that the diagnosis can be difficult to make upfront, and unfortunately, patients have many of the symptoms that you described, which in retrospect, they're all very classic. Chest pain and passing out and palpitations or racing heart are all easily attributed to hypertrophic cardiomyopathy in retrospect, and then treatment can be both successful, but come with its own complications and challenges.

You highlighted the need for surgery, and I'm sure the recovery from that was not straightforward and having to have the device placed, followed by some issues with diuretics and the impact tit can have on the kidneys. Our heart goes out to you and I really, really want to thank you for sharing your story with us today. It's very educational. Dr. Kittleson, Kathryn mentioned the need for a pacemaker or defibrillator. I do just want to touch on for clarity's sake. Does the fact that someone has either the obstructive variant or nonobstructive variant contribute to their need for a defibrillator, or is that a different discussion?

Michelle Kittle...: [29:22](#) Great point and I also want to thank Kathryn. It's so humbling and important for us to realize, in addition to knowing all the medical facts, the patient experience is so critical. So to get to your question, the short answer is no. The guidelines for primary prevention defibrillator sudden cardiac death risk stratification are the same whether you have obstructive versus nonobstructive cardiomyopathy. A big update in the 2020 hypertrophic cardiomyopathy guidelines is that the degree of left ventricular outflow tract obstruction no longer impacts the decision as a risk modifier of whether or not you place a defibrillator for primary prevention because it was shown not to be an independent factor. So regardless of their phenotype, you use the other measures which were discussed in a recent podcast to risk stratify patients appropriately.

Robert Fraser: [30:15](#) Thank you for clarifying, and Dr. Burke, if you could, I have just one more question I want to wrap up with because it's somewhat of a common clinical conundrum, that is patients with hypertrophic cardiomyopathy can develop routine cardiovascular disease, most commonly hypertension. Can you just speak to the implications of treating someone who has both hypertension and either variation of hypertrophic cardiomyopathy?

Michael Burke: [30:42](#) Sure. So the simple answer is you have to treat the hypertension because we obviously can't have people walking around with blood pressures of 190 over 100 just because they have HCM, but it is important to highlight that particularly with

patients that have obstructive, whether it be resting or latent obstruction, we generally try to avoid vasodilators because that can worsen the obstruction by lowering the afterload, but if you have someone that has concomitant hypertension, you do have to give them something to treat the hypertension. So now what do you give them? That's tricky. I think my first go-to is to try to get them on one of the non-dihydropyridine calcium channel blockers. So verapamil or diltiazem, which are both as we know, very good blood pressure agents as well, but they also provide you a bit of that negative inotropic effect that can help with obstructive disease.

Beyond that though, it's hard to know what to do. You just have to be cautious and you have to be gentle and I think you need to follow these patients in clinic fairly quickly with slow, careful up titration of blood pressure medicines. This is where patient education and engagement is also really helpful. I find it's very helpful if these people have a home blood pressure monitor and they can record some blood pressures and bring that into clinics so that I can be very assured that their blood pressure is not dropping too low periodically. You also have to be very careful with your history in these people. You've got to ask them each time they're coming into clinic and you're seeing them for potential up titration of what are your symptoms? If they're having dizziness and lightheadedness when they first stand up, that could be a sign that their gradient is worsening and you may need to do more testing in that case.

So the patient with significant obstruction and hypertension is very hard to manage, and to some extent, that might lead you down the path of considering several reduction therapies, which we won't cover here since you mentioned that will be another podcast. Nonobstructive disease is a little bit more straightforward because if they're nonobstructive, you have a little bit more of a cushion to safely add on some afterload reducing agents to get the blood pressure down, but as I mentioned before of course, if you've got a nonobstructive patient and you start them on diuretics and you dry them out too much, you could actually provoke a gradient that wasn't there before.

Now, another important aspect to this question really is, are you sure this is HCM versus hypertensive heart disease? This is a particularly important issue because we're diagnosing HCM in more and more cases of mild disease, not like what Kathryn is describing to us, but more mild types of HCM, and that typically presents later in life. Now, things that can help make the diagnosis are if you have the classic features, ASH, SAM, apical

hypertrophy, severe LVH. Those things point towards it being HCM. Certainly, genetic testing can be really helpful in this setting because even though the field has settled out with genetic testing, we have pathogenic variants in about one in three and that's not expected to increase, but if you have a pathogenic variant, you know that this ventricular hypertrophy with concomitant hypertension is likely still HCM.

One more interesting caveat that is relatively new is that hypertension is likely causal of the HCM phenotype in some cases. So there was a landmark paper, actually two in fact, but one that directly showed the effect of hypertension. These were published in Nature Genetics just in February of this year. The first study is really important because it shows the first really conclusive evidence that at least a portion of HCM patients are actually, it's actually a polygenetic disorder, not monogenic.

But with regards to hypertension in this, they used a worldwide HCM cohort, a huge cohort of thousands of patients and they showed an extraordinarily strong association that was likely causal between HCM and hypertension, particularly for sarcomere gene negative disease, and that's important because it makes the whole spectrum of HCM a little bit more complicated because it suggests that at least in some cases of HCM, HCM may actually be an exaggerated response to hypertension in a genetically susceptible individually.

Robert Fraser:

[34:54](#)

Thank you. It's a very important topic and overlapping topic so I think it's important that we touch on it. With that being said, I want to thank our listeners for tuning in today, special thanks to our guests, Dr. Kittleson and Dr. Burke for sharing their expertise. Very special thanks to our patient guest, Kathryn, for sharing her story. We've had a really nice thorough discussion about two different phenotypes of hypertrophic cardiomyopathy, and as a reminder, this podcast has been a part of the American Heart Association HCM initiative, which is sponsored by Bristol Myers Squibb. In closing, I'd like to advocate all patients and providers to engage in shared decision-making for all aspects of HCM care because one size does not fit all. For more educational material, please visit the American Heart Association HCM patient website. Thank you very much. (music).