00:00 – 00:45 Welcome and thank you for joining this podcast titled Hypertrophic Cardiomyopathy. 7 introductory insights. I'm Rob Fraser, a cardiologist at the Minneapolis Heart Institute. I'm joined today by Dr. Miguel Leal, a clinician, educator and the director of the arrhythmia and electrophysiology service at the University of Wisconsin, Madison. As well as Doctor Ferhaan Ahmad, a physician scientist, cardiologist, cardiovascular geneticist and director of the HCM Center at the University of Iowa. The purpose of the AHA HCM Podcast series is to educate healthcare professionals on hypertrophic cardiomyopathy to improve the care of affected patients through early symptom recognition, diagnosis, and treatment. The American Heart Association's HCM initiative is sponsored by MyoKardia, so let's jump into the discussion.

00:46-00:50 To kick things off, Doctor Ahmad. How much of a societal problem is hypertrophic cardiomyopathy?

00:50-2:29 Well, that's an incredibly important question Rob, because, it's really quite under recognized in general. We don't have an exact number in terms of the prevalence, we think, it totally is, was likely the most common sort of heritable single gene cardiovascular disorder. Initial estimates were that 1 in 500 people in the population might have hypertrophic cardiomyopathy. And that was based mostly answered imaging studies but now that we have some understanding of the genetic basis for hypertrophic cardiomyopathy, the we think that it might actually be as high as 1 in 200 in the general population, so that really means that somewhere between 650,000 and a million Americans might have hypertrophic cardiomyopathy, which really makes it not only the most common disorder, but also in terms of cardiovascular disease, also probably more common than many other sort of heritable disorders like cystic fibrosis, ALS, multiple sclerosis for example. And it really does affect people of all ages, so children can get it. More commonly we start seeing it in puberty and beyond, but we can diagnose it even in the elderly. And it's not just an American problem, but really, it's a worldwide problem and I think probably almost every country in the world has cases of HCM themselves recognized, but it's already been documented over 120 countries, and so the problem is I mentioned is that it's really kind of under recognized and the majority of individuals who have HCM probably don't even realize they have it. So based on claims data, for example, we think that maybe you know only one out of seven individuals that has HCM is actually receiving appropriate care for it.

02:30-03:34 Doctor Fraser, if I might, I'd like to add the fact that this is actually a very timely podcast because we're finally now beginning to understand the natural history of this disease condition. In the past it was really hard to appreciate what hypertrophic cardiomyopathy can do to a patient's life span, because it is true that the later stages of this disease sometime result in what we call systolic heart failure or decompensated clinically manifested heart failure. But a lot of those patients they never make it to that stage, because sudden cardiac death, which is one of the most unforgiving aspects of hypertrophic cardiomyopathy, claimed so many of those lives and now, thanks to a lot of treatment modalities that we finally have available to offer to these patients on a routine basis, we have been able to understand this disease from its very onset when the diagnosis is made and hopefully such diagnosis is made at earlier stages nowadays than it used to be in the past, but also to prognosticate to tell these patients and their families what is the expected course of that disease progression and more importantly, trying to not only alleviate any pain or suffering, but also improve their quality of life throughout their lifetime.

03:34-03:42 It's clear we've learned a lot about hypertrophic cardiomyopathy. Can either of you speak to its history and how long we've known it exists?

03:42-05:43 Absolutely, this is an interesting story that began outside of our field of cardiovascular medicine. So back in London all the way back to the 1950s. So we're talking about a disease condition that has over seven decades of knowledge. Dr. Teare, pathologist at St. Georges Hospital. And he began to notice that there were autopsied hearts of patients who had suffered sudden, unexplained death, they had one thing in common. Those hearts were very hypertrophied. They were very thick. The musculature in the heart, did not appear normal either macroscopic or microscopically, and initially the first presumption was that there could be a tumor. Maybe this was another neoplastic process that happened to infiltrate amidst the myocardial fibers and caused some degree of decompensation, either electrical, mechanical or both. And then over the last 70 years, as you pointed out, a lot has been learned and the source of that knowledge has been very, very diffuse. We learned through the advancements in our cardiac imaging studies. It is undeniable that echocardiography has played a major role in letting us understand what businesses can do to patients, and also even to propose some type of diagnostic modalities or diagnostic criteria that allow us to understand what is hypertrophy that comes from, say, high blood pressure, systemic hypertension versus the true genetic disease that essentially occurs at the sarcomere level within myocardial cells. It is also true that clinical genetics have allowed us to move leaps and bounds forward because like many other inherited arrhythmia conditions or inherited cardiomyopathic syndromes, we do not have a full understanding of what genes can lead to this disease, and moreover, and even if a patient has a certain mutation, it does not necessarily mean that he or she will manifest what we call week the phenotypical characterization of the disease, but all of those pieces of knowledge that have added to each other over the past seven decades have allowed this to move forward from a pathological observation from a hospital in London, to the widespread knowledge that we have about this condition today.

05:44-05:56 That is a fascinating history and you make a nice point regarding the genetics. Doctor Ahmad you have considerable experience with hypertrophic cardiomyopathy genetics. Can you speak a little bit about it?

05:56-10:41 Sure, when I was in medical school, this disorder was idiopathic. In fact, that one of the first terminologies for this disorder in in the mid-20th century was idiopathic hypertrophic subaortic stenosis. And indeed, it was idiopathic and is only actually just about to graduate from medical school that the first genetic variant in a family with hypertrophic cardiomyopathy was reported. And, really, it's only at that point that we no longer considered hypertrophic cardiomyopathy to be an idiopathic disorder, because we actually did finally have some idea what the causes might be. So it turns out that I still have a lot to learn, but in terms of the genetics, we have identified collectively and almost all investigators around the world...we've identified some around 11 genes that have variants that can lead to hypertrophic cardiomyopathy. That number of 11 genes is a little bit fluid. In fact, the level of evidence is probably strongest for these eleven genes or so, but in fact, there's probably another 10 or 15 genes that have been proposed also, to be associated with hypertrophic cardiomyopathy, but with varying levels of evidence. The interesting thing is about the story about the genes where the evidence is strongest that they are associated with hypertrophic cardiomyopathy. All encode proteins that are in the sarcomere or associated with the sarcomere. So, in one sense, hypertrophic cardiomyopathy is could be considered a disease of the sarcomere, and we have so many hundreds of thousands of

variants that have been described in different individuals and families with hypertrophic cardiomyopathy at this time. Having said that, uhm. We still are not able to identify variance in every individual in every family. So, depending on whether there's a positive family history or not in any individual patient with hypertrophic cardiomyopathy, roughly somewhere between 30 and 50% of the time, or 30 and 60% of the time, you would actually find a pathogenic variant that you're confident is causing hypertrophic cardiomyopathy in that individual. So that still leaves quite a large proportion of patients where we are unable to identify a pathogenic variant. And that's due to a number of reasons, some are technical some are related to the fact that variance can be present in non-coding parts of genes where we really have much less knowledge and we really can't necessarily interpret a variant in a non-coding part of a gene to be definitely pathogenic or not. Also, there are probably other genes that can be associated with hypertrophic cardiomyopathy at a lower prevalence and we just haven't yet identified them as being associated with hypertrophic cardiomyopathy, so we don't have a screen for them for variance. There is also some hope that we can use genotype information, or specific variant information in patients to prognosticate or to guide therapy. And that still a work in progress. In general, I define specific variances, specific genes doesn't necessarily let us tell the patient as an individual what their prognosis is going to be. Although at the more population level, we do have some degree of genotype/phenotype correlation now For example, the SHaRe registry has shown that individuals who have variance in genes identified in the sarcomere protein and coding genes identified tend to have poor outcomes compared to patients that do not have an identifiable variant in their genes. So that is sort of a 30,000-foot level birds eye view of genotype/phenotype correlation. We are still not that good at using that information for specific patients. However, genetic testing extremely valuable for several reasons. One is just to confirm the diagnosis where the diagnosis is unclear and ambiguous. And if you do identify a pathogenic variant that is very helpful and so confirming that diagnosis. Also, we can get fooled as to what the diagnosis is on the basis of just imaging data. For example, there are phenocopies, these are disorders that look like hypertrophic cardiomyopathy but are actually distinct disorders that have distinct therapies. And so genetic testing can sometimes distinguish between these different disorders. So, for example Fabry disease is a completely different storage disorder for which there is a distinct therapy namely enzyme replacement therapy and so you obviously don't want to miss that diagnosis. It's also helpful for families to identify a pathogenic variant in a patient that information can be used to screen individuals and families to determine whether that risk of developing hypertrophic cardiomyopathy or whether they already have hypertrophic cardiomyopathy. And it's a faster, easier and cheaper way of screening family members than doing serial gene studies for example over a lifetime

10:41-10:46 So, for a variety of reasons genetic testing is extremely helpful in many patients and many families.

10:46-10:55 So, in summary, it sounds like we learned a tremendous more knowledge about hypertrophic cardiomyopathy in genetics although we still have a lot to learn.

10:55-11:06 I'd like to shift gears a little bit and Dr. Leal, I have a question for you. And that is can you talk to me a little bit about the intersection of hypertrophic cardiomyopathy and athletes?

11:06-13:39 This is a great question Rob because it essentially comes down to the very core of how this disease became of common knowledge in the United States and beyond. I think by now everyone

has read an article or watched some type of media production on an athlete, typically a young person, potentially with the promising career ahead of him or her, who unfortunately succumbed to this condition. Because as we mentioned before, one of the very unforgiving features of hypertrophic cardiomyopathy is that it can have it's very first clinical manifestation be sudden cardiac arrest. And we all know from several registries that this survivability of an out of hospital cardiac arrest scenario is not high. It depends on the availability of resources such as AEDs, and also folks that are invested and trained to bring patients back from arrhythmias can be fatal. So, athletes are known to be affected by hypertrophic cardiomyopathy to an extent that has caused a significant degree of commotion in the public. Because some data suggest that hypertrophic cardiomyopathy is the single most common cause of sudden cardiac death in that patient population, and the deaths of young or professional athletes have certainly brought attention to this condition. We are all familiar with Reggie Lewis, and Reggie Lewis is a very famous basketball player who devoted preparing for a successful career with the Boston Celtics and he died suddenly during practice back in 1993. And Reggie Lewis was 27 years when he died and that immediately brought media attention to a condition that apparently can affect anyone and there is no specific predilection for disease condition or for health status. In fact, those individuals, those professional athletes, are what we consider the pinnacle of health. These are people that we do not see dropping dead in the street or doing the practice of any professional exercise activity. So, one of the consequences of this concern in this reality, is that people began to wonder and ponder if we should have a universal screening recommendation for athletes. Should we be looking for hypertrophic cardiomyopathy in each and every single professional athlete, men and women, regardless of age and regardless of sport. And some interesting observations have stemmed over the years, number one is that we still do not have a current universal recommendation. Because of the fact that you have to screen a massive amount of individuals to collect a very small number of potential problems, potential cases, and that has not been either feasible or proven to be the way that a standard of care should go about when it comes to these large, collegiate type athletic associations. The other interesting feature is that the type of modality that is played or practiced seemed to matter as well.

13:39-13:57 So it is a very important condition to be made aware of for folks who deal with young adults, especially with a sports medicine professionals, this is something that has to be in your mindset because if this disease is unrecognized or left unattended, it could be responsible for tragedies as we have seen over the last few decades.

13:57-14:04 Doctor Ahmad can you talk a little bit about how we diagnose hypertrophic cardiomyopathy and how we might differentiate it from some other conditions?

14:40-17:12 Well the cornerstone of diagnosis is history, physical exam, electrocardiography and then really probably the most important aspect is imaging which is usually echocardiography and now increasingly is cardiac MRI as well. And on imaging, some criteria we use, essentially as the name implies, hypertrophic cardiomyopathy is characterized by hypertrophy or abnormal left ventricular wall thickening. And it doesn't just have to the left ventricle, it can be biventricular as well, but so that the traditional criteria we've used is that if left ventricular wall thickening is greater than 15 millimeters in all-comers or at least 13 millimeters in someone has a family history of hypertrophic cardiomyopathy that's usually sort of our general guideline to make a positive diagnosis for hypertrophic cardiomyopathy. But it's important to remember that unfortunately life isn't always that

simple. Individuals, certainly through genetic testing now we know that individuals who may have pathogenic variants, but even individuals who don't have genetic information, they may have early hypertrophic cardiomyopathy with relatively mild or no hypertrophy and yet may still be at risk of certain adverse outcomes, so it is actually some of the difficult diagnoses to make sometimes. Aside from thickening, other abnormalities that may come up, certainly on cardiac MRI imaging, you may see evidence of late enhancement or fibrosis, T1 mapping might be abnormal suggesting that there is indeed some sort of abnormal fibrotic process occurring in the myocardium of these patients. Most patients with early hypertrophic cardiomyopathy do have some perhaps non-specific abnormalities, still some abnormalities on electrocardiogram too so that can help a little bit. The issues are again the differential diagnosis, so individuals may have some degree of cardiac hypertrophy but not attributable to hypertrophic cardiomyopathy. So, for example individuals with hypertension or valve disease like aortic stenosis, may have some degree of hypertrophy. Usually it is milder than what is typical for hypertrophic cardiomyopathy, and it's usually concentric whereas individuals with hypertrophic cardiomyopathy can certainly have concentric hypertrophy but the more sort of classical patterns are asymmetric septal hypertrophy or sometimes apical hypertrophy. Sometimes the pattern of hypertrophy and the degree of severity of hypertrophy can help you distinguish from other acquired forms of cardiac hypertrophy verses hypertrophic cardiomyopathy. And again, as we kind of discussed earlier, we want to rule out other potentially genetic phenocopies of hypertrophic cardiomyopathy that are actually due to other disease processes. So, for example, amyloidosis, some of the storage cardiomyopathies are due to genes that are not sarcomere protein encoding genes and have distinct disease processes are distinct therapies. And again, genetic testing can help in those situations. In addition, imaging, especially cardiac MRI imaging, is helpful in identifying infiltrative processes of storage processes that look different than what we see in a patient with hypertrophic cardiomyopathy.

17:12-17:22 That's a very nice overview, I'm gonna again segue, Dr. Leal can we talk a little bit about the symptoms of those who have hypertrophic cardiomyopathy.

17:22-17:32 Certainly this is a disease condition that is very complex as we've come to learn in this podcast as illustrated it really well so far, and one of the complexities comes in the fact that these patients can present in a variety of ways.

17:32-17:44 So, first of all, there are those patients are truly never really present you with any symptoms at all and their disease condition is incidentally discovered by imaging studies that may have been ordered for a completely different indication.

17:44-18:12 It is fascinating to appreciate how some patients reached the age of 60 or 70 or even beyond that without having had any discernible events that can be attributed to hypertrophic cardiomyopathy. And that essentially tells us that we have a lot to learn from those people. What exact mutations do they carry if their genetic mutation can be identified? What about their lifestyle, what about their life choices as far as the other risk factors that we all are concerned about for the onset of cardiovascular disease in general?

18:12-18:54 - So, there is a huge cohort of patients and it's estimated that it could be up to half of these individuals who have no symptoms throughout their lifetime. But that leaves an entire other half

with symptoms. Patients that can present to the clinic complaining of shortness of breath with mild to moderate levels of physical activity that was simply not the case six months before or a year prior. And that is a consequence of the fact that they have the obstruction that we were describing before. That their cardiac output is not as vigorous and healthy as it should be when the demand is there, because the septum is thickened, because there is that hypertrophy that effects the subvalvular apparatus making the heart struggle a lot harder than it should to deliver cardiac output to the rest of the body.

18:54-19:41 And as a consequence, we start having increased cardiac filling pressures and every time their heart's filling pressures go up, one of the very first symptoms then comes is shortness of breath because our lungs do not like to see that elevated pulmonary capillary pressure that is consequential to a heart chamber that has a hard time relaxing, what we call diastolic dysfunction, it is sometimes years and years before true systolic failure ensues. And about 40 to 45% of our patients will present with those symptoms. They will claim that they have inability to carry on their activities of daily living as they did before. And again, the obstructive component of hypertrophic cardiomyopathy is responsible for the vast majority of their clinical scenario, which also means that patients who do not have the obstructive components may not present with heart failure.

19:41-20:38 And now we open another chapter of presentations which is the arrhythmia syndromes, the electrical imbalances of the heart, the myocardial disarray that is the hallmark of this condition, makes the traditional organized electrical system within their hearts act in a very unpredictable manner. And now not only can you have islands of myocardial fibrosis in scar tissue that can serve as a perfect niche for reentrant arrhythmia circuits, but you also can have cells that are under overload and overcharge and they're essentially firing at will. Cells that normally would not be causing electrical activity may now be triggered by scenarios that essentially results in ventricular arrhythmias. And we know that, unlike atrial arrhythmias, with which patients sometimes can live for years or decades in a reasonable state of health, ventricular tachyarrhythmias are life threatening and they cannot just be dealt with through rhythm control strategies. You really have to abort them at the very onset otherwise you may have a sudden cardiac death case.

20:38-22:24 And the unfortunate estimate is that somewhere between 5 and 6% of these patients will present after having survived a sudden cardiac death event. Which is often the under representation of the many others will never make it to the cardiology office to the electrophysiology clinic to discuss the event that they just survived. It is also important to mention that this is a patient population with particular high rates for atrial fibrillation, again back to the analogy as they can before those increased filling pressures in the heart, they are responsible for morphologic changes in the heart and our atria, our top chambers are not really designed to handle significant pressure overload or volume overload. And as a consequence, they do dilate, they become morphologically altered, and they also become electrically remodeled. And there is a significant higher prevalence of atrial fibrillation in patients with hypertrophic cardiomyopathy. Every time we see a patient atrial fibrillation before the age of 50 or 60 years of age, this is a disease condition that is always in our mind because A fib, or atrial fibrillation is very prevalent in this patient population. In one of the main disadvantages of atrial fibrillation which is the risk of stroke or thromboembolic phenomenon is a true reality in these patients to the extent that we prescribe anticoagulants regardless of any other risk factors. If you have hypertrophic cardiomyopathy and develop atrial fibrillation you belong on anticoagulant medication to

make sure that your risk of stroke is minimized to what it should be for somebody with your age and gender in the general population without the condition. So again to summarize a very complex disease that can present as heart failure, as arrhythmias, both atrial and ventricular, and ultimately as aggressively as a sudden cardiac death events with the important caveat that a large component of patients, approximately half of them, appears to have no symptoms whatsoever

22:25-22:32 Thank you, Dr. Leale, this is a very complex condition that clearly has a very diverse presentation and set of symptoms.

22:32-22:50 Can we talk a little bit about the prognosis of patients with hypertrophic cardiomyopathy? We've talked somewhat about how we diagnose it, as well as the symptoms and the intersection of HCM and athletics, but what can we expect as far as a lifespan and the course of care for patients who are diagnosed with hypertrophic cardiomyopathy?

22:50-23:31 Rob, as Miguel was saying you know we do have all these dire consequences that had can happen. The good news and that's what I can tell most my patients is that even though these are possibilities, the vast majority of patients do very well, have a pretty much normal lifespan and reasonable quality of life. Especially if their diagnosis is made and they are under constant surveillance. And if problems arise then we mitigate those problems, the prognosis can actually, overall be pretty good. But as our job as cardiologists and physicians is to make sure that we do recognize people who might be at high risk of adverse outcomes, and then go ahead and mitigate that risk.

23:31-24:01 So probably the majority of patients, we can say that their annual risk of dying is on 1% per year, which is about the same as the general population. However, we do need to identify individuals who might be at high risk of, for example, sudden cardiac death, which is probably the most feared complication of hypertrophic cardiomyopathy. And you know when you have individuals that we think are high risk of sudden cardiac, then the usual course of action is to offer them an implantable cardioverter defibrillator, or ICD.

24:01-24:36 Now the challenge for us is to identify who is at high risk. You don't have a crystal ball, but there are a number of methods that we kind of use, or criteria we used to identify those who might get higher risk. And some of them are pretty much common sense you know, so individuals obviously who have had a sudden cardiac arrest event are going to be at high risk of having another event. Individuals who have had unexplained syncope or documented ventricular tachycardia or repetitive episodes of non-sustained ventricular tachycardia, those are individuals are more likely to have sudden cardiac death.

24:36-25:33 If they have extreme septal thickening, and the usual cut off is 30 centimeters that's considered to be at risk factor, but again it's not really a dichotomous variable. It’s not like 29 millimeters is fine and 31 millimeters is really bad. It’s really more of a continuous variable. Family history, if you have a very strong family history of people having sudden cardiac death then obviously that may lead you to think that your patient may also be at high risk for sudden death. Syncope is sometimes a very difficult thing to kind of get a handle on, but if a patient presents with a history of syncope that does sound cardiac then again, that would be a risk factor. We do have some sort of

emerging risk factors that have really been so recognized only in the past few years, and this is partly because of our improvement in imaging technology, so individuals who have extensive myocardial fibrosis or individuals who have left ventricular apical aneurysms as part of an apical pattern disease, they're probably at higher risk of sudden cardiac death as well.

25:33-25:54 There's also other potential factors we look at in terms of their hemodynamic response to exercise that can help to gauge what their risk would be. So we have to put all these risk factors together see what the patient has and come up with our own estimate of what their risk might be and if whether they would benefit from an ICD or not.

25:54-26:12 There are also some calculators that have been developed inputing a lot of the same variables we just discussed and some additional variables that we can actually just enter online if you like into a risk calculator and it will give us an estimated risk of sudden cardiac death over the course of the next five years.

26:12-26:46 And generally if you estimate the risk of being greater than 6% over the next five years, then an ICD would be warranted. But none of these ways of gauging risk is perfect, and a lot of it is still clinical judgment and often if we have a certain intermediate risk estimate and that's where it becomes shared decision making where you have a discussion with your patient to figure out what the what did what the patient would like, what level of risk are they willing to tolerate. Would they rather have a safety net in place in the form of an ICD, or would they rather wait until it's much more definitive that they would benefit from an ICD.

26:46-27:54 So again very complex, but these are some of the issues that we have to discuss in terms of prognosis when it comes to sudden death. And as Miguel mentioned patients who have atrial fibrillation, even if they have been in, sinus rhythm has been restored, CHADS-VASc scores are irrelevant in the setting of someone who has hypertrophic cardiomyopathy. And then of course, the minority of patients will actually need some sort of intervention for heart failure symptoms. People who have severe symptoms that are no longer responsive to medical therapy and have evidence of obstruction, left ventricular outflow track obstruction, and they would benefit from septal reduction therapy, either surgical septal myectomy or alcohol septal ablation. The minority of patients that have severe symptoms without obstruction, they may have symptoms because of diastolic dysfunction or because of systolic dysfunction that does occur in a small minority of patients. They may end up being candidates for cardiac transplant. So those are sort of things that we look at. A lot of dire consequences, but the good news again is that the vast majority of patients do not need any of these interventions.

27:54-28:10 Thank you, very thorough answer. It sounds like the prognosis is very individualized to the extent that each patient manifests any one of the many symptoms that patients with hypertrophic cardiomyopathy can have, and then to what extent they need and any particular therapy.

28:10-28:22 With that being, said we've had a really nice broad, introductory discussion on hypertrophic cardiomyopathy today. In regard to the condition we've covered in epidemiology, its history, its genetics, how to diagnose it, the symptoms patients experience with hypertrophic cardiomyopathy.

28:22- 28:52 We've touched on the treatment, as well as the prognosis. To our listeners, the American Heart Association is sponsoring a 6 webinar and 18 podcast curriculum focused on HCM. The first webinar was launched in May 2020 and is available for viewing online on the AHA website. Thank you for joining us today for the hypertrophic cardiomyopathy a 7-point introduction podcast. Please continue to visit the American Heart Association website for future episodes in this podcast series, as well as future webinar content.