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Innovative therapeutic approaches in hypertrophic cardiomyopathy

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CHAPTER ONE

Dr. Pantazis:
Welcome to this symposium on hypertrophic cardiomyopathy, and we will try to unhide all hidden aspects of this disease.

Let's start from the basics. Hypertrophic cardiomyopathy is a thick heart, hypertrophied heart. According to the scientific definition, what is hypertrophied in this heart, what is thick is the myocytes, the cells. We expect to see hypertrophied cells, and we also expect to see scar tissue between the cells, fibrosis, and we also expect to see loss of the myocyte architecture, which we call disarray. This is when the cells are not aligned anymore, and they lose their normal structure. On top of these, and additionally, we sometimes see microvascular ischemia, which has a number of different mechanisms. Although these are common markers, common features of hypertrophic cardiomyopathy, we don't always see them together, and we don't see them in the whole heart, they can affect different areas of the heart, and therefore we may not be able to identify them in certain parts of the heart.

Since hypertrophic cardiomyopathy is associated with hypertrophied cells, it is important that we discriminate it from other conditions that appear with a thick heart, but the cells are not hypertrophied, and the thickness and the appearance of the thick heart is because of deposits. Deposits can be lipids, such as in Fabry disease, or amyloid, such as in amyloidosis. It's important that we diagnose and discriminate those conditions early because they have different prognosis, different pattern of inheritance in the family, but also, they have different treatment. Nowadays, these conditions can be treated, can be stabilized, and sometimes reversed if we diagnose them early, so it's very important that the diagnosis happens timely. Hypertension is followed by question marks because hypertension has historically been one of the conditions that we need to eliminate from the diagnostic list before we diagnose hypertrophic cardiomyopathy. In hypertensive patients, we do see a degree of hypertrophy. Nowadays, although hypertrophic cardiomyopathy is a separate disease, we believe that hypertension sometimes can play a role in the development of hypertrophic cardiomyopathy, and therefore the two are studied very carefully together, although they're separate diseases.

The etiology of hypertrophic cardiomyopathy at a genetic level is usually associated with the sarcomeric genes, the genes that encode information for the sarcomeric proteins, and follows an autosomal dominant pattern of inheritance. The commonest genes which are affected in hypertrophic cardiomyopathy are the myosin heavy chain and the myosin-binding protein C gene. The genetic testing has a number of challenges. Patients often present with mutations, DNA changes, which have not been observed elsewhere. We call them private mutations. These are difficult to study because we don't have data on how they will behave in the future, what clinical conditions they will produce. When we send a DNA sample to the lab, we expect the lab to identify a pathogenic change in the DNA. This means that the change in the DNA can be safely associated with the clinical condition, and is expected to cause the same condition in all people who carry it. However, we often get from the lab, the result which is a VUS, which means Variant of Unknown Significance, and

it's self-explanatory. It means that the DNA change cannot safely be associated with the clinical condition. Although it may not be benign, equally, it cannot be confirmed that it is pathogenic. When we are in this situation, we need to study both the genetic change and the family in more depth and possibly follow both in the future because sometimes the classification of the VUS changes and they become either benign or pathogenic. Until we have a new classification, the VUS is a result from the lab that is not actionable. We cannot do anything with that. Another complex issue is that the changes in the DNA in hypertrophic cardiomyopathy have incomplete penetrance, so they don't give the full phenotype in all patients, and this variability can exist also within the same family. Therefore the study of both the genetic change in the family and the clinical expression in the same family, as well as in other families who have similar genetic change is both challenging and very helpful, and we have to do it when we are uncertain about the genetic result. When there is history of hypertrophic cardiomyopathy in the family, then the possibility of getting back a positive genetic result, a genetic result which is pathogenic, is higher, which means that we are in the right direction. When we confirm pathogenicity in one genetic change, in one mutation, then it does affect and cause the condition in more people in the same family.

How does the genetic change translate to the clinical condition? Obviously, it's a very long pathway. Since there are multiple genes involved and multiple mutations, it's not a straight line. The starting points can be different, but what happens, in a very short summary, is that the protein produced is either not good quality or it is produced at low levels. This is not only because it is not translated, the DNA change, but it's also because the body itself rejects the proteins which are not of good quality, and therefore the overall volume of them is reduced. In the cell, in the myocardial cell, what happens is that the actin and the myosin are bound together more firmly than what they should, and sometimes the unbinding is problematic and doesn't happen. The metabolism of the calcium is affected and this complicates this binding of actin and myosin even more, and at the end, the metabolism of the cell is more demanding. This triggers a number of pathways, some of them are gene-specific, others are nonspecific to the gene, which at the end cause hypertrophy.Many other factors play a role in this long journey, epigenetic factors, post-translational protein modifications, factors from the environment, and we are looking also into modifier genes which means that some other genes may play a role in the expression of the responsible gene and they can either enhance or reduce the expression of the main gene, causing more or less severe clinical condition.

When the patient comes to our clinic, though, all this information is in the background. What the patient is expecting from us to look at is three main domains. One is the risk of complications, and usually what is in people's mind is the risk of sudden death. It's a real risk, it does happen in some patients with hypertrophic cardiomyopathy, but fortunately, it's a low risk. The second question that the patients have is their symptoms. This is an interesting question because there are patients who don't experience any symptoms despite the diagnosis, there are patients who experience mild symptoms, and there are patients who experience quite significant symptoms which can be debilitating. The challenges here are quite few. The two main challenges are that these symptoms are quite dynamic and the patients typically describe good and bad days, good and bad periods, and therefore to get a full and holistic understanding of their symptoms needs a lot of work. The other challenge is that patients suffer from this chronic disease, and over the time they adapt their physical activities and their lifestyle to the symptoms in order to prevent them. Of course, that's the right thing to do. However, this gives us possibly a false impression of mild symptoms or sometimes nonexistent symptoms because the patients are not doing many physical activities and they have given up a number of hobbies and other activities that would have caused symptoms. Finally, we need to look at the family and consider the genetic testing, which we have discussed, but also the screening of the family members in order to diagnose them early and to make sure that they don't have risks.

Assessing the heart with hypertrophic cardiomyopathy is not very different than assessing any other heart at the beginning. However, the individual morphology and anatomy of this heart poses a number of challenges here as well. When assessing the systolic function, we usually look at the ejection fraction, which is sometimes incorrect because of the hypertrophy and the small end-diastolic volumes and overestimates the systolic function. End-diastolic function is always difficult to assess in these patients because it's multiparametric, and in probably 70% of these patients, we can detect left ventricular outflow tract obstruction which is responsible for their symptoms. This is the obstruction of the outflow of the left ventricle during systole. It's a very dynamic event, and to this, contribute the hypertrophied interventricular septum, the abnormalities of the mitral valve, the position in the left ventricle of the papillary muscles, the angulation of the interventricular septum, the contractility of the heart, the loading conditions, and many other factors which are not listed here. Essentially, this is a pathology of the whole left ventricle and not of the left ventricular outflow tract, or of the hypertrophied septum. The very detailed study of this can assist, can help us make the correct diagnosis and treat it in an appropriate way. Some patients, though, do not have obstruction in the left ventricle. When this is our impression, we need to confirm it with a number of tests and provocation tests, and if all these tests suggest that there is no obstruction, then we need to start looking at the heart muscle and how the heart muscle's stiffness contributes to the symptoms of these patients. For both obstructive and non-obstructive hypertrophic cardiomyopathy, in an ideal situation, we would like to use specific treatment and specific drugs. However, we don't have those. For many years, we have been using nonspecific treatment, treatment that has been developed for other cardiac conditions and has been used in hypertrophic cardiomyopathy, hoping that it will help these patients. The commonest medication used here is the beta blocker which have a negative inotropic effect. A small number of these patients will end up with heart failure and reduced systolic function, and

then maybe invasive and advanced options and escalation of the management are necessary, such as transplantation.

From this presentation, I think a number of points can be identified as action points, and one of them is the early and accurate diagnosis of the hypertrophic cardiomyopathy and the discrimination from other causes of a thick heart. The recertification is an ongoing challenge, which will be massively helped by big data and artificial intelligence. In terms of assessing the patient's clinical condition, we need to focus on the real life symptoms and try to evaluate them in a way that will give us useful information about who needs treatment, when, and what type of treatment. This treatment needs to be more efficient, needs to be disease-specific, it needs to address the problems which cause symptoms in hypertrophic cardiomyopathy in obstructive and non-obstructive. In an ideal situation, again, knowing now the root cause of this condition, we should be able to modify the condition or even prevent it from expressing altogether.

CHAPTER TWO

Dr. Michels:
Hypertrophic cardiomyopathy making the diagnosis.

Hypertrophic cardiomyopathy is defined by an increased left ventricular wall thickness equal or exceeding 15 millimeters. In the left upper panel, you can see the typical echocardiography image of a patient with hypertrophic obstructive cardiomyopathy with asymmetrical hypertrophy systolic anterior motion of the mitral valve, and this is a patient with obstruction.

Half of the patients with hypertrophic cardiomyopathy don't have any complaints, patients that do have complaints often complain about shortness of breath, syncope, pre-syncope, and heart failure symptoms. We are of course afraid of sudden cardiac death, especially during exercise. The pathological hallmark of hypertrophic cardiomyopathy is depicted in a right upper panel where you can see the myocardial disarray. Below that, you can see a typical CMR image of a patient with hypertrophic cardiomyopathy with late gadolinium enhancements depicting replacement fibrosis. We do have treatment options for patients with hypertrophic obstructive cardiomyopathy, like the myectomy and an alcohol septum ablation in the lower panel, and we can prevent sudden cardiac death by the implantation of ICDs. Hypertrophic cardiomyopathy is often a familiar disease with an autosomal dominant pattern of inheritance, which means you also have to take attention and care about the family members, and in patients with genetic hypertrophic cardiomyopathy, pathogenic DNA variants and sarcomere genes are present.

If we'd like to make the diagnosis in hypertrophic cardiomyopathy, we should identify patients with cardiac hypertrophy, and this starts with an index of suspicion. Of course, the patient can have symptoms like shortness of breath, chest pain, palpitations, pre-syncope, or syncope, but we often get patients referred with just an abnormal ECG without complaints or cardiac murmur. Of course, we have patients that come from a family of unknown hypertrophic cardiomyopathy and especially in first-degree relatives you should have a high index of suspicion. If you are making the diagnosis of hypertrophic cardiomyopathy, clinical assessment is focused on etiology, including genetic testing, pathophysiology, treatment options, and recertification for sudden cardiac death. The etiology of hypertrophic cardiomyopathy, in almost half of the patients a pathogenic DNA variant in the sarcoma protein gene is involved, and especially myosin binding protein C3, and myosin heavy chain are involved in hypertrophic cardiomyopathy. In almost a third of the patients, we have unknown etiology, and of course, there are also other genetic and non-genetic causes like cardiac amyloid Fabry or Denon disease, which we should call hypertrophic cardiomyopathy, phenocopies. It's really important in making the diagnosis that we also have some information about etiology, especially with new treatments entering the field.

This clinical evaluation of a patient with left ventricular hypertrophy, it's crucial to pay attention to the family history. Just draw a little pedigree signs, of course, symptoms, the ECG, cardiac imaging, and some really routine laboratory test. If you have features of a specific disease, you can either really go in that direction, or ask for specific genetic testing. If you don't have any clue which specific disease is underlying this left ventricular hypertrophy, then we continue with genetic testing. In history and physical examination, it's important to pay attention on the age and the gender of your patients as most inherited diseases occur in younger patients, and most left ventricular hypertrophy caused by hypertension, or cardiac amyloid will happen in older patients. Gender, you should also take into account gender in hypertrophic cardiomyopathy. Race ethnicity is also important, especially in inherited TTR cardiac amyloids, there's a high prevalence of pathogenic DNA variants in Blacks. You should pay attention to extracardiac manifestations like carpal tunnel in cardiac amyloid and also pay attention in the mode of inheritance, for example, mitochondrial diseases are inherited in a X-linked pattern.

The ECG is often overlooked but it's really important in hypertrophic cardiomyopathy as first of all it could raise the suspicion of hypertrophic cardiomyopathy if you see left ventricular hypertrophy on the ECG, but also, ECGs abnormalities may suggest a specific diagnosis or morphological variants like giant negative T wave inversion that can be present in a patient with apical hypertrophic cardiomyopathy, low or normal QRS voltages in the presence of left ventricular hypertrophy should point to the direction of cardiac amyloids, pre-excitation in a patient with storage diseases like Pompe, Danon, or PRKAG2 and abnormal Q waves can point in asymmetrical left ventricular hypertrophy or replacement fibrosis.

In this slide, you see some examples of ECGs of patients with left ventricular hypertrophy. Then in the lower part, this is a patient with apical hypertrophy, and actually, his first echo came back normal but that was because they didn't pay attention to the apex of the heart. In the upper right panel, you can see a patient with Danon disease, extensive left ventricular hypertrophy with regularization abnormalities, but also a really short PR interval and pre-excitation. Then in the lower panel on the right, this is a patient with cardiac amyloid with extensive hypertrophy on echo but you see actually normal voltages or even lower voltages and also the presence of pathological Q waves. This is a patient with cardiac amyloid. Then echo, echocardiography in cardiology, in general, is central in making the diagnosis and also monitoring of hypertrophic cardiomyopathy. It can give us a really good impression of the left ventricular wall thickness, but also the systolic function, diastolic function, left atrial enlargement, mitral valve abnormalities, and of course, if we're talking about left ventricular hypertrophic obstructive cardiomyopathy also in the left ventricular outflow tract obstruction both in rest and during provocation. Left ventricular outflow tract obstruction is a typical hallmark of hypertrophic cardiomyopathy and you should really look for it so you should make echo images both in rest and during physiological provocation with Valsalva or exercise and a definition of left ventricular gradient obstruction is equal or exceeding 30 mm of mercury. If it's above 50, it's hemodynamically important and might point in a specific treatment option.

Then a word on cardiovascular magnetic resonance imaging. It can show us many of the things that echo can also do, but I think it's really important for myocardial tissue characterization and also plays an important role in patients with less optimal echo images. Patients with poor echo windows or echocardiography inconclusive, suspicion of an alternative diagnosis, but also, for risk stratification, the maximum wall thickness, ejection fraction, presence of apical aneurysms, and extended fibrosis. It can also help us to guide our invasive therapy, especially on mitral valve abnormalities, papilloma muscle abnormalities. These are some clinical images of patients with hypertrophic cardiomyopathy from our own clinic. On the left side, you see a patient with an extensive apical aneurysm which is really nicely shown by their CMR. In the middle panel, this is a patient with hypertrophic cardiomyopathy carrying a myosin heavy chain mutation, you can see the extensive late gadolinium enhancement. On the right part, you can see the typical image of late gadolinium enhancement in cardiac amyloid pointing in another direction, then classical hypertrophic cardiomyopathy.

To conclude, I think it's important that we all have an index of suspicion of hypertrophic cardiomyopathy in patients that we are encountering. We start with a classical clinical evaluation including cardiac images with a special focus on both history of the patient for extracardiac manifestations, but also the family history. Don't forget about the ECG. I think there's a central role for echo including provocation of left ventricular outflow tract obstruction. CMR really has an added value in hypertrophic cardiomyopathy, and I think it should be performed in any patient presenting with left ventricular hypertrophy. I'd really like to thank you for your attention.

CHAPTER THREE

Dr. Olivotto:
Hello. My name is Iacopo Olivotto. I'm a clinical cardiologist working in Florence. I'm privileged to be part of this symposium. I will be speaking about the therapeutic landscape of patients with hypertrophic cardiomyopathy, and these are my disclosures.

We now know very well that hypertrophic cardiomyopathy is not as rare as we thought. It is a complex disease, and is far more complex than just a thick heart. We know that obstruction is an important determinant of symptoms. We know that the metabolic, energetic, and electrophysiological consequences of the disease are far-reaching and important. We also know that treatment of these patients is complex. It is not just giving drugs, it's not just sending patients to operations or interventions, it is a chronic, slowly, progressive disease, with low event rates. We need to comprehensively treat patients and take into account everything from the quality of life, to treatment of complications, to professional lifestyle decisions, and much more.

When we talk about comprehensive management, this is really what we mean. Of course, in terms of actual treating complications and treating the disease, I've been in this business for over two decades, and for a long time, the best landscape has been those of the interventional, the surgical, and interventional cardiologist. Simply because they were fantastic options, they still are fantastic options, which includes surgical myectomy for obstructive disease, alcohol septal ablation, the defibrillator that has really changed the outlook of high-risk patients for prevention of arrhythmia complications and treatment of atrial fibrillation. Of course, when you move to the landscape of pharmacological interventions, this is what the landscape looked like for a long time. We do have some palm trees, a little oasis here and there, but that's mostly because we have used with good effect drugs that have been developed for other diseases, such as beta-blockers or Verapamil. There's had been some joy, but not too much with drugs like ranolazine or paraxylene, trying to modify some of the substrates of disease, and of course, disopyramide which we use as a negative inotrope for control of arrhythmias, and particularly for control of obstruction. As you see, however, not much, and particularly, none of these drugs have ever been developed thinking about the real mechanism of disease. They have just been used because they were available and did some good things to our patients. Made our patients feel better to some extent.

Of course, if we move to the actual mechanism of disease, HCM is a disease caused by mutations in sarcomere gene proteins, which

are the actual machinery of the heart. Of course, there's nothing as sensitive as the sarcomere in heart pathophysiology. We do know now that one of the determinants, particularly in the model of HCM caused by these myosin heavy chain mutation, is the fact that the conformation of the myosin dimers is altered, so that mutations in the dimers, as you see here, favor the on or the activated form of the molecule, as opposed to the super relaxed or inactive form of the molecule which is prevalent in nature. This is essential because the sarcomere needs time to recover, it needs to be sustainable. We cannot possibly use all our myosin heads in contraction at any given time. That in fact, in normal sarcomeres, 40-50% of the myosin heads are estimated to be in a super relaxed state. Therefore, not involving contraction. When you have mutations, in particular regions of the myosin molecules, this leads to a natural doping of the heart. Hyperactivation of these molecules, which tend to be much more commonly in inactivated state, which leads to a hypercontractile, but also high energy-consuming state. Which is, to some extent, what is really the main, the original thing behind the disease, leading to a number of downstream complications to anything to with regard to energy propagation, to an electrophysiological remodeling of the cardiomyocytes. Small defects leading to huge complications. In the clinical arena, this translates to the progressive build-up of complications of ventricular dysfunction, heart failure-related complications, and arrhythmias.

Although, the actual risk of arrhythmic events is definitely not as high as we thought. We can see from these data from the shared registry that the sooner you have a clinical-evident disease, the more likely you are to have some complication during your lifetime because of the pathophysiology I was referring to. Of course, in some unfortunate patients, about 7% to 10% of the patients, the progression of disease become so severe as to dominate the clinical picture and lead to dysfunction and heart failure subtended by severe diffuse fibrosis. In fact, we can make this a case of too much of a good thing, too much contractility leading to adverse consequences, which is really the essence according to the most brilliant minds that have thought about HCM is the actual essence of the disease.

It was about time that we had a molecule that could actually counter this mechanism. This is exactly what Mavacamten is. Mavacamten is a first-in-class allosteric ionotropic negative myosin modulator which binds to the myosin head, reduces its affinity for actin, and therefore, tries to restore, to normalize the state of things with less has involving contraction in a given time. Really normalizing the core mechanism of disease in HCM, at least as far as we know on patients that have a secondary gene mutation-associated disease. Does Mavacamten work? We know it does work because there's been extensive experimental work particularly in animal models, transgenic, HCM animal models. In the mouse model, of course, in which we can have a lot of information, a lot of tissue available, and also prognosis because of the short lifespan of these animals, we know that the drug treatment with Mavacamten, so normalization of sarcomere status, is to reduce hypercontractility, improves diastolic function, stops the development or even sometimes reverses development of hypertrophy, and to some extent normalizes fibrosis and disarray. It is really a disease-modifying agent in the animal model. What about humans? Of course, it's much harder to study a drug like this in humans, but we do have a lot of information now and information is building up the studies we do. We know that in patients with obstructive disease, which has been the original target simply because obstructive disease is easier to study because symptoms are so correlated to obstruction and relieve LVOT gradient really translates into clinical improvement. In patients with obstructive HCM, we know that the drug is capable by its negative inotropic action to relieve the gradient, improve performance, improve quality of life, and to some extent, positive cardiac remodeling as well as improved the biomarker profile of these patients.

This is data from the EXPLORER-HCM trial which is the first and the largest phase three study performed in HCM so far with Mavacamten looking at obstructive symptomatic HCM patients. You can see here how, on the left, the gradient in patients who are treated with Mavacamten is very clearly very nicely reduced by Mavacamten as opposed to virtually no change in placebo. This is exercise-related gradient. On the right, how this effect is obtained with only a very small reduction in ejection fraction, only 4% drop in ejection fraction. In a safe and well-tolerated manner, very huge effect on the gradient. This is one patient from my center. You can see at baseline, the typical gradient, and you can see here after 30 weeks of treatment, the gradient on Valsalva has disappeared.

Quality of life increases very extensively. There was a nine-point improvement with KCCQ which is a massive improvement in patients simply because they're not obstructive anymore. Even more interestingly in terms of thinking ahead, and for long-term prognosis, the biomarkers, as I was referring to, NT-proBNP and troponin I, which are very heavily impacted in a beneficial way by the drug. In terms of cardiac function, we know that diastolic function improves in patients treated with Mavacamten. There are other evidence of positive remodeling from CMR; sub-studies of Explorer and other studies. What we were not expecting to see is this. This is an ECG from one patient with my center participating in EXPLORER. You can see the typical and huge evident ECG abnormalities, repolarization abnormalities typical of HCM. This is the same patient same heart rate at the end of the study. This is something we have not really seen, this kind of normalization of repolarization abnormalities with other drugs. Even though you may drop the gradient, you never see this happen with disopyramide for example. We don't really know what this is due to, but it's quite intriguing to think that some of the disease-modifying effect we have seen in animal model may actually translate in clinical practice into this sort of effect. We're definitely looking more into this because this is a consistent effect. If you use artificial intelligence algorithm to detect HCM, you can see that at

the beginning of the trial with mavacamten, most of the patients are picked up by artificial intelligence. At the end of the study, the same patients are not diagnosed anymore by the same algorithm because their ECGs have improved so much.

We hope to show more and more with time, but this is only the tip of the iceberg in terms of what the drug can do for disease modification. This is the most recent trial, the VALOR-HCM trial, which aimed to understand whether patients who were candidates for surgery, so obstructive patients, candidates for surgery, surgical myomectomy, could actually benefit from mavacamten. You can see randomized with placebo. You can see that, in green, the patients that were candidates for surgery at the beginning of the study were basically, became non-eligible at the end of the study, and therefore dropped from the waiting list as opposed to very little effect into that respect in the placebo arm.

While we are waiting to know more about long-term effect of the drugs, we definitely know that in a shorter term, this is a very effective drug in controlling obstruction symptoms and even may postpone or delay or even eliminate, who knows, the need for surgery.

In conclusion, we are now at the beginning of a new era for treatment of hypertrophic cardiomyopathy. Simply because the first drug that has been designed specifically for the disease, has been developed successfully and is now entering clinical use in the US. It is already approved by the FDA. In Europe, we're still awaiting EMA approval. We think that the drug will initially be positioned in patients with symptomatic obstructive disease as a sort of intermediate step, will probably be used in patients who have failed to respond to the standard pharmacological options, and before moving on to surgery, and hopefully, will stop the need for these patients to go on into invasive, and sometimes potentially dangerous interventions. Of course, we hope that the era that has just begun with the advent of myosin modulators, there are other molecules along this pipeline that have been developed, will change the treatments landscape of HCM forever, bringing more and more opportunities to our patients, and hopefully, demonstrating that treating patients with this kind of approach not only improves symptoms in the short term, but really modifies the disease and is capable of interfering with the natural history of the disease. Thank you very much.

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