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What are the challenges in making the right diagnosis in HCM?

**Dr. Elliot:**
Hello, my name is Perry Elliott. I'm a professor of cardiovascular medicine at University College in London, and today we're going to be talking about the challenges in making the right diagnosis in people with hypertrophic cardiomyopathy. Most of what I'm saying today can be found in the latest European Society of Cardiology guideline on the management of cardiomyopathies, published in 2023.

So let's start by what we mean by cardiomyopathy. Cardiomyopathy at one level is very simple. It's an abnormal heart muscle which is not explained by abnormal loading conditions such as hypertension or aortic stenosis. But in cardiomyopathy diagnosis, we often look at other traits beyond, for example, ejection fraction or wall thickness. We'll look at both the left and the right ventricle and increasingly, we characterize diseases by the presence of scar. So these phenotypes that we describe, hypertrophic, dilated, non-dilated left ventricular cardiomyopathy, and so on, are basically a descriptive term of the structure and the physiology of both the left and the right ventricle.

In the case of hypertrophic cardiomyopathy, however, the diagnosis is relatively simple in that you simply have to have a wall thickness in an adult of more than 15 mm in the absence of hypertension or aortic valve disease sufficient to cause that level of thickening. In children, we make the diagnosis when we see a wall thickness more than 2 standard deviations from the norm, corrected for their body size and age.

Now obviously, when making the diagnosis, the fact that we have to detect hypertrophy means that we are heavily reliant on cardiac imaging. And the techniques we use have evolved with the technology that we have available to us. But in everyday practice, this means echocardiography and, in selected patients, cardiac magnetic resonance.

So here you see a typical patient with unequivocal hypertrophic cardiomyopathy with thickening of the interventricular septum. This asymmetric distribution being highly characteristic of HCM. We can see the same on cardiac magnetic resonance imaging, again, showing this marked asymmetry between the septum and the other myocardial segments.

However, we also recognize that pretty much any pattern of thickening in the left ventricle is possible in this disease. So, here you see another phenotype which maybe as present in 10% of patients, where you have thickening confined to the left ventricular apex.

In addition to hypertrophy, we may also see other features, and this is a feature we see maybe in 25% of patients at rest, which is a form of dynamic left ventricular outflow tract obstruction caused by systolic anterior motion, usually of the anterior mitral valve leaflet, sometimes the posterior leaflet, or sometimes both leaflets. This is often, as you can see in the lower panel on the left, associated with a degree of mitral regurgitation.

In addition to this form of dynamic obstruction, we may see other structural abnormalities, so we may see elongation of the mitral leaflets or abnormalities in the submitral apparatus with fractionation of the papillary muscles or anomalous insertion of the papillary muscles into the mitral leaflets themselves.

But hypertrophic cardiomyopathy is not really a diagnosis. As with all of the cardiomyopathy subtypes, this is basically a description of the anatomy and the physiology of the ventricle. It doesn't tell you the underlying cause. Even in the most classical disease, asymmetric hypertrophy associated with the characteristic histopathology of myocyte disarray and fibrosis, outflow tract obstruction, this is probably

in about 40% of patients caused by inheritable variants in the genes that encode cardiac sarcomeric proteins. The sarcomere being the basic contractile apparatus of the cardiomyocyte.

But we recognize that even in the classical phenotype or in less typical phenotypes, concentric hypertrophy, hypertrophic apex, and so on, there are many different genetic and some acquired disorders that can result in this phenotype of hypertrophic cardiomyopathy.

So in the approach to diagnosis as laid out here in this figure from the 2023 ESC guideline, in order to make a correct diagnosis, you have to integrate a number of pieces of information. What is the scenario here? Who is this person? What is their age? Why are they presenting? Do they have a family history? All of these things condition how you interpret the tests that you subsequently perform in the patient.

Yes, we image the patient and ascribe them to a phenotype, but remember a phenotype is more than just a wall thickness measurement. It's also what you see on the electrocardiogram, whether the patient has AV block, whether there are extracardiac signs of disease which may point you towards a particular etiology.

And this is what we often call the cardiomyopathy mindset. And as outlined in the guideline, this basically means that to make a definitive diagnosis of the cause of any cardiomyopathy, including hypertrophic, you need to take this multiparametric approach, which includes clinical evaluation, pedigree analysis, ECG, laboratory tests, and multimodality imaging.

Just to highlight a few elements of this process, scenarios, I've already said that if you have a parent who has unequivocal disease and one of their children presents with an abnormal ECG with borderline wall thickness, they already have a 50/50 chance of having hypertrophic cardiomyopathy. So the diagnostic criteria would be conditioned by the clinical scenario that you face.

We often create tables like this of lists of extracardiac features, but this doesn't have to be too complicated in ordinary everyday practice. Just simply noting the age of the patient. A 75-year-old patient with concentric hypertrophy is much more likely to have cardiac amyloidosis than a 30-year-old in which amyloidosis is almost certainly not the cause. I've spoken about family history, but the pattern of inheritance may help you decide the cause. And there are some specific noncardiac signs and symptoms which are readily elicited in the cardiac clinic.

Every test has value, including an electrocardiogram. So the electrocardiogram can give you clues as to the distribution of hypertrophy, whether it's myocardial fibrosis. It's very sensitive in the early diagnosis of disease in relatives, and it provides some diagnostic red flags.

Here you see an example of classical apical involvement with deep T wave inversion in the lateral leads. But in this patient, you have numerous red flags. Not only do you have evidence for atrioventricular conduction block, so 2 to 1 block, but the conductive beats are pre-excited and you have DT wave inversion typical of apical hypertrophy. This is classical phenotype of a rare variant in a gene called PRKAG2, which causes about 1% of HCM, but the clues are conduction disease, pre-excitation, and LVH.

So think about the phenotypes, describe the patterns of hypertrophy, describe the physiology, but look for diagnostic clues.

Here's another one. Here you have a patient, concentric LVH, impaired systolic function. That combination of impaired systolic function with LVH points you to the direction of metabolic disease, amyloidosis, depending on the age of the patient.

In the modern era of imaging, we do have ways of interrogating the substrate, if you like, the myocardium itself. We use MRI, and we have signals which could be highly suggestive of specific diagnoses, such as Fabry disease, amyloidosis. But these still have to be integrated into an overall clinical picture, and I'll close with yet another example of how this iterative approach helps you towards diagnosis.

This is a 79-year-old male, has a cardiac history, previous myocardial infarction, 2-vessel disease, now presents with heart failure. But he also has trifascicular block. He's complained of bilateral neuropathic symptoms in his hands and has bilateral carpal tunnel syndrome. He also has a history of lumbar stenosis. Already, we're moving towards a precise diagnosis

His echocardiogram, here in the short axis and here in the apical long axis, shows the anterior infarct he previously sustained, but the posterior wall is thick. And if we do the appropriate test as here on the right, a bone scan where you see the heart lights up, we have our diagnosis. This man has cardiac amyloidosis. But we knew that from the age, from the noncardiac symptoms, from the presence of AV block, and the presence of hypertrophy.

So in summary, hypertrophic cardiomyopathy is a term that describes a family of disorders. Many, if not majority, are genetic in origin, but not all. And you should think about some of these rarer phenocopies, particularly in those patients who have these readily determined diagnostic red flags.

Thank you very much.