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Evaluation of the complex cardiac pathophysiology in HCM

Dr. Masri:
Hello, my name is Ahmed Masri, and I'm a cardiologist and hypertrophic cardiomyopathy specialist at Oregon Health and Science University in Oregon, Portland, United States. I'll be talking to you today about the cardiac physiology and pathophysiology of hypertrophic cardiomyopathy. Those are my disclosures.

And so HCM is a fairly complex phenotype of disease. It's a collection of different phenotypes that we see depending on what the actual disease leads to. And as you can see, it's not just hypertrophy. It depends on the location of the hypertrophy, the amount of obstruction that happens with that, the level of the obstruction, and if we develop an apical aneurysm or not. At the histological level, you can see multiple different things affecting the myocyte sheaths, including myocyte disarray. You can see also the blood vessels being affected in such a disease. And ultimately, fibrosis is one of the biggest issues that we have to deal with.

And so it's not just the complexity at what we see in our own eyes, both histologically as well as on the imaging, but also the genetic bases of the disease are fairly complex. This is the machinery with how our muscle contracts and we're not going to go through it, but just to give you a flavor of how complex the spaces of the disease is. Just focusing on the 2 most common gene mutations in hypertrophic cardiomyopathy gives you an idea of what is going on. In one of them, you have myosin-binding protein C, which is the braking mechanism of the heart function. If you have deficiency in your brakes, then the heart, essentially, is going to be hypercontractile and be hyperactive in a way. So you could be just sitting down, but your heart thinks that you're running a marathon, in a way.

The flip side of that is the beta-myosin heavy chain mutations or variants. Normally, the beta-myosin heavy chain is your gas supply for the heart muscle. So if you have excessive amount of gas, you also would end up with the same concept as deficiency of the braking system. And so we really have to change the way we think about this. Normally we think about HCM as being left ventricular hypertrophy, but the left ventricular hypertrophy is the downstream effect of the hypercontractility. So it's just like any skeletal muscle as well, you go to the gym, you build muscle up; it's the same concept. The heart starts being hypercontractile without regulation, leading to left ventricular hypertrophy and the muscle thickening that we see in HCM.
On top of that, we have to think about, at the molecular level, what's going on with this hypercontractility. The mechanochemical cycle of myosin is the primary example where you need ATP so that you can disengage the myosin from actin, and then you hydrolyze ATP to ADP and inorganic phosphorus, and then the cycle repeats itself.

That's really how you end up getting this engagement/disengagement cycle between actin and myosin, which leads to the power stroke. And so if you make this cycle strong, that's what happens in hypertrophic cardiomyopathy. If it's weak, that's what happens in dilated cardiomyopathy. If you try to do the opposite using a myosin inhibitor or an activator, then you can manipulate the cycle. And the reason behind this is what was found over the last, you know, decade or so, that myosin has another state. It's not just either bound to actin or off actin and available. There's also a third state, which is that so-called super relaxed state. The myosin head is totally folded inward; it is not available to engage with actin. Normally, about 30% or so of our myosins are in that state. But with HCM you have a disordered state where most of these myosins are just available for engagement, leading to this hypercontractility.

And so all of what I told you so far is that hypertrophic cardiomyopathy is a sarcomere problem. However, if you think about it, not until

recently, most of the therapies we had have nothing to do with the sarcomere, from beta-blockers, calcium channel blockers, metabolic modulators, septal myectomy, alcohol septal ablation, and disopyramide, none of them actually target the sarcomeres directly. And so what else are their kind of problems? So all of this culminates eventually into an effect on exercise tolerance. And so patients don't come to you with being swollen in profound heart failures presentation. They do have heart failure symptoms, but they mainly have exercise intolerance, and their symptoms are typically on exertion. And if you think about it, the way to think about that is that exercise can encompass all of these issues that you see, from small vessel disease to diastolic dysfunction, fibrosis, pulmonary hypertension, myocardial ischemia, the LVOT obstruction, the hypertrophy. All of that cycle ends up culminating in affecting exercise tolerance, which can be measured for peak exercise using maximum oxygen consumption or peak oxygen consumption.

So peak VO2, while it's not familiar to many of you, it's a measure of the maximum oxygen that the body is using while exercising at maximum exercise. And that gets affected by having a complex situation such as hypertrophic cardiomyopathy. And so this is a summary of all the studies in hypertrophic cardiomyopathy that have shown what is the effect on peak VO2 with intervention. And you see a lot of variability. The news is, if you do observational studies, the peak VO2 change will be high. But those are all biased studies, and we can't really use them without having a control group. Once you focus on randomized and placebo-controlled trials, blinded ones, you see that the effect size ranges anywhere from, you know, 1, 1.4 with mavacamten, and then 1.7 with aficamten in the SEQUOIA-HCM trial. And all of these things essentially show you that a 1.0 increase in peak VO2 is meaningful because that means you are getting at, essentially, at being able to do a lot more than you normally would have done if you are limited with symptoms.

This is not necessarily to say that, you know, an athlete can do tons more by increasing 1.0 of peak VO2, but these patients with HCM are limited. The average peak VO2 for these patients is about 18 mL/kg/min, so they are fairly limited patients.

And so what else is important with peak VO2 is that it does predict outcome, and hard outcomes, not just any outcome. So we're looking at not just exercise intolerance, but we're looking at heart failure, heart failure hospitalizations, death. And you know, and the certifying peak VO2 into different groups, in multiple studies, shows the same consistent thing, which is the lower your peak VO2 is, the worse your outcomes are.

And so why CPET? Why don't we just put people on a treadmill? Because we can also monitor not just the peak VO2, but also how much effort they're doing using the disparity exchange ratio. And so this is essentially how much the relationship between oxygen and CO2 production. And so we like to see a ratio of above 1 to 1.1. That means that you actually worked hard enough during the exercise, and that tells us about peak exercise. What if we want to look at submaximal exercise? We have another measure which is VE/VCO2. This is minute ventilation relation to carbon dioxide production, and this is a submaximal exercise measure. So you can look at the slope between any 2 points that you decide on. You can choose the beginning of the exercise, the anaerobic threshold, or peak exercise, and you can measure that. And that tells you a lot about patients, even if they are unable to achieve peak exercise like they did at baseline. And this also correlates with outcomes. And this also is a known measure for VE/VCO2, the higher the slope measurement is, the worse the outcomes are as well.

And so in conclusion, HCM is a complex disease, both genetically and phenotypically. Hypercontractility due to excessive myosin actin interaction is the primary underlying mechanism of disease. And peak VO2 provides a comprehensive evaluation of the complex pathophysiology of HCM at peak exercise. And cardiopulmonary exercise testing is not just peak VO2; it has multiple metrics of maximal and submaximal exercise capacity assessment, which helps us understand the effect size of different treatments and put things into context when we see patients in clinic.

Thank you.