

**RICHARD G. BACH:** I'm empowered or asked here tonight to speak to you on an update on evaluation and nonsurgical treatment strategies for symptomatic patients with hypertrophic cardiomyopathy. These are my disclosures.

We all, in this audience it goes without saying, know what hypertrophic cardiomyopathy is. A definition that I think rings true is unexplained hypertrophy that is not due to some other secondary cause. This is a highly variable disease, though. I think one of the hallmarks of hypertrophic cardiomyopathy is that it is not the same from patient to patient, which in fact highlights the fact that the evaluation and treatment strategies need to be carefully tailored to the patient. That the patient needs to be comprehensively evaluated. That'll be the topic that I'll be focusing on over the next few minutes and the next few slides.

The prevalence. The prevalence, you'll probably read from many traditional publications, has been estimated at about one in 500. But more recently, one of my co-panelists here tonight and others have looked very carefully at this question on how prevalent is this within the population. And a revised estimate, which was recently published in the Journal of the American College of Cardiology, is about one in 200 patients.

I'll be pointing here on the right side. I'm sorry for those looking on the left side, but I only have one pointer. But in any case, the point of making this estimate known-- one in 200-- I think all of us will encounter patients commonly in our practice that have hypertrophic cardiomyopathy, relatives with hypertrophic cardiomyopathy, or some question or suspicion of hypertrophic cardiomyopathy.

Understanding how to enter the evaluation phase, how to manage those patients, how to manage them comprehensively-- not just themselves, but their family members-- is a very important aspect of the care of any individual with hypertrophic cardiomyopathy.

Another fact to mention here is that approximately 70% of the population has what we call left ventricular outflow tract obstruction to what we consider to be a significant degree, either at rest or with provocation. So a very important component of the evaluation and management of these patients relates to left ventricular outflow tract obstruction.

There is a relatively short list-- although these patients may present with many different syndromes-- short list of their common clinical scenarios. They include heart failure, angina, syncope, and sudden death. None of these is obviously more important than the other, but as we're talking about the symptomatic management of patients, we're really talking about dyspnea on exertion, dyspnea, angina, and episodes of syncope. That is probably the most common three syndromes these patients present with.

In our treatment goals, to mention it, are symptom relief obviously, but in addition, we have a sort of teachable moment when we encounter a patient with hypertrophic cardiomyopathy to very importantly assess their risk of sudden death and try to prevent that if, in fact, the patient is identified to have risk factors. You will hear more about that in subsequent presentations, the identification and management of patients with respect to their risk of sudden death.

Now, I apologize that from the back this may be difficult to see. I liked this algorithm for management that was published in a perspective piece by Dr. Barry Maron and Rick Nishimura very recently. But it highlights the fact that we'll encounter these patients in practice at many stages in the evolution of their symptoms, from the asymptomatic patients all the way to those with very severe symptoms.

In the middle here, shown in green if it shows up, are the target aspects of their clinical care that we want to be targeting-- we want to be evaluating. The risk of sudden death, even for the individual who is completely asymptomatic, is a very important aspect we need to be paying attention to. But as the patient develops mild to moderate symptoms, or severe symptoms, we realize that we're trying to estimate their quality of life and the impact their symptoms are having on that quality, and maintain this perspective on a dynamic risk assessment for sudden cardiac death.

One thing that is advocated, both in the recent European society guidelines and the ACC/AHA guidelines from 2011, is that as patients become more symptomatic in their management, referral to a hypertrophic cardiomyopathy center may be beneficial to these patients. That is something advocated in both sets of guidelines, and I'll try to show you over the next few slides why that may be something worthwhile in tailoring their evaluation strategies.

And for patients who are refractory, who have severe symptoms where medical management-- the short list of medical management shown here on the right-- medical management may not necessarily be efficacious enough. We have certain treatment strategies. If they have severe obstruction, septal myectomy or alcohol septal ablation there may be treatment strategies that can be beneficial for these patients. For patients who are non-obstructive, these are patients who may be, as necessity, referred to centers for transplantation.

Now, what can a hypertrophic cardiomyopathy center provide? I just show this slide up as a cartoon to illustrate the kinds of resources that we've put together at Washington University Medical Center to try to really target this population, hypertrophic cardiomyopathy.

First of all, one needs advanced imaging technologies and advanced imaging personnel. Not just the techniques, but dedicated personnel who are skilled in the evaluation of these patients, either by echocardiography or cardiac MR shown here. We also need, in fact, skilled electrophysiologists. One of them on the panel tonight, Dr. Marye Gleva is our electrophysiologist at Barnes-Jewish Hospital dedicated to hypertrophic cardiomyopathy. So she has the expertise to manage both arrhythmias and profile a patient's risk of sudden death. And the skill to be using the proper devices for those individuals.

We need the genetics component of the picture for hypertrophic cardiomyopathy, meaning these individuals have a certain familial possibility. When they have that possibility, assessing their gene likelihood and/or sending them for genetic testing may be something important. In addition, we need to have individuals who have the skill to counsel such patients. And so one person on tonight's panel who will be presenting towards the end, Dr. Sharon Cresci fulfills that role for our hypertrophic cardiomyopathy center at Barnes Jewish Hospital.

In addition, for the patients who need interventional treatments, we need a surgeon, we need interventional cardiologists who are skilled in the types of interventions that can help individuals, particularly with those with severe left ventricular outflow tract obstruction. I'll highlight one more fact, which is that we've added to our team an individual who crosses over between our Center for Hypertrophic Cardiomyopathy and Advanced Heart Failure and Transplantation. Dr. Shane LaRue at our institution keeps his hats in both of these environments so that he can take patients who require treatments that are quite advanced for heart failure from the hypertrophic cardiomyopathy population and put them on the road to heart transplantation when it's necessary. And having this integrated into one group has actually been very beneficial for the care of patients at our institution.

Now, what's specialized about this evaluation? There are some common tests you'll see here listed for the patient with hypertrophic cardiomyopathy. Stress echocardiography, cardiac catheterization, cardiac MR, and transesophageal echocardiography. But I would want to highlight the fact that we've put together dedicated personnel who do these in very specialized protocols. These are not routine stress echoes. These are not routine cardiac cath. These are not routine cardiac MRIs. And neither are they routine transesophageal echos. We have a team dedicated to this particular protocol for hypertrophic cardiomyopathy that takes this to the next level, so to speak.

Let me give you a case example. I always find it illustrative to talk about case examples when we're talking about how to evaluate these patients. Here's a relatively young man, 29-year-old male. He has shortness of breath and chest discomfort on exertion that's been increasing in frequency and severity over the last several months. He's short of breath with even walking less than one block at the time we first encounter him.

So he already has advanced to the point where he has quite severe symptoms. In fact, he develops chest pressure after heavy meals, or even at rest. He's had multiple episodes of lightheadedness and near syncope, although no frank syncope. He's a former construction worker but now on disability, unable to work because of these symptoms that have developed. And on examination, he has a relatively harsh murmur. Not an atypical story for a patient presenting with severe symptoms with hypertrophic cardiomyopathy.

The evaluation for such a patient involves, first, a screening echocardiogram. And just to show you an example here, the parasternal long axis view of this patient's echo shows the characteristic features of hypertrophic cardiomyopathy, or at least for many individuals with hypertrophic cardiomyopathy highlighting the variability from person to person.

There is asymmetric septal hypertrophy with a septal thickness that is, in fact, about 2.6 centimeters. There is systolic anterior motion of the anterior leaf of the mitral valve, which touches the interventricular septum during systole. And by Doppler estimation shown on the lower right, in fact there is a resting gradient which is almost 100 millimeters of mercury for this individual. So quite severe left ventricular outflow tract obstruction even at rest.

For such an individual, we don't leap immediately to invasive management strategies. In fact, this is an individual we start therapy with the first and the foremost agent that's useful for individuals for hypertrophic cardiomyopathy that's endorsed in the guidelines, which is a beta blocker. And so he was started on metoprolol. But unfortunately, as is the case for many individuals, he only had minor improvement in his symptoms and really didn't tolerate an increase in dose on the metoprolol

So let's ask, what else is available for medical therapy? We don't immediately stop after trying one agent and route that patient towards invasive management strategies. We try to explore additional medical therapy options, and I think it's very important to recognize that disopyramide, an agent that is probably underutilized in this population, is a very effective therapy for many patients with obstructive hypertrophic cardiomyopathy.

Here's a study, the multi-center study for use of disopyramide in hypertrophic cardiomyopathy. Several centers put together their experience. 118 patients, which were treated over a period of about three years. And you'll see that for many individuals there was success both in about a 50% using disopyramide in reducing their left ventricular outflow tract gradient. But in addition, you can see that their symptoms were strongly benefited, and about 2/3 of the population both tolerated therapy and were symptomatically improved enough that they could avoid an invasive management strategy or interventional therapies.

On the opposite side of that coin, however, about a third of patients-- 40 out of the total-- that either did not tolerate therapy or benefit from it-- and this patient group really needed to move on to more interventional strategies to manage their left ventricular outflow tract obstruction. So back to our patient. We started disopyramide on this individual. But unfortunately, he was one of those in the third or so of the population that really didn't tolerate the therapy very well at all.

He didn't like the side effects and really refused to take the therapy after a couple weeks, unfortunately, and remained as symptomatic as he had been despite this now combination of agents. So we could ask, what's the next step in such an evaluation? And I would say, in our institution, we're looking for more advanced imaging strategies for such a patient to try to then more clearly define a management strategy with respect to septal reduction therapy. That's kind of the target that we're looking for in such an individual who's failed medical therapy.

And our approach, just to show you what our experience has been, is to use a specialized stress echo protocol, but in addition move on to more advanced imaging. In this case, one could argue either for CMR-- I'm going to talk a little bit over the next few slides about transesophageal echocardiography.

In this specialized Hokum Protocol Stress Echo, we get a very careful analysis of the resting 2D echo, but in addition look very carefully at peak exercise at the peak provokable gradient, which is something that is not done in most routine stress echocardiographic laboratories. It does take a skilled technician to be able to acquire this information reliably and look very carefully at the patient's exercise tolerance and other aspects of the results of the test.

And for this one individual-- that's the example that we're talking about-- he's only able to exercise for three minutes and 56 seconds on a Bruce protocol. Very poor exercise tolerance. Only five mets. He has to stop due to his typical symptoms-- shortness of breath, chest heaviness-- and it's sort of gratifying to me, gratifying in a sense, to say we've now correlated some of the findings on the stress echo physiologically with his symptoms that he's having in his day-to-day life. And to me, that really puts together information that's very useful therapeutically.

One additional aspect-- he drops his blood pressure at peak exercise, so we've now identified another fairly high-risk indicator for this gentleman that he has a high risk of sudden death. Another teachable moment in this evaluation strategy where we can now triage him towards a preventative measure like a defibrillator.

We take this patient, therefore, and want to ask, what are our treatment recommendations. As I said earlier, we want to think about where do we go to determine his candidacy for septal reduction therapy. And the next step is this specialized hypertrophic cardiomyopathy protocol, transesophageal echocardiogram. We find this most useful to assess the left ventricular outflow tract and very importantly exclude fixed left ventricular outflow tract obstruction, but in addition assess the mitral valve anatomy.

It turns out, as you probably are aware, many of these patients have abnormalities of their mitral valve apparatus that are quite important to know about before we decide whether or not surgery is indicated or potentially alcohol septal ablation might be a strategy to recommend. And in fact, we want to look very carefully at one particular aspect, which is the mitral regurgitation in these patients.

Many individuals, you'll find, on a transthoracic echocardiogram with hypertrophic cardiomyopathy and significant obstruction, have severe mitral regurgitation. We use transesophageal echo for a number of features of that valve morphology, and the mitral regurgitation jet direction and timing and the valve motion. So all of these are features of the mitral valve that can really not be adequately profiled by a transthoracic echocardiogram. But then we take this test one step further and do a dynamic drug suppression test, all with the goal of determining what is the etiology of this mitral regurgitation? Is it amenable to either surgical or interventional therapy? And what will the likelihood of outcome be if the patient is triaged into one or another treatment strategy?

And so, looking at this particular patient's transesophageal echocardiogram, you'll notice the typical features. There is a bulge in the basal interventricular septum, which is typical of this asymmetric septal hypertrophy. And you can see these mitral valve leaflets being pulled over, so there is dramatic systolic anterior motion seen very well by transesophageal electrocardiography.

You can even see that the leaflets are getting pulled apart during systole such that, if you look at the Doppler interrogation of this patient's particular TEE, you can see that there's a dramatic jet of severe mitral regurgitation. But the features are quite important, and the features come-- in fact, I think we should give credit to the group in Toronto, which in the early 1990s really mapped out these features. When mitral regurgitation is secondary to left ventricular outflow tract obstruction and systolic anterior motion, it tends to be posteriorly directed as it is in this case, and it tends to be late in its timing during systole, and related to these leaflets being pulled apart during systole by a systolic anterior motion.

And when we look with a little more detailed perspective-- we actually are using phenylephrine during these transesophageal echos to try to get a dynamic suppression of that mitral regurgitation for more confidence that is in fact due to the left ventricular outflow tract obstruction. In a series of patients that we've been doing over the last few years, this is a representative example in this patient. You can see the very severe mitral regurgitation at rest. After the patient is administered phenylephrine, and the blood pressure responds, you can see that there seems at least, and this is, again, a work in progress.

Some preliminary information, but I just want to share this with you. There seems to be a reduction in the mitral regurgitation implying that it is most likely secondary to this systolic anterior motion and left ventricular outflow tract obstruction. Giving us some confidence that we can offer septal reduction therapy as a means of both reducing his left ventricular outflow tract obstruction, but most likely also reducing his severity of mitral regurgitation.

Now, there's one additional aspect of the TEE that I find most critical, and this is very, very important because, although it is stated even in the most recent ESC guidelines that transthoracic echo can be used to examine the mitral valve apparatus, and only if one has suspicion of problems does one have to move on to more advanced imaging. I think more advanced imaging is indicated in almost every patient. Because quite unexpectedly-- the Mayo Clinic reported this a few years back-- a few patients in their population-- we don't have a denominator, but in their population referred for septal reduction therapy turned out to have fixed left ventricular outflow tract obstruction.

In our experience, looking back over the last 175 patients or so that we've had referred, we actually had eight patients identified who had abnormalities of the mitral valve, or membranes, or some form of fixed left ventricular outflow tract obstruction which would not be ameliorated by any other technique but surgery. And we like to tell our surgeon, Dr. Dan [INAUDIBLE], who you'll be hearing from in a few minutes that there is fixed left ventricular outflow tract obstruction before he goes into the operating room rather than having him discover it afterwards.

Now, back to our patient. So our patient fits into this category of individuals who have refractory symptoms after a reasonable attempt at drug therapy. And so we have two choices here. One, septal myectomy, that you'll hear more about later tonight. And the second one, as it is termed in the guidelines, both the European guidelines and the ACC/AHA guidelines, and I think a very balanced discussion in those guidelines if you're interested in it, calls this an alternative to surgery.

I think it's an important alternative to surgery. It's an alternative available for those patients who have high risk for surgery, especially perhaps elderly patients. But in addition, those patients who are unwilling to have surgery, who by personal preference will not have surgery. And that population is not, in fact, trivial within the overall population of hypertrophic cardiomyopathy patients in my own experience.

But in this particular patient, he has his symptoms refractory to therapy, his MR appears to be secondary to systolic anterior motion of the mitral valve, but we have a relatively lengthy discussion, as I typically do with these patients and our physicians who manage the patients with the hypertrophic cardiomyopathy center are obliged to do, regarding the options for septal reduction therapy.

He had a relative who had had a bad outcome from cardiac surgery unrelated to hypertrophic cardiomyopathy, but he would not consider surgery under any circumstances and in fact, we then triaged towards the treatment by alcohol septal ablation. And now, let me go through some of the aspects of alcohol septal ablation because I think it is an important aspect of the non-surgical management of these patients that is a viable alternative to surgery.

Here's the technique shown schematically-- beautifully-- in a perspective piece by Eugene Braunwald a few years back, showing that using a balloon catheter we can isolate a septal branch of the left anterior descending artery, use that septal branch to in fact isolate a portion of the myocardium within the hypertrophied septum, and by doing so deliver alcohol to cause an ablation or a controlled heart attack, or whatever you want to call it, a way of ablating the tissue there to try to achieve some of the results non-surgically.

We guide every procedure with contrast echocardiography shown here. And in fact, shown on the next slide is just the results of that for this individual. You can see truncation of his first septal perforator branch. I'll show you the results with respect to his hemodynamics. There is a marked reduction in his left ventricular outflow tract obstruction, which is almost immediate. Some feel that takes a few months to deliver the production in the gradient, but in fact it happens immediately in the cath lab. And it is sustained. It may be variable in the first few weeks, but most patients feel better almost immediately after the procedure.

And here is his post-three month echocardiography evaluation, which we do routinely in every patient, showing that there is now what we like to call a divot out of his proximal septum, and that divot is hard to distinguish in some patients, at least, when there's been successful alcohol septal ablation from the kind of divot that you might get from septal myectomy.

His results are shown here, on a treadmill exercise stress test, showing that he's had a marked increase in his exercise capacity. He no longer has a drop in his blood pressure and his gradient was reduced to a resting gradient of 12 and a peak provokable gradient in the 30s.

This is the overall results from our study of our 100 patients or so in our series, showing that we have a dramatic reduction of the resting and provokable gradient, at the cost of about 12% requiring a permanent pacemaker because of complete heart block.

The symptomatic status of these patients is markedly improved. You can see in one year, the vast majority, in fact over 90% of these patients are classed one to two. In our series, less than 10% of these patients need either a second procedure, either myectomy or alcohol septal ablation the second time.

And it reiterate some of the outcomes that have been shown in series. This is a series of-- a relatively larger series of patients from South Carolina and Baylor-- showing that the gradient is reduced and the reduction is sustained over a period of several years. It does not recur, as some patients are concerned and physicians are concerned it may recur. It doesn't appear to, and in fact the symptomatic response is sustained over a period of years as well.

So gratifying results in a non-surgical approach for patients who are reasonable and good candidates. There is a wider experience. You'd say these anecdotal experiences don't necessarily convince anyone of the success of this strategy. There is a multi-center experience that we participated in, a prospective study from nine centers. Over 800 patients were enrolled and studied for about 10 years starting in the year 2000. The published results are favorable. I'll just read this bottom line. You already have this in your slide set, but compared to hypertrophic cardiomyopathy patients who did not undergo septal reduction therapy included in other series, survival appears better after alcohol septal ablation.

Now, you'd say, well, I'm not sure I understand or believe that compared to myectomy, but we fortunately have some comparative data more recently published from the Mayo Clinic experience. Paul [INAUDIBLE] and colleagues put together a very nice experience. A follow-up on an earlier series, but in this follow-up-- over a period of about eight years of follow-up-- you can see the expected survival after alcohol septal ablation was pretty equivalent.

And in fact, in their series-- and it is arguable in any series how comparable these patients are-- myectomy versus alcohol septal ablation-- that absolutely has to be admitted. But it appears that there's very little in the way of difference between the outcomes of this very selected patients series.

So I would conclude that for severely symptomatic patients with hypertrophic cardiomyopathy and outflow tract obstruction, septal ablation remains an early and sustained hemodynamic and symptomatic improvement-- results in. And alcohol septal ablation, like myectomy, carries risks of death and significant morbidity mandating careful patient selection and meticulous technique by experienced operators for appropriately selected patients. And that's very important that they be comprehensively evaluated to be selected, but long-term results support a highly favorable risk/benefit balance.

Now, I'm hopeful over the next few years we may need to do less myectomy and less alcohol ablation. I just want to share with you, since we're talking about nonsurgical strategies, an approach, in fact a new agent that's being developed by Gilead, which is a late sodium current blocker. The national PI on the trial is next to me here right now. The Liberty HCM trial, which is a very important study in my mind because it's one of the first randomized controlled experiments testing a new agent for symptomatic benefit and disease modification in patients with hypertrophic cardiomyopathy.

I show on the left of this slide some of the in-vitro data on isolated cardiomyocytes from hypertrophic cardiomyopathy hearts. It shows the action potential duration is markedly prolonged compared to normal and normalizes to some degree with application of this particular agent in vitro. And this is just a protocol that we are pursuing at our center, and many worldwide, to test whether or not this medication can be beneficial.

Using these strategies, and the current strategies available, I'm gratified to see some information that was recently published that suggests that the current outcomes for patients managed with guideline-type approaches in our modern therapeutic interventions may be comparable to that of the general population. And I thank you for your attention.