Adult with Systemic Right Ventricle Failure: Which Medications Work?

Announcer: Welcome to the Mayo Clinic Cardiovascular Continuing Medical Education podcast. Join us each week to discuss the most pressing topics in cardiology and gain valuable insights that can be directly applied to your practice.

Dr. Burchill - Welcome back to "Interview with the Experts," a podcast series from Mayo Clinic Education. This is from the cardiovascular team. I'm Luke Burchill, and I'm your host today. I'm leading the development of the new heart failure care pathway here at Mayo Clinic, and joining me is my friend and colleague, Dr. Charlie Jain. So Dr. Jain is an adult congenital heart specialist, and also our expert in invasive hemodynamics, and working with me in the heart failure clinic. So welcome today, Dr. Jain.

Dr. Jain - Thank you very much, Dr. Burchill. I'm honored to be here with you, thank you.

Dr. Burchill - So today we're talking about the systemic right ventricle, so maybe we should just start there, actually, and say who are these systemic right ventricle patients that we're talking about?

Dr. Jain - Yeah, that's a great point, 'cause you know, sometimes that term, there's different ways to word this in the literature, but so when I think about systemic right ventricles in the context of all adults with congenital heart disease and heart failure, we're talking about patients with transposition of the great arteries who now have a systemic right ventricle, so that's either DTGA, or complete TGA post atrial switch, or congenitally corrected transposition of the great arteries, also known as LTGA, and so those are the two major populations I'm thinking of. There's others that fall into more of a univentricular morphology, which we won't really be focusing on as much.

Dr. Burchill - And recently, I had a patient who had congenitally corrected transposition of the great arteries, and she was told by her local team it was not possible that she could be alive without having had a surgery. So let's just, I know that there'll be listeners who haven't seen a patient with congenitally corrected transposition, or CCTGA, as we call it. Is it possible for you to be an adult and to have CCTGA, and not to have had surgery, and there, if so, why do we say corrected?

Dr. Jain - Yeah, it is a confusing term sometimes, and it's a wild concept. I know when I first started to wrap my head around it, it was pretty mesmerizing and it still is in many respects, but you're absolutely right. So patients with CCTGA, and it's called that because it's congenitally corrected, so by the time they're born, they have a viable way of blood flow, which I'll explain in a moment. But sometimes those patients are diagnosed much later in adulthood, 50 years, 60 years of age occasionally, and sometimes they can go their entire life without any surgery or really needing a lot of medical intervention. Now, many can present much earlier too, so there's

an extremely wide spectrum of patients with CCTGA, with patients requiring surgeries in infancy too, so it runs the spectrum, but it's pretty incredible. So CCTGA, congenitally corrected transposition, also known as LTGA, they have what we refer to as atrial ventricular and ventricular arterial discordance, and so it kind of cancels out. So the ventricles are connected to the wrong arteries, but the atria are also connected to the wrong ventricles. So you still have two circuits that work, and they're in series rather than in parallel as it is in DTGA. Those patients either need a preductile shunt or surgery usually within the first year of life.

Dr. Burchill - And so yeah, it's referring to the physiologic correction that comes with that, as you say, the double discordance, rather than referring to the work of a surgeon. That's what CCTGA, the correction is referring to the physiologic correction, meaning that the blue blood is going to the lungs, and the red blood's going to the brain and the body, even though everything's reversed. So good, good, so you and I, I mean, we see patients with normal hearts as well. That's the non-congenital patients we see, but let's also make this clear. Today we're talking about these patients, they have a morphological anatomic right ventricle in the wrong place, so what I'm saying there is that this right ventricle is subaortic. It is pumping blood to the brain and the body. So maybe let's talk about this, what's wrong with that? Why can't a right ventricle sit in the wrong place?

Dr. Jain - That was well put there, Dr. Burchill. So the reasons why right ventricle may be sitting in the wrong place is for a few reasons, but the simplest thing to think about is just the afterload mismatch. So when we think about in typical anatomy, the right ventricle pumping into the pulmonary circulation, and the pressure's there usually about one fifth or so of the systemic circulation. So now if a right ventricle is suspected to do the work for the aorta as a subaortic or systemic ventricle, it's essentially doing five times the workload, from a pressure afterload situation, its entire life. So the major thing that we think about is progressive loading, pressure loading, and then remodeling as a consequence of that to the right ventricle. So over time, for some patients this happens sooner than others, but they get progressive right ventricular enlargement and dysfunction. Along with that, they may get tricuspid regurgitation, tricuspid referring to the systemic AV valve, so the AV valve always connecting to the ventricle there. And then there's a number of other things that can go wrong, depending on if they're more of the DTGA post atrial switch or CCTGA. But in short, it's that longstanding pressure afterload with subsequent consequences.

Dr. Burchill - And I know that sometimes there's patients listening to this who might have these conditions, so I'm gonna further emphasize that right ventricle, for most people, has a pretty lazy job. It just sort of sits below the lungs, and that's a low pressure circuit. It's the easy job. The left ventricle's got the hard work, it's gotta pump blood through the brain and the body. This is not that situation. This is that lazy ventricle that's being put into the spotlight, and it has to pump blood to the brain and the body, as you say, under high pressure. And I think it's quite amazing how the heart adapts to these differences, but over time, it becomes maladaptive. We see thickening of that ventricle enlargement of the chamber, and in most, almost all, we see a reduction in function that increases over each decade of life. So that sort of brings up this question, okay, if we know that the function of the systemic right ventricle is declining, why

can't we just sort of take from the playbook of normal or acquired heart failure, and just use the medications that we use there?

Dr. Jain - Great question, why can't we? You know, I mean, I think it depends on who you ask, and there's a lot of varying opinions out there, and you probably have much more historical context on this than I do, but my understanding is basically is-

Dr. Burchill - Hey, is that because I'm older? Is that why you're saying that?

Dr. Jain - Can we delete that part? No, but you know, I think I'm just saying in terms of having a good historical context here is important, because when we think about the trials, that was the question initially, why can't we just use the medications that we would use for systemic left ventricle? And from my understanding, the trials that were done mostly on beta blockers, ACE inhibitors, ARBs, now over a decade ago and even further back than that, they were not overwhelmingly positive, showing the same effects that we see in patients with systemic left ventricles, and so essentially, they didn't show this overwhelming mortality benefit, and they didn't even necessarily show a significant improvement in ejection fraction or functional capacity, quality of life. But I think there's a lot of potential caveats when we look at how do we interpret those studies and are they applicable to our patients. And so there's varying opinions on here, but because of those studies being somewhat equivocal or conflicting, not overwhelmingly positive, I think historically, there's been a lot of reluctance or lack of enthusiasm to starting goal directed medical therapy in patients with systemic right ventricles.

Dr. Burchill - I agree, and I think that the challenge has been just, as you mentioned, the design of those clinical trials. So I talk about horses, zebras, and unicorns. I know you love this, I know you love it when I talk about this. But the clinical trials were the horses, thousands of the horses, so thousands of people with the standard forms of heart failure in anatomically normal hearts, and they were statistically powered, that's a statistical concept, but they had enough people to answer the question that was being asked about improvements in function, but ultimately, those hard endpoints like survival. Look back at our studies, it's like five, we had five people, we had eight people, we had 12, we had 15, and so I don't even know if they were positive or negative. I just know that they could not really answer the questions. They gave us some information about, you know, tolerability, and you know, response in small numbers of patients, but I completely agree, we were not excited by the findings. But now fast forward a couple of decades, and I think we're tired of the clinical inertia, we're tired of really kicking the can, and not being able to prescribe something as we see the function of these hearts declining. So maybe update the listener here, so we're talking to cardiologists, but again maybe some patients listening. What do you think's changed just in these last few years, some new trials, particularly coming out of Europe, and how is that influencing the conversations you are having with patients, and the medications that you might be more interested in using?

Dr. Jain - Yeah, great question, and I guess I'll probably answer it in two ways in terms of what's changed from my understanding. One is the design of the trial, the endpoints of the trial, the patient selection, so there's a big difference there, and that I think that is driven from the inertia,

as you described. And then the other is the new kids on the block, you know? RNAs or sacubitril-valsartan, as well as the SGLT two inhibitors have really revolutionized a lot of the way that we manage patients with acquired heart failure, and because of the excitement and all the progression of medication management even just in acquired heart failure in the past few years, I think it's really just kind of lighted the fire for us in adult congenital heart disease with heart failure to say that we need to do something, we can do something, let's take a look at it. So in terms of the patient design, though, so many of those prior trials, which were somewhat equivocal or hard to interpret, as you said, they had, like you said, small numbers, a lot of patients with relatively preserved systemic right ventricular ejection fractions, many of those patients were NYHA class one, and it was short follow-up. And so trying to prove mortality benefit with a one year follow-up in patients who are well and with good pump function is gonna be hard, even in acquired heart disease. So now the more recent trials, as you mentioned, the ones from Europe, particularly the groups in Belgium and Italy, they've looked at patients with systemic right ventricular function that's reduced, and generally patients who are more symptomatic as one difference, and then the endpoints aren't necessarily mortality, but there are changes in systemic right ventricular ejection fraction or even strain on echo, as well as changes in six minute walk distance, changes in quality of life, so more patient-centered outcomes related research, and it's showing more promise. So I think the more recent enthusiasm is for those two reasons, one, in the change in the study design and the patient selection, and then two, I think there is hope that the newer medications may have more benefits for our patients on some of the prior generations of the medication, so there's some thought that the sacubitril-valsartan combination has more benefits for the RV. SGLT2 is, I don't think we've had much data yet, but they're so overwhelmingly helpful in acquired heart disease, it's hard to imagine that they wouldn't be in congenital heart disease.

Dr. Burchill - Yeah, so again, the listener, they might have a patient, either a patient or a CCTGA, they might already have them on something like lisinopril, or losartan, valsartan. So if you're listening to this, one of the questions that's coming up in my mind, our minds when we see these patients is, is this someone who we might consider upgrading to the angiotensin receptor neprilysin inhibitor? Entresto is the one option that we have right now. What are you doing, Charlie, when you identify that patient, what are you saying to the patient, and how are you navigating just the conversation about why should we even consider switching this medication that they might've already been on for a couple of years?

Dr. Jain - Yeah, that's a great question, and I think it comes down to the heart of clinical medicine. It's an art to many respects, and we don't have enough guidance or data to tell us what to do in this situation, you know? So I'm relatively frank with the patients and open, saying that we don't know necessarily how much this will help you in five years, 10 years, 20 years down the road compared to just staying on your current medication. But I try to share my enthusiasm with them, and say that I am hopeful that this medication will be better for you. Now, whether or not how hard we kind of advocate for that or push for that, I'm curious to hear your thoughts too. But at least in my practice, what I've been doing is, you know, if things are smooth and steady, and the patient feels well and the systemic RV ejection fraction's good and stable, I don't advocate for it as strongly, because one, we just don't have the data there, but I at least bring up the discussion. Alternatively, if things are going downhill, the patient's not feeling as well, the

systemic RV ejection fraction's getting worse, or their functional capacity is declining, then I more strongly advocate for them and I share the data with them. But then there's also just another part of clinical medicine, there's cost associated with these. And so if the patient's already on a good dose of lisinopril and they tolerate it, and the newer medication's gonna cost them a few hundred dollars a month, I don't know if it's really fair to tell the patient that you need to take it, in my opinion. If you know they can't get food on the table, I don't know know if getting the medication with their morning meds is worthwhile. I don't know if it has enough benefit there, honestly, compared to taking one of the trusted, tried, and true medications, but curious to hear your thoughts too.

Dr. Burchill - No, I love your emphasis, it's the art, not just the science of medicine, and I sort of go through all those points as well. I find that my patients are very interested in the patient reported outcomes, and understandably so, like talking about a change in right ventricular strain is a very abstract thing. It doesn't really mean much if you're a patient, other than your doctor's telling you maybe it's an indication of improved function. But they are interested in, oh, the patients are walking a little farther, and also they're reporting better quality of life, or better or maybe improvements in symptoms. So definitely, this is all about shared decision making, and to undertake shared decision making, patients need to be informed. So I think one of the unexpected, or maybe you can say it's not surprising, but the change in my practice is the extra time that this takes. And so I keep in mind, you know, the patient's coming from an adult congenital heart visit. Sometimes that conversation is really beyond what you can achieve in that time, and so that I see is a barrier that we as a team and as the individual providers, we sort of need to think a little bit differently about that being a follow-up call, perhaps something that's tackled, because for it to be proper shared decision making, it does require quite a bit of time including, you know, the side effect profiles, and the financial side effects for patients.

Dr. Jain - Right.

Dr. Burchill - So any thoughts on that?

Dr. Jain - Well, yeah, no, I think that's a great point, and I guess I'll just, you know, speak to the team efforts here. I think we're incredibly grateful and lucky for our nursing team and our nurse practitioner team who are key players in our successful rollout of these medications, 'cause it is intensive, you know? The conversation doesn't stop when the patient walks out of the office that day. It's ongoing checking labs. It takes, it's a big effort, and I think that makes a huge difference if you have a team that we can all work together and accomplish this for the patient. In the absence of that, I find it even more challenging than it already is. So yeah, just kind of kudos or shout-out to the team, so thank you for developing the team, and yeah.

Dr. Burchill - Yeah, I couldn't agree more. I think if this was just a solo marathon, it's actually very difficult to be prescribing these properly with the information that the patients need. So just in the last few minutes that we have, let's talk about the SGL2 inhibitors. One thing I wanted to pick your brains on is these SGL2 inhibitors. I think for me what's exciting is the demonstration of benefit for both heart failure with reduced ejection fraction and heart failure with preserved

ejection fraction. I think many of our patients do have mixed systolic and diastolic dysfunction, so that's partly why I'm particularly eager to see what the future outcomes are gonna be like with our patients who are choosing to trial the SGL2 inhibitors. What's your early experience?

Dr. Jain - Great question, and I'm excited about them just for the reasons you said. And I think two other particular reasons that I'm excited in addition to the fact that the diastolic function are more preserved ejection fraction patient, one is that they're relatively hemodynamically neutral. So some of our patients walking around with systolic blood pressure in the 80s or so, and we're nervous about starting Entresto. These medications tend to be better well tolerated in my experience with them, and then two is that it seems like there's more symptomatic benefit. You know, in the acquired heart failure literature, it shows that it decreases exercise wedge pressure and things like that, and so it fits that these patients have better patient-centered outcomes improvement. And so I'm particularly excited about them for patients who are quite symptomatic. In terms of the experience, I'll be honest, in systemic RVs, I don't have much yet. I know the Penn Group recently published their experience, and they had eight DTGAs with systemic RVs, and they showed that it was safe. So in terms of side effects from them, there weren't any significant side effects, and so that's encouraging, and it makes me feel more confident on starting it up with patients. But I think so far, I'll be honest, it's certainly less than a handful of systemic RV patients that I've had them on yet, but I'm excited, and I think it gets back to the patient centered discussion, though, shared decision making, 'cause the cost is an issue, and then we don't really have efficacy data yet in this patient population, and so it's somewhat hearsay to the patient, so it depends on how they're doing and their willingness to try something new.

Dr. Burchill - Thank you, that's fantastic. This has been a great conversation today, thank you. Was there anything else that you wanted to say before we finish?

Dr. Jain - No, just very grateful to people like you who are leading the efforts and trying to improve the awareness and the care of our patients with adult congenital heart disease and heart failure, and also grateful for our patients who entrust in us, and we do the shared decision making with, so thank you.

Dr. Burchill - Thank you. Well, as always, it's not a me, I think this is a we, and it's only possible because of the team that we work with, so thank you again, Dr. Jain.

Dr. Jain - Thank you, Dr. Burchill.

Dr. Burchill - And for listeners, stay tuned for our next episode on "Interview with the Experts."