**SickKids VS Sudden Cardiac Death**

**COLD OPEN**

**Hannah**: In 1990 Heather Cartwright is on the varsity rowing team at Western University in London, Ontario. She's 20 years old and in the best shape of her life.

**Heather**: I really felt like I was at the top of my game. I had rowed all summer, had tried out for the Canadian national team.

**Hannah**: That fall, Heather is competing in the annual rowing regatta at Trent University in Peterborough.

**Heather**: And for anyone who knows Canadian rowing, it's like our homecoming. There's a big beer garden. There's oom-pah-pa bands. The banks of the river are lined with students and alumni and families and dogs.

**Hannah**: The race is 5 kilometres and Heather is seated second from the bow among 8 rowers. She's rowing extra hard that day to impress her coach. She wants to make the crew that will row at the big regatta at Harvard in a few weeks. But in the final thousand metres…

**Heather**: My vision, it's almost like it was-like a wrapper or something came down in front of my eyes and I couldn't see clearly in front of me. Now, I've been at the end of some very, very hard races. And this was not an unfamiliar feeling

to have sort of a tunnel vision. But what was unfamiliar was I felt like I could put my oar in the water, but I couldn't pull. I couldn't push hard with my legs.

**Hannah**: As they cross the finish line, Heather collapses over her oar.

**Heather**: And usually that's typical. The coxswain would wait a minute and let the rowers recover and then we would turn the boat and row back but I couldn't move. I think I was semi-conscious at that point. I was definitely extremely dizzy and just did not know what was going on.

**Hannah**: Heather is pulled onto shore, her toes dragging on the dock. She's rushed to the local hospital, where she's stabilized and monitored. Four days later, she's transferred to St. Mike's in Toronto, where she's told she'd had an exercise-induced tachycardia. It means her heart rate had become so fast that it couldn't pump blood to her body.

But this isn't a diagnosis. It's a symptom of something more serious. At the time, her cardiologist doesn't know exactly what. In the meantime, Heather is prescribed beta blockers and told to take a break from rowing.

**Heather**: I had no concept of what the beginning of this journey was—that I had already started

the journey. I thought I was healthy, I was fine. It was easily to be explained. And easily fixed.

**Hannah**: But Heather's problem wasn't easy to explain or fix. It would take four years to get a diagnosis: arrhythmogenic right-ventricle cardiomyopathy, or ARVC. It's a rare, hereditary heart disease that the medical community had only just officially defined.

**Heather**: I was sort of marching along the same timeline as they were discovering things about this disease.

**Hannah**: There are two hallmarks of ARVC. It's brought on by intense exercise and it can cause sudden cardiac death, striking mostly the young and athletic. Many of them die not knowing they had the disease. It's estimated that 80% of people with ARVC are undiagnosed. By the time it's identified, it's too late.

**Heather**: This disease kills children. Suddenly, unexpectedly. Seemingly healthy, athletic, happy kids who are just out on a soccer field or in a hockey rink or on a basketball court or on a rowing course.

**Hannah**: But this shadow may be lifting. With help from donors like Heather and her family, researchers at SickKids and Toronto General Hospital are casting new light on ARVC and exposing this once-invisible disease.

[MUSIC INTRO]

**Hannah:** You're listening to SickKids VS, where we take you to the frontlines in the fight for child health. I'm Hannah Bank. And this is SickKids VS Sudden Cardiac Death.

## ACT ONE

**Hannah:** The main feature of ARVC is frequent arrythmias. These are spells of erratic or fast heartbeats that, if severe enough, can short-circuit the heart. ARVC can present at a young age, but unless there's a known family history, the signs are easy to miss. Looking back, Heather recognizes glimmers of ARVC in childhood.

**Heather**: I would throw up after athletic events multiple times. I would be dizzy. I wouldn't be able to recover. And, you know, the effect of exercising hard—sweating, rapid heart rate, you know, dizziness—is the same as the effect of ARVC.

**Hannah**: By the time Heather was diagnosed at 24, she'd been coming to terms with the end of her rowing career.

**Heather**: I had my sights set on making the Canadian national team to compete at the Olympics, to row at the highest elite level. So to be told that that door was closed —and that's how I identified myself—was excruciating as a young person.

**Hannah**: Heather was also told that she shouldn't have children.

**Heather**: Because of the stress that it would likely put on my heart. I just tucked that away and kind of didn't deal with it for years. But that was a really hard one.

**Hannah**: Beyond limiting exercise, the only treatment for ARVC is an implantable cardiac defibrillator, or ICD. It's a battery-powered device surgically implanted in the chest that sends electric shocks to the heart. (Like the metal paddles, but inside the body.)

**Heather**: And what happens is the defibrillator fires to try to stop your heart so that when your heart restarts, it starts back in the right rhythm—just like unplugging a computer and plugging it back in. It's like a little death, but it's a little death that saves your life.

**Hannah**: At 52, Heather is on her 4th ICD. Years of competitive sports and near misses have taken a toll. She is in the early stages of heart failure. She's learned to manage the daily threat of ARVC. But as she's made peace with her limitations, the long grasp of this genetic disease has started to reach her family.

**[MUSIC TRANSITION]**

**Hannah**: In 1994, when ARVC becomes an official diagnosis, SickKids cardiologist Dr. Bob Hamilton

is paying close attention. As a researcher he studies similar disorders that cause sudden death. As a clinician, he would finally have a framework to diagnose patients. But the testing process is convoluted.

**Dr. Bob Hamilton:** The diagnosis currently requires a detailed series of clinical tests of each patient every year.

**Hannah**: This involves MRI, ECG recordings, an exercise stress test, blood work. It's onerous and the results are not always definitive.

**Dr. Bob Hamilton:** It's probably only by guess about 70% sensitive. Unfortunately, there's no perfect gold standard for the disease, but we think we're probably missing 30%.

**Hannah:** It isn't until 2004—10 years later—that the first ARVC gene is discovered. Today there's roughly 20 implicated genes. In 2012 Heather was found to have one of them. But the result wasn't inevitable. Only 60% of ARVC patients have a known genetic cause.

**Dr. Bob Hamilton:** There's still genetics that we don't understand for this disease.

**Hannah**: In 2012 Bob starts working closely with Dr. Danna Spears, a cardiologist who runs the Heritable Arrythmia Clinic at Toronto General Hospital across the street from SickKids. It's an important relationship. Because ARVC is

inherited, mapping and testing family members is the main way to identify people at risk.

**Dr. Bob Hamilton:** When we see children presenting with the disease, one of the things we do once we get the workup started is to refer the parents or adult siblings to Toronto General. When they make a diagnosis, they will refer the kids to us to be evaluated. And we actually meet monthly to discuss families as a group.

**Hannah**: Bob and Danna follow Heather's family—her sister and brother, and a niece. ARVC is thought to run deep in the Cartwright bloodline. There are stories of a cousin several times removed who collapsed after a long-distance race. And Heather's grandmother was said to have a weak heart. She died suddenly in her 40s.

Along with Bob and Danna's clinical partnership, they work together on ARVC genetic research. (Heather and her siblings have funded some of this work.) But in 2013, Bob begins looking for other disease markers in an unexpected place. He joins a dermatology lab at SickKids to study a possible connection between certain skin disorders and cardiac symptoms. As he learns more about skin disease, Bob makes a startling discovery about ARVC.

## ACT TWO

**Hannah:** Since Heather's diagnosis nearly 30 years ago, ARVC continues to cast a long shadow over the family. They worry about Heather having another major cardiac event. And she worries about her siblings and their children. Would ARVC keep rearing its ugly head again and again? Despite genetic advances, 40% of people with ARVC have no known genetic cause. A negative genetic test isn't necessarily a free pass. Six years ago, Heather's sister Meredith found this out the hard way.

**Meredith**: I was 51 and was actually at a family meeting with my brother and sister and one of our advisors. And my sister looked at me and she said, you look terrible. I think there's something happening. And I was clammy. I don't think at the time I realized my heart was racing. But, you know, I felt nauseous. And so my sister called an ambulance.

So the next day I'm literally on a stress test, like in jeans and loafers, running. And they basically pushed me off the treadmill, like put me on a bed. And I'm like, what was that for? And the reason was, is that on my stress test, the reading was that I had ARVC and which is exactly what my sister has.

**Hannah:** Despite the family history, Meredith is shocked. Six years earlier, she and her daughter

Brooke had tested negative for the known genes. But the clinical results are compelling. She is diagnosed with ARVC and prescribed an implantable defibrillator Fairly quickly, her daughter Brooke, who's 13 at the time, is sent to SickKids for testing. She's already an athlete. She'd been swimming competitively and dabbling in other sports. It was important that Bob start monitoring her.

Brooke is now a student at Queen's University. She's been cleared to play rugby, which is high-intensity, but for shorter periods. It doesn't put the same strain on her heart as the long endurance of, say, rowing. And so far, things look ok. But a couple of years ago, Brooke started showing signs of ARVC. Meredith won't get into the specifics, but it weighs on her.

**Meredith:** Being an athlete and participating in sports is a huge piece of who she is. The other thing is that, you know, as a young athlete and as a young woman, she regulates her mood and mental health through exercise. What's being taken away with a diagnosis of ARVC is your vitality, literally, your health.

**Hannah**: Meredith and Heather's brother, Brian, is also negative for the ARVC mutations. And so far, his clinical tests have been good. But, like Meredith, Brian worries about *his* young daughter.

**Brian:** My daughter is now six years old, grade one. She is a very sporty, energetic spirit and always on the go. She's a going concern. This this hits a raw nerve. And this is this is where I really am terrified that this is something that she will be diagnosed with.

**Hannah**: There have been a few scary moments. During a soccer practice last summer, she ran off the field to tell Brian that her heart was beating fast.

**Brian:** And I literally caught my breath and went, oh my god. And I said to the parents: does anyone have a heart monitor? And thankfully, one of the other parents said, I'm wearing my Apple Watch. And he took off his watch. He put on my daughter and we took her heart rate and it was racing. And Dr. Hamilton had suggested that it's hydration and rest and you've got to kind of watch it. And that was that was like a pivotal moment for me.

**Hannah**: The clinical tests can’t detect ARVC this young. For reasons that aren’t well understood, the disease usually presents in adolescence or early adulthood. So for now, Brian can only watch his daughter for signs—and hold his breath on the soccer field. ARVC will be an ever-present worry.

**Brian:** It's sort of like this dark hovering cloud overhead on the horizon, that once in a while it comes right over top of us.

**Hannah**: Brian recalls a day years ago at the family cottage, watching Heather as her defibrillator fired.

**Brian**: And she literally sat down, crossed her arms. And so we sat down quietly with her and watched her. And if you've ever seen those television shows where they take the paddles and put it on someone's chest and the body jumps—it's that. It's like she's being struck by a bolt of lightning. She jumps and then she goes back down and it's exhausting. And then the tears are coming down over her face. And then there's the...it's like a tsunami wave and there's another wave that comes. I remember watching my mother's face to see her...daughter [pauses, chokes up] and her face. I can't...[pauses] You know...it's your *child*.

Watching your siblings—now one, now two. And I'm thinking, OK, who's next? The hardest part is the helplessness of not knowing that you could have a ticking time bomb that could reveal itself at any time. I don't know. And this is where, you know, we need to know more as fast as possible.

## ACT 3

**Hannah**: In the 70s and 80s, when ARVC wasn't well defined, if a person had died from a sudden cardiac event, doctors would illuminate the heart from the inside. A telltale sign of the disease was that the heart would be yellow and transparent. A Chinese lantern is how doctors described it. Scar tissue and fatty deposits had replaced the healthy red muscle tissue. Bob explains.

**Dr. Bob Hamilton:** Where we know the mutations in arrhythmogenic cardiomyopathy, the most common ones are mutations of proteins that make a structure called a desmosome. And this holds heart muscle cells together at their ends, very much like a hitch on a train. If you can think about a hitch being made up of several different pieces of metal, if any one of those pieces of metal are deformed, then that hitch may be weak and allow the train cars to separate. When cells separate, something has to come in and replace them. And scar tissue and fat may be what's doing that.

**Hannah**: These detachments are thought to cause the arrythmias.

**Dr. Bob Hamilton:** In addition to having these mechanical hitches, there are also these tubes that allow information and electricity to pass from cell to cell. And so when the heart muscle cells separate because the hitch is weak, those electrical connections also separate. And

therefore the conduction in the heart slows down.

**Hannah**: Years of competitive rowing had put major stress on Heather's failing desmosomes, or train hitches, to use Bob's analogy. Desmosomes are also found in other body tissues, but most abundantly in skin cells. So it makes sense that Bob begins collaborating with a dermatology lab at SickKids.

**Dr. Bob Hamilton:** I think I got the better end of the stick out of that relationship because I learned so much about skin disease and particularly about the skin-blistering diseases called pemphigus.

**Hannah**: Bob learns that pemphigus diseases are caused by autoantibodies, or just antibodies for short. These are immune proteins that mistakenly attack the body's own tissue. For example, in rheumatoid arthritis, antibodies damage healthy cells in the joints. In pemphigus, antibodies attack the desmosomes in the skin, causing blistering and rashes.

**Dr. Bob Hamilton:** So I really got to thinking maybe there's an autoantibody to the heart's desmosome. And we went searching for that.

**Hannah**: Initially, Bob homes in on the fraction of ARVC patients with no family history or known genetics. He gets a small grant from the Labatt

Family Heart Centre's innovation fund at SickKids, set up to support out-of-the-box ideas. But his lab has trouble spending the money. These ARVC patients are so rare, there aren't enough of them to test. And it would likely take years.

**Dr. Bob Hamilton:** We realized we had to test everybody that had a clear cause and a clear gene and a clear family history.

**Hannah**: This fluke decision leads to an astonishing discovery for Bob and his team.

**Dr. Bob Hamilton:** And we were actually astounded to see that everybody had exactly the same autoantibody. It didn't matter whether you had a gene cause or not, or whether you even knew which gene it was.

**Hannah**: It is the strongest, clearest indication of ARVC out there. And it was gleaned from a blood test. It also identifies the trigger of the disease: antibodies attacking desmosomes in the heart.

**Dr. Bob Hamilton:** Well, you know, when you see these things at first it seems too good to be true. So the first thing we did was basically I said to Diptendu Chatterjee, who's the scientist in my lab that really does all the work on this and, basically said to Diptendu, well, now you have to do a whole bunch more patients to confirm this. So it wasn't really a moment to celebrate and relax. It

was, oh, wow. And now we have to work even harder.

**Hannah**: Bob and the team had made the discovery using patient samples from SickKids and Toronto General. But to validate the results, they would need to test a few thousand samples from many different cohorts. The problem is, they've burned through their grant money.

At the time, Meredith's daughter Brooke is a patient of Bob's. And Meredith hears about his study.

**Meredith**: I looked at him and said: so if you had one hundred thousand dollars, how much faster could you go? He's like, a lot faster.

**Dr. Bob Hamilton:** The gift really came in exactly the right time. I mean, it's amazing. It really directly supported my research and it led to, you know, further validation and the publication of our finding. It allowed us to, you know, be confident about our funding, and really get down to work. It brings notice to your work that then either other donors or other successful funding applications can then arise out of that.

**Hannah**: And they do. Bob's ARVC research team would subsequently receive more than $1.3 million in external grants.

Back at the lab, the team begins the validation process and connects with an ARVC research

group in Zurich. Of the 25 samples tested, all of them have the antibody.

As news breaks about the discovery, Bob is asked to present his late-breaking science at the annual meeting of the European Society of Cardiology in 2017. The next year his team publishes their stunning results. Though the sample size is small, the antibody test has been 100% accurate in detecting ARVC. Bob is humble about the implications.

**Dr. Bob Hamilton:** Well, I think it gives a nice, simple test, it provides the opportunity to diagnose patients quickly in their own community rather than coming into an academic center and having, you know, a thousand dollars worth of tests each year and spending the entire day here and sometimes a day on each side for travel.

**Hannah**: Bob and his team continue to validate the test with groups around the world. They're aiming for 2,600 samples. Bob figures they're still a year or two from having a clinical test. The vision is to include the ARVC antibody test in routine blood-tests at hospitals and commercial labs anywhere. The antibody is even present in saliva, which opens the possibility of a spit test. For patients like the Cartwrights, it's exhilarating to imagine the ultimate outcome.

**Meredith:** And the fact that this could now, you know, give a diagnostic tool but eventually be

used to create a remedy and a cure in our lifetime is mind blowing, it's so exciting, like it gigantic.

## CODA

**Hannah:** Being able to easily and accurately detect ARVC will no doubt save countless lives. Sudden death is rare among people who've been diagnosed. They can be monitored, educated about exercise and, if needed, fitted with a defibrillator.

Family testing could be expanded and easily deployed anywhere in the world. In the not faraway future, kids might be tested before joining a sports team.

For Meredith's daughter, Brooke, the test would give certainty about whether to pursue an athletic career. And Brian could know much sooner if his daughter will develop ARVC, and how severely.

Implicating antibodies in this disease and others like it, will likely lead to their reclassification as autoimmune diseases. And this opens up all kinds of new treatment directions, ones that are already in use.

In their lifetimes, Heather and Meredith, who already have their diagnosis, might be able to take a drug that stops the antibodies from doing

more damage to their hearts. The next generation of Cartwrights—and scores of other affected people—will have the power of knowing.

**Meredith:** What an impact it can make in communities, because you actually don't have to go very far to hear about the guy that died in the arena. The girl who died in the gymnasium. Like, every town has one of these stories. They can be solved within our lifetimes. And if solved, saves lives. And so to be able to give that gift to your next generation and to everybody else's next generation? That's incredible.

**[END/OUTRO]**

**Hannah:** From SickKids Foundation, this is SickKids VS. Thanks for listening. If you want to support work like this, visit sickkidsfoundation.com/podcast to donate. And if you like this podcast, please subscribe and rate us on Apple podcasts, Spotify, or wherever you listen to SickKids VS.

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