University of Manitoba: "What's the Big Idea?"
Series 4, Episode 4: Matters of the Heart: Uncovering Sex Differences in Heart Failure with Dr. Lorrie Kirshenbaum

INTRO MUSIC FADES IN

INTRODUCTORY MONTAGE

News clip
https://globalnews.ca/video/11026424/womens-heart-health-highlighted

"The then 51-year-old had experienced what's called a Spontaneous Coronary Artery Dissection. SCAD is a condition that, in 90% of cases, affects women. Heart disease is on the rise and it's the number one cause of death for women, globally."

LORRIE KIRSHENBAUM:
"So why does it happen predominantly in women, not men?

Women have different kinds of heart disease. They manifest different kinds of symptoms and signs of heart disease. And this has largely been underrepresented, largely because, in the early 60s and 70s, clinical trials were performed predominantly in men, males.

Next to the reproductive organs, the heart is the most different between males and females. And that was something that was really unknown. A woman would go to their doctor with some form of heart disease, vague symptomology that didn't correlate with the man. They were often dismissed as having anxiety, being tired, and they were having a cardiac event."

INTRODUCTION

MUSIC FADES IN

MICHAEL BENARROCH: Welcome to What's the Big Idea? I'm your host, Michael Benarroch, President and Vice Chancellor at the University of Manitoba. February is Heart Month, and this episode explores heart health from a perspective many haven't considered. My guest is Dr. Lorrie Kirshenbaum, a former Canada Research Chair in Molecular Cardiology, at UM's Max Rady College of Medicine and the Director of the Institute of Cardiovascular Sciences. Through international partnerships and groundbreaking research, Dr. Kirshenbaum has helped reshape how we understand heart failure, including answering a historically overlooked question: do women's and men's hearts fail in the same way?

He is a member of the Order of Manitoba, a UM Distinguished Alumni Award recipient, and a widely honoured leader in cardiovascular research. This episode unpacks his big ideas about how we prevent and treat heart disease. Check your pulse. Things are about to get exciting.

MAIN INTERVIEW

MUSIC FADES OUT

MICHAEL BENARROCH: Hello Lorrie, it's great having you here today. I'm really looking forward to this conversation.

Your big idea is that heart failure unfolds differently in men and women. And in 2024, you received $5 million in federal funding to establish a lab to investigate this. Sex differences in heart failure was a blind spot in medicine. That kind of surprised me. But what led you to see something worth being curious about? What got you to ask the question and have the idea that women and men's hearts fail in different ways?

LORRIE KIRSHENBAUM: I'm delighted to be here and thank you for taking the time to give me the opportunity to share some of our research and some of these long-term plans we have here and investigating sex differences and heart disease.

What's become very apparent over the past, I would maybe 10 years, 15 years is that women have different kinds of heart disease. They manifest different kinds of symptoms and signs of heart disease. And this has largely been underrepresented, largely because, in the early 60s and 70s, clinical trials were performed predominantly in men, males. In some of our studies, we recognize that female animals, our and model systems behave differently. They displayed greater incidence of heart damage after heart attack. And it was consistent with the clinical presentations of women having greater incidence and severity of heart disease, which contradicted what people originally believed.

The statistic really is one in three women are likely to have heart disease, have some form of heart disease, and if they experience their first heart attack, it's usually more severe than it would occur in males. So, this led us to ask the question, what is this related to? And we discovered that this was tied to cell metabolisms that are different between males and females, within the heart muscle itself. The way the heart protects itself, in response to oxygen deprivation, lack of oxygen, ultimately results in heart attack conditions, and the heart muscle becomes damaged.

And the lack of understanding was that next to the reproductive organs, the heart is the most different between males and females. And that was something that was really unknown. So, a woman would go to their doctor with some form of heart disease, vague symptomology that didn't correlate with the man. They were often dismissed as having anxiety, being tired, and they were having a cardiac event.

MICHAEL BENARROCH: Hmm.

LORRIE KIRSHENBAUM: And so, this is obviously a problem. And so, we decided that we were going to try to understand why this was the case. And women are not necessarily smaller men and as a result, the treatment modalities were built around men and not women. And so, our interest in this whole program was to find a way to better understand heart disease in female hearts, better understand how we could treat female hearts and decrease morbidity and mortality, improving quality of life.

MICHAEL BENARROCH: So, let's break this down. Let's start with what is heart failure.

LORRIE KIRSHENBAUM: So, in the most rudimentary sense, heart failure is a condition where the heart's ability to pump blood does not meet the body's needs. And heart failure can result from many different sources; it has many different origins but predominantly it occurs after a heart attack. And the question is, what is a heart attack? So, the heart attack that we talk about really refers to the fact that the heart muscle requires a constant supply of oxygen. And when that oxygen delivery is interfered with because there's blockage in the coronary arteries, which otherwise supply the heart muscle cells that make up the heart, the heart muscle cells die. They become damaged. And the ability for the heart muscle to contract or pump blood is diminished. And so, you need these cells for the heart muscle to contract blood. And if that is interfered with, the person is said to have heart failure because the ability of the heart to function is abnormal. It can be acute, after a heart attack, a person can go into heart failure, or it can be chronic.

The chronic heart failure is a real problem because it really, ultimately leads to palliative care. The only real treatment for heart failure is a heart transplant. And in most cases, that's really impractical.

MICHAEL BENARROCH: Right. So, we have heart failure. How does it differ in men and women? And what causes these differences?

LORRIE KIRSHENBAUM: The presentation is different. Typically, a male having a heart attack, the classic symptoms is, a male will complain about an elephant on their chest, radiating pain down the arm, pins and needles. They may have jaw pain.

MICHAEL BENARROCH: Right.

LORRIE KIRSHENBAUM: That doesn't often happen in a female. The symptoms may be just very vague. They may be nonspecific. They may not have any symptoms at all. They just might feel off. And we don't really understand why the presentation is different, but we believe, at the cellular level, how the heart cells are connected to the rest of the body, etc., the response mechanism is different between females and males, and for that reason, we want to investigate why. By understanding that mechanism, we can develop new therapies and treatments and obviously better diagnostics to ameliorate heart disease, predominantly in females.

MICHAEL BENARROCH: So, how does a doctor approach this with a female patient?

LORRIE KIRSHENBAUM: There are different risk factors that lead to heart disease, in general. And so, the risk factors for women are largely different than they would be for men. Beyond just the smoking and the obesity and diabetes and hypertension, which we're now seeing more of. Pregnancy is a form of stress on the heart. Every time a woman has a baby, it causes the heart to work harder. Anytime the heart has to work harder, it's a stress to the heart.

Typically, if a patient is concerned, about they're not feeling well, I mean, we advocate call 911, go to the emergency. Don't treat yourself and don't dismiss symptoms. But they often dismiss it. So, that's the problem. It's recognizing this. And so, when they appear at the doctor's office, we have built a program now. It's not only educating our physicians and our medical students, it's educating the public that if they feel unwell, something is not right, they should go to their doctors. And now we're educating the doctors to say, hey, you know, there may be symptoms that you are missing.

MICHAEL BENARROCH: I think one of the other things that I found interesting about your work, a pretty major discovery in your lab, was identifying a distinct protein that plays a role in heart failure.

LORRIE KIRSHENBAUM: Right, right.

MICHAEL BENARROCH: Keeping in mind that I'm an economist, so you know, I tried to read some of your research, but it got a little technical for me, which people say that about economists' research, but can you explain what this protein does and why finding it, in both of these contexts, is significant?

LORRIE KIRSHENBAUM: Sure. Well, for an economist, you're asking some terrific questions. So, thank you. So, how did we get to the protein and why does this link to the woman heart health? This protein, we discovered, is important in basically regulating the cell's ability to respond to stresses like the lack of oxygen. What we discovered was that heart muscle cells, in contrast to other cells of the body, don't respond well to the lack of oxygen, they die. And they don't replicate; they don't repair themselves. Skin cells, liver cells will regenerate. Heart muscle cells don't. So, we asked the question early on, if we couldn't get the cells to regenerate, could we get them to live longer? And in that process, we identified a series of proteins that were genetically regulated, that basically told the cells when to live and die.

MICHAEL BENARROCH: And you also found this same protein shows up in cancer patients undergoing chemotherapy.

LORRIE KIRSHENBAUM: Okay, so cell death in the heart is not a good thing because, I mentioned, it leads to heart failure. If you look at the converse, the converse in cancer, a cancer effectively, at its most rudimentary level, is our cells that don't know how to die. They've lost this mechanism to self-correct and so the tumor grows because the cells are proliferating, they're growing.

There were several genes that were identified in cancer biology called tumor suppressor genes that actually suppress the tumor because they block the cells from growing. They are missing or deficient in cancer. So, the cancer has an advantage, it grows. So, how do I contrast cell death of heart cells and cell growth, in cancer cells, to this protein that we identified? And we discovered that if you blocked the activation of this protein, you could actually prevent the heart muscle cells from dying, and you could minimize the amount of heart damage, following a simulated heart attack. So, what does this have to do with cancer? This particular gene, that inappropriately gets activated inappropriately during heart attack, is switched off in cancer. And so, the converse happens. And so, now we develop the cancer direction in the lab to see how we can activate this particular gene and again, mitigate cell, tumor formation by playing with dialing up or dialing down the expression of the protein.

How does this link to women heart health? It links to women heart health because there is a class of drugs, anthracycline type drugs, that are commonly used to treat breast cancer, non-Hodgkin's lymphoma, etc., and uterine cancers and several others, predominantly in women. The chemotherapy itself tends to be very effective, but one of the side effects is it causes heart failure.

MICHAEL BENARROCH: Right.

LORRIE KIRSHENBAUM: It causes the heart muscle to die. And we linked this particular protein, that's switched on when people are having heart attacks, to the same cardiac dysfunction that we see, in patients or in animal models, treated with this particular chemotherapy. There are other things going on with this chemotherapy, but this protein again seems to be involved. And why it became important to us is because it's women, with ovarian cancer, with endometrial cancer, with breast cancer, that are treated with this particular drug. And if they develop symptoms, early on, after taking this drug, the drug has to be withdrawn.

It ultimately leads to the fact, if we see that there's a cardiac effect of the drug immediately, the person basically goes without chemotherapy, without cancer treatment. So, there's a very fine connection in evolution, in biology, how these different genes and proteins got activated in different organ systems and they got activated in a sex specific manner. And that's what we're trying to tease out with this entire program.

MICHAEL BENARROCH: So, would it be possible one day to target this protein with a drug?

LORRIE KIRSHENBAUM: Yes, so we developed a variety of peptides, small proteins that target this particular protein and we can prevent it from being activated in the heart. And at the same time, we've developed mimetics that kind of fool the cancer cell, into thinking that this gene is no longer, because it's inactivated, we can kind of fool the cancer cell into thinking it's active and we can kill the cancer cell. So, we're playing it at both ends. It's very exciting. And with new technologies, in precision medicine, this is something that we're hoping. And we're also planning of using this protein as a diagnostic because if a person has a heart attack, we want to know if this protein is elevated in the blood, you know, in addition to some of the other diagnostics that are currently being used.

MICHAEL BENARROCH: That's really interesting. Basically, you would stop the cells, stop the process of killing the cells. And so then, in minimizing that damage, what's the prospects for the future? So, the heart is healthier, in a sense, after a heart attack.

LORRIE KIRSHENBAUM: That would be the end goal. If we can prevent or minimize the amount of heart muscle damage after a heart attack, or in response to chemotherapeutic drugs, it would have a positive effect on outcome.

MICHAEL BENARROCH: I know that also some of your research is supported by the Women's Heart Health Fund.

LORRIE KIRSHENBAUM: Yes. I also want to illustrate the importance of the funding because this is the very first dedicated Women Heart Health research program that will be translated into patient care.

MICHAEL BENARROCH: So, how has this helped you take a more holistic view of women's heart health?

LORRIE KIRSHENBAUM: So, we're not looking at just the heart itself. We've developed this program in partnership within the university and stakeholders within the province. The plan is to have this not only service the local centre in Winnipeg, but also northern regional communities, particularly vulnerable and underserved individuals. St. Boniface Hospital, in general, is the regional centre for cardiac care in the province. And now we have this program that we're hoping to translate this into recruitment of clinician scientists that will be able to help patient care. But it's more than just the heart. We are interested in education. We're interested in having nursing involved. We're interested in having psychologists involved. So, the holistic view is not just looking at the heart, we're actually looking at the person. And that's what's really important because we're treating the person, we're looking at lifestyle, diet. So, it's not just the heart in isolation.

MICHAEL BENARROCH: Right, so not just having a physician look at your heart but thinking about your entire lifestyle.

LORRIE KIRSHENBAUM: Yeah, and that's really important because our health care system, the way it's set up, is not designed for that, and so, we have to take that into account. I think education is really

important, not only at the public level, but also at the healthcare delivery level. The awareness is what's really important.

MICHAEL BENARROCH: And so, are there different approaches for men and women? Is the treatment more or less the same, at this time?

LORRIE KIRSHENBAUM: The treatment is typically tailored to address the symptoms. In terms of treating men and women currently, yes, that's the answer. But the treatment would be not necessarily cookie cutter. It was what the person needed, if they're short on breath or need a drug to help their blood pressure go down or a drug to lower their lipids, you know, they'd be treated accordingly.

MICHAEL BENARROCH: With that, what are some of the big unanswered questions about sex differences and heart disease that you still want to examine?

LORRIE KIRSHENBAUM: Women develop a disease predominantly called SCAD. It's called spontaneous coronary artery dissection. If you'd looked at the coronary arteries, and I use by analogy a garden hose, if you were to take a look at a garden hose, you'd see an outer rubber layer and there's an inner core, they're multiple layers.

What happens in predominantly women, these layers begin to separate, like an onion. They just peel apart. And ultimately what happens is that the blood gets trapped between the layers and it occludes, it narrows the blood vessel and then ultimately the flowing of the blood to the heart is diminished. It's lethal, it can just rupture or it can be stable over time, but treatment is required immediately. So why does it happen predominantly in women, not men? And so, we're actually looking at those questions. How can you better diagnose SCAD? Because it goes undiagnosed. It's not something that someone would have pre-symptoms. They may not feel well, but when it happens, it happens.

There's another condition called Takotsubo cardiomyopathy, and it predominantly occurs in women. It's called broken heart syndrome. It was identified by a Japanese physician. You hear of stories where a male husband or whoever dies and shortly after the partner dies.

And that's typically because the catecholamines, the norepinephrine, epinephrine chemicals are very high in these individuals, and they profoundly affect the heart. Why does that happen predominantly in women and not males?

So, there are other forms of heart disease. Women develop heart attacks and if you looked at their heart, their blood vessels are squeaky clean. A man, they would have plaques and everything. Why does it happen? And that's a disease where women have microvascular disease that we don't really understand. Microvascular disease meaning very, very tiny blood vessels. That the disease of origin and they have perfectly good coronaries. So, when you ask the question, those are three predominant areas that remain uncharted. And we'd like to understand why.

MICHAEL BENARROCH: Well, and just from that, you could see how diagnosis, it's so important to understand, right? Because if you're looking at it from the perspective of male heart disease, you're not gonna be looking for the right things or all of the things you should, in females.

LORRIE KIRSHENBAUM: Yes. And everything that we do now, in terms of funding, the granting agencies actually require it. We were doing it before, but the granting agencies require now sex differences between males and females to be identified. And you're quite right. We wouldn't identify that there'd be a difference between males and females, if we weren't looking.

MICHAEL BENARROCH: I know a lot of our research requires that we get research funding, especially your research. And so, let's get a bit philosophical. You once said that you could offer me a million dollars, I'm quoting you, but that won't solve heart disease, that won't cure cancer, it's the idea. And I know we hear over and over, when you have an idea, to conduct research which is a little bit outside the box, which I think, probably when you got started with this, it was a little bit outside the box. Did you have challenges getting funded for this? Did you have to convince people that this was, in fact, a line of research that was important and that there was something substantial to this?

LORRIE KIRSHENBAUM: Yes, I think the ideas are really important and thinking outside the box is where the evolution comes from. The innovation is thinking outside the box. Yes, getting funding for these kinds of programs were very challenging. There was a lot of pilot studies we had to do and there was a lot of demonstration that this has legs, so to speak, and it holds water.

People are really resistant to change. I think this is part of the issue. I would tell my graduate students that just because it's published doesn't mean it's real. We have to challenge it. And the other thing is I've always instilled, in my trainees, as a mentor or even faculty, if you have an idea, if you have knowledge, you have an inkling, you know, follow it because you don't know where it's going to go.

MICHAEL BENARROCH: Now, your research has kind of taken you in a number of different directions and it's really interesting to read. You partnered with NASA to study the circadian rhythms and heart attacks. Tell us a little bit about that.

LORRIE KIRSHENBAUM: The work with NASA was really, really quite exciting. It was the most profound experience. I can't put it to words. And knowing that we're from University of Manitoba. And when I went there, I gave a lecture, it had our billboard. They had the U of M logo, the St. Boniface logo. And I was so proud to be there.

I had always wanted to be an astronaut, so this was the closest, I think, we could get. In collaboration with one of our most recent recruits, Ina Rabinovich Nikitin, she's an Assistant Professor in our Department of Physiology and Pathophysiology, and at the Institute, we had been working together to look at the effects of shift work and the incidence of shift work on heart disease and how it affects women greater than in men.

So, that's where this started. And so, we identified differences in circadian effects on the heart. And historically, it was established that heart attacks occur greater in the morning hours, usually a transition from Sunday to Monday, than any time of the week. And they occur typically greater, in the morning. And the severity would be greater in a woman than in a male.

So, we were talking about this, and we have a publication that's currently under review at a major journal. But the crux of it is that, if we were able to condition animals with exercise, prior to the shift work, we could mitigate the amount of cardiac injury.

So, what does this have to do with space flight? What does this have to do with NASA? Well, if you looked at the heart itself, the heart basically has a shape of a football. But in space, because of the lack of gravity or the microgravity, the heart muscle basically becomes more like a soccer ball, more round.

That's because the gravity, which would be otherwise pulling down, the heart doesn't have to work hard. And so, the blood moves upward. And that's why when you see on TV, the astronauts, they've got these swollen heads.

MICHAEL BENARROCH: Right.

LORRIE KIRSHENBAUM: Cause they're not working, you know? And so, their heart muscle changes. It becomes more like a soccer ball than it does a football. So, what does this have to do with my interest in heart failure? When you look at a person who has heart failure, their heart also remodels. Their heart actually becomes more round than ovoid. We say that's remodeling. It changes its shape. So, we wanted to know, first of all, when the astronauts come back to Earth, the heart doesn't always return to normal.

MICHAEL BENARROCH: For those astronauts.

LORRIE KIRSHENBAUM: For those astronauts and we wanted to know if we could learn from these healthy individuals anything about shape change, remodeling in those individuals, and adapt that to individuals on the Earth, in terms of heart failure. So, we're continuing our work with NASA. We're trying to see if we can learn about how the muscle remodels and the impact on circadian events.

MICHAEL BENARROCH: The astronauts whose hearts change shape and doesn't change back, does their heart perform differently afterwards?

LORRIE KIRSHENBAUM: It does. Actually, it does. And in fact, they resemble some element of heart failure. The amount of function when they return is somewhat diminished. It takes some time. They can't walk. Beyond just the muscle atrophy and the muscle weakness. The heart is a muscle. It too has to recover.

MICHAEL BENARROCH: It's fascinating. It's always so interesting to hear about the work and then, you know, the different contexts and how we can learn from space to help humans on Earth. So, on the personal level, happy birthday. I understand it's your birthday.

LORRIE KIRSHENBAUM: Thank you.

MICHAEL BENARROCH: And so, I won't ask how old you are, but what North American kid born in the 60s and 70s didn't want to be an astronaut? But how have you changed your lifestyle? You're doing research in this area. You must take it home and think about what you need to do yourself.

LORRIE KIRSHENBAUM: I actually had this discussion with my wife not long ago; we were just traveling. We were walking every day. I used to cycle quite avidly. I still do, but it's difficult, in Manitoba, with the winter. And I used to run and because of the age, knees and things like that. I think it's important to stay active. I think diet is really important. The amount of food and when we eat it. I've watched or try to watch what I'm eating. I stay away, although I love fries, I stay away from fries where I can and fried saturated fats.

I don't know if exercise, necessarily, to say this is what you should be doing high intensity or low intensity. It's that you should be doing something. That's the only thing I can advocate if people are thinking, at any time, at any age, they should be considering what their lifestyle really is.

MICHAEL BENARROCH: So, you've built partnerships with the Mayo Clinic, the Barbara Streisand Heart Centre, you've worked with research centres across Europe, you've worked with NASA. I'm sure you've gotten job offers at other places. I know what some of the big hospitals in America offer. What's kept you in Manitoba? And what do you tell young researchers who are building their careers about working here in Manitoba?

LORRIE KIRSHENBAUM: It's a really important question. So, I had trained in the U.S., and I had wanted to come back to Canada, close to 30 years ago. And the reason was there was something in Canada that I saw that was a little bit different than in the U.S.

But particularly U of M. This was really quite open. When I came back, I was recruited back. I wasn't sure I was going to come back to Winnipeg, but there were opportunities here, that were created for me, because it was a smaller place, because it was U of M, that allowed me to flourish. I had a foundational support, not only financially to support the program, but there was a lot of support within the program and within the university, to be able to talk with you, as the president of the university, being able to talk to your predecessors, being able to go to the department head, going to the deans, having a connection with people really made a difference, as a smaller institution, that people knew who I was and people supported the research. And that made a huge difference because I developed a program that didn't otherwise exist here. And now that became a nucleus for spawning off recruitment. We were recruiting not only faculty, but trainees.

And there's something special about U of M, in terms of the support, whether it be CFI applications, whether it be internal money support, that the grass is always greener. But if you look closely what you want, you can find it right here. This is exactly what I tell our trainees. A lot of them run off because they feel that they may be getting something that they may not be getting here and that may be the case. But I think, you can see from my own research program, I took the initiative to build a program, and if it wasn't here, I found a way to do it, and if it wasn't here, we found networks and I found a way to bring or go myself to places if it wasn't here and I don't believe that would have happened so readily if I was in another institution. So, I'm grateful to be here. I'm honoured to be a professor. I'm honoured to run the Institute and be part of this research enterprise.

MICHAEL BENARROCH: Lorrie, thank you so much. You've just described the Manitoba way. And we're thrilled that you stayed here. Your research is impactful. It's changing the way we treat heart failure, especially in women. And look forward to your continued work. Thanks for being a guest.

LORRIE KIRSHENBAUM: Thank you very much.

MUSIC FADES IN

EXTRO

MICHAEL BENARROCH: I hope you enjoyed this episode. I'm continually in awe of UM's research excellence and the talent we have here in Manitoba. We are at the center of bold ideas that have an impact around the world. If you want to learn more about this important work, check our show notes or visit umanitoba.ca.

Join me next time when my guest is Zahra Moussavi, who has big ideas on how non-pharmaceutical interventions can help treat Alzheimer's disease. Until then, take care of your heart and keep thinking big.