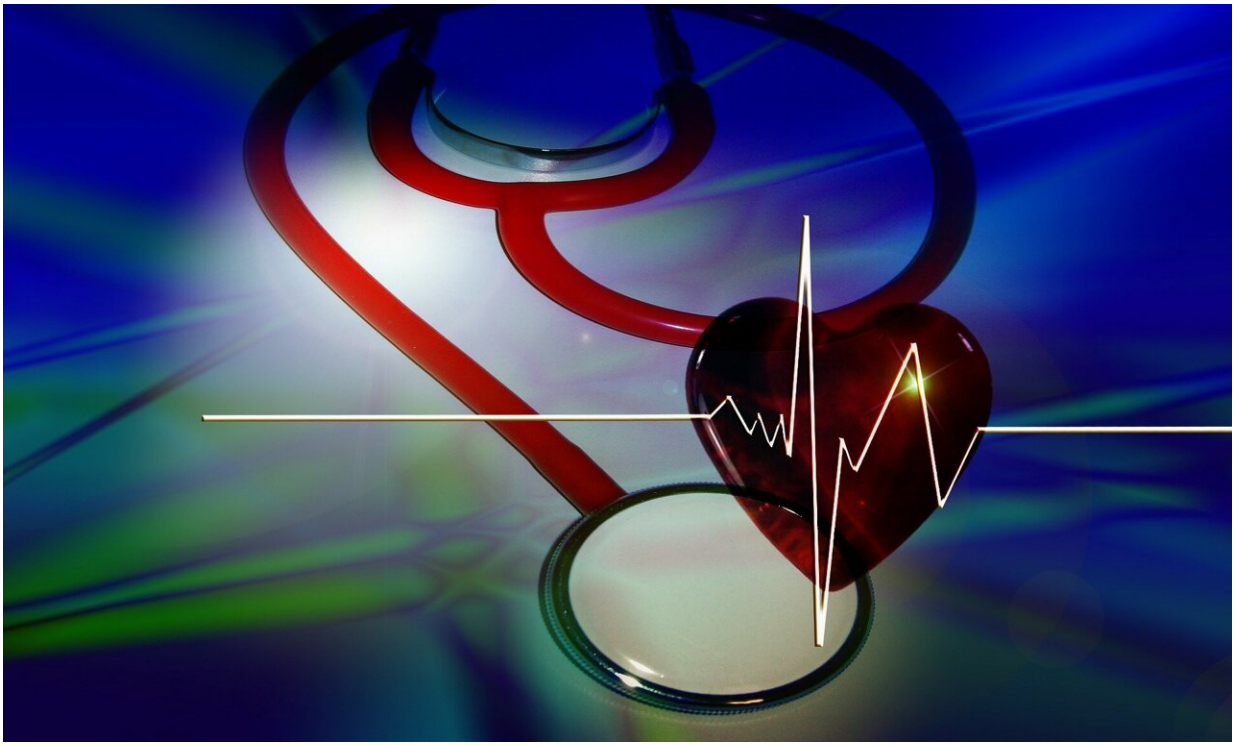
Teasing apart sex differences in heart disease

June 5 2024, by Kate Ledger, Mayo Clinic News Network



Credit: Pixabay/CC0 Public Domain

Damian Di Florio, Ph.D., remembers the lightning-bolt moment five years ago when he began thinking differently about the questions scientists ask. He was a summer undergraduate student working in the lab of cardiovascular researcher DeLisa Fairweather, Ph.D., when she and another scientist gave a lecture about vitamin D. The lab's studies had found stark differences between how vitamin D affects the heart

function of male and female models of disease.

"That was the first alarm bell for me," says Dr. Di Florio, who recently completed his Ph.D. in Clinical and Translational Science at Mayo Clinic Graduate School of Biomedical Sciences under Dr. Fairweather's mentorship. "It made sense that sex differences would be an important feature of biology to consider in any type of research, and especially in cardiovascular disorders, which women and men experience differently."

A disease more deadly in men

Dr. Fairweather has long studied myocarditis, an inflammation of the heart that's set off by a viral infection and can result in heart failure. The disease is rare, but it predominantly affects men under age 40. It can reduce the heart's ability to pump and can even be instantly fatal.

Several viruses, including SARS-CoV2, the virus that causes COVID-19, are known to set off the inflammatory process, but no disease-specific tools exist to detect myocarditis in its early stages.

For Dr. Fairweather, who serves as director for translational research for the Department of Cardiovascular Diseases, a key research goal is using the preclinical model of myocarditis that she developed to depict the disease process and provide new information relevant to human disease. She closely examines data for differences between males and females, including immune signaling which is affected by hormonal differences.

Translational research studies the mechanisms of disease with the goal of finding cures. Dr. Fairweather's lab aims to develop diagnostic tools and treatments that are tailored appropriately to men and women. "The mechanism of what's causing disease differs by sex," she says. "We should be looking for treatments according to that framework."

The perspective helped shape Dr. Di Florio's graduate work and it also yielded important results. "If we had not analyzed a certain data set by sex, we would have missed some of the most important and interesting features of that data," he says.

Differences in genes that affect the heart

During his Ph.D. research, Dr. Di Florio found differences in the male and female responses to viral infection, including genes activated during acute stages of myocarditis. He looked at genes affecting the energy-producing structures in cells—organelles known as mitochondria—that are especially essential in a pumping heart.

He found female mice with myocarditis have genes engaged that help mitochondria function; males have the same genes turned off. The lab is characterizing the genes, aiming to identify a target they can manipulate with the goal of making the genes more active in males during the disease process.

Dr. Di Florio also explored whether there might be sex-based variations in how myocarditis affects the pumping of the heart. Using three-dimensional echocardiography, he found that both male and female mice showed a reduction in blood squeezed out of the heart, a measurement known as ejection fraction. But when it came to the motion that pushes blood from the heart and to the rest of the body, a force known as global latitudinal strain, males showed worse function than females.

Further, that pumping difference correlated with the presence of immune cells in the heart—a sign of inflammation. The findings suggest that measuring global longitudinal strain could be the basis to develop a much-needed clinical test to detect myocarditis at an early stage.

A step toward treatment

During her graduate studies in Clinical and Translational Science, Danielle Beetler, Ph.D., looked at a potential treatment for myocarditis using particles that exist in the body. Her work in Dr. Fairweather's lab also took sex differences into account, focusing on the fact that the symptoms in women with myocarditis tend to be less severe than those in men.

"The idea was that maybe women who are most protected from these cardiovascular conditions have some kind of messaging in their body that can be applied in the context of male-driven disease," says Dr. Beetler, who also graduated this year.

Her experiments looked at extracellular vesicles, or EVs—tiny "envelopes" that are shed by cells and contain molecular messages, including mRNA. The studies found EVs from healthy donors not only shut down the replication of the virus and reduced damage caused by the immune system, but also protected cardiac function.

The research also found that the effect of the EVs differed by age and sex of the donor. The researchers speculate that some donors may have had an undetected infection, suggesting that specialized screening would be necessary in the development of a therapy.

"The studies overall are a step toward a novel, biocompatible treatment for myocarditis and maybe other cellular messaging-related diseases," says Dr. Beetler.

An outlook that could change medicine

The National Institutes of Health granting system has a policy for

researchers to include consideration of sex as a biological variable in clinical and preclinical studies. Dr. Fairweather and her mentees are committed to this approach for the benefit of patients.

She believes a close examination of sex differences will lead to better biomarkers for diseases that predominantly affect men, such as heart disease, and those that predominantly affect women, such as autoimmune diseases, which she also studies.

Research in her lab looks at sex differences in other cardiovascular conditions, particularly disease pathways that overlap with myocarditis. The lab has recently developed a new model of cardiovascular injury that can occur during cancer treatment. During chest radiation, a patient may incur damage to the heart and later develop cardiomyopathy, a disorder that interferes with the heart's ability to pump.

Emily Whelan, a second-year student in the Clinical and Translational Science graduate track, is looking for genes that may differ by sex and may affect inflammatory and functional responses to injury. The goal is to identify early indicators of cardiomyopathy and possible therapeutic targets, and to improve guidelines for diagnosis and surveillance.

For Dr. Di Florio, who is continuing his research as a postdoctoral fellow at Mayo Clinic, sex differences are now part of his thinking as a researcher and are how he'll evaluate data in future studies.

"The approach has the benefit of more precisely describing mechanisms of disease," he says. "It also has far-reaching sociological implications for how to more justly study and treat disease. It's information we absolutely need to address the biological differences that affect how frequently disease occurs, how severe the damage is and how well the body handles injury."