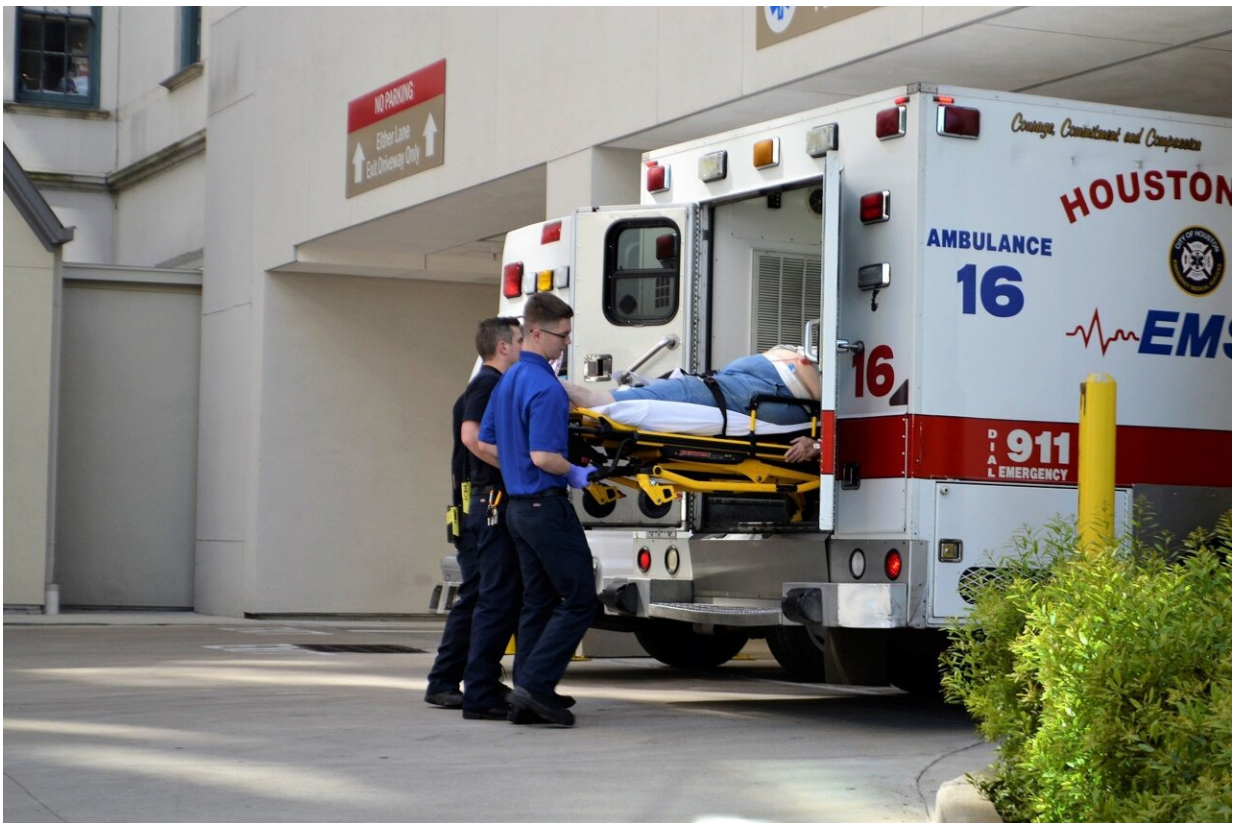


Study uncovers connections between obesity and heart failure

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A new small [study](#) led by Johns Hopkins Medicine researchers and published July 25th in the journal *Nature Cardiovascular Research* has revealed the impact of obesity on muscle structure in patients having a

form of heart failure called heart failure with a preserved ejection fraction (HFpEF).

According to the [Journal of Cardiac Failure](#), HFpEF represents more than half of all [heart failure](#) world-wide. In the United States, it accounts for over 3.5 million heart failure cases. Originally, this form of [heart disease](#) was associated with having a [high blood pressure](#) and along with this, excess muscle growth (hypertrophy) to help counter the pressures. Over the past 2 decades, HFpEF is occurring more often in patients with [severe obesity](#) and diabetes according to the [Journal of the American College of Cardiology](#). However, there are still very few effective HFpEF therapies, and a challenge in developing therapies has been the lack of studies in human heart tissue to determine exactly what is abnormal. As hospitalization and [death rates](#) in HFpEF patients are quite high, (30-40% over 5 years), understanding its underlying causes is critical.

"HFpEF is a complex syndrome, involving abnormalities in many different organs", says lead investigator David Kass, M.D., Professor of Medicine at the Johns Hopkins University School of Medicine. "We call it heart failure (HF) because its symptoms are similar to those found in patients with hearts that are weak. However, with HFpEF, heart contraction seems fine, yet heart failure symptoms still exist. While many prior efforts to treat HFpEF using standard HF drugs have not worked, success has since come from drugs used to treat diabetes and obesity."

More specifically, the drug used to treat diabetes, known as an SGLT2 inhibitor (sodium glucose transporter 2 inhibitor) is currently the only evidenced based drug for HFpEF that has improved not only its symptoms but also reduced long-term rehospitalization rates and endpoints of mortality. The weight loss drug GLP1-receptor agonist has been tested and found to improve symptoms in patients with HFpEF,

and ongoing studies are determining if a similar hard end-point (mortality reduction, hospitalization for HF reduction) are also possible outcomes. As such, these drugs have already been shown to be effective not only in diabetes where they started, but also in HFpEF.

To perform the study, the research team obtained a small piece of muscle tissue from 25 patients who had been diagnosed with varying degrees of HFpEF caused by diabetes and obesity and compared them to heart tissue from 14 organ donors whose hearts were considered to be normal. They examined the muscle using an [electron microscope](#) that shows [muscle structure](#) at a very high magnification.

Mariam Meddeb, M.D., MS, cardiovascular disease specialist at the Johns Hopkins University School of Medicine, who conducted the study says, "Unlike viewing the heart with a traditional microscope, the electron microscope allows us to magnify the image to 40,000 times its size. This provides a very clear picture inside the muscle cell, what we call ultrastructure, such as mitochondria that are the energy power plants, and sarcomeres (unit of muscle fiber) that generate force".

The researchers found notable ultrastructural abnormalities were particularly present in tissue of the most obese patients who had HEpEF, which had mitochondria that were swollen, pale, and disrupted, had many fat droplets, and their sarcomeres appeared tattered. These abnormalities were not related to whether the patient had diabetes, and were less prominent in patients who were less obese.

"These results will help those trying to develop animal models of HFpEF, since they show what one wants to generate at this microscopic level", notes Dr. Kass. "It also raises the key question of whether reducing obesity, as is now being done with several drug therapies, will reverse these ultrastructural abnormalities, and in turn improve HFpEF outcome."

The new findings help move the needle in understanding HFpEF and bring some clarity about the impact of obesity in heart disease, and provide a target for therapies to improve to benefit the many millions of HFpEF patients.

Other Johns Hopkins researchers who contributed to the study are Navid Koleini, Mohammad Keykhaei, Seoyoung Kwon, Celia Aboaf, Mohamed Lehar, Kavita Sharma, Virginia S. Hahn.

More information: Mariam Meddeb et al, Myocardial ultrastructure of human heart failure with preserved ejection fraction, *Nature Cardiovascular Research* (2024). [DOI: 10.1038/s44161-024-00516-x](https://doi.org/10.1038/s44161-024-00516-x)

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