Health Matters

Cause of heart failure may differ for women & men

A new study from the UC Davis School of Medicine found striking differences at the cellular level between male and female mice with heart failure with preserved ejection fraction (HFpEF).

The findings could determine how HFpEF is treated in women compared to men.

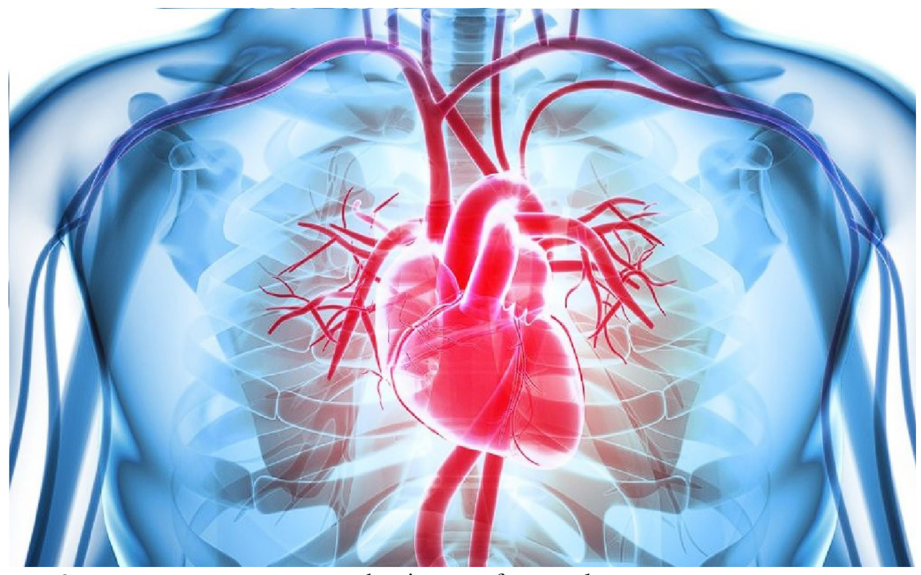
With HFpEF, the heart muscle contracts normally but the heart is unable to fully relax and refill properly between beats. This condition is known as diastolic dysfunction. It can occur if the heart is too stiff or if the contraction process doesn't shut off quickly enough between beats.

The study showed that the diastolic dysfunction in female mice resulted from altered heart filament proteins. In male mice, it resulted from the slow removal of calcium from heart cells between heartbeats, causing a slight contraction to remain between beats.

"This study demonstrates the importance of conducting research on both male and female populations," said Donald M. Bers, a senior author of the study. Bers is the chair of the Department of Pharmacology and the Joseph Silva Endowed Chair for Cardiovascular Research at the UC Davis School of Medicine. "If these same molecular male-female distinctions occur in obese diabetic patients with HFpEF, it may mean that the best therapeutic strategies for HFpEF in women may differ from those for men."

Heart failure is when the heart cannot pump enough blood and oxygen to support the body. Approximately 6.2 million people in the U.S. have heart failure. The five-year mortality rate for heart failure is around 50%, although many factors can influence survival. About half of those with heart failure have HFpEF, and almost twice as many women have HFpEF compared to men. Men with the heart failure may be more at risk of cardiac arrhythmias and sudden cardiac death.

Obesity and diabetes are common in people with HFpEF. To study the disease, the researchers created a unique "two-hit" mouse model combining



two factors.

For the first factor, the researchers used mice genetically lacking a leptin receptor. Leptin is a hormone that promotes satiety. Without it, appetite remains high and the animals become obese and diabetic. For the second factor, mice were exposed to an aldosterone infusion. Aldosterone is a hormone made by the adrenal gland. High levels of aldosterone cause fluid retention.

This animal model of heart failure and diabetes develops HFpEF, allowing researchers to analyze the cellular and molecular mechanisms of muscle contraction and relaxation in male and female mice.

Calcium is critical in the activation of contraction and relaxation of heart muscle cells as well as the heart's electrical activity. Calcium entering the heart cell at each beat causes the muscle to contract. It also helps drive the electric signal that synchronizes the contraction of the millions of heart muscle cells required for the heart to function as an efficient pump. Calcium is removed from the cell at each beat. This allows the heart to relax between beats and fill for the next beat.

In the male mice with HFpEF, the calcium removal from the heart muscle cells was slowed, preventing complete relaxation between beats. The male HFpEF mice also exhibited more abnormal heart rhythms, known as arrhythmias.

In contrast, the females with HFpEF exhibited normal calcium movements into and out of the heart cells. Instead, the researchers observed an increase in a shorter and stiffer form of titin (N2B). Titin is a protein in the heart that acts like a supportive spring. Researchers also observed phosphorylation (a molecular reaction) of titin and another heart filament protein, troponin I. Both the titin and troponin changes made the female heart cells functionally stiffer - making the heart harder to fill - even though calcium removal was normal.

Chicken feathers to deliver chemotherapy drugs

A new method of drug delivery using proline, an amino acid found in chicken feathers and skin tissue, could be used to limit the side effects of chemotherapy and repair important enzymes, new research suggests.

Published recently, researchers have designed a cage (a box made of single molecules) from biologically compatible peptides, short amino acids that form the basis of proteins. These cages can house drugs of different sizes and transport them in the body with high levels of precision.

The negative side effects associated with chemotherapy, such as hair loss and nerve damage, are a result of 'off-site toxicity', where the treatment kills healthy cells surrounding tumours as well as the tumour itself. By creating a nano-sized cage to house the drug and carry it into the tumour before releasing it, this effect can be channelled more directly to the tumour, shielding healthy cells.

The cage can be tuned to different sizes, enabling different payloads of drugs. This flexible structure allows for chemotherapy drugs, antibiotics, and antivirals to potentially be delivered. Previously, cages of this kind could only be made using hydrocarbon molecules found in tar, which can often be toxic to humans.

This structure, researchers believe, also opens the door for faulty enzymes to be replaced within the body, which has previously not been possible. Historically, enzymes, which are composed of proteins and perform important functions in the body, could only have their activities blocked by drugs. The blocking of this functionality would then have an impact in the body, like reducing inflammation. Now, the cages could replace this function which may lay the groundwork for a new form of treatment.

Principal author Dr Charlie McTernan, Lecturer in Chemistry at King's College London and Group Leader at the Francis Crick Institute, said "What we've created is essentially a biologically compatible molecular teabag. We can fill this teabag, or cage made from widely available proline and collagen, with several different medicines and deliver them in a much more targeted way than we could before."

"In time, we hope that this could mean that we can limit the hair loss, nausea, and other unpleasant side effects of chemotherapy. We might even be able to repair malfunctioning enzymes that have an influence on the development of cancer. The best part is we can do this sustainably and at scale."

Proline is very straight and rigid in shape, while also being soluble in water, which makes it uniquely suited for drug delivery, as water makes up roughly 60% of the human body. By binding the peptide to small amounts of metal such as palladium, the researchers could create a tuneable structure they could rapidly increase or decrease in size.

As proline and collagen are widely available and don't rely on chains of hydrocarbons like previous methods, the team hope to sustainably scale up their current production in the lab.

Changes in brain lead to memory problems

People who report early memory problems and whose partners also suspect they have memory problems have higher levels of tau tangles in the brain, a biomarker associated with Alzheimer's disease, according to a study published recently.

Subjective cognitive decline is when a person reports memory and thinking problems before any decline is large enough to show up on standard tests.

"Understanding the earliest signs of Alzheimer's disease is even more important now that new disease-modifying drugs are becoming available," said study author Rebecca E. Amariglio, PhD, of Harvard Medical School in Boston. "Our study found early suspicions of memory problems by both participants and the people who knew them well were linked to higher levels of tau tangles in the brain."

The study involved 675 adults with an average age of 72 who did not

have cognitive impairment on formal testing. All had brain scans for amyloid plaques. Of this group, 60% had elevated levels of amyloid, meaning they were at risk for developing cognitive impairment due to Alzheimer's disease even though, at the time of the scan, they were cognitively normal. Participants did not know if they had elevated levels of amyloid.

Each participant had a study partner - a spouse, child or friend - who could answer questions about the participant's thinking and memory skills and ability to perform daily tasks. In 65% of cases, partners lived with participants.

Each participant and their partner completed a questionnaire to assess the participant's subjective cognitive decline. Questions included, "Compared to one year ago, do you feel that your memory has declined substantially?" and "Compared to one year ago, do you have more difficulty managing money?" Participants' and partners' scores were recorded with higher scores indicating greater complaints about memory.

Researchers also reviewed brain scans for levels of tau tangles. Greater tau is also a risk factor for Alzheimer's disease and is at higher levels in people with elevated amyloid.

Researchers found participants with higher levels of tau tangles in the brain had higher scores of complaints on the memory questionnaire. Their partners also scored them higher. This association was stronger in participants who had elevated levels of amyloid plaques.

"Our study included a high percentage of people with elevated amyloid, and for this reason we were able to also see that memory complaints were associated with higher tau tangles," said Amariglio. "Our findings suggest that asking older people who have elevated Alzheimer's disease biomarkers about subjective cognitive decline may be valuable for early detection. This is particularly important since it is predicted that treatments given at the earliest diagnosable form of the disease will be the most effective in slowing the disease."

Existing drugs show promise for rare genetic disorder

A drug approved to treat certain autoimmune diseases and cancers successfully alleviated symptoms of a rare genetic syndrome called autoimmune polyendocrine syndrome type 1 (APS-1). Researchers identified the treatment based on their discovery that the syndrome is linked to elevated levels of interferon-gamma (IFN-gamma), a protein involved in immune system responses, providing new insights into the role of IFN-gamma in autoimmunity.

The study, led by researchers at the National Institutes of Health's National Institute of Allergy and Infectious Diseases, was published recently.

In a three-stage study, conducted in mice and people, the researchers examined how APS-1 causes autoimmune disease. The syndrome is marked by dysfunction of multiple organs, usually beginning in childhood, and is fatal in more than 30% of cases. This inherited syndrome is caused by a deficiency in a gene that keeps the immune system's T cells from attacking cells of the body, leading to autoimmunity; chronic yeast infections in the skin, nails, and mucous membranes; and insufficient production of hormones from endocrine organs, such as the adrenal glands. Symptoms include stomach irritation, liver inflammation, lung irritation, hair loss, loss of skin coloring, tissue damage, and organ failure.

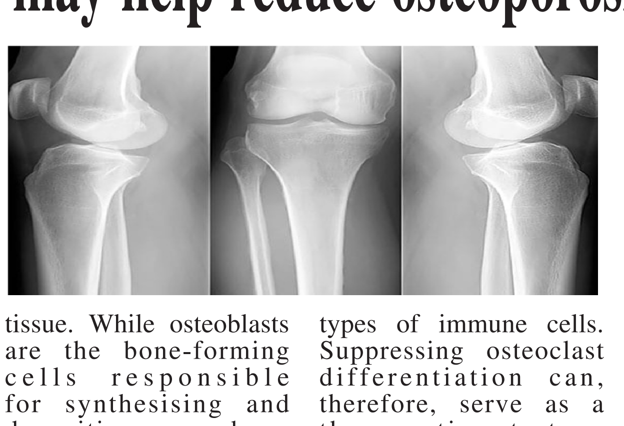
In the first stage of this study, researchers led by scientists in NIAID's Laboratory of Clinical Immunology and Microbiology examined the natural history of APS-1 in 110 adults and children. Blood and tissues were analyzed to compare gene and protein expression in people with and without APS-1.

They found elevated IFN-gamma responses in the blood and tissues of people with APS-1, indicating that IFN-gamma may play an important role in the disease and providing a pathway to target for treatment.

Key protein may help reduce osteoporosis bone loss

Osteoporosis, a condition characterised by porous and fragile bones, poses a significant threat to skeletal health. As the very framework of the human body, bones provide crucial structural support. When bone mass diminishes, it not only compromises this support but also impairs overall function, leading to a diminished quality of life. With the aging population experiencing a surge in osteoporosis cases, the strain on healthcare resources for long-term care is evident. Hence, there is a need to understand the mechanisms that contribute to osteoporosis and develop effective targeted therapies to minimise its long-term impact.

Osteoblasts and osteoclasts are two types of cells crucial for the maintenance and remodeling of bone



tissue. While osteoblasts are the bone-forming cells responsible for synthesising and depositing new bone tissue, osteoclasts are the bone-resorbing cells involved in the breakdown and removal of old or damaged bone tissue. An increase in the proportion of osteoclasts leads to loss of bone mass in conditions like osteoporosis, rheumatoid arthritis (joint inflammation), and bone metastases (cancer that has spread to the bones). Osteoclasts arise from the differentiation of macrophages or monocytes, which are types of immune cells. Suppressing osteoclast differentiation can, therefore, serve as a therapeutic strategy to prevent bone loss. However, the precise molecular mechanisms governing the complex process of bone remodelling remain unclear.

In a new groundbreaking study, Professor Tadayoshi Hayata, Mr. Takuto Konno, and Ms. Hitomi Murachi from Tokyo University of Science, along with their co-workers, delved deeper into the molecular regulation of osteoclast differentiation. Receptor activator of nuclear factor kappa B ligand (RANKL) stimulation induces the differentiation of macrophages into osteoclasts. Further, bone morphogenetic protein (BMP) and transforming growth factor (TGF)-□ signaling pathways have been implicated in the regulation of RANKL-mediated osteoclast differentiation. In the current study, the researchers sought to investigate the role of Ctdnep1 - a phosphatase (an enzyme that removes phosphate groups) that has been reported to suppress BMP and TGF-□ signalling.Prof. Hayata states, "RANKL functions as an 'accelerator' for osteoclast cell differentiation. Driving a car requires not only the accelerator but also the brakes. Here, we find that Ctdnep1 functions as a 'brake' on osteoclast cell differentiation."