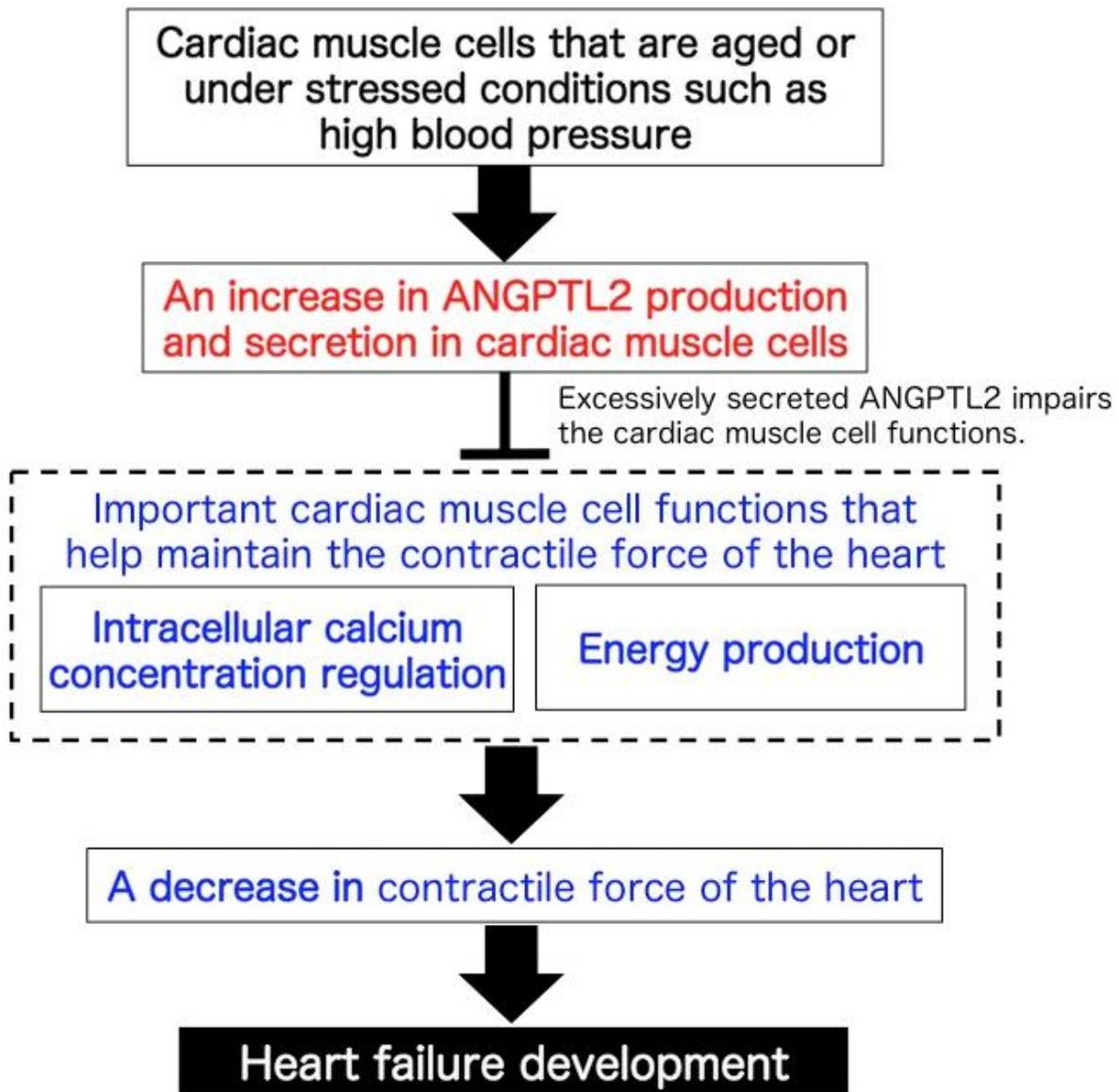


Discovery and gene therapy treatment of a novel heart failure mechanism

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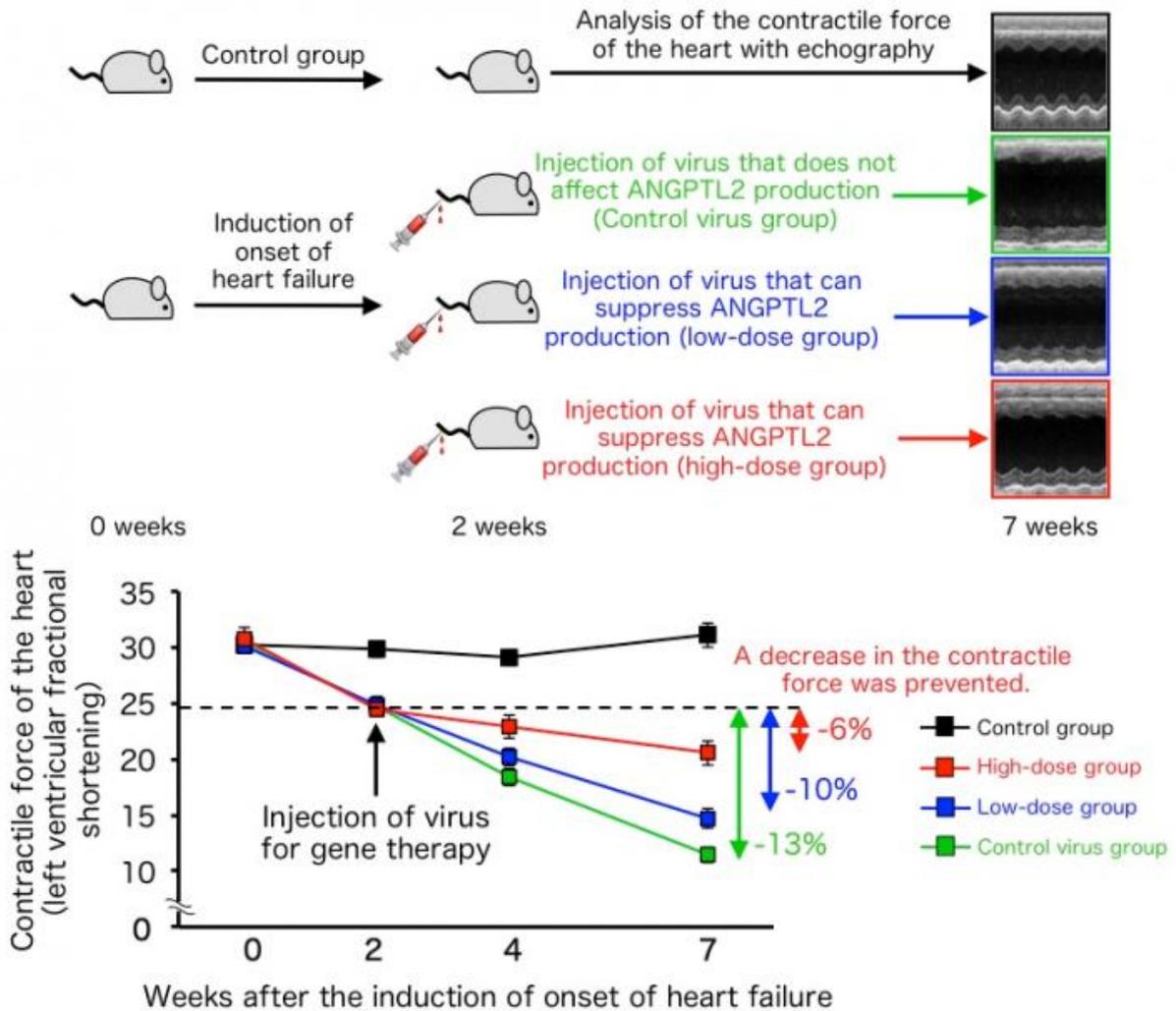
Aging and stress, such as high blood pressure, are causes of heart failure. These factors increase ANGPTL2 production and secretion in cardiac muscle cells. Excessively secreted ANGPTL2 impairs important cardiac muscle cell functions, such as intracellular calcium concentration regulation and energy production, that help maintain the contractile force of the heart and promotes the development of heart failure. Credit: Professor Yuichi Oike

A key protein that causes heart failure has been revealed through new research from a collaboration based in Kumamoto University, Japan. The protein ANGPTL2 (Angiopoietin-like protein 2) is secreted by cardiac muscle cells and decreases the contraction force of the heart by reducing energy production and the regulating function of the calcium concentration in cardiac muscle cells. Utilizing gene therapy to inhibit the production of ANGPTL2, researchers were able to produce beneficial therapeutic effects in both a heart failure mouse model and in human cardiac muscle cells which were differentiated from iPS cells.

Heart failure occurs when heart function is reduced making it no longer able to pump enough blood to body. Patients with severe heart failure have a very [poor prognosis](#), with a five-year survival rate of 50-60% despite advances in modern medicine and medical technology.

Professor Yuichi Oike's research team found that cardiac muscle cells that were from heart failure patients, were aged cells, or were under the stress of high blood pressure had increased production and secretion of the protein ANGPTL2. The research team previously reported that excessive secretion of the ANGPTL2 protein by aged or stressed cells causes chronic inflammation and promotes the development of lifestyle-related diseases such as atherosclerotic disease, obesity, diabetes, or cancer.

ANGPTL2 is also related to heart failure. Excessive ANGPTL2 secretions by cardiac muscle cells impair important functions, such as intracellular [calcium concentration](#) regulation and energy production, that help maintain the contractile force of the heart. On the other hand, moderate exercise reduces the production of ANGPTL2 in cardiac muscle cells which helps keep the heart healthy.



In mice treated with a virus that does not affect ANGPTL2 production in cardiac muscle cells (green), the rate of decrease in contractile force of the heart was 13 percent from virus injection. On the other hand, in mice treated with a virus that

can suppress ANGPTL2 production in cardiac muscle cells (blue or red), a reduction in the contractile force was prevented. In particular, treatment with a high-dose of the virus more effectively suppressed progression of heart failure (red), producing a rate of decrease in the contractile force of 6 percent. It is expected that this new gene therapy will become a novel therapeutic strategy for heart failure. Credit: Professor Yuichi Oike

"We found that ANGPTL2 is significantly involved in heart failure. Among knockout mice that could not produce the protein, the development of heart failure was suppressed in a manner similar to moderate exercise," said Professor Oike. "Furthermore, we genetically engineered a non-pathogenic virus which was designed to infect cardiac muscle cells and reproduce a special RNA molecule that inhibit the production of the ANGPTL2 protein." This new gene therapy in the heart failure mouse model was successful in suppressing ANGPTL2 production in cardiac muscle cells thereby reducing the pathological progression of heart failure.

Additionally, in [cardiac muscle cells](#) that were differentiated from human iPS cells, the suppression of ANGPTL2 promoted calcium concentration regulation and enhanced energy production. It is considered that the newly developed gene therapy may also be effective for human heart failure patients.

Current treatment for [heart failure](#) is mainly symptomatic. The gene therapy developed here is expected to become a fundamental treatment that corrects the mechanism of reduced heart function itself.

More information: Zhe Tian et al, ANGPTL2 activity in cardiac pathologies accelerates heart failure by perturbing cardiac function and energy metabolism, *Nature Communications* (2016). [DOI:](#)

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Provided by Kumamoto University

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