Researchers pinpoint new drug target for heart failure patients

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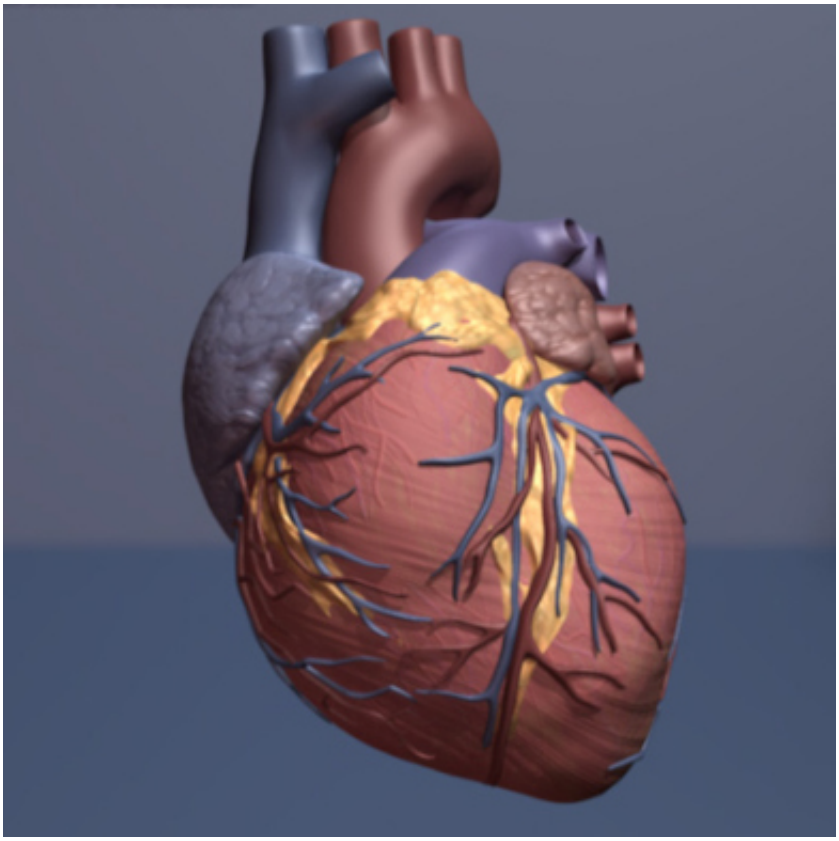

Human heart. Credit: copyright American Heart Association

Researchers led by Julian E. Stelzer, PhD, associate professor in the department of physiology and biophysics at Case Western Reserve University School of Medicine, have found a new target for drug developers seeking straightforward ways to improve cardiac output in

heart failure patients. In a recent study published in *Science Advances*, the researchers bypassed complex cell signaling pathways that are dysregulated in failing hearts by directly targeting proteins that help heart muscles contract. The team discovered modifying one protein in particular—myosin binding protein-C, or MyBP-C—can significantly enhance cardiac output in mouse models, providing the first evidence that this protein could be specifically targeted to modulate heart function in humans.

The target protein is found inside contractile machinery of the cardiac muscle cells that keep the heart pumping, called cardiomyocytes, and contains three locations where chemical phosphate groups commonly attach. When phosphate groups attach, the "phosphorylated" protein helps the heart contract more vigorously in response to stress. But researchers wanted to know which of the three phosphate attachment sites is most responsible for enhancing the heart's pumping ability, in hopes that they could directly target it to improve heart function, instead of the complex cascade of proteins involved in the stress response.

"Phosphorylation of MyBP-C enhances both the magnitude and rate of cardiomyocyte contraction, which at the whole heart level translates to enhanced systolic left-ventricular pressures, and ultimately cardiac output," said Stelzer. "Our findings show that a specific amino acid on MyBP-C, serine 302, can be directly targeted to enhance the rate and magnitude of cardiac pump function, which would be of benefit to a large number of heart failure patients."

Stelzer created transgenic mice with MyBP-C modified at specific amino acids where phosphate attaches, to help narrow down the important binding sites. Mice with only serine 302 modified couldn't maintain appropriate systolic blood pressures in response to specific stressors, even with their other phosphate attachment sites intact. The mice experienced a dangerously reduced blood supply to their outer

tissues, similar to when humans experience heart failure. The experiments indicate the serine 302 binding site is specifically required to help the heart keep up its force and pressure. For drug developers interested in improving cardiac output, serine 302 on MyBP-C may be the primary amino acid to target.

The findings also explain the molecular underpinnings of how hearts respond to stress. Phosphate groups are added to MyBP-C by an enzyme called protein kinase A, or PKA. In this new study, the team zeroed in on the effects of PKA-mediated attachment of phosphate groups to specific locations on MyBP-C, and the contribution of each attachment site to heart function.

"We found that the functional effect of preventing phosphorylation of serine 302 alone, is equivalent to the impact observed by preventing phosphorylation of all three PKA phosphorylatable sites in MyBP-C, which pinpoints serine 302 as the main molecular target of PKA phosphorylation in MyBP-C for cardiac muscle contraction," said Ranganath Mamidi, PhD, lead author of the study and postdoctoral scholar in the department of physiology and biophysics at Case Western Reserve University School of Medicine. Other contributors from the Stelzer laboratory included Kenneth S. Gresham, PhD, and Jiayang Li, MD/PhD Candidate.

Together the researchers demonstrated their findings in several models, including isolated cardiac muscle fibers and intact mouse hearts. "In the intact heart, phosphorylation of serine 302 increased the rate and magnitude of pressure development, and therefore cardiac output, but this effect was abolished in mice with modified serine 302 MyBP-C," said Mamidi. "Therefore, our studies have identified a critical downstream target of stress signaling that can modulate cardiac output in vivo."

Stelzer suggests drugs that help phosphate molecules bind to serine 302 on MyBP-C could markedly improve cardiac output in people with heart failure due to reduced pumping capacity. Said Stelzer, "Now that serine 302 in MyBP-C has been identified as a molecular target to boost cardiac performance, efforts are underway to design small molecules that can elicit similar functional effects in the intact human heart."

More information: Ranganath Mamidi et al, Cardiac myosin binding protein-C Serphosphorylation regulates cardiac β-adrenergic reserve, *Science Advances* (2017). DOI: 10.1126/sciadv.1602445

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