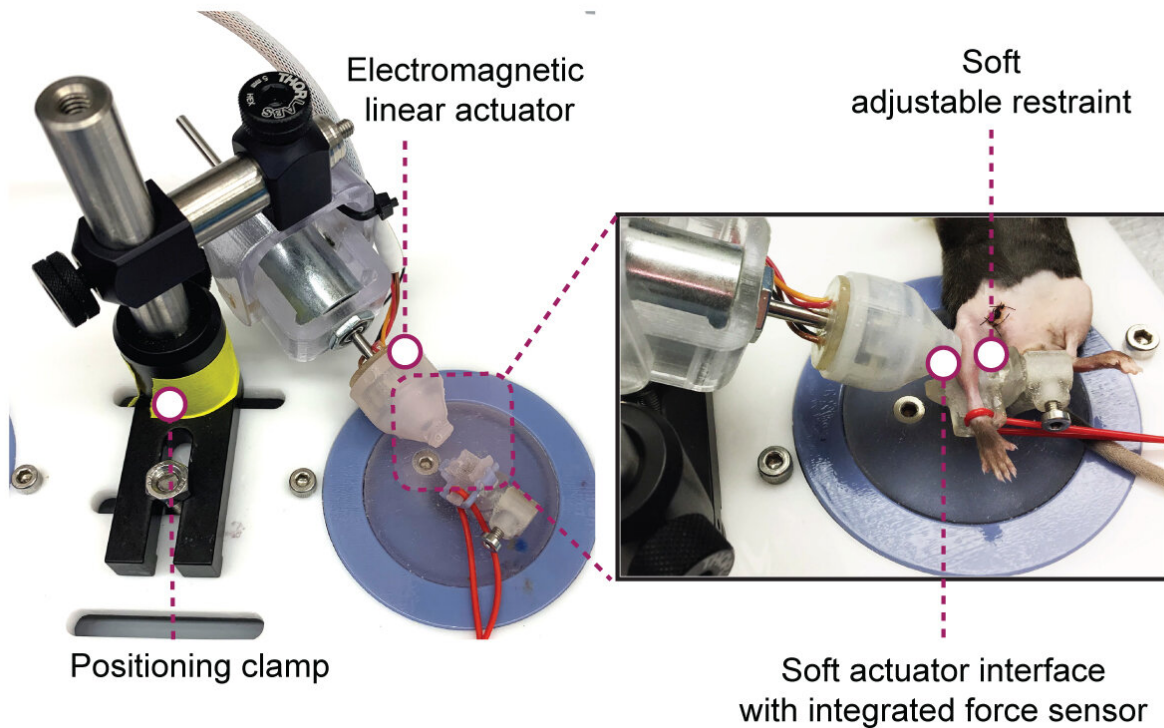


# Massage doesn't just make muscles feel better, it makes them heal faster and stronger

October 6 2021



A photograph of the robotic soft-interface device, which is equipped with an electromagnetic actuator and an integrated force sensor. Credit: B.R. Seo, et al., Science Translational Medicine (2021)

Massage has been used to treat sore, injured muscles for more than 3,000 years, and today many athletes swear by massage guns to rehabilitate their bodies. But other than making people feel good, do

these "mechanotherapies" actually improve healing after severe injury? According to a new study from researchers at Harvard's Wyss Institute for Biologically Inspired Engineering and John A. Paulson School of Engineering and Applied Sciences (SEAS), the answer is "yes."

Using a custom-designed robotic system to deliver consistent and tunable compressive forces to mice's [leg muscles](#), the team found that this mechanical loading (ML) rapidly clears [immune cells](#) called neutrophils out of severely injured [muscle tissue](#). This process also removed [inflammatory cytokines](#) released by neutrophils from the muscles, enhancing the process of muscle fiber regeneration. The research is published in *Science Translational Medicine*.

"Lots of people have been trying to study the beneficial effects of massage and other mechanotherapies on the body, but up to this point it hadn't been done in a systematic, reproducible way. Our work shows a very clear connection between mechanical stimulation and immune function. This has promise for regenerating a wide variety of tissues including bone, tendon, hair, and skin, and can also be used in patients with diseases that prevent the use of drug-based interventions," said first author Bo Ri Seo, Ph.D., who is a Postdoctoral Fellow in the lab of Core Faculty member Dave Mooney, Ph.D. at the Wyss Institute and SEAS.

## **A more meticulous massage gun**

Seo and her coauthors started exploring the effects of mechanotherapy on injured tissues in mice several years ago, and found that it [doubled the rate](#) of muscle regeneration and reduced [tissue](#) scarring over the course of two weeks. Excited by the idea that mechanical stimulation alone can foster regeneration and enhance muscle function, the team decided to probe more deeply into exactly how that process worked in the body, and to figure out what parameters would maximize healing.

They teamed up with soft robotics experts in the Harvard Biodesign Lab, led by Wyss Associate Faculty member Conor Walsh, Ph.D., to create a small device that used sensors and actuators to monitor and control the force applied to the limb of a mouse. "The device we created allows us to precisely control parameters like the amount and frequency of force applied, enabling a much more systematic approach to understanding tissue healing than would be possible with a manual approach," said co-second author Christopher Payne, Ph.D., a former Postdoctoral Fellow at the Wyss Institute and the Harvard Biodesign Lab who is now a Robotics Engineer at Viam, Inc.

Once the device was ready, the team experimented with applying force to mice's leg muscles via a soft silicone tip and used ultrasound to get a look at what happened to the tissue in response. They observed that the muscles experienced a strain of between 10-40%, confirming that the tissues were experiencing mechanical force. They also used those ultrasound imaging data to develop and validate a computational model that could predict the amount of tissue strain under different loading forces.

They then applied consistent, repeated force to injured muscles for 14 days. While both treated and untreated muscles displayed a reduction in the amount of damaged muscle fibers, the reduction was more pronounced and the cross-sectional area of the fibers was larger in the treated muscle, indicating that treatment had led to greater repair and strength recovery. The greater the force applied during treatment, the stronger the injured muscles became, confirming that mechanotherapy improves muscle recovery after injury. But how?

## **Evicting neutrophils to enhance regeneration**

To answer that question, the scientists performed a detailed biological assessment, analyzing a wide range of inflammation-related factors

called cytokines and chemokines in untreated vs. treated muscles. A subset of cytokines was dramatically lower in treated muscles after three days of mechanotherapy, and these cytokines are associated with the movement of immune cells called neutrophils, which play many roles in the inflammation process. Treated muscles also had fewer neutrophils in their tissue than untreated muscles, suggesting that the reduction in cytokines that attract them had caused the decrease in neutrophil infiltration.

The team had a hunch that the force applied to the muscle by the mechanotherapy effectively squeezed the neutrophils and cytokines out of the injured tissue. They confirmed this theory by injecting fluorescent molecules into the muscles and observing that the movement of the molecules was more significant with force application, supporting the idea that it helped to flush out the muscle tissue.

To pick apart what effect the neutrophils and their associated cytokines have on regenerating muscle fibers, the scientists performed *in vitro* studies in which they grew muscle progenitor cells (MPCs) in a medium in which neutrophils had previously been grown. They found that the number of MPCs increased, but the rate at which they differentiated (developed into other [cell types](#)) decreased, suggesting that neutrophil-secreted factors stimulate the growth of muscle cells, but the prolonged presence of those factors impairs the production of new muscle fibers.

"Neutrophils are known to kill and clear out pathogens and damaged tissue, but in this study we identified their direct impacts on muscle progenitor cell behaviors," said co-second author Stephanie McNamara, a former Post-Graduate Fellow at the Wyss Institute who is now an M.D.-Ph.D. student at Harvard Medical School (HMS). "While the inflammatory response is important for regeneration in the initial stages of healing, it is equally important that inflammation is quickly resolved to enable the regenerative processes to run its full course."

Seo and her colleagues then turned back to their *in vivo* model and analyzed the types of [muscle fibers](#) in the treated vs. untreated mice 14 days after injury. They found that type IIX fibers were prevalent in healthy muscle and treated muscle, but untreated injured muscle contained smaller numbers of type IIX fibers and increased numbers of type IIA fibers. This difference explained the enlarged fiber size and greater force production of treated muscles, as IIX fibers produce more force than IIA fibers.

Finally, the team homed in on the optimal amount of time for neutrophil presence in injured muscle by depleting neutrophils in the mice on the third day after injury. The treated mice's muscles showed larger fiber size and greater strength recovery than those in untreated mice, confirming that while neutrophils are necessary in the earliest stages of injury recovery, getting them out of the injury site early leads to improved muscle regeneration.

"These findings are remarkable because they indicate that we can influence the function of the body's immune system in a drug-free, non-invasive way," said Walsh, who is also the Paul A. Maeder Professor of Engineering and Applied Science at SEAS and whose group is experienced in developing wearable technology for diagnosing and treating disease. "This provides great motivation for the development of external, mechanical interventions to help accelerate and improve muscle and tissue healing that have the potential to be rapidly translated to the clinic."

The team is continuing to investigate this line of research with multiple projects in the lab. They plan to validate this mechanotherapeutic approach in larger animals, with the goal of being able to test its efficacy on humans. They also hope to test it on different types of injuries, age-related muscle loss, and muscle performance enhancement.

"The fields of mechanotherapy and immunotherapy rarely interact with each other, but this work is a testament to how crucial it is to consider both physical and biological elements when studying and working to improve human health," said Mooney, who is the corresponding author of the paper and the Robert P. Pinkas Family Professor of Bioengineering at SEAS.

"The idea that mechanics influence cell and tissue function was ridiculed until the last few decades, and while scientists have made great strides in establishing acceptance of this fact, we still know very little about how that process actually works at the organ level. This research has revealed a previously unknown type of interplay between mechanobiology and immunology that is critical for [muscle](#) tissue healing, in addition to describing a new form of mechanotherapy that potentially could be as potent as chemical or gene therapies, but much simpler and less invasive," said Wyss Founding Director Don Ingber, M.D., Ph.D., who is also the *Judah Folkman Professor of Vascular Biology* at (HMS) and the Vascular Biology Program at Boston Children's Hospital, as well as Professor of Bioengineering at SEAS.

**More information:** Skeletal muscle regeneration with robotic actuation–mediated clearance of neutrophils, *Science Translational Medicine* (2021). [www.science.org/doi/10.1126/scitranslmed.abe8868](http://www.science.org/doi/10.1126/scitranslmed.abe8868)

Provided by Harvard University

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