

MARTÍN DONATO <sup>MTSAC</sup>**Acute exercise modifies titin phosphorylation and increases cardiac myofilament stiffness**

Müller AE, Kreiner M, Kötter S, Lassak P, Bloch W, Suhr F, et al. Acute exercise modifies titin phosphorylation and increases cardiac myofilament stiffness. *Front Physiol* 2014;5:449. <http://doi.org/zc3>

The beneficial effect of regular physical activity is generally accepted, not only in healthy individuals, but also in the setting of some cardiovascular diseases, such as heart failure, where exercise has been shown to improve patient outcome.

Several recent studies suggest that exercise might also contribute to modify myocyte passive stiffness, by changing titin phosphorylation. This protein is expressed in all striated muscles and is encoded by a single gene. Titin is a giant sarcomere protein which enables correct sarcomere assembly, acting as a kind of “molecular spring” that contributes to restore original sarcomere length. Thus, titin participates directly in the regulation of myofilament distensibility.

Skeletal muscle expresses one titin isoform called N2A (3,3-3,7 MDa), while in mammals cardiac titin is expressed as two isoforms: the shorter and stiffer N2B (3,0 MDa) isoform and the longer and more distensible N2BA (3,2-3,7 MDa) isoform. Myofilament stiffness is determined by the ratio of N2BA and N2B titin isoforms and post translationally by phosphorylation of the Band N2 PEVK region.

Changes in titin phosphorylation are critical in certain cardiovascular pathologies involving increased myocardial stiffness. Thus, the authors raise the hypothesis that exercise might alter titin properties.

To test this hypothesis, Müller et al. exercised adult rats in a treadmill for 15 min (20 m/min) and then sacrificed the animals isolating cardiac and skeletal muscle myocytes.

Titin phosphorylation was determined in Ser4099 and Ser4010 in the N2-Bus region (PKG and PKA-dependent, respectively) and in Ser11878 and Ser12022 in the PEVK region (PKC $\alpha$  and CaMKII $\delta$ -dependent, respectively). Passive tension was also evaluated by sarcomere force-length curves.

An interesting finding of this study is that acute exercise induces divergent post translational modifications of titin in cardiac and skeletal muscle. While acute exercise increased PEVK phosphorylation of cardiac titin, the same intervention had an opposite effect in skeletal muscle, indicating that both types of muscle react differently to the mechanical stimulus. Thus, the results of this work show for the first time a different response in titin phosphorylation of cardiac and skeletal muscle after an acute bout of exercise.

Consequently, the authors conclude that acute exercise results in stiffer cardiac myocytes as a result of increased PEVK phosphorylation, whereas the lower PEVK phosphorylation decreases myofilament stiffness in skeletal muscle. Therefore, as previously mentioned, acute exercise induces divergent effects on cardiac and skeletal muscle, specifically on titin phosphorylation.

*Considering that titin is a key regulator of sarcomere assembly and myocardial stiffness, the observations of Müller et al. regarding the differences between cardiac and skeletal muscle could be important to maintain structural integrity, especially in skeletal muscles submitted to training. For the cardiac muscle, acute exercise induces a titin-regulated change in myofilament stiffness, which could improve ventricular filling and hence stroke volume, supporting the Frank-Starling mechanism, crucial during exercising conditions.*