The Journal of Physiology

LETTER

Stress-induced increase in muscle force: truth or myth?

In their elegant study, Andersson and colleagues (2012) further our understanding of the molecular mechanisms of Ca^{2+} regulation that mediate the positive inotropic effect exerted by adrenergic agonists on fast twitch skeletal muscle fibres. Their initial assumption for the study is that 'under conditions of acute adrenergic stress (i.e. the fight or flight response) the contractile force of muscle is enhanced' (Andersson *et al.* 2012). The concept of stress-induced force enhancement is reported in the title and emphasized in several parts of the paper. Nonetheless, in this study, as in several previous studies (Williams & Barnes, 1989), the focus is not on stress (which is a physiological body reaction associated with a prominent activation of the sympathetic nervous system) but on the exposure of muscle fibres to (exogenous) adrenaline and its agonists in non-physiological conditions. Notwithstanding the relevance of the results of the study by Andersson *et al.* (2012), we would like here to challenge the view that stress induces an increase in contractile muscle force in physiological conditions since this concept is not adequately supported by the available experimental evidence. The concept stems from the syllogism 'stress is associated with adrenaline release, adrenaline enhances muscle force, thus stress enhances muscle force'. This chain of relations, to our knowledge, has never been observed in response to physiological stress, neither in animal models nor in humans.

Indeed, most studies on this topic are based on anaesthetized or decerebrate animal models, or on isolated muscles and muscle fibres in which a *physiological stress response cannot be elicited*. This limitation also applies to the two papers (Brown *et al.* 1948; Cairns & Dulhunty, 1993) cited by Andersson *et al.* (2012) in support of their assumption. The study by Cairns & Dulhunty (1993) investigated the inotropic effect of terbutaline, a β2-adrenergic agonist, on isolated muscle fibres, and the study by Brown *et al.* (1948) investigated the effect of adrenaline on pre-fatigued muscles in isolated nerve–muscle preparations and in decerebrate animals. Incidentally, the adrenergic-induced recovery of force exhibited by fatigued muscle (*anti-fatigue* or Orbeli effect) investigated by Brown *et al.* (1948) was later found to be largely dependent on mechanisms other than the Ca^{2+} handling by the sarcoplasmic reticulum, namely the potentiation of the Na^+/K^+ pump of the sarcolemma (Overgaard *et al.* 1999; Clausen & Nielsen, 2007).

Besides the positive inotropic effect, adrenaline also exerts a less known *weakening* effect, specifically on slow-twitch muscle fibres, consisting of a shortening of the twitch force duration, i.e. a *positive lusitropic* effect (Bowman, 1980; Roatta & Farina, 2010), similar to the one exerted on cardiac muscle. As early as 1958, Bowman & Zaimis (1958) reported that the force enhancement in the fast-twitch tibialis anterior muscle of the cat was attained with a much higher I.V. dose of adrenaline (3–10 μg kg^{-1}) than the force reduction in the slow-twitch soleus muscle (0.06–0.5 μg kg^{-1}). They considered the former dose to result in blood concentration beyond the physiological range and they expressed doubts about the physiological relevance of the positive inotropic effect. Therefore, the positive lusitropic effect may be the main effect of stress in physiological conditions. Nevertheless, we should mention that 20 years later, in his comprehensive review, Bowman also referred to unpublished observations concerning the occurrence of some positive inotropic effects at lower adrenaline concentrations (I.V. dose of 0.5 μg kg^{-1}), which he considered to be compatible with a physiological condition of *extreme* stress (Bowman, 1980). In addition, we note that the paper by Andersson *et al.* (2012) did include an *in vivo* measure, in which transgenic stressed rats showed greater grip forces than control rats. However, since an adrenergic positive inotropic effect is not the only possible explanation for the results, this test cannot provide a strong support for the existence of a stress-induced enhancement of muscle force *in vivo*.

Very recently, the adrenergic effects on skeletal muscles have been investigated during a physiological stress response in humans (Roatta *et al.* 2008; Roatta & Farina, 2011). Interestingly, these studies showed weakening of selectively activated low-threshold (thus presumably slow-twitch) motor units during activation of the sympathetic nervous system by the cold pressor test (painful stimulus induced by immersion of one hand in icy water; Roatta *et al.* 2008), in accordance with the positive *lusitropic* effect. Further, it was not possible, using the same physiological stressor, to identify a positive inotropic effect when assessing all muscle fibres in the soleus and in the tibialis anterior muscles (Roatta & Farina, 2011). Of course, we cannot exclude that a stronger or different type of stress is necessary to produce a detectable enhancement of force. Even so, a lusitropic effect seems to occur in a greater range of physiological conditions than the inotropic effect, in agreement with the observations of Bowman (1980). Administration of adrenaline and β2-agonists in humans indeed results in a weakening effect (Marsden & Meadows, 1970; Crivelli *et al.* 2013), so that the functional consequences of a potential inotropic effect due to stress actually seem to be marginal for force production, at least in humans.

In conclusion, while we appreciate the useful data provided by Andersson *et al.* (2012), we challenge the view that *physiological stress* enhances muscle force, which is assumed in their paper as an established fact. Conversely, we find the scientific evidence for this effect very limited, to the extent that the force enhancement with stress may be a myth generated more by a very appealing functional explanation of the phenomenon than by strong experimental evidence. We contend that the main physiological effect of stress on muscle contractility is the positive lusitropic effect, for which there is more experimental evidence. This results in an increased relaxation rate of the muscle fibres which may serve to increase the speed of rapidly alternating movements (Roatta & Farina, 2010). While less intuitive than an increase in force, this effect would also be beneficial in the context of *fight or flight*.

Silvestro Roatta[1] and Dario Farina[2]

[1] *Department of Neuroscience, University of Torino, C.so Raffaello 30, 10125, Torino, Italy*
[2] *Department of Neurorehabilitation Engineering, Bernstein Focus Neurotechnology Göttingen, University Medical Center Göttingen Göttingen, Germany*

Email: silvestro.roatta@unito.it

DOI: 10.1113/jphysiol.2013.251553

References

Andersson DC, Betzenhauser MJ, Reiken S, Umanskaya A, Shiomi T & Marks AR (2012). Stress-induced increase in skeletal muscle force requires protein kinase A phosphorylation of the ryanodine receptor. *J Physiol* **590**, 6381–6387.

Bowman WC (1980). Effects of adrenergic activators and inhibitors on the skeletal muscles. In *Handbook of Experimental Pharmacology, Adrenergic Activators and Inhibitors*, ed. Szekeres L, pp. 47–128. Springer, Berlin, Heidelberg, New York.

Bowman WC & Zaimis E (1958). The effects of adrenaline, noradrenaline and isoprenaline on skeletal muscle contractions in the cat. *J Physiol* **144**, 92–107.

Brown GL, Bülbring E & Burns BD (1948). The action of adrenaline on mammalian skeletal muscle. *J Physiol* **107**, 115–128.

Cairns SP & Dulhunty AF (1993). The effects of β-adrenoceptor activation on contraction in isolated fast- and slow-twitch skeletal muscle fibres of the rat. *Br J Pharmacol* **110**, 1133–1141.

Clausen T & Nielsen OB (2007). Potassium, Na^+,K^+-pumps and fatigue in rat muscle. *J Physiol* **584**, 295–304.

Crivelli G, Borrani F, Capt R, Gremion G & Maffiuletti NA (2013). Actions of β2-adrenoceptor agonist drug on human soleus muscle contraction. *Med Sci Sports Exerc* (in press).

Marsden CD & Meadows JC (1970). The effect of adrenaline on the contraction of human muscle. *J Physiol* **207**, 429–448.

Overgaard K, Nielsen OB, Flatman JA & Clausen T (1999). Relations between excitability and contractility in rat soleus muscle: role of the Na^+–K^+ pump and Na^+/K^+ gradients. *J Physiol* **518**, 215–225.

Roatta S, Arendt-Nielsen L & Farina D (2008). Sympathetic-induced changes in discharge rate and spike-triggered average twitch torque of low-threshold motor units in humans. *J Physiol* **586**, 5561–5574.

Roatta S & Farina D (2010). Sympathetic actions on the skeletal muscle. *Exerc Sport Sci Rev* **38**, 31–35.

Roatta S & Farina D (2011). Sympathetic activation by the cold pressor test does not increase the muscle force generation capacity. *J Appl Physiol* **110**, 1526–1533.

Williams JH & Barnes WS (1989). The positive inotropic effect of epinephrine on skeletal muscle: a brief review. *Muscle Nerve* **12**, 968–975.