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COMMENTARY

Exercise may be detrimental in hypertension: too much of a good thing!

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It is well accepted that regular physical activity is beneficial for a person's health, specifically, but not solely, with respect to the cardiovascular system. This has led to the advice that exercise is wise for the general population. Aerobic exercise lowers arterial pressure moderately in healthy humans with the effect being more pronounced in hypertensive groups, as demonstrated by a large meta-analysis.[1] The beneficial effect was evident (with subtle differences) for endurance and resistance training,[1–3] and aerobic exercise has reduced arterial pressure even in resistant hypertension.[4] Therefore, guidelines for the management of hypertension include, among other lifestyle changes, recommendations for regular exercise ('at least 30 min of moderate-intensity dynamic aerobic exercise 5–7 days per week').[5] However, it is unknown whether too much of a good thing could be wonderful or, in fact, do harm.

In this issue of *Hypertension Research*, Chen *et al.*[6] studied the effect of different intensities of exercise on vascular function in spontaneously hypertensive rats (SHR). The key findings were a beneficial effect of mild exercise but a poor outcome with strenuous exercise due to a modulated (decreased or increased) expression of voltage-gated Ca^{2+} (CaV) channels in vessels with concomitant functional effects on vascular function. SHR rats ran on a treadmill at ~60 or 80% of their maximal aerobic exercise capacity (moderate- or high-intensity exercise) for 8 weeks at 1 h per day and 5 days per week and were compared with sedentary SHR or normotensive Wistar–Kyoto (WKY) rats. As expected, moderate exercise reduced systolic pressure (by 30 mm Hg), whereas intense exercise unexpectedly exacerbated the systolic pressure even further. The body weight decreased in both exercise groups, and this decrease was pronounced in the high-intensity animals, which led to a significant increase in the heart-to-body weight ratio in this group.

Vascular function was assessed *in vitro* using isolated mesenteric arteries and revealed an enhanced contraction upon administration of norepinephrine and an activator of CaV channels (BayK 8644) in the SHR arteries compared with the normotensive WKY controls. This expected enhancement in the hypertensive rats was reversed through moderate exercise, but, surprisingly, this was not the case in the SHR animals that were subjected to intense exercise. In fact, the contractile response was exaggerated in this group compared with the sedentary rats. The authors report that the depolarization-induced contractile responses (using high potassium) were similar, which, at first glance, is a bit surprising, as such responses invoke CaV channels as well. However, at a K^+ concentration of 120 mM, tissues may already be depolarized to such a level that further Ca^{2+} influx through the CaV channels elicits no further contractile response. The accentuation of the CaV channels on the vascular function in SHR was also reflected by a greater sensitivity of the constricted arteries to a CaV channel blocker (nifedipine) compared with the WKY controls. Moderate exercise partially normalized the sensitivity, but intense exercise again had no beneficial effect; however, conversely, sensitivity was increased. These data on vascular function suggested an emphasized role of CaV channels in SHR compared with normotensive rats, which, in part, was reversed by moderate exercise (Figure 1a). Importantly, this protective effect of exercise was turned back to a detrimental effect in the animals that exercised at ~80% of their maximal aerobic capacity (Figure 1b).

Thereafter, Chen *et al.* studied currents through CaV channels in smooth muscle cells isolated from mesenteric arteries and confirmed the functional contractile responses. Peak currents were enhanced in the SHR compared with the WKY, and this enhancement was partially reduced by moderate exercise. However, intense exercise enhanced the currents through the CaV channels compared with sedentary rats. These alterations in whole-cell currents were similarly retrieved after stimulation using BayK 8644. In contrast, the current–voltage relationship and the activation and inactivation properties of the channel remained unaltered, indicating an enhanced number of channels, whereas individual channels exhibited similar properties in all groups. Channel density was then examined through immunostaining and western blots targeting the alpha1C subunit using an appropriate antibody, which verified the assumption. Likewise, this CaV channel subunit was similarly modified at the mRNA level. However, the increases did not exactly parallel the protein levels, suggesting regulation not only at the transcriptional level but also involving posttranscriptional modulatory mechanisms (Figure 1). Taken together, results by Chen *et al.* demonstrated that too much of a good thing is not wonderful but is, in fact, harmful (in this model). The beneficial downregulation of CaV channels by moderate exercise reverses into the opposite after intense exercise: CaV channels are found at greater levels in vessels from this group with concomitant functional consequences.

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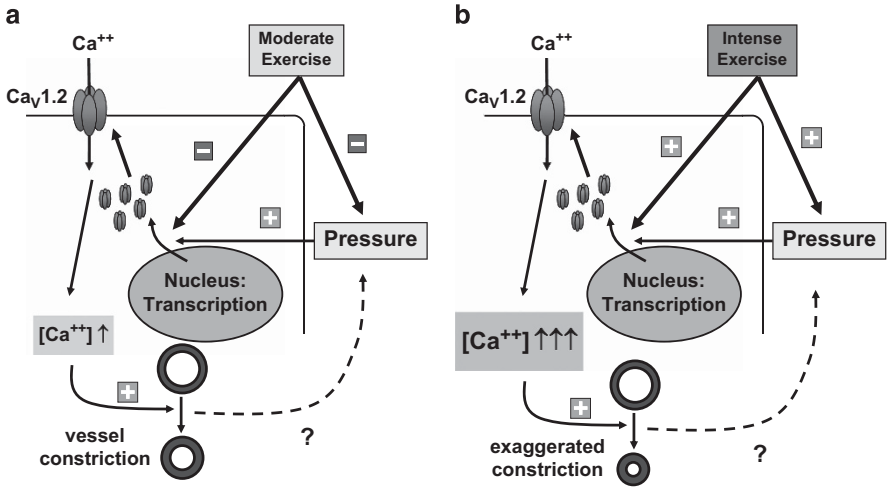

Figure 1 (**a**) Arterial hypertension (pressure) upregulates the expression of $Ca_V1.2$ channels in vascular smooth muscle cells through transcriptional and post-transcriptional (not shown) mechanisms. The enhanced expression increases the inward Ca^{2+} currents upon depolarization and exaggerates contractile behavior upon stimulation (norepinephrine or an activator of CaV channels (BayK 8644)). This may further increase pressure (indicated by the dashed arrow). Moderate exercise exerts beneficial effects in hypertensive rats by reducing the arterial pressure and attenuating CaV expression through concomitant functional changes. It remains unclear whether the effect is mediated through the pressure decrease or is independent of the pressure decrease (indicated by arrows). (**b**) In marked contrast, intense exercise did not exert beneficial effects but exaggerated arterial pressure and CaV expression in hypertensive rats. It remains to be determined whether this effect on CaV expression is mediated (in part) through a pressure increase. A full color version of this figure is available at the *Hypertension Research* journal online.

These interesting findings do not resolve the original 'the chicken or the egg' question: is it the pressure that modulates CaV channel expression or does the CaV channel upregulation boost the pressure? The effect of exercise can also not be determined in this puzzle: is the initial effect a pressure decrease or is the first target the expression level of the CaV channels? In either case, moderate exercise is good for you: it decreases arterial pressure and CaV channel expression, as previously demonstrated by these authors.[7] However, too much of a good thing neither decreases pressure nor downregulates CaV channels but, in fact, induces the opposite, which is an important finding in itself. Therefore, this animal study focuses our attention on the detrimental effect of strenuous exercise in uncontrolled hypertension. In addition, excessive exercise may have a negative impact on cardiac remodeling in hypertensive rats, as reported by others.[8,9]

There are indications that a dose–response relationship exists for physical activity and vascular disease in humans, that is, additional benefits occur with more physical activity.[10] In addition, a recently published large cohort study demonstrated that women who engaged in physical activity had a lower incidence of coronary heart and cerebrovascular disease than women who were inactive.[11] Interestingly, increases in the frequency of strenuous exercise (>3 times per week) were associated with enhanced vascular risk, indicating that also in humans, there can be too much of a good thing. The data from this study suggest that strenuous exercise should be limited in frequency (2–3 times per week), whereas moderate exercise (no sweating) had a maximal impact if performed 4–6 times per week.[11] Sex differences may exist,[12] but more importantly, patients with metabolic risk factors are prone to larger pressure increases during exercise[13] and may be more susceptible to harmful effects. Defining the fine line between the beneficial and detrimental effects of exercise seems to be crucial, but precisely defining the location of this line is extremely difficult to achieve.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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