It is generally accepted that exercise training reduces the risk of cardiovascular diseases (CVD), but the precise mechanisms for this reduction are not fully understood. Mora and colleagues followed up 27,055 women for 11 years and found the risk factors investigated in their study explained 59% of the physical activity-related reduction in CVD. Green and colleagues thought that this result suggests at least 40% of the risk reduction by exercise cannot be explained by traditional risk factors and they proposed direct effects of exercise on the vascular wall and attributed it to improvement of endothelial function by shear forces (Figure 1).

Goto and colleagues reported that moderate-intensity exercise for 12 weeks augmented endothelium-dependent vasodilation in healthy young men, whereas high-intensity training increased oxidative stress and did not improve endothelial function. These results show that the balance between the production of reactive oxygen species and release of nitric oxide is important in the maintenance of vascular function.

Hypertension, one of the most famous traditional risk factors of CVD, sometimes becomes resistant to pharmacological therapy, and is called resistant hypertension. Recently, Dimeo and colleagues confirmed aerobic exercise reduces blood pressure in resistant hypertension. Their results suggested that a low responsiveness to pharmacological therapy does not mean a low responsiveness to exercise in resistant hypertension.

In this issue of the Journal, Silva and colleagues demonstrate that aerobic training reduced high arterial pressure and the vasoconstrictor axis of the renin-angiotensin system (RAS) in spontaneously hypertensive rats (SHR). As the subtitle of their report indicates, they focused on the balance between the vasoconstrictor and vasodilator axes of the RAS. Interestingly, they found the concentrations of angiotensin II (AngII) and angiotensin (1-7) [Ang (1-7)] in the renal arteries than in other arteries such as the femoral and carotid, and the thoracic aorta. Aerobic training quickly decreased the AngII content in the renal artery of the SHR. The Ang (1-7) content was also reduced by training, but the reduction was much smaller. After 12 weeks of training, the ratio of AngII/Ang (1-7) content in the renal artery was significantly decreased and may be responsible for the reduction of arterial blood pressure in SHR.

Ang (1-7) is generated by angiotensin-converting enzyme 2 (ACE2) from AngII and has many protective effects on the cardiovascular system through its receptor. Shah and colleagues used 2-kidney 1-clip (2K1C) hypertensive rats and assigned them to either a sedentary or trained group. Chronic infusion of Ang (1-7) attenuated hypertension and cardiac hypertrophy only in the trained rats, but not in the sedentary rats. In ventricular tissue, the Mas receptor and the angiotensin type 2 receptor (AT2R), both putative Ang (1-7) receptors, were more upregulated in the trained 2K1C rats than the sedentary 2K1C rats. They also showed that the levels of phosphorylated endothelial nitric oxide synthase (p-eNOS) was highest in the ventricular tissue of trained 2K1C rats after Ang (1-7) infusion. Costa and colleagues revealed that acute infusion of Ang (1-7) to SHR diminished mean arterial pressure and the antihypertensive effect of Ang (1-7) was blocked by an AT2R antagonist and bradykinin B2 receptor antagonist, but not by the Mas receptor antagonist.

Putative receptors of Ang (1-7) are controversial. Santos argued about the specificity of the AT2R antagonist, and Xu...
et al showed elevated blood pressure and endothelial dysfunction caused by increased oxidative stress in Mas gene-deleted mice. Currently, the situation has become more complex. Ohshima and colleagues revealed both the ACE2/Ang (1-7)/Mas axis and ACE2/Ang (1-7)/AT1R axis are competing. The Mas receptor and angiotensin type 2 receptor (AT2R) are putative Ang (1-7) receptors. The mechanism for the exercise-induced increase in Ang (1-7) is unknown; however increased Ang (1-7) may induce phosphorylation of endothelial nitric oxide synthase (eNOS). Exercise may also increase the responsiveness of vascular tissues to Ang (1-7) through unknown mechanism(s); Ang, angiotensin.

Figure 2. The angiotensin II/angiotensin type 1 receptor (AT1R) axis and angiotensin-converting enzyme 2 (ACE2)/angiotensin (1-7)/Ang (1-7)/Ang (1-7) receptor axis are competiting. The Mas receptor and angiotensin type 2 receptor (AT2R) are putative Ang (1-7) receptors. The mechanism for the exercise-induced increase in Ang (1-7) is unknown; however increased Ang (1-7) may induce phosphorylation of endothelial nitric oxide synthase (eNOS). Exercise may also increase the responsiveness of vascular tissues to Ang (1-7) through unknown mechanism(s); Ang, angiotensin.

Recently, analogs of Ang (1-7) and other Mas agonists have been developed as therapeutic agents that counteract the action of AngII. These compounds may also be beneficial for improving insulin resistance and oxidative stress.

Ang (1-7) is a small peptide, consisting of 7 amino acids. Nevertheless, there are many unsolved questions about it, such as the control mechanism for its production, and putative receptors responsible for its function. Exercise is necessary for good health. Similarly, further experiments are required to figure out the role of Ang (1-7) in the maintenance of good health.

References