Oxidative stress (OS), caused by an imbalance between oxidants and antioxidants, is generally considered to damage cells by degrading cellular proteins and lipids or by damaging DNA. OS has been shown to increase in elderly people, and accumulating evidence indicates that OS plays a central role in the development of comorbidities such as cardiovascular disease (CVD: coronary artery disease and stroke), neurodegenerative disease (eg, Alzheimer disease and Parkinson disease), various human malignancies, and muscle atrophy in the elderly. OS increases because of overproduction of reactive oxygen species (ROS) such as nicotinamide adenine dinucleotide oxidase, xanthine oxidase, and lipoxygenase or because of the uncoupling of nitric oxide synthase. Vascular cells release ROS, which mediate various signaling pathways that underlie vascular inflammation in atherogenesis. ROS are produced by endothelial cells, smooth muscle cells (SMCs), and macrophages, and they oxidize low-density lipoprotein (LDL) to form oxidized LDL, which is taken up by macrophages to form foam cells. These in turn secrete growth factors that induce SMC migration into the intima, followed by fibrous plaque formation. Subsequent rupture of fibrous plaques leads to thrombus formation and vessel occlusion.

Data from the REACH registry indicate that peripheral artery disease (PAD) patients often have CVD as comorbidities. Importantly, even if the PAD stage is mild, 60% of individuals with intermittent claudication (IC) die from myocardial infarction and 10% die from stroke. Therefore, for patients with IC,
disease management should involve reducing the risk of pre-mature cardiovascular death. For this purpose, anti-OS strategies may be effective. Various anti-OS compounds, such as vitamin C, vitamin E, and resveratrol, have been proposed to reduce cardiovascular risk, but their use has yielded mixed outcomes, partly because of the lack of sensitive biomarkers by which the various levels of OS can be assessed.

In the current issue of the Journal, Ebisawa et al report a study in which they measured the levels of diacron-reactive oxygen metabolite (d-ROM) as a marker of OS, reflecting the serum hydroperoxide concentration, and found that patients with IC (Rutherford stages 2 and 3; average ankle-brachial index [ABI]: 0.61±0.15) showed elevated OS. They performed endovascular therapy (EVT) as first-line treatment for IC and reported that the elevated OS (increased d-ROM levels) decreased significantly at 3 months later. Interestingly, the reduction in the d-ROM levels corresponded with improvements in the ABI and changes in walking distances compared with preoperative distances. The results suggested that the improvements in exercise capacity brought about by revascularization were associated with systemic OS reduction.

Several previous studies have reported that exercise can reduce OS and that the resultant progressive physical activity is an effective means of reducing mortality and cardiovascular events in patients with PAD. To date, exercise therapy has been considered to play a key role in the management of patients with IC, as it significantly improves the pain-free walking distance and absolute walking distance and lowers the risk of CVD. Moreover, among the exercise therapies available, supervised exercise therapy (SET), which is programmed training under the supervision of trained physiotherapists or doctors, has been demonstrated to provide better results than non-interventional exercise. However, a large, randomized controlled trial for patients with IC and superficial femoral arterial disease that compared SET with EVT or combined treatment (EVT plus SET) found no difference among the groups after 1 year of intervention. Considering the cost of EVT (using stents) and the risk of operative complications, including incidental occlusion of collateral vessels, which would exacerbate ischemia, the ideal treatment strategy for patients with IC seems to be SET plus best medical treatment (BMT) rather than EVT, at present. However, randomized mild to moderate IC (MIMIC) trials showed that the EVT group had a longer maximum walking distance than the SET group 24 months after therapy. Further, the result of the Endovascular Revascularization and Supervised Exercise (ERASE) Trial, which compared the clinical effectiveness of EVT plus SET (n=106) with that of standard SET care only (n=106) among patients with IC, reported that the combination of EVT plus SET showed a 282-m (99% confidence interval [CI], 60–505 m; P=0.001) greater improvement in the maximum walking distance and a 408-m (99% CI, 195–622 m; P<0.001) greater improvement in the pain-free walking distance compared with the SET-only group at 12 months. The VascuQol scores were also significantly better in the combination therapy group. Taken together, the results of Ebisawa et al’s study and the ERASE trial cast doubt on the current practice of using SET as first-line therapy for patients with IC. In many countries, including Japan, there is either no reimbursement or no available program for SET. Additionally, many patients seem to drop out from SET, and patient compliance with SET may differ among treatment strategies. Considering all the findings collectively, new trials should be performed to answer the question of whether SET with BMT should precede EVT or whether SET with BMT should follow EVT (Figure). In these trials, the outcome measures should include not only walking distances and ABI but also the occurrence of CVD during long-term follow-up. Further, no previous trial has utilized biomarkers to monitor systemic OS in patients. Measurement of OS using the d-ROM test may be helpful to compare groups objectively and estimate the risk of CVD, reducing which should be the ultimate goal of the treatment.

References