Prevention of transient endothelial dysfunction in acute exercise: A friendly fire?

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Long-term exercise training probably represents an effective antioxidant and antiatherogenic therapy (1). It has been shown to induce arterial remodelling, plaque stabilization and functional adaptations which decrease the risk of acute cardiovascular events (2, 3). These activities are believed to reduce morbidity and mortality among physically active cardiovascular patients as compared to sedentary controls (1). However, at the same time it is recognized that acute bouts of exercise may represent a transient ischaemic, prothrombotic and arrhythmogenic stimulus (3). Exercise is also known to initiate an increase in vascular oxidative stress and provides a challenge to the antioxidative capacity of tissues (1). For example, during acute exercise training endothelial production of reactive oxygen species is increased by enhanced vascular shear (4).

The delicate balance between pro- and antioxidant capacity and the subsequent positive versus negative influence of free radicals in the vasculature appears to be crucial. At low concentrations, free radicals, and their reactive non-radical derivatives, such as hydrogen peroxide, may act as mediators and modulators of cell signaling which contribute to key functions such as regulation of smooth muscle tone and blood pressure (5). Numerous data indicate that activation of redox-sensitive signaling pathways in response to non-exhaustive exercise is induced by transient oxidative stress that in turn stimulates the longer lasting expression of certain antioxidant enzymes and thereby increases the antioxidative capacity of the vascular wall (Fig. 1). Data supporting this hypothesis have been evaluated in different transgenic animals and in clinical trials (1).

In-vivo studies in animals and humans demonstrated that exercise results in an increased vascular expression of eNOS (1) suggesting an important role of endogenous production of nitric oxide (NO) as beneficial effects of exercise. Interestingly, increased NO-production appears to be directly linked to vascular oxidative stress, since endogenous hydrogen peroxide, a well known vascular oxidant, seems to play a key role in this process (6). Furthermore, the effect of hydrogen peroxide on eNOS expression by exercise training was shown to be followed by an induction of SOD3 expression (7) which, in turn, facilitates the generation of hydrogen peroxide from superoxide. In addition, a recent study of Richardson et al. (8) suggested that reactive oxygen species contribute to brachial vasodilatation during acute handgrip exercise. Thus, oxidative stress during exercise may actually play an important role in the normal vascular response to exercise.

In this issue of Thrombosis and Haemostasis, Gresele et al. (see article beginning page 444) compared the effects of aspirin with those of the aspirin derivative NCX-4016 in preventing acute endothelial dysfunction (9). This is likely provoked by exercise-induced ischemia and subsequently increased oxidative stress of the lower limbs in a group of cardiovascular patients with intermittent claudication. A head-to-head comparison between these two drugs under the conditions of acute exercise in cardiovascular patients appears to be an exciting approach and extends numerous previous studies on this new and potentially useful drug. NCX-4016, the NO-donating derivative of aspirin, is the ether of acetylsalicylic acid and 3-nitrooxyxymethyl phenol. In a physiological environment, NCX-4016 is enzymatically metabolized to produce NO at low rates, an enzymatic denitration reaction known to also occur prior to the pharmacologic actions of organic nitrates such as nitroglycerin, isosorbide mononitrate or pentaerythrityl tetranitrate (10). The release of NO from NCX-4016 appears to be time and concentration-dependent. Recent studies suggested that this pathway depends on the cytochrome p450 system and possibly involves the cytosolic glutathione-S-transferase (11).

NO has proven to be an important component in numerous signalling pathways, its biological activity is remarkable, spacious, and complex. It induces vasodilation, likely protects the vasculature and the gastric mucosa and inhibits platelet aggregation, inflammation, cellular proliferation and apoptosis (12). Thus, the combination of aspirin with an NO-generating residue in order to correct the endogenous deficit of NO in cardiovascular diseases appears a promising approach. Indeed, animal studies with NO-aspirin showed that it can control hypertension, reduces tissue damage after myocardial infarction and stroke and inhibits restenosis after percutaneous intervention (13). Furthermore, NCX-4016 treatment produced a significant reduction of plasma LDL-oxidation, oxidative stress and athero-
genesis, while treatment with aspirin itself had no effect. It seems to be better than aspirin alone in preventing or controlling colonic adenocarcinoma (14) and is a potent inhibitor against colon cancer in azoxymethane-treated rats (15). Moreover, unlike aspirin, NCX-4016 did not show any gastrointestinal adverse effects due to increased mucosal blood flow and reduced leukocytes adherence to postcapillary mesenteric venule walls (13). Altogether, these studies suggest unique and therapeutically useful properties of nitroaspirin over aspirin.

However, in the present investigation Gresele et al. demonstrated that nitroaspirin, but not aspirin, prevents exercise-induced endothelial dysfunction in peripheral arterial disease which is presumably mediated by increased vascular oxidative stress. What do the results of this study add to the current knowledge on NCX-4016? First, it extends the list of clinical studies which are important to estimate the therapeutic value of NCX-4016. Secondly, it shows that transient endothelial dysfunction occurring during exercise training appears to be sensitive to effects of NCX-4016 which presumably extends the known antioxidative effects of aspirin (16). Third, it shows that NCX-4016, unlike aspirin, also prevented exercise-induced increases of plasma elastase and soluble VCAM. As pointed out by Gresele et al., these effects are likely a consequence of reduction by NCX-4016 of exercise-induced vascular oxidative stress. However, the differences observed between aspirin and NCX-4016 are small. Furthermore, the potentially important role of a transient increase of vascular oxidative stress on the expression of antioxidative enzymes as described above raises the intriguing question whether or not the selective reduction of exercise-induced transient endothelial dysfunction by NCX-4016 is beneficial compared to aspirin or beneficial at all.

There is at least a reasonable possibility that transient endothelial dysfunction during acute exercise as observed by Gresele et al. is a functional outcome of transiently increased vascular oxidative stress which over the long-term appears to be a rather beneficial signal. While reactive oxygen species produced in large amount during acute bouts of exhaustive exercise may mediate cellular damage, lower levels of reactive oxygen species such as hydrogen peroxide have important signaling properties in blood vessels (5, 6). Therefore, suppression of cellular production of reactive oxygen species during exercise training, as suggested for NCX-4016, might lead to a loss of important vascular signaling events such as increased expression of eNOS and ecSOD which, over the long run, presumably increase the antioxidative capacity of the vascular wall (Fig. 1) and protect the vasculature against permanent oxidative stress known to be present in cardiovascular disease.

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References


