Outstanding Effect of Physical Exercise on Endothelial Function Even in Children and Adolescents

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Improving endothelial function is well known to prevent cardiovascular damage. Also, endothelial function is becoming established as a remarkable surrogate marker of cardiovascular disease. Indeed, endothelial dysfunction is an initial step of atherosclerosis, which is evoked by various factors such as hypertension, diabetes, dyslipidemia, smoking habit, metabolic disorder, excess salt intake, lack of exercise, etc., in which lifestyle-associated diseases are included. Endothelium secretes not only vasodilative substances (e.g., nitric-oxide (NO), prostacyclin, and endothelium-derived hyperpolarizing factor (EDHF)), but also vasoconstrictive substances (e.g., angiotensin-II, endothelin, and reactive oxygen species (ROS)).

Classically, endothelial function has been evaluated by coronary catheter, strain-gauge plethysmography, etc., most of which are specific, but invasive. Recently, noninvasive methods have become prevalent, such as flow-mediated dilation (FMD) and reactive hyperemia peripheral arterial tonometry (RH-PAT), both of which have beneficial properties, viz. noninvasiveness and reproducibility. Concerning sex differences, endothelial function in premenopausal women is higher compared with coeval men. Even in healthy children and adolescents, several studies have reported that endothelial function is higher in girls than boys, which is consistent with the study by Mueller et al in this issue of the Journal. Also of great interest, the finding in this study of age-related increases in endothelial function in children is in accordance with previous studies. Meanwhile, it is well known that endothelial function in older subjects is worse than in younger subjects. To our knowledge, there is no evidence concerning the exact age of the highest level of endothelial function over the lifetime of men and women.

Several studies have suggested that microvascular development may not be complete until late adolescence. The exact correlation of endothelial function with age should be resolved to uncover the whole picture of endothelial function in humans.

Of great importance, a novel suggestion was given in the present study. In fact, several types of intervention to improve endothelial function have been reported to date (Table). Of them, this study focused on the relationship of endothelial function with physical exercise (PE) at school. They divided children into control and intervention groups. In the control group, the children undertook 45 min of PE twice weekly. In the intervention group, the children practiced 60 min of PE daily and the high-level group with sports students in Sports School was included. They demonstrated that the intervention group had higher reactive hyperemic index (RHI), an index of endothelial function by RH-PAT, compared with the control group after adjustment for sex and age. Interestingly, they further investigated the PE-mediated effect on cardiopulmonary function, which was evaluated by VO2peak, a cardiopulmonary indicator, from treadmill cardiopulmonary exercise test with spirometry. They found that PE improved VO2peak in the first 2 years, but less after 4 years of PE lessons. These findings indicate that the beneficial effect of PE on endothelial function lasts longer than cardiovascular performance. PE is well known to prevent cardiovascular disease via several beneficial mechanisms, in which improvement of endothelial function, at least in part, is included. Surprisingly,
this study may be the first to show that a daily PE program could further increase endothelial function in children beyond their aging, which would provide them with future clinical benefit for a long period of time. Additionally, they showed that the extent of increased endothelial function in the high-level PE group compared with the control group was higher than in the intervention group. Even in healthy subjects, excessive PE is known to enhance excess ROS production, which would lead to endothelial dysfunction. However, there is still no accurate evidence of the cardiovascular outcome by high-intensity exercise. Further studies regarding the beneficial and/or harmful effects of high-intensity exercise in children, adolescents, and adults are awaited with great anticipation to determine whether we people can continue high-intensity exercise.

Definitely, it is important to determine the appropriate device to use for evaluation of endothelial function in targeted subjects. In this study, RH-PAT could evaluate the increase in endothelial function concomitant with age, similar to previous studies. Concerning FMD, a previous study demonstrated that it could not detect the age-related change of endothelial function in children. Meanwhile, Hopkins et al. showed an adverse finding in which the effect of age on FMD remained significant after adjustment for baseline brachial artery diameter. Also, their regression models revealed that age still affected FMD in females, but not in males. However, their findings included some discrepancy. For instance, FMD at age 8 was higher compared with other age groups except for ages 6 and 10, and FMD at age 10 was higher compared with ages 7, 14, and 15. Regarding the difference between RH-PAT and FMD, there were interesting studies evaluating the effect of dipeptidylpeptidase 4 inhibitor (DPP4-I) on endothelial function in diabetic patients. In a study of RH-PAT, DPP4-I improved endothelial function, whereas the other study of FMD showed that DPP4-I did not. Indeed, RH-PAT mainly evaluates the EDHF-mediated microvascular response by measuring finger pulse wave amplitude during reactive hyperemia, whereas FMD mainly evaluates NO-mediated conduit artery dilative response by measuring brachial artery diameter. Also, it is well known that the microvasculature is likely to be impaired compared with the conduit artery. Therefore, RH-PAT may be, even to a small extent, sensitive to slight changes in endothelial function compared with FMD, although the extent of that sensitivity remains undetermined. Collectively, RH-PAT may be suitable for evaluations in children, adolescents, and young healthy subjects, while FMD may be suitable in subjects with cardiovascular diseases. Understandably, both RH-PAT and FMD may be suitable to evaluate subjects with lifestyle-associated diseases (Figure). However, the appropriate application on how to select RH-PAT and/or FMD still remains unknown.

The present study contains several messages about endothelial function in children and adolescents, such as the relationships of endothelial function with age, sex, PE, and choice of evaluating device. Among them, the clinical importance of PE in healthy children and adolescents is a key message, which is actually similar to the importance of PE in adults and patients with cardiovascular diseases. This novel finding suggests the clinical effect of PE which could reduce future mortality and morbidity not only in adults but also in children. Further studies are needed to accumulate the evidence of PE’s importance to convince us that PE is definitively essential to extend lifespan and a healthy lifespan.

Conflict of Interest
There is no conflict of interest to report for the authors.

References

