Flow-mediated dilation and cardiovascular disease

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A cornerstone of the “exercise is medicine” movement is that regular exercise has widespread health benefits. Compared with the number of studies that have characterized health outcomes, relatively few address the mechanisms for the health outcomes. The study by Birk et al. (1) in the Journal of Applied Physiology presents evidence for the role of increased blood flow as the mechanism for enhancing the health of arteries following exercise. By using regular leg-based exercise (cycling) to induce a training effect in the brachial artery in the arm, improvements in brachial artery flow-mediated dilation (BAFMD) were seen only in the arm where exercise-related increases in blood flow occurred and not in the arm where pressure restriction prevented the increase in blood flow. The authors argue that non-flow-related effects of exercise could not account for their results. The concept being proposed is that an important mediator of the cardiovascular benefits of exercise are the increases in blood flow exercise produces (5) even in arteries perfusing tissues considered to be inactive during exercise.

The main outcome measurement in the Birk et al. (1) paper is BAFMD. Flow-mediated dilation (FMD) and the brachial artery FMD test have become a cornerstone of assessments of cardiovascular function and cardiovascular risk (4, 18, 22). There are currently 1,346 publications using the BAFMD test, including 199 publications in the year 2011 (PubMed). When performed under strict guidelines, the BAFMD test is thought to reflect nitric oxide bioavailability (4). The shear stimulus from the reactive hyperemia causes the release of nitric oxide, which is a potent vasodilator. Numerous studies have shown that a reduced FMD response is associated with many cardiovascular risk factors and conditions, such as impaired glucose metabolism (8), obesity (6), and smoking (3). Future cardiovascular events and mortality have also been associated with reduced FMD as assessed by the BAFMD test (9, 12).

The study by Birk et al. (1) presents an important mechanistic link between leg-based exercise training and changes in cardiovascular disease risk as assessed by BAFMD. Given the potential importance of the reduced FMD in the onset of cardiovascular disease, understanding how FMD can be measured is important. Although there are a number of different approaches to measuring FMD (10), the most common approach is the BAFMD test (4). The test is easy to administer (by a skilled technician with the proper equipment) and can be performed in 15 min. By using current guidelines with the testing site located on the brachial artery in the upper arm and the ischemic cuff placed distal to the elbow, a typical BAFMD test on a healthy subject results in ~6–8% increase arterial diameter from resting arterial diameter. Diseased conditions typically have reduced BAFMD, often 50% lower.

A number of methodological issues are important when performing and interpreting BAFMD tests. The primary challenge is the relatively small signal change with the BAFMD test. With a FMD value of 5%, even a 1% difference in the measurement of initial diameter will result in a 20% difference in the resulting FMD value. When performing tests on patients with reduced FMD (say 2–3% at baseline), this variability becomes even more important. Performing a BAFMD test requires careful attention to the measurement of arterial diameter, as well as the use of sophisticated ultrasound equipment and digital analysis routines (16, 19). It also means that FMD studies will require relatively large sample sizes (7, 11, 23). The Birk et al. (1) paper represents a state-of-the-art example of how to perform BAFMD tests.

One of the keys to measuring FMD is the role of exercise–or reactive hyperemia-induced shear stress (15, 17). A current debate on BAFMD is whether to account for changes in shear stimulus when comparing results of a training study like the one by Birk et al. (1). Previous studies have strongly suggested that the BAFMD is proportional to the magnitude of the shear stimulus (15, 17, 20). Normalizing for shear stress may be necessary when comparing across conditions in which relatively large differences in shear stimulus are expected (such as younger and older adults). However, the errors in measuring the shear stimulus and the small differences in shear stimulus between tests can result in a normalization that may not reduce the variance of the measurements (21). The study by Birk et al. (1) reported their shear stimulus values, but chose not to normalize their BAFMD values. Studies that measure FMD should present values for the shear stimulus in their results. Ideally, FMD values should be normalized to the shear stimulus, as this should reduce the variance of a measurement that has a lot of inherent variability. The choice to normalize or not normalize can influence the statistical outcome of a study.

An important component of normalizing the shear stimulus in a FMD test is how the shear stimulus is measured. In the current study, shear stimulus is estimated from the mean velocity across the vessel wall divided by 4 (13). This assumes a constant velocity profile for all participants, perhaps a good assumption in the current study in which all the participants are healthy. The study also uses the recommended shear stimulus calculation of the area under the curve for the hyperemic response (14). The area under the curve is determined from the entire shear stimulus added up from the release of ischemia to the time of the peak diameter response (2). The rationale for this determination of area under the curve is that the nitric oxide releasing shear stimulus is a combination of how long the stimulus is occurring as well as the magnitude of the shear stimulus. However, it might be worth reconsidering this approach. The hyperemic stimulus in healthy adults after 5 min of ischemia lasts ~30–40 s. Including velocity values after this period of elevated blood flow may add little to the stimulus to release nitric oxide. Indeed, the low velocities 40–60 s after

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release of the ischemia might be a signal to reduce the release of nitric oxide and to allow the return to resting diameter.

Birk et al. (1) chose to perform their study using healthy adults with unimpaired values for BAIFMD prior to exercise. The limitation to this approach is that it is difficult to enhance BAIFMD above normal healthy levels. Highly trained endurance athletes do not have enhanced BAIFMD over that of untrained but healthy individuals. Complete understanding of the benefits of exercise-induced shear stimulus in enhancing vascular health requires that similar studies be performed on people with impaired BAIFMD prior to training.

In conclusion, BAIFMD has become a major tool in studies that evaluate cardiovascular health. The measurement is non-invasive and relatively easy to perform, although it does have methodological challenges that influence the interpretation of the results. The study by Birk et al. (1) points out that leg exercise training, as performed in this study, increases the shear stimulus in the arms, which appears to account for the vascular adaptations that occur in the arteries of the arms with training. Future studies need to confirm this finding in people with impaired FMD. But this study highlights an important concept, that exercise is more than a black box and we should think of the exercise in terms of the various signals for adaptation it produces. Rather than reporting exercise in terms of walking speed, work in a cycle ergometer, or even heart rate, perhaps we should report the intensity of a training stimulus in terms of the magnitude of loads placed on the muscle, the metabolic energy turnover, and, yes, the shear stimulus (5).

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DISCLOSURES

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