EXERCISE AND CARDIOVASCULAR RISK REDUCTION:
TIME TO UPDATE THE RATIONALE FOR EXERCISE?

Running Title:  Exercise and Vascular Risk Reduction

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Whilst it is generally accepted that the promotion of exercise accords with clinical best practice, the anecdotal experience of many primary care physicians, cardiologists and exercise physiologists is that, even when exercise prescriptions are adhered to, risk factors often fail to demonstrate marked improvement. Since modification of traditional risk factors fails to fully explain the magnitude of exercise-mediated risk reduction (18), we propose that there are direct effects of exercise on the vascular wall, which confer cardioprotection via a “vascular conditioning” effect.

Magnitude of Risk Reduction With Exercise Training or Physical Fitness.

The Health Professional’s Study (25) included 44,452 men whose adjusted relative risk of myocardial infarction was 0.7 (P<0.001), providing strong evidence for the cardiovascular benefits of exercise in primary prevention. Meta-analyses of exercise-based cardiac rehabilitation, including trials conducted in the contemporary medications/interventions era, estimate reduction in mortality of 20-32% (26), although the lack of impact on non-fatal infarction remains unexplained. Nonetheless, exercise is associated with ~30% benefit in terms of decreased cardiac risk (27), a magnitude similar to that associated with antihypertensive and lipid lowering interventions (32, 35).

Does Risk Factor Modification Explain the Risk Reduction Associated with Exercise?

A recent AHA expert statement (27) suggested that, in normocholesterolemic subjects, exercise decreases LDL-cholesterol by 1-5%. The impact of exercise on blood pressure averages ~3/2mmHg in normotensive subjects and the impact of cardiac rehabilitation is similar (26). The impact of physical activity on glycometabolic control in healthy subjects appears small and transient (17, 30), although exercise is clearly an important intervention in diabetes/insulin resistance as its effects exceed those associated with the use of metformin (4, 31).

A recent analysis of 27,000 subjects (18) reported that differences in risk factors explained 59% of the cardiovascular risk reduction associated with exercise. The impact of HbA1c, lipid sub-profiles,
lipoprotein(a), apolipoproteinA1, apolipoproteinB-100, creatinine, homocysteine, hs-CRP, fibrinogen, s-ICAM-1, weight, height, BP and diabetes were taken into account. Blood pressure and inflammatory/hemostatic markers were responsible for the major contributions to exercise-mediated risk reduction, whilst lipids, body mass index and HbA1c contributed to a lesser degree. This statistical modelling suggests that at least 40% of the risk reduction associated with exercise cannot be explained by establish risk factors. Furthermore, a proportion of each of these risk factor contributions may be mediated through improvements in endothelial function (21, 22).

Whilst the impact of exercise may be greater in subjects with raised cholesterol, blood pressure or glycated hemoglobin, the effects of exercise on risk factors are generally smaller than those achieved with pharmacological interventions (27, 32, 35) and less than that which would account for the impact of exercise on cardiovascular outcomes. It is, of course, probable that the small benefits in each risk factor summate, but other explanations for the cardioprotective benefits of exercise seem likely.

What Could Account for the Positive Effects of Exercise Beyond Traditional Risk Factors?

The endothelium produces numerous paracrine hormones, including nitric oxide (NO), which are anti-atherogenic. Endothelial dysfunction precedes and predicts the development of atherosclerotic disease and initially occurs at coronary branch points, as do atherosclerotic plaques. Interventions of known cardiovascular benefit improve endothelial function. Coronary and peripheral endothelial dysfunction predict cardiovascular events, and improvement in endothelial function improves prognosis. Endothelial dysfunction can be considered an early and integral manifestation of vascular disease and improvement in endothelial function should impact on CV risk (9).

An important physiological stimulus to endothelium-mediated vasodilation is shear stress. Removal of the endothelium abolishes flow- and pharmacological NO-mediated arterial dilatation and NO-
dependent, flow-mediated, vasodilation normalises endothelial shear (23). There is strong evidence that exercise training of small and large muscle groups is associated with improvement in NO-vasodilator function (9).

Since cardiovascular risk factors are associated with impaired endothelial function, which is reversible via pharmacological treatment (21, 22), it is conceivable that exercise training improves endothelial function by virtue of its impact on risk factors. However, exercise training improves endothelial function in the absence of changes in lipid levels (10, 15), blood pressure (10, 13), glucose tolerance (10), or BMI (34). Improvement in risk factors is therefore not an obligatory requirement for improvement in endothelial function as a result of exercise training.

**How Does Exercise Training Directly Affect the Vascular Wall?**

*Vascular function:* Hambrecht and colleagues (11) studied the impact of 4 weeks cycle exercise on the internal mammary artery of CAD patients. Training significantly increased endothelium-dependent dilation. From analysis of a section of artery harvested during bypass surgery, the authors concluded that exercise increases NO-synthase protein expression and phosphorylation, effects consistent with a shear-stress mechanism for enhanced NO bioactivity.

Another mechanism may relate to the impact of exercise on oxidative stress. Repeated NO production as a result of exercise may reduce its degradation by free radicals, directly decrease free radical production, or increase the expression of antioxidant enzymes. Goto and colleagues (5) observed improvement in endothelial function after moderate-intensity training which did not alter oxidative stress, whereas high-intensity training increased oxidative stress and endothelial function did not improve. The impact of exercise on endothelial function may depend upon the balance between reactive oxygen species, antioxidant defences and their impact on NO bioavailability.
Vascular structure: Autopsy and angiographic studies suggest that physical conditioning increases arterial cross-sectional area (2, 16) and athletes consistently exhibit enlarged skeletal muscle conduit (3, 19) and resistance (8) arteries, compared to controls. Longitudinal studies provide further support for an arteriogenic impact of exercise training (3, 7, 19). Arterial remodelling is shear stress and NO(endothelium)-dependent (33) and acts in a manner which homeostatically regulates wall shear (28).

Exercise Training, Heart Rate Variability and Vascular Adaptation

Fatal arrhythmias can occur in conjunction with ischemia, in tissue previously damaged by ischemia, and as primary events. Emerging evidence suggests that low heart rate variability (HRV) at rest or during exercise is an independent predictor of cardiovascular mortality (29). Exercise training/physical activity are associated with enhanced HRV (14, 24). There are several possible explanations. As described above, exercise training is associated with increased compliance and arterial remodelling of great vessels, including those in barosensitive areas. This may increase baroreceptor afferent activity, evoking increased reflex parasympathetic outflow. In addition, recent studies indicate that endurance training remodels cardiorespiratory centers, thereby reducing sympathetic, and enhancing parasympathetic, outflow (1, 20). Whether these adaptations occur in humans is not known, but seems likely. Increased parasympathetic, and decreased sympathetic, outflow to the heart would typically be cardioprotective (1).

Clinical Relevance of the Direct Effects of Exercise Training on the Vasculature.

A recent study compared the effects of stenting to exercise training. After 12 months, the “stent” group exhibited decreased stenosis diameter (81%→12%), whereas exercise training had no impact (78%→77%) (12). Nonetheless, significantly higher event-free survival occurred with exercise training (88% vs 70%). Coronary interventions treat a short segment of the diseased coronary tree, whilst exercise exerts beneficial effects on endothelial function and disease progression in the entire
arterial bed. In contrast to exercise training, interventional cardiology represents palliative care with respect to the underlying atherosclerotic disease process (12). Exercise training should be the cornerstone of prevention efforts.

SUMMARY.

Exercise training reduces cardiovascular events. The effects of exercise on traditional risk factors do not fully account for the magnitude of risk reduction. Exercise exerts direct effects on the vasculature via the impact of repetitive increases in shear stress on the endothelium, which transduce functional and structural adaptations that decrease atherosclerotic risk. Direct effects of exercise on the vasculature therefore provide a plausible contribution to the reduction in cardiac events associated with exercise training. Since different forms of exercise are associated with different patterns of shear stress and arterial adaptation, future studies should focus on the direct impacts of exercise on vasculature function and structure rather than on surrogate measures of vascular health.
ACKNOWLEDGEMENTS

DJG received research funding support from the National Heart Foundation of Australia.

MJJ was supported by NIH HL-46493, NS-32352 and HL-83947

The authors would like to thank Dr David Dunstan of the International Diabetes Institute for his helpful discussion and advice regarding exercise and glycometabolic control.
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