Coronary flow responses to exercise training: further evidence of the benefit of an underutilized therapeutic modality

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ABSTRACT

Inactivity is associated with endothelial dysfunction and the development of cardiovascular disease. Exercise training has a favourable effect in the management of hypertension, heart failure and ischaemic heart disease. These beneficial effects are probably mediated through improvements of vascular function and, in this issue of Clinical Science, Hägg and co-authors propose a coronary artery effect. The use of a Doppler technique for non-invasive assessment of coronary flow reserve in a small animal model is an exciting aspect of this study. If feasible in the hands of other investigators, the availability of sequential coronary flow measurements in animal models may help improve our understanding of the mechanisms of disorders of the coronary circulation.

Exercise capacity is a very powerful determinant of outcome, and an inactive life style is associated with endothelial dysfunction and the development of cardiovascular disease [1]. A number of studies have shown that exercise training has a favourable (albeit small) effect in the control of hypertension [2], improvement of quality of life and functional capacity in heart failure [3], and may be as effective as percutaneous coronary intervention in angina [4]. The weight of evidence suggests that these beneficial effects are probably mediated through improvements in vascular function, perhaps through replenishment of the endothelium by circulating endothelial progenitor cells released during exercise [5]. Although much interest has focused on peripheral vascular function, Hambrecht et al. [6] have proposed effects on coronary vascular function in patients with coronary artery disease and, in this issue of Clinical Science, Hägg and co-workers [7] propose a coronary artery effect in an animal model without coronary disease.

In the study by Hägg et al. [7], spontaneously hypertensive rats were exercised for 6 weeks, and the effects of exercise training were studied using transthoracic Doppler evaluation of left anterior descending artery flow at rest and in response to adenosine–induced hyperaemia. Gene and protein expression in cardiac tissue were assessed using immunohistochemistry and real-time PCR. The authors [7] found significantly greater adenosine-induced hyperaemia in exercising rats compared with controls, with a 2.6-fold increase in velocity in exercised animals compared with a 1.5 times increase in the controls. These changes were matched by increased gene expression of superoxide dismutase, without a change of endogenous nitric oxide synthase. The authors conclude that physical exercise is associated with improved coronary flow velocity reserve corresponding to improved antioxidant capacity.

The concerns that clinicians often express about animal models are applicable to the study by Hägg et al. [7]: the effect could relate to the animal selected (whose vasculature may not parallel that of humans), the different physiological responses of a relatively acute model compared with chronically abnormal coronary arteries, and the difficulty in delivering an equivalent intensity of exercise to patients with cardiovascular disease in ‘real life’. Nonetheless, the consistency of the findings

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with existing clinical studies [6], and the associated gene and protein studies suggest this is a plausible phenomenon.

Although the direct benefits of exercise on coronary vascular function are provocative, the use of a Doppler technique for non-invasive assessment of coronary flow reserve in a small animal model is sensational. Transthoracic Doppler measurement of coronary flow velocity, especially in the left anterior descending artery, is feasible in humans, although it does require significant training [8]. Measurement of flow reserve may be used to complement standard stress echocardiography, to understand the physiological significance of intermediate-grade coronary stenoses and to understand the mechanism of chest pain with apparently normal coronary arteries. The thin chest wall of the animals would certainly increase the feasibility of this technique, but to keep the sample volume stable in a small animal preparation could be challenging indeed. It will be important to see how readily other investigators can pick up this skill, which opens up new vistas for the sequential follow-up of coronary vascular function in animal models, and may help us address the new frontier of diseases of coronary vascular function.

Perhaps because of the marvels of coronary imaging and intervention, the clinical approach to diseases of the coronary vasculature has for a long time been dominated by assessment of the conduit vessels. However, many patients with ischaemic pain have anatomically normal coronary arteries, with either chronic or acute disturbances of myocardial perfusion, presumably attributable to disturbances of vessel function [9]. The study by Hägg et al. [7] offers a non-invasive means of measuring this problem with coronary flow reserve, as well as proposing exercise training as a modality for its management. Better understanding the mechanisms of these disorders and the treatment responses will be facilitated by the availability of sequential coronary flow measurements in animal models.

REFERENCES