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EDITORIAL COMMENTARY

Of mice and men ... does exercise decrease progression of transplant coronary vasculopathy?

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See related article on pages 330-7.

In this issue of the *Journal*, Sommer and colleagues from the Hannover Medical School present the results of a well-designed study demonstrating reduced intimal

proliferation after allogeneic transplant of a segment of abdominal aorta in mice thereafter subjected to 28 days of an exercise program, as compared with a group not subjected to exercise. The exercise group also demonstrated increases in endothelial integrity, circulating endothelial cells (ECs), and EC function as measured by counts of ECs staining positive for the anti-endothelial nitric oxide synthase antibody ab5589. The results are not subtle. The percentages of luminal area reduction were 81% in the control group and 60% in the exercise group. In major histocompatibility complex-matched groups (ie, only minor mismatch present), the reductions were 75% in the control group and 49% in the exercise group.

In general, exercise is known to improve metabolic function, lipid profile (particularly, increase in high-density lipoprotein cholesterol), insulin sensitivity, and

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FIGURE 1. Schema representing our best current understanding of the mechanism of transplant coronary artery vasculopathy. DC, Donor cell; CMV, cytomegalovirus; MHC, major histocompatibility complex; TLR, Toll-like receptor; eNOS, endothelial nitric oxide synthase; SMC, smooth muscle cell. (Adapted from: Schmauss D, Weis M. Cardiac allograft vasculopathy: recent developments. *Circulation*. 2008;117:2131-41.)

immunologic functions. It increases the perfusion of myocardium and fibrinolytic activity and reduces the adherence of thrombocytes as the result of increased synthesis of prostaglandin (PGI₂). Exercise reduces visceral fat volume and also interleukin 6 and high-sensitivity C-reactive protein concentrations. Exercise increases the activity of endothelial nitric oxide synthase and the concentration of circulating EC progenitor cells. A range of studies have shown that these collective effects reduce endothelial damage, EC dysfunction, and vascular inflammation. Because the latter pathologic states are central to the formation and progression of atheromas, it is not surprising that the atheroprotective effects of exercise and physical activity in both peripheral and coronary artery disease are well documented.¹

Consider the schema, adapted from Schmauss and Weis,² shown in Figure 1. This schema represents our best understanding of the mechanism of transplant coronary artery vasculopathy (CAV). The central features leading to CAV are endothelial dysfunction and vascular inflammation—identical to those leading to coronary artery disease. If at least some of the effects of exercise listed previously act directly at the level of the endothelium and

inflammatory chain and with sufficient strength, then it makes complete sense that exercise should impede the effect that the alloimmune response has on CAV. This is what Sommer and colleagues have shown.

There has been but one randomized clinical trial (RCT) examining the relationship between exercise and CAV, conducted by Nytrøen and coworkers at the University of Oslo.³ Forty-three cardiac allograft recipients were randomized to receive either high-intensity interval training or standard care alone for 1 year. The effect of training on CAV progression was assessed by intravascular ultrasonography. Nytrøen and coworkers found a significantly smaller mean increase in atheroma volume (0.9%; 95% confidence interval, 0.3%-1.9%) in the high-intensity interval training group compared with that in the control group (2.5%; 95% confidence interval, 1.6%-3.5%; $P = .021$).

Compared with that seen in the RCT, the rate of intimal proliferation was much greater in the current study of Sommer and colleagues. The clinical group was, of course, immunosuppressed, whereas the mice were not. The mice were studied immediately after transplant, when one might expect an intense immune response

(even ongoing acute rejection) in the absence of induction therapy. Sommer and colleagues did not report the histomorphology of the acute process; on the basis of previous work, however, it is unlikely to be identical to that seen in chronic CAV.

On the other hand, it is known that the progression rate of CAV is greatest in the first 12 months after transplant. The RCT may have underestimated the potential impact of exercise because patients underwent the high-intensity interval training regimen an average of 4 years after receiving the transplant. In addition, the control group in the RCT in fact generally exercised—67% of control group patients exercised at least twice per week in the last 3 months before follow-up. The study of Sommer and colleagues did not have such limitations.

The strength of the study of Sommer and colleagues, even though it was done with mice and had the limitations listed previously, is that it adds significantly to a limited body of evidence that exercise is acting at the “end points” of the atherogenesis process (the center boxes in [Figure 1](#)).

Furthermore, the effect is strong enough to impede significantly the effects of the alloimmune response (the top box in [Figure 1](#)), even in the absence of pharmacologic immune suppression. Finally, the effect of exercise is present across a broad range of donor-recipient antigenic mismatch (at least between the groups studied). Of mice and men, the remaining questions are what type of exercise regimen is best applied to transplant recipients, when should it be instituted, and whether this therapy actually reduces the need for or delays the time to consideration for retransplant.

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