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Reply

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We agree with Underwood and his colleagues that changes in blood flow, pressure and shear stress influence the development of intimal hyperplasia as shown most clearly in the excellent article by Dobrin et al. [1]. In our experiments there is no reason to assume that there is a difference in the hemodynamic environment into which the control and treated grafts were placed, as vessels from either group were inserted into the same circulation in rabbits of equivalent weight. We have previously published the data on the flow parameters in this model [2]. Any hemodynamic contribution to the formation of intimal hyperplasia should be common to the two groups. Therefore, the suggestion that changes in intimal thickness reported in our experiments are flow related, which is only one of a multiplicity of processes contributing to the development of intimal hyperplasia, is unlikely.

We also agree that the rabbit model used in our studies, or any animal model, may not produce exactly the same result as in the clinical situation which is perhaps not surprising to most researchers in this field or in any other area of investigation. The study [3] cited by Underwood et al, which purportedly questions the clinical relevance of this model, suggests that the only difference that was observed between the rabbit jugular vein and the human saphenous vein was the responsiveness to serotonin. This preliminary report in fact found a high degree of correlation between human and animal results aside from this change in serotonin reactivity. Our previous comparative investigations with this model to the clinical situation additionally concur that the homology between this model of vein grafting and human saphenous vein grafts are greater than any perceived differences with respect to both endo-thelial and smooth muscle cell pathophysiology. We believe that the overall similarities of the model to man and the insight previously gained from these types of studies warrant their continued application for advancing experimental investigations to reduce intimal hyperplasia in human vein grafts.

The comment made regarding our previous study on the beneficial effect of aspirin and dipyridamole on the formation of intimal hyperplasia [4] not correlating with the clinical situation and therefore further implying that the rabbit model is not clinically relevant, is mistaken, as this study was actually performed in the rhesus monkey. Although we have not investigated the use of aspirin and dipyridamole in this rabbit model, other pharmacologic interventions we have reported in this model [5] adequately reflect the human situation.

Furthermore, it is important to note that in our monkey model, the treatment with aspirin and dipyridamole was initiated 3 weeks prior to grafting, whereas in the study [6] cited by Underwood et al., the aspirin was initiated 7 h after surgery. A recent statement by the American Heart Association [7] reviews the available data and suggests that the time of initiation of therapy is crucial to the therapeutic outcome. Based on the numerous clinical trials discussed in this statement, the recommendation by the American Heart Association is that low-dose aspirin should be administered following surgery and continued for at least 1 year to reduce vein graft occlusion. When the result of a large multicenter trial sponsored by the United States National Institutes of Health investigating aspirin and lipid-lowering drugs is completed, a clearer therapeutic recommendation may be forthcoming as to how to minimize the development of graft atherosclerosis.

In spite of whatever reservations Underwood and his colleagues may still have regarding our study, we hope that they recognize the potential important implication of this study – that this finding of a single ex vivo treatment at the time of grafting represents a novel approach to the prevention of long-term graft occlusion. We recognize that as with all therapies which are successful in an animal model, clinical trials to validate the results are required.

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