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## INVITED COMMENTARY

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A major limitation in developing molecular therapies for critical limb ischemia has been the lack of a clinically relevant model to test efficacy. The existing animal models primarily depend on acute limb ischemia generated by femoral artery ligation or excision. These models have provided insights into cellular and molecular mechanisms that underlie collateral artery growth, primarily because young rodents collateralize quickly in response to ischemia. This trait is less helpful when trying to test potential treatments that will be effective in older, atherosclerotic, diabetic human patients. Many single growth factor therapies have showed efficacy in these rodent-based models, only to fail in human clinical trials. Furthermore, these surgical models require invasive isolation of the femoral artery, creating an inflammatory milieu for arteriogenesis different from that caused by atherosclerosis. They also lack the tibial level occlusions seen in diabetic patients.

The current article addresses the last two concerns. The authors have modified the model developed by Liddell et al,[1] where the authors used a percutaneous transauricular approach to coil embolize the rabbit superficial femoral artery, by instead using 300- to 500-μm microspheres to embolize more distal targets: the saphenous (posterior tibial equivalent) and anterior tibial arteries and their outflow beds. The resulting acute ischemia resulted in significant hindlimb ulcerations, similar to the pedal gangrene seen in patients with critical limb ischemia. The ulcerations and decreased saphenous artery blood flow were persistent up to 14 days at the time of humane killing.

It is likely that this model will need further refinement to be made practical for use in testing arteriogenic therapies. The embolization resulted in a significant acute ischemic injury to the muscle, with a large inflammatory cell infiltrate and muscle necrosis. The footpad necrosis in most of the rabbits was severe,

with high pain scores, resulting in ethical concerns for maintaining the model for longer than 14 days. Staged embolizations of the anterior tibial and saphenous arteries with particles sized for the tibial arteries rather than their outflow beds might better reflect the tibial level occlusions seen in diabetic humans and provide a less severe and more chronic ischemia that would better support therapeutic testing. This method would also facilitate use of the model in hypercholesterolemic or diabetic rabbits, who would presumably be less tolerant of the severe arterial ischemic insult generated by the current protocol.

Limitations aside, this percutaneous embolization-based model of hindlimb ischemia represents a step forward in the creation of a more relevant animal model of critical limb ischemia. It remains to be seen whether it is enough of a step forward to support robust preclinical testing of arteriogenic therapies.

*The opinions or views expressed in this commentary are those of the authors and do not necessarily reflect the opinions or recommendations of the Journal of Vascular Surgery or the Society for Vascular Surgery.*

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