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Dear Editor:

We are honored to provide a revised manuscript, "*Preclinical Model of Hind Limb Ischemia in Diabetic Rabbits*," for potential publication in the Journal of Visualized Experiments. We have included a detailed response to the reviewers' comments as a separate attachment.

In this work, we describe an optimized large animal model of peripheral ischemia in rabbits that have diabetes and hyperlipidemia. Despite use of this surgery as a preclinical model for many years, a detailed description of this type of surgery is lacking in the literature and there is a lack of standardization in how the surgery is performed by different groups. Moreover, the procedure is primarily performed in healthy animals rather than those with diabetes or another factor that compromises vascular regeneration. Studies using healthy animals with hind limb ischemia were used to justify clinical trials for patients with peripheral ischemia that subsequently failed to show benefit. We believe a major contributor to this failure in clinical translation stems from the use of healthy animals that have exceptional regenerative capacity in contrast to patients with PVD. The method we describe in this work addresses these issues and provides a detailed description of the ligation method to produce reproducible and comparable results between experiments. In addition, the described methods incorporate several innovations that have not been used in previous studies or have been used in separate studies and brought together in this protocol. We have also included an additional supplementary protocol for analysis of histological samples that are optimized to work on rabbit tissues as well as protocols for creating high fat diets that can provide cost savings over purchasing commercially available diets.

The Journal of Visualized Experiments is the ideal format to present the complex surgical methods described in our studies and there is a broad set of groups that would benefit from a detailed description of the methods we describe in our manuscript. The surgical method for performing hind limb ischemia in rabbits is inadequately described in the vast majority of scientific papers employing this model. We hope that this protocol will provide a more consistent preclinical model that reduces the disconnect between

results of preclinical studies and clinical trials for peripheral ischemia. Thank you for your consideration.

Sincerely,



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