A novel intracoronary microsyringe system (MicroSyringe) was developed for regulated drug injection into the adventitial space. In this report, the feasibility, safety, and distribution pattern of vascular treatment with this modality were tested in 17 swine by delivering Oregon green-labeled paclitaxel (OGP) and tacrolimus. Coronaries were harvested 0.5-96 hr postinjection and analyzed for drug by fluorescence histochemistry (OGP) and liquid chromatography-mass spectrometry (tacrolimus). Histopathological analysis was subsequently performed. The microsyringe deliveries were performed safely in all cases. In the OGP-injected group, within 2 hr postprocedure there was intense staining of the adventitia, media, and endothelium around the injection site, and by 23 hr staining extended distally by 27.5 mm. With tacrolimus, similar longitudinal drug distribution was seen; furthermore, by 48 hr there was detectable drug over 40 mm proximal and distal to the injection site. Significant levels of tacrolimus were detectable in coronaries at 96 hr. Percutaneous adventitial delivery is safe, feasible, and provides consistent dosing for complete treatment of a vascular territory.