

#5 **DOSE-DEPENDENT INHIBITION OF MYOINTIMAL  
HYPERPLASIA BY ORALLY-ADMINISTERED RAPAMYCIN**

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**Objective:** It is known that stent-bound, interstitially eluted drug Rapamycin impregnated stents (designed to release drug locally for 2 to 4 weeks) inhibit adjacent myointimal hyperplasia (MIH). Although Rapamycin (sirolimus) is an effective inhibitor of localized MIH, the effects of orally administered drug is unclear. Our goal is to study the effect of orally administered rapamycin on MIH in a rabbit post-injury aorta model.

**Methods:** MIH was induced in 35 New Zealand white rabbit (2.5-3.0 kg) aortas by passage of a 2-Fr balloon catheter via a femoral cutdown. The aortic intima was abraded by withdrawing the inflated balloon 3 times. 3 groups of 10 to 15 rabbits each were administered 1) no rapamycin (control), 2) low dose (0.1 mg/kg) or 3) high dose (0.4 mg/kg). Drug was started 1 week before operation and continued for 3 to 6 weeks post-injury. Aortas were harvested at 3 weeks (n=15) or 6 weeks (n=20). Triplicate elastin stained paraffin sections of the distal aorta analyzed to measure the intima/media cross sectional area ratio (I:M ratio).

**Results:** Aortas harvested at 3 weeks showed control I:M ratio=53.0±10.2%; low dose 16.9±13.2%; high dose 23.8±7.5%, representing 68% inhibition of MIH in the low dose and 55% inhibition in the high dose group. The differences between low dose and control, high dose and control groups were both significant (p<0.01); the difference between low and high dose groups was not significant (p=0.39). Aortas harvested at 6 weeks showed a control I:M ratio =51.8±12.2%; low dose (4 weeks administration) 28.8±14.8%; low dose (7 weeks) 33.0±7.5%; high dose (4 weeks) 47.5±15.6% representing 44%, 36% and 8% inhibition of MIH in the low and high dose groups. The difference between the low dose (4 weeks) and control groups at six weeks was significant (p = 0.0045).

**Conclusions:** Low dose oral rapamycin inhibits MIH at 3 weeks post-injury, but the effect is less pronounced at 6 weeks post-injury. The high dose oral regimen was less effective at three weeks and induced minimal inhibition at 6 weeks. These results suggest: 1) oral rapamycin administration induces potentially useful inhibition of myointimal hyperplasia, 2) low doses may be paradoxically more effective than high doses, and 3) inhibition is not necessarily enhanced by longer periods of oral administration.