

#12 INHIBITION OF INTIMAL HYPERPLASIA BY DIRECT THROMBIN INHIBITORS IN AN ANIMAL VEIN BYPASS MODEL

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Objective: Direct thrombin inhibitors (DTI) are clinically utilized as anticoagulants. As other anticoagulants have previously been proposed to limit intimal hyperplasia (IH), administration of these drugs during performance of bypass procedures may assist mid-term patency of bypass grafts. The specific objective of this study was to determine the effect of DTI on IH and whether any reduction in IH was solely due to inhibition of thrombin.

Methods: A vein bypass model was created by interposing a segment of inferior epigastric vein into the carotid artery of young male Sprague-Dawley rats (6 animals per treatment group). Vein grafts were topically treated (soaking of the vein grafts for 15 minutes and irrigation of the graft and adjacent artery for one minute prior to restoration of flow) with either saline or a DTI (argatroban 1 mg/ml or lepirudin 25 mg/l). At 30 days, grafts and adjacent vessels were perfusion-fixed at the animals' antemortem mean arterial pressure and harvested. Sections of the common carotid (C), proximal anastomosis (Px), graft (G), and distal anastomosis (Dt) were stained and analyzed for intimal hyperplasia (intima to media ratio –IM, and luminal area).

Results: There was a statistically significant reduction in intimal hyperplasia in the DTI treated groups as compared to control. There was better preservation of luminal area in the DTI groups, most notably in the graft segment of the argatroban group. Values are mean ±1 SD.

Conclusions: Both argatroban and lepirudin produced a statistically significant reduction in intimal hyperplasia. As both argatroban and lepirudin are direct thrombin inhibitors, the difference between the 2 treatment groups, observed in preservation of graft luminal area, likely represents an additional action of argatroban, which is distinct from its direct inhibition of thrombin.

		IM	Lumen
Saline	C	1.00 ± 0.00	1.00 ± 0.00
	Px	4.31 ± 3.10	1.04 ± 0.39
	G	4.39 ± 3.59	1.27 ± 0.86
	Dt	6.16 ± 2.54	0.88 ± 0.62
Argatroban*	C	1.00 ± 0.00	1.00 ± 0.00
	Px	2.29 ± 1.88	1.57 ± 0.40
	G	2.08 ± 1.49	1.86 ± 1.04** (vs. lepirudin and saline)
	Dt	2.27 ± 1.05	1.78 ± 0.46
Lepirudin*	C	1.00 ± 0.00	1.00 ± 0.00
	Px	2.60 ± 1.37	1.11 ± 0.15
	G	3.38 ± 1.10	1.40 ± 0.96
	Dt	3.49 ± 1.48	1.19 ± 0.36

*p< .05 by one-way ANOVA against saline; **p< .05 by independent t-test against same section, alternate treatment