HIGH DOSE INTRAVENOUS ASPIRIN VS LOW DOSE INTRAVENOUS OR ORAL ASPIRIN IN EXPERIMENTAL CORONARY VASCULAR INJURY

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Inhibition of platelet aggregation in response to vessel wall injury has been used to stabilize acute coronary syndromes. Delivering 100 μA anodal direct current to the intima of the left circumflex coronary artery (LCCA) of canines, at a site of moderate stenosis, provides a thrombogenic model of vascular injury. We explored the anti-thrombotic effects of aspirin (ASA) [GpI: 20mg/kg iv, GpII: 4.6 mg/kg iv, GpIII: 4.6 mg/kg po 18h prestudy) and placebo (CT). Time to thrombosis was prolonged and incidence of thrombosis was lower in GpI ($p<0.05$). Thrombi were smaller in GpI ($p<0.05$). Indium-labeled platelet adherence to vasculature (LCCA/LAD ratios) was decreased in proximal and distal vessel segments after ASA ($p<0.05$). *Ex vivo* arachidonic acid induced aggregation decreased in all groups with ASA ($p<0.0001$). In summary, high dose iv ASA had saltatory effects: stabilized CBF, prolonged the time to thrombosis, reduced the incidence of thrombosis, reduced thrombus mass, and limited platelet adherence to sites of vessel wall injury. Low dose ASA, given iv or po, was ineffective. With persistent intracoronary thrombi, high dose iv ASA may be useful despite the fact that platelets continue to interact with injured vascular segments *via* ASA insensitive mechanisms.

	GpI (n=11)	GpII (n=6)	GpIII (n=7)	CT (n=11)
CBF (ml/min)	31±2→26±4*	26±4→10±5	27±5→7±7	29±4→0
Thrombosis time (min)	237±7*	127±25	156±35	90±11
Incidence thrombosis	2/11*	3/6	6/7	11/11
Thrombus mass (mg)	5.0±1.0*	12.2±2.6	11.6±3.9	9.1±1.2
LCCA/LAD prox	1.5±0.4†	1.5±0.3†	1.2±0.1†	3.7±1.3
LCCA/LAD mid	5.6±1.0	5.6±1.5	10.2±2.9	12.6±8.0
LCCA/LAD distal	1.5± 0.3†	1.3±0.2†	2.1±0.5†	7.3± 2.7
Serum ASA levels(mg/dl)	10.1±1.2*	3.1±0.4¥	<2.4	

*$p<0.05$ compared other groups, †$p<0.05$ compared control, ¥$p<0.05$ compared GpIII

LOW BLOOD OXYGEN AFFINITY IMPROVES CARDIAC FUNCTION DURING REGIONAL MYOCARDIAL ISCHEMIA IN PIGS

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Definitive experiments characterizing the effects of blood oxygen affinity (BOA) on the function of ischemic myocardium have not been previously performed. We used the osmotic pulse method to incorporate inositol hexaphosphate into red blood cells (RBC) (low affinity, LA, P_{50}=35.1 ±0.6, n=6). High affinity RBC (HA, P_{50}=23.4 ±0.2, n=4) were prepared by incubating with KCNO. These methods produce stable changes in BOA (normal affinity, NA, P_{50}=31.4±0.5, n=6). Graded myocardial ischemia was induced by step reductions in LAD coronary blood flow (CBF). At baseline, coronary vascular resistance (CVR) was increased by 26.0±4.3% with low BOA and decreased by 12.0±1.2% with high BOA ($p<0.05$). Coronary venous pO2 (mmHg) was highest in the LA group (42.6±1.1), lower in the NA group (32.5±1.5), and lowest in the HA group (19.7±1.9). CBF could be reduced by 75±3% in the LA group, but only by 33±2% in the HA and 58±4% in the NA groups, before significant loss of myocardial shortening occured. Systemic hemodynamics were stable in both LA and NA groups, and at a low O_2 delivery (3.6 ml O_2/min/100 g) O_2 extraction was 66% higher in the LA compared to HA and NA groups ($p<0.05$). CVR was similar in all groups at low CBF. These cardiac and extracardiac responses suggest that low affinity blood may offer potential cardiac protection during reduced coronary blood flow.

DETECTION OF CORONARY CLOT LYSIS WITH AN IMPROVED ELISA FOR CROSS-LINKED FIBRIN DEGRADATION PRODUCTS

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Concentrations of cross-linked fibrin degradation products (XL-FDP) increase *in vivo* during pharmacologic thrombolysis. The extent to which increases reflect clot lysis has been controversial because of overestimation of XL-FDP concentrations with currently available ELISAs due to detection of noncross-linked fibrin(ogen) products complexed with XL-FDP by tag antibodies not specific for cross-linked fibrin. To overcome this difficulty, a new ELISA was developed in which the monoclonal antibody 3B6 (AGEN), which is specific for XL-FDP, was used as both the capture and tag antibody. Concentrations of XL-FDP with the new ELISA did not increase in plasma samples incubated with 2.5 μg/ml t-PA *in vitro* in the absence of clot. To determine whether increases in XL-FDP reflect clot lysis *in vivo*, we measured concentrations of XL-FDP in 61 patients with acute infarction, treated with 100 mg of t-PA . In patients with evidence of coronary recanalization (n=50) defined by rapid rates of increase of myoglobin or the MM_3 isoform of creatine kinase and coronary angiography, plasma concentrations of XL-FDP were higher than in those without reperfusion or evidence of coronary thrombosis (n=11; 385±54 [SE] vs 148±34 ng/ml at 1 hr [p=.04], and 529±59 vs 278±80 ng/ml at 2 hr after t-PA [p=07]. Only 3 patients without reperfusion had XL-FDP >300 ng/ml by 2 hr after treatment compared with 32 patients with reperfusion (p=.03). In two patients without coronary thrombosis, XL-FDP did not change. Thus, increases in the concentration of XL-FDP with this more specific assay appeared to detect clot lysis. However, clot lysis per se did not always result in reperfusion, perhaps due to the persistence of concomittant coagulant activity.

ARGATROBIN REDUCES PLATELET DEPOSITION AT THE SITE OF BALLOON ANGIOPLASTY IN AN *EX VIVO* WHOLE ARTERY MODEL

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Platelet thrombus formation at the site of balloon angioplasty induced arterial injury is associated with early reocclusion and late restenosis. In addition to its role in fibrin formation, thrombin is a potent activator of platelets (plts). We studied the effect of the strong thrombin inhibitor argatrobin ((2R,4R)-4-methyl-1-[N-(3-methyl-1,2,3,4-tetrahydro-8-quinolinesulfonyl-l-argyinyl]-2-piperidinecarboxylic acid monohydrate) (K_i = 19 nM) on platelet deposition at the site of balloon injury (BI) in an *ex vivo* whole artery model. Freshly prepared rabbit aortas were mounted in a perfusion chamber. One half of the mounted arterial segment underwent BI with a standard angioplasty balloon catheter with the uninjured half serving as the control segment. The arteries were then perfused with human blood at physiologic pressure and shear rates of 150-330 sec^{-1} (low shear) and 700-1250 sec^{-1} (high shear) for 30 minutes. Plt deposition was measured with 111-Indium labeled plts. Blood was anticoagulated with heparin (2 U/ml) or argatrobin (20 μg/ml). The results are expressed as plts x $10^6/cm^2$ with Mean±SEM.

AGENT	Control (low shear)	BI (low shear)	BI (high shear)
Heparin	0.6±0.1§	6.9±1.0+	11.7±2.3
Argatrobin	0.5±0.2§	2.8±0.9+	6.1±1.1

(+$p<0.05$, §$p<0.01$ vs BI-Heparin segments) (n=5)
At low shear rates there was a 59 % decrease in plt deposition ($p<0.05$). At high shear rates there was a 48% decrease in plt deposition.

CONCLUSIONS: 1) At shear rates seen in non-stenotic coronary arteries argatrobin is significantly more effective than heparin in reducing platelet deposition at the site of balloon angioplasty induced injury. 2) These results demonstrate the importance of thrombin in platelet thrombus formation. 3) Argatrobin may be a useful clinical agent in reducing early reocclusion and late restenosis following angioplasty.