1197-30 Intracoronary Irbesartan Increases Myocardial Perfusion and Microvascular Blood Volume in a Pig Model of Acute Ischemia

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Angiotensin II (Ang II) is a potent direct vasoconstrictor. In acute ischemia, blockade of Ang II may have beneficial effects on the coronary microcirculation. We evaluated irbesartan (Irb), a novel specific Ang II receptor antagonist, in a pig model at baseline and during acute ischemia.

Electron-beam CT (EBCT) was performed in 9 pigs for quantification of myocardial perfusion (MP) and intramyocardial vascular blood volume (BV) at the mid-ventricle. Iodinated contrast was injected into the LAD to define the myocardium "at risk" and into the right atrium for examination of MP and BV at baseline, during infusion of 50 μg/kg/min adenosine (Aden) into the LAD, and after injection of a bolus of 0.2 mg/kg Irb into the LAD. To induce acute ischemia (ST-segment and T-wave changes), 1.2 M 15 μm microspheres were injected into the LAD, and MP and BV were again examined at rest, during Aden, and after Irb. MP and BV were compared between the LAD region "at risk" (L) and an infero-lateral control region (C), and L/C was calculated (table, values are mean [SD]).

	MP			BV		
	Rest	Aden	Irb	Rest	Aden	Irb
Ratio L/C (Baseline)	1.04 [0.09]	2.22* [0.36]	1.12 [0.23]	0.91 [0.16]	1.65* [0.25]	1.07* [0.19]
Ratio L/C (Ischemia)	0.63* [0.14]	0.78*† [0.26]	0.74*† [0.26]	0.63* [0.19]	0.74 [0.32]	0.73 [0.33]

* = p < 0.1 vs. "Baseline Rest", † = p < 0.1 vs. "Ischemia Rest"

Conclusion: Intracoronary Irbesartan preserves regional BV during acute ischemia and increases regional MP similar to adenosine. Irbesartan is a coronary vasodilator at rest and during acute ischemia.

1197-31 Isoprostane, 8-Epi Prostaglandin $F_{2\alpha}$, in the Pathogenesis of Ischaemic Heart Disease

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Background: Isoprostanes have been shown to be a reliable index of oxidant stress in vivo. We have also shown that one of these compounds, 8-epi prostaglandin (PG) $F_{2\alpha}$, has a potent vasoconstrictive action in bovine and porcine coronary arteries. In this study we measured levels of 8-epi $PGF_{2\alpha}$ in patients with acute and chronic ischaemic heart disease and assessed the motor response of isolated human coronary arteries to the administration of isoprostane.

Methods and Results: Levels of 8-epi $PGF_{2\alpha}$ in systemic venous plasma were measured by enzyme immunoassay. Reactivity of coronary artery rings to 8-epi $PGF_{2\alpha}$, the thromboxane mimetic, U46619 and $PGF_{2\alpha}$ were determined *in vitro*. Control levels of free isoprostane were 50.57 ± 7.63 pg/ml (n = 12), whilst levels in age matched coronary artery disease patients were greatly elevated with chronic stable, unstable and myocardial infarction patients having levels of 181.16 ± 32.85, 280.30 ± 58.06 and 348.77 ± 79.81 pg/ml respectively (n = 13). This increase in isoprostane levels was independent of risk factors such as cigarette smoking and diabetes mellitus. 8-epi $PGF_{2\alpha}$ also constricted human coronary artery rings in a concentration-dependent fashion with an EC_{50} of 395.4 ± 62.9 nmol/L (n = 9). The thromboxane A_2 mimetic, U46619 and $PGF_{2\alpha}$ also constricted human coronary vessels as did the prostanoid $PGF_{2\alpha}$ with EC50 values of 26.2 ± 8.1 nmol/L (n = 9) and 997.4 ± 150.1 nmol/L (n = 9) respectively.

Conclusions: Venous levels of 8-epi $PGF_{2\alpha}$ are increased in ischaemic heart disease, presumably as a consequence of synthesis in the coronary vasculature where they have a potent vasoconstrictor effect. Isoprostanes produced locally in the coronary arteries during conditions of oxidant stress may play a role in the pathophysiology of myocardial ischaemia.

1197-32 Lovastatin Inhibits Plasminogen Activator Inhibitor Type-1 Production by Adipocytes

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Background: Obesity predisposes to attenuated fibrinolysis attributable to increased concentration in blood of plasminogen activator inhibitor type-1 (PAI-1). We have previously reported that tumor necrosis factor-alpha (TNF-α), known to be increased in association with human obesity and insulin resistance, stimulates PAI-1 production mediated by reactive oxygen centered radicals. Lovastatin, a hydroxymethyl glutaryl coenzyme A (HMG-CoA) reductase inhibitor can bind free radicals and transitional metal ions and thus may act as an antioxidant.

Methods: To determine whether antioxidant properties of lovastatin reduce adipocyte generation of PAI-1, 3T3-L1 mouse preadipocytes were differentiated into adipocytes and co-incubated with lovastatin (6 μg/ml) for 5 days. The conditioned media were assayed for PAI-1 by Western blotting and for plasminogen activators (PA) activity by zymography.

Result: TNF-α (10 ng/ml) significantly increased adipocyte PAI-1 production (6.2 ± 2.4 fold) (mean ± SE) (n = 6) compared with that in controls (p < 0.01) and decreased PA activity in the media. The effect of TNF-α was completely inhibited by the concomitant presence of hydroxyl radical scavenger, tetramethylthiourea (20 mM) (1.1 ± 0.1 fold) or lovastatin (1.2 ± 0.5 fold). Urea (20 mM), used as control, had no effects. Furthermore, lovastatin reduced basal (without TNF-α) PAI-1 production by adipocytes.

Conclusions: These results suggest that lovastatin inhibits PAI-1 production by adipocytes and may normalize the otherwise diminished fibrinolytic activity in obese subjects. Beneficial effects of lovastatin in ischemic heart disease may be attributable in part to its antioxidant properties and normalization of fibrinolytic system dysfunction.

1197-33 Effect of Troglitazone in Nondiabetic Patients With Coronary Artery Disease

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Background: Insulin resistance is a common finding in patients with coronary artery disease (CAD). Compensatory hyperinsulinemia and associated lipid disorders have been suggested to play an important role in the development of CAD. Troglitazone, a novel insulin sensitizing and antioxidant agent, may improve these metabolic disorders.

Methods: We performed a standard 75 g oral glucose tolerance test before and after the administration of troglitazone 400 mg daily for 4 weeks in 6 nondiabetic CAD patients, all of whom had hyperinsulinemic response to oral glucose load. Lipoprotein lipase (LPL) levels in post heparin plasma and thiobarbituric acid reactive substances (TBARS) as an index of lipid peroxidation were also determined.

Results: After the treatment, the plasma insulin response significantly decreased with the mean incremental area under the curve (AUC) from 162 ± 46 to 93 ± 28 μU·h/mL (p < 0.01). The AUC of the plasma glucose was unchanged. (267 ± 55 to 249 ± 82 mg·h/dL, p = NS). Although troglitazone improved neither elevated plasma triglyceride (228 ± 114 to 172 ± 53 mg/dL, p = NS) nor decreased high density lipoprotein levels (39 ± 9 to 42 ± 9 mg/dL, p = NS) to a significant degree, a rise in LPL levels was observed in all of the patients (167 ± 68 to 199 ± 88 ng/mL, p < 0.05). Additionally, improvement in susceptibility to lipid peroxidation was also observed with mean plasma TBARS level from 3.67 ± 1.07 to 2.62 ± 0.84 nmol/mL (MDA Eq, p < 0.01).

Conclusion: Troglitazone improved the atherogenic lipid profiles as well as the insulin response in patients with CAD and insulin resistance. These data suggest troglitazone may confer clinical benefits in the selected patients.

1197-34 Response of Antibodies to Oxidized LDL in Hypercholesterolemic Patients Treated With HMG-CoA Reductase Inhibitors

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HMG-CoA reductase inhibitors slowed anatomic progression of atherosclerosis and decreased cardiovascular events. Twenty six patients with hypercholesterolemia were treated for one year, 18 with HMG-CoA reductase inhibitors (11 men, mean age = 55 ± 6), 8 with diet (4 men, mean age = 66 ± 9). Lipid concentrations and Ab titers to OxLDL were measured at baseline, 6 months, and 12 months. In patients treated with HMG-CoA reductase inhibitors, LDL cholesterol decreased by 26 ± 8% and 30 ± 12% at 6 months and 12 months, respectively. The Ab to OxLDL rose from baseline value (optical density) of 0.101 ± 0.07 to 0.160 ± 0.07 at 6 months (p = 0.008) and remained elevated at 0.136 ± 0.06 at 12 months (p = 0.048). Patients treated with diet showed similar degree of LDL cholesterol reduction to the other group at 6 months (p = 0.99), and at 12 months (p = 0.74). Autoantibodies to OxLDL, 0.145 ± 0.123 at basline, remained unchanged at 0.091 ± 0.136 (p = 0.454) at 6 months and 0.102 ± 0.079 (p = 0.428) at 12 months. Changes in LDL cholesterol levels from baseline did not correlate with changes in Ab levels in either groups.

Conclusions: Hypercholesterolemic patients treated with HMG-CoA reductase inhibitors revealed a rise in titers of Ab to OxLDL after six months, and titers remained elevated at 12 months. Mechanisms may involve mobilization of OxLDL within the plaque, as well as removal of the OxLDL from the plaque. The rise in Ab to OxLDL may stabilize plaque as well as protect uninvolved segments of the blood vessels, hence, a reduction in cardiovas-