cular events. This is consistent with recent study showing protective effect of immunizing LDL receptor-deficient rabbits with OxLDL.

1197-35 Circulatory Effects of Nicorandil After First Dose and After Repeated Dosing

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Nicorandil (NIC) is a nicotinamide derivative (n-[2 Hydroxyethyl] nicotinamide nitrate), which improves coronary blood flow and is an anti-ischemic agent, but unlike nitrates is claimed not to be associated with development of tolerance during chronic therapy.

In a double blind randomized crossover study in 14 patients with stable angina pectoris, effects of 10 mg NIC or placebo (PL) on cuff blood pressure (BP) and heart rate were evaluated after the first dose and after 2 weeks of bid therapy. Measurements were made before and 1, 4 and 8 hours post dose. Compared to baseline values changes in systolic (S) and diastolic (d) BP and heart rate (HR) in the standing position after the first dose and after 2 weeks of bid therapy were:

	1 Hours		4 Hours		8 Hours	
	NIC	PL	NIC	PL	NIC	PL
(S) BP 1st Dose	-28*	-3	-19*	0	-16*	-4
Day 14	-11	-4	-5	-12	-3	
(D) BP 1st Dose	-13*	-1	-13*	-1	-12	-5
Day 14	-7	-3	-7	-4	-4	-2
(HR) 1st Dose	12	1	3	4	2	3
Day 14	3	-2	-5	4	4	8

* $P < 0.05$ compared to respective placebo (PL).

Data show that first dose of 10 mg NIC exerted significant circulatory effects for at least up to 8 hours but the peak effect and duration of effects were markedly attenuated after repeated dosing. Thus, contrary to prevailing view, this study shows that circulatory tolerance develops following repeated exposure to nicorandil.

1197-36 What Role Does Mannitol Play in Preventing Contrast Nephropathy? a Prospective Analysis

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Recent studies have shown that the use of mannitol may increase renal oxygen demands, and despite causing an osmotic diuresis, may be injurious to renal function after vascular contrast exposure. It's use, therefore, as a prophylactic agent to prevent contrast nephropathy after coronary intervention remains controversial. As part of the PRINCE (Prevention of Radiocontrast Induced Nephropathy Evaluation) Trial, patients who were randomized to a forced diuresis protocol (furosemide 1 mg/kg IVP and dopamine 3 μg/kg/min IV) and had a mean pulmonary capillary wedge pressure <20 mmHg at the start of the procedure, received intravenous mannitol 12.5 g/kg over 2 hours. This administration occurred during the contrast exposure and was followed by hydration with 0.5 NS IV at a rate to match the urine output. As dictated by the protocol, those who were selected for mannitol had a lower mean PCWP, 14.4 vs. 26.1 mmHg, p = 0.0009. The mean baseline serum creatinine (Cr) was 2.2 ± 0.38 vs. 2.59 ± 0.94 in the mannitol-exposed (group 1, n = 22) vs. the mannitol-unexposed (group 2, n = 76), p = 0.05. Groups 1 and 2 were otherwise similar with respect to confounders including diabetic status and contrast volume received. The mean induced urine flow rates were 167.62 ± 58.00 vs. 133.20 ± 55.63 ml/min/over 24 hours, p = 0.02, in groups 1 and 2 respectively. The resultant mean Cr at 48 hours after contrast exposure was 2.72 ± 1.19 vs. 3.11 ± 1.21 mg/dl, p = 0.22, and the mean individual increase in Cr was 0.61 ± 0.98 vs. 0.58 ± 0.72 mg/dl, p = 0.88, respectively.

Conclusions: Despite its use in patients with more favorable renal function and hemodynamic profiles, the controlled, prospective IV administration of mannitol was not effective in preventing renal injury despite augmentation of a forced diuresis with other agents.

1197-37 A Randomized Trial of Prevention Measures in Patients at High Risk for Contrast Nephropathy: Initial Results of the PRINCE Study

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Recent studies from series of PTCA and CABG patients indicate that baseline renal dysfunction is an independent predictor of mortality after these procedures. We have previously shown a graded relationship with the degree of renal failure and the probability of in-hospital death in patients undergoing coronary intervention. Earlier studies of singular prevention strategies (ANF, loop diuretics, mannitol) have shown no clear benefit across a spectrum of patients at risk. We set out to test the hypothesis that a forced diuresis after the contrast exposure with a combination of therapies would result in a reduced degree of renal injury in high-risk patients. We randomized 98 patients to forced diuresis with IV crystalloid, furosemide, mannitol (if PCWP <20 mmHg), and low-dose dopamine (n = 43) vs. matching IV placebo (n = 55) in patients with baseline renal dysfunction (Cr = 2.4 ± 0.8 and Cr = 2.5 ± 0.9 mg/dl). The groups were similar with respect to age, weight, diabetic status, LV function, degree of prehydration, contrast volume and ionicity, and extent of peripheral vascular disease. The forced diuresis resulted in higher urine flow rates, 163 ± 54 vs. 123 ± 55 ml/hr, over the 24 hours after contrast exposure (p = 0.001). Those patients in the highest quintile of urine flow had the smallest increase in serum Cr, 0.3 ± 0.5 vs. 0.9 ± 0.9 mg/dl in the lowest quintile of flow, p = 0.08. Two patients in the forced diuresis arm vs. 5 patients in the placebo arm required dialysis with all seven cases having measured flow rates <145 ml/hr in the 24 hours after the procedure.

Conclusions: Forced diuresis with IV crystalloid, furosemide, and mannitol if hemodynamics permit, beginning at the start of angiography or intervention to achieve a urine flow rate of >145 ml/hr in the 24 hours after the procedure, is a protective strategy against post-contrast exposure nephropathy.

1198 Heart Failure: Beta Antagonists

Wednesday, April 1, 1998, Noon–2:00 p.m.
Georgia World Congress Center, West Exhibit Hall Level
Presentation Hour: 1:00 p.m.–2:00 p.m.

1198-38 Carvedilol Inhibits Endothelin-1 Biosynthesis in Cultured Human Coronary Artery Endothelial Cells

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It has been recently reported that CHF patients treated with carvedilol have significantly reduced circulating endothelin-1 (ET-1) levels as compared to placebo-treated patients. The reductions in plasma ET-1 levels corresponded with a significant functional improvement in various parameters used to measure the symptoms and severity of heart failure. However, the mechanism for the decrease in ET-1 was not known. Therefore, the present study was designed to investigate the direct effects of carvedilol on ET-1 biosynthesis in cultured human coronary artery endothelial cells (HCAECs). HCAECs were treated with carvedilol 15 min prior to the addition of serum and ET-1 levels were measured in the conditioned medium 24 hr later. Carvedilol produced a concentration-dependent inhibition of serum-mediated stimulation of ET-1 biosynthesis with an IC_{50} = 1 uM. PreproET-1 mRNA expression was also inhibited by carvedilol treatment. Other β-adrenoceptor antagonists such as propranolol (10 uM) or celiprolol (10 uM) did not effect ET-1 biosynthesis. Furthermore, the antioxidant probucol (10 uM) did not effect ET-1 production. Immuno-histochemical analysis of HCAECs also demonstrated that carvedilol inhibited ET-1 expression. These data indicate that carvedilol directly inhibits the biosynthesis of ET-1 in HCAECs, and this effect may contribute to its vasodilating and antiproliferative actions. Furthermore, these effects may contribute to the ability of carvedilol to improve clinical outcome in CHF patients.

1198-39 Does Carvedilol Inhibit Aortal Smooth Muscle Cell Proliferation?

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Carvedilol [C] is a multiacting antihypertensive drug recently also approved for the treatment of heart failure and combines β- with α_1-blocking and antioxidant activities. It was shown that C protects the vasculature from chronic pathological processes such as ischemia, atherosclerosis and remodelling that is observed in the cardiovascular system after pressure overload and shear stress. To evaluate the antiproliferative activity of C on human aortic vascular smooth muscle cells [SMC], we tested the influence of C and of different agents which contribute to C's activity. SMC were cultured under serum free conditions and either treated for 6 hrs with different concentrations of C, C's metabolite BM 91.0228 [BM] [without β-blocking, but 30-fold