Conclusion: We suggest that coronary artery remodeling is a major contributing factor to angiographic misinterpretation of disease eccentricity that can be determined accurately only by the IVUS.

1217-82 Comparison of the Restenosis Mechanism of Cutting Balloon Angioplasty and Plain Old Balloon Angioplasty: A Serial Intravascular Ultrasound Study

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Background: The Cutting Balloon (CB) is a novel dilation device that longitudinally incises the coronary plaque during balloon dilation. This incision limits the degree of arterial trauma associated with balloon dilation, potentially reducing the late injury response compared with plain old balloon angioplasty (POBA).

Methods: To evaluate the restenosis mechanism of CB in comparison with POBA, We performed intravascular ultrasound (IVUS) in 146 lesions (98 CB and 48 POBA) before and after the procedure and at a mean follow-up of 6 months. There were no significant differences in the patient and lesion characteristics between the two groups. Vessel area (VA), lumen area (LA) and plaque area (PA) were measured.

Results: There were no differences among CB and POBA in pre and post changes in VA, LA and PA.

		CB (n = 98)	POBA (n = 48)	P value
Restenosis	ΔVA	1.4 ± 2.4	1.4 ± 2.3	NS
	ΔPA	1.5 ± 2.3	1.0 ± 2.4	NS
	ΔLA	2.9 ± 1.2	2.4 ± 1.7	NS
Non-restenosis	ΔVA	0.2 ± 2.0	1.2 ± 3.6	NS
	ΔPA	0.4 ± 2.3	1.6 ± 3.2	0.04
	ΔLA	0.2 ± 2.6	0.4 ± 2.2	NS
Binary restenosis (QCA)		27%	38%	NS

(Δ: changes between post and follow-up)

Conclusion: In the restenosis group, there were no differences between CB and POBA. In the non-restenosis group, CB resulted in less plaque increase and plaque increase after POBA caused compensatory enlargement of coronary arteries, which may suggest a smaller degree of arterial trauma by CB.

1218 Newer Agents of Vascular Injury

Wednesday, April 1, 1998, 3:00 p.m.–5:00 p.m.
Georgia World Congress Center, West Exhibit Hall Level
Presentation Hour: 3:00 p.m.–4:00 p.m.

1218-6 Acute Phase Proteins vs Traditional Risk Factors as Markers of Arterial Wall Impairment

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Background: Acute phase proteins (APP), such as C reactive protein (CRP), fibrinogen (FBG) and the 3rd complement component (C3), are associated with the risk of ischemic events, often more closely than traditional risk factors (tRF). In this study the relation of APP and tRF with arterial wall impairment has been assessed.

Methods: In 317 unselected men aged 55–64 years, carotid and femoral arteries were examined at the bifurcation by ultrasonography. For each subject the maximum intima-media thickness (IMT) and the maximum % stenotic area were related to CRP, FBG, C3, C4 and tRF.

Results: IMT correlated with CRP (Spearman's $\rho = 0.21$; P = 0.0004), FBG ($\rho = 0.19$, P = 0.0013) and C3 ($\rho = 0.12$; P = 0.0374). Stronger correlations were found, however, with tRF such as cigarettes/day ($\rho = 0.38$; P < 0.0001) and cholesterol ($\rho = 0.26$; P < 0.0001). Twenty-one subjects had at least one arterial stenosis ≥ 50%; compared with the rest of the sample, they had higher levels (mg/dl) of C3 (80.6 ± 12.5 (1 SD) vs 73.8 ± 11.3; P = 0.0274), C4 (33.8 ± 8.5 vs 29.7 ± 7.2; P = 0.0380), CRP (0.38 ± 0.33 vs 0.29 ± 0.41; P = 0.0669) and FBG (277.6 ± 67.6 vs 252.6 ± 60.8; P = 0.0784). In multiple logistic regression, of these 4 APP only C3 was independently associated with a stenotic area ≥ 50% (P = 0.0165) but, after addition of tRF, only triglycerides (P = 0.0008), systolic blood pressure (P = 0.0111) and cigarette smoking (P = 0.0164) remained in the model, and all APP were excluded.

Conclusions: The quantitative relation of arterial wall impairment with APP is weaker than the one with tRF. Thus, this relation does not account for the closer association of APP with the risk of acute ischemic events.

1218-7 Hyperhomocystcinemia Is an Independent Risk Factor for Carotid Atherosclerosis

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Recent studies suggest a relationship between vascular occlusive disease and hyperhomocysteinemia, which may damage cells lining blood vessels and favor atherosclerosis. This study evaluated if patients with carotid atherosclerosis (CAS) had higher blood levels of homocysteine. CAS was defined as intimal media thickness of ≥2 mm on the far wall at carotid bifurcation or at internal carotid measured by B-mode ultrasonography. Total homocysteine levels (tHcy, μmol/L) were determined by HPLC with fluorescent detector. The study studied 191 consecutive patients (48% males, mean age 58 ± 14 years, 50% dyslipidemia, 41% hypertension, 28% smokers, 14% coronary artery disease, 10% diabetes). Patients with CAS (n = 91), when compared to patients without CAS (controls, n = 100), had older age (64 ± 10 vs. 52 ± 10 yrs, p < 0.001), male gender (61% vs. 36%, p < 0.01) and hypertension (57% vs. 27%, p < 0.001). Dyslipidemia, smoke, diabetes, body mass index, serum creatinine, folic acid and vitamin B12 were similar in the two groups. In contrast, tHcy levels were significantly higher in patients with CAS (11.7 ± 6.5 μmol/l, 95% confidence intervals (95% CI) 10.3–13.0) than in controls (8.1 ± 4.4 μmol/l, 95% CI 7.2–8.9; (p < 0.0001). Females had lower they levels than males both in patients with CAS and in controls. tHcy levels were positively correlated with age (p = 0.02) and negatively correlated with folic acid (p < 0.001), but were not correlated with B12 or creatinine. By logistic regression, independent predictors of CAS were male gender (odds ratio (OR) 2.56; 95% CI 1.30–5.40; p < 0.0001), hypertension (OR 2.55; 95% CI 1.26–5.17; p < 0.0001), age (OR per 10 year increments 2.15; 95% CI 1.57–2.94; p < 0.01) and they levels (OR per unit increments 1.10; 95% 1.03–1.19; p < 0.005). In conclusion, hyperhomocysteinemia is an independent risk factor for carotid atherosclerosis. Since hyperhomocysteinemia may be corrected by folic acid and vitamin B12 supplements, homocysteine blood levels should be screened in patients at risk of atherosclerosis and vascular occlusive disease.

1218-8 Increased Soluble Form of Vascular Cell Adhesion Molecule-1 and Intercellular Adhesion Molecule-1 in Intermittent Claudication

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Background: A rapid increase in leukocyte adhesion to endothelium is one of the earliest events in response to inflammation and in the pathogenesis of vascular damage. Vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1) are members of the immunoglubulin gene superfamily that play a major role in the leukocyte adhesion process. We assessed the effect of treadmill exercise on circulating soluble form of VCAM-1 and ICAM-1 in patients with intermittent claudication.

Methods: In 12 claudicants and 8 age-matched control subjects, venous plasma levels of VCAM-1 and ICAM-1 were determined by sensitive ELISA tests at rest, at maximal tolerated exercise and 5, 15 and 30 min after exercise. Patients were selected who did not present any condition known to interfere with adhesion molecule modulation.

Results: In controls, exercise did not affect plasma levels of adhesion molecules. VCAM-1 was 610 ± 42 ng/ml at rest and 592 ± 53 ng/ml at peak exercise. The corresponding values for ICAM-1 were 232 ± 17 and 233 ± 21 ng/ml. Conversely, all claudicants showed increased plasma levels of both VCAM-1 and ICAM-1 at maximal tolerated exercise. VCAM-1 increased from 691 ± 65 to 832 ± 83 ng/ml (p < 0.05). ICAM-1 returned from 249 ± 20 to 275 ± 22 ng/ml (p < 0.01). Thirty minutes after exercise, VCAM-1 and ICAM-1 returned to resting values, being 709 ± 70 and 244 ± 21 ng/ml, respectively. No relationship was found between plasma values of adhesion molecules and treadmill performance.

Conclusion: In patient with intermittent claudication, exercise increase plasma levels of VCAM-1 and ICAM-1. This probably reflects endothelial activation or damage and thus may have potential implications on the pathophysiology of the arterial disease.

1218-9 Inhibition of Arterial Thrombosis: Synergistic Interaction Between Platelet IIb/IIIa Receptor and Tissue Factor

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Background: Recent studies have suggested the importance of platelet IIb/IIIa receptor in arterial thrombosis. Equally the release of tissue factor (TF) and its interaction with factor VII, at sites of vascular injury may promote thrombosis.

We tested whether there is a synergistic interaction between these two mechanisms in promoting thrombosis in a rabbit model of arterial thrombus formation.

Methods: Carotid artery was instrumented with Doppler flow probe and a needle electrode. Partially occlusive thrombus was formed by applying 150 μA of current which damages the endothelium. After development of 50% occlusion of the artery by thrombus, the current was stopped and a murine monoclonal antibody against rabbit TF (AP-1) (0.35 mg/kg) or IIb/IIIa (AZ-1) (0.5 mg/kg) or vehicle (control) was administered. The changes in carotid blood flow were continuously monitored by the Doppler flow probe. Bleeding was assessed by weighing the amount of blood absorbed in a preweighed sponge, placed in a cut wound that was 5 cm long and 0.5 cm deep.

Results: The control rabbits (n = 12) occluded their arteries in 46.2 ± 13.6 min after stopping the current by a fibrin-platelet thrombus. In contrast, AP-1 or AZ-1 prevented carotid artery occlusion for >200 min (n = 12) (p < 0.0001). Lower doses of AP-1 or AZ-1 were ineffective. However, when subthreshold concentrations of AZ-1 or AP-1 were given together thrombus formation was totally blocked. The deep incisional blood loss were not different between the control animals and the treated group receiving both AP-1 and AZ-1.

Conclusion: Data suggest that subthreshold inhibition of two different mechanism of thrombus formation may be superior than an attempt to inhibit a single pathway.

1218-10 Increased Expression of Tumor Necrosis Factor-α in Diabetic Macrovasculopathy

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Background: In common atherosclerosis and especially forms of accelerated vasculopathy, immunoinflamatory mechanisms participate in the disease process, however it is unclear whether this is present in diabetic vasculopathy which also has an accelerated pattern. We hypothesized that diabetic macrovasculopathy, compared to classical atherosclerosis, is related to increased immunoinflammatory features and matrix accumulation.

Methods: Vessel segments obtained, after limb amputation, from diabetic (n = 20) and nondiabetic (n = 16) patients were analyzed histologically to characterize the vascular lesions, and immunohistologically to identify the presence of T cells, accumulation of fibronectin, and expression of tumor necrosis factor (TNF)-α in the lesions.

Results: Similar histological features of advanced atherosclerotic lesions between the two lesion types were seen. By immunohistochemistry, a similar pattern of T cell infiltration and fibronectin accumulation was observed. Nevertheless, increased expression of TNF-α was observed in 13/19 diabetic lesions and only in 2/16 lesions from the nondiabetic group (p < 0.003).

Conclusion: Increased TNF-α expression was observed in diabetic vasculopathy which may be important for the development of this disease process.

1218-11 Haptoglobin Polymorphism and Peripheral Arterial Occlusive Disease

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Background: Haptoglobin (Hp) is a hemoglobin-binding antioxidant plasma protein protecting against the hemoglobin/iron driven oxidation and is characterized by a genetic polymorphism with three functionally different phenotypes: Hp 1-1, Hp 2-1 and Hp 2-2. As the functional differences between Hp types may influence progression of atherosclerosis, we tested the hypothesis whether one of the phenotypes is overrepresented in peripheral arterial occlusive disease (PAOD), which is a high oxidative stress atherosclerotic disorder.

Methods: PAOD patients (n = 121, 87 males, 34 females, age: 60 ± 10 years) and controls (n = 255) were phenotyped by starch gel electrophoresis. PAOD was defined by an ankle/brachial systolic blood pressure index <0.85 at the walking capacity-limiting leg.

Results: In PAOD, Hp 1 allele frequency was significantly (P < 0.01) lower than in controls (0.29 versus 0.40).

Relative Phenotype frequency (n)	PAOD (n = 121)	Controls (n = 255)
Hp 1-1	0.09 (n = 11)	0.16 (n = 41)
Hp 2-1	0.40 (n = 48)	0.48 (n = 122)
Hp 2-2	0.51 (n = 62)	0.36 (n = 92)

The low Hp 1 allele frequency was mainly due to a strong overrepresentation (Table) of the Hp 2-2 phenotype (P < 0.001). The overrepresentation of Hp 2-2 was observed for both males (Hp1 allele freq. 0.31) and females (Hp1 allele freq. 0.23). Control data were in Hardy-Weinberg equilibrium. Systolic and diastolic blood pressure were comparable for the three Hp phenotypes.

Conclusion: Hp 2-2 type is overrepresented among PAOD patients. Our observation may point to a contributing role of haptoglobin polymorphism in the process of atherosclerosis.

1218-12 Effect of Cigarette Smoking on the Elastic Properties of the Human Aorta: A Non-Invasive Study

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Background: Aortic elasticity is a major determinant of LV function and coronary flow. We have previously shown, using invasive methodology, that active smoking acutely deteriorates aortic elastic properties (Circulation 1997; 95: 31–38). In the present study we applied a non-invasive, readily available method for the investigation of the effect of smoking on aortic function.

Methods: Distensibility (Dist) of the ascending aorta was studied in 20 long-term, active smokers (men, age 34 ± 7 yrs) before and 5 min after smoking of one standard cigarette (nicotine: 1.0 mg). Aortic Dist was calculated from the formula: = 2 × pulsatile change in aortic diameter/diastolic aortic diameter × pulse pressure). Aortic diameters were recorded by echocardiography (using a high resolution, 5 MHz transducer) 3 cm above the aortic valve, in the M-mode tracings, guided by the 2-D echocardiogram in the parasternal long axis view. Pressures were obtained by sphygmomanometry.

Results.

	Baseline	Smoking	p value
Systolic Pressure (mmHg)	116.8 ± 6.8	125.7 ± 7	<0.001
Diastolic Pressure (mmHg)	80.3 ± 4.9	87 ± 5.8	<0.001
Pulse pressure (mmHg)	36.4 ± 5.2	37.9 ± 5.9	NS
Systolic Diameter (cm)	3.02 ± 0.3	3.05 ± 0.3	<0.02
Diastolic Diameter (cm)	2.86 ± 0.29	2.94 ± 0.3	<0.001
Aortic Dist (10^{-6} cm^2 dyn^{-1})	2.36 ± 0.58	1.65 ± 0.53	<0.001

Conclusions: Smoking results in an acute reduction of the elastic properties of the aorta. This non-invasive methodology is best suited to large-scale epidemiological studies regarding the effects of smoking on the aortic function (long-term studies, studies after cessation, passive smoking studies, etc).

1218-13 Cardiovascular Effects of Hypercholesterolemia in Normotensive Adults

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Background: Hypercholesterolemia is a well known risk factor for atherosclerosis, a condition associated to reduced arterial compliance. The effects of hypercholesterolemia on cardiac geometry and arterial function were investigated in the absence of arterial hypertension.

Methods: Echocardiograms were performed in 197 normotensive patients (age 52 ± 10; 112 men; 171 white) with hypercholesterolemia (cholesterol >240 mg/100 ml) (HC) and in 183 normotensive controls (age 46 ± 10; 103 men; 123 white) with plasma cholesterol <220 mg/100 ml (N).

Results: HC were older than N (p < 0.01), while body mass index and gender distribution were comparable. Prevalence of non-white race was significantly higher in N than in HC (p < 0.0001). Systolic (129 ± 15 vs 118 ± 12 mmHg), diastolic (77 ± 10 vs 74 ± 8 mmHg) and pulse pressure were higher in HC than in N (always p < 0.001). HC had lower stroke volume/pulse pressure ratio (SV/PP) than N, as both absolute value and percentage of predicted by a prognostically validated multiple regression equation, including age, body weight and heart rate (both p < 0.001), even after controlling for difference in age and race. HC also exhibited higher LV mass (38 ± 9 vs 34 ± 7 $g/m^{2.7}$) and relative diastolic wall thickness (0.38 ± 0.05 vs 0.34 ± 0.06, both p < 0.0001). Differences in LV mass and relative wall thickness were confirmed after controlling for systolic blood pressure, age and race (both p < 0.05).

Conclusion: Thus, hypercholesterolemia in the absence of clear-cut arterial hypertension in adults is independently associated with: 1) reduction in arterial compliance, 2) increased values of LV mass with tendency to concentric LV geometry.