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.