Methods and Results: Porcine arterial SMCs were incubated with ethyl dihydroxybenzoate (EDHB) or dehydroproline (DHP), two mechanistically distinct inhibitors of collagen synthesis. Western blot analysis revealed that both reagents reversibly inhibited secretion of type I collagen, with no effect on SMC viability or fibronectin production. SMCs treated with either inhibitor attached normally to a preformed collagen substrate, but cell spreading was inhibited by 42% (EDHB, $p < 0.05$) and 33% (DHP, $p < 0.05$). Migration velocity, quantified in single cells by digital time-lapse videomicroscopy, was significantly and reversibly reduced by EDHB (6.2 ± 0.9 vs 12.0 ± 1.5 μm/h, $p < 0.01$) and by DHP (6.9 ± 1.0 vs 11.1 ± 1.3 μm/h, $p < 0.01$). Flow cytometry revealed that expression of β1 integrins, through which SMCs interact with collagen, was unaffected by EDHB or DHP. However, both inhibitors prevented normal clustering of β1 integrins, as shown by immunofluorescence microscopy, consistent with the lack of appropriate extracellular matrix ligands for integrin engagement. Moreover, there was impaired recruitment of vinculin into focal adhesion contacts and disassembly of actin stress fibers, as downstream consequences.

Conclusions: The concordant results from two biochemically different inhibitors suggest that de novo production of collagen is required for SMC migration and appears necessary to maintain the transcellular traction system required for locomotion. Inhibition of collagen synthesis may thus be a novel means of controlling SMC migration following vascular injury.

9:30

874-5 Extent and Distribution of Intimal Cell Death in Human Target Lesions: Implications for the Development of Intimal Hyperplasia Found in Restenosis

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Background: Beyond smooth muscle cell proliferation and extracellular matrix secretion, deregulated programmed cell death (apoptosis) may also contribute to restenotic intimal hyperplasia by prolonging the life span of intimal cells with their subsequent accumulation. The objectives of the present study were as follows: (i) to identify cell death, (ii) to distinguish and quantify apoptosis from necrosis, and (iii) to compare restenotic with primary lesions.

Methods: Human atherectomy specimens from 24 primary and 13 restenotic coronary and peripheral lesions were studied by TUNEL test (Tdt mediated dUTP nick end labeling, pretreatment with 3% citric acid; detection of cell death by the presence of fragmented DNA), transmission electron microscopy (TEM) and morphometric analysis.

Results: Intimal hyperplasia was more consistent with restenosis than with primary lesion origin, and was mainly attributed to increased smooth muscle cell density (652 ± 256 *vs.* 215 ± 168 cells/mm^2; $p < 0.001$). As the main finding of the present study, cell-rich restenoses compared to primary hypocellular plaques contained less TUNEL$^+$-cells, indicating nucleus-associated apoptosis (2 ± 2% *vs.* 12 ± 3%; $p < 0.001$). Most importantly, ultrastructural plaque evalua on confirmed these data by a markedly decreased portion of apoptotic cells in restenotic vs. primary lesions (3 ± 5% *vs.* 12 ± 11%; $p < 0.001$). In particular, most of these cells were smooth muscle cells exhibiting distinct morphologic signs of apoptosis, i.e. nuclear alterations, membrane budding, cytoplasmic condensation and loss of adhesion due to cell shrinkage (anoikis phenomenon). Intimal cellularity and density of apoptotic cells showed significant inverse correlation ($r = -0.45$; $p = 0.001$). In contrast, the frequency of accidental cell death (necrosis) did not differ between both lesion types (13 ± 12% *vs.* 12 ± 10%; $p = 0.52$).

Conclusions: Our quantitated data demonstrate that apoptotic cells can be highly reproducibly found in human plaque tissue by nuclear DNA strand breaks (TUNEL) and their distinct ultrastructural features (TEM). Apoptosis and not necrosis is the crucial cell death form to account for the apparent discrepancy seen between both lesion types. The findings of this study suggest that a decrease in apoptosis is significantly implicated into intimal hyperplasia as commonly found in human restenosis post angioplasty.

9:45

874-6 A Requirement for Rac1 in Platelet-derived Growth Factor Stimulated Migration

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Cellular migration is a complex process allowing for the coordinated and directional movement of cells. The intracellular pathway by which directional migration is achieved is incompletely understood. Since cell movement requires the dynamic remodeling of the actin cytoskeleton, we have focused on the role of rac1 in chemotaxis. Previous studies have shown that rac1 belongs to the Rho-A family of small GTP-binding proteins which function to regulate cellular morphology. We have used recombinant adenoviruses to transiently express in fibroblasts either a dominant negative (N17rac1) or a constitutively active (V12rac1) isoform of the small GTP-binding protein rac1. Expression of N17rac1 inhibits random and platelet-derived growth factor (PDGF) stimulated migration of cells. Surprisingly, expression of V12rac1 also inhibited the chemotactic response to PDGF. Since migration in the Boyden Chamber requires adhesion to a filter containing 5 micron pores and subsequent migration, we separately tested the role of N17rac1 on adhesion. We observed no significant effect of dominant negative rac1 expression on cellular adhesion to either plastic or fibronectin-coated surfaces. Furthermore, expression of N17rac1 had no effect on PDGF stimulation of mitogen activated protein kinase (MAPK). Similar to what was observed in fibroblasts, expression of N17rac1 inhibited the PDGF-stimulated migration of primary vascular smooth muscle cells. These results suggest that rac1 activity is required for PDGF-stimulated cell migration in a variety of cell types, and suggest that inhibition of rac-dependent pathways may be useful to control undesirable cellular migration in a variety of disease states.

875 Implantable Defibrillators: Highlighted Abstract Session With Discussion of Current Perspectives

Wednesday, April 1, 1998, 8:30 a.m.–10:00 a.m.
Georgia World Congress Center, Room 261W

8:45

875-2 Automatic Conversion of Atrial and Ventricular Tachyarrhythmias Using a New Dual Chamber Defibrillator

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Introduction: A new dual chamber defibrillator (Medtronic model 7250) was implanted in 77 patients in 14 European centers in a clinical study. The device interpretes the atrial and the ventricular rhythm and delivers pacing or shock therapies in either chamber as appropriate. It measures 55 cc and 93 g and has 2 pace/sense (P/S) ports, 2 or 3 high voltage ports (HV) and an active can. Rhythm analysis uses PP and RR intervals and the sequencing of P and QRS complexes.

Methods: All patients (pts, 80% male) had a history of VT and/or VF; 42% had also suffered episodes of atrial fibrillation (AFib), 15% had atrial flutter (AFlut). Mean ejection fraction was 42% (range 12–86%), mean age was 60 years (range 19–78). Underlying cardiac disease was myocardial infarction or coronary artery disease in 56%, cardiomyopathy in 30%, valvular disease in 10% and none in 4%. In all pts, atrial and ventricular leads (P/S and HV) were implanted, none in the coronary sinus.

Results: Data were collected on 82 episodes of AFib (29 induced), of which 53 were successfully converted. Also, 215 episodes of AFlut were documented (50 induced). In 42 cases, high frequency burst therapy successfully terminated the episode, 116 episodes were converted by antitachy pacing, and in 23 cases a low-energy shock was used to restore sinus rhythm. Four pts received a total of 10 automatic ambulatory shocks for AFib. Dual (ventricular and atrial) tachycardias were simultaneously registered 34 times and correctly treated. All 235 VT (44 induced) and 267 VF (211 induced) were appropriately treated. Only 3 pts received ventricular therapies for inappropriately detected episodes.

Conclusion: The data confirm that the new dual chamber defibrillator is capable of automatically and safely detecting and treating both ventricular and atrial tachyarrhythmias.

9:00

875-3 A Prospective Randomized Comparison of High-Frequency Burst Pacing With Antitachycardia Ramp Pacing for Termination of Induced Atrial Tachycardias

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High-density mapping studies of type I atrial fibrillation (AFib) have suggested the presence of an excitable gap. Recently, local capture during AFib has been shown by atrial pacing. However, the efficacy of high-frequency burst pacing (HFBP) for termination of induced episodes of AFib and atypical atrial flutter (AF) has not been demonstrated. Thus, we examined the clinical efficacy of HFBP and antitachycardia ramp pacing (ARP) for termination of induced episodes of AFib and atypical AF in 15 patients (pts) who received the new Arrhythmia Management System (AMS), the model 7250 (Medtronic