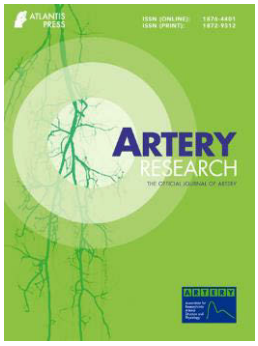

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P1.07: ROSUVASTATIN INCREASES EXTRACELLULAR ADENOSINE IN HUMANS IN VIVO: A NEW PERSPECTIVE ON CARDIOVASCULAR PROTECTION

P. Meijer, W.J.G. Oyen, D. Dekker, P.H.H. van den Broek, C.W. Wouters, O.C. Boerman, G.J. Scheffer, P. Smits, G.A. Rongen

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Results: Brachial BP was similar between atorvastatin and placebo groups. Carotid systolic BP was slightly lower in the atorvastatin group but there was a statistically significant interaction between lipid-lowering and antihypertensive regimen; carotid SBP was lower in people randomized to atorvastatin + amlodipine-based therapy (placebo + atenolol = 130.6±2.4mmHg; atorvastatin + atenolol = 132.1±2.3mmHg; placebo + amlodipine = 131.0±2.8 mmHg; atorvastatin + amlodipine = 122.5±2.3 mmHg; Interaction p = 0.04; comparison placebo + amlodipine vs. atorvastatin + amlodipine p < 0.01).
Conclusions: The combination of atorvastatin with amlodipine-based antihypertensive treatment lowers central BP. This effect may contribute to the reduced incidence of cardiovascular events seen in people receiving this combination in ASCOT-LLA.

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P1.03
DIFFERENCES IN THE LATE SYSTOLIC SHOULDER PRESSURE (SBP2) OF THE RADIAL ARTERY PRESSURE WAVEFORM BY ANTIHYPERENSIVE REGIMEN IN THE ANGLO SCANDINAVIAN CARDIAC OUTCOMES TRIAL (ASCOT)

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Previous work using a transfer function to estimate central systolic blood pressure (SBP) from the pressure waveform in the radial artery reported that, central SBP was lower in the amlodipine-based regimen compared with the atenolol-based regimen in the Anglo Scandinavian Cardiac Outcomes Trial (ASCOT) [1]. However use of a transfer function to estimate central BP has been criticised and more recently Munir et al.,[2] have proposed that the late systolic shoulder ($pSBP_2$) may be a direct estimate of central SBP. We compared $pSBP_2$ between patients randomized to the amlodipine-based and atenolol-based regimens in a substudy of ASCOT.
229 patients participated in the substudy. Applanation tonometry was performed at the right radial artery using a Millar tonometer. Waveforms were ensemble averaged and calibrated to brachial artery pressure. All data are means (SD).
Brachial BP did not differ significantly (137.5 (12.2)/79.6 (7.4) vs. 142.1 (15.3)/80.5 (9.2) mmHg; NS), but $pSBP_2$ was significantly lower in the amlodipine-based regimen (112.4 (10.4) vs. 119.3 (13.1) ; p< 0.01). $pSBP_2$ occurred earlier in the amlodipine-based group (415.8 (53.0)vs. 453.5 (51.6) ms; p < 0.01) probably due to the lower heart rate in the atenolol-based regimen.
Lower $pSBP_2$ in people randomized to the amlodipine-based regimen in ASCOT are in keeping with previous findings using a transfer function applied to the radial pressure waveform and direct measurements in the carotid artery and suggest that $pSBP_2$ may be a useful indicator of central SBP.
1. Williams et al., Circulation 2006; 113:1213-25
2. Munir et al., Hypertension. 2008;51:112-8.

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P1.04
THE INFLUENCE OF QUINAPRIL ON ARTERIAL STIFFNESS, BLOOD VISCOSITY AND ARTERIAL SHEAR STRESS IN PATIENTS WITH ESSENTIAL ARTERIAL HYPERTENSION

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Aim: to analyze the influence of quinapril on aortic PWV, whole blood viscosity (WBV), shear stress in the ascending aorta (AA) and common carotid artery (CCA), prometaloproteinase-1 (proMMP-1) and its tissue inhibitor (TIMP-1) plasma concentration in patients with essential arterial hypertension (HT).
Methods: 55 patients, (mean age 55,8 ± 13,8 yrs.) with HT 1 and 2 gr. were treated with quinapril in stepwise increased doses from 10 to 40 mg/d till BP goal <140/90 mmHg was achieved. At baseline and then after 3 and 6 months of treatment PWV, WBV, proMMP-1 and TIMP-1 were determined. Shear stress in AA and CCA was calculated from WBV, internal vessel diameter and blood flow velocity (Vmax) measured ultrasonographycally.
Results: After 6 months of treatment by quinapril we observed decrease of BP (155.6/92.0 mmHg vs. 135.9/82.9 mmHg, p<0.001), PWV (10.35 m/s vs. 9.64 ms, p<0.001), WBV (5.14 cP vs. 4.86 cP, p<0.05) and TIMP-1 (111.0 ng/ml vs. 94.1 ng/ml, p<0.001) and increase of Vmax in AA (127.1 cm/s vs.131.3 cm/s, p<0.05, Vmax in CCA (69.9cm/s vs. 78.4 cm/s, p<0.05) and shear stress in CCA (22.2 dyne/cm^2 vs. 24.7 dyne/cm^2 , p<0.05). Significant positive correlation was observed for PWV and TIMP-1, and negative correlations for PWV and Vmax in AA, PWV and Vmax in CCA, as well as PWV and shear stress in CCA.
Conclusions: Quinapril reduces arterial stiffness by inhibition of collagen metabolism. This effect is mediated by influence on arterial shear stress.

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P1.05
INFLUENCE OF FELODIPIN ON BLOOD PRESSURE AND ARTERIAL PROPERTIES IN OLDER HYPERTENSIVE PATIENTS

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Pulse wave velocity (PWV) and endothelial function are prognostic factors in arterial hypertension. Modification of them, apart from blood pressure (BP) lowering seems to be important in the evaluation of antihypertensive drugs. The AIM of this study was to prove otherwise while assessing the direct effect of felodipin (Felodip, Teva) on arterial properties in patients (more then 55 years old) with mild, moderate and severe hypertension.
Materials and methods: 30 hypertensive patients (mean age 63,98±6,46 years, 22 male, 8 female) received felodipin in individual titrated doses 2,5-10mg (mean dose 7,96 mg) daily for 3 months. The examination comprised routine tests, ECG, blood glucose, total cholesterol, triglycerides. The assessment of arterial stiffness was done by way of measuring brachial-ankle pulse wave velocity (baPWV). Endothelial function was calculated based on flow-mediated dilatation (FMD) parameters.
Results: The treatment produced a significant reduction in systolic (-30.4mmHg) and diastolic BP (-15.2mmHg). Significant decrease of baPWV (by 7.0%) and increase of FMD (by 21.5%) was observed. There was an insignificant rise in the levels of cholesterol, triglycerides, glucose. Felodipin has been well tolerated in most patients.
Conclusion: These results demonstrate that felodipin increases arterial distensibility. This effect of felodipin should be attributed to BP lowering and endothelial function improvement.

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P1.06
THE EFFECT OF SPINAL ANESTHESIA ON BLOOD PRESSURE AND AUGMENTATION INDEX

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Objectives: Parameters characterizing arterial stiffness - augmentation index (AIx) and pulse wave velocity (PWV) - are autonomous and independent cardiovascular risk factors. In this study we examined if the spinal anesthesia has considerable effects on the peripheral and central blood pressure, augmentation pressure, AIx and PWV.
Methods: The measurements were carried out using SphygmoCor (AtCor Medical, Australia) device. Spinal anesthesia was performed in all patients because of surgery, due to varicosity of lower extremity. Spinal anesthesia was performed uniformly by 3.2 milliliters of bupivacaine (0.5 %) via the L3 interstice. One liter of crystalloid infusion was administrated before the procedure. Patients were examined before anesthesia, and after enrollment of sensory analgesia and motor block.
Results: 29 patients (10 males and 19 females, aged: 53.7±12.9 years) were included in the study. As a result of spinal anesthesia not only the systolic (143.4±20.4 vs. 119.5±16.4 mmHg, p<0,0001) and diastolic peripheral (83.2±11.3 vs. 68.3±10.7 mmHg, p <0.0001), but also the systolic 132.6±18.3 vs. 105.2±14.8 mmHg, p<0.0001) diastolic (85.8±12.1 vs. 69.3±11.2, p<0.0001) central BP, mean pressure (105.8±13.9 vs. 84.7±13.1, p< 0.0001) and pulse pressure (60.2±13.9 vs. 51.2±10.8, p<0.02) decreased. We also observed a significant difference in the augmentation pressure (14.6±7.9 vs. 6.1±3.8 mmHg, p<0.001), and AIxHR75 (26.8±6.9 vs. 15.1±10.9%, p<0.001), respectively. There were no significant difference in PWV (9.3±3.7 vs. 9.1±3.4 m/s, p=0.8).
Conclusion: As a result of spinal anesthesia and so regional sympathetic nervous block not only the peripheral and central BP, but also the AIx decreased significantly, while PWV remained unchanged.

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P1.07
ROSUVASTATIN INCREASES EXTRACELLULAR ADENOSINE IN HUMANS IN VIVO: A NEW PERSPECTIVE ON CARDIOVASCULAR PROTECTION

P. Meijer, W.J.G. Oyen, D. Dekker, P.H.H. van den Broek, C.W. Wouters, O.C. Boerman, G.J. Scheffer, P. Smits, G.A. Rongen.
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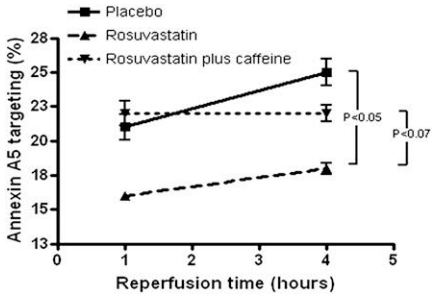
Background: Increased extracellular adenosine formation provides a cholesterol-independent explanation for the therapeutic benefit of statins. This theory was tested in humans in-vivo using dipyridamole-induced vasodilation as a read out for local adenosine formation. Its relevance was explored using a foream model of ischemia-reperfusion injury.
Methods: Twenty-one healthy volunteers were randomly allocated to receive either rosuvastatin (20 mg/day for eight days) or placebo in a double-blind parallel design. The vasodilator response to the nucleoside transport inhibitor dipyridamole was determined in the absence and presence of the adenosine antagonist caffeine. In two additional studies, healthy volunteers were randomly divided in four groups to receive either placebo (n=10), rosuvastatin (20 mg/day for 7 days; n=22), or rosuvastatin combined with intravenous caffeine (4 mg/kg, single dose; n=12). Subsequently, volunteers performed ischemic exercise of the non-dominant forearm. At reperfusion, Tc-99m-labeled annexin A5 was infused intravenously and scintigraphic images were acquired using a gamma camera, providing an early marker of injury.
Results: Rosuvastatin treatment significantly increased the vasodilator response to dipyridamole. This effect was completely abolished by caffeine. Rosuvastatin increased tolerance to ischemia-reperfusion injury, an effect which was attenuated by adenosine receptor blockade.
Conclusion: Rosuvastatin increases extracellular adenosine formation and protects against ischemia-reperfusion injury in humans in-vivo. Our observations prove the concept that statins and dipyridamole interact synergistically whereas caffeine consumption hinders the therapeutic action of statins.



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P1.08
EFFECTS OF ANTIOXIDANTS ON SERUM URIC ACID AS A MARKER OF VASCULAR FUNCTION

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Introduction: Serum uric acid is linked to vascular nitric oxide activity and therefore can blunt endothelium-dependent vasodilation. Antioxidants may increase nitric oxide activity and endothelial function and this might result in decreased uric acid levels.
Aim: The objective was to investigate if supplementation with antioxidants has a beneficial effect on uric acid.
Method: 74 borderline hypertensive Caucasian men participated (aged 45-65 years) in a randomized double-blind, cross-over intervention trial receiving either an antioxidant cocktail (vitamin C, E and folic acid) or placebo. Cardiovascular parameters were recorded with the Finometer. The Complior SP was used to measure the carotid-radialis PWV.
Results: Folic acid (as an indicator of compliance to antioxidant intake) increased significantly with 30% (P=0.005) with no changes in the placebo group. Uric acid was lower after the antioxidant intervention (changed from 0.53 mmol/L to 0.49 mmol/L (p=0.007), with no change in the placebo group. No significant differences were found between the pre and post intervention values for blood pressure, total peripheral resistance and PWV for both interventions . Significant correlations were found between uric acid and total cholesterol (placebo r=0.54: P< 0.001; antioxidant r=0.25: P=0.04).
Conclusion: With antioxidant intervention the lowered uric acid level point to a improvement in vascular function and oxidative stress. The weaker correlation between uric acid and cholesterol also points to improved vascular function since uric acid is strongly linked to cholesterol in vascular disease.

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P1.09
THE EFFECTS OF RIMONABANT-INDUCED WEIGHT LOSS ON ARTERIAL FUNCTION AND GLYCAEMIA IN OBESE ADULTS WITH TYPE 2 DIABETES

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Premature large artery stiffening is a major contributor to the development of cardiovascular disease in type 2 diabetes. Intentional weight loss through lifestyle intervention is associated with a reduction in arterial stiffness. Rimonabant is a cannabinoid-1 receptor blocker that reduces body weight and improves the cardiovascular risk profile in obese subjects. The purpose of this study was to examine the effects of rimonabant therapy on arterial function in obese subjects with type 2 diabetes.
Twenty-nine obese subjects (age range 30-72yrs) (13 male, 16 females) with type 2 diabetes (13 insulin-treated) were studied. Twenty subjects were studied before, during and after 6 months therapy with rimonabant in conjunction with dietary and lifestyle advice. Nine subjects received dietary and lifestyle advice only without rimonabant. Arterial function was assessed by measuring aortic and brachial pulse wave velocity (PWV) and augmentation index (Sphygmocor).
After 6 months, Rimonabant therapy led to significant weight loss (mean weight loss 5±4Kg, p<0.0001), improved glycaemia (HbA1c reduction 0.6±1.1%, p<0.05) and lipid profile (HDL cholesterol increase of 0.1±0.1mmol/L, p<0.01). Aortic systolic pressure was lowered by 5±9mmHg (p<0.05) but there were no changes to peripheral blood pressure, augmentation index or aortic PWV.
In conclusion, rimonabant therapy in association with dietary and lifestyle change leads to significant weight loss and improved glycaemic control in obese adults with type 2 diabetes. However, these clinical benefits do not appear to be accompanied by a reduction in arterial stiffness or wave reflection.

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P1.10
CIMT MEASUREMENT IS MORE RELIABLE THAN WEIGHT REDUCTION IN OVERWEIGHT YOUNG ADULTS TO ASSESS LIFESTYLE IMPACT

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The Insulin Resistance Syndrome is characterized by decreased tissue sensitivity to the action of insulin, obesity and a thick Carotid Intima Media Thickness (CIMT). Homeostasis Model Assessment (HOMA) remains an excellent to assess the level of insulin resistance. We studied the impact of a healthy lifestyle modification in young overweight BMI >27 and non-overweight adults BMI <22 m/kg2. The intervention consisted of a 16 weeks dietary consultation, exercise and a personalized vascular image.
Results:

overweight	BMI>27	(n=18)	normal weight	BMI <22 (n=10)
age	8-12 years		8-12 years	
HOMA glucose x Insulin/22.5	4.6	2.4	1.9	1.8
glucose mg/dl	92	88	78	77
insulin µU/ml	21	17	9.7	9.5
CIMT µ	539	530	522	520
Cholesterol mg/dl	160	162	148	143
HDL-C mg/dl	38	41	57	59
BP mmHg	130/76	126/72	110/68	108/70

Discussion: Both groups lost some weight and showed an improvement in different parameters. The relative change in CIMT was significantly more in the obese group A positive correlation between HOMA and CIMT was observed, (r= 0.717, p< 0.02). in the overweight cases increasing significantly (r=0.832, p<0.01) (delta change p<0.05).