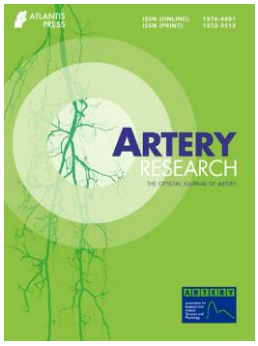

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4.4: ARTERIAL PHENOTYPE MODULATION AND REGULATION OF VASCULAR FIBROSIS IN MICE BY CONDITIONAL INACTIVATION OF INTEGRIN AV SUBUNIT IN VASCULAR SMOOTH MUSCLE CELLS

Ekaterina Belozertseva, Huguette Louis, Zhenlin Li, Mustapha Bourhim, Dominique Dumas, Veronique Regnault, Patrick Lacolley

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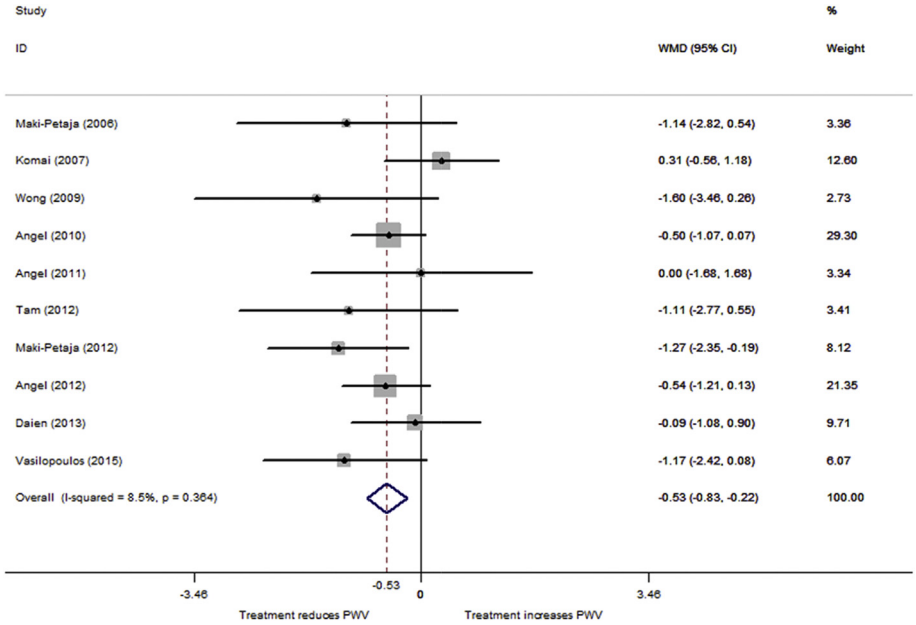

Conclusions: The balance of evidence suggests that TNF-antagonists may have a beneficial effect on arterial stiffness in RA patients. Given the predictive role of aortic stiffness for adverse cardiovascular outcomes, TNF-antagonists might confer reduction of the cardiovascular risk of these patients beyond their anti-inflammatory effect. However, larger longitudinal studies are warranted to confirm recent findings.

4.2
WITHDRAWAL OF STATINS THERAPY IN PATIENTS AFTER CAROTID ENDARTERECTOMY ASSOCIATED WITH INCREASING RISK OF SIGNIFICANT RESTENOSIS

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Background: The benefit of carotid revascularization is decreased by the occurrence of restenosis at the site of surgery, which is associated with a modestly increased risk of stroke. Preventing restenosis plays pivotal role in the overall treatment and prevention of stroke in patients with carotid artery disease.
Purpose: To evaluate influence of discontinuing of statins therapy on occurrence of restenosis in patients after carotid endarterectomy.
Methods: We studied 240 patients after carotid endarterectomy, mean age — 64.4±6.8 years. All the patients were divided into two groups: 1 group comprised 124 patients, who had taken atorvastatin in dose 10-40 mg daily and 2 group — 116 patients who discontinued statins therapy due complication 3 %, poor tolerance 9% or personal reluctance 88%. All the patients also underwent serial standardized ultrasound examination on 1, 3, 6, 12 month during first year after operation and then annually. Mean observation time was 5.6±2.1 years. Significant restenosis carotid artery (more than 70%) was established by standard Doppler velocity criteria.
Results: The significant restenosis of internal carotid artery was found in 2,4% patients with statins therapy and in 7,8% patients without statins. Statins withdrawal increased the incidence of late significant restenosis of internal carotid artery (odd ratio: 3.393 95% confidence interval: 0.895—12.857). Patients with withdrawal of statins had higher wall thickness: 4.3±0.8 against 2.9±0.9 (#1088 p<0,05).
Conclusion: Withdrawal of statins therapy in patients after carotid endarterectomy associated with increasing risk of significant restenosis carotid artery.

4.3
ELECTRONIC CIGARETTE SMOKING INCREASES AORTIC STIFFNESS IN YOUNG SMOKERS

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Purpose/Background/Objectives: Smoking increases aortic stiffness which is an important predictor of cardiovascular risk. Electronic cigarettes (EC) simulate tobacco cigarette (TC) and have been advocated as a less harmful alternative. We investigated the acute effect of EC smoking on aortic stiffness compared to the effect of TC smoking.
Methods: We studied 24 healthy smokers (mean age 30±8 years, 13 females), who were free of risk factors X from smoking. Each participant visited our unit on four separate occasions (96 in total) and smoked: a) TC over 5 minutes b) EC over 5 minutes c) EC for a period of 30 minutes. During the sham procedure, participants did not smoke anything. Carotid-femoral pulse wave velocity (PWV) was used to assess aortic stiffness.
Results: Both TC and EC smoking increased systolic and diastolic BP, and the differences in changes of BP responses between the two smoking forms were not significant. Compared to TC, EC5 min smoking resulted in a less potent PWV increase throughout the study (F=4.425, P=0.005). On the other hand, EC30min resulted in a PWV increase similar to that of TC smoking throughout the study period (F=0.268, P=0.615). EC30 min smoking resulted in a more potent effect on PWV compared to EC5 min smoking (F=3.167, P=0.030).
Conclusions: EC over 30 minutes induces an unfavorable effect on aortic stiffness similar to TC smoking. The influence of EC smoking over 5 minutes on aortic stiffness is not as prompt and is less potent compared to the effect of TC smoking.

4.4
ARTERIAL PHENOTYPE MODULATION AND REGULATION OF VASCULAR FIBROSIS IN MICE BY CONDITIONAL INACTIVATION OF INTEGRIN AV SUBUNIT IN VASCULAR SMOOTH MUSCLE CELLS

Mrs Ekaterina Belozertseva [1], Dr Huguette Louis [1], Dr Zhenlin Li [2], Dr Mustapha Bourhim [1], Dr Dominique Dumas [3], Dr Veronique Regnault [1], Dr Patrick Lacolley [1]
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Integrin α_v functions as a receptor for adhesion proteins and is expressed at high density in vascular smooth muscle cells (VSMC)[1,2,3,4,5] whose phenotypic modulation plays a crucial role in arterial ageing and atherosclerosis[6,7].

Our aim was to define the arterial phenotype in mice conditionally inactivated for the integrin α_v subunit in VSMC[8,9,10](α_v ^{SMKO}) and its role in angiotensin II (AngII)-induced arterial fibrosis. Transgenic mice α_v ^{SMKO} and their control littermates (WT) were treated with two doses of AngII, low (0.3 mg/kg/day) and high (1.5 mg/kg/day), for 4 weeks.
At baseline, blood pressure was lower in α_v^{SMKO} compared to WT mice. Carotid distensibility was increased in α_v ^{SMKO} mice (13.3±0.7 vs 10.3±0.6 $mmHg^{-1}\cdot10^{-3}$). With low dose AngII isobaric distensibility remained higher in α_v^{SMKO}mice (12.4±1.2 vs 10.7±1.0 $mmHg^{-1}\cdot10^{-3}$).With high dose AngII the increase in collagen content in carotid media was lower in α_v^{SMKO}than in WT (19 vs 35%) for a similar increase in blood pressure (30 mmHg) and arterial wall hypertrophy. Collagen immunostaining and fluorescence measurements (multiphoton microscopy second harmonic generation) confirmed that high dose AngII induced lower increases in collagen content in α_v^{SMKO} mice versus WT (8.9±1.7 vs 14.2±1.4 greyscale mean/pixel). The combination of similar arterial wall hypertrophy with less fibrosis in mutant mice explains an increased distensibility in response to AngII.
The α_v subunit regulates AngII-induced arterial fibrosis as determined by collagen staining, immunostaining and fluorescence. Pharmacological targeting of vascular α_v integrin may have clinical applications in the treatment of patients with fibrosis associated with hypertension and atherosclerosis.

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4.5

U-SHAPED RELATIONSHIP OF RESERVOIR PRESSURE TO CARDIOVASCULAR EVENTS IN PATIENTS WITH HEART FAILURE WITH REDUCED EJECTION FRACTION

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Objectives: Parameters of aortic stiffness are considered important indicators of cardiovascular risk. However, in heart failure with reduced ejection fraction (HFrEF), their association to outcome was found to be inversed. The aim of this work was to analyze the relationship of the amplitude of reservoir pressure (PresAmp) to cardiovascular events in HFrEF.
Methods: Patients with HFrEF were collected from a cohort undergoing coronary angiography at the hospital Wels-Grieskirchen, Austria. PresAmp was computed from central pressure obtained from radial readings by a generalized transfer function. A combination of myocardial infarction, death, stroke and cardiovascular revascularization served as primary endpoint. Cox-regression analysis and Kaplan-Meier estimates were used for survival analysis.
Results: 83 (9 female) patients were included with a mean age of 61 years. During a median follow-up of 1272 days, 30 patients suffered from the combined endpoint. No significant linear association to outcome was found for PresAmp, brachial or central pulse pressure in Cox-analysis. In all three cases, Kaplan-Meier analysis comparing the respective quartiles indicated a nonlinear, U-shaped relation, but only for PresAmp the increase in risk was significant ($P<0.05$) in both directions. Although patients with low (16.6 (2.8 SD) mmHg) and high (26.1 (3.2 SD) mmHg) PresAmp showed similar risk, they differed in blood pressure, age, presence of hypertension, presence of coronary artery disease, ventricular dimensions, ejection fraction and diastolic function (table).
Conclusion: We found a U-shaped relation of reservoir pressure to outcome in our population. Pulsatile hemodynamics seem to separate patients with HFrEF into different phenotypes with different prognosis.

Table: Comparison of patients with low (1st quartile) and high (4th quartile) PresAmp. PP, pulse pressure. EF, ejection fraction. LVEDV, left ventricular end-diastolic volume. LVESV, left ventricular end-systolic volume. Values are presented as mean (standard deviation).

Parameter	1st quartile PresAmp	4th quartile PresAmp	P-value
N patients	21 (19m/2f)	21 (19m/2f)	
Age, years	57.1 (9.68 SD)	69.4 (9.24 SD)	<0.001
Hypertension	6 (29 %)	19 (90 %)	<0.001
Coronary artery disease	8 (38 %)	14 (67 %)	0.06
Brachial PP, mmHg	31.0 (6.87 SD)	63.0 (8.32 SD)	<0.001
Central PP, mmHg	20.4 (4.08 SD)	48.6 (9.33 SD)	<0.001
E/E'medial	30.8 (15.8 SD)	19.3 (10.0 SD)	0.008
EF, %	22.5 (7.33 SD)	31.6 (7.49 SD)	<0.001
LVEDV, ml	253 (91.3 SD)	162 (64.5 SD)	<0.001
LVESV, ml	199 (75.8 SD)	112 (50.8 SD)	<0.001

4.6

BEAT-BY-BEAT ASSESSMENT OF CARDIAC AFTERLOAD USING AORTIC PU LOOP — A PILOT STUDY

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Purpose/Background/Objectives: Cardiac afterload evaluation is crucial during general anesthesia (GA) especially during hypotension episode. Using beat to beat aortic pressure (P) / flow velocity (U) loop constructed from routine signals recorded during GA might allow to track afterload changes.
Methods: We defined 3 angles characterizing the PU loop (alpha, beta and Global After-Load Angle (GALA) angles). Augmentation index (AIx) and total arterial compliance (Ctot) were also measured via radial tonometry and transfer function. Twenty patients were recruited and classified into low and high cardiovascular (CV) risk group. Vasopressors were administered, when baseline mean arterial pressure (MAP) fell by 20%.
Results: We studied 118 pairs of pre/post bolus measurements. At baseline, patients in the lower CV risk group had higher cardiac output (6.1±1.7 vs