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Jahrestagung der Österreichischen Gesellschaft für Internistische Angiologie (ÖGIA)

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Abstracts

(in alphabetischer Reihenfolge nach Erstautor)

Low-density Lipoprotein Receptor-Related Protein 1B impairs Cellular Proliferation in Human Cell Lines

A.G. Beer, C. Zenzmaier, P. Marschang
Department of Internal Medicine III – Cardiology, Angiology, Innsbruck Medical University

Introduction Low-density lipoprotein (LDL) receptor-related protein 1B (LRP1B) is one of three very large receptors (4599 amino acids) of the LDL receptor family, several members of which have been implicated in the pathogenesis of atherosclerosis. The unusually large LRP1B gene was discovered during studies of lung cancer cell lines, where alterations of the receptor were frequently found and LRP1B was therefore postulated as a putative tumor suppressor. Since the receptor has also been described in smooth muscle cells of the arterial wall, it may be involved in the pathogenesis of atherosclerotic lesions.

Methods Expression of LRP1B was analyzed by qRT-PCR using primers specific for human LRP1B or mouse *Lrp1b* as well as by Western blotting with a specific polyclonal antibody. For introduction of the receptor into LRP1B-negative cells, a mammalian expression vector containing the full-length 13.800 bp murine *Lrp1b* cDNA was constructed. In cells with high endogenous LRP1B expression, the receptor was downregulated using specific siRNA (Dharmacon). Cellular proliferation was analyzed using a BrdU-incorporation ELISA and adhesion-independent growth using a soft agar colony formation assay, respectively.

Results Using qRT-PCR, different cell lines with detectable or absent endogenous LRP1B expression were identified. Transfection of the vector containing the full length *Lrp1b* cDNA resulted in efficient receptor expression as demonstrated by qRT-PCR and appearance of a 600 kDa band in Western blotting. Expression of *Lrp1b* in cells lacking endogenous LRP1B significantly reduced both cellular proliferation and anchorage-independent growth compared to empty vector-transfected control cells. Conversely, in cells with endogenous LRP1B expression, LRP1B knockdown with siRNA significantly enhanced cellular proliferation.

Conclusions These findings demonstrate that, consistent with the postulated tumor suppressor function, overexpression of full length *Lrp1b* leads to impaired cellular proliferation, while LRP1B knockdown has the opposite effect. These data and further experiments may help in unraveling the largely unknown physiological role of LRP1B and its potential functions in cancer and atherosclerosis.

Impact of Age and Body mass index on Skin Temperature in Raynaud's Phenomenon

G.-A. Giurgea, W. Mlekusch, S. Charwat-Resl, M. Mueller, A. Hammer, M. E. Gschwandtner, R. Koppensteiner, O. Schlager
Division of Angiology, Department of Medicine II, Medical University of Vienna

Background Previous studies suggested that sympathetic nerve-dependent vascular tone regulation could be affected by age and body weight. Whether age and the body mass index (BMI) are associated with skin temperature and skin perfusion in patients with Raynaud's phenomenon (RP) is not known. This study aimed to assess the relation of age and BMI to skin perfusion and skin temperature in patients with RP and in controls.

Methods In patients with RP and controls skin temperature und skin perfusion of the non-dominant hand were measured by infrared thermography and laser Doppler imaging. After resting measurements patients underwent cold provocation by exposure to 20° tempered water. Temperature and perfusion measurements were repeated after cold exposure.

Results Before cold exposure age was related to skin temperature ($r = 0.683$; $p < 0.0001$) and skin perfusion ($r = 0.595$; $p = 0.002$) in patients with RP. Further, the patients' BMI was related to skin temperature ($r = 0.657$; $p < 0.0001$) and skin perfusion ($r = 0.653$; $p < 0.0001$) in patients with RP. In controls, no correlation was found between baseline skin temperature/perfusion and age/BMI. In patients with RP cold provocation led to a –7% (median, IQR –13.1; –4.1) change in skin temperature and to a –26.4% (–36.2; 2.9) change in skin perfusion, while in controls cold exposure resulted in a –15.7% (–18.3; –11.6) change in skin temperature and a –26.4% (–36.2; 2.9) change in skin perfusion. The cold-induced changes in skin temperature and perfusion were inversely related to age ($r = –0.518$; $p = 0.003$) and BMI ($r = –0.662$; $p < 0.0001$) in patients with RP.

Conclusion Age and BMI are related to skin temperature and skin perfusion in patients with RP. In contrast to controls age and BMI are inversely related to cold-induced changes of skin temperature and skin perfusion in RP patients.

Auswirkung multifaktorieller Intervention auf die Prognose von Patienten mit peripherer arterieller Verschlusskrankheit und Glukosetoleranzstörungen

C. Höbaus[1], R. Koppensteiner[1], G. Schernthaner[2], G.-H. Schernthaner[1]
[1]Abteilung Innere Medizin II – Angiologie, Medizinische Universität Wien;
[2]Abteilung Innere Medizin I, Krankenanstalt Rudolfstiftung

Einleitung Die Kombination aus peripherer arterieller Verschlusskrankheit (PAVK) und Diabetes mellitus Typ 2 (DMII) führt zu einem verminderten Überleben. In der Literatur wird eine 50-%-Mortalität und eine 25-%-Amputationsrate nach 6 Jahren Beobachtungszeit beschrieben. In dieser Studie analysierten wir, ob rezente Verbesserungen in der Behandlung dieser Patienten dieses Risiko vermindern kann.

Material und Methoden In einer prospektiven Studie wurden 366 Patienten (34 % Frauen) mit PAVK und folgenden Glukosetoleranzstörungen eingeschlossen: 29 % normale Glukosetoleranz (NGT), 33 % gestörte Glukosetoleranz (PRE) sowie 38 % DMII. Diese Kohorte zeigte ein hohes kardiovaskuläres Risiko (KVR): 92 % arterielle Hypertonie, 97 % Hyperlipidämie, 74 % aktive oder ehemalige Raucher. Zusätzlich war bei 32 % eine koronare Herzerkrankung und bei 39 % eine arterielle Gefäßerkrankung der Karotiden (CAVK) bekannt. Die Zielwerte zur Reduktion des KVR konnten innerhalb der ersten 6 Studienmonate bei 58 % LDL-Cholesterin < 100 mg/dl, bei 69 % Blutdruck < 140/80 mmHg und bei 69 % HbA1c bei T2DM < 7,0 % erreicht werden.

Ergebnisse Das gesamte Überleben der Kohorte betrug nach 4,9 Jahren 89,3 %. Das MACE- (Kombination aus Tod, nicht-tödlichem Herzinfarkt und Schlaganfall) freie Überleben lag bei 84,3 %. Das ereignisfreie Überleben, inklusive interventioneller und chirurgischer Eingriffe wegen PAVK, lag bei 68 %. Patienten mit DMII zeigten ein Überleben von 87,8 % verglichen mit 89,3 % PRE und 95,2 % NGT

(p = 0,161). Das MACE-freie Überleben betrug 81,3 % für DM II, 87,6 % für PRE und 92,4 % für NGT (p = 0,059). Das ereignisfreie Überleben lag bei 85,5 % für DMII, 71,9 % für PRE und 77,1 % für NGT (p = 0,155)

Diskussion Ein multifaktorielles Management dieser Patienten führt zu einer dramatischen Reduktion der jährlichen Todesrate (2,8 für Patienten mit PAVK und DMII), MACE und PAVK-Ereignissen. Eine zentrumsbasierte Therapie dieser Patienten könnte daher einen Überlebensvorteil für diese spezielle Patientengruppe darstellen.

Successful Ultrasound-assisted Catheter-directed Thrombolysis followed by Secondary Prophylaxis with Rivaroxaban in a Patient with acute Intermediate-risk Pulmonary Embolism – a Case Report

P. Marschang, R. Kirchmair, W.-M. Franz
Department of Internal Medicine III – Cardiology, Angiology, Innsbruck Medical University

Background Intermediate risk pulmonary embolism, which is characterized by echocardiographic and laboratory signs of right heart dysfunction without haemodynamic compromise, carries a significant risk of short-term mortality (3–15% within the first 3 months). Recently, a randomized trial comparing ultrasound-assisted catheter-directed thrombolysis with conventional anticoagulation in patients with intermediate risk pulmonary embolism has provided evidence for the efficacy and safety of this treatment [1].

Case description A 76 year old female patient was admitted to our department with extensive pulmonary emboli with involvement of the right main pulmonary artery as assessed by computed tomography. Ultrasound showed proximal thrombosis of the right great saphenous vein and the patient was initially treated with low molecular weight heparin. Echocardiography revealed right ventricular enlargement (right-to-left-ventricular- [RV/LV-] ratio 1.08) and laboratory analyses showed elevated levels of troponin T (27.5 mg/ml) and NT-proBNP (8352 ng/l). Therapy was switched to unfractionated heparin and ultrasound-assisted catheter-directed thrombolysis (EKOS) with 20 mg rtPA for 18 hours was performed successfully. Periprocedural bleeding with transient hematemesis and a groin hematoma requiring the transfusion of two units of packed red cells were observed. With the exception of a transient rise in creatinine in the following days, no other adverse reactions were encountered. Re-evaluation after 5 days showed striking regression of pulmonary thrombi as well as normalization of the RV/LV-ratio (0.62). Subsequently, anticoagulation therapy with rivaroxaban (2 × 15 mg p. o. for 3 weeks, followed by 1 × 20 mg p. o.) was initiated. Follow-up after 3 months showed no signs of right ventricular dysfunction or incipient pulmonary hypertension by echocardiography and nearly complete normalisation of laboratory parameters.

Discussion The optimal management of intermediate risk pulmonary embolism is still controversial. Here we report successful ultrasound assisted catheter-derived thrombolysis in a 76 year old female patient with submassive pulmonary embolism. Compared to systemic thrombolysis, this method requires only 20% of the usual dose of the thrombolytic compound, thereby reducing the bleeding risk of the patients. With the initiation of rivaroxaban therapy shortly after the procedure, we observed a favourable outcome during hospitalization and three months of follow-up.

Reference:

1. Kucher N, Boekstegers P, Müller OJ, et al. Randomized, controlled trial of ultrasound-assisted catheter-directed thrombolysis for acute intermediate-risk pulmonary embolism. Circulation 2014; 129: 479–86.

Vascular Strain in Predefined Arterial Segments in Healthy Adults: a Pilot Study

O. Schlager, S. Charwat-Resl, A. Willfort-Ehringer, R. Koppensteiner
Division of Angiology, Department of Medicine II, Medical University of Vienna

Background Vascular strain can be analysed non-invasively by duplex ultrasound (DUS) using speckle tracking. In peripheral arteries vascular strain potentially mirrors vascular elasticity. Vascular strain analysis could therefore serve as a screening tool for early atherosclerosis. The aim of this pilot study was to determine vascular strain at various parts of the arterial tree and to assess its reproducibility.

Methods The abdominal aorta, the common carotid arteries (CCA), the common femoral arteries (CFA) and the popliteal arteries were investigated in healthy subjects using DUS. Cross-sectional DUS clips of the respective arteries were obtained on 3 consecutive days, 3 times each day. Vascular strain was determined offline and the inter-/intraday reproducibility as well as the components of variance of vascular strain were calculated.

Results A total of 589 DUS clips were obtained in 10 healthy subjects (7 males, mean age 28.3 ± 3.2 years). Vascular strain was highest in the abdominal aorta (7.2 ± 3.0%). Lower vascular strain was found in the CCA (5.7 ± 2.1%), in the CFA (2.1 ± 1.1%) and in the popliteal artery (1.9 ± 1.1%). The intraday coefficients of variation of vascular strain were 6.2% (abdominal aorta), 3.9% (CCA), 3.3% (CFA) and 6.1% (popliteal artery), and the interday coefficients of variation were 5.9% (abdominal aorta), 8.4% (CCA), 10% (CFA) and 4.6% (popliteal artery), respectively. The variance component analysis showed that the variance of vascular strain mainly depended on the investigated vessel and subject, while individual clips of one vessel, the day of examination and the body side (right/left) hardly had any impact on the variance of vascular strain. The variance components were similarly distributed in the abdominal aorta, CCA, CFA and popliteal artery.

Conclusion Vascular strain can reliably be determined at various arterial sites with an acceptable reproducibility. Between different segments of the arterial tree, we found substantial differences of vascular strain with highest values in the abdominal aorta.

Lipocalin 2 – a Novel Factor in Limb Ischemia

M. Theurl[1], A. Schroll[2], D. Lener[1], I. Theurl[2], W.-M. Franz[1], G. Weiss[2], R. Kirchmair[1]
[1]Department of Cardiology and Angiology; [2]Department of Infectious Diseases, Medical University Innsbruck

Introduction Lipocalin 2 (Lcn-2) is a 25-kDA secreted acute phase protein, which is produced by immune cells, renal tubule cells and a variety of epithelial cancer cells. Recent data suggest that Lcn-2 is up-regulated in acute ischemic kidney injury and promotes tumor progression by induction of angiogenesis. Thus, we hypothesized this protein might be a therapeutic target for the treatment of peripheral arterial disease (PAD).

Methods and Results To test our hypothesis the unilateral mouse hind limb ischemia (HLI) model was conducted. Briefly, limb ischemia was induced by ligation of the femoral artery and blood flow was measured weekly by laser Doppler perfusion imaging. Interestingly, in this animal model knockout of Lcn-2 resulted in an impressive phenotype. Compared to background mice (C57BL/6 = wild type = WT) the Lcn-$2^{-/-}$ mice showed significantly more tissue defects after ligation of the femoral artery. Moreover, the ischemia-associated lesions were more severe as determined by necrosis score (necrosis score Lcn-2 1.8 ± 0.16 vs WT 0.67 ± 0.19; n = 5; p < 0.01) and amputation rate was higher among the Lcn-$2^{-/-}$ mice. The decreased expression of mitogen activated protein kinase (MAPK) in ischemic hind limbs of Lcn-$2^{-/-}$ mice might be responsible for the poor outcome in this animal model. Transplantation of WT-bone marrow to irradiated Lcn-$2^{-/-}$ mice had no influence on the outcome of the animals suggesting that observed effects depend more on the endothelium than on inflammatory cells.

To clarify possible effects of Lcn-2 on endothelial cells (EC), in-vitro experiments were performed. Indeed, Lcn-2 induced EC-proliferation as determined by BrdU incorporation (rel. proliferation Lcn-2 10 nM vs. control: 1.4 ± 0.09; n = 3; p < 0.001) and mechanistically these results can be traced back to the induction of the MAPK signaling pathway and phosphorylation of eNOS. Intriguingly, Lcn-2 associated MAPK-activation was blocked by a neutralizing VEGF-antibody suggesting an involvement of this prominent angiogenic factor in Lcn2-induced effects. Real-time PCR analyses showed expression of Lcn-2 and the Lcn-2-receptor by EC as well as a hypoxia dependent up-regulation (rel. Lcn-2 mRNA hypoxia vs normoxia 1.6 ± 0.2; p < 0.05; rel. Lcn-2-receptor mRNA hypoxia vs. normoxia 2.62 ±

0.22; $p < 0.001$) being a hint for a physiological relevance of this peptide in limb ischemia.

Conclusion Lcn-2 seems to be an interesting therapeutic target for the treatment of PAD.

The Neuropeptide Catestatin for the Treatment of Myocardial Ischemia

M. Theurl, D. Lener, A. Beer, W.-M. Franz, R. Kirchmair
Department of Cardiology and Angiology, Medical University Innsbruck

Introduction Myocardial infarction (MI) induces irreversible tissue damage, eventually leading to heart failure. Exogenous induction of angiogenesis is recognized to positively influence ventricular remodeling after a MI. Recently, we could show that therapy with the neuropeptide catestatin (CST) restores perfusion in the hind limb ischemia model by the induction of angiogenesis, arteriogenesis and vasculogenesis. Thus, we assumed that CST might exert beneficial effects in experimental MI.

Methods/Results To test the effect of CST on cardiac angiogenesis in-vitro matrigel assays with human coronary artery endothelial cells (HCAEC) were performed. CST significantly mediated capillary like tube formation comparable to basic fibroblast growth factor (bFGF), which was used as positive control (rel. tube formation vs. ctr.: CST 1 nM 2.69 ± 0.2; $n = 3$; $p < 0.001$). Interestingly, blockade of bFGF either by a bFGF-antibody (Ab) or a specific receptor blocker (PD173074) resulted in abrogation of observed effect suggesting a bFGF-dependent mechanism.

Moreover, CST induced proliferation of HCAEC and human coronary artery smooth muscle cells (HCASMC) as determined by BrdU-incorporation. Similar to the matrigel assay blockade of bFGF attenuated the effect (HCAEC: rel. proliferation vs ctr.: CST 1 nM 1.5 ± 0.1; $p < 0.001$; CST+bFGF-Ab 1.1 ± 0.1; $p < 0.01$ vs CST; CST+PD173074 0.7 ± 0.1; $p < 0.001$ vs CST; HCASMC: rel. proliferation vs ctr.: CST 1 nM 1.8 ± 0.03; $p < 0.01$; CST+bFGF-Ab 1.2 ± 0.1; $p < 0.001$; CST+PD173074 0.9 ± 0.1; $p < 0.001$; $n = 3$). Consistent with these findings Western blot assays revealed bFGF-dependent phosphorylation of extracellular-signal regulated kinase 1/2.

To evaluate the effect of CST on cardiomyocyte apoptosis in cardiac ischemia the ischemia/reperfusion model was performed (1 hour ischemia, 24 hours reperfusion). After reversible ligation of the left anterior descending artery an intra-myocardial injection of CST or saline 0.9% (control) was performed. In this model CST-treatment was associated with a significant reduction of cardiomyocyte apoptosis (apoptotic cardiomyocytes/HPF: CST 9.16 ± 0.95 vs ctr. 19.36 ± 1.74; $n = 8$/group; $p < 0.01$).

Conclusion CST represents a promising candidate for the treatment of myocardial ischemia.

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