P5.1: PROTEOMIC ANALYSIS ON HUMAN ARTERIAL TISSUE: RELATIONS TO ARTERIAL STIFFNESS

M. Hansen, H. Beck, A. Imukhamedov, P. Jensen, L. Rasmussen

To cite this article: M. Hansen, H. Beck, A. Imukhamedov, P. Jensen, L. Rasmussen (2014) P5.1: PROTEOMIC ANALYSIS ON HUMAN ARTERIAL TISSUE: RELATIONS TO ARTERIAL STIFFNESS, Artery Research 8:4, 142–143, DOI: https://doi.org/10.1016/j.artres.2014.09.138

To link to this article: https://doi.org/10.1016/j.artres.2014.09.138

Published online: 7 December 2019
In the population-based Maastricht Study, we evaluated the associations between carotid stiffness (cPWV) and ΔPWV, and glucose metabolism status (GMS). Additionally, we investigated the interdependency of cPWV and ΔPWV with GMS to find out whether remodeling may act differentially upon cPWV and ΔPWV.

Methods: The study consisted of 594 individuals (312 normal glucose metabolism [NGM], 98 impaired glucose metabolism [IGM] and 184 T2D). cPWV and ΔPWV were determined by ultrasonography and tonometry. Regression analyses were used to investigate the associations of cPWV and ΔPWV with GMS (NGM as reference). Models were adjusted for age, sex, mean arterial pressure (MAP), and central pulse pressure, cPWV or ΔPWV as appropriate, and additionally for: anti-hypertensive medication, prior cardiovascular disease, estimated glomerular filtration rate, or body mass index.

Results: After adjustment for age, sex and MAP, T2D was associated with greater cPWV (β (95% CI): 0.284 (0.012-0.556)) and ΔPWV (0.299 (-0.005-0.603)). Further adjustments did not change these associations. After additional adjustment for cPWV or ΔPWV the associations with ΔPWV and cPWV attenuated (0.209 (-0.083-0.502) and 0.208 (-0.053-0.470), respectively). IGM was not associated with either cPWV or ΔPWV.

Conclusions: In T2D both cPWV and ΔPWV are increased. The associations were only partially interdependent, which suggests that remodeling impacts on both stiffness and its pressure-dependency.

P4.12
AGE, WAIST CIRCUMFERENCE AND BLOOD PRESSURE ARE ASSOCIATED WITH SKIN MICROVASCULAR FLUSMOTION: THE MAASTRICHT STUDY
MUMC/M-CARIM, Maastricht, The Netherlands

Introduction: Skin microvascular flowmotion (SMF) plays an important role in optimal delivery of nutrients/oxygen to tissue and in maintaining normal peripheral resistance. It is unclear however, which determinants influence SMF. Therefore, we investigated which cardiovascular risk factors are associated with SMF.

Methods: We measured SMF in 506 participants without a prior cardiovascular event. SMF was investigated using Fourier transform analysis of skin laser Doppler flowmetry. The associations of the cardiovascular determinants age, sex, waist circumference, 24-h systolic blood pressure (SBP), total-to-HDL cholesterol, fasting plasma glucose (FPG), and cigarette smoking with SMF were analyzed by use of multiple linear regression analysis.

Results: The mean age of the study population (n = 506) was 58.8 ± 8.5 years, 260 (51.4%) were men, mean waist circumference was 95.7 ± 13.0 cm, mean 24-h SBP was 119 ± 12 mmHg, and 73 (14.4%) were smokers. After adjustment for cardiovascular risk factors and medication, per 1SD higher age SMF was 0.17 SD (95SC: 0.08; 0.26; P < 0.001) higher; per 1SD higher waist circumference SMF was -0.12 SD (-0.23; -0.01; P = 0.03) lower; per 1SD higher 24-h SBP SMF was 0.17 SD (0.07; 0.27; P < 0.001) higher. No other associations with SMF were found.

Conclusions: Age and blood pressure were directly, while waist circumference was inversely associated with SMF. The exact mechanisms underlying these findings remain elusive. The present data support the hypothesis that microvascular dysfunction, specifically, impaired SMF, plays a role in the development of obesity-related insulin resistance and hypertension.

P4.13
TYPE 2 DIABETES IS ASSOCIATED WITH ALTERED CAROTID ARTERY MECHANICS INDEPENDENTLY OF AGE AND MEAN ARTERIAL PRESSURE—THE MAASTRICHT STUDY
Maastricht University Medical Centre, Cardiovascular Research Institute Maastricht (CARIM), Maastricht, The Netherlands

Introduction: Type 2 diabetes (T2D) is characterised by accelerated vascular ageing, which changes arterial wall structure and hence artery mechanics (e.g., pressure-area (P-A)). Pulse wave velocity (PWV) is affected by both blood pressure and changes in wall mechanics. To investigate changes in wall mechanics in T2D, we aimed to disentangle the vascular ageing phenomena (characterised by PWV) from pressure effects.

Methods: We studied young (<55y) and older (>70y) individuals without and with T2D matched at the group level for age, sex and MAP (n = 29 each) from the Maastricht Study. Non-linear P-A curves were derived from carotid tonometry and echo-tracking, using Langewouters-model fits. Isobaric PWV (Bramwell-Hill) was determined at MAP.

Results: In individuals without T2D, the average P-A curve in older, as compared to younger individuals, was shifted rightward (diastolic area (Ad), mean ±SD: 48.8 ± 10.3 vs. 42.5 ± 8.3mm², P = 0.003), which led to higher PWV (9.9 ± 2.0 vs. 7.4 ± 1.6m/s, P = 0.001). Next, in younger individuals with T2D, as compared to those without, a similar pattern was found (Ad: 45.7 ± 9.6 vs. 42.5 ± 8.3mm², P = 0.068 and PWV: 8.2 ± 1.6 vs. 7.4 ± 1.6m/s, P = 0.027). Finally, in older individuals with T2D, as compared to those without, the P-A curve was again shifted rightward (Ad: 51.3 ± 10.4 vs. 48.8 ± 10.3mm², P = 0.034), but PWV was not significantly different (10.1 ± 1.7 vs. 9.9 ± 2.0mm/s, P = 0.29).

Conclusion: Independently of blood pressure, both ageing and T2D have a dilatory effect on carotid arteries, with ageing also clearly demonstrating stiffening. Although T2D is associated with additional stiffening in individuals younger than 55y, this was not observed in individuals older than 70y.

P5.1
PROTEOMIC ANALYSIS ON HUMAN ARTERIAL TISSUE: RELATIONS TO ARTERIAL STIFFNESS
M. Hansen, H. Beck, A. Imukhamedov, P. Jensen, L. Rasmussen
Odense University Hospital, Odense, Denmark

We hypothesized that arterial stiffness is associated with changes in the arterial protein profile, particularly in relation to extracellular matrix (ECM) components, and aimed at determining differentially expressed proteins in human arterial tissue by quantitative proteome analysis in patients with different degrees of arterial stiffness. Arterial stiffness, assessed by carotid-femoral pulse wave velocity (PWV), central blood pressure and augmentation index by pulse wave analysis, as well as carotid intima-media thickness were measured the day prior to surgery in a group of patients undergoing coronary artery bypass grafting. Protein extracts of well-defined, homogenous, non-atherosclerotic individual samples of the left mammary artery from 10 of these patients with high PWV and 9 with low PWV, were compared by quantitative proteome analysis, using iTRAQ-labeling and nano-LC-MS/MS. Of 504 quantified proteins, 28 were differentially expressed between groups with high and low PWV (P < 0.05). Six out of eight members of the extracellular matrix family of small leucine-rich repeats were upregulated. In T2D, no significant differences between the two groups (P > 0.001, Fisher’s Exact Test). Only one other of 43 identified ECM proteins were differentially regulated (collagen alpha-1(VIII)). Several proteins related to smooth muscle cell function and structure were found in different amounts between the two groups.
Changes in the arterial amounts of small proteoglycans, known to be involved in collagen fibrillogenesis, are associated with arterial stiffness. In addition, several proteins related to function of the human arterial smooth muscle are changed as well.

P5.2 QUANTITATIVE PROTEOMICS REVEAL INCREASED CONTENT OF BASEMENT MEMBRANE PROTEINS IN ARTERIES FROM PATIENTS WITH TYPE 2 DIABETES, BUT REDUCED AMOUNTS AMONG METFORMIN USERS

S. Prell 1, L. Kristensen 2, H. Beck 1, P. Jensen 3, T. Steinecke 1, M. Bjørling-Poulсен 4, M. Larsen 5, M. Hansen 6, L. Rasmussen 7
1Odense University Hospital, Odense, Denmark
2University Hospital of Aarhus, Aarhus, Denmark
3University of Southern Denmark, Odense, Denmark

We hypothesized that metformin intake influence the molecular composition of arterial tissue from patients with type 2 diabetes. We analyzed non-atherosclerotic, internal mammary arteries, gathered at coronary by-pass operations from 30 patients with type 2 diabetes (16 treated with metformin, 14 without), as well as from 30 age- and gender-matched non-diabetic individuals. Quantitative proteome analysis was done by iTRAQ-labeling and LC-MS/MS analysis on individual trypsinized extracts of formalin fixed, paraffin embedded tissue. Sections were also analyzed by histology and immunohistochemistry.

We were able to quantitate 129 proteins. The amounts of the basement membrane (BM) component, alpha-1-type IV collagen were increased in patients with diabetes (0.96 +/- 0.05 (non-DM, n=30) vs 1.35 +/- 0.09 (T2DM, n=30), t-test: p = 0.00015, Benjamini-Hochberg correction: p = 0.02), as was other BM-components, i.e. laminins and nidogen. The expression of type IV collagen, laminin and other altered proteins were significantly lower among metformin users, compared to patients not treated with metformin (alpha-1-type IV collagen: 1.63 +/- 0.1 (no metformin treatment, n=14) vs 1.17 +/- 0.10 (metformin treated, n=16) (arb.units)), p = 0.013). Patients treated with or without metformin had similar levels of HbA1c, cholesterol and blood pressure. Accumulation of basement membrane proteins as part of the arteriopathy of type 2 diabetes link the diabetic macro- and micro-angiopathy and provides a molecular substrate for altered functions of the arteries in diabetes, as for example dysfunctional remodeling. Reduced amounts of basement membrane components in metformin treated individuals, despite similar glycemic control, are compatible with the hypothesis that metformin influence the vasculature.

P5.3 INFLUENCE OF DIABETES MELLITUS ON ARTERIAL STIFFNESS PARAMETERS, RESPECTIVELY ON CENTRAL SYSTOLIC BLOOD PRESSURE - A MATTER OF SEX?

A. Sitar-Taut, A. Cozma, M. Cebanu, D. Zdrenghea, D. Pop
"Iuliu Hatieganu" University of Medicine and Pharmacy, Cluj-Napoca, Romania

Diabetes represents an important cardiovascular risk factor, arterial stiffness being responsible, partially at least, for cardiovascular disease initiation. Objective to evaluate the arterial stiffness changes in diabetic patients, identifying differences between two sexes. Design and method The study included 285 patients, (67% women), with a mean age of 59.27 +/- 11.05 years. 69 (42 women) patients (24.2%) were diabetics. All patients underwent biochemical and arterial determinations. Arterial parameters (brachial augmentation index -Aixb-, aortic augmentation index -Aixo-, pulse wave velocity -PWVao-, central systolic blood pressure -SBPAo, aortic pulse pressure-PAPAo-) were determined using the TensioMedArteriograph. Results: 74% of patients were hypertensive, 24.2% diabetics, 40% obese, 16.8% smokers, 68.1% with dyslipidemia, 70.9% with metabolic syndrome, 37.8% with cardiovascular diseases. A significant correlation (p = 0.05) was found between brachial augmentation index and age (r = 0.375), weight (r = 0.427), abdominal circumference (r = -0.286), systolic blood pressure (r = 0.359), HDL-cholesterol (r = 0.352). In addition aortic augmentation index correlated with diastolic blood pressure (r = 0.173). Pulse wave velocity significantly correlated with age (r = 0.266), systolic blood pressure (r = 0.376), diastolic blood pressure (r = 0.168), triglycerides (r = 0.192). A relationship was found between SBPAo and age (r = 0.155), systolic blood pressure (r = 0.423), diastolic blood pressure (r = 0.390), glyceria (r = 0.155). All arterial stiffness parameters correlated with SBPAo (for Aixo a = 0.405, for Aixb r = 0.291, for PWVao r = 0.214). Conclusion: Despite the fact that all parameters quantify aortic and brachial stiffness, they seem to be different influence by anthropometric and biochemical parameters. This paper was published under the frame of European Social Found, Human Resources Development Operational Programme 2007-2013, project no. POSDRU/159/1.5/S/138776

P5.4 IDENTIFICATION OF FACTORS THAT INFLUENCE AORTIC AND BRACHIAL STIFFNESS

A. Cozma, A. Sitar-Taut, O. Orasan, A. Fodor, D. Zdrenghea, D. Pop
"Iuliu Hatieganu" University of Medicine and Pharmacy, Cluj-Napoca, Romania

Knowing the predictive value of arterial stiffness for cardiovascular events, it is mandatory to identify the factors responsible for the increase in arterial stiffness.

Objective: Identification of factors that influence arterial stiffness, i.e. brachial and aortic augmentation index (AixAo), pulse wave velocity (PWVao), respectively central systolic blood pressure (SBPAo).

Design and method: The study included 285 patients with a mean age of 59.27 +/- 11.05 years. All patients underwent anthropometric measurements, biochemical and arterial determinations. Arterial parameters were determined using the TensioMedArteriograph.

Results: 74% of patients were hypertensive, 24.2% diabetics, 40% obese, 16.8% smokers, 68.1% with dyslipidemia, 70.9% with metabolic syndrome, 37.8% with cardiovascular diseases. A significant correlation (p = 0.05) was found between brachial augmentation index and age (r = 0.375), weight (r = 0.427), abdominal circumference (r = -0.286), systolic blood pressure (r = 0.359), HDL-cholesterol (r = 0.352). In addition aortic augmentation index correlated with diastolic blood pressure (r = 0.173). Pulse wave velocity significantly correlated with age (r = 0.266), systolic blood pressure (r = 0.376), diastolic blood pressure (r = 0.168), triglycerides (r = 0.192). A relationship was found between SBPAo and age (r = 0.155), systolic blood pressure (r = 0.423), diastolic blood pressure (r = 0.390), glycemia (r = 0.155). All arterial stiffness parameters correlated with SBPAo (for Aixo a = 0.405, for Aixb r = 0.291, for PWVao r = 0.214).

Conclusion: Despite the fact that all parameters quantify aortic and brachial stiffness, they seem to be different influence by anthropometric and biochemical parameters. This paper was published under the frame of European Social Found, Human Resources Development Operational Programme 2007-2013, project no. POSDRU/159/1.5/S/138776

P5.5 IN VIVO ASSESSMENT OF REGULATORY MECHANISM OF THE SYSTEMIC ARTERIAL AND VENOUS SYSTEM FOR THE PREVENTION OF ORTHOSTATIC INTOLERANCE

C. Leguy a, b, A. Blamber, J. Rittweger a, L. Beck a
aGerman Aerospace Center, Cologne, Germany
bSimon Fraser University, Vancouver/BC, Canada

To reduce the risk of post-flight orthostatic intolerance for astronauts, a better understanding of the response of the cardiovascular system to changes in hydrostatic pressure is essential. The objective of this study is to assess the regulatory mechanisms of the arterial and venous system in response to acute changes in hydrostatic pressure. The experimental protocol applied to twelve volunteers consisted of: 3x3min 70-degree head-up tilt (HUT) and 3x3min 45-mmHg Lower Body Negative Pressure (LBNP). Blood Pressure, 4-segment electrical impedance (thorax, splanchnic, upper leg, and lower leg-Zleg) and Femoral artery blood flow (FABF) was assessed. FABF responses were characterized by a half-time decay constant, τ, of 6.10 +/- 0.34a and a volume increase of 27.2 +/- 3.4 mL. Zleg after tilting and LBNP onset decreases faster with HUT (τ = 6.9 +/- 0.75a LBNP and 2.7 +/- 0.75 HUT, p < 0.001), whereas upon tilting-back and removal of LBNP no differences were obtained (τ = 3.3 +/- 0.75a LBNP and 2.1 +/- 0.75 HUT).

We can assume that the extra FABF volume and dynamics is mainly related to a vasocostriction sympathetic reaction independent of the stress conditions. The faster decrease in Zleg for HUT indicates a faster fluid shift in the lower leg than with LBNP, whereas the similar time course upon tilt-back and removal of LBNP may mainly be related to the compliance of the tissues in the lower limb, and thus independent of the stress conditions. With this study, we have shown that LBNP onset induces a delayed blood fluid shift compared to HUT whereas fluid emptying on removal coincided with lower limb tissue properties.