P1.13: CHANGES IN PULSE WAVE VELOCITY ALONE CANNOT PREDICT THE PULSE PRESSURE INCREASE WITH AGE

Berend Westerhof*, Thomas Weber, Siegfried Wassertheurer, Bernhard Hametner, Nico Westerhof


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Abstracts

days) using osmotic minipumps. Blood pressure was recorded using tail cuff measurement and telemetry carotid implants. Vascular reactivity was assessed in isolated aortic segment, and thrombin generation was measured using calibrated automated thrombography.

Results: ATII induces an upregulation of tissue factor, thrombin-dependent endothelial cell VCAM-1 expression and integrin αv-6 and platelet-dependent leukocyte adhesion to arterial conductance vessels. The resulting vascular dysfunction unexpectedly involved the activation of FXI but not FXII. The platelet FXI receptor glycoprotein Ibα supports the upregulation of thrombin feedback activation in ATII-treated mice. Importantly, pharmacologic inhibition of FXI synthesis is sufficient to prevent thrombin propagation on platelets, to reduce vessel wall leukocyte infiltration, and to diminish ATII-induced endothelial dysfunction and arterial hypertension in mice and rats.

Conclusion: Our results reveal a critical role of platelet GPIbα to promote localized thrombin amplification and a FXI-thrombin feedback loop in ATII-induced vascular inflammation. Targeting FXI could be a novel therapeutic possibility to interrupt this heterotypic cellular coagulation-inflammatory circuit.

P1.10
PULSE PRESSURE IN RELATION TO 24-HOUR URINARY SODIUM EXCRETION IN A SAMPLE OF HIGH-SALT INTAKE POPULATION

Adam Bednarski 1,*, Katarzyna Stolarz-Skrzypek 1, Grzegorz Klebasa 1, Agata Francyz 1, Małgorzata Kloch-Badelek 1, Kalina Kawecka-Jaszcze 1, Danuta Czarnecka 1

1st Department of Cardiology, Interventional Electrocardiology and Hypertension, Jagiellonian University Medical College, Krakow, Poland

Objectives: In recent years, many studies emphasized the role of arterial rigidity in the development of cardiovascular diseases. Pulse pressure in an easy-obtained, reproducible marker of arterial stiffness and an independent cardiovascular risk factor. On the other hand it was observed that sodium restriction could improve large elastic artery compliance. The aim of the study was to investigate the relation between salt intake and pulse pressure in high salt intake population.

Methods: The study group included 303 subjects recruited from the general population of Southern Poland. Ambulatory blood pressure (ABP) monitors (SpaceLabs 90207) were programmed to obtain measurements each 15 min. during the day and each 30 min. nighttime. Based on the ABP data, we calculated pulse pressure (PP) over 24h, daytime and nighttime. Sodium intake was assessed based on 24h urinary sodium excretion. Database management and statistical analysis were performed with SAS software.

Results: The study group included 136 men and 167 women, with 165 hypertensive individuals, 105 of them on antihypertensive treatment, mean age = 47.1 ± 15.7 yrs. While adjusting for age, sex, body mass index, 24h blood pressure, antihypertensive treatment, and lifestyle, we observed positive relation between sodium intake and 24h and daytime PP ({β1:SE}: 0.016 ± 0.006 = 0.0075, daytime PP (β1:SE): 0.011 ± 0.005, p = 0.029) and non-significant trend regarding nighttime PP (β1:SE): 0.009 ± 0.005, p = 0.094).

Conclusion: In our high salt intake population, sodium intake was positively related to calculated pulse pressure over 24h and daytime.

P1.11
SOLUBLE IL-6 RECEPTOR CONCENTRATIONS ARE ASSOCIATED WITH AUGMENTATION INDEX IN HEALTHY YOUNG MALES

Matthew Armstrong 1,*, Cat Singh, Laura Watkeys, Linnet Thekkumuriyil, Jordan Tucker, Zoe Marshall, Richard Webb, Barry McDonnell

Cardiff Metropolitan University, Cardiff, UK

Background: Augmentation Index (Alx) is considered a sensitive marker of arterial stiffness in young individuals. Increased levels of inflammatory markers such as interleukin-6 (IL-6) are associated with increased levels of arterial stiffness in older and diseased populations. However, little is known about these associations in young healthy individuals, as concentrations are prone to fluctuation. Data suggests that increased levels of the soluble IL-6 receptor (sIL-6R), facilitate the detrimental pro-inflammatory signalling of IL-6, which may highlight sIL-6R’s role as a mediator of chronic inflammation and associated disease states. Therefore, the aim of the study was to determine the associations between sIL-6R and IL-6 with Alx in a young healthy cohort.

Methods: In 20 healthy male subjects (age 22±3 years), self-reported physical activity levels (PA) were determined via International Physical Activity Questionnaire. Peripheral and central blood pressure and Alx@75 were measured using the Mobil-O-Graph system (IME). Plasma concentrations of sIL-6R and IL-6 were assessed via enzyme-linked immunosorbent assay (R&D systems).

Results: Alx@75 was significantly associated with levels of sIL-6R (r = 0.5, P = 0.02) but not associated with levels of IL-6 or PA (P>0.05).

Conclusion: These novel pilot data suggest that elevated concentrations of sIL-6R at an early age may be indicative of an underlying vulnerability to inflammation-associated vascular stiffening. Furthermore, the absence of any association between IL-6 and Alx in our study implies that sIL-6R may be a more suitable biomarker than IL-6 for use in understanding the mechanisms by which inflammation affects vascular stiffening. However, larger studies are required to confirm our findings.

P1.12
IN IDIOPATHIC PULMONARY ARTERIAL HYPERTENSION ARTERIAL NARROWING IS LIMITED AND HETEROGENEOUS

Nina Rol 1,*, Esther Timmer, Theo Faes, Harm Jan Bogaard, Anton Vonk Noordegraaf, Katrien Grunberg, Nico Westerhof

VU University Medical Center, Amsterdam, The Netherlands

Rationale: In severe idiopathic pulmonary arterial hypertension, iPAH, pulmonary vascular resistance is increased due to remodeling of the small (resistance) arteries. Most information on arterial remodeling is limited to assessments of averaged increases in wall thickness. Quantitative information on the number of arteries affected and their internal diameter decrease in relation to vessel size is limited. Our objective was therefore to quantify numbers of affected small arteries and their internal diameter decrease for the differently sized vessels.

Methods: Internal and external arterial diameters were measured in 5 controls and 6 iPAH subjects. Resistance arteries (13 to 500 μm) were classified in Strahler orders (1-8), and the number of fraction of affected vessels and their internal diameter decrease calculated.

Results: In iPAH not all resistance arteries are affected, on average about 70% of arteries have diameters not different from the control subjects, with the number of affected arteries varying between 20 and 50%. Within each order the diameters of affected vessels vary greatly and are decreased to 70-20% of control with on average to about 60% of control. We conclude that narrowing of resistance arteries a feature of iPAH and is heterogeneous: not all arteries are narrowed, and internal diameters of narrowed arteries, even within single orders vary largely. Determination of total vessel numbers of arteries and of veins is necessary to gain insight into the possible role of rarefaction and of changes in the venous system.

P1.13
CHANGES IN PULSE WAVE VELOCITY ALONE CANNOT PREDICT THE PULSE PRESSURE INCREASE WITH AGE

Berend Westerhof 1,2,*, Thomas Weber 1, Siegfried Wasserdüfer 1, Bernhard Hametner 4, Nico Westerhof 5

1Edwards Lifesciences, Amsterdam, The Netherlands
2Academic Medical Center, Amsterdam, The Netherlands
3Klinikum Wels-Grieskirchen, Wels, Austria
4Austrian Institute of Technology, Vienna, Austria
5VUmc Medical Center, Amsterdam, The Netherlands

Recently Weber et al. invasively obtained aortic Pulse Wave Velocity (PWV) as a function of age. [1] Systolic and diastolic arterial pressure were determined as well. PWV can be used to derive total arterial compliance, Ctot, as Ctot = k/PWV2. With Ctot and Stroke Volume (SV), aortic Pulse Pressure (PP) can be approximated from Ctot = SV/PP. However, the PWV-derived value for Ctot predicted a larger PP increase with age than measured. [1] PWV increased from 5.6 to 12m/s between <40 and >80 years of age thus aortic compliance (Cao) decreased by a factor (12/5.6) 2 =4.6. [1] Setting Ctot equal to Cao, PP would increase by the same factor, while measured PP increased from 50 to 90 mmHg. SV decreasing with age may play a role but certainly not a factor 2. We hypothesize that Ctot is not equal to Cao as calculated form PWV: compliance of the conduit arteries, Cao, also contribute. This can be seen as follows. In the young Cao = 0.6, Cao = 0.16 and Cao = 0.25 (cgs units). At high age Cao reduces to 0.6/4.6 = 0.076 and Cao to 0.25/1.2 = 0.20, thus Cao = 0.28; about halved. PP then approximately doubles, in agreement with the pressure data. In aging Ctot decreases considerably less than Cao since the relatively smaller changes in Cao play a role as well. Changes in aortic PWV alone cannot predict the PP increase as a function of age.

P1.14
ANALYSIS OF LEFT VENTRICULAR FILLING DYNAMICS
Lindsay Burrowes 1,*, Alessandro Satriano 1, Richard Thompson 2, Nigel Shrive 1, John Tyberg 1
1University of Alberta, Calgary, Alberta, Canada
2University of Calgary, Calgary, Alberta, Canada

Diastolic filling of the left ventricle (LV) occurs in two phases, early and late filling. Early filling, manifest as the “E-wave”, is thought to be substantially due to diastolic suction (DS), a phenomenon where the LV aspirates blood and fills itself, independent of atrial activity. Late filling, resulting in the mitral flow “A-wave” is a result of left atrial contraction. Adequate filling of the LV is necessary to maintain normal heart function at rest and under stress. DS is thought to be an important mechanism in the efficiency of filling.

To study DS, we have invasively measured pressure and used cardiac MRI to evaluate cavity volume and flow in an animal model to quantify different measures of DS under varied experimental conditions.

The amount of filling due to DS (VDS), determined by the change in volume between mitral valve opening and LV pressure minimum of the pressure-volume loop (Katz 1930), is related to the measured end systolic volume (ESV). As ESV decreases the VDS increases. The smaller the ESV, the larger the recoil energy of the LV as it relaxes towards resting volume. This contributes increased energy for the suction of blood into the ventricle in early filling.

Wave intensity analysis (the separation of forward and backwards waves and wave type) and intraventricular pressure gradients will also be considered in order to determine which best describes DS and whether they can be used together to better understand changes in filling dynamics under varied loading conditions.

P1.15
CONDITIONAL INACTIVATION OF INTEGRIN AV SUBUNIT IN VASCULAR SMOOTH MUSCLE CELLS REGULATES FIBROSIS IN VESSELS
Ekaterina Belozertseva 1,*, Melusine Didelot 1, Amel Mohamadi 1, Zheng Li 2, Huguette Louis 2, Jean-Baptiste Michel 2, Véronique Regnault 1, Patrick Lacolley 1
1UMR 5 1116, Vandoeuvre-les-Nancy, France
2UMR 8256, Paris, France
3UMR 5 1148, Paris, France

Integrin avb3 is expressed at high density in vascular smooth muscle cells (VSMCs). It functions as a receptor for adhesion proteins in VSMCs and plays a pivotal role in arteriosclerosis and atherosclerosis. The aim was to study the role of integrin avb3 in angiotensin II (Ang II)-induced arterial fibrosis in mice and in human samples of atherosclerotic arteries in situ. Transgenic mice conditionally inactivated for integrin av subunit in VSMCs (avSMKO) were treated with Ang II (1.5 mg/kg/day) for 4 weeks. Immunostained slices of atherosclerotic plaques at different stages of development and primary cultures of human aortic VSMCs were used. At baseline, blood pressure was lower in avSMKO compared to control (WT) mice. Isobaric carotid distensibility was increased and remained higher in avSMKO in response to Ang II. The increase in collagen content response to Ang II was lower in avSMKO than in WT (15 vs 36%) for similar increase in blood pressure (20 mmHg) and arterial wall hypertrophy. The immunohistochemistry of aortic slices showed stronger staining for integrin avb3 in atherosclerotic plaques compared to healthy aortas. In VSMC cultures, the mRNA of av was decreased.

In conclusion, these results show that avb3 is strongly expressed in neointimal proliferation and in fibrous plaques. The av integrin subunit seems to regulate arterial fibrosis in response to hypertension and plaque growth. Low RNA quantities of av subunit of VSMCs contrasted with strong protein staining in plaques suggesting the participation of inflammatory cells in the synthesis of this integrin.

P1.17
THE VENTRICLE’S PROMINENT ROLE IN PRESSURE AMPLIFICATION: AN INCREMENTAL EXPERIMENTAL STUDY
Nicholas Gaddum 1,*, Jordi Alastruey 1, Tobias Schaeffter 2, Phil Chowienzyk 3
1King’s College London, Division of Imaging Sciences and Biomedical Engineering, St. Thomas’ Hospital, London, UK

Despite central pressure’s predictive power of cardiovascular risk, brachial pressure is the clinical standard. However, amplified brachial systolic pressure varies significantly with age, and during therapy. Our aim was to modulate individual arterial and ventricular parameters in an experimental model of the cardiovascular system, to quantify each parameter’s contribution to arterial pressure and its amplification.

A piston driven ventricle provided computer-controlled flow waveforms into various silicone arterial trees. Silicone tubes diameters (20, 15, 10mm), wall thicknesses (0.5, 0.7, 1.0, 1.5mm), lengths (30-400cm), taper (20mm inlet to 20, 15, 10 and 5mm outlets), were each applied with various ventricular stroke profiles (sawtooth to sinewave). Intravascular pressure-tip wires and ultrasonic flow probes measured pressure and flow. MAP, Flow and HR were maintained between tests for comparison.

Ventricular stroke profile independently augmented pressure amplification from 16% to 82% between sinewave and sawtooth ejections profiles. As expected for any arterial model, the transfer function from central to distal pressure measurement sites remained constant. Decreasing taper, wall thickness, and length, and increasing diameter each increased amplification by shifting the peak of the amplifying transfer function towards the more prominent lower frequencies, (1-3Hz). However, the amplification variation between all vascular parameters was <30%.

Despite the arterial tree dictating how the ventricular pulse will propagate, the ventricle provides the wave packet of frequencies with which to be amplified. These findings correlate well with observations of decreasing amplification with age as the native inevitability decreases, and increasing amplification associated with decreased LV mass during hypertensive drug therapy.

P2.1
AGING AND STRUCTURAL ALTERATIONS OF SUBCUTANEOUS SMALL RESISTANCE ARTERIES IN HYPERTENSIVE PATIENTS
Carolina De Cucles, Claudia Rossini, Claudia Agabiti Rosei, Enzo Porteri, Alice Gavazzi, Stefano Caletti, Paola Pileri, Maria Antonietta Coschignano, Enrico Agabiti Rosei, Damiano Rizzoni
Clinica Medica, Department of Clinical and Experimental Sciences, University of Brescia, Brescia, Italy

Background: It was proposed that early vascular ageing may be an important mechanism of vascular damage in large conductance arteries. However it is not known whether ageing may also affect small resistance artery morphology.

Patients and methods: For this reason, we investigated 100 patients with essential hypertension. Secondary forms of hypertension were excluded according to standard clinical evaluations and biochemical or instrumental assessments. In all patients, an evaluation of small resistance arteries morphology was performed by wire micromyography. A small amount of subcutaneous tissue was obtained by local biopsy or during election surgery and subcutaneous small resistance arteries were dissected and mounted on a myograph; the media to lumen ratio (M/L) was then measured.

Results: The age range of our population was 22-81 years, with a mean value of 57±12 years; 14% of them were current smokers, 32% had alterations in lipid patterns, none of them had diabetes mellitus, 58 were males and average blood pressure values were 156/95 ± 19/12 mmHg. We found a significant correlation between M/L and age (r = 0.30, p = 0.002): the statistical significance of the correlation persisted after correction for confounding variables (gender, serum cholesterol, smoking status, serum glucose, systolic or diastolic blood pressure values). A statistically significant inverse correlation was also observed between internal diameter and age (r = -0.20, p = 0.046).

Conclusion: Our data suggest that age may affect microvascular structure in hypertensive patients. It is also possible that hypertension may anticipate the effects of physiological aging, and this should be explored in a relatively large population of normotensive subjects.

P2.2
RESISTANT HYPERTENSION AND STRUCTURAL ALTERATIONS OF SUBCUTANEOUS SMALL RESISTANCE ARTERIES
Claudia Agabiti Rosei, Carolina De Cucles, Claudia Rossini, Maria Lorenza Mulesan, Massimo Salvetti, Enzo Porteri, Alice Gavazzi, Anna Paini, Stefano Caletti, Maria Antonietta Coschignano, Paola Pileri, Enrico Agabiti Rosei, Damiano Rizzoni
Medical Physics and Metrological Information Technology at Physikalisch-Technische Bundesanstalt (PTB), Berlin, Germany
King’s College London British Heart Foundation Centre, St Thomas’ Hospital, London, UK

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