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P1.15: CONDITIONAL INACTIVATION OF INTEGRIN AV SUBUNIT IN VASCULAR SMOOTH MUSCLE CELLS REGULATES FIBROSIS IN VESSELS

Ekaterina Belozertseva*, Melusine Didelot, Amel Mohamadi, Zhenlin Li, Huguette Louis, Jean-Baptiste Michel, Véronique Regnault, Patrick Lacolley

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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 Calgary, Calgary, Alberta, Canada

²University of Alberta, 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, Zhenlin Li ², Huguette Louis ¹, Jean-Baptiste Michel ³, Véronique Regnault ¹, Patrick Lacolley ¹

¹UMR_S 1116, Vandoeuvre-les-Nancy, France

²UMR 8256, Paris, France

³UMR_S 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 which phenotypic modulation 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 in 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 Chowienczyk ³

¹King's College London, Division of Imaging Sciences and Biomedical Engineering, St. Thomas' Hospital, London, UK

²Medical Physics and Metrological Information Technology at Physikalisch-Technische Bundesanstalt (PTB), Berlin, Germany

³King's College London British Heart Foundation Centre, 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 inotropy 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 Ciuceis, 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 aging 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 Ciuceis, Claudia Rossini, Maria Lorenza Muiesan, Massimo Salvetti, Enzo Porteri, Alice Gavazzi, Anna Paini, Stefano Caletti, Maria Antonietta Coschignano, Paola Pileri, Enrico Agabiti Rosei, Damiano Rizzoni *