



## Artery Research

ISSN (Online): 1876-4401

ISSN (Print): 1872-9312

Journal Home Page: <https://www.atlantis-press.com/journals/artres>

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### **3.5: INVESTIGATING THE ROLE OF HEMODYNAMICS IN AAA FORMATION THROUGH COMBINED IMAGING AND MODELING: A LONGITUDINAL IN-VIVO STUDY IN APOE MICE**

B. Trachet, M. Renard, G. De Santis, S. Staelens, J. De Backer, B. Loeys, P. Segers

**To cite this article:** B. Trachet, M. Renard, G. De Santis, S. Staelens, J. De Backer, B. Loeys, P. Segers (2010) 3.5: INVESTIGATING THE ROLE OF HEMODYNAMICS IN AAA FORMATION THROUGH COMBINED IMAGING AND MODELING: A LONGITUDINAL IN-VIVO STUDY IN APOE MICE, Artery Research 4:4, 147–147, DOI: <https://doi.org/10.1016/j.artres.2010.10.170>

**To link to this article:** <https://doi.org/10.1016/j.artres.2010.10.170>

Published online: 21 December 2019

### 3.3 CARDIOTROPIN-1 IS A DETERMINANT OF ARTERIAL STIFFNESS AND THICKNESS IN RODENTS

N. Lopez-Andres <sup>1,\*</sup>, C. Laurent <sup>1</sup>, M. A. Fortuno <sup>2</sup>, C. Labat <sup>1</sup>, J. Diez <sup>2</sup>, F. Zannad <sup>1,3</sup>, P. Lacolley <sup>1</sup>, P. Rossignol <sup>1,3</sup>

<sup>1</sup>Inserm U961, Vandoeuvre-les-Nancy, France

<sup>2</sup>CIMA, Pamplona, Spain

<sup>3</sup>CIC Pierre Drouin, Vandoeuvre-les-Nancy, France

**Background & aims:** Cardiotropin-1 (CT-1), a cytokine belonging to the interleukin-6 family, exerts proliferative and secretory effects in vascular smooth muscle cells. We aimed to investigate the functional and morphological vascular changes induced by chronic CT-1 administration in rats and its involvement in the arterial phenotype of CT-1-null mice.

**Methods:** A) CT-1 (20 µg/Kg, IP) was administered to Wistar rats for six weeks (n = 10/group). B) 2 year-old wild-type (WT) (n = 12) and CT-1-null mice (n = 12) were studied. Vascular structure and function were evaluated by an echo-tracking device. Circumferential wall stress, incremental elastic modulus (Einc), media cross-sectional area and pulse wave velocity (PWV) were measured. Aortic wall collagen, elastin and fibronectin contents were determined using immunohistochemistry, RT-PCR and Western blot.

**Results:** A) Neither vehicle nor CT-1 treatment modified BP. The Einc/wall stress curve from CT-1-treated was shifted to the left as compared with vehicle group. CT-1-treated rats also showed increased media cross sectional area (p < 0.01), collagen content (p < 0.01) and fibronectin expression (p < 0.01). B) CT-1-null mice presented an increased wall stress (p < 0.05) and Einc (p < 0.05) as compared with WT mice. Media cross sectional area, collagen and fibronectin content were reduced (p < 0.05) in mice lacking CT-1.

**Conclusions:** Normotensive rats subjected to CT-1 overloading developed impaired vascular function, characterized by an increment in arterial stiffness accompanied by an augmented media thickness and extracellular matrix production. Accordingly, CT-1-null mice presented a reduced arterial stiffness and a reduced media thickness and collagen content. Our data show that CT-1 is a key player in arterial thickness and stiffness.

### 3.4 INSTANTANEOUS BLOOD PRESSURE IS A DETERMINANT OF AORTIC AUGMENTATION INDEX AND PULSE WAVE VELOCITY: OBSERVATIONS IN PATIENTS WITH AUTONOMIC FAILURE

A. M. T. Huijben <sup>\*</sup>, F. U. S. Mattace-Raso, A. H. van den Meiracker  
Erasmus University, Rotterdam, Netherlands

**Objective:** Acute lowering of blood pressure (BP) with vasodilating agents is associated with a reduction in aortic augmentation index (Alx), whereas carotid-femoral pulse-wave velocity (cfPWV) is largely unaffected. We explored the effect of acute BP lowering on Alx and cfPWV in patients with autonomic failure (AF).

**Design and method:** Finger BP, Aix, cfPWV, heart rate (HR), left ventricular ejection time (LVET) and time to aortic wave reflection (TR) were obtained in supine rest and after 30° and 60° passive head-up tilting for 5 min in 10 subjects with autonomic failure (age 61 ± 15 yrs, 4 males).

**Results:** At baseline, MAP was 127 ± 22 mmHg, HR 72 ± 13 bpm, LEVT 338 ± 30 msec and TR 139 ± 4 msec. In response to 30° and 60° tilting MAP decreased by 18.7 ± 9.8 and 39.6 ± 11.6%, LEVT by 11.5 ± 3.2 and 20.4 ± 5.5%, Alx by 39.2 ± 27.5 and 100.9 ± 78.1%, cfPWV by 12.0 ± 10.5 and 27.5 ± 13.5% and HR increased by 5.2 ± 7.7 and 13.9 ± 17.6% (all p < 0.05), whereas TR did not change. Postural decreases in Alx were not related to changes in cfPWV. In adjusted analysis, 68% of the Alx variation during tilting could be explained by MAP and TR and 76% of the cfPWV variation by MAP and by gender.

**Conclusion:** Instantaneous BP is a determinant of Alx and cfPWV in AF patients. Moreover, changes in Alx are unrelated to changes in cfPWV, indicating that these measures of vascular stiffness provide different information.

### 3.5 INVESTIGATING THE ROLE OF HEMODYNAMICS IN AAA FORMATION THROUGH COMBINED IMAGING AND MODELING: A LONGITUDINAL IN-VIVO STUDY IN APOE MICE

B. Trachet <sup>1,\*</sup>, M. Renard <sup>3</sup>, G. De Santis <sup>1</sup>, S. Staelens <sup>2</sup>, J. De Backer <sup>3</sup>, B. Loeys <sup>3</sup>, P. Segers <sup>1</sup>

<sup>1</sup>BioMMeda - IBiTech, Ghent University, Ghent, Belgium

<sup>2</sup>Medisip - IBiTech, Ghent University, Ghent, Belgium

<sup>3</sup>Centre for Medical Genetics, Ghent University, Ghent, Belgium

The pathophysiological mechanisms underlying abdominal aortic aneurysm (AAA) formation are not yet fully understood. Hemodynamics have been suggested to play an important (modulating) role, but no longitudinal studies have been performed yet due to (a.o.) a lack of (human) data in the pre-diseased state. We used an established mouse model of AAA to perform a longitudinal hemodynamical study in 10 male apoE-deficient mice. All animals were scanned at baseline using micro-CT (Triumph, Gamma Medica) with a dedicated contrast agent (Aurovist, Nanoprobes) to assess the AA geometry, immediately followed by a baseline ultrasound scan (Vevo 2100, Visualsonics) to assess aortic structures and diameters and to measure Doppler velocity waveforms at the proximal and distal aorta and at the celiac, mesenteric, left and right renal arteries. All animals subsequently underwent implantation of a subcutaneous pump, continuously delivering angiotensin II for 28 days. End stage micro-CT and ultrasound scans were performed 31 days after pump implantation. Eight animals survived the complete experiment, and 5 of them developed an AAA. The micro-CT images were subsequently used to reconstruct a geometric 3D computer model (Mimics, Materialise) and combined with the measured flows in a Computational Fluid Dynamics (CFD) simulation (Fluent, Ansys). This procedure will provide unique data on the pre- and post-AAA hemodynamic situation (blood flow and wall shear stress patterns) over the abdominal aorta and side branches in great detail and will allow to further analyze the potential link between local hemodynamics, AAA formation and the location at which the aneurysm develops.

### 3.6 NANOMECHANICAL PROPERTIES OF A MODEL OF TYPE 1 DIABETIC AORTA

R. Akhtar <sup>\*</sup>, N. Gardiner, B. Derby, J. K. Cruickshank, M. J. Sherratt  
The University of Manchester, Manchester, United Kingdom

Although it is well established that in both Type 1 and Type 2 diabetes arterial stiffening occurs, the differential roles played by constitutive arterial components remain unknown. Here, we characterised the nano-mechanical properties of fibrillin microfibrils, a key elastic fibre component, extracted from diabetic arteries.

We isolated fibrillin microfibrils from the aortae of rats with a Streptozotocin-induced model of Type 1 diabetes, and age-matched controls. Fibrillin microfibrils have a 'beads-on-a-string' structure with a periodicity of approximately 56 nm. Atomic force microscopy (AFM) was used to image the microfibrils to determine whether there were any structural changes. Molecular combing was also used to apply a known tensile force (4000 pN) to partially adsorbed fibrillin microfibrils. Combed microfibrils were also imaged with AFM. Fibrillin microfibril periodicity was significantly reduced in the diabetic rats; 52.7 ± 0.3 nm (diabetic) compared with control animals; 59.5 ± 0.4 nm (n = 1500 periodicity measurements, 3 animals per group; p < 0.01). Following combing, periodicity was significantly increased in microfibrils isolated from diabetic aortae (62.3 nm, SEM 0.51 nm, t-Test, N = 1500, P < 0.01) as compared with control animals (58.5 nm, SEM 0.40 nm, p < 0.001, t-test). Eight weeks after islet cell destruction and hyperglycaemia, in vivo, profound changes in microfibril structure are induced, which in turn appear to weaken these important macro-molecular assemblies. This study also demonstrates that it is possible to localise structural and mechanical changes in diabetic aortae at the nanoscopic length scale.

### 5.1 ENHANCED COMMUNICATION VIA GAP JUNCTIONS PROTECTS THE ENDOTHELIUM FROM ISCHAEMIA-REPERFUSION INJURY IN VIVO IN MAN

S. Venkatasubramanian <sup>1,\*</sup>, C. M. Pedersen <sup>1,2</sup>, J. P. Langrish <sup>1</sup>, G. Barnes <sup>1</sup>, C. M. Cheong <sup>1</sup>, H. E. Botker <sup>2</sup>, R. K. Kharbanda <sup>3</sup>, N. L. Cruden <sup>1</sup>, D. E. Newby <sup>1</sup>, N. N. Lang <sup>1</sup>

<sup>1</sup>University of Edinburgh, Centre for Cardiovascular Science, Edinburgh, United Kingdom

<sup>2</sup>Aarhus University Hospital Skejby, Dept of Cardiology, Aarhus, Denmark

<sup>3</sup>The John Radcliffe Hospital, Dept. of Cardiovascular Medicine, Oxford, United Kingdom

**Background:** Endothelial dysfunction is the hallmark of ischaemia-reperfusion (IR) injury and intercellular gap junctions appear to play a role in this process. Rotigaptide (ZP-123) is a novel anti-arrhythmic agent that increases inter-cellular communication via gap junctions. We tested the hypothesis that rotigaptide protects the human forearm arterial circulation from IR induced endothelial dysfunction.

**Methods:** Healthy male subjects (n = 21) were recruited into a randomised double-blind cross-over study. IR injury (upper arm cuff inflated to 200 mmHg for 20 min) was induced in the presence of intra-arterial rotigaptide