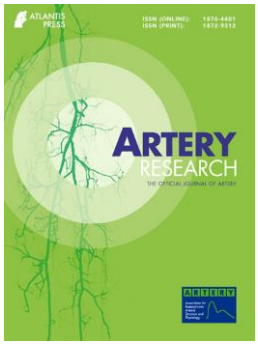

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P3.05: THE ROLE OF HYALURONAN IN AORTIC STIFFENING IN PATIENTS WITH RHEUMATOID ARTHRITIS

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P3.03

NEW METHOD TO ASSESS ARTERIAL STIFFNESS IN CONSCIOUS UNRESTRAINED RATS BY TELEMETRY

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Pulse wave velocity (PWV) is considered as "the gold standard" to assess arterial stiffness. However, PWV is very dependent of blood pressure (BP) and is affected by anaesthesia, largely used in animal experimentation. Thus, the goals of the present study were: 1) To validate the PWV measurement in awake unrestrained rats using a new telemetry implant from Data Science International equipped with two pressures probes. 2) To measure PWV at different BP levels by using the circadian change of BP during the day or after acute BP reduction.
One catheter was placed in aortic arch and the other in abdominal aorta at the level of iliac bifurcation in Wistar Kyoto rats (18weeks-old, n=5). Hemodynamic parameters were recorded for 24h during baseline period and during an acute decrease in BP induced by diltiazem (100mg/kg/po). PWV was calculated by using the foot-to-foot method.
This new implant allows to measure heart rate, BP, BP amplification and PWV (Table1). The changes in PWV due to circadian or pharmacological changes in BP are shown in Fig.1. Both conditions exhibit similar linear regressions, allowing the assessment of PWV at different BP levels and thus independently of the BP.
In conclusion, we show for the first time that the evaluation of arterial stiffness dependent and independent of the BP in chronically instrumented awake unrestrained rats is now possible. It will be a good tool to assess the effects of drugs on arterial wall stiffness.

Table 1

	Central BP	Distal BP
SBP mmHg	118 ± 2	122 ± 2
DBP mmHg	101 ± 2	99 ± 2
MBP mmHg	110 ± 2	110 ± 2
PP mmHg	18 ± 1	22 ± 1
Heart rate bpm	355 ± 8	
Amplification	1,25 ± 0,11	
PWV m/s	4,7 ± 0,2	

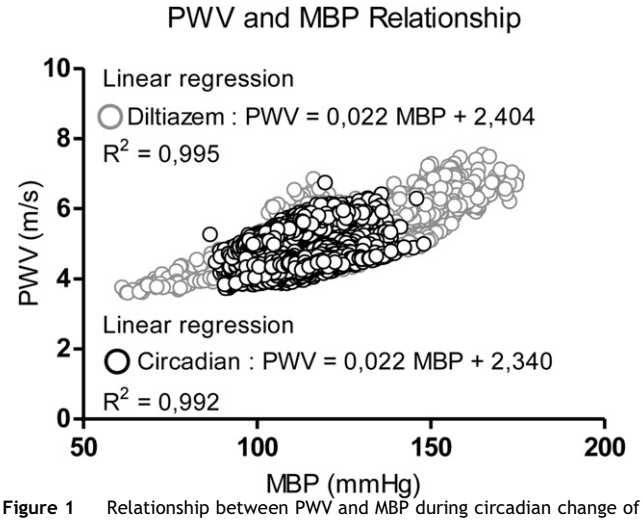

Figure 1 Relationship between PWV and MBP during circadian change of BP or acute administration of diltizem on 24h period. PWV : Pulse Wave Velocity, MBP : Mean Blood Pressure

P3.04

INCREASED THROMBIN GENERATION AND VASCULAR REMODELING IN OBESE ZUCKER RATS

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The metabolic syndrome associates obesity, inflammation and arterial stiffness. We characterized the coagulation phenotype in 25 and 80 week old Zucker rats, that mimics human metabolic syndrome. We adapted a calibrated automated thrombography technique which follows thrombin activity after in vitro stimulation by tissue factor. The endogenous thrombin potential (ETP) which represents the area under the curve of thrombin generation was higher in 25 week old obese rats than in control lean rats of the same age (428 ± 29 nM.min versus 328 ± 27 nM.min) and still higher at 80 weeks (422 ± 30 versus 306 ± 11 nM.min). The most striking finding was an increase in thrombin generation characterized by a widening of the area under the curve associated with an increase in plasma fibrinogen. This hypercoagulability was corroborated by F1+2 test *in vivo* at 25 weeks and did not depend on platelets because it was observed in platelet free plasma. Endothelial dysfunction was shown by a high plasma concentration of von Willebrand factor and inflammation by an increase in several cytokines in a cytokine array and in metalloproteinase activity by zymography. In contrast, there was no increase in thrombin generation *in vitro* with ageing whatever the strain. To conclude, we have shown that thrombin generation increased *in vitro* with obesity, independently of platelet activation as early as 25 weeks of age. We suggest an implication of fibrinogen whereby thrombin interacting with fibrinogen is protected from its inhibition by antithrombin.

P3.05

THE ROLE OF HYALURONAN IN AORTIC STIFFENING IN PATIENTS WITH RHEUMATOID ARTHRITIS

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Introduction: Patients with rheumatoid arthritis (RA) have increased aortic stiffness, which can be improved with anti-inflammatory therapies. However, how inflammation leads to aortic stiffening remains unclear. One potential mechanism is by overproduction of hyaluronan (HA) in the extracellular matrix, which results in stiffening of the arterial wall by thinning of elastic lamellae in animal models. However, the effect in man is unknown. The aim was to evaluate 1) whether serum HA concentration is a valid surrogate of aortic tissue level and 2) to compare serum HA in patients with RA and control subjects and to relate this to aortic pulse wave velocity (aPWV).
Methods: 18 aortic tissue samples were homogenised and HA concentration in the homogenate and corresponding serum sample was assessed using commercially available ELISA kit (DY3614, R&D Systems, U.K). Also, aPWV using SphygmoCor system, and Serum HA was assessed in 40 patients with RA and in 40 matched control subjects.
Results: There was a correlation between tissue and serum HA (R=0.68; P=0.01). Patients with RA had higher serum HA compared to controls (66.6±65.2 v. 11.0±7.9 ng/ml; P<0.0001). In patients with RA, the serum HA levels correlated with aPWV (R=0.3; P=0.01).
Conclusion: This study demonstrates that serum HA is increased in patients with RA in comparison to control subjects, and this correlates with aortic stiffening. The data suggests that increased HA synthesis may be the mechanism behind inflammation-induced aortic stiffness in patients with RA. However, further experiments are needed to study causality between tissue HA concentration and aortic stiffness.

P3.06

CYCLIC STRETCH-INDUCED THROMBIN GENERATION BY RAT VASCULAR SMOOTH MUSCLE CELLS IS MEDIATED BY THE INTEGRIN (V(3) SIGNALING PATHWAY)

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Vascular smooth muscle cell (VSMC) phenotypic modulation plays a pivotal role in atherothrombotic diseases. Thrombin generation at the surface of