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

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Pulse wave velocity (PWV) is considered as "the gold standard" to assess arterial stiffness. However, PWV is very dependent on blood pressure (BP) and is affected by anesthesia, 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 (18 weeks old, n = 5). Hemodynamic parameters were recorded for 24 h during baseline period and during an acute decrease in BP induced by diltiazem (100 mg/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 (Table 1). 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 is now possible. It will be a good tool to assess the effects of drugs on arterial wall stiffness.

### Table 1

<table>
<thead>
<tr>
<th></th>
<th>Central BP</th>
<th>Distal BP</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP mmHg</td>
<td>118 ± 2</td>
<td>122 ± 2</td>
</tr>
<tr>
<td>DBP mmHg</td>
<td>101 ± 2</td>
<td>99 ± 2</td>
</tr>
<tr>
<td>MBP mmHg</td>
<td>110 ± 2</td>
<td>110 ± 2</td>
</tr>
<tr>
<td>PP mmHg</td>
<td>18 ± 1</td>
<td>22 ± 1</td>
</tr>
<tr>
<td>Heart rate bpm</td>
<td>355 ± 8</td>
<td></td>
</tr>
<tr>
<td>Amplification</td>
<td>1.25 ± 0.11</td>
<td></td>
</tr>
<tr>
<td>PWV m/s</td>
<td>4.7 ± 0.2</td>
<td></td>
</tr>
</tbody>
</table>

![Figure 1](image1.png)

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

**P3.03**

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

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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 106 ± 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.

**P3.04**

**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 106 ± 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.