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### **6.3: OXIDATIVE STRESS AND INFLAMMATION: IMPLICATION IN ENDOTHELIAL DYSFUNCTION AND CARDIOVASCULAR AGING ON MURINE MODELS**

S. Baron\*, T. Bedarida, M.M. Strelcyn, C.H. Cottart, F. Vibert, G. Renault, B. Saubamea, E. Veissieres, D. Henrion, J.L. Beaudoux, V. Nivet-Antoine

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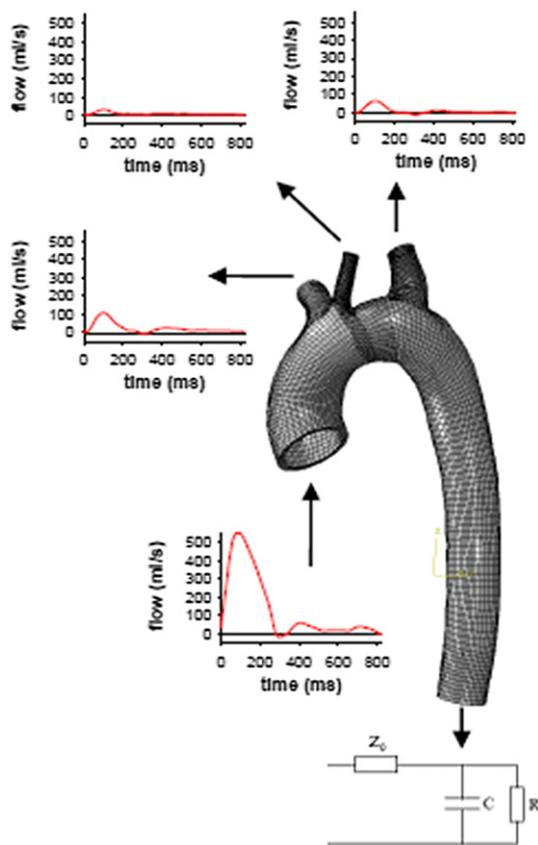


Figure 1 Patient-specific geometry and boundary conditions.

### 6.3 OXIDATIVE STRESS AND INFLAMMATION: IMPLICATION IN ENDOTHELIAL DYSFUNCTION AND CARDIOVASCULAR AGING ON MURINE MODELS

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The aim of the study was to characterize cardiovascular aging with functional (Doppler) and molecular (RT-qPCR and immunohistochemistry quantifications) approaches using three murine models. Molecular studies on aorta (AO) and mesenteric arteries (MA) were used to explore the role of oxidative stress and inflammation. Time-induced aging model corresponded to 25 months-old C57Bl/6J mice feed with standard diet. Doppler exhibited a concentric left ventricle hypertrophy with a decreased aortic distensibility, and an increased aortic thickening. This model presented both a decreased Thioredoxin1 expression (AO and MA) and an increased NADPH oxidase (MA) expression. Inflammation markers were increased in MA (IL-1beta in MA and in AO (IL-6, TNF-alpha). Three months with High Fat and Protein Diet (HFPD) at 9 months induce a major hyperlipidemia. This model exhibited a dilated cardiopathy with both a decreased aortic distensibility and an increased aortic thickening. HFPD increased NADPH oxidase, IL1-beta and TNF-alpha expressions and decreased Thioredoxin1 expression (AO and MA). The mixed model corresponded to 25-months old C57Bl/6J mice feed for 3 months with HFPD. They presented a major cardiopathy with a decreased aortic distensibility, and exhibited both a major oxidative stress (increased NADPH oxidase and decreased Thioredoxin1 in AO and MA) and a major endothelial inflammation (increased IL-1beta, IL-6 and TNF-alpha in AO and MA). eNOS gene was not modify in any model. We conclude

that NADPH oxidase and Thioredoxin1 seem to play a key role in the arterial aging process and might be interesting potential targets for therapeutics assays.

### 6.4 CARDIOTROPHIN-1 INDUCES STRUCTURAL AND MECHANICAL CHANGES IN AORTA

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**Aims:** Cardiotrophin-1 (CT-1), a cytokine belonging to the interleukin-6 family, exerts proliferative and secretory effects in vascular smooth muscle cells. We investigated the morphological, micromechanical and molecular vascular changes induced by chronic CT-1 administration in rats.

**Methods:** Recombinant rat CT-1 (20 µg/Kg, IP) or vehicle (n=10/group) was administrated to Wistar rats for six weeks. Vascular structure and function were determined with an echo-tracking device. Aortic extracellular matrix (ECM) protein production and attachments were quantified by immunohistochemistry, RT-PCR and Western blot. Acoustic wavespeed within the aorta was determined using a novel scanning acoustic microscopy (SAM) method at 1 GHz which enables tissues stiffness to be determined with a ~1 µm spatial resolution.

**Results:** In normotensive CT-1-treated rats, the incremental elastic modulus-circumferential wall stress curve was shifted leftward compared to vehicle, indicating increased arterial stiffness. Aortic media thickness was higher (40%) in CT-1-treated rats. Aortic collagen type I (80%), fibronectin (80%), metalloproteinases activities (40%), integrins (70%) and focal adhesion proteins (60%) were also increased in whereas elastin levels were similar to controls. Further, increased acoustic wavespeed in CT-1 rats ( $1694 \pm 2 \text{ ms}^{-1}$  compared to  $1673 \pm 2 \text{ ms}^{-1}$ ,  $p < 0.001$ ) was found in parallel with increases in collagen volume fraction (21 % as compared to 9 % in controls).

**Conclusions:** We demonstrate that CT-1 is a key player in arterial remodeling and stiffness by modulating aortic mechanical properties, media thickness, ECM production and attachments. Thus, CT-1 could be a new biotarget to reduce arterial stiffness and decrease ECM deposition in vascular diseases.

### 6.5 ACUTE β-ADRENERGIC BLOCKADE INCREASES AORTIC WAVE REFLECTION IN YOUNG MEN AND WOMEN: DIFFERING MECHANISMS BETWEEN SEXES

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Acute β-adrenergic blockade increases aortic wave reflection, however, the mechanisms remain unclear. Evidence suggests that β-adrenergic receptor sensitivity in the peripheral vasculature differs between sexes. Therefore, the goal of this study was to examine whether β-adrenergic blockade alters aortic wave reflection and forearm vasoconstrictor responsiveness to a similar extent in young men and women. In thirty-one subjects (16M/15F;  $26 \pm 1$  years) non-invasive aortic pressure waveforms were synthesized from high-fidelity radial pressure waveforms via applanation tonometry before and during systemic β-blockade (0.25 mg/kg bolus, followed by 0.004 mg/kg/min continuous infusion of propranolol). Forearm vasoconstrictor responses to exogenous intra-arterial norepinephrine (NE) were also assessed in a subset of subjects (13M/9F). Wave reflection characteristics are summarized in Table 1. β-blockade increased aortic augmentation index (Alx) and wave reflection amplitude (aortic augmented pressure (AG)) in both sexes. However, the increase in wave reflection tended to be greater ( $P < 0.05$  and  $P = 0.07$  for AG and Alx, respectively) in women following β-blockade. Alx adjusted for HR (Alx@75bpm) increased in women following β-blockade, whereas it was unchanged in men. Moreover, the change ( $\Delta$ ) in Alx was inversely associated to  $\Delta$ HR only in men ( $r = -0.54$ ,  $P < 0.05$ ). Finally, β-blockade caused an enhanced forearm vasoconstrictor response to exogenous NE in women (Figure 2). Our data suggest that: 1) aortic wave reflection is increased to a greater extent in women following systemic β-blockade; and 2) the mechanism for enhanced aortic wave reflection