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


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for 3 months with HFPD. They presented a major cardiopathy with
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oxidase (MA) expression. Inflammation markers were increased in MA (IL-
6.3
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 fed with standard diet. Doppler exhibited a concentric left ventricle hypertrophy with a decreased aortic distensibility, and an increased aortic thickening. HFPD increased NADPH oxidase, IL1-beta 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 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. 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 presented both a decreased aortic distensibility and an increased 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 modified 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.

6.4
Alims: 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 whereas elastin levels were similar to controls. Further, increased acoustic wavespeed in CT-1 rats (1694 ± 2 ms⁻¹ compared to 1673 ± 2 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±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 (AIx) 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 AIx, respectively) in women following β-blockade. AIx adjusted for HR (AIx@75bpm) increased in women following β-blockade, whereas it was unchanged in men. Moreover, the change (A) in AIx was inversely associated to ΔHR 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...