Hemodynamic and endocrine factors in the biomechanical remodeling of the vascular wall

PhD Thesis

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INTRODUCTION

The vascular system plays a diverse role in the human body. It is capable of mechanical adaptation depending on the hemodynamic and endocrine environment.

Hypertension is a well-recognized risk factor for cardiovascular and renal diseases and may lead to increased risk of stroke. Small resistance arteries play a key role in the control of blood pressure. Sex differences in hypertension have been described but little is known about the mechanisms through which sex hormones affect the remodeling of coronary resistance arteries.

Varicose veins affect the adult population adversely however the pathomechanism of the formation of varicose veins is still unclear. Little is known about the effects of flow disturbances on venous pathology.

Biomechanical remodeling of resistance arteries in hypertension, sex differences, effects of sex hormones

Sex differences in hypertension have been described, and are at least in part thought to be due to the effects of estradiol and testosterone. Sex differences in the early stages of hypertensive vascular adaptation in the heart and in the intramural small coronary arteries that are fundamentally

responsible for the blood supply of the heart muscle have not been studied thoroughly.

Mechanisms leading to the development of varicose veins

There is evidence to suggest that chronic flow alterations induce morphological remodeling processes in the affected vessels. Unfortunately, despite the emerging significance of flow disturbances in the development of pathological varicose morphology, there is a lack of experimental studies addressing the flow induced remodeling processes of the venous side of the circulation.

Experiments centered on inducing venous hypertension showed that reduced flow may trigger inflammatory processes. However histological evidence of macrophage invasion, and new cell formation in association with a newly developed venous collateral system is hard to come by in the literature.

AIMS OF STUDY

Our aim was to study hemodynamic and endocrine factors in the biomechanical remodeling of the vascular wall. Our intention was to focus on vessel wall remodeling in diseases that have a large adverse impact on the well-being of the population. Therefore our research centered on coronary pathologies in hypertension and the possible effects of sex hormones of coronary pathologies. The other field chosen was the development of varicosities.

The following questions were intended to be answered by this study:

- **Is there a difference between the sexes regarding vascular remodeling in the coronary resistance arteries of the rat following angiotensin II (AngII) induced hypertension?**

- **How does ovariectomy and hormone replacement affect this remodeling in the intramural coronaries, which play a cardinal role in cardiovascular pathophysiology?**

- **How does the increase in venous pressure and decrease of venous flow affect the geometrical and biomechanical characteristics of the saphenous vein main branch in chronic main branch stricture model in rats?**

- **Is there evidence of collateral network formation following partial clipping of the main branch of the saphenous vein of the rat?**

- **Is there evidence of macrophage invasion and new cell formation at the clipping site?**

METHODS

Experiments carried out to fulfill the aims listed above are summarized in Table 1.

Table 1.

Summary table of experiments performed.

Chronic Angiotensin II infused animals					
male	female				
10	10				
Chronic Angiotensin II infused animals					
hypertensive controls -female	ovariectomy - female	estrogen therapy - female			
11	11	11			
Clipped veins					
Videomicroscopy	Hemodynamic measurements	Batson 17 cast	Angiometry 4 weeks	Angiomerty 8 weeks	Histopathology
6	12	12	12	8	13

First series included chronic Angiotensin II infused, Sprague Dawley rats male vs. female, and the left descending coronary was studied via angiometry under the induced hypertensive conditions.

The second series included chronic Angiotensin II infused Sprague Dawley rats, where one group was ovariectomized, one group was ovariectomized and given estrogen therapy, and the third, "control hypertensive group" underwent a sham abdominal operation, the left descending coronary was studied via angiometry under the induced hypertensive conditions.

In the third series, the saphenous vein and its tributaries were studied in a low-flow high-pressure model. Videomicroscopy studies were performed on the first group hemodynamic measurements were made on the second group. The third group underwent preparation with Batson#17 Corrosion Kit, and plastic casts were prepared to study the developed venous collateral system. The fourth and fifth group was sacrificed at 4 and 8 weeks respectively and angiometry was performed. Histopathology was performed in the sixth and final group.

Chronic Angiotensin II infusion

An osmotic minipump was implanted into Sprague-Dawley rats containing AngII acetate and remained in situ for 4 weeks.

Sex differences between Male vs. Female Animals

Four weeks after implantation of the minipump the animals were sacrificed, and the intramural coronary arteries from the left descending artery were prepared.

Ovariectomy and estrogen therapy

Following 4 weeks of AngII treatment via the subcutaneous osmotic minipump we investigated intramural coronaries taken from ovariectomized rats, rats that were also given estrogen therapy following the ovariectomy and the

‘‘hypertensive control’’ group underwent an abdominal sham operation, and received AngII.

Partial chronic occlusion (‘‘clipping’’) of the saphenous vein in the rat

We induced a combined flow-pressure disturbance in the saphenous system of the rat by performing chronic partial clipping of the main branch. The most proximal segment of the main branch of the saphenous vein was dissected and a longitudinally slit 4mm long semi-rigid, thick-walled piece of a plastic tube with a lumen diameter of 500 μm was placed around the vein.

Measurement protocols

Pressure-angiometry was performed for all dissected segment (both coronaries and venous segments), and for venous segments videomicroscopy, hemodynamic measurements, Batson#17 casting, and histological examination were performed also.

Biomechanical calculations for all vessel segments

From the original calibrated pressure-diameter plots, geometric and biomechanical parameters were computed for each intraluminal pressure level.

RESULTS

Sex differences in the remodeling of rat coronary resistance arteries in angiotensin II hypertension

The relative heart weight of the hypertensive females was greater compared with hypertensive males. In hypertensive females, we observed significantly smaller inner radii and greater wall thickness than in males. Tangential wall stress values, which show the mechanical loading of the vessel, were significantly higher in males than in females.

Effects of ovariectomy and estrogen replacement

Ovariectomy reduced the lumen while estrogen treatment not only restored lumen diameter but resulted in even higher values than in control AngII treated rats. We found similar results regarding the outer radius. In our series spontaneous myogenic tone was higher in the estrogen treated group compared with the ovariectomized group.

Estradiol treatment restored nitric oxide (NO)-dependent, bradykinin (BK)-induced relaxation to the hypertensive control level.

The effects of high-pressure low-flow conditions on the saphenous main branch and collaterals

A reduction in diameter of the clipped segments in comparison with their contralateral unclipped controls was

found in our series. The wall thickness and wall mass values of the clipped segments were significantly reduced compared to those found in the contralateral side. We also found massively reduced contractility and reduced endothelial dilation capacity in venous segments following occlusion.

A rich bypassing collateral system was found on the clipped side under video-microscopic examination, and Batson#17 casting. Histological analysis proved the presence of macrophage invasion and new cell formation and at the occlusion site and a massive remodeling of the elastic components in the wall. Quantitative image analysis was performed and we found that the inner elastic membrane became less condensed, and less organized in the clipped, remodeled segments.

The applied low flow–high pressure hemodynamic challenge also induced a remodeling of the contractile elements: age-induced accumulation of the contractile protein in the inner medial layers was found to be less effective in clipped segments.

CONCLUSIONS

The aim of this thesis was to gain a more thorough understanding some of the hemodynamic and endocrine factors that play a role in the remodeling of the vascular wall of coronaries in hypertension, and the network of the saphenous vein in varicosity.

Differences between the sexes in terms of vascular remodeling in the coronary resistance arteries of the rat following early stages of angiotensin II induced hypertension was studied in a chronic Angiotensin II infusion model via in vitro pressure-angiometry. Different adaptation mechanisms were observes in males and females. Relaxation to bradykinin was greater in females. Although we observed inward eutrophic remodeling in females, an increase in wall stress and elastic modulus dominated in males.

The effects of ovariectomy and hormone replacement on the remodeling of intramural coronaries were studied in the same chronic angiotensin II model, and via in vitro pressure angiometry. In hypertension, intramural small coronaries show inward eutrophic remodeling after ovariectomy comparing with hypertensive controls. Estrogen therapy had an opposite effect on vessel diameter. Hormone therapy led to an increase in spontaneous tone, allowing for greater dilatative capacity.

Estrogen may therefore be considered to counterbalance some of the adverse changes seen in the wall of intramural coronaries in the early stages of chronic hypertension.

The effects of an increase in venous pressure and decrease of venous flow on the saphenous vein in chronic main branch low-flow high pressure stricture model in rats was studied via a partial chronic occlusion model. In vitro pressure-angiometry, intravital videomicroscopy, hemodynamic measurements, histology and immune-histology of the main branch and preparation of Batson#17 plastic casts were performed. Contrary to expectations, the main branch did not dilate morphologically, instead involution with morphologically reduced lumen, reduced wall thickness and reduced wall mass was observed. A rich collateral system appeared on the clipped side. Loosening of the force-bearing elements during flow-induced wall remodeling may be an important pathological component in varicosity

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