9. ENDOTHELIAL CHANGES IN HYPERTENSION

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Introduction

Hypertension is the second cause of death in developed countries. Human hypertension and several animal models of hypertension are associated with increased peripheral vascular resistance and changes at the endothelial layer of the vessels. The endothelium is a dynamic organ which responds to several stimuli triggered by a wide plethora of effectors in order to restore the loss of function [1]. There is accumulating evidence pointing towards a dysregulation of endothelial function as key in the development of cardiovascular diseases like hypertension. As a consequence of such dysregulation, the endothelium suffers changes in structure and function, which under certain circumstances contribute to the genesis of different cardiovascular diseases. Here we will summarize the most important changes occurring within the vascular endothelium in response to hypertension.

Structural changes in hypertension

As a result of their location, endothelial cells are exposed to mechanical forces: pressure, tension, and shear stress. Of these forces, shear stress appears to be very important in mediating endothelial changes both morphological and metabolic. Cells exposed to positive shear stress exhibit a reorientation in respect to the blood flow. It is of particular interest that regions experiencing laminar blood flow tend to be protected against atherogenesis. By contrast there is a strict correlation between areas suffering high shear stress forces (such as those in the bifurcation of coronary arteries) with the formation of atherosclerotic lesions [2], although the mechanism by which shear stress is transduced into metabolic pathways remains poorly understood. Mechanical forces activate the cascade of the Mitogen Activated Protein Kinases (MAPK) ERK1/2 (Extracellular signal Regulated Kinase), inducing gene expression [3]. However, the link between shear stress and ERK activation is not well documented.
Arterial pressure plays a pivotal role in the maintenance of the vessel architecture. Hypertension is associated with alterations in the structure and number of arteries, and these modifications affect the whole artery layer system from the endothelium to the adventitia. The endothelial response to hypertension is correlated with a re-orientation, polarity loosening, and a dramatic change in cell morphology turning the cells into a polyedric-like shape. As a result of these changes, endothelial uniformity is lost and protrusion of the cells into the lumen of the vessel wall takes place [4]. One of the causes by which hypertensive patients acquire atherosclerotic lesions is thought to be mediated by the loss of the ability of endothelial cells to respond to shear stress forces, although it is not the sole cause of this vascular pathology. Hypertension-mediated phenotypic changes of the endothelium wall are also associated with the modification in the composition of the extracellular matrix (ECM) at the intima layer, and the balance between the expression and activity of metalloproteinases, ECM degrading enzymes, and their specific inhibitors TIMPs [5]. As we will further discuss, hypertension is strongly associated with severe cardiovascular pathological entities like atherosclerosis.

Metabolic changes in hypertension

The endothelial wall is the main sensor of dynamic stress, arterial pressure, and chemicals, and it is the signal transducer of the cardiovascular system from the blood flow to the vessels. Endothelial cells are in charge of maintaining vascular tone and of regulating cell adhesion and platelet aggregation to the vascular wall. Endothelial changes in response to hypertension are mediated by the synergistic effect of mechanical and chemical stimuli, and the consequence is the release of vasoactive factors, which are intended to restore the functionality of the endothelium. We can classify these factors into the following categories: relaxing factors, contracting factors, reactive oxygen species, growth factors, and coagulation and fibrinolysis factors. A brief description of the physiologic functions of these factors follows.

Relaxing factors

In response to different stimuli, endothelial cells synthesize the relaxing factors nitric oxide, prostacycline (PGI2), and the endothelium derived hyperpolarizing factor (EDHF) [1](figure 1).

Nitric Oxide
Nitric oxide (NO) is a free radical gas molecule produced by the activity of the enzymes nitric oxide synthases (NOSs). Three NOS isoforms have been described. Two constitutive isoforms are expressed in endothelial cells and central nervous