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# Vascular Repair and Remodeling: A Review

Nicolás F. Renna, Rodrigo Garcia, Jesica Ramirez and
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## Abstract

Vascular remodeling is alterations in the structure of resistance vessels contributing to elevated systemic vascular resistance in hypertension. In this review, physiopathology of vascular remodeling is discussed, and the impact of antihypertensive drug treatment on remodeling is described, emphasizing on human data, fundamentally as an independent predictor of cardiovascular risk in hypertensive patients. Then we discussed a vascular repair by endothelial progenitor cells (EPCs) that play important roles in the regeneration of the vascular endothelial cells (ECs). The normal arterial vessel wall is mostly composed of ECs, vascular smooth muscle cells (VSMCs), and macrophages. Endothelial impairment is a major contributor to atherosclerosis and restenosis after percutaneous coronary intervention (PCI). Reendothelialization can effectively inhibit VSMC migration and proliferation and decrease neointimal thickening.

**Keywords:** endothelial progenitor cells, fructose-fed hypertensive rats, metabolic syndrome, hypertension, oxidative stress, vascular remodeling

## 1. Role of endothelial progenitor cells in vascular repair

Vascular diseases, including atherosclerosis, media calcification, and microangiopathy, are prevalent in patients with diabetes mellitus and are considered to be primary causes of death and disability in these individuals [1]. Atherosclerosis occurs earlier in patients with diabetes, frequently with greater severity and a more diffuse distribution. Patients with diabetes have increased prevalence of vascular disease and, as a result, increased morbimortality from acute myocardial infarction. Diabetes and metabolic syndrome (MS) are associated with vascular function abnormalities and ensuing morphological changes associated with vascular remodeling and atherosclerosis [2, 3].

The arterial vessel wall is mostly composed of endothelial cells (ECs), vascular smooth muscle cells (VSMCs), adventitial connective tissue and macrophages. Endothelial impairment is believed to be a major contributor to atherosclerosis or restenosis after percutaneous coronary intervention (PCI). Reendothelialization with ECs can effectively inhibit VSMC migration and proliferation and decrease neointimal thickening. It is for this reason that we studied a mechanism to achieve a rapid reendothelialization, through, for example, autologous translators of endothelial progenitor cells (EPC), mature or immature, as a fundamental hypothesis in the prevention of these two pathologies: atherosclerosis and restenosis, which derive in the same clinical entity: acute coronary syndrome.

EPCs are divided into different evolutionary stages from mother cells to mature ECs. Both early and late EPCs can repair blood vessels, but late EPCs that have a strong proliferation capacity are more involved in the formation of new vessels or angiogenesis. By measuring EPC in patients by flow cytometry in patients by flow cytometry, we found that in patients with atherosclerosis are decreased compared to control subjects without atherosclerosis [4–6]. Several studies show that EPCs can be recruited to sites of endothelial injury then mature in site, changing cluster of differentiation (CD), and playing a major role in reendothelialization [7–9].

Atherosclerosis is an inflammatory disease with leukocyte infiltration, accumulation of smooth muscle cells, and formation of neointima. Damage of the endothelial monolayer triggers the development of thrombosis with consequent occlusion versus arterial subocclusion. Recent studies demonstrated the recruitment and incorporation of EPC into atherosclerotic lesions and therefore provided evidence supporting the role of vascular cells in the pathophysiology of atherosclerosis. Moreover, there is evidence that EPC are capable of regenerating cells, vascular grafts, and native vessels [10, 11].

The EPCs can mediate vascular repair and attenuate atherosclerosis progression even in the continued presence of vascular injury. Although the mechanisms involved are still not clear, EPCs seem to contribute to the restoration of the endothelial monolayer [12]. In addition to bone marrow, spleen-derived EPCs also have the capacity to repair damaged endothelium [13]. EPCs derived from spleen homogenates also enhanced reendothelialization and reduce neointima formation after induction of endothelial cell damage using the carotid artery model [14].

Other models have also been used, such as the balloon injury model, mobilization of circulating EPCs, and accelerated repair of the nude endothelium [15]. In addition, autologous EPCs that overexpress endothelial nitric oxide synthase (eNOS) ameliorates endothelial integrity when transplanted into mice after carotid artery balloon injury. Increased NO bioavailability significantly strengthens the vasoprotective properties of the reconstituted endothelium, leading to inhibition of neointimal hyperplasia [16].

Transfer of progenitor cells is not always beneficial. ApoE KO mice receiving mononuclear bone marrow cells, following induced hind limb ischemia, showed increased neovascularization, accelerated atherosclerotic plaque formation, and lesion size compared to control groups [17]. In an alternate study, because of proinflammatory properties of these cells, as reduction in IL-10 levels in the atherosclerotic aortas was observed accelerated atherosclerosis along with reduced plaque stability [18]. Similarly, even though implantation of an arteriovenous anti-CD34-ePTFE

graft in pigs, it also stimulated intimal hyperplasia [19, 20]. Besides obvious differences in various experimental models, it is difficult to reconcile these findings and it seems that excessive mobilization of progenitor cells may lead to restenosis, but its absence may impair reendothelialization [21]. It is important to mention term EPC is loosely used to describe a vastly heterogenic cell population that is consisted of different progenitors. Recent studies have highlighted the impact of cell isolation protocols on the functional capacity, that is, different phenotypes.

## 2. Flow cytometric characteristics of EPC

EPCs are identified by expression of CD34, CD133, or VEGFR2. Their accurate characterization is very difficult, because as these cells may originate from multiple precursors: the hemangioblast, nonhematopoietic mesenchymal precursors, such as the bone marrow, monocytic cells, and also tissue resident stem cells. Two methods for isolation of EPCs from the peripheral blood have been described [22]:

1. From isolated monocytic cells onto fibronectin-coated plates and cultured in the presence of growth factors, form colonies after 5–7 days, denominated endothelial cell colony-forming units (CFU-EC) [23].

2. From monocytic cells from peripheral blood plated onto collagen-I-coated plates in endothelial growth media (EGM-2) can give rise to CFU-EC after 14–21 days [24]. The expression of VEGFR2 on peripheral blood monocytes is essential for their endothelial-like function [25].

How was it exposed beforehand, there are two distinct phenotypes: early EPCs and late outgrowth EPCs [26, 27] which differ fundamentally from each other their proliferation potential. The first, that are derived from monocytic cells, have low proliferative capacity but express of eNOS and they fail to form perfused vessels in vivo. The late outgrowth EPCs have a high proliferation rate and can be maintained in culture extensively. These cells play a key role in angiogenesis [22]. Some studies further identified these cells as CD34$^+$CD45$^-$ precursors [28] and clarified their origin from the peripheral blood monocytes. CD14$^+$ cells seem to give rise to early EPCs, whereas late EPCs develop exclusively from the CD14$^-$ subpopulation [29].

In experimental studies, where EPCs are infused into ischemic lower limbs, only a small number of these can be seen in capillaries of the patient, although the perfusion improves considerably [30–33]. This suggests the potential release paracrine of angiogenic factors. This supportive function of EPCs may be crucial in ensuring the survival of tissue-residing cells and enhancing blood vessel formation and tissue repair. Early outgrowth EPCs produce higher levels of growth factors [34, 35]. To summary, it can say that EPC phenotype vary depending on their origin and their clutters of differentiation, with different functions:

1. immature EPCs that have proliferative ability

2. mature EPCs that can physically engraft into neoendothelial layer

3. supportive EPCs that produce growth factors to promote endothelial repair.

## 3. Angiogenesis in the vessel wall

An interesting question could be: How do the vessel wall progenitor cells migrate to the endothelial and intima layer of the vessel? The answer is the vasa vasorum. These play a significant role in transporting cells to the intimal region and have positively correlated with the development of atherosclerosis [35, 36]. In atherosclerotic lesions abundant microvessels can be observed. The vasa vasorum are considered to significantly contribute to:

1. atherosclerosis progression

2. plaque instability

3. also authors, support that contribute to plaque regression.

The real thing is that decreased blood supply through the adventitial vasa vasorum can trigger atherogenic intima thickening [37, 38]. Using the Lac-Z mice, Xu et al. [10] provided unique insights into the formation of these microvessels. It was clearly demonstrated that endothelial cells of microvessels within allografted vessels were derived from bone marrow progenitor cells (**Figure 1**). These results suggest a potentially dual role of EPCs in transplant atherosclerosis, protective through the repair of the denuded endothelium and promoting plaque
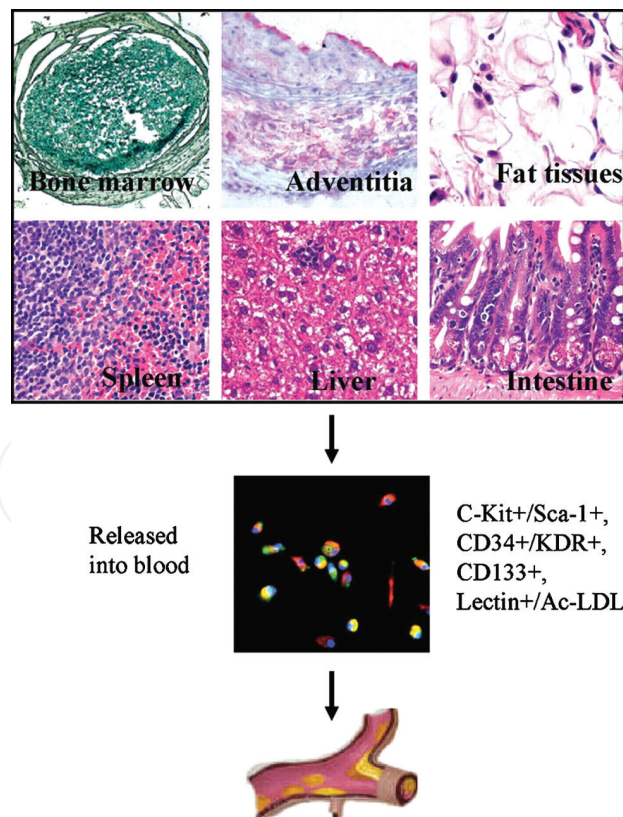


**Figure 1.** EPC origins. EPCs could be released from bone marrow, fat tissues, vessel wall, especially adventitia and spleen, liver, and intestine, where they form a circulating EPC pool. They can then contribute to the repair of damaged vessels in pathological conditions.

angiogenesis. Some studies have shown the potential detrimental EPC transplantation as lung cancer or multiple myeloma [38]. Additional experiments are required to fully delineate the functional significance of stem cell incorporation into the microvasculature and define the role of progenitors in tipping the balance between atheroprotection and atherogenesis.

## 4. Definition of vascular remodeling

The vascular wall is formed by endothelium cells, smooth muscle cells, and fibroblasts interacting to form an autocrine-paracrine complex. During vascularization, the vascular wall cells detects changes in the environment, releasing communication signals as growth factors, inflammation mediators, and paracrine mediators that influences on vascular structure and function. The results are vascular remodeling. This is an active process of structural change that involves changes in at least four cellular processes: cell growth, cell apoptosis, cell migration, and the synthesis or degradation of extracellular matrix.

Vascular remodeling is dependent on dynamic interactions between: (1) local growth factors, (2) vasoactive substances, and (3) hemodynamic stimuli, and is an active process that occurs in response to long-standing changes in afterload conditions; that it may subsequently contribute to the pathophysiology of vascular diseases and circulatory disorders [39].

Increased peripheral vascular resistance in hypertension was uniformly ascribed to a higher volume of wall material per unit length of vessel or "hypertrophy." It was always thought that the process of vascular hypertrophy was only due to increased muscle cells, as in the left ventricle, the term remodeling was first applied to the resistance vessels by Baumbach and Heistad to indicate a structural rearrangement of existing wall material around a smaller lumen [39–41].

Mulvany proposed that vascular remodeling should encompass any change in diameter noted in a fully relaxed vessel, not explained by a change in transmural pressure or compliance, and therefore due to structural factors [42–44]. With the objective of to be operational, the classification necessitates appropriate methods for the measurement of resistance vessels dimensions, supplying factors either removed or controlled for: (i) vascular tone, (ii) transmural pressure, and (iii) vessel compliance [38, 45].

## 5. Classification of vascular remodeling

Consideration of morphological changes has changed over time. Gibbons proposed a classification based on the response to increased blood pressure. These changes are displayed predominantly in media-to-lumen ratio (M/L), changing the vessel wall width for increased muscle mass (**Figure 2A**) or in the reorganization of cellular and noncellular elements (**Figure 2B**). These changes increase vascular reactivity, thus enhancing peripheral resistance. Another mechanism are mainly involves changes in the dimensions of the lumen (**Figure 2C** and **D**). In this case, the restructuring of the active components and cell signals does not
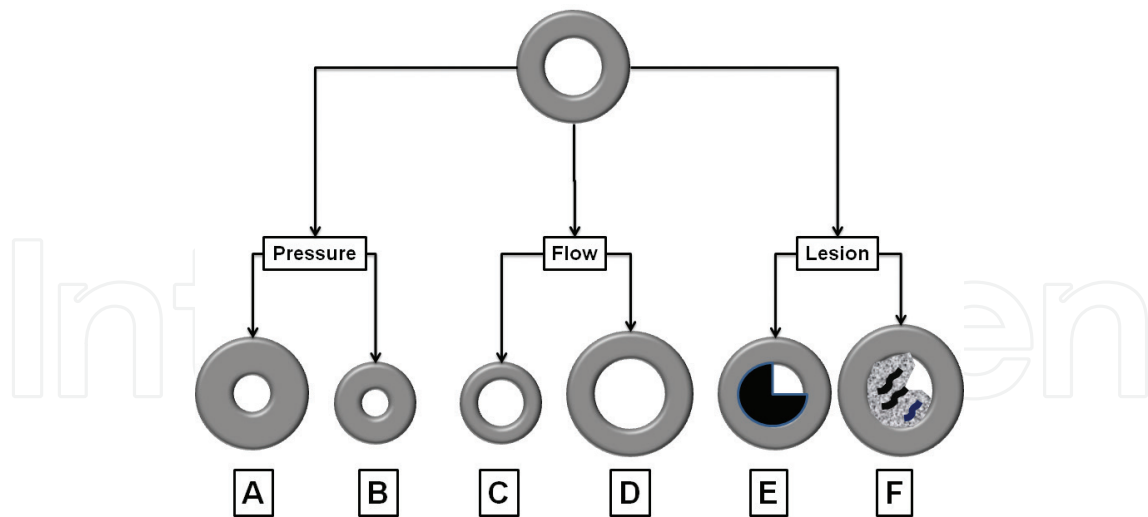
**Figure 2.** Changes are predominantly in media-to-lumen ratio (M/L), changing the vessel wall width for increased muscle mass (A) or in the reorganization of cellular and noncellular elements (B). Another mechanism of remodeling are mainly involves changes in the dimensions of the lumen (C) and (D). In this case, the restructuring of the active components and cell signals does not result in significant changes in the dimensions of the vascular lumen. Another form of vascular remodeling is microcirculation rarefaction (E) and (F).

result in significant changes in the dimensions of the vascular lumen; the changes in vessel wall thickness are relatively small. Clinical examples of this type of restructuring include the dilation of vascular remodeling associated with a constantly high blood flow (**Figure 2D**) (e.g. arteriovenous fistula) or the loss of cellularity and extracellular matrix proteolysis, resulting in the formation of an aneurysm. Equally, a reduction in the diameter of the vascular mass results from a long-term reduction in blood flow (**Figure 2C**). In fact, microcirculation rarefaction is another form of vascular remodeling that promotes hypertension and ischemic tissue. The vascular wall is also markedly changed in response to vascular injury (**Figure 2E** and **F**). In neointima, forms of reparative response to injury, as thrombosis, migration and vascular smooth muscle cells (VSMCs) proliferation, increased matrix production, and infiltration of inflammatory cells also exist.

Hypertension is associated with structural changes in the resistance vessels such as reduction in lumen diameter and increase in M/L ratio. This mode of structural change has been called "remodeling" [46].

Structural changes in resistance vessels are described as a rearrangement process to understand the pathogenesis of the disease and its therapeutic approach. However, it has been discussed that the term "remodeling" is not ideal because it is frequently used to describe any change in the structure of the vessel or myocardium. To avoid this difficulty, some authors make four proposals [47].

First, the term "remodeling" is limited to situations where there is a change in the lumen of a relaxed vessel, as measured under standard intravascular pressure. The changes in the characteristics of the wall material do not take into account the change in the vascular lumen.

Second, the process of changing the vessel wall without changes in the amount or characteristics of the materials are termed eutrophic remodeling. This process can be characteristic from

situations involving an increase in the amount of material (hypertrophic remodeling) and those involving a reduction in the amount of material (hypotrophic remodeling).

Third, changes associated with decreased or an increased in lumen diameter should be classified as internal remodeling and external remodeling, respectively.

Finally, the remodeling process should be quantified. The term "remodeling index" refers to the variations of lumen referred to as eutrophic remodeling, depending on the changes in the wall section area.

The four proposals above allow for accurate terminology. Thus, the increase in the M/L ratio and decrease in the lumen diameter in resistance vessels of patients with essential hypertension without any change in the amount of wall material is called inner eutrophic remodeling. The decrease in the lumen diameter of the renal afferent arteriole with a decrease in the amount of wall material is called inner hypotrophic remodeling.

Chronic changes in hemodynamic forces structurally alter the vascular wall. In addition, hemodynamic changes are not the only production mechanisms of vascular remodeling. The inflammatory response and changes in the components of the matrix have been suggested as important mediators in the vascular adaptation process [48].

**Figure 3** highlights schematically the adaptation of these changes in different pathologies, including structural changes to the intima layer that contribute to remodeling of the vascular wall. Thus, outward remodeling compensates for atherosclerotic plaque growth and delays the progression of blood flow limitation during stenosis, whereas during restenosis, intimal hyperplasia causes a narrowing of the lumen.
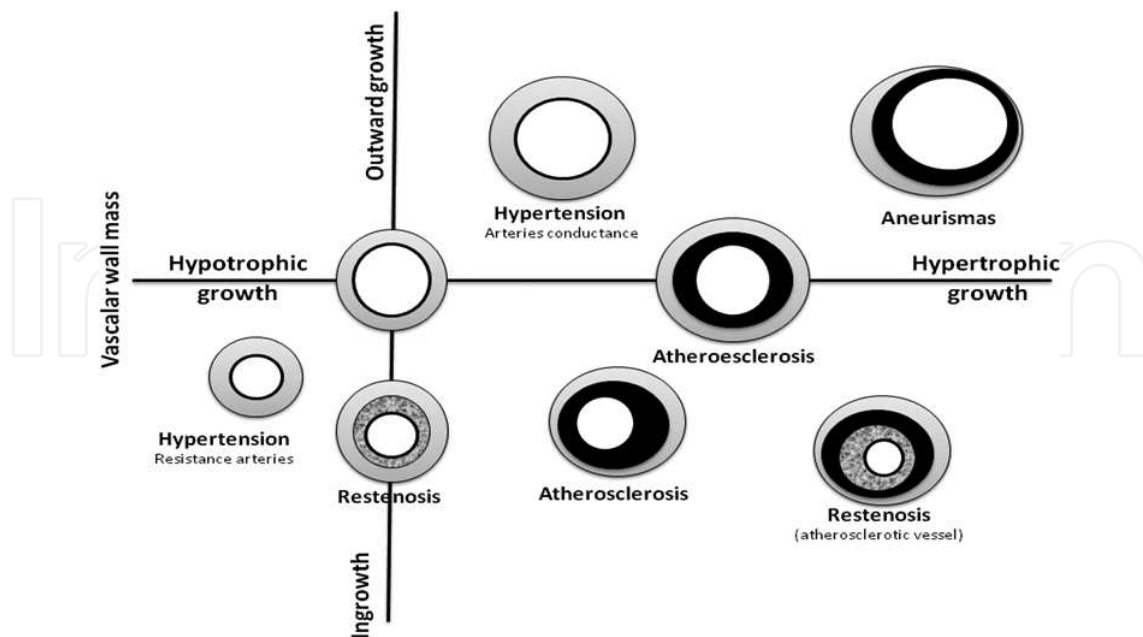


**Figure 3.** Schematic adaptation of changes in different pathologies, including structural changes to the intima layer that contribute to remodeling of the vascular wall. Thus, outward remodeling compensates for atherosclerotic plaque growth and delays the progression of blood flow limitation during stenosis, whereas during restenosis, intimal hyperplasia causes a narrowing of the lumen.

In summary, vascular wall remodeling is the result of changes in cellular and noncellular components, depending on the disease process causing the changes. Changes in the growth and migration of VSMC, endothelial dysfunction, inflammatory processes, and the synthesis or degradation of extracellular matrix components may be present during the disease process.

# 6. Pathophysiology of vascular remodeling in hypertension

## 6.1. Hypothesis of inflammatory and endothelial dysfunction

The traditional view of atherosclerosis as a lipid storage disease is crumbling with growing evidence that inflammation is involved during all stages, from the initial injury to the final stage of thrombotic complications. The narrowing of the arterial lumen is not necessarily a sign of myocardial infarction, and treating narrowed blood vessels does not prolong life. Although invasive procedures are needed in some cases, we understand that medical treatment and lifestyle modification (diet and physical activity) produce benefits that may result from reductions in inflammatory processes [49].

Usually, endothelial cells (EC) prevent leukocyte adhesion. However, the triggers of atherosclerosis can initiate the expression of adhesion molecules on EC, mediating leukocyte adhesion to the arterial wall. A key part of this interaction is VCAM-1. It is likely that oxidized lipids can induce gene expression via the pathway initiated by the nuclear transcription factor-kB (NF-kB), such as IL-1β and TNF-$\alpha$ [50].

This concept of vascular inflammatory disease allows a new approach for risk stratification and treatment. Increased levels of CAM are predictive of cardiac events and are an independent risk factor in men with coronary disease [51]. In our previous study, we demonstrated the presence of the endothelium as well as the products of NF-kB signaling and VCAM-1 in an experimental model of metabolic syndrome in hypertensive rats receiving a fructose-rich diet fructose-fed hypertensive rats (FFHR) [52].

Chemokines are low molecular weight cytokines responsible for mediating the maturation, differentiation, and migration of cells involved in the inflammatory response. In addition to this role, chemokines could promote reactive oxygen species (ROS) production and other cytokines during leukocyte infiltration of the vessel wall. Monocyte chemotactic protein-1 (MCP-1) is a chemokine that regulates the migration and infiltration of monocytes and macrophages into the site of inflammation. It is overexpressed in the presence of cardiovascular risk factors, especially in atherosclerotic lesions. Differential activation induces nuclear transcription factors such as NF-kB and AP-1, which leads to the release of IL-6 and the proliferation of VSMC [53].

Cytokines are soluble proteins that form a complex signaling network critical in the regulation of innate and adaptive inflammatory response. Cytokines modulate the inflammatory response through their influence on the growth, development and activation of leukocytes, and other inflammatory cells. TNF-$\alpha$ is a key mediator in systemic inflammation with a significant role in the Th1 inflammatory pathway. The activity of TNF-$\alpha$ is varied and includes

the production of interleukin CAM expression, cell migration and activation, and activation of metalloproteinases (MMP) and COX activity, promoting the procoagulant state. TNF-$\alpha$ is detected in endothelial cells and smooth muscle cells at all stages of the formation of atheromatous plaques [54].

There are over 30 members of the interleukin family. They are subdivided by the similar structure or homology of the receptor. The transformation from a vascular homeostasis inflammatory state is influenced by an imbalance between the pro-inflammatory and anti-inflammatory activities of interleukins. The role of IL-1 includes the stimulation of CAM, chemokines, growth factors, tissue factor, and other cytokines. The expression levels of the receptor antagonist IL-1Ra significantly increase in unstable angina compared with stable angina. Decreased levels of IL-1Ra after coronary stent placement may be linked to a low association with recurrent ischemia [55]. IL-6 is a multifunctional cytokine with a central role in inflammation. Elevated levels of IL-6 increase the risk of myocardial infarction and mortality in patients with coronary heart disease [56].

IL-10 has pleiotropic properties and influences different cell populations. Its most important role is in inflammatory vascular disease as part of the Th2 response. The expression of IL-10 decreases the expression of inflammatory cytokines, decreasing the Th1 phenotype. IL-10 also decreases NF-kB signaling reducing synthesis of pro-inflammatory cytokines, CAM, chemoattractants, and growth factors [57, 58].

Endothelial dysfunction in FFHR causes an increase in the expression of NF-kB and AP-1 and the posttranscriptional product VCAM-1. The expression of NF-kB (p65) and AP-1 (c-fos) predominates throughout the vessel wall. Increased VCAM-1, as discussed in the literature, is a marker of vascular inflammation, vascular permeability, and endothelial dysfunction.

This experimental model produced an increased expression of several cytokines. This finding demonstrates that the vascular bed FFHR model presents a pro-inflammatory and proatherogenic microenvironment that favors vascular remodeling. C-reactive protein (CRP) was used to evaluate whether this local inflammatory process is also systemic and revealed significantly increased IL-6 expression in the liver.

The potential importance of vascular wall inflammation as a therapeutic target remains an area not yet fully explored, where understanding the involvement of inflammatory mediators in vascular remodeling is relevant. The data suggest that oxidative stress and the subsequent activation of genes involved in the inflammatory process are actively involved in organ damage at the vascular level.

## 6.2. Vascular remodeling and extracellular matrix metalloproteinases

MMPs are tools for maintaining the homeostasis of extracellular structures. Their synthesis is induced by cytokines as well as cell-cell and cell-matrix interactions. Acute coronary syndromes are an example of an increase in clinical conditions, specifically in the vulnerable region of the plaque [59]. Exposure to oxidized low-density lipoproteins or TNF-$\alpha$ induces the expression of MT3-MMP, a protease that degrades atherosclerotic plaques and is expressed in macrophages [60, 61].

MMPs with accessory signaling molecules can modulate cell-cell interactions through the activation of signal transmission and release of cytokines and chemokines. By these effects, accessory signaling molecules can propagate the inflammatory response.

## 6.3. Vascular remodeling and acute phase reactants

The production of acute phase reactants is a normal physiological response to cytokine release in acute and chronic inflammatory conditions. Ultrasensitive quantification of CRP, when it is below the detection limits of the common assay, has a very important role in the detection of vascular inflammation and cardiovascular risk prediction. There is evidence that CRP is involved in atherosclerosis, especially during the early stages. It stimulates the production of pro-inflammatory cytokines in monocytes and macrophages [62] and mediates the expression of CAM, allowing for increased leukocyte adhesion and migration. Their increased expression suppresses endothelial nitric oxide synthase [34] and promotes a procoagulant state.

Multiple studies have determined that increases in CRP are an independent risk factor for developing atherosclerosis. Data from clinical studies indicate that this association is less important when viewed in healthy subjects and controls inflammatory markers such as IL-6 and fibrinogen [63, 64], whereas another study identified CRP as a predictor of diabetes mellitus independent of established risk factors. CRP also indicated a correlation with the risk of cardiovascular events in women with metabolic syndrome [65].

## 6.4. Vascular remodeling and the renin-angiotensin-aldosterone system

Another important pillar in the vascular remodeling process is the renin-angiotensin-aldosterone system (RAAS) [66, 67]. To evaluate its participation, we studied the expression of AT1R and AT2R at the vascular level. In the experimental model of FFHR, we observed increased expression of AT1R and decreased expression of AT2R, promoting growth, vascular hypertrophy, and endothelial dysfunction. The release of ROS and initiation of vascular inflammation through different intracellular signaling cascades foster interconnections with other routes such as NAD(P)H oxidase and the growth factor receptor associated with insulin (IGFR).

**Figure 4** allows us to appreciate the AT1R-associated intracellular cascades. In this experimental model, the route associated with the satellite receptor and the IGFR subunit associated with NAD(P)H oxidase are the most important pathophysiological mechanisms. The FAK pathways PI3K and JAK2 generate stimuli and trigger contraction, migration and cell adhesion via intranuclear promoters that synthesize ICAM-1 and VCAM-1. Endothelial Growth Factor Receptor (EGFR) and Insulin Growth Factor Receptor (IGFR) amplified pathways are associated with cellular growth and hypertrophy as a result of insulinogenic stimuli and permit activation of collagenase, which modifies the extracellular matrix. Finally, the oxidative stress pathway stimulated by angiotensin activates redox-sensitive inflammatory molecules such as AP-1 and NF-kB, which amplify the inflammatory response by cytokines, chemokines, and lymphokines to ultimately induce more vascular inflammation.

Angiotensin II is the main effector of the RAAS in the homeostatic regulation of the cardiovascular system and in the pathogenesis of cardiovascular disease. Aldosterone interacts with mineralocorticoid receptors (MR), causing endothelial dysfunction, facilitating thrombosis,
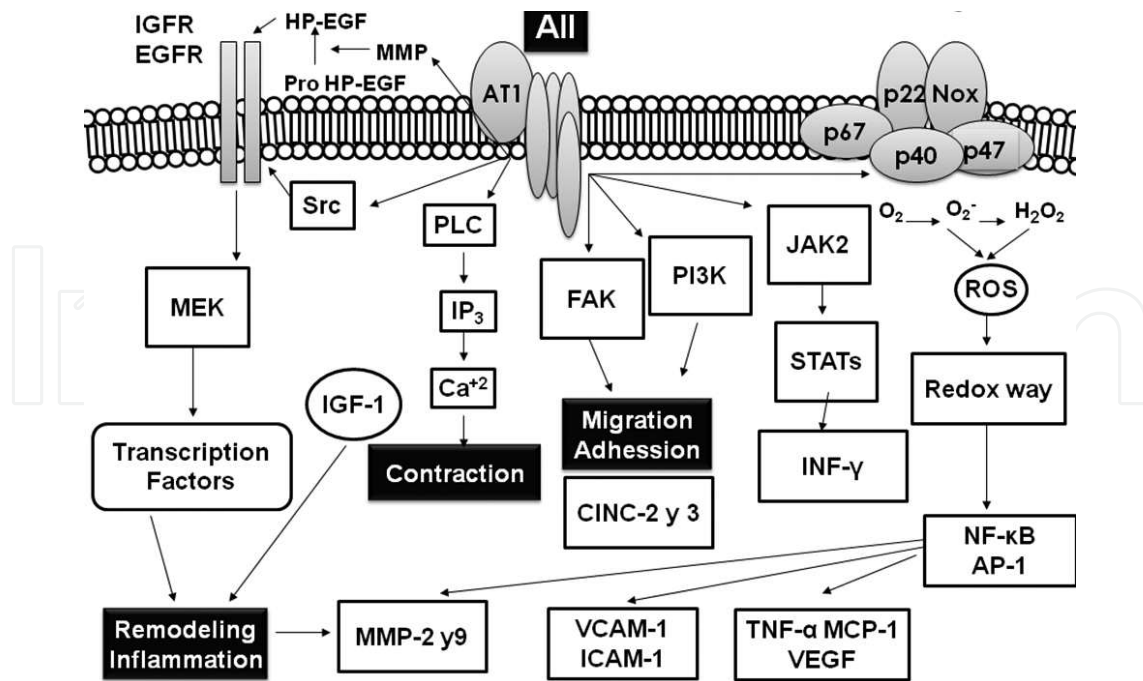
**Figure 4.** Associated intracellular cascades to physiopathology of vascular remodeling. In FFHR experimental model, the route associated with the satellite receptor and the IGFR subunit associated with NAD(P)H oxidase are the most important pathophysiological mechanisms. Also, the oxidative stress pathway stimulated by angiotensin activates redox-sensitive inflammatory molecules such as AP-1 and NF-kB, which amplify vascular inflammatory response.

reducing complacence, causing vascular hypertrophy and cardiac fibrosis, and generating pathological remodeling. Aldosterone also induces the growth and proliferation of VSMC. A classical genomic action of aldosterone on MR is the translocation of this Aldo-MR complex into the nucleus, where it interacts with promoters to post-transcriptionally regulate gene and protein expression. For this path, increased Ki-ras2A expression (small and monomeric GTP-binding protein), which is associated with cardiac remodeling, generates fibrosis, and cell proliferation by ERK1/2 possibly [68]. Recently, some authors have demonstrated that aldosterone stimulates EGFR intracellularly in CHO cells. The transactivation of this receptor has also been described as a crucial step in the cascade of MAPK signaling activated by angiotensin II. This pathway allows for "cross-talk" and mutual activation that allows the development of cardiovascular injury and subsequent remodeling. The latter route is via "fast" activation, which is different from genomic stimulation and stimulates MKP-1 and Ki-generated ras2A proliferation and vascular remodeling; this discovery explains the changes previously observed in other studies [69].

Noting the role of aldosterone in vascular remodeling in FFHR, we observed that chronic administration of spironolactone did not change the variables of metabolic syndrome that were partially reversed by oxidative stress. This can be explained by the relationship between aldosterone and the angiotensin II receptor AT1R, which sensitizes the effects and increased the post-receptor response [67].

In summary, abundant evidences indicate the involvement of the RAAS in the pathophysiology of vascular remodeling; our observations in experimental pathology highlight the structural and functional changes.

In this special issue, different authors have tried to demonstrate the involvement of different pathophysiological mechanisms to clarify the vascular changes associated with hypertension and metabolic syndrome.

## 7. Clinical data

The most feasible possibility for studies of resistance vessels in humans relies on the examination of small muscular arteries from biopsies of subcutaneous gluteal fat. Small arteries can also be obtained from omental fat [70–73]. The dissected vessels are mounted in a wire or pressure myograph, but due to the invasive character of these procedures, most relevant studies are of modest size [74–76]. In other cases, untreated hypertensives in place of patients newly diagnosed. In this studies, a data indicate that small subcutaneous arteries of nondiabetic hypertensives undergo inward eutrophic remodeling. Evidence suggests that diabetes, on top of essential hypertension, is associated with media hypertrophy (eutrophy remodeling). The same hypertrophy was also shown by one of these studies in normotensive diabetics, supporting a pressure-independent effect.

Finally, hypertension secondary as renovascular disease could promote media growth in arteries [77–80].

When evaluating the clinical data, there are two problems.

1. sampling problem.

2. subcutaneous vasculature is not necessarily representative of other vascular beds. In opposition to this idea, a positive correlation has been found in hypertensive patients between coronary flow reserve and the M/L ratio of subcutaneous arteries, indeed supporting that hypertensive changes of microvascular structure were not limited to the subcutis tissue.

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