Over the last decade, a number of investigations have recognized a relationship between lipids and hypertension, in particular with hypertensive renal disease, independently from co-morbidities such as Obesity, Diabetes and Metabolic Syndrome. In the next few pages, we will review some of the salient aspects of this relationship. It is not the aim of this presentation to cover the very extensive bibliography on the subject, but rather to validate therapies aimed to control hyperlipemia in renal diseases associated to arterial hypertension.

1 - Mechanisms of Arterial Hypertension

a) The Critical Role of Sodium Balance

Sodium retention and the subsequent volume expansion are thought to be an important (if not the most important) cause in the development of Renal Hypertension. In this view, physiologists and clinicians have classically visualized the *excessive volume* as exerting a greater than normal pressure on vessel walls. This initial effect, easily demonstrated by a rapid saline infusion, is eventually replaced by a rise in total peripheral resistance, the so-called Bayliss myogenic effect. Oddly enough, if the aim were the maintenance of normal blood pressure, peripheral resistance should decrease, not increase and thus, the observed physiologic response fails to explain why the small resistance vessels should contract and stay contracted for a long time in fixed hypertension. This issue is relevant because it implies that blood pressure may be only a subservient of volume regulation, or better said, sodium balance. The degree of expansion by itself is inconsequential. Witness conditions of volume expansion such as Pregnancy or Liver Cirrhosis, where autoregulation remains intact and blood pressure does not increase. In fact, in Congestive Heart Failure, volume expansion and increased vascular resistance co-exists while blood pressure remains unchanged.

To answer this question, Guyton suggested that whatever the renal abnormality causing salt retention, it would upset sodium balance leading to the much dreaded cardiovascular congestion. To correct the balance, the kidney generates a number of mechanisms that increase blood pressure and thereby enhance renal sodium excretion. Once sodium balance is corrected, blood pressure decreases only if the salt retaining mechanism is not longer present. In other words, blood pressure accommodates to whatever level is needed to maintain salt balance. That is to say, as long as the renal excretory defect is present blood pressure will remain elevated. This notion is the basis of the pressure-diuresis curve [1] that basically establishes a direct and very sensitive relationship between blood pressure and renal salt excretion. (Figure 1).
This compensating mechanism operates in all forms of hypertension not only in hypertension of renal origin. According to this notion, the development of chronic arterial hypertension, requires the "renal permission". If blood pressure increases for any of the many reasons known to us, the normal kidney would certainly make sure that salt output increases and that a negative balance eliminates the need to keep the blood pressure elevated. However, a diseased kidney, or a kidney constrained in its regulatory function (by genetic milieu, drugs, hormones, sympathetic activity, etc) may not be able to handle a given salt load at the usual blood pressure level; consequently, blood pressure will rise to reinstate the sodium balance.

This notion establishes the superior rank of perfusion over blood pressure.

b) Renin-Angiotensin System, Oxidative Stress and Salt Retention.

Many mediators of salt retention have been postulated, (Table 1) and it is quite possible that several of them participate causing changes in kidney function that ultimately rise blood pressure. In this respect, it is important to bear in mind that all hypertension models available, (including the genetic models), affect renal function in one way or another. The consequences of the separate actions of these different regulators cause changes in renal hemodynamics, in particular vascular reactivity that increases very early in the pre-hypertensive state. This increased pressor response (hypereactivity) may be the consequence of an imbalance between factors that are vasoconstrictors and antidiurectic and factors that are vasodilator and natriuretic.

![Image](image.png)

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<table>
<thead>
<tr>
<th>Table 1: Mediators of Arterial Hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Renal sodium balance</td>
</tr>
<tr>
<td>2. Renin-Angiotensin – Aldosterone System</td>
</tr>
<tr>
<td>3. Sympathetic Nervous System</td>
</tr>
<tr>
<td>4. Nitric Oxide</td>
</tr>
<tr>
<td>5. Prostaglandins and other Eicosanoids</td>
</tr>
<tr>
<td>6. Endothelinilys</td>
</tr>
<tr>
<td>7. Renalase</td>
</tr>
<tr>
<td>8. ANP – Uroguian and other endopeptidases</td>
</tr>
<tr>
<td>9. Other</td>
</tr>
</tbody>
</table>

Undoubtedly, the imbalance between the actions of the prohypertensive renin-angiotensin system and the antihypertensive Nitric Oxide (NO) play a pivotal role. Angiotensin (Ang II) stimulates membrane oxidases and thereby increases the production of superoxides. These are quenched by NO leading to the formation of the very potent oxidant peroxinitrite. As a result, NO availability decreases [2-4]. The combined effects of increased superoxides and decreased NO is associated with increased vasoconstriction, sodium retention and vascular inflammation, all of which may perpetuate not only arterial hypertension but also the renal defect in sodium handling.
2 - The Role of LDL-Cholesterol in Hypertension

Increased LDL Cholesterol and Arterial Hypertension frequently co-exists [5,6]. This association is quite important because both, LDL and Hypertension can cause endothelial dysfunction and vascular inflammation. In fact, in many aspects, the mechanisms leading to inflammation are shared by both, the renin-angiotensin system and LDL. And yet there are no clear-cut arguments showing that LDL may directly or indirectly lead to hypertension.

a) High Serum Lipids and High Blood Pressure

It has been suggested that the interactions of lipoproteins, in particular LDL, with other neurohumoral systems could play a pathogenic role in blood pressure elevation [7]. In effect, serum triglycerides and LDL cholesterol levels correlate with blood pressure levels [8] and the prevalence of dyslipidemia increases with rising blood pressure [9]. In addition, blood pressure is increased not only by a high cholesterol diet in normal rats, but also by acute cholesterol elevations induced by blood exchange from hypercholesterolemic rats [10]. Similarly, the infusion of cholesterol emulsions increases blood pressure in rabbits [11] whereas intralipid and heparin infusions increase blood pressure in normotensive normocholesterolemic subjects [12]. In most studies, these blood pressure elevations are associated with increased Reactive Oxigen Species (ROS) and/or decreased NO activity. For instance, Atarashi et al found increased MDA, a marker of tissue oxidation, in animals with acutely increased serum cholesterol [10]. These findings suggest that ROS may be involved in the mechanisms leading to hypertension.

b) Hypertensive Mechanisms in Dyslipemias.

Studies in human and in animal models have shown that hypercholesterolemia is associated with vascular hyperreactivity. In fact, normotensive hypercholesterolemic subjects have an increased vasoconstrictor response to stress test [13], and LDL increases intracellular free calcium concentration in vascular smooth muscle [14] thus providing an explanation for the increased vascular reactivity.

However, this exaggerated state of vasoconstriction could result from increased activity of the Sympathetic Nervous System. Indeed, hypercholesterolemic subjects have higher blood levels of NE [15] and a high cholesterol diet increases urinary NE excretion rate [16]. This activation of the Sympathetic Nervous System may be responsible, at least in part, for the oxidative stress-induced inflammation. On the other hand, NE induces similar increase of blood pressure in normocholesterolemic and hypercholesterolemic subjects suggesting that other mechanisms may be necessary to induce blood pressure elevation [16].

Prominent amongst other potential mechanisms is the activity of the Renin Angiotensin System. Indeed, patients with Familial Hypercholesterolemia, AngII-mediated pathways are enhanced [17] and Ang II-induced vasoconstriction is increased. This enhanced activity of the Renin Angiotensin System may result from LDL induced AT1 receptor up-regulation. Indeed, studies by Nickenig et al in isolated vascular smooth muscle cells from hypercholesterolemic rabbits showed enhanced vascular expression of AT1 receptors and a significant correlation between AT1 receptor density and LDL plasma concentration [18,19]. On the other hand, LDL increases Ang II release in cell cultures [20].

In summary, LDL may amplify the activity of the Renin Angiotensin System not only by enhancing receptor activity, but also by increasing Ang II synthesis. That LDL affects endothelial function through the renin angiotensin system is supported by studies showing that the AT1 receptor antagonist Candesartan improves the abnormal endothelial response to acetylcholine in hypercholesterolemic subjects [21].

In keeping with this notion and because the AT1 receptor is a major source of reactive oxygen species (ROS) in the vascular wall, it has been proposed that LDL-mediated AT1 receptor overexpression may account for enhanced vascular release of free oxygen radicals and by these means increase vasoconstriction and cell proliferation. Indeed, hypercholesterolemia increases de synthesis of ROS in endothelial cells by stimulating membrane NADPH oxidase [22], and also by promoting the release of xantine oxidase into de circulation. Atarashi et al. found that acute hypercholesterolemia induced by blood exchange from hypercholesterolemic rats increases the concentration of Malonyl dialdehyde.

The effects of LDL on Ang II release are most probable related to lysophosphatidylcholine (LPC), a component of the LDL particle. Indeed, LPC increases Ang II-induced pressor response, but in the absence of Ang II, neither OxLDL nor LPC show significant effects on resting tone of aortic rings. Thus, the renin angiotensin system seems necessary for LDL to cause changes in vascular tone. [23]

This mechanism has been further defined by adding the Rho kinase inhibitor Y27632 after Ang II/LDL-induced vasoconstriction. The inhibitor reverses the Ang II-induced constriction and has no effect in its absence [23]. Thus, vascular tone can be increased by two Ang II-mediated mechanisms. (Figure 2) On the one hand, Ang II increases cytosolic Ca++ concentration and on the other Rho kinases increase light chains myosin.
Hypercholesterolemia may then increase the activity of the Renin Angiotensin System and by this means the production of ROS is enhanced. O2- quenches NO and thereby reduces its availability. In this respect, it has been shown that hypercholesterolemia alters NO mediated endothelial dependent vasodilation in coronary and forearm vessels[24, 25].

Concurring with this notion, atorvastatin lowers blood pressure in normocholesterolemic, spontaneously hypertensive rats (SHR), improves endothelial dysfunction and reduces ROS. Atorvastatin induced downregulation of AT1 receptor expression and decreased expression of the NAD (P)H oxidase subunit p22phox. The activation of the AT1 receptor plays a pivotal role for the induction of this redox system in the vascular wall.[26]

In summary, there are clear evidences supporting the effects of serum cholesterol on vascular tone. These effects may result from the direct action of ROS and oxidized LDL, or from increased activity of the renin angiotensin system. In both cases, oxidant stress seems of overriding pathophysiologic impact. Indeed, anticholesterolemic agents such as the HMG Co reductase inhibitors (statins) increase flow-dependent vasodilation as efficiently as Losartan, an angiotensin II receptor antagonist. The individual effects are added when these two agents are combined [27]. Delbosc et al suggested that the antioxidant action of HMG CoA reductase inhibition in Ang II–dependent hypertension is responsible for the beneficial effects on cardiovascular alterations.[28].

3) Renal Effects of LDL

Hypercholesterolemia is associated to oxidized low-density-lipoprotein (ox-LDL) and increased oxidative-stress. Because oxidants affect systemic vascular structure and function, it is reasonable to expect the LDL-induced ROS could cause similar renal vascular changes. In effect, hypercholesterolemia functions as an independent risk factor for renal injury. In our laboratory, we found that a high cholesterol diet in normotensive rats causes early glomerular inflammation, increased proteinuria and glomerular mononuclear cell infiltration and hypertrophy even before blood pressure rises. These inflammatory changes were coupled to abnormal renal vascular reactivity (Figure 3). Of interest, all of these abnormalities were prevented by atorvastatin. (Figure 4)
Our findings are in agreement with clinical observations in humans and animal models showing that hyperlipidemia causes abnormalities in renal hemodynamics, glomerulosclerosis and progressive renal damage. Because similar harmful effects of ROS have also been documented on renal parenchyma, mesangial cells culture, and on matrix components [29-32], it could be surmised that ROS are the mediators of LDL-induced renal damage. [33,34]

Although we did not find an elevation of blood pressure during the short span of our study, the introduction of a high salt intake worsened the histological features. These additional injurious effects of salt could result from further increases in oxidative stress [35]. In our studies, we found that Atorvastatin was able to reverse glomerular hypertrophy and inflammation and at the same time to improve the anomalous renal endothelial dysfunction. Our findings are in agreement with those of Jing and Roman who found that chronic treatment with lovastatin in SHR shifts the relations between renal medullary blood flow, renal interstitial pressure, sodium excretion, and renal perfusion pressure to lower blood pressure and to attenuate the development of hypertension and renal vascular hypertrophy in SHR.[36]

In contrast to studies performed in human forearm and in the coronary circulation, our results suggest that hypercholesterolemia does not primarily impair L-arginine-induced renal vascular relaxation [37]. Instead, hypercholesterolemia seems to decrease renal cortical NO Synthesis via an Ang II Type 1 Receptor-sensitive mechanism [38]. All these data suggests that LDL-mediated increases in ROS lead to renal damage. In effect, there is increasing evidence to suggest that lipid disorders play a role in the progression of renal disease [39,40] For instance, esterified and unesterified cholesterol (present in LDL) accumulate in sclerotic glomerular segments as the glomerular lesions progress. This is associated to a progressive decrease in apo B .[41] Thus, LDL may act as one of a major endogenous modulator for mitogenic signaling response and cell proliferation within the glomerulus.
Studies with HMG Co A reductase inhibitors support these findings. For instance, Simvastatin attenuates the inflammatory and pro-oxidative environment as well as fibrosis in kidneys in pigs with diet-induced hypercholesteroleemia. Renal perfusion is enhanced in these animals. [42] Similarly, monocyte infiltration and the expression of the adhesion molecule VCAM-1 were shown to be reduced by Cerivastatin treatment [43].

Platelets are known to enhance monocyte activity, and Cerivastatin reduces monocyte and platelet activities [44]. The decrease in proteinuria by statins may be due in part to the decrease in monocyte and/or platelet activity. The beneficial effects of statins have been shown in hypercholesterolemic rabbits and in diet-induced hypercholesterolemia superimposed on an activated renin-angiotensin system[45]. This combination accelerates the development of fibrosis in the stenotic kidney by amplifying profibrotic mechanisms and disrupting tissue remodeling. These alterations might contribute to renal disease progression in Atherosclerotic Renal Disease and might account for the increased propensity for end-stage renal disease [46]. Buemi et al. [47] have reported that fluvastatin is effective in decreasing proteinuria in patients with IgA nephropathy.

Downregulation of AT1 receptor gene expression and reduced oxidative stress may contribute to the beneficial therapeutic effects observed with statins that are beyond the lowering of plasma cholesterol. In effect, lipid-lowering therapy decreases AT1 receptor density [16]. Be that as it may, several studies, have shown that HMG Co reductase inhibitors preserve endothelium-dependent and endothelium-independent function, before any lipid lowering effect. Thus, the correction of endothelial dysfunction seen with Fluvastatin may follow pathways not identical to the hypercholesterolemia-induced dysfunction [48].

4) LDL and Renal Hypertensive Disease

Despite all the functional and structural abnormalities described, all hypercholesterolemic models show a sluggish hypertensive response. For instance, in the salt-sensitive Dahl hypertensive model, hypertension develops only if the hypercholesterolemic diet is accompanied by high sodium intake. Salt is certainly responsible for this effect and yet the treatment with Atorvastatin in this model causes a reversal of hypertension [49].

In the presence of structural or hemodynamic renal alterations (inflammation, fibrosis, etc) LDL could facilitate the hypertensive process. To test this hypothesis we study the effects of statins in the 5/6 Nephrectomy rat. In this model, renal damage progresses to renal failure and leads to salt-sensitive hypertension, proteinuria, and renal fibrosis. As expected, we found that a normal salt diet caused no changes in blood pressure, whereas a high sodium intake readily increased it. (Figure 5)

This marked salt-sensitivity, was accompanied by increased proteinuria, decreased renal indices of NO, and increased renal oxidant stress. (Figure. 6 and 7).
Atorvastatin, prevented the blood pressure from rising in the high sodium group and decreased the blood pressure in the normal sodium group (Figure 5). These effects were accompanied by improved salt balance in both groups but proteinuria (Figure 6) and renal NO/ROS balance were improved only in the normal salt diet group. In the high sodium group, the beneficial effects of Atorvastatin on blood pressure and on sodium balance were not reflected by significant improvement in proteinuria, NO indices and oxidative stress (Figure 6 and 7).

The effects of Atorvastatin on blood pressure could be related to decrease tubular reabsorption\[50\]. In our study, Atorvastatin attenuated sodium retention (via enhanced excretion), although the net effect was partial and the animals remained with a milder positive sodium balance. Interesting, this partial correction of sodium balance was accompanied by total control of blood pressure. This suggests that while part of the beneficial effects of atorvastatin on blood pressure may be due to enhanced sodium excretion, separate mechanisms reducing peripheral resistance are likely. In effect, atorvastatin had a mild though significant blood pressure lowering effect in the rats on normal salt intake with neutral sodium balance.

Thus, it is tempting to postulate that atorvastatin may have prevented endothelial dysfunction as has been described by other investigators and it is consistent with prior studies describing statins as improving endothelial function and decreasing blood pressure in non-salt-sensitive hypertensive models [51,52].

The natriuretic effect of atorvastatin was not unexpected as statins have been shown to decrease Na and/or Cl reabsorption in various nephron segments [50]. These effects have been postulated to be due to decreased oxidant stress and/or increased NO, [53] either of which may inhibit tubular sodium excretion or increase renal medullary blood flow with the consequent increase in renal interstitial pressure and passive back-diffusion of sodium through the paracellular pathway [54].

Finally, in our study Atorvastatin improved proteinuria together with NO and oxidant stressing the normal salt group. While the NO/ROS balance did not appear to be entirely implicated in the salt-sensitive hypertension induced by Nx, it closely paralleled proteinuria, suggesting that it may be a culprit in the renal injury. Indeed, the beneficial effect of atorvastatin on proteinuria in the normal salt diet rats was accompanied by normalization in renal NO indices, whereas the lack of effect of atorvastatin on proteinuria in the high salt diet rats was accordingly associated with a lack of
improvement in the renal NO indices and a no significant improvement in oxidant stress. This suggests that Atorvastatin has beneficial effects on renal injury even in the absence of hyperlipidemia and independently of its ability to lower blood pressure and enhance sodium excretion. In keeping with this notion, our results also suggest that atorvastatin may exert its favorable effect on renal injury (as evidenced by decreased proteinuria) by normalizing the NO/ROS balance.

The effects of a high salt intake deserve a further comment. The beneficial actions of Atorvastatin on renal NO and on protein excretion rate were completely abrogated by the high sodium diet. This comes as no surprise: high salt intake may blunt the beneficial effects of other agents including ACE inhibitors [55]. Furthermore, high salt intake causes severe hemodynamic renal dysfunction and proteinuria in SHR in the absence of changes in blood pressure [25]. High salt diet may not only influence urinary albumin excretion independently from its effects on blood pressure, but also may independently predict the risk for coronary artery disease [56]. Nonetheless, considering atorvastatin’s efficacy in preventing salt-sensitive hypertension [49], and the role of hypertension in promoting renal injury, we would have expected a significant improvement in proteinuria. Because the lack of benefit in the proteinuria was accompanied by unimproved renal NO, it seems likely that at this early stage of Nx, the major stimulus for renal injury is due to the NO/ROS imbalance rather than the hypertension. On the other hand, salt may have prevented the beneficial effects of atorvastatin by a direct pro-oxidant effect of NaCl [57].

In summary, in subtotal nephrectomy Atorvastatin lowered the blood pressure, prevented the rise in proteinuria and normalized the NO/ROS balance in animals on a normal salt intake. In sodium loaded rats Atorvastatin prevented the rise in blood pressure, and yet it could not reverse other deleterious effects of high-salt intake.

While it remains irrefutable that salt sensitive is a key instigator in sub-optimal blood pressure control, the remarkable protective action of HMG-CoA inhibition on renal indices and blood pressure cannot be negated.

Summary
LDL can activate the renin angiotensin system by releasing Ang II from the cells and by up-regulating the AT 1 receptor (Figure 8). Ang II stimulates NADH oxidases and Xantine Oxidases thus increasing ROS. These compounds not only can oxidize LDL but also can decrease NO availability thereby increasing peroxinitrates. As a result, inflammatory genes are induced and this is followed by structural and functional abnormalities in vascular tissue. These abnormalities are manifested by endothelial dysfunction and increased vascular reactivity.

Similar effects have been described in the kidney. The immediate consequence is the stimulation of renal hypertensive mechanisms that lead to sodium retention and hypertension.
Bibliography

36. Fleischmann EH, Schlach MP, Schmidt BM, Oehmer S, Schmieder RE. Hypercholesterolaemia and...
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