Nitric Oxide in Hypertension: Relationship With Renal Injury and Left Ventricular Hypertrophy

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Abstract—Hypertension is accompanied by architectural changes in the kidney, heart, and vessels that are often maladaptive and can eventually contribute to end-organ disease such as renal failure, heart failure, and coronary disease. Nitric oxide, an endogenous vasodilator and antithrombotic agent synthesized in the endothelium by a constitutive nitric oxide synthase, inhibits growth-related responses to injury in vascular cells. Specifically, in the presence of hypertension, nitric oxide may work in the kidney by inhibiting both mesangial cell hypertrophy and hyperplasia as well as synthesis of extracellular matrix and in the heart and systemic vessels by modulating smooth muscle cell hypertrophy and hyperplasia. The effects of nitric oxide are antagonistic of the effects of angiotensin II. Shear stress and cyclic strain, physical forces known to operate in hypertension, are accompanied by increases in endothelial nitric oxide synthase expression, nitric oxide synthase protein, and nitric oxide synthase activity in endothelial cells. Experimental studies using genetic models of hypertension show a variation in hypertension-modulated vascular nitric oxide synthase activity in different strains of rats. These studies suggest that upregulation of vascular nitric oxide synthase activity is a homeostatic adaptation to increased hemodynamic workload in hypertension and that this may help prevent end-organ damage. If these findings apply to humans, differences in end-organ disease seen in patients with similar degrees of hypertension may be due in part to genetic differences in vascular nitric oxide synthase activity in response to hypertension (Hypertension. 1998;31[part 2]:189-193.)

Key Words: nitric oxide ■ hypertension ■ angiotensin II ■ renal injury ■ left ventricular hypertrophy

Epidemiological studies have demonstrated that in hypertensive patients, increased serum creatinine, proteinuria, and microalbuminuria are independent predictors of an increased cardiovascular morbidity/mortality due to LVH/heart failure and coronary artery disease. Furthermore, in patients with end-stage renal failure who are receiving hemodialysis, the incidence of myocardial ischemia/infarction approaches 20 times that in the general population. In these patients the prevalence of cardiac death is higher during the first few years of dialysis, suggesting that cardiac disease is preexistent and not acquired during chronic hemodialysis. In the aggregate these studies clearly suggest that in hypertension end-organ injury is diffuse, affecting all organs (albeit the severity of the individual end-organ injury varies in different patients). On the other hand, it is also clear that in hypertensive patients the prevalence of LVH, renal failure, and coronary artery disease, which are the major causes of morbidity and mortality, varies in different populations of hypertensive patients, suggesting that susceptibility to cardiovascular and renal disease is not uniform.

In hypertension, an increase in pressure-workload fosters adaptive changes in the endothelium, the vascular smooth muscle, and the extracellular matrix of vessels and the heart. However, in many patients, the adaptive changes to hypertension, which occur in the kidney, heart, and vessels, are in fact maladaptive because they are harbingers of renal failure, cardiac failure, and coronary artery disease. Obviously, there is a need for ways to identify those patients who are at higher risk for development of end-organ disease. In this context, recent studies have shown that a deletion polymorphism of the ACE gene is associated with target-organ damage in hypertension. Specifically, the D allele of the ACE gene is associated with microalbuminuria, LVH, and coronary artery disease as well as the renal complications of insulin-dependent diabetes.

The endothelium plays a crucial role in the regulation of vascular tone and vascular remodeling. NO synthesized by a constitutive endothelial NOS is an endogenous vasodilator and antithrombogenic agent, which inhibits vascular smooth muscle and mesangial cell growth and therefore may participate in vascular as well as glomerular remodeling in response to hypertensive injury.

The association between increased activity of the local tissue renin-angiotensin system and vascular pathophysiology has been well demonstrated. NO appears to be the major endogenous antagonist of the vascular actions of Ang II and, therefore, a balance between Ang II and NO appears pivotal for the maintenance of vascular homeostasis.

Given the close association between abnormal renal parameters and cardiovascular morbidity/mortality and the growing evidence for NO in vascular physiology and pathology, recent studies have focused on the role of NO in hypertensive renal disease as well as its relationship with concomitant injury affecting the left ventricle and large vessels such as the aorta.

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The Kidney and NO: Relationship Between Structure and Function

The glomerulus is made up of the glomerular basement membrane, the epithelial cells outlining the glomerular basement membrane in the urinary space, and the mesangium forming the glomerular centrolobular area. The glomerular basement membrane reflects over the mesangium between the capillary loops but is absent at the point of contact between the glomerular endothelial cells and the mesangial cells. A barrier between circulating glomerular blood and the mesangium is thus formed by the single layer of fenestrated endothelium. Passage of plasma carrying large as well as small molecules is possible through the mesangial area because of the large size of the glomerular endothelial fenestrae. The products synthesized by the endothelial and mesangial cells are able to reach each other in high concentrations because of their close proximity.

Mesangial cells contain actin-myosin filaments and change their contractile state in response to vasoactive substances, much as vascular smooth muscle cells do. Agents such as Ang II, eicosanoids, ET-1, and NO synthesized and released locally can act on these cells in autocrine and paracrine fashion. The antagonistic interaction of locally synthesized Ang II and NO is important in the regulation of renal physiology and renal pathology. In the glomerulus, modulation of the glomerular microcirculation is possible under physiological and pathological conditions when these vasoactive agents act on the mesangium or the afferent and efferent arteriole, or both. The responses of glomerular cells to injury and resulting architectural changes of the glomerulus such as mesangial hypertrophy, mesangial hyperplasia, and increased mesangial cell matrix production are often due to the added effects of hemodynamic (glomerular hypertension) and nonhemodynamic actions of these vasoactive agents, much as occurs in systemic vascular beds.

Ang II has been found to control growth factors such as platelet-derived growth factor and transforming growth factor β, which have been implicated in the pathological remodeling of the glomerulus in response to injury. However, NO not only antagonizes the effects of Ang II on arteriolar tone and mesangial contraction but inhibits the response of mesangial cells to growth stimulating signals driven by Ang II that lead to mesangial cell hypertrophy and/or hyperplasia as well as to increased matrix production.

A dose-dependent increase in blood pressure and renovascular resistance occurs in response to systemic administration of NO synthesis inhibitors. These changes are accompanied by a significant reduction in renal plasma flow and a moderate decrease in glomerular filtration rate. NO inhibition also leads to an increase in afferent arteriolar resistance and to a decrease in the ultrafiltration coefficient, the latter probably being mediated by mesangial cell contraction. In addition, macula densa NO appears to control glomerular hemodynamics by way of tubuloglomerular feedback mechanisms. Renal sodium excretion may also be affected by the direct action of NO on the tubules and its ability to modify medullary blood flow and interstitial pressure. Selective inhibition of NO synthesis in the renal medullary interstitium decreases papillary blood flow and diminishes urinary sodium excretion but does not alter glomerular filtration rate or systemic blood pressure.

Interaction Between Ang II and NO

Increased actions of Ang II or NO may be due to an actual increase in the local concentration of the individual agent and/or to a concomitant decrease in the concentration of the other. Moreover, chronic NO synthesis inhibition induces glomerular and tubulointerstitial injury as well as coronary vascular remodeling and LVH that is accompanied by increased ACE expression and activity. This would suggest that decreased vascular NO bioactivity due to endothelial dysfunction as seen in hypertension may promote vascular hypertrophy due to a combined deficit of NO and local excess of Ang II. Indeed, experimentally, in vivo transfection of excess ACE to arterial segments results in localized vascular hypertrophy mediated by Ang II.

Ang II has been reported to activate NADH/NADPH oxidase in vascular smooth muscle cells and more recently in mesangial cells, leading to the cells' protracted synthesis of O$_2^-$, which has great affinity for NO, causing interaction between the two and resulting in either NO inactivation or the production of toxic peroxynitrite. Furthermore, in the glomerulus as in the vasculature in general, decreased NO bioactivity not only reduces the ability of NO to counteract Ang II actions on vascular tone but also diminishes the homeostatic role of NO in preventing vascular thrombosis, leukocyte adhesion to endothelium, and Ang II-driven mesangial cell hypertrophy/hyperplasia and production of extracellular matrix.

ET-1, a powerful vasoconstrictor, is capable of reducing renal blood flow and glomerular filtration rate by acting on preglomerular resistances and inducing mesangial cell contraction. The interaction between NO and ET-1 appears to be more important under pathological than under physiological conditions. In addition, ET-1 synthesis is upregulated by Ang II and downregulated by NO. ET-1 may thus play its role late rather than early in renal pathophysiological processes in that its importance may build as the renal bioactivity of NO decreases.

Hypertensive Renal Injury

Capillary pressures and flows in the glomerulus are regulated by independent changes in resistance of the afferent and efferent arterioles and coordinated by the concomitant contraction (or relaxation) of the mesangium. Under normal physiological conditions, an increase in systemic blood pressure is accompanied by an increase in preglomerular resistances.
The endothelium and the mesangium are the most vulnerable glomerular structures in glomerular hypertension. The endothelial dysfunction and pathological remodeling that occur in the kidney as well as in other vascular beds as a consequence of increased blood pressure may not be entirely explained by the increased hemodynamic workload imposed by hypertension, however, except perhaps when it is very severe.12-14,37

**NOS and Hypertensive Injury**

In vitro studies have demonstrated that hemodynamic forces such as shear stress36 and cyclic strain38 increase vascular NO production by increasing endothelial NOS expression, NOS protein, and NOS activity. Our laboratory has used age-matched SHR and DS rats with hypertension of similar severity and duration to investigate the relationship between hypertension and vascular NOS activity.12-15 Endothelium-dependent relaxation mediated by NO is normal in hypertensive SHR, whereas it is dramatically impaired in DS rats. Aortic calcium-dependent NOS activity measured by the conversion of L-[14C]arginine to L-[14C]citrulline was increased 106% in SHR but reduced by 73% in DS rats compared with their normotensive counterparts.21,23 These results explain why endothelium-dependent relaxation mediated by NO is impaired in DS rats but not in SHR. Endothelium-dependent relaxation was also impaired in renal and mesenteric vessels of hypertensive DS rats.21,23 Increased NOS activity in SHR would thus suggest that these rats are able to upregulate and maintain high levels of vascular NOS in response to hypertension.12-14 These findings also suggest that, by contrast, the endothelium of DS rats not only fails to increase NOS activity but in fact decreases it in response to hypertension.12-14 Hence, heightened vascular NOS activity probably represents “normal physiological” adaptation to the increased hemodynamic forces (ie, cyclic strain) in hypertensive states. On a similar note, serum levels of NO2/NOx, which are stable metabolites of NO, increase in Sprague-Dawley rats rendered hypertensive by placement of a clip in one of the renal arteries.34

High dietary salt did not foster hypertension, cardiac and aortic hypertrophy, or renal injury in Dahl salt-resistant rats.12,14 Complementarily, in DS rats, antihypertensive therapy consisting of an ACE inhibitor and a diuretic prevented hypertension, the fall in NOS and abnormal aortic endothelium-dependent relaxation, LVH, and renal injury.13 This further supports the notion that in DS rats, end-organ injury and the fall in NOS activity are a consequence and not a cause of hypertension. If these observations made in the genetic rat models of hypertension apply to humans, they may provide important insights into the pathogenesis and therapy of cardiovascular disease.

**Link Between NOS Activity and Renal, Vascular, and Cardiac Injury in Experimental Hypertension**

Findings in comparative studies of SHR and hypertensive DS rats suggesting a link between NOS activity, vascular remodeling, and end-organ injury are particularly striking. In SHR, aortic hypertrophy did not occur and LVH increased only
Nitric Oxide and Hypertensive Injury

15% 12 In hypertensive DS rats on the other hand, the aorta and left ventricle hypertrophied 36% and 88%, respectively, and there was in fact a significant negative correlation between NOS activity and aortic and left ventricular hypertrophy 2-14. In the kidney, increased NOS activity in SHR was accompanied by minimal glomerular and tubulointerstitial disease as well as minimal urinary protein excretion. In hypertensive DS rats, however, renal NOS activity fell, and severe glomerular injury, heavy proteinuria, and marked tubulointerstitial disease occurred44 (Figs 1 and 2).

In conclusion, our experimental findings and those of others strongly suggest that in hypertension, NOS activity is linked to the development of end-organ disease, particularly LVH and renal disease 40,41. Further, clinical studies in humans have suggested that impaired endothelin-dependent relaxations mediated by NO may not be a universal finding in hypertension 45,46. The prevalence of LVH, renal failure, and stroke, which are major causes of morbidity and mortality, varies in different populations of hypertensive patients 21,27. Recent human studies, genetic polymorphism in the renin-angiotensin system has been associated with cardiovascular and renal disease in hypertension 7,8. Inspired by these associations and the findings described, it is tempting to speculate that vascular NOS activity in response to hypertension is genetically determined and that the heterogeneity may at least partially explain the different rates of occurrence of end-organ disease in humans with hypertension of similar severity 21,47,48.

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