Endothelial Dysfunction and the Kidney: Emerging Risk Factors for Renal Insufficiency and Cardiovascular Outcomes in Essential Hypertension

Carmine Zoccali
Consiglio Nazionale delle Ricerche–Istituto di Bio-Medica, Clinical Epidemiology & Pathophysiology of Renal Diseases and Hypertension, Ospedali Riuniti, Reggio Calabria, Italy

Renal insufficiency in essential hypertension represents the expression of a medium- and small-size arteriolopathy characterized by intimal hyperplasia, hyalinosis, and smooth muscle cell hypertrophy (nephroangiosclerosis). Because in animal models endothelial dysfunction plays a role in this alteration, nephroangiosclerosis and the attendant renal insufficiency may be the expression of a systemic dysfunction of vascular endothelium. Endothelial function in the kidney vasculature of hypertensive individuals has been investigated little because studies on the hemodynamic response of the kidney to nitric oxide activation and blockade are laborious to perform. There is no direct proof that endothelial dysfunction in the forearm or in the coronary circulation is paralleled by a similar hemodynamic dysfunction in the kidney. A recent study in a large population of patients with essential hypertension showed that, independent of other risk factors, the GFR in these patients is strongly related to the forearm blood flow response to acetyl choline (an established test of endothelial function). Furthermore, in this study, C-reactive protein was inversely related to the GFR and with the vasodilatory response to acetyl choline, pointing to inflammation as a likely mechanism to explain the association between endothelial dysfunction and impaired renal function in essential hypertension. A dysfunctional endothelium may represent a critical link accounting for the risk for both renal impairment and cardiovascular complications in essential hypertension.


Nephroangiosclerosis: The Cinderella of Renal Diseases

According to major renal registries, nephroangiosclerosis is a disease that is responsible for at least one third of cases of ESRD. Comparatively, the contribution of glomerulonephritides is just one fifth to one sixth that of nephroangiosclerosis. In general, the epidemiologic burden of this disease still is not appreciated by internists and renal physicians. This is because only in a minority of patients (approximately 1:1000) does nephroangiosclerosis evolve to the end stage. Although rarely progressing to advanced renal failure, it is so prevalent in the general population that it eventually represents the most frequent cause of ESRD. That the epidemiologic burden of nephroangiosclerosis still is overlooked is transparent also from the scanty research efforts focused on this disease. Indeed, search of the major medical database PubMed shows that during the last 10 yr, the publication rate of papers that deal with glomerulonephritides has remained stably at approximately 1000 papers per year, whereas the corresponding figure for nephroangiosclerosis has been a mere 50 papers per year. This is a sort of scientific paradox because research efforts seem to be diverted toward relatively rare causes of ESRD and inexplicably overlook the most common cause of ESRD.

Chronic Kidney Disease Epidemic

During the past 5 yr, substantial knowledge has been accrued on the high frequency of minor degrees of renal insufficiency. In the United States, approximately 8 million Americans, or approximately 7% of the general population, display moderate (GFR 30 to 60 ml/min) chronic kidney disease (CKD). Such a high frequency cannot be attributed to immunologic or genetic diseases because these are rare, affecting less than 0.01% of the population. The most common causes of CKD are atherogenic diseases (hypertension, dyslipidemia, and type 2 diabetes [1]), diseases in which the underlying histologic alteration is commonly represented by nephroangiosclerosis. It is just the extension of atherogenic diseases to the kidney vasculature that establishes the perverse cardiovascular–renal link that is responsible for the current epidemic of CKD in Western countries and that propels the high rate of cardiovascular complications in this population (2). The importance of a moderate degree of renal insufficiency in the high cardiovascular risk of hypertensive individuals is epitomized by observations made in the Progetto Ipertensione Umbria Monitoraggio Ambulatoriale (PIUMA) study cohort (3). Indeed, on the basis of the data reported in this study, we calculated that, independent of other risk factors, including left ventricular hypertrophy, and 24-h average ambulatory BP monitoring, the presence of a moderate degree of renal insufficiency entails a 90% increase in the risk for incident cardiovascular complications. Therefore, nephroangiosclerosis and the attendant renal
function loss are important not only because they may be conducive to ESRD but also because they trigger cardiovascular events.

Nephroangiosclerosis, Intimal Hyperplasia, and Endothelial Dysfunction

The most typical finding in nephroangiosclerosis is represented by intimal hyperplasia of medium and small renal arteries. Such an alteration is the expression of systemic endothelial damage being extended to the whole arterial system, from small vessels to the aorta (4). Therefore endothelial damage seems to be the basic anatomic alteration that eventually leads to disastrous vascular events in the heart, brain, and kidney (5). In line with this interpretation, the inability of medium and small vessels to respond appropriately to vasodilatory stimuli (6) that are mediated by the nitric oxide (NO) system, such as the parasympathetic neuromediator acetylcholine (ACh), is an established functional correlate of intimal hyperplasia.

The cause of nephroangiosclerosis in hypertension still is incompletely understood. In the rat, renal alterations that are similar to those of nephroangiosclerosis can be induced by the NO inhibitor NG-nitro-l-arginine methyl ester (7), suggesting that endothelial damage is a critical element in the pathogenesis of this disease. There is consistent evidence that the endothelial response to ACh in the forearm vasculature of individuals with essential hypertension is compromised (8). Such an alteration largely is independent of arterial pressure, overweight, smoking, and hypercholesterolemia, all factors that may be conducive per se to endothelial dysfunction (9). Of note, endothelium-dependent vasodilation in the forearm is closely related to that in coronary arteries (10), again pointing to a systemic rather than to a local disorder (5). Endothelial function in the kidney vasculature in hypertensive patients has been investigated little because studies of the hemodynamic response of the kidney to NO activation and blockade are laborious to perform. There is no direct proof that endothelial dysfunction in the forearm or in the coronary circulation is paralleled by a similar hemodynamic dysfunction in the kidney. As alluded to before, animal models suggest that nephroangiosclerosis and the attendant renal insufficiency are expected consequences of endothelial dysfunction in the renal circulation (7). Therefore, testing the association between indicators of renal function and the forearm blood flow response to ACh may provide circumstantial evidence in support of the hypothesis that nephroangiosclerosis is the expression of endothelial dysfunction in the kidney.

We recently investigated this relationship and renal function in 500 patients with uncomplicated, never treated, essential hypertension and serum creatinine <1.5 mg/dl (11). Such a population seemed ideally suited to test the hypothesis because drug treatment and background cardiovascular complications are notorious confounders in the interpretation of studies of endothelial function. Remarkably, we found a strong link between the vasodilatory response to ACh and the GFR (Figure 1). Such a link was independent of arterial pressure and other risk factors, suggesting that systemic endothelial dysfunction is an important mechanism that contributes to mild renal dysfunction in essential hypertension.

Endothelial Dysfunction, Inflammation, and Renal Dysfunction in Essential Hypertension

It is well established that the endothelium synthesizes a variety of inflammatory molecules, such as intercellular adhesion molecule and vascular cellular adhesion molecule, and that, in turn, it is the target of inflammatory processes. Subtle elevations in plasma concentration of C-reactive protein (CRP), a reliable marker of inflammation, were associated with similarly subtle reductions in creatinine clearance in the Prevention of Renal and Vascular Endstage Disease (PREVEND) study (12). In line with these observations in the general population, we found that CRP was inversely related both with the response to ACh and with the GFR (Figure 2). These associations suggest that endothelial dysfunction may be an intermediate mechanism mediating the effect of inflammation on renal function.

Collectively, these studies document that an impaired vasodilatory response to ACh is a risk marker for renal function loss
in patients with essential hypertension and suggest that inflammation may be the mechanism triggering both endothelial dysfunction and renal insufficiency in essential hypertension. In this perspective, it seems to be of particular interest that high levels of asymmetric dimethylarginine (ADMA) may represent a possible mechanism that is conducive to endothelial dysfunction in essential hypertension. The synthesis of this substance is increased in inflammatory states (13), and acute inflammation may trigger a fully reversible endothelial dysfunction in healthy young humans (14). Such a hypothesis is specifically supported by our findings showing that ADMA is increased in patients with uncomplicated hypertension and by the parallel observations that in these patients, the response to ACh is inversely related to plasma ADMA concentration \( r = 0.58, P < 0.01 \) (15). The role of ADMA as a critical player in endothelial dysfunction in essential hypertension is also suggested by the fact that L-arginine infusion fully restores endothelium-dependent vasodilation in these patients (15).

As alluded to before, consistent evidence now has been accrued that in individuals with essential hypertension, even minor degrees of renal insufficiency entail a high risk (3). Likewise, endothelial dysfunction now has emerged fully as a feature of major clinical relevance in hypertensive patients (5,8) because independent of arterial pressure levels and other risk factors, it is associated with left ventricular hypertrophy (16) and predicts cardiovascular events (17).

**Conclusion**

A dysfunctional endothelium seems to be a key factor in the risk for renal insufficiency in individuals with essential hypertension. The inverse links between CRP and the GFR and the vasodilatory response to ACh coherently suggest that inflammation is a likely mechanism explaining this association. The endothelium seems to be at the crossroads of the risk for renal insufficiency in patients with essential hypertension.

**References**