Hypothesis Paper

Arterial Stiffness and Kidney Function

Michel E. Safar, Gérard M. London, Gérard E. Plante

Abstract—The vascular hallmark of subjects with end-stage renal disease undergoing hemodialysis is increased aortic stiffness, a phenomenon independent of mean arterial blood pressure, wall stress, and standard cardiovascular risk factors such as plasma glucose, cholesterol, obesity, and smoking. These observations suggest that subtle links might associate arterial stiffness and kidney function in normotensive and hypertensive populations. Recently, aortic pulse wave velocity and creatinine clearance have been shown to be statistically associated in subjects with plasma creatinine $\leq 130$ $\mu$mol/L, again independently of mean arterial blood pressure and classical cardiovascular risk factors. This association was even shown to predominate in subjects younger than age 55 years. In addition, acceleration of aortic pulse wave velocity with age was more important in these subjects than in untreated normotensive control individuals, and the phenomenon was consistently predicted by baseline plasma creatinine values. Among all antihypertensive drugs, angiotensin-converting enzyme inhibitors only were shown to exhibit a significant and independent effect on aortic stiffness. The use of these drugs was significantly associated with improvement of large aortic stiffness in subjects treated for hypertension. In conclusion, increased stiffness of central arteries is independently associated with reduced creatinine clearance in subjects with mild to severe renal insufficiency, indicating that kidney diseases may interact not only with small but also with large conduit arteries, independently of age, blood pressure level, and classical cardiovascular risk factors. Whether sodium, divalent ionic species (calcium, phosphates), and the renin-angiotensin-aldosterone system play a role in such alterations remains to be elucidated. (Hypertension. 2004;43:163-168.)

Key Words: hypertension $\bullet$ kidney $\bullet$ blood pressure $\bullet$ arteries $\bullet$ vascular

Bright’s disease involves relatively well established links between uremia, high blood pressure, and cardiovascular (CV) complications, which were elegantly described from clinical observations at the end of the 19th century. In those days, biological and imaging tolls were of course quite limited, and exquisite clinical skill was critical for establishing such relationships of unique pathophysiological importance. The tremendous development of renal replacement therapy to handle chronic uremia, including dialysis techniques, over the past half century is associated with an increasing number of CV complications, which are poorly defined at this point in time, illustrating the complex relationships between renal failure and hypertension. Traditionally, one refers easily to three different mechanisms to explain these relationships. First, renal failure is associated with structural and/or functional alterations exclusively located in small resistance arteries. Second, hypertension-related CV complications affecting larger blood vessels of the brain and the heart are related to atherosclerosis, a morbid condition not necessarily immediately and exclusively linked to hypertension. Third, the kidney itself, also a major target for atherosclerosis, is most likely responsible for vascular dysfunction and hypertension through failure in maintaining the milieu intérieur, particularly divalent ions homeostasis, even when best replacement therapy is initiated. Not precisely identified when Richard Bright described his classical clinical condition a century ago, it becomes more evident that some of the uremic “poisons” suspected to be responsible for the vascular disorders associated with renal failure in those days could now be identified as the calcium/phosphate soft tissue deposition.

Large arteries exhibit two different but quite important functions: a conduit function, expressed by mean blood pressure and blood flow, and a buffering function, expressed by pulsatile pressure and flow. The former enables oxygen to be adequately delivered to tissues. The alterations of the conduit function result almost exclusively in CV complications caused by atherosclerosis, with resulting stenosis and ischemia mainly observed in the brain, the heart, or even the kidney. In contrast, the latter function enables the pulsatile flow arising from the heart to be transformed into a continuous flow at the peripheral level. This function is intimately related to the visco-elastic properties of the aorta and its major branches. With age, increased arterial stiffness results in a selective elevation of pulse pressure (PP) caused by an increase of systolic blood pressure (SBP) and a decrease of diastolic blood pressure (DBP), causing deleterious consequences for the heart. Increased arterial stiffness through an elevation of SBP enhances the left ventricular load and favors cardiac hypertrophy and, through reduction of DBP, results in a...
decrease in the perfusion pressure of the coronary arteries, thus contributing to myocardial ischemia. To our knowledge, in such conditions, the potential relationships between the kidney (with or without terminal uremia), the mechanical properties of the large arteries, and arterial stiffness and PP have never been clearly established in animal models as well as in human models.

The purpose of this review is 2-fold: (1) to establish the statistical relationship between arterial stiffness and kidney function in subjects with normal and elevated blood pressure and (2) to confirm that this relationship might develop independently of age, mean arterial blood pressure, and, mainly, the presence of atherosclerotic disease. Because the reported observations were obtained from human subjects, the final goal of this review is to define the clinical relationships between conduit artery alterations and renal dysfunction. This objective, if confirmed, should help the promotion of basic as well as of clinical research in domains connecting large arteries, high blood pressure, and renal function.

**Arterial Stiffness, Renal Function, and Guyton Model**

In the classical Guyton model, hypertension is primarily defined from the so-called pressure–diuresis mechanism. The kidney is considered to be a filter and, for each given value of sodium intake (equal, in steady-state and normal conditions, to urinary sodium output), a given steady mean blood pressure is achieved. As hypertension develops, the renal filter is altered and a higher mean blood pressure is required to maintain sodium external balance, as under normal conditions. Thus there is a shift of the pressure–diuresis curve toward higher blood pressure values. Different patterns of pressure–diuresis curves have been described according to different etiologic profiles of hypertensive disorders (hyperactivity of the renin–angiotensin system, abnormal external sodium balance, etc.).

Within the organism, the pressure–diuresis mechanism is achieved through a negative feedback loop that, in animals, is defined by equations (with their corresponding specific coefficients), which characterize the resulting changes in fluid volumes, cardiac output, vascular resistance, and compliance. In 1978, we added to the Guyton model new mathematical and statistical procedures to determine conditions that could be applied and used for investigation of hemodynamic data in humans. We defined the changes in the equation coefficients for the negative feedback loop required to describe the hemodynamic characteristics of normotensive and hypertensive human populations introduced in the model. The results indicated that in hypertensive subjects, only 8 of the 21 coefficients of the model should be modified to obtain the same cardiac output as normotensive controls. These coefficients included not only the kidney, the autonomic nervous system, and the arterioles but also the veins and large arteries.

Using rapid infusion of dextran in hypertensive subjects, we provided evidence that compliance in large collecting veins was reduced, therefore contributing to maintaining filling pressure of the heart despite a significant reduction of intravascular blood volume. Large vein compliance was shown to be highly correlated with the increased renal filtration fraction, which characterizes renal adaptive behavior in subjects with essential hypertension. However, during these investigations, we were unable to find a substantial link between reduced aortic compliance, a classical index of arterial stiffness, and renal function. In subjects with essential hypertension, renal parameters such as inulin clearance, renal plasma flow, and calculated filtration fraction were more strongly correlated with SBP than with DBP. Since, in these hypertensive subjects, increased SBP could not be explained exclusively on the basis of an increase in mean blood pressure or in ventricular ejection, the reported findings indirectly suggested the presence of specific links between arterial stiffness and the kidney. Because, in this first approach, the Guyton model was used, and because, in such conditions, the primary alteration was a renal defect, the first hypothesis to consider was that the kidney alterations may be a causal factor in the mechanism(s) of increased arterial stiffness. Under these conditions, it is thus important to evaluate whether this causal link may be mediated or not by high mean arterial blood pressure. Of course, the standard description itself of the Guyton model implies that atherosclerosis of the large arteries was absent from the studied relationships between large arteries and the kidney.

**Large Artery Damage in End-Stage Renal Disease**

In recent years, numerous clinical observations indicated that the majority of all deaths in dialysis patients are attributed to CV diseases. These observations reported over several years in several populations of patients treated with different modes of renal replacement therapy and with a variety of different CV disease profiles from a general population suggested a strong connection between uremia and CV disorders. Although a frequent underlying cause responsible for these complications is represented by occlusive lesions associated with atherosclerosis, it is obvious that many other vascular complications found in end-stage renal disease (ESRD) patients were also present despite clinically undetected atherosclerotic plaques.

In patients with ESRD undergoing hemodialysis, clinical studies have shown that blood pressure values are most frequently characterized by increased SBP alone with normal or even low DBP. Such alterations are consistently associated with increased stiffness of large conduit arteries and early wave reflections. Increased stiffness was shown to be independent of mean blood pressure level but largely influenced by the diffusion of large artery calcifications, often related to poorly controlled calcium-phosphate homeostasis. Recent studies demonstrate that phosphate retention caused by reduced urinary excretion in renal patients is associated with human aortic smooth muscle cell calcification, an early morbid phenomenon that has been recognized as a major factor contributing to large artery stiffness several decades ago. This hemodynamic pattern is associated with vascular remodeling, characterized by dilation of elastic and muscular-type arteries, and increased wall thickness. In ESRD patients, arterial remodeling and, more importantly, increased arterial stiffness, as measured from aortic pulse wave velocity (PWV), are strong independent predictors of all causes and mainly CV mortality. Moreover, a therapeutic trial in ESRD patients by Guerin et al has shown that after long-term blood pressure reduction, CV survival is observed mainly in
those patients showing adequate blood pressure and PWV control. However, patients with appropriate blood pressure reduction but who maintain elevated PWV do not survive, which is an observation that clearly shows the critical deleterious role of increased stiffness and morbid arterial remodeling.

The mechanisms responsible for arterial stiffening in patients undergoing hemodialysis are incompletely understood but are observed in nondiabetic subjects and cannot be exclusively related to standard CV risk factors such as glucose intolerance, hypercholesterolemia, overweight, or increased tobacco consumption. Furthermore, studies comparing structural and functional alterations of carotid and radial arteries in ESRD patients have shown that the observed vascular alterations are largely independent of age and of mechanical factors, such as increased local wall stress and high blood pressure (Figure 1). Such findings are observed on central elastic and peripheral muscular arteries. In particular, in vivo studies performed on the radial artery, a blood vessel poorly altered by aging and unmodified by atherosclerosis, have shown that the major mechanism of vascular alterations was characterized by an increased stiffness of the vascular wall matrix, a parameter consistently associated to “uremia” and not to high blood pressure. Studies in experimental uremia and in vitro in arteries of uremic patients have shown striking structural alterations involving an increase in wall thickness, cross-sectional media, and total extracellular matrix including collagen but no elastin. In addition, important calcifications of elastic lamellae are present, suggesting the potential role of parathormone. Such structural changes are not similar to those observed in aging, atherosclerosis, or standard hypertension. Thus the role of renal factors may be logically proposed, as those related to fluid redistribution, the accumulation of advanced glycosylation end product and/or the accumulation of an endogenous inhibitor of nitric oxide synthesis, and, finally, oxidative stress-related tissue damage. Nevertheless, whether the status of large vessels depends on the primary cause of the renal disease or even precedes kidney alterations remains largely ignored and needs to be explored.

Large Artery Damage in Mild to Moderate Renal Insufficiency

In experimental rat models of moderate renal insufficiency, changes in aortic structure involving increased wall thickness and accumulation of collagen, but not of elastin, have been reported independent of age, mean blood pressure, and conventional CV risk factors such as plasma glucose or cholesterol. Unfortunately, in such animals, arterial stiffness was not evaluated. Only in recent clinical studies have significant relationship between arterial stiffness and renal function been reported in subjects with mild to moderate renal insufficiency and normal or high blood pressure level.

In 1290 untreated subjects with plasma creatinine <130 µmol/L, creatinine clearance was calculated from the Cockcroft and Gault formula, itself compared with directly measured creatinine clearance. On that basis, the population was divided into 3 tertiles adjusted for age and gender. Only in the lower tertile was elevated aortic PWV significantly associated with reduced creatinine clearance. This phenomenon was independent of mean blood pressure values and was shown to be more important in younger (≤55 years) than in older subjects. This latter finding was of major importance because it is well known that the age term is included in the Cockcroft-Gault formula. In addition, plasma glucose and cholesterol, obesity, smoking habits, and heart rate did not influence the correlation. Furthermore, in a subset of untreated hypertensive subjects, creatinine clearance was independently and positively correlated with common carotid artery compliance (but not radial artery compliance). In this latter finding, the contribution of creatinine clearance to the total variance of carotid compliance was 20%, a relatively high value.

In cross-sectional studies involving subjects treated for hypertension with serum creatinine <300 µmol/L, aortic PWV and serum creatinine level were positively and independently correlated. Age, blood pressure, and the presence of diabetes mellitus were other important factors independently influencing the level of PWV. Among antihypertensive drugs used in these subjects, only angiotensin-converting enzyme inhibitors (ACEIs) influenced PWV values. More specifically, in these cross-sectional studies, ACEI were associated with low PWV, independent of blood pressure and other standard CV risk factors (Table 1). For the interpretation of this finding, it is important to recall that it is extremely hazardous to attribute lower PWV to nonrandomized ACEI use. Many factors may affect the clinical decision to use or not use an ACEI, and this confounding indication may explain the apparent association. Thus, it is important to note that in long-term randomized follow-up, increased plasma creatinine and high PWV are significantly and independently associated with CV mortality. It is noteworthy that treatment with ACEI was found to improve CV survival independently of brachial blood pressure values in subjects with high CV risk factors, and multiple or recurrent strokes. In a randomized trial of subjects with ESRD, CV mortality was reduced only when two different prerequisites were achieved. First, the blood pressure reduction was associated with PWV attenuation. Second, an ACE inhibitor was constantly present among the antihypertensive drugs used and its presence was significantly associated with the reduction of CV risk (Table 2).
Finally, more recent longitudinal studies have provided evidence that independently of mean blood pressure, aortic PWV increases more rapidly with age in subjects treated for hypertension than in untreated normotensive control subjects. Furthermore, from all factors known to influence the increase in PWV with age, the most important was shown to be baseline plasma creatinine level.

To summarize, in normal subjects and in those with high blood pressure, either treated or untreated, high PWV and reduced creatinine clearance are significantly and independently associated. However, in subjects treated for hypertension, the elevation of PWV with age is steeper in those with higher baseline plasma creatinine values. Increased plasma creatinine and elevation of aortic PWV are independent predictors of CV risk that respond to ACEIs. Finally, increasing clinical evidence indicates that the use of ACEIs is independently associated with CV survival in populations with high risk.

**Hypothesis and Prospective Views**

Because in this review the primary approach to the interactions between large arteries and the kidney was issued from the Guyton model, the principle message was that renal changes could directly affect the viscoelastic arterial properties of large arteries. An important aspect was that the renal-induced alterations of the viscoelastic arterial properties were largely independent of the presence of atherosclerosis and/or mean arterial pressure changes. However, to relate large artery structure and function and kidney alterations, other reasonably straightforward possibilities may be suggested. First, increased arterial stiffness leads to increased PP, which in turn may lead to kidney damage (glomerular and/or tubular). Second, one or several common mechanisms may act on the kidney and large arteries. Some of these potential physiopathological steps are summarized in Figure 2, with particular emphasis on the vicious cycle starting from kidney disease to vascular calcification and rigidity (blood pressure-independent features) to atherosclerosis, hypertension, and target organ damage, including the kidney (blood pressure-dependent features).

In recent years, novel methodological approaches enabled better development of these different hypotheses. In the past, aortic stiffness was evaluated in vivo, from simple Windkessel models of the circulation, or in vitro from determinations of the static pressure–diameter relationship of various arterial segments. Today, arterial stiffness can be evaluated from direct in vivo measurements of local PP and pulsatile diameter, the latter being determined by high-resolution echo-tracking techniques. Therefore, the subtle relationships observed between kidney function and arterial stiffness that may be described are those relating the kidney to changes in PP or large artery diameter, or a combination of these parameters.

Limited data are presently available in the literature to establish relationships between PP and renal structure and function characteristics. The relationships between blood pressure and the kidney are exclusively analyzed in terms of SBP, DBP, or mean blood pressure but never in terms of PP. However, there is no doubt that pulsatile pressure can be detected and measured across the renal glomerular microcirculation network, at least in superficial nephrons, in normal and spontaneously hypertensive rats, which are the classical animal model of essential hypertension. In a recent study using an elegant in vitro perfused hydropneumatic kidney model, Louzenviser et al were able to show that the degree of hypertension-dependent glomerular injury in the kidney correlates remarkably with isolated SBP, a well-established physiological marker of large artery rigidity and increased pulsatility. Thus, this finding was the first to suggest that increased arterial pulsatility is associated with more vasoconstriction within the kidney.

In humans, a positive relationship has been observed between systemic PP and the degree of proteinuria. Furthermore, there is no doubt that increased mechanical strain and shear stress

**TABLE 1. Cross-Sectional Study**

<table>
<thead>
<tr>
<th>Independent Variable: Aortic PWV</th>
<th>Standard Coefficient</th>
<th>R² Increment</th>
<th>P Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>0.43</td>
<td>0.15</td>
<td>0.000</td>
</tr>
<tr>
<td>Gender (male/female)</td>
<td>0.13</td>
<td>0.01</td>
<td>0.000</td>
</tr>
<tr>
<td>Treatment duration (y)</td>
<td>0.11</td>
<td>0.01</td>
<td>0.000</td>
</tr>
<tr>
<td>Plasma glucose (mmol/L)</td>
<td>0.14</td>
<td>0.02</td>
<td>0.000</td>
</tr>
<tr>
<td>Smoking (packs/y)</td>
<td>0.05</td>
<td>0.003</td>
<td>0.07</td>
</tr>
<tr>
<td>ACEI (yes/no)</td>
<td>0.07</td>
<td>0.005</td>
<td>0.01</td>
</tr>
<tr>
<td>Plasma creatinine (µmol/L)</td>
<td>0.11</td>
<td>0.009</td>
<td>0.000</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>0.12</td>
<td>0.013</td>
<td>0.000</td>
</tr>
<tr>
<td>Brachial SBP (mm Hg)</td>
<td>0.25</td>
<td>0.06</td>
<td>0.000</td>
</tr>
</tbody>
</table>

Covariates of aortic PWV in a population of 712 hypertensive subjects treated by antihypertensive drug regimen (personal data). Measurement were performed during chronic treatment including multiple drug approach. PWV indicates pulse wave velocity; ACEI, angiotensin-converting enzyme inhibition; SBP, systolic blood pressure; MSE, mean standard error. $R^2=0.47$; MSE=1.98

**TABLE 2. Randomized Longitudinal Trial Factors Influencing CV Mortality in a Single Blind Therapeutic Trial in Subjects With ESRD Undergoing Hemodialysis**

<table>
<thead>
<tr>
<th>Variable: Cardiovascular Mortality</th>
<th>RR (95% CI)</th>
<th>z Statistic</th>
<th>P Value</th>
<th>Pseudo $r^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>CVD (yes/no)</td>
<td>4.72 (1.91–11.61)</td>
<td>3.36</td>
<td>0.00077</td>
<td>0.13097</td>
</tr>
<tr>
<td>LV mass index (10-g increase)</td>
<td>1.11 (1.03–1.19)</td>
<td>2.63</td>
<td>0.00844</td>
<td>0.00847</td>
</tr>
<tr>
<td>ΔPWV (1 = positive; 0 = negative)</td>
<td>2.35 (1.23–4.51)</td>
<td>2.57</td>
<td>0.01004</td>
<td>0.08110</td>
</tr>
<tr>
<td>ACE inhibitor (1 = yes; 0 = no)</td>
<td>0.18 (0.06–0.55)</td>
<td>-3.00</td>
<td>0.00274</td>
<td>0.10689</td>
</tr>
</tbody>
</table>

CVD indicates previous cardiovascular disease. LV, left ventricular; PWV, pulse wave velocity; RR, relative risk; CI, confidence interval.

Adjustments were made on all prognostic variables considered in model. Results of analyses were model $\chi^2=59.54, P<0.00001$, and pseudo $r^2=0.44254$ for cardiovascular mortality.
contribute to renal structural alterations. However, the intrarenal distribution of mechanical forces has not yet been directly investigated, nor have the associated changes in endothelial integrins and cytoskeleton, which on the contrary have been elegantly demonstrated in endothelial cell culture preparations. More importantly, recent experiments performed in vitro on isolated proximal tubularveal vessel, for the first time to our knowledge, that shear stress reproduced by increased flow rates under these conditions exerts similar alterations on cytoskeleton reorganization. It is likely that such morphological and functional changes on the epithelial luminal membrane is to be associated with alterations in membrane transport proteins, similar to what has been reported in large artery endothelial cell barriers from both the luminal and adventitial (vasa vasorum) sides of these conduit vessels.

The highly significant relationship between large artery stiffness and creatinine clearance shown in this review indicates that mostly muscular-elastic, rather than pure muscular, arteries are involved, at least in the early phase of renal functional alterations. Therefore, if a common factor interacts between large muscular-elastic arteries and the kidney, it seems likely that the extracellular matrix of vascular and renal cells should be mainly involved. These changes may obviously affect several pathways involving the sodium and water balance, the renin–angiotensin–aldosterone system, the calcium–phosphate metabolism, or even vasoactive factors, such as nitric oxide and endothelin, or other compounds of endothelial origin.

The potential relationship between extracellular matrix, sodium, and the renin–angiotensin system may affect different pathophysiological mechanisms. First, collagen fibers, mainly types I and III, represent the more rigid components of the arterial wall and also contribute to the development of renal fibrosis. In both organs, angiotensin II and aldosterone participate in the collagen accumulation and are known to be prevented by converting enzyme inhibition and/or aldosterone antagonism. Interestingly, aldosterone has been shown in rats to increase the stiffness of aortic wall material independently of wall stress. Second, in renal and vascular tissues, abnormal collagen cross-linking caused by the accumulation of endoglycosyl products are reversed by amino guanidine and/or related compounds.

Third, positive sodium and fluid balance, frequently related to renal dysfunction, may contribute to pressure-independent alterations of large artery structure and function and may be reversed by diuretic therapy. Fourth, in large artery matrix and renal interstitial compartments, proteoglycans contribute to alterations in sodium and water content, either through changes in the spatial configuration of these complex macromolecules or through their capacity to bind sodium and/or calcium ions.

In conclusion, in human and animal models of hypertension, the relationship between kidney function and high blood pressure should no longer be restricted to the exclusive role of resistance arterioles. We hypothesize that large arteries, the major site of CV complications, should urgently be taken into consideration and become a priority in basic and clinical research activity.

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