Cross-Talk between the Kidney and the Cardiovascular System

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In recent years, increasing evidence has been provided that even minor renal dysfunction is a powerful cardiovascular risk factor that induces typical cardiovascular alterations and thus predisposes to coronary heart disease as well as to noncoronary cardiovascular problems. This first had been noted in patients with diabetes but now has been confirmed amply in patients without diabetes as well. Numerous heterogeneous abnormalities have been described in patients with early renal dysfunction (e.g., microalbuminuria, reduced estimated GFR). One final common pathway seems to be endothelial cell dysfunction. The link between albuminuria and generalized endothelial cell dysfunction (as indicated by diminished flow-mediated vasodilation, markers of endothelial cell dysfunction, sloughed off endothelial cells, and high transcapillary albumin escape rate) is unclear. In patients with early renal dysfunction, a long list of classical and nonclassical cardiovascular risk factors have been identified: Elevated asymmetric dimethyl-L-arginine concentrations, markers of microinflammation, oxidative stress, features of metabolic syndrome, abnormal adipokine concentrations, dyslipidemia, inappropriate activation of the renin-angiotensin system, and sympathetic overactivity. The mechanisms that link dysfunction of the kidney and the cardiovascular system are being sought. The most interesting unifying concept, however, is deranged fetal programming linking nephron underdosing to the increased cardiovascular risk.


Types of Cardiovascular Events Observed in Patients with Minor Renal Dysfunction

Although the high risk for cardiovascular death, particularly from coronary heart disease (CHD), had been recognized early after introduction of maintenance hemodialysis (1), it is only relatively recently that the high cardiovascular risk in patients with minor renal dysfunction has been appreciated fully (2). This link first had been noted in patients with diabetes. This observation prompted Deckert et al. (3) to propose the concept that albuminuria was a marker for and linked to a generalized endothelial cell defect as documented by an increased transcapillary albumin escape rate (4,5). Only much later was it recognized that albuminuria and proteinuria (6,7) are cardiovascular risk factors in patients without diabetes as well. This by now has been well documented by several large population-based studies (8–10) and by controlled intervention trials. The latter also suggested that the prediction of cardiovascular events by albuminuria extends into the range of albumin values that conventionally have been considered to be within the normal range (11,12) as had been found previously also in diabetes (13). The observation that changes in albuminuria during treatment translate into changes of cardiovascular events is suggestive for but not definite proof of a causal role of albuminuria (14).

In parallel, after the unexpected observation in the Hypertension Detection and Follow-up Program (HDFP) study (15), it by now also has been confirmed amply that even minor elevations of serum creatinine or reductions in estimated GFR—even more sensitive, increases of cystatin C (16)—predict cardiovascular events and cardiovascular death in the general population (17,18) and particularly in patients who undergo cardiac interventions (19) or ischemic events (20).

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4D, and stroke accounted for 10% in USRDS and 6% in 4D. It is obvious that despite undoubted experimental (21–23) and clinical (24) evidence of accelerated atherogenesis in renal failure, there is more to cardiac death in renal patients than CHD. What is remarkable in the context of cardiovascular risk in patients with minor renal dysfunction is our observation that in the experimental model of the apoE−/− mouse, atherogenesis is accelerated by as little reduction of renal function as uninephrectomy (21).

For patients with early stages of renal dysfunction, there is little information on the exact breakdown of the types of cardiovascular death. It has been well documented that the frequency of atherosclerotic disease and congestive heart failure is increased in patients with minor reduction of GFR (25). Furthermore, an excess of coronary events and death according to CHD criteria has been noted even in microalbuminuric patients (26). Many aspects of this relation have not been clarified, and this issue will continue to be an important task for future epidemiologic work. That cardiac abnormalities are seen with minor renal dysfunction also is illustrated by our past experimental studies: Even relatively modest resection of renal parenchyma caused striking left ventricular hypertrophy (LVH), cardiac fibrosis, microvessel disease with a selective capillary deficit, and wall thickening of intramyocardial arterioles in the hypertrophied heart (Figure 1) (27,28).

Because in renal patients sympathetic overactivity is seen (29) and may occur even before GFR decreases, at least in hypertensive patients with autosomal dominant polycystic kidney disease (30), we suspect that sudden death makes a major contribution even at this early stage. This caveat of the heterogeneity of factors is appropriate to prevent overly simplifying paradigms to explain the elevated cardiovascular risk.

**Potential Pathogenetic Mechanisms**

As indicated in the previous section, it would be naïve to assume that one single mechanism accounts for all that there is to cardiovascular dysfunction in renal disease. Nevertheless, one mechanism that seems to be central in the genesis of many different aspects of cardiovascular dysfunction in renal patients stands out as one potential final common pathway, namely endothelial cell dysfunction. Endothelial cell dysfunction has been documented directly by measuring indices such as flow-mediated vasodilation (31,32) and indirectly by measuring circulating markers of endothelial cell dysfunction (33,34) and markers of processes that are known to interfere with endothelial cell function, e.g., oxidative stress (32,35,36), microinflammation (35,37–40), adipokine abnormalities such as low serum adiponectin levels (41), and others. More direct evidence for endothelial damage is also provided by the observation of circulating endothelial cell–derived microparticles’ adversely affecting endothelial cell function (42) and of circulating endothelial cells that had been sloughed off the endothelial cell layer (43,44). Furthermore, it is increasingly recognized that atherosclerosis is the combined result of damage to the resident cells and repair by circulating bone marrow–derived endothelial precursor cells (45). Against this background, it is of interest that the number and the function of such precursor cells are diminished in renal patients (46,47) for reasons that have not been clarified fully.

Numerous factors that have an adverse impact on endothelial cell function are demonstrable in patients with primary renal disease even when whole-kidney GFR still is normal. An incomplete list comprises apolipoprotein abnormalities (48,49), elevated concentrations of asymmetric dimethyl-γ-arginine (ADMA) (50), and elevated concentrations of homocysteine (51), the role of which as a cardiovascular risk factor is dubious, however (52). Furthermore insulin resistance, a powerful predictor of cardiovascular events, is seen even when whole-kidney GFR still is normal (53). This finding is of note because
Cardiac Consequences of Disturbed Renal Function

It is widely known that in patients with renal dysfunction, cerebrovascular events are more frequent (57), and malfunction as well as remodeling of central arteries occur (58). Because of limitations of space, we focus here on the heart.

A number of potential pathogenetic factors that cause cardiac malfunction in renal disease have been identified in experimental studies using the renal ablation model. Among others, a potential pathogenetic role of parathyroid hormone on LVH, interstitial fibrosis, and thickening of intramyocardial arterioles has been found (59). This observation is consistent with several clinical studies showing that parathyroid hormone concentrations correlate with cardiac morbidity and cardiac death in dialysis patients (60).

Apart from increased afterload (elevated BP, aortic stiffening) and preload (hypervolemia, anemia), the cardiac abnormalities are amplified by the activation of local systems such as the renin-angiotensin system (RAS) and the endothelin (ET) system. Using PCR, in situ hybridization, and immunohistochemistry, increased mRNA and protein expression of ET-1 were found in the heart of subtotally nephrectomized rats compared with controls (61). This is of particular interest because high ET-1 serum levels together with increased protein expression of ET-1 also were found in the heart of uremic patients (62). In addition, LVH was found to correlate closely with serum ET-1 concentrations (63).

Intervention studies using experimental models of renal failure were of interest because they identified some potential pathogenetic principles in renal–cardiac interaction. Persistence of LVH was noted in rats with moderate renal failure despite correction of anemia by blood transfusion and hypertension by sympatholytic agents (64). In contrast, in recent studies, LVH was ameliorated but not abrogated by administration of angiotensin-converting enzyme (ACE) inhibitors, sympatholytic agents, ET receptor blockers, and recombinant human erythropoietin (rhEPO) (65–67). An experimental study using the bradykinin receptor blocker Hoe140 documented that in uremic animals, the beneficial effect of ACE inhibition on LVH is mediated via bradykinin (67).

In the same experimental model, treatment with ACE inhibitors, ET receptor blockers, and calcium channel blockers also prevented wall thickening of intramyocardial arteries after subtotal nephrectomy (65) (Figure 1). In this case, the effect of ACE inhibitors could be dissociated from accumulation of bradykinin. In contrast, nonspecific antihypertensive treatment (dihydralazine and furosemide), sympatholytic agents, or correction of anemia with rhEPO did not prevent intramyocardial micro-arteriopathy (68).

In addition to arteriolar changes, reduction of capillary density is another factor that interferes with oxygen delivery. In subtotally nephrectomized rats with moderate renal failure of short (65) and long duration (69), cardiac capillary length density, i.e., the total length of all capillaries contained within a unit volume of myocardium, was reduced approximately 25% (Figure 1). Capillary rarefaction occurs not only in the hypertrophied heart of patients or rats with renal failure but also in other types of hypertension or LVH, respectively. The decrease in capillary density is significantly more pronounced in uremia, however, and leads to an increase in intercapillary distance, potentially compromising blood and oxygen supply of cardiomyocyte under conditions of increased demand. These conditions render the myocardium more susceptible to ischemic injury and may particularly increase the cardiac risk in uremic patients (70). The finding of lower capillary supply suggests that in the LVH of uremic patients, capillary growth does not keep pace with cardiomyocyte growth, apparently because the expression of angiogenic signals (vascular endothelial growth factor) is diminished or because inhibitors of capillary angiogenesis are present. Clarification of these points requires further experiments.

Intervention trials also gave some hints as to the pathomechanisms underlying the decrease in cardiac capillary supply: It was prevented by the central sympatholytic agent moxididine (65) by selective and nonselective ET receptor blockers (66,71) and in recent studies also by the ß blocker metoprolol (72). In contrast, treatment with the calcium channel blocker nifedipine or the ACE inhibitor ramipril or correction of anemia with rhEPO did not affect myocardial capillary density. It is interesting that administration of the bradykinin receptor antagonist Hoe140 resulted in a further decrease of myocardial capillary supply (67). The sensitivity of the cardiac vasculature to bradykinin presumably is explained by the fact that uremia is a state of decreased bioavailability of nitric oxide (NO) (73).

The relation between kidney malfunction and heart malfunction is a two-way process. Renal malfunction causes cardiac problems, and, conversely, in both experimental studies (74) and clinical observations (75), cardiac malfunction causes progressive renal malfunction. The study of van Dokkum et al. (74) examined the effects of myocardial infarction on the loss of renal function in unilaterally nephrectomized rats. The degree of focal segmental sclerosis and of proteinuria was more pronounced in the animals with myocardial infarction, and a significant correlation was found between left ventricular pressure and proteinuria. The data suggest that cardiac damage aggravates mild renal dysfunction, possibly via neurohumoral signals. This mutual interaction justifies the concept of a “cardio-renal syndrome” (76).

Link between Kidney and Heart: Open Questions

It presumably is easy to convince the reader that renal dysfunction is bad for cardiovascular outcome. It is much more difficult to explain why there is a link between kidney and the cardiovascular system. For instance, why do endothelial cells, say, of a coronary artery, “know” that the glomerulus leaks protein. It is easy to envisage that in the glomerulus, endothe-
lial cells are affected by altered function of podocytes, the main controller of glomerular permeselectivity. There is overwhelming evidence of intense cross-talk between podocytes and glomerular endothelial cells that is mediated primarily by vascular endothelial growth factor (77,78). The interaction between leaking glomeruli and endothelial cells in the systemic circulation, however, remains enigmatic. Little evidence has come forward for the original hypothesis of a common abnormality of charge or composition of the basal membrane of glomeruli and extra-renal vessels, respectively (3). Although the role of podocytes in controlling glomerular permeselectivity is paramount, one little discussed possibility is that the endothelial glyocalyx, which is heavily involved in the genesis of vascular pathology (79,80), also controls vascular permeability (81). Possibly, this also is the case in the glomerulus, as suggested, for instance, by the observation that injection of proteases that digest the glyocalyx causes almost instantaneous massive proteinuria without changes in podocyte morphology (82). The possibility of a common glyocalyx defect in the glomerulus and in the systemic circulation is worth considering in future studies.

Several pathways through which reduced glomerular filtration theoretically may influence endothelial function are conceivable. These possibilities are not mutually exclusive: (1) Accumulation of substances that normally are excreted via the kidney; (2) failure of the kidney to produce active substances such as the recently described renalase (83); (3) reduced metabolic function of the kidney as illustrated by the example of ADMA: In patients with mild to moderate renal failure, the concentration of ADMA is correlated to surrogate markers of cardiovascular risk (84) and also is a powerful predictor of progression of renal dysfunction and of cardiovascular events (85,86). Although the plasma concentration in renal patients are not dramatically elevated, at these concentrations as found in renal patients, ADMA modifies gene expression patterns in endothelial cells (87). ADMA acts as an inhibitor of NO synthase, reducing the bioavailability of NO (88,89); it is well established that diminished production of NO is a feature of renal failure (73,90). Although both asymmetric ADMA and its isomer symmetric SDMA are excreted via the kidney, we had noted that SDMA concentrations went in parallel with creatinine, whereas ADMA concentrations did not (91). We had postulated that ADMA metabolism by dimethylarginine dimethylaminohydrolase, an enzyme whose activity is high in the kidney, was diminished in renal disease (91). This hypothesis is supported by recent genetic experiments (92).

Unknown are the exact mechanisms by which sympathetic activity is dramatically increased in patients with renal disease even when whole-kidney GFR still is normal (30). Increased afferent signals that emanate from the damaged kidney raise the activity of hypothalamic centers, but the triggering intrarenal signals have not been identified (93). Sympathetic overactivity is of course particularly deleterious in patients with cardiovascular disease and may contribute to the excessive frequency of sudden death and high case fatality rate of ischemic events in renal patients.

A further unresolved issue that is relevant in this context is whether in renal disease there is inappropriate activation of local RAS of cardiovascular structures, as suggested by the observation of increased angiotensin II formation in the isolated perfused hind limb of uremic rats (94) and increased expression of components of the RAS in the heart of subtotally nephrectomized rats (28). As a further possibility, it was suggested recently that the LVH and LV fibrosis in uremia are caused by increased concentrations of the cardiotoxic steroid marinobufagenin (95) and possibly also telocinobufagin (96), which not only inhibit the Na⁺,K⁺-ATPase but also generate oxidative stress.

The metabolic syndrome is a widely known factor that predisposes not only to cardiovascular events but also to chronic kidney disease (97). An attractive hypothesis that suggests a link between the predisposition to renal disease and to the metabolic syndrome is the hypothesis of “neprhon undersizing” proposed by Brenner et al. (98). They postulated that aberrant fetal programming by genetic factors or malnutrition and other insults to the pregnant mother leads to the formation of fewer glomeruli. The hypothesis of a relation between fewer nephrons and hypertension has been proved (99), at least in white individuals (100). Suggestive, although not definitive, evidence points also to a link between malnutrition during the fetal period and albuminuria (101). A link between preexisting predisposition to hypertension and development of renal disease is suggested by the observation that diabetic (102) and nondiabetic (103) renal disease is seen more frequently in families with hypertension and that in patients with normal urinary findings at baseline, the risk for future ESRD is predicted by BP at baseline (104). Finally, numerous experimental observations support the concept of a link between nephron number and susceptibility to glomerular damage (105,106). Conversely, Barker et al. (107) originally proposed the hypothesis that he recently confirmed in a retrospective study that impaired intrauterine development predisposes also to increased cardiovascular risk and cardiovascular events in adult life. Whether fetal programming can cause adverse cardiovascular effects by directly affecting the intrauterine development of cardiovascular structures is a possibility that has not been explored so far.

Perspectives

In the past, in view of the devastating cardiovascular prognosis of patients who are on dialysis, the main emphasis of research was on ESRD. Patients who reach ESRD constitute only a minority who have survived; indeed, the risk for death, mainly from cardiovascular causes, has been reported to be much higher than the risk for starting dialysis (25). It is obvious from the evidence here that the cumulative cardiovascular risk builds up progressively throughout the earlier stages of chronic kidney disease, and this must be the focus of future research and intervention.

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