Cardiovascular Problems on Hemodialysis: Current Deficits and Potential Improvement

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High cardiovascular mortality is the major cause of reduced life expectancy of patients who are on hemodialysis. Classical risk factors cannot fully explain the magnitude of the risk. This article addresses some nontraditional approaches to deal with the excessive cardiovascular risk for patients who are on hemodialysis. Although improvements have been made in the past decade, survival of dialysis patients continues to be unsatisfactory in most countries. There are glaring differences of survival between countries as indicated by the Dialysis Outcomes and Practice Patterns Study (DOPPS) (1) (Table 1), although significant differences are certainly also found between centers (2) (Table 2). Important factors that account for differences in outcome are duration of dialysis sessions, ultrafiltration rate (4), and differences in vascular access, which are beyond the scope of this article. According to the US Renal Data System (http://www.usrds.org) and the Die Deutsche Diabetes Dialyse Studie (4D Study) (5), approximately 50% of deaths of dialysis patients are from cardiovascular causes (Figure 1).

Epidemiologic Facts

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Underlying Cardiac Disease

In the past, cardiovascular death was mainly viewed as the result of accelerated coronary heart disease (CHD). Although CHD is undoubtedly more frequent than in the background population, the importance of two other, largely unresolved cardiovascular problems stand out today: Sudden death and cardiomyopathy (6), the latter mainly the result of cardiac fibrosis and microvesSEL disease. In the following, we emphasize selected new aspects of these cardiac complications and point out nonclassical risk factors that presumably have an impact on cardiac complications. We proceed from there to propose plausible targets for future investigations.

In the past, it was assumed that the major cause of cardiovascular death on hemodialysis was myocardial infarction as the result of accelerated coronary atherosclerosis. Recently, however, it has turned out that cardiac arrest is the most important cause both in the United States and in Europe (7). This was also documented by the 4D Study (Figure 2).

The frequency of cardiac arrest is 100 times higher in dialysis patients than in the background population (8), and there are notable differences between the two groups. In the general population, coronary artery disease accounts for approximately 80% of sudden deaths, the rest being accounted for by channelopathies (i.e., genetic defects that cause disturbed function of cardiac ion channels) and cardiomyopathy (9). In contrast, cardiac arrest of hemodialysis patients occurs most frequently in the absence of clinically manifest and adjudicated coronary artery disease (5). Cardiac arrest in dialysis patients differs also from what is observed in the general population by preferentially occurring at nighttime (“patient found dead in the bed”), similar to what is found in patients with sleep apnea. In patients without sleep apnea, sudden death occurs in the early morning hours and the arousal reaction is thought to be the trigger.

It follows that in dialysis patients, the primary “killer” and most frequent cause of cardiac death is not CHD but cardiomyopathy. Such cardiomyopathy occurs very early in the course of impaired renal function, both in experimental studies (10) and in human observations. It is characterized by a composite of inappropriate ventricular hypertrophy, marked interstitial fibrosis, microvesSEL disease with thickening of intramycocardial arteries, and capillary deficit (11). In a small biopsy controlled study, it was shown that cardiac fibrosis was a predictor of death (12). Cardiac fibrosis (causing arrhythmia as a result of reentry circuits) as well as diastolic malfunction (the result of reduced compliance [11]) are the most important causes of cardiac death and potentially future therapeutic targets.

A study that used magnetic resonance imaging came to the conclusion that left ventricular dilation and systolic dysfunction point to (possibly latent) ischemic heart disease (12). Systolic dysfunction is a potent predictor of poor survival in hemodialysis patients (13), but the relative contributions of CHD and of primary abnormalities of the myocardium (14,15) unrelated to CHD remain unclear. In the following section, we point to specific voids in our knowledge and discuss potential new targets of future research and intervention.

New Therapeutic Targets

Salt and Salt-Mediated Hormones

There is no doubt that, at least in the long term, hypertension is a powerful predictor of mortality for patients who are on hemodialysis (16), despite that in patients with cardiovascular...
damage low BP rather than high BP is associated with higher mortality (17). In the first article ever on maintenance hemodialysis, Scribner, a prophet in the desert, stated (18): “In the case of dialysis patients a low normal level of ECV is maintained by the powerful tool of ultrafiltration which, if properly used along with moderate dietary sodium restriction and maintenance of natriuresis by diuretics (19), are the only proven method of controlling BP in the hemodialysis population.” Unfortunately, such wise insight into pathomechanisms by the nestor of our specialty has not remained the focus of attention of nephrologists. It is fair to say that the issue has been neglected. Salt as the cause of hypertension has recently gained much support outside nephrology (20,21), and there is good evidence that salt induces target organ damage even by mechanisms other than hypertension (22,23).

Scribner had suspected that in patients with predialysis hypertension digitalis, like substances played a causal role in the genesis of hypertension (24). Today it is known that one of the salt-induced digitalis analogues, the bufadienolide marinobufagenin, an inhibitor of Na\(^+\)/K\(^+\)ATPase (25), reproduces cardiomyopathic features and cardiac fibrosis of uremia in experimental animals. Its pathogenetic role is further supported by the observation that neutralizing antibodies to marinobufagenin prevent the cardiac lesions in subtotally nephrectomized rats (26,27). In dialysis patients, a relationship was reported between left ventricular mass and another cardiotonic steroid: Ouabain (28). It is of interest that an inhibitor of ouabain—rostafuroxin—is currently in clinical evaluation (29).

These and several other recent observations (e.g., concerning salt and sympathetic activity [30] or salt and endothelial dysfunction [31]) point to novel therapeutic targets and potential future approaches:

- Reduction of salt intake (32) is an elementary approach to decrease the sodium load.
- Apart from the sodium load, the serum sodium concentration is presumably of major importance as well. Essential hypertension is associated with a minor but significant increase in serum sodium (33). A minor increase in serum and cerebrospinal fluid sodium concentration (34) stimulates central pressor mechanisms, including sympathetic activation (30) and release of cardiotonic steroids. Furthermore, in the presence of aldosterone, even a small increase in sodium concentration increases the stiffness of human endothelial cell function and suppresses nitric oxide production (31). The role of these effects of serum sodium concentration in dial-

### Table 1. Mortality on hemodialysis in different regions (1)

<table>
<thead>
<tr>
<th>Region</th>
<th>Annual Mortality of HD Patients (%)</th>
<th>Risk Ratio Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Crude</td>
<td>Adjusted</td>
</tr>
<tr>
<td>United States</td>
<td>22</td>
<td>5.34</td>
</tr>
<tr>
<td>Europe</td>
<td>16</td>
<td>3.12</td>
</tr>
<tr>
<td>Japan</td>
<td>7</td>
<td>1.00</td>
</tr>
</tbody>
</table>

Adjusted for age, gender, race, coronary artery disease, congestive heart failure, other cardiac disease, diabetes, lung disease, dyspnea, smoking, cancer, HIV, gastrointestinal bleeding, peptic ulcer disease, hepatitis B virus, hepatitis C virus, neurologic disease, psychiatric disease, recurrent cellulitis/gangrene, and vision problems. HD, hemodialysis.

### Table 2. One-year crude mortality rates on HD in various European countries (3)

<table>
<thead>
<tr>
<th>Country</th>
<th>Crude Mortality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>France</td>
<td>13.3 (11.7 to 15.2)</td>
</tr>
<tr>
<td>Germany</td>
<td>16.3 (14.4 to 18.5)</td>
</tr>
<tr>
<td>Italy</td>
<td>13.8 (12.1 to 158.8)</td>
</tr>
<tr>
<td>Spain</td>
<td>15.3 (13.3 to 17.7)</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>18.6 (16.3 to 21.2)</td>
</tr>
</tbody>
</table>

Adjusted for age, gender, and diabetes as cause of ESRD 95% confidence interval.
ysis patients deserves further studies. The reduction of vascular nitric oxide production and the associated vascular stiffening are of particular concern in view of the known vascular stiffness of central vessel and the impact of this abnormality on heart work (35).

- An additional option may be the administration of antagonists of the cardiotoxic steroid ouabain (e.g., rostafuroxin [29]). It reverses the ouabain-dependent increase of vascular resistance.

- The same may be true for aldosterone antagonists. Intervention with spironolactone effectively lowered BP in dialysis patients with anuria (36) without provoking hyperkalemia (36-38). In the patient with anuria, obviously, mechanisms other than sodium excretion must account for lowering of BP, suggesting a direct vasodilatory action of aldosterone. In this context, the finding that aldosterone causes stiffening of human endothelial cells is highly relevant (39). The BP effect of aldosterone is dependent on and amplified by administration of salt: In the presence of a positive salt balance, aldosterone is also a permissive factor for the development of cardiac fibrosis and other cardiomyopathic features (40).

**Sympathetic Activity**

In the earliest stages of chronic kidney disease (CKD) (41), sympathetic overactivity has been documented by microneurography, and the overactivity is pronounced in end-stage kidney disease (42). Experimental studies showed that sympathetic overactivity is explained by increased afferent signals emanating from the kidney (43). In models of renal failure, one finds release not only of catecholamines but also of co-transmitters (44), and both may account for accelerated progression. The adverse effect of catecholamine excess on cardiac function is widely known, and a strong case can be made for the use of β blockers in renal patients (45). In models of impaired renal function, β receptor blockade attenuates progression even when given on top of renin-angiotensin system blockade (46). In experimental studies, β blockade affects cardiac function and ameliorates even one facet of uremic cardiomyopathy: the capillary deficit (47).

It has been shown that phagocytic cells produce catecholamines (48), which amplify inflammatory reactions (49). Microinflammation is a hallmark of the cardiovascular complications of uremia (50). The known increase of sympathetic activity and catecholamines in kidney disease may potentially further amplify microinflammation.

An entirely new dimension has been introduced by the observation that an enzyme generated in the kidney (renalase) is involved in the catabolism of circulating catecholamines. As a result, in its absence, catecholamine half-life is increased (51), which is of obvious interest particularly in the context of the high frequency of sudden death. Catecholamines predict cardiac death in nonrenal patients with cardiac disease (52) and in dialysis patients (53). In the past, concerns about the metabolic adverse effects of the first generations of β blockers were a deterrent to their use, but the introduction of new β blockers with fewer adverse effects, carvedilol and nevibolol, has revitalized the discussion on the use of β blockers in patients with CKD (45).

**Phosphate and Vitamin D**

An unanticipated finding was originally the observation (54) that cardiovascular mortality is significantly correlated with high predialytic phosphate concentrations. More recently, it has been documented that in patients with CKD (55) and even in cardiac patients without kidney disease, the serum phosphate concentration is a predictor of cardiovascular death (56). The underlying mechanisms are presumably complex given the interaction of phosphate with active vitamin D (57); with cellular calcium handling; with fibroblast growth factor 23, a predictor of survival of dialysis patients (58); and with klotho.

It has also long been known that endothelial cells express vitamin D receptors (59) and produce active vitamin D. Apart from the vasculature, the heart is another target of vitamin D (60). Ongoing studies will show whether normalization of 25-hydroxyvitamin D concentrations and administration of active vitamin D or vitamin D analogues will have an impact on cardiovascular function and on cardiac death.

The mechanisms of the vascular and cardiac effect of phosphate have not been clarified, and the same is true for vitamin D and the hormones involved in phosphate homeostasis. These issues are beyond the scope of this article, but this is not to say that they are not important.

**Neglected Cardiovascular Risks**

**Sleep Apnea**

Sleep apnea is considerably more frequent, at least by a factor of 10, in the dialysis population. In symptomatic dialysis patients, a frequency of 70% was found (61) and a frequency of 20 to 30% in dialysis patients overall (62) compared with 1 to 2% in the general population (63), for whom it is associated with increased mortality (64). Sleep apnea seems to be an important contributor to mortality in dialysis patients as well, because nocturnal lowering of Po2 is a predictor of death on dialysis (65). The issue to what extent this abnormality in dialysis patients is more a form of peripheral or of central apnea is still unresolved. Interventional studies of nonrenal patients showed that treatment of sleep apnea improved survival (66). Sleep apnea for patients who are on dialysis is one factor that may require changes in dialysis strategies, because daily nocturnal dialysis caused a dramatic reduction of sleep apnea (67).

**Depression**

Depression has been found in at least 20 to 30% of dialysis patients, and mortality increases with increasing time that the patients feel depressed (68). In nonrenal patients with cardiovascular disease, a similar prevalence has been reported (69,70); in such patients, depression is an independent and powerful predictor of death (71). It is uncertain whether the link is causal. This remains a difficult area to study. In the cardiology literature, a number of pathogenetic mediators that may also be operative in kidney disease have been proposed: Autonomic imbalance, hypercorticism, insulin resistance (72), and microinflammation (73–75). Whether interventions to reduce micro-
inflammation might also safely reduce depression in patients with CKD, as suggested by interventions for patients with nonrenal disease (76), is unclear. The issue of whether microinflammation causes depression also is of interest: In patients with malignancies, depression that was provoked by treatment with IFN-α could successfully be treated with an antidepressant (77). Less depression may explain the positive effect of spirituality (78) and the potential positive role of caregivers (79) for the quality of life of patients who are on renal replacement therapy.

Disrupted Biorhythm

Another neglected aspect of cardiovascular risk is disrupted biorhythm (80). Sleep disturbances and altered day/night rhythm have been frequently documented in dialysis patients (81). Adverse cardiac events show significant diurnal variations (82), and mortality is higher for people whose professions expose them to frequent disruption of the biorhythm (e.g., flight crews, shift workers) (83). A recent animal experiment showed that in the long run, disruption of the biorhythm by genetic manipulation caused target organ damage in kidney and heart (84). Against this background, the findings of the observational DOPPS are remarkable that self-reported disturbed sleep is a powerful predictor of mortality (85), most tightly related to pain, pruritus, and depression. Melatonin antagonists have recently become available for at least the treatment of transient insomnia after sleep-time shift (86).

Attractive Areas for Future Investigations

Scribner left the following statement as a legacy: “Although we have accomplished much, we still have much to do to improve the lives and the wellbeing of our patients...we owe them continued research” (87). This requires some “thinking outside the box.”

Overall, one has to state that in nephrology, despite a rich repertoire of observational studies, very few interventional studies are available, so current guidelines are mostly opinion based. This contrasts with, for instance, cardiology, for which abundant controlled, prospective evidence is available (88); so future interventional studies are a high priority, but these must be based on solid insight into pathophysiology, which remains an equally important topic.

If priorities for future studies should be defined, it is good to remember the answer of the bank robber Willie Sutton: “Why did you break into the bank?” “Because that’s where the money is.” If we are to devise strategies to have the greatest impact and to reduce the most frequent causes of death, we should go after sudden death; it is here where “the money is” and greatest benefit can be expected.

A fascinating new development was the recognition that cardiac development and function is to a large extent under the control of micro-RNAs, which control entire patterns of transcription by RNA interference switching on and off transcription. Two specific micro-RNA species, miR-1 and miR-133, have been recognized to be related to arrhythmia and two, miR-21 and miR-29, to cardiac fibrosis (89). To study their potential role in kidney disease would be a promising topic (15).

In view of the fact that typical lesions and functional disturbances of uremic cardiomyopathy can be reproduced by marinobufagenin and that neutralizing antibodies against marinobufagenin prevent such lesions (26), two lines of studies immediately offer themselves: First, because cardiotonic steroids are released by salt loading in the absence of renal disease, it will be important to determine whether their plasma concentration is influenced by salt intake in patients with CKD as well as in dialysis patients. Second, because of the role of plasma sodium concentration discussed above, it will also be important to study whether the dialysate sodium concentration influences the concentrations of marinobufagenin and ouabain independent of the salt balance. On a more basic level, interventions that block the action of marinobufagenin should be a considerable priority.

In view of the importance of arrhythmia and sudden death, mechanistic studies on sympathetic overactivity are a hot topic, and in view of the high cardiovascular mortality, a controlled trial on β blockade with the metabolically neutral new β blockers on top of standard therapy should also be a priority.

Oxidative stress is known to be involved in the cardiomyopathy of CKD (90). In our own study (10), we found that in the ApoE−/− mouse, even uninephrectomy caused cardiac fibrosis, capillary rarefication, and arteriolar thickening (Table 3). This initial stage of cardiomyopathy was completely prevented by the administration of the superoxide dismutase mimetic tempol, which abrogated oxidative stress. Although administration of folate did not provide benefit as expected on the basis of the hypothetical role of homocysteine (91,92), the issue may not yet be completely settled (93), and more sophisticated and specific medications to reduce oxidative stress remain a high priority.

One of the most pressing clinical problems is the issue of target BP on dialysis. Observational studies in prevalent dialysis populations yielded controversial results: Low BP values

<table>
<thead>
<tr>
<th>Table 3. Early onset of uremic cardiomyopathy: Uninephrectomy of ApoE−/− mice (10)</th>
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</thead>
<tbody>
<tr>
<td>Parameter</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td>Sham operation</td>
</tr>
<tr>
<td>Uninephrectomy</td>
</tr>
<tr>
<td>Uninephrectomy + tempol</td>
</tr>
</tbody>
</table>

VV, volume density; LV, length density; IMT, intima media thickness.
were associated with the highest risk (17,94). Studies of patients who had less morbidity and were on long, slow dialysis clearly showed that low BP values within the normal range provided a survival benefit (16). The issue is very complex, and problems such as central versus peripheral BP, circadian BP profile, pre-existing cardiovascular morbidity, and differential effect of antihypertensive agents on different endpoints have not been fully investigated. A recent meta-analysis documented an overall beneficial effect of antihypertensive treatment in hemodialysis patients (95). In the future, it will be important to address the risk that low diastolic pressures may have in jeopardizing coronary perfusion in patients with CHD, because cardiac perfusion occurs only in diastole. Higher rates of myocardial infarction have been documented in patients with cardiovascular disease (96) and in patients who had diabetes and CKD (97) and had low diastolic BP. The differential effect of antihypertensive agents on various end points is also nicely illustrated by the Irbesartan Diabetic Nephropathy Trial (IDNT), in which irbesartan was superior to amlodipine with respect to the renal end point (98) but amlodipine was superior to irbesartan with respect to prevention of stroke and myocardial infarction (99).

Although it is urgent to address the pathomechanisms that are involved in studies with appropriate methods, it is unrealistic to believe that the issue of the most appropriate BP on dialysis can be resolved in one single big study. The future challenge will certainly be to individualize treatment and to get off the naive view that one BP is optimal for all dialysis patients.

Disclosures
None.

References
loss of function of the thiazide-sensitive cotransporter have reduced blood pressure. *Hum Mol Genet* 17: 413–418, 2008


