EDITORIAL REVIEW

Cardiovascular Complications in Renal Failure[1,2]

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ABSTRACT

Cardiovascular diseases are a leading cause of death in end-stage renal disease (ESRD) largely as a result of the progressively increasing age of ESRD patients and the broad constellation of uremia-associated factors that can adversely affect cardiac function. Hypertension, one of the leading causes of renal failure, is a major culprit in this process, causing left ventricular hypertrophy, cardiac chamber dilation, increased left ventricular wall stress, redistribution of coronary blood flow, reduced coronary artery vasodilator reserve, ischemia, myocardial fibrosis, heart failure, and arrhythmias. In addition to impairing the coronary microcirculation, hypertension may contribute to the development of atherosclerotic coronary artery disease, particularly in the presence of the many lipid abnormalities observed in ESRD. These patients have reduced high-density lipoprotein cholesterol and increased plasma triglyceride concentrations, and there is a defect in cholesterol transport. Other abnormalities that may contribute to atherosclerotic coronary artery disease in ESRD are reduced high-density lipoprotein cholesterol synthesis and reduced activity of the reverse cholesterol pathway. Treatment with fibric acids, nicotinic acids, and lovastatin may be useful in lowering cholesterol and triglyceride concentrations in some of these patients. The incidence of coronary artery disease in ESRD populations is difficult to determine. About 25 to 30% of ESRD patients with angina have no evidence of significant coronary artery disease, and an undetermined number have silent coronary disease. The presence of resting electrocardiographic abnormalities caused by hypertension or conduction defects makes it difficult to accurately diagnosis coronary artery disease in ESRD populations by noninvasive methods, including exercise testing and thallium scintigraphy with or without the use of dipyridamole. Hypotension is a frequent complication of the dialytic process. Many factors have been implicated, including autonomic neuropathy. There is no concensus on the function of the efferent limb of the sympathetic nervous system. The afferent limb (arterial baroreflex function) is felt to be impaired. Further, there may be defects in the ability of the cardiovascular system to respond to sympathetic nerve activity. Most studies of autonomic function have used indirect measurements. Studies are underway that use techniques to assess sympathetic function directly. Such experiments with microneuropathy suggest greater skeletal sympathetic muscle discharge in uremic patients than in normal patients.

Key Words: *Cardiovascular complications, ischemic heart disease, autonomic neuropathy, lipid abnormalities*

Cardiovascular diseases, including cerebrovascular disease, are the leading causes of death in end-stage renal disease (ESRD) populations and account for 30 to 50% of all deaths. Moreover, this frequency has not changed appreciably during the past 15 yr. This finding may be best explained by the broad constellation of uremia-associated hemodynamic, metabolic, and treatment- and disease-associated factors that can adversely affect cardiac function; among them are hypertension, abnormalities of lipid and carbohydrate metabolism, and abnormali-

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ties of the pituitary gonadal axis. Other factors associated with the dialysis prescription, the use of corticosteroid and androgen therapies and complications of altered parathyroid and vitamin D metabolism, also contribute significantly.

Sustained cardiovascular morbidity and mortality in the ESRD population also reflect the age of this group, which has become increasingly skewed toward the elderly. Patients over age 65, who comprise 12% of the United States population, represent nearly 40% of the ESRD population. These patients are at increased risk for mortality of all causes but especially from cardiovascular and cerebrovascular diseases whose excess mortality in the general population has been shown to be largely related to the presence of hypertension and elevated serum lipids. Data from the United States Data System 1989 Report (1) show that in ESRD populations, as in the general population with advancing age, there is an increasing mortality from cardiac disease, largely heart failure and arrhythmia, and from myocardial infarction, with peak mortality over age 60.

Black individuals, who comprise approximately 12% of the United States population, are also overrepresented in ESRD populations. They are at the highest risk for hypertension (2) and also have an increased morbidity and mortality from all causes and from cardiovascular disease, particularly in age-matched data in the general population. As will be discussed later, this increased cardiovascular morbidity and mortality may, in part, be related to an increased prevalence of left ventricular hypertrophy and increased left ventricular mass index, largely as a consequence of hypertension (3). In this regard, Silverberg *et al.* (4) have shown that increased left ventricular mass index is associated significantly with cardiovascular morbidity and mortality in ESRD patients. This, together with age and hypertension, may serve as a predictor of mortality in the chronic renal failure population.

The poor, too, are overrepresented in the ESRD population, resulting from this high proportion of black and elderly patients. A zip code analysis that we performed for Jefferson County, AL, showed that the number of patients per zip code entering ESRD programs in the county was directly related to the percentage of households in the zip code with low incomes (less than $7,500/yr; $r = 0.914$; $P < 0.001$). This highly significant correlation suggests a strong association between poverty and the development of ESRD and has important implications for treatment and outcome.

HYPERTENSION: CONTINUED CAUSE OF ESRD AND COMPLICATIONS DURING DIALYSIS THERAPY

Hypertension is one of the leading causes of renal failure in the United States. Current studies now suggest that antihypertensive therapy can delay, but not necessarily prevent, the onset of renal failure (5–8). Moreover, as renal function deteriorates, blood pressure increases and blood pressure control becomes increasingly difficult to achieve. As a result, the rate of deterioration of renal function accelerates and the risks for cardiovascular complications increase. In the Jefferson County, AL, ESRD population, deaths from stroke, myocardial infarction, and congestive heart failure occurred more frequently in patients with ESRD because of hypertensive renal failure. This study also revealed that ESRD patients dying of stroke and heart failure had poor blood pressure control at the time of initial referral for nephrological care.

The greatest number of patients in Jefferson County referred with hypertensive renal disease were blacks who had significantly higher blood pressures and more severe retinal vascular disease than did whites (9). A significant proportion of these patients were receiving no antihypertensive therapy at the time of referral and had not been recipients of regular medical care before their initial referral to a nephrologist. Although it is uncertain what the explanation for this might be, cultural, and especially economic, factors may contribute significantly to the problem. As noted previously, there is a strong association between poverty and the development of ESRD. Poverty not only can impact negatively on therapeutic interventions for hypertension before dialysis, but it may also adversely affect the success of blood pressure control after dialytic therapy has commenced because government entitlement programs often do not cover the cost of medications necessary to control blood pressure. In this regard, although it has been observed that mean blood pressure tends to be significantly lower once dialysis has begun (10), Cheigh *et al.* recently reported (11) that only 15% of patients maintained blood pressures within the normotensive range at all times, suggesting that blood pressure control in the interdialytic period, as determined by continuous ambulatory blood pressure monitoring, is much worse than had previously been thought.

It is not surprising, therefore, that anatomical abnormalities of the heart, such as left ventricular hypertrophy and left atrial and left ventricular chamber dilation, strongly associated with hypertension, are the most common abnormalities of cardiac structure seen in ESRD patients (12). In addition to hypertension, intermittent and sustained extracellular fluid volume overload and anemia may cause increased cardiac work and cardiac chamber dilation. Increased ventricular chamber size together with hypertension and left ventricular hypertrophy may produce increased left ventricular wall stress, redistribution of coronary blood flow (causing ischemia and subsequent development of myocardial fibrosis), systolic and diastolic dysfunction, and heart failure

(13,14). Anemia also contributes to a high-output state, further placing the left ventricle at risk for failure. It has been reported that correction of anemia with erythropoietin can decrease left ventricular chamber size and reduce cardiac indices (15).

Sustained hypertension together with an increased prevalence of abnormalities of lipid metabolism in patients with ESRD may cause vascular endothelial damage and may contribute to the development of atherosclerosis and subsequent occlusion of one or more main coronary vessels. It is now well described that atherosclerotic heart disease is a major problem affecting the older white male dialysis population (16).

Ischemic heart disease may also result from disturbances in the coronary microcirculation, which may reduce the compliance of these vessels, thereby limiting their vasodilatory response to increasing myocardial oxygen demands. Such abnormalities may result from hypertension-induced structural abnormalities of the small coronary vessels, as mentioned above. Alternatively, they may result from functional disorders of the microcirculation that reduce the coronary vasodilator reserve. Some of the factors that may influence this are noted in Table 1. Among those associated with uremia are reduced blood viscosity due to anemia, abnormalities in responses to local relaxing or constricting factors, the consequences of left ventricular hypertrophy induced either by pressure or volume, and altered myocardial oxygen consumption (17). Such abnormalities of the microcirculation or of the main coronary circulation, as noted previously, may lead to ischemia and fibrosis and to stiffness of the myocardium with subsequent development of myocardial failure. The frequent occurrence of diastolic dysfunction in ESRD patients may be a manifestation of these changes and may contribute significantly to dialysis-associated angina and hypotension.

The importance of altered coronary microcirculation is not theoretical and should not be underestimated. Rostand and Rutsky have shown that approximately 27% of patients with ESRD developed ischemic heart disease in the absence of significant main coronary arterial occlusion, a percentage not dissimilar to that in the general population (18). An examination of the characteristics of these ESRD patients revealed that those with absent main coronary lesions had substantially more left ventricular hypertrophy, lower hematocrits, and higher cardiac indices than did those with significant main coronary lesions (16). Importantly, they also had significantly greater degrees of hypertension at the onset of dialysis (16). Because black patients with symptoms of ischemic heart disease had significant coronary stenosis half as often as did white patients (18), alterations in coronary microcirculation may play a major role in ischemic heart disease in Americans of African descent. It would appear then that hypertension developing before the onset of dialysis may contribute to the development of left ventricular hypertrophy and reduced cardiac performance that may be sustained as a consequent of inadequate blood pressure control during dialysis.

TABLE 1. Factors contributing to ischemic heart disease in ESRD

Increased Myocardial Oxygen Demand
Increased myocardial mass
Increased systolic and diastolic wall stress
Decreased Oxygen Supply
Decreased capillary/myocyte density
Increased diffusion distances
Abnormal diastolic relaxation
Compression of myocardial circulation
Fibrous replacement of microcirculation
Small vessel disease
Abnormal vasomotor tone
Coronary artery disease
Anemia

Diligent antihypertensive therapy should be undertaken before the onset of renal failure in order to delay its progression and to minimize subsequent cardiac hypertrophy, ischemia, and failure. The association between poverty and ESRD suggests that there are still major economic barriers to antihypertensive therapy despite the availability of government entitlement programs, and every effort should be made to enhance the availability of antihypertensive medications for patients before and after the development of renal failure. Drugs such as beta-blockers, calcium channel blockers, and angiotensin converting enzymes inhibitors are useful in such a strategy. Although it is argued whether left ventricular hypertrophy, once established in uremia, can be reversed by dialysis or by antihypertensive agents, recent data (19) suggest that blood pressure control, at least with angiotensin converting enzyme inhibitors, can minimize cardiac hypertrophy. Close follow-up is also needed to assure optimal blood pressure for it cannot be assumed that well-controlled pre- or postdialysis blood pressures represent adequate blood pressure control in the interdialytic period.

LIPID ABNORMALITIES IN ESRD

Many forms of hyperlipidemia have been observed in patients with renal disease. For example, patients with the nephrotic syndrome have marked increases in low-density lipoprotein (LDL) cholesterol that are often associated with an increase in the concentration of very low-density lipoproteins. As renal function progressively deteriorates, lipid abnormalities become increasingly obvious. Although the reasons for this are debated, the parallel development of parathyroid hormone hyperactivity has suggested a rela-

tionship between the two (20,21). However, in these patients, there is an inverse relationship between parathyroid hormone and triglyceride concentration (22). Patients with ESRD undergoing maintenance dialysis are observed to have an increase in plasma triglycerides due to reduced very low-density lipoprotein degradation and decreased concentrations of high-density lipoprotein (HDL) cholesterol. Although a defect in cholesterol transport has been reported, LDL cholesterol levels are usually low (23–25). Patients undergoing successful renal transplantation demonstrate a somewhat different form of hyperlipidemia associated with an increase in very low-density lipoprotein and LDL cholesterol, most likely reflecting the use of immunosuppressive therapy.

As a consequence of these lipid abnormalities and other risk factors for ischemic heart disease, patients with ESRD have been described to be at increased risk for atherosclerotic coronary artery disease and its complications. Lindner *et al.* (26) reported on the experience of the initial 44 patients placed on chronic maintenance hemodialysis in Seattle and found that the probability of death due to cardiovascular disease approached 50% after 10 yr on hemodialysis. More than half of this mortality was accounted for by coronary artery disease. Subsequently, Haire *et al.* (27) reported that patients who continue to smoke after the initiation of dialysis or who had persistent hypertension despite dialysis also had very high cumulative mortality rates, approaching 80% in 7 yr in smokers compared with a cumulative mortality rate of less than 20% in nonsmokers.

In 1976, a prospective study was begun in Seattle involving 147 patients at the Veterans Affairs Medical Center and 63 patients at the Northwest Kidney Center. Between 1976 and 1978, 186 additional patients were entered into this prospective study. An interim evaluation in April 1984 (L. Haas unpublished observations), indicated that about half of these patients were still alive. Of those who had died, 99 had cardiovascular deaths, 50 died of myocardial infarction, and 49 died of sudden death. Ninety-three patients died from noncardiovascular deaths, which included sudden death associated with hyperkalemia. The cardiovascular disease was early in onset in both men and women. Of the 30 women who died of cardiovascular disease, the mean age at the onset of dialysis was 50 ± 14 yr and the mean age of death for the group was 53 ± 14 yr. Sixty-nine men began dialysis at the age of 54 ± 10 yr with the mean age of death at 59 ± 9 yr. Hypertriglyceridemia was the predominant lipoprotein abnormality associated with death due to coronary artery disease in both men and women when compared with patients still living and with those dying of noncardiovascular diseases.

Brunzell *et al.* (28) evaluated the prevalence of hypertriglyceridemia and hypercholesterolemia in 127 patients in the Seattle dialysis population. They found that several of the abnormalities associated with hypertriglyceridemia, independent of renal failure, were common in the dialysis population and included diabetes mellitus, the use of androgen therapy, and the use of the antihypertensive propranolol. Nevertheless, hypertriglyceridemia existed in the remaining subset of the dialysis population when compared with a Seattle-based control population. Total serum cholesterol concentrations were lower than normal in the dialysis group and were accounted for by a decrease in both LDL and HDL cholesterol fractions. The decrease in HDL cholesterol concentration was, in part, associated with hypertriglyceridemia but, when compared with controls matched for triglyceride concentration, HDL cholesterol concentration was still depressed. Of interest was the finding that the HDL apoprotein A1, the major protein of HDL, was normal in the dialysis population subset that did not have the other acquired causes for hypertriglyceridemia. This finding suggested that the number of HDL particles was normal but that the composition of HDL was abnormal.

The hypertriglyceridemia and decreased serum concentration of HDL cholesterol in dialysis patients were associated with a decrease in both lipoprotein lipase in adipose tissue and in postheparin plasma (29). However, HDL cholesterol concentration may also be reduced because of a decreased synthetic rate (30) or because of a reduction in the enzyme lecithin-cholesterol acyl transferase (31). When these patients were treated with clofibrate at a markedly reduced dose, the abnormality of lipoprotein lipase in adipose and in postheparin plasma corrected toward normal as did the abnormalities in lipoproteins (32). Studies of the half-life of a single 1-g dose of clofibrate in normal subjects revealed the half-life to be about 16 ± 5 h, whereas in patients on chronic maintenance dialysis, its half-life was increased to 110 ± 36 h (33). For this reason, the dose of clofibrate used in patients on maintenance dialysis was markedly decreased to 1.5 g/wk in order to reduce myopathy. The unusual patient who has an elevated LDL cholesterol may be treated with the hydroxymethylglutaryl coenzyme A reductase inhibitor, lovastatin, which in doses of 20 to 40 mg daily can significantly lower serum total cholesterol levels and increase HDL concentrations with few, if any, side effects. Nonpharmacological approaches have also been suggested and have proven successful (34). Recently, abnormalities in intermediate-density lipoproteins and lipoprotein (Lp) (a) have been observed in patients undergoing chronic maintenance dialysis. Such abnormalities have been associated with atherosclerosis (35), but therapy directed toward these abnormalities has not yet been evaluated.

Although the hypertriglyceridemia and reduced HDL cholesterol concentrations seen in chronic renal failure patients and patients on chronic maintenance

hemodialysis may be treated with low doses of clofibrate or other fibric acids, nicotinic acids and lovastatin may be useful in lowering cholesterol and triglyceride concentrations in patients with nonuremic nephrotic syndrome or with hyperlipidemias associated with transplant therapy. It is important to note, however, that renal transplant recipients who are receiving cyclosporine as their immunosuppressive agent must take reduced doses of lovastatin, because the interaction of cyclosporine and lovastatin may accelerate the appearance of the lovastatin-associated rhabdomyolysis syndrome.

ISCHEMIC HEART DISEASE IN ESRD

As alluded to at the outset, ischemic heart disease continues to be a leading cause of death in ESRD associated with increasing numbers of diabetic and older patients who may have had ischemic heart disease before the initiation of hemodialysis therapy. Further, the risks for the development of symptomatic disease are increased in patients with ischemic heart disease because of the prevalence of extracellular fluid volume overload, left ventricular hypertrophy, inappropriate increases in peripheral vascular resistance, anemia, and dialysis-associated factors, such as rapid volume and electrolyte shifts and hypoxemia not encountered in the non-ESRD population.

The prevalence of coronary artery disease in the ESRD population is uncertain because all published series represent populations selected for cardiac catheterization on the basis of either symptoms or risk factors for coronary artery disease. Recently, Rostand and Rutsky (18) found that 59 of 81 ESRD patients who had angina pectoris (73%) were noted to have coronary artery lesions with greater than 50% luminal narrowing when studied by cardiac catheterization. Their predictive model developed by discriminant function analysis found the best predictors of significant coronary disease to be age (>50 yr), white race, male gender, elevated total serum cholesterol, angina or myocardial infarction before hemodialysis initiation, and the presence of left ventricular wall motion abnormality on echocardiogram or radionuclide angiogram (16). Castro *et al.* (36) found that 49 of 77 (64%) of high-risk patients had coronary artery disease on angiography. Of those, 28 (57%) had significant obstructive lesions. Only 9 of these 28 (32%) were symptomatic, suggesting that myocardial ischemia may not be appreciated in many ESRD patients. In this regard, Pochmalicki *et al.* (37) recently reported electrocardiogram (ECG) monitoring performed for 4 h before, during, and after hemodialysis in 62 consecutive ESRD patients. Thirty-seven percent of these patients demonstrated ST segment depression consistent with myocardial ischemia in the absence of any symptoms. They found the presence of silent ischemia correlated with diabetes mellitus, advanced age, smoking, and known coronary artery disease. Noteworthy also was the finding that during a 14-month follow-up, 11 patients died, 8 of whom had had silent ischemia on monitoring during hemodialysis. Thus, silent ischemia may be as common a problem in patients on hemodialysis as in the chronic stable angina population with normal renal function and may be of ominous prognostic significance.

Unfortunately, noninvasive testing for diagnosis and risk stratification in patients with coronary artery disease is less satisfactory in ESRD patients than in the general population. The ECG response to exercise may be difficult to interpret because of left ventricular hypertrophy or conduction abnormalities that distort the baseline ECG. Further, effort tolerance may be poor in patients with ESRD for noncardiac reasons. Thus, despite experiencing angina during hemodialysis, patients may not be able to generate adequate stress during exercise treadmill testing. Thallium scintigraphy, similarly, may be less sensitive or specific for coronary artery disease in the hemodialysis population. Just as effort limitation may preclude interpretation of ECG responses to exercise, impaired effort tolerance for noncardiac reasons may also make thallium scintigraphic identification of relatively underperfused myocardiums difficult. In recent years, dipyridamole thallium scintigraphy has become increasingly popular, particularly for those whose effort tolerance is poor and, thus, would seem an ideal test in ESRD patients. However, Marwick *et al.* (38) have reported that this test may have much lower sensitivity and specificity in ESRD patients than in the coronary disease population with normal renal function. They found that 19 of 45 patients undergoing pretransplant evaluation (42%) had significant coronary artery disease at catheterization, but only 14 had abnormal dipyridamole thallium scintigrams. Only seven of these were true positives. Thus, the overall sensitivity of this test for identifying patients with significant coronary disease in the renal failure population was 37% with a specificity of 73%, significantly worse than that in the nonrenal failure population in which the sensitivity was 95%. Resting or exercise-induced wall motion abnormalities by radionuclide angiography or by echocardiogram may be more specific for coronary artery disease, providing that patients are able to exercise to ischemia.

Rostand and Rutsky (18) have found that 27% of 81 patients with angina pectoris and angiographic-defined coronary arteries had normal or minimally plaqued coronary arteries. Although chest pain in this patient population could represent noncardiac pain (e.g., esophageal motility dysfunction or acid reflex), there is evidence that at least a subset of these patients may have had ischemic pain in the

absence of obstructive coronary artery disease. Delano *et al.* (39) reported isoproterenol stress studies with sampling of myocardial venous lactate concentrations in six asymptomatic dialysis patients with no evidence of ischemic heart disease. All patients had increased coronary serum lactate concentrations—evidence of myocardial ischemia. In these circumstances, it is likely that ischemia may be the consequence of left ventricular hypertrophy, which limits the coronary flow reserve available to the myocardium during stress (40). This limitation in flow reserve, as previously mentioned, reflects multiple abnormalities present in left ventricular hypertrophy that prohibit matching myocardial oxygen demands during stress with an appropriate coronary blood flow response for oxygen delivery (Table 1).

Medical management of ischemic heart disease in end-stage renal failure includes careful attention to risk factors such as smoking, hypertension, and lipid abnormalities, just as in the population without renal disease (Table 2). Nitrates, beta-blockers, and calcium channel blockers all have anti-ischemic benefits and can be used in the ESRD population. Although aspirin use is becoming increasingly common in patients with chronic stable angina, the widespread use of aspirin in ESRD patients on hemodialysis has not yet been studied. Given the high prevalence of hypertension and the possibility of hemorrhagic stroke and risks for gastrointestinal bleeding, aspirin should be used cautiously. Nevertheless, aspirin may be useful for preventing platelet activation during hemodialysis, which may contribute to ischemia during this procedure. Although exercise is encouraged in patients with chronic stable angina and normal renal function, regular strenuous exercise may be particularly beneficial in the ESRD patient. Goldberg *et al.* (34) have reported the benefit of routine exercise in a small number of dialysis patients.

TABLE 2. Approaches to management of coronary artery disease

Risk Stratification
Emphasis on Prevention
Aspirin
Exercise
Treatment of lipid disorders
Antihypertensive therapy
Treatment of anemia
Anti-Ischemic Therapy
Medical
Nitrates
Beta-blockers
Calcium-channel blockers
Angiotensin converting enzyme inhibition
Invasive
Coronary artery bypass grafting
PTCA,[a] atherectomy, stents

[a] PTCA, percutaneous transluminal coronary angioplasty.

They found that after 3 to 18 months of exercise, there was a significant increase in hemoglobin, hematocrit, and HDL cholesterol concentrations and a reduction in serum triglyceride and total serum cholesterol concentrations. Furthermore, there was an improvement in glucose and insulin responses to a glucose load. More recently, erythropoietin has been shown to increase not only hemoglobin and hematocrit, exercise tolerance, and maximum oxygen consumption but also to prevent ischemic ECG response to exercise (41).

ESRD patients who fail to respond to medical management can be treated with coronary artery bypass grafting although at a higher risk than in patients with normal renal function (42,43). However, it is not known whether coronary artery bypass grafting offers survival advantages in patients with ESRD, even those considered to be at high risk. In recent years, percutaneous transluminal coronary angioplasty has been more frequently performed in ESRD patients with symptom benefit, although published series describing risk and long-term benefit have not been yet appeared.

AUTONOMIC DYSFUNCTION AND ITS CONSEQUENCES IN RENAL FAILURE

Although sustained hypertension, among other factors, contributes significantly to cardiovascular and cerebrovascular morbidity and mortality in patients with chronic renal failure, hypotension is a frequent complication of the hemodialysis process and may also be a significant contributor to cardiovascular and cerebrovascular morbidity and mortality in the hemodialysis population. The etiology for hypotension is multifactorial and may include such problems as extracellular fluid volume loss during the dialysis process, use of bioincompatible dialysis membranes, redistribution of blood volume, hypoxemia, heart failure resulting from systolic and/or diastolic dysfunction, dialysis-associated shifts in intra- and extracellular calcium, acquired valvular disease, or disturbances of heart rhythm. In addition, alterations in sympathetic nervous system activity have been implicated as a cause for alteration in vascular reactivity seen in uremic and dialysis patients.

Three principal concepts have been postulated regarding sympathetic nervous system function in uremia. First, it has been suggested that the efferent limb of the sympathetic nervous system functions normally. Several studies suggest that chronic renal failure is accompanied by tonic overactivity of the sympathetic nervous system because plasma norepinephrine levels were noted to be elevated (44–46). Such findings, though indirect, have also suggested that hyperactivity of the sympathetic nervous system

may have contributed to the genesis of hypertension in the uremic patient (47). However, other investigators have found that chronic renal failure is accompanied by normal or even decreased plasma norepinephrine levels (46,48). The large variability in plasma norepinephrine concentrations among hemodialysis patients may be related to individual differences in sympathetic outflow and/or plasma catecholamine clearance, particularly because catecholamines are partially cleared during hemodialysis and represent only a small fraction of the total amount of catecholamine released. To complicate matters further, plasma concentrations of dopamine beta-hydroxylase, also released from the peripheral sympathetic nerve endings, are decreased in patients with chronic renal failure, suggesting that central sympathetic outflow may be lower, not higher, than normal (44). Thus, at the present time, there is little consensus concerning the effects of chronic renal failure on the efferent limb of the sympathetic nervous system.

In contrast to the first concept, arterial baroreflex (i.e., afferent) function is thought to be impaired in many patients with chronic renal failure. This proposed baroreflex impairment is thought to contribute both to poor blood pressure regulation associated with hypotension during hemodialysis and to increased tonic levels of circulating catecholamines, which might contribute to chronic hypertension. It has been widely observed that arterial baroreflex control of heart rate is frequently impaired in chronic renal failure (49–53). Sudden changes in arterial pressure typically evoke much smaller reflex changes in heart rate in uremic patients than in healthy individuals. This reflex attenuation appears greatest in uremic patients with hypertension but may also be found in uremic patients with normal blood pressure (54). Impaired baroreflex control of heart rate is thought to contribute to the development of hypotension during hemodialysis because the degree of this impairment is generally greater in hypotension-prone than in hypotension-resistant dialysis patients (50,51,53). Of note is the finding that patients with dialysis-induced hypotension show blunted changes in heart rate with baroreflex maneuvers (e.g., Valsalva) but show normal increases in blood pressure with the cold pressor test, a nonbaroreflex stimulus to sympathetic outflow (50,53,54). These observations have been interpreted as meaning that the autonomic defect in uremia is localized to the afferent arm of the baroreceptor reflex and that the efferent sympathetic pathways remain intact (50,55). However, Nakashima *et al.* (56) suggest that the problem may not be with baroreceptors *per se* but rather with the ability of the cardiac branch of the vagus nerve to respond to changes in baroreceptor input (e.g., an efferent rather than an afferent defect). In this study of a large group of chronic hemodialysis patients, it was found that heart rate and plasma norepinephrine increase normally with head-up tilt (even in hypotension-prone patients), suggesting a normal baroreflex arc. However, heart rate slowing was blunted during acute hypertension produced by fistula occlusion and this change was accompanied by a marked attenuation of normal sinus arrhythmia, suggesting a selective defect in the parasympathetic innervation of the sinus node.

Last, chronic renal failure may be accompanied by defects in the ability of the cardiovascular system to respond to sympathetic neural activation, which may further exacerbate hypotension during hemodialysis (57,58). In this regard, Mann *et al.* (59) found that rats with experimental uremia had blunted chronotropic responses to an infusion of isoproterenol when compared with controls but had identical decreases in blood pressure. Although those authors were unable to find a reduction in beta-adrenoreceptor density, they did find reduced basal and stimulated adenylate cyclase activity in uremic rats as compared with controls. These results suggested that chronotropic responses of the heart are reduced in uremia. However, there are other studies showing that isoproterenol evokes normal increases in heart rate in uremic patients, which suggests that the beta-adrenergic receptors function normally (56). Campese *et al.* (47) have demonstrated that uremic patients have reduced changes in mean arterial blood pressure and heart rate in response to the alpha-adrenergic agonist norepinephrine when compared with controls. Similar findings have been reported in animals with experimental uremia. The reasons for this are unclear, but it has been suggested that parathyroid hyperactivity found in chronic uremia may blunt the pressor effects of norepinephrine as a consequence of its vasodilatory properties. Thus, there is no unanimity of opinion regarding either the state of the sympathetic nervous system in uremia or its contribution either to hypertension or to dialysis-associated hypotension.

In order to address the controversy that has arisen regarding the state of the sympathetic nervous system in patients with chronic renal failure and to avoid the pitfalls that may have resulted from indirect measurements of sympathetic function, direct assessments of efferent sympathetic nerve activity would be preferable. The microneurographic technique of Vaibo *et al.* (60) may provide such an opportunity. This technique involves the percutaneous insertion of a unipolar microelectrode into a peripheral nerve (usually the peroneal nerve) in order to selectively record action potentials from sympathetic fibers innervating the peripheral circulation of the skeletal muscle bed. The technique is well tolerated and safe and permits continuous recording of spontaneous sympathetic nerve activity in conscious humans (60). Microneurography offers several specific

advantages over indirect assessments of sympathetic function for the study of uremic autonomic neuropathy. First, it provides a reproducible and valid means of comparing basal rates of sympathetic discharge targeted to a specific vascular bed between different groups of individuals. Second, it permits a quantitative assessment of baroreflex control of a sympathetic nerve activity, thereby avoiding potential defects in end-organ reactivity that may complicate the interpretation of baroreceptor function when heart rate or blood pressure is used as the reflex endpoint. A third advantage is that by simultaneously measuring sympathetic nerve traffic and blood flow, it is possible to examine in detail the relationship between sympathetic nerve discharge and vascular resistance in the same vascular bed. This would allow a determination of whether uremia alters the ability of the peripheral vasculature to respond appropriately to changes in sympathetic neural traffic. Preliminary data in uremic patients suggest that baseline rates of skeletal muscle sympathetic discharge are frequently greater than normal in chronic hemodialysis patients (61). The implications of these data remain unclear and will need to be interpreted in the light of future data gathered by the same methodology. At the present time, hypotension remains a frequent and troublesome hemodynamic consequence of hemodialysis. The importance of alterations in the sympathetic nervous system in this process remains to be elucidated.

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