MEDICINE GRAND ROUNDS

UREMIC AUTONOMIC NEUROPATHY

The Ups and Downs of Blood Pressure in Patients with Chronic Renal Failure

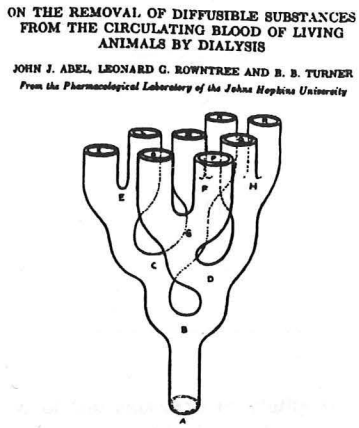
October 22, 1992

Ronald G. Victor, MD

TABLE OF CONTENTS

I. INTRODUCTION

The idea of removing solutes from body fluids by dialysis dates back to the beginning of the century. In 1913 Abel and colleagues at Johns Hopkins performed the first experimental hemodialysis in dogs (1). The first viable dialyzer for the treatment of acute renal failure in patients was invented in 1943 (2); however, dialysis became a viable treatment for chronic renal failure only with the surgical development of a long-term arteriovenous access in 1966 (3). Financial access to maintenance dialysis became a reality in the United States in 1973 with the creation of the Medicare End-Stage Renal Disease (ESRD) Program, which now includes over 150,000 patients (4).


ON THE REMOVAL OF DIFFUSIBLE SUBSTANCES FROM THE CIRCULATING BLOOD OF LIVING ANIMALS BY DIALYSIS

JOHN J. ABEL, LEONARD G. ROWNTREE AND B. B. TURNER

From the Pharmacological Laboratory of the Johns Hopkins University

Figure 1. Schematic diagram of the first dialyzer. From JJ Abel et al., *J Pharmacol Exp Therap*, 1914 (1).

A. Excessive Mortality in Dialysis Patients.

Despite the life-saving benefit of dialysis, long-term survival rates on dialysis are disappointing.

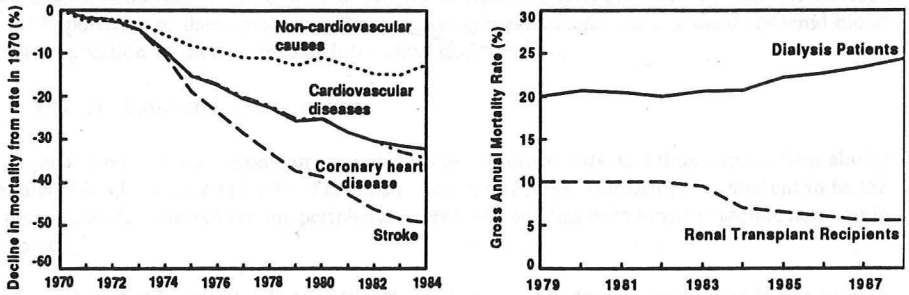


Figure 2. Trends in Mortality Rates in the General Population (Left Panel) and in the ESRD Population (Right Panel). Adapted from *NHLBI Vital Statistics of the United States* (5); Parker and Hull, *Am J Kidney Dis*, 1990; (6) NJ Feduska et al. and D Fries et al., *Cyclosporine: Therapeutic Use in Transplantation*, 1988 (7,8).

In the past two decades in this country, there has been a remarkable 30% decline in death rate from heart disease and a 50% decline in death rate from stroke (5), presumably related to better treatment of hypertension and healthier life styles. In contrast, the annual death rate for dialysis patients in the U.S. has not decreased but rather increased from 20 to 25% (4), which is considerably higher than the death rates for dialysis patients in Europe and Asia: 7% in France, 14% in Australia, 10% in Germany, and 9% in Japan (6). The high death rate for dialysis patients in the U.S. stands in sharp contrast to the much lower death rate after cadaveric renal transplantation, which has decreased from about 10 to 6% with the advent of cyclosporine (7,8).

TABLE 1. Mean Life Expectancies of Dialysis Patients in the United States.

AGE (yrs)	- DIABETES	+ DIABETES
15-24	14.4	4.7
25-34	11.1	4.2
35-44	9.2	3.6
45-54	6.7	3.5
55-64	4.8	3.0
65-74	3.2	2.4
75-85	2.2	1.9

Adapted from PW Eggers, *Am J Kid Dis*, 1990 (4).

Cardiovascular disease is unquestionably the major cause of the excessive mortality in patients with chronic renal failure (9-13), and hence my cardiologic interest in this nephrologic problem. Hypertension, for example, occurs in ~90% of patients with end stage renal disease and is a major risk factor for an extraordinarily high prevalence of both heart attack and stroke (10,12,14). In addition, acute, severe hypotension is a frequent complication of maintenance hemodialysis, occurring in up to 40% of chronic dialysis patients (15-17). Despite the obvious clinical importance of these problems, the underlying mechanisms causing the disordered blood pressure regulation in uremia are not fully understood.

B. Uremic Autonomic Neuropathy.

One popular theory is that chronic uremia poisons the baroreceptors, and thus impairs their ability to regulate blood pressure (18-23). This postulated baroreceptor impairment is thought to be the autonomic manifestation of uremic peripheral neuropathy and has been termed "uremic autonomic neuropathy."

The first aim of this exercise is to critically review what is known and what is not known about the neural control of blood pressure in uremia. My other aim is to review very recent work suggesting some new concepts about the mechanisms and treatment of blood pressure problems in chronic hemodialysis patients.

II. HYPERTENSION IN CHRONIC RENAL FAILURE

A. Cardiovascular Disease as the Major Cause of Death in Chronic Renal Failure.

Cardiovascular disease is the leading cause of death in end stage renal disease, accounting for about one-half of all deaths, with infectious disease being second.

TABLE 2. Major Causes of Death in Chronic Renal Failure.

CARDIOVASCULAR	%
Congestive Heart Failure	15
Sudden Cardiac Death	13
Acute Myocardial Infarction	12
Cerebrovascular Accident	11
Hemorrhage	4
Pericarditis and Tamponade	2
Pulmonary Embolism	1
Mesenteric Infarction	1
TOTAL	**59**
INFECTIOUS DISEASE	15
OTHER	26

Adapted from J. Bommer. In *Oxford Textbook of Clinical Nephrology*, 1992 (24).

Among patients with chronic renal failure, the prevalence of myocardial infarction is 10-100 times greater than that in the general population and the prevalence of cerebrovascular accident is increased 250 times (24).

Hypertension is thought to be a key factor for this excessive cardiovascular morbidity and mortality (10,14,24). Hypertension accelerates the development of coronary atherosclerosis, left ventricular hypertrophy, and congestive heart failure.

Preliminary results of 24 hour ambulatory blood pressure monitoring suggest that in the majority of ESRD patients hypertension is not being adequately controlled on current regimens of dialysis and antihypertensive medications (25). In a study of 53 treated hypertensive dialysis patients, the average blood pressure for the entire inter-dialytic period was 158/88 mmHg, which simply may be inadequate to halt the progression of target organ damage.

B. Accelerated Target Organ Damage.

In this regard, the rate of progression of target organ damage from hypertension may be particularly accelerated in dialysis patients for several reasons:

1. Age. Patients over 65 comprise 12% of the Unites States population but 40% of the end stage renal disease population (10).

2. Race. African-Americans comprise approximately 12% of the United States population but 30% of the ESRD population (10). There is increasing evidence that race is an important determinant of the rate of development of left ventricular hypertrophy, myocardial infarction, and other target organ damage produced by a given level of hypertension (26).

3. Poverty. The poor also are clearly over represented among the ESRD population, raising health care issues that have received considerable attention in this presidential election year. A study in Jefferson County, Alabama, for example, showed that the number of patients per zip code entering hemodialysis programs in the county was directly related to the percentage of households in the zip code with annual incomes less than $7500 (r=0.914, P<0.001) (10).

4. Lipid Abnormalities. Dialysis patients often have increased plasma triglycerides due to reduced VLDL clearance (10). Although LDL cholesterol generally is normal, lipoprotein (a), Lp(a) recently has been found to be markedly elevated in dialysis patients (10,27). Lp(a) is a cholesterol-rich lipoprotein that is structurally related to LDL, but also contains apo(a), a glycoprotein with sequence homology to plasminogen. Recently, Lp(a) has been shown to be an independent risk factor for myocardial infarction and stroke and Dr. David Moliterno and colleagues recently have found that it also predicts persistent coronary artery occlusion after myocardial infarction (28).

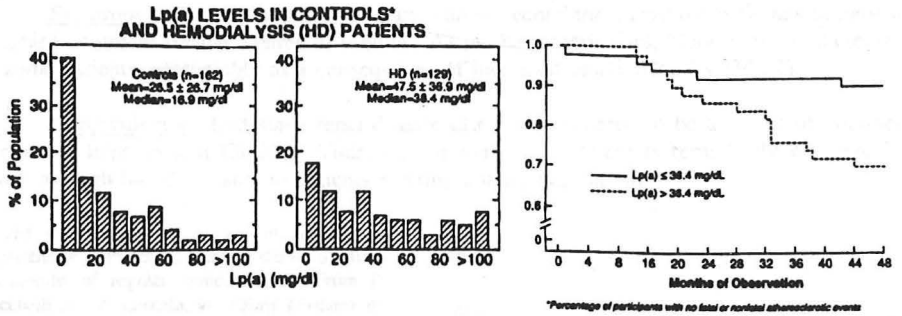


Figure 3. The left panels compare the distribution of Lp(a) in patients with coronary artery disease (and normal renal function) with that in dialysis patients. From Cressman et al., *Circulation*, 1992 (27).

Lp(a) values are skewed to the lower end of the scale in the coronary patients but not in the dialysis patients, in whom the mean serum Lp(a) values are two-times higher (and eight times higher than that in the general population). The far right panel shows that among dialysis patients Lp(a) is an independent predictor of event-free survival.

5. Cigarette Smoking. Dialysis patients who continue to smoke have a much higher cumulative mortality rate compared with nonsmokers (29).

6. Diabetes. About 20% of dialysis patients in the U.S. now are diabetic, accounting in part for the greater ESRD mortality rate in the United States vs. Europe and Asia, where fewer diabetics are accepted for hemodialysis (6). The 3-fold higher cardiovascular death rate among young diabetics vs. nondiabetic dialysis patients is related mainly to coronary artery disease and diabetic cardiomyopathy with microvascular angiopathy.

When hypertension is combined with several such risk factors, the cumulative risk for morbid cardiovascular events is multiplicative.

Given that hypertension is a major risk factor for the excessive cardiovascular morbidity and mortality in hemodialysis patients, what are the underlying mechanisms causing the hypertension?

C. Postulated Mechanisms and Treatment of Hypertension in Chronic Renal Failure.

Approximately 90% of all patients with end-stage renal failure exhibit hypertension, the etiology of which is undoubtedly multifactorial (30,31). In this regard, it is important to remember that systemic arterial pressure is the product of cardiac output and total peripheral resistance, the latter being proportional to blood viscosity and inversely proportional to the fourth power of the vessel radius.

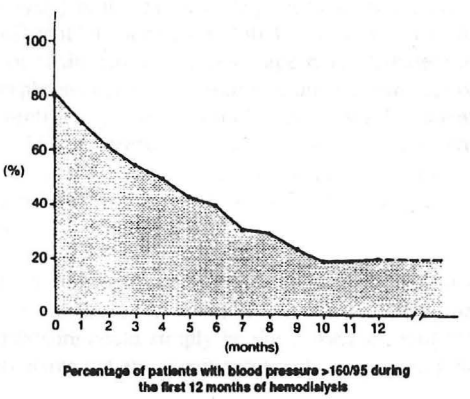
1. Pre-existing Essential Hypertension.

2. Erythropoietin. In the past few years, human recombinant erythropoietin has become a standard treatment for the anemia of uremia. As the hematocrit rises, blood pressure increases in some patients, presumably as a consequence of increased blood viscosity (30-32).

3. Hypervolemia. End stage renal disease often is considered to be a model of volume-dependent hypertension (30,31). Thus, regular dialysis treatment is remarkably effective in lowering high blood pressure in patients entering a dialysis program.

Figure 4. Percentage of patients remaining hypertensive (BP>160/95 mmHg) during the first 12 months of regular hemodialysis. From P Zucchelli and A Zuccala, in *Oxford Textbook of Clinical Nephrology*, 1992 (31).

These data are from 102 uremic patients entering chronic hemodialysis treatment. During the first 12 months of maintenance hemodialysis, the number of patients considered to be hypertensive decreased from 80 to 20%. The remaining 20% were considered to have volume-resistant hypertension.



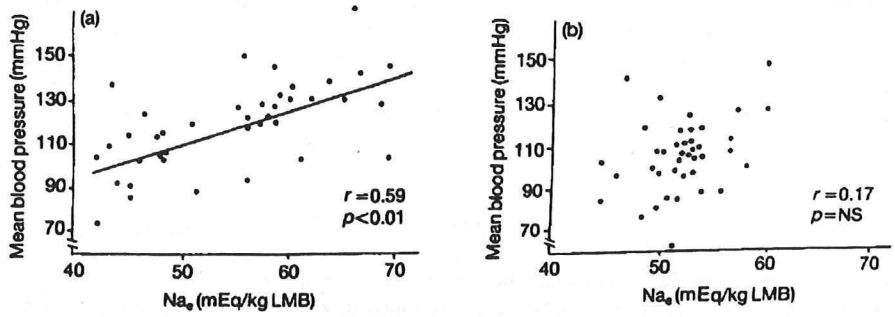


Figure 5. Relationship between exchangeable sodium (Na_e) and mean blood pressure in uremic patients before (a) and after (b) the start of regular hemodialytic treatment. From P Zucchelli and A Zuccala, "Control of blood pressure in patients on hemodialysis" in *Oxford Textbook of Clinical Nephrology*, 1992 (31).

Before initiation of dialysis, a strong correlation is observed between exchangeable sodium and blood pressure, suggesting "volume-dependent" hypertension. However, this correlation disappears after patients have been treated with dialysis for several months, suggesting that factors other than plasma volume contribute to this form of hypertension.

The current thinking is that such "volume-resistant" hypertension is related to activation of vasoconstrictor mechanisms, such as the renin-angiotensin and sympathetic nervous systems, and to inhibition of vasodilator mechanisms, such as that produced by nitric oxide (an endothelial dependent relaxing factor).

4. Activation of the Renin-Angiotensin System.

It has been widely hypothesized that excessive stimulation of the renin-angiotensin system (by the volume removal that accompanies hemodialysis) is the cause of hypertension in the great majority of dialysis patients with "volume-resistant" hypertension (30,31,33). In order to maintain a normal or even high plasma level of renin activity in end stage renal disease, the juxtaglomerular cells from the few remaining nephrons must be secreting renin at a remarkably high rate. In the 1970's, the terms "dialysis-refractory hypertension" and "renin-dependent hypertension" were considered synonymous. The evidence was as follows: a) a positive correlation in such patients between plasma renin activity and blood pressure, b) an antihypertensive effect of saralasin and angiotensin-converting enzyme inhibitors, and c) an antihypertensive effect of bilateral nephrectomy.

Recent studies, however, suggest that the role of the renin-angiotensin system in "dialysis-refractory hypertension" previously has been overestimated for several reasons (31). First, the observed correlation between renin and blood pressure could simply be the consequence of the higher rate of ultrafiltration to which the hypertensive patients were subjected in attempting to

lower the blood pressure. Thus, the high plasma renin activity may be the result of the attempted treatment and not the cause of the hypertension. Second, baseline plasma renin activity is a poor predictor of the blood pressure lowering effect of angiotensin converting enzyme inhibitors. Third, the effects of nephrectomy are not limited only to removal of the renal renin-angiotensin system. As discussed below, bilateral nephrectomy may affect the activity of the sympathetic nervous system, another important mechanism of blood pressure regulation.

5. Activation of the Sympathetic Nervous System.

Animal studies have indicated that the kidney is not only an elaborate filtering device, but also a sensory organ that is richly innervated with sensory, or afferent, nerves (34-36). There are two main functional types of renal afferent nerves: a) renal baroreceptors, which increase their firing in response to increases in renal perfusion pressure; and b) renal chemoreceptors, which increase their firing during exposure to ischemic metabolites or uremic toxins.

The chemosensitive renal afferent nerves have been implicated in the pathogenesis of hypertension by causing reflex activation of sympathetic outflow to the heart and peripheral circulation (36-38).

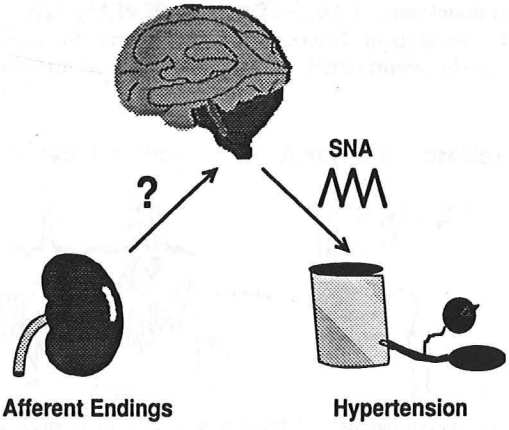
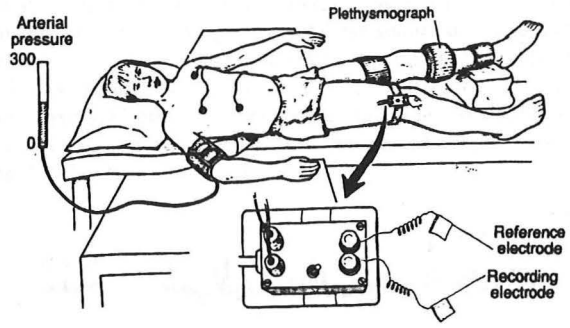


Figure 6. Renal afferents are thought to cause reflex increases in efferent sympathetic nerve activity, leading to hypertension.

Stimulation of these afferent nerves by either ischemic metabolites, such as adenosine, or by uremic toxins, such as urea, evokes reflex increases in sympathetic nerve activity and blood pressure in experimental animals (34,38). We therefore hypothesized that chronic stimulation of these afferent nerves in hemodialysis patients causes chronic sympathetic overactivity, which might contribute to hypertension. Because renal denervation can reduce efferent sympathetic overactivity and blood pressure in experimental hypertension (37), we further hypothesized that in patients with chronic renal failure sympathetic overactivity might be reduced by bilateral nephrectomy, which eliminates the renal afferent nerve endings. To test this hypothesis, we performed direct microelectrode recordings of postganglionic sympathetic action potentials (39) in chronic hemodialysis patients with and without bilateral nephrectomy.

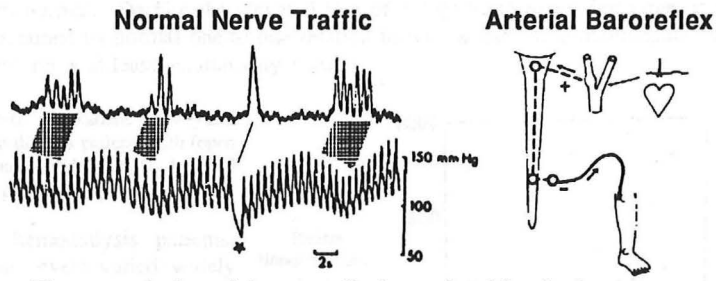
Figure 7. Experimental setup.



With the patients supine, we recorded sympathetic nerve impulses targeted to the skeletal muscle vasculature in the leg. This is accomplished by inserting tungsten microelectrodes into the peroneal nerve (39). We placed a plethysmograph on the contralateral leg to measure calf blood flow, since an increase in regional vascular resistance would be the expected consequence of increased sympathetic nerve activity. The principal investigator on this project was Dr. Rick Converse, who now is a third year cardiology fellow. Our coinvestigators included Drs. Tage Jacobsen and Charles Jost, two other cardiology fellows in my lab, Troy Obregon, who now is an MS-II, Dr. Bob Toto, and Dr. Fetnat Fouad-Tarazi who is a hypertension specialist at the Cleveland Clinic.

Previous attempts to determine the level of sympathetic nerve activity in patients with chronic renal failure were based solely on measurements of plasma norepinephrine levels, which have varied greatly from very low (40-43) to very high (14,19,20,44,45). This lack of correlation is probably related to the confounding effects of uremia on prejunctional modulation of norepinephrine release and on plasma catecholamine clearance (46,47). Furthermore, plasma catecholamines are cleared during hemodialysis.

Figure 8. Baroreceptor regulation of muscle sympathetic nerve activity. From Fagius and Wallin, *TINS*, 1986 (48).



This is a typical recording of muscle sympathetic nerve traffic from a normal human subject. The sympathetic activity normally is regulated by the baroreceptors. Increases in blood pressure stimulate the carotid sinus baroreceptors, which in turn inhibit the efferent sympathetic activity. Decreases in blood pressure, as occurs with a premature ventricular contraction, deactivates the baroreceptors triggering a large burst of sympathetic activity. Because the baroreceptors are relatively deactivated during each diastole, the sympathetic discharge is locked to the cardiac cycle such that the minimum interval between bursts equals the cardiac cycle length.

We used this technique to determine if the rate of sympathetic discharge is elevated in uremia and if baroreceptor regulation is normal or abnormal. We performed these studies on 18 patients undergoing chronic maintenance hemodialysis whose native kidneys were intact, five patients undergoing chronic maintenance hemodialysis who previously had undergone bilateral nephrectomy, and 11 healthy, normotensive subjects with normal renal function. We excluded from study any patients with diabetes mellitus or congestive heart failure. Antihypertensive medications were discontinued at least 48 hours prior to study.

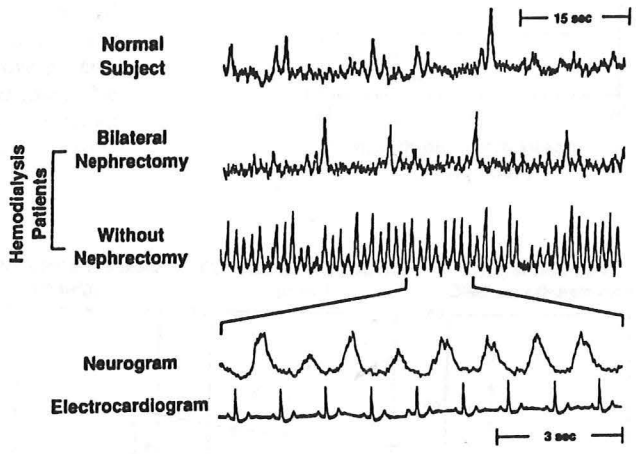


Figure 9. Recordings of muscle sympathetic nerve activity in a normal subject and in two hemodialysis patients, one with and one without bilateral nephrectomy. The first three panels are representative segments of the neurograms from the three different subjects and the last two panels display the neurogram and simultaneous electrocardiogram from the third subject on an expanded time scale. From RL Converse et al., *N Engl J Med*, 1992 (49).

The rate of sympathetic nerve discharge was much higher in the dialysis patient with native kidneys than in the patient with bilateral nephrectomy, the latter being indistinguishable from normal. Despite the elevated rate of sympathetic nerve discharge, the sympathetic activity retained its normal one-to-one relation to the cardiac cycle (demonstrating that baroreceptor function is at least qualitatively normal).

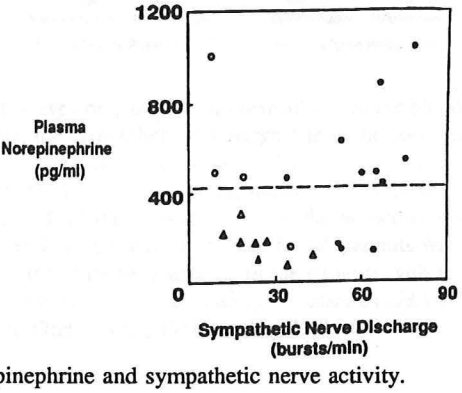


Figure 10. Relation between sympathetic activity and plasma norepinephrine in dialysis patients with (open triangles) and without (solid circles) bilateral nephrectomy, and normal controls (open triangles) (49).

In both groups of hemodialysis patients, plasma norepinephrine levels varied widely from normal to markedly elevated (the upper limit of normal being indicated by the dotted line). Although there was marked overlap between norepinephrine levels in the two groups of patients, muscle sympathetic nerve activity was consistently lower in the patients with than in those without nephrectomy. There was no correlation between plasma norepinephrine and sympathetic nerve activity.

Figure 11. Relation between muscle sympathetic nerve activity and plasma renin activity in hemodialysis patients without bilateral nephrectomy (49).

Plasma renin activity was markedly elevated in four patients being treated with an angiotensin-converting enzyme inhibitor (open circles), but was normal in the remaining dialysis patients (upper limits of normal for hypertensive patients being indicated by the dashed line). No correlation was found between sympathetic nerve activity and plasma renin activity.

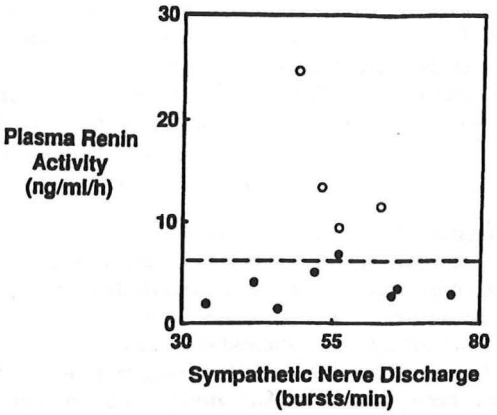
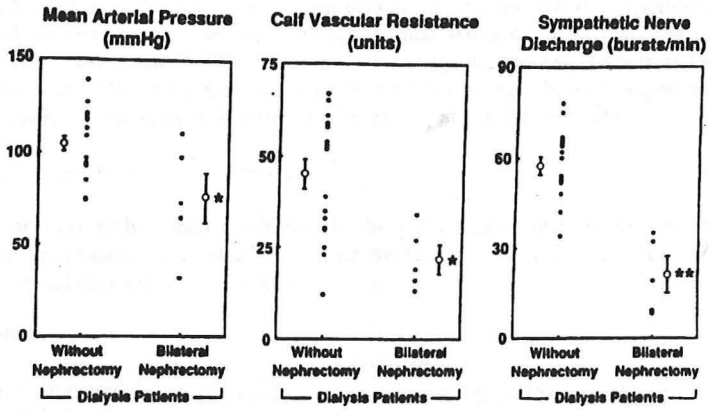


Figure 12. Individual and mean data from the dialysis patients with and without bilateral nephrectomy showing mean arterial pressure (left panel), calf vascular resistance (middle panel), and muscle sympathetic nerve activity (right panel). Group data are mean ± SEM, * P<0.05 vs. patients without nephrectomy; **P<0.01 vs. patients without nephrectomy (49).



Although the two groups of hemodialysis patients were comparable with respect to routine blood chemistries, arterial blood gases and body weights, the sympathetic discharge rate in the patients without nephrectomy was almost 3 times higher than in the patients with bilateral nephrectomy (58±3 vs. 21±6 sympathetic bursts per minute, P<0.01), the latter being indistinguishable from normal. The sympathetic nerves fired during 82±4% of the cardiac cycles in the hemodialysis patients with native kidneys, but during only 25±6% of the cardiac cycles in the patients with bilateral nephrectomy. The lower levels of sympathetic nerve discharge in the patients with vs. without nephrectomy were accompanied by lower levels of regional vascular resistance (22±4 vs. 45±4 units, P<0.05) and of mean arterial pressure (76±14 vs. 106±4 mmHg, P<0.05).

In the hemodialysis patients with native kidneys, elevated sympathetic activity was remarkably constant throughout the inter-dialysis period despite large increases in total body water. This finding was unexpected because in normal humans muscle sympathetic nerve activity decreases over time with increases in total body water, a decrease mediated presumably by baroreceptor reflexes (50). Thus, the reproducibility of elevated sympathetic activity at different points in the inter-dialysis period suggests that uremia activates some excitatory neural influence that overrides the inhibitory baroreflex-mediated influence of an expanded plasma volume.

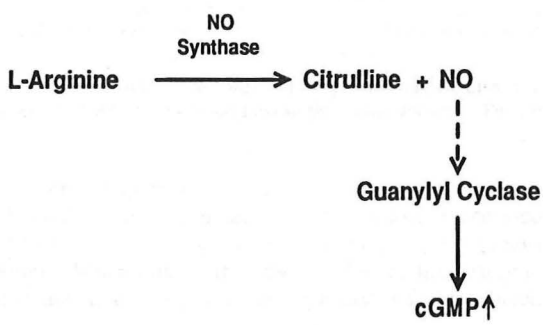
The observation that sympathetic outflow was normal in dialysis patients with bilateral nephrectomy suggests that sympathetic overactivity in chronic hemodialysis patients without bilateral nephrectomy is not caused by: 1) the hemodialysis procedure per se; 2) stimulation of arterial chemoreceptors (e.g., by acidosis or hypoxia), since the two groups of dialysis patients were comparable with respect to arterial blood gases, as well as to hematocrit, serum creatinine, blood urea nitrogen, and other blood chemistries; or 3) permanent alterations in the sympathetic nervous system. In contrast, this observation strongly suggests that bilateral nephrectomy removes some afferent signal arising in the failing kidney.

Although the precise nature of this signal is unknown, our data are consistent with the hypothesis that uremic toxins, such as urea, might selectively stimulate renal afferent nerves that lead to reflex activation of sympathetic outflow. In chronic hemodialysis patients, hypertension undoubtedly is multifactorial. However, reduced sympathetic activity may be one important mechanism by which bilateral nephrectomy lowers blood pressure in dialysis patients.

6. Inhibition of Nitric Oxide (NO).

Another mechanism that recently has been implicated in the pathogenesis of hypertension in patients with end stage renal disease is inhibition of nitric oxide, which now is thought to be synonymous with endothelial-derived relaxing factor (51-55).

Figure 13. Nitric oxide (NO) Synthesis.



NO synthase was first discovered in visceral endothelial cells but appears to ubiquitous, including a high concentration in the central nervous system. This enzyme converts the amino acid L-arginine to citrulline (which is inert) and nitric oxide (NO), an unstable gas. NO readily diffuses into the cytosol where it binds to guanylyl cyclase, resulting in an increase in cyclic GMP which is the main second messenger mediating its biologic effects. In vascular smooth muscle this results in vasodilation. In the nervous system, NO seems to function as a neurotransmitter.

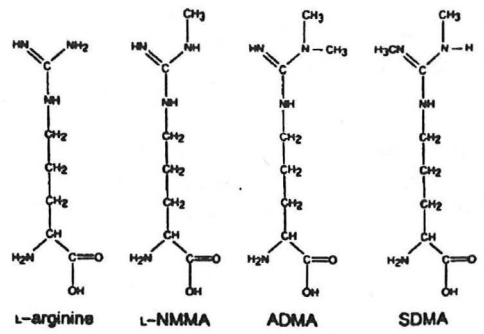


Figure 14. Structures of L-arginine, N^G-monomethyl-L-arginine (L-NMMA), asymmetric dimethylarginine (ADMA) and symmetric dimethylarginine (SDMA). From S. Moncada, *Acta Physiol Scand*, 1992 (53).

L-NMMA, a synthetic pharmaceutical, is a competitive inhibitor of NO synthase. It is structurally very similar to two endogenous substances SDMA and ADMA which have been isolated from human plasma and urine. SDMA is inert but ADMA is an endogenous inhibitor of NO synthase and is as potent as L-NMMA. ADMA normally is excreted unchanged in the urine and therefore accumulates to very high levels in the plasma of patients with chronic renal failure (55). In patients with end stage renal disease, plasma levels of ADMA were found to be eight times higher than normal (8.7 vs. 1.15 µmol/l, $P<0.001$) (55).

When compared with L-NMMA, endogenous ADMA isolated from human urine is of equal potency in inhibiting NO synthase in macrophages and in vascular smooth muscle (55).

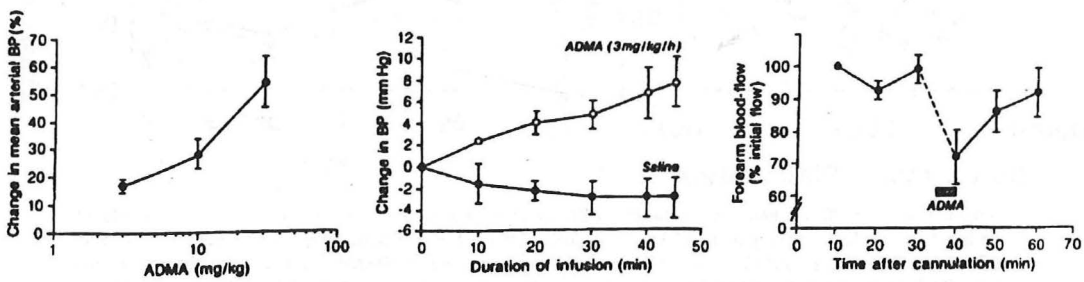


Figure 15. Hemodynamic effects of ADMA in vivo. Left and middle panels: blood pressure raising effects of ADMA in anesthetized guinea pigs; right panel: effect of ADMA on blood flow in the human forearm. From P Vallance, et al., *Lancet*, 1992 (55).

In the guinea pig, ADMA causes a dose-dependent increase in blood pressure. The continuous infusion at 3 mg/kg/h gradually increased blood pressure by about 10 mmHg; this dose increased the plasma concentration of ADMA by 9-fold, which is comparable to the levels of endogenous ADMA in patients with chronic renal failure. When infused directly into the brachial artery in normal humans, ADMA caused vasoconstriction as shown by the sharp decrease in forearm blood flow.

Although not shown on the slide, ADMA also inhibits NO synthase in macrophages, resulting in decreased bacteriocidal activity.

So, these results raise the intriguing possibility that accumulation of endogenous ADMA and blockade of nitric oxide synthase contributes to hypertension and to infection, the two most important causes of death in chronic dialysis patients. Could L-arginine be an effective antihypertensive agent in these patients?

A causal relation between accumulation of ADMA and high blood pressure has not yet been established in human patients. Over the summer, however, three articles were published providing evidence that chronic oral administration of an NO synthase inhibitor (L-NAME) produces chronic hypertension in rats (56-58).

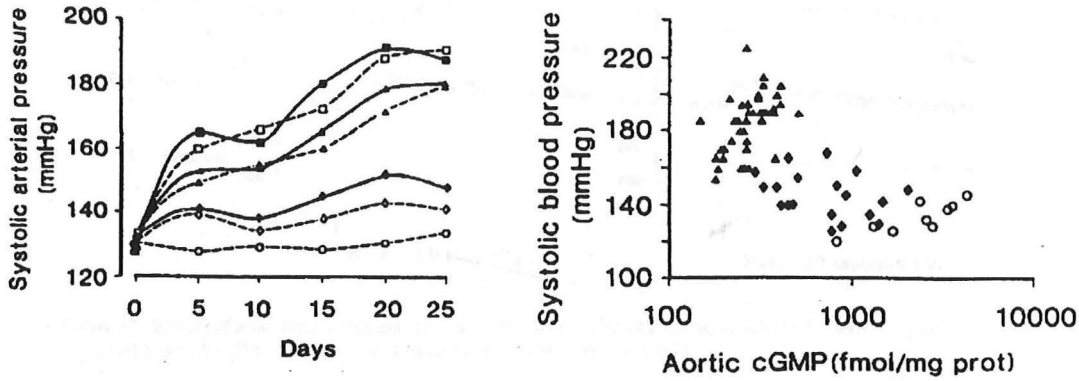


Figure 16. Effects of chronic oral administration of L-NAME on blood pressure and cGMP in vascular smooth muscle. Left panel: time-dependent and dose-dependent increase in systolic blood pressure (tail cuff) induced by chronic oral administration of L-NAME in Wistar rats (n = 10 per group). (○) 0, (◊) 1, (◆), 5, (Δ) 10, (▲) 20, (□) 50, (■) 100 mg of L-NAME per kg/d. Right panel: relation between systolic blood pressure and aortic cGMP (○) Control rats; (1-5 mg of L-NAME per kg/d; (▲) 10-100 mg of L-NAME per kg/d ($r = 0.67$, $P < 0.0001$, n = 69). From J Arnal et al., *J Clin Invest*, 1992 (57).

These data indicate that chronic inhibition of NO synthase produces dose-dependent increases in blood pressure in rats. The magnitude of the hypertension is inversely related to the concentration of aortic cGMP, which is the putative second messenger. Although not shown on the slide, the hypertension was reversed by L-arginine.

Another study demonstrated that L-NAME-induced hypertension causes glomerular damage in the rat (56).

In addition to its presence in vascular endothelial cells and macrophages, NO synthase is ubiquitous in both the peripheral and central nervous system, where there is increasing evidence

that it functions as a neurotransmitter (53,59-63). These considerations led to the hypothesis that the hypertensive effects of NO synthase inhibitors might be caused in part by activation of the sympathetic nervous system (62,63).

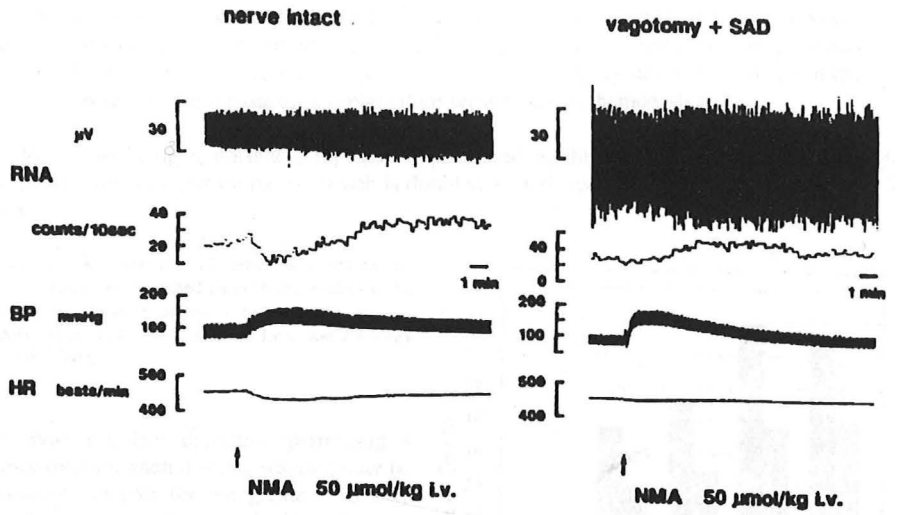


Figure 17. Effects of acute intravenous injection of L-NMMA on efferent renal nerve activity (RNA), blood pressure (BP), and heart rate (HR) in rats. From I Sakuma et al., *Circ Res*, 1992 (62).

The left panel shows the effects of L-NMMA in rats with intact baroreceptor nerves. Bolus intravenous injection of a single dose of L-NMMA causes a robust and long-lasting increase in blood pressure, which was accompanied by a biphasic response in renal sympathetic nerve activity (and in heart rate): an initial decrease followed by a subsequent increase. The initial decrease in sympathetic activity is the expected baroreflex response to a sudden increase in blood pressure. However, the subsequent increase in sympathetic activity despite a persistent elevation in blood pressure suggests that inhibition of NO synthase has an excitatory effect on the sympathetic nervous system which eventually overrides the inhibitory effect of the baroreceptor reflex.

The right panel shows that after surgical denervation of the baroreceptors (vagotomy plus sinoaortic denervation, SAD), the neuroexcitatory action of L-NMMA is amplified, as shown by the monophasic increase in renal sympathetic nerve activity.

Thus, an intriguing, but as yet unanswered, question is whether accumulation of endogenous ADMA in hemodialysis patients contributes to sympathetic overactivity and hypertension. If so, L-arginine should be an effective antihypertensive treatment.

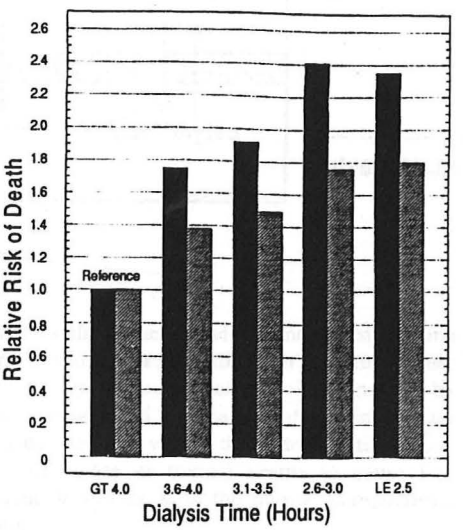
III. HEMODIALYSIS-INDUCED HYPOTENSION

A. Magnitude of the Problem

In the early days of dialysis, a main goal was to treat problems related to chronic volume overload, hypertension and congestive heart failure. As the time of a typical dialysis session was reduced from eight to three hours, symptomatic hypotension emerged as a major problem, occurring in 30-50% of chronic dialysis patients (15,17). These hypotensive events often require aggressive resuscitative measures and premature termination of hemodialysis.

In addition to being a nuisance, repeated hypotension might contribute in the long run to excessive cardiovascular mortality, which is doubled as dialysis time is shortened from 4 to 2.5 hours.

Figure 18. Relative risk of death increases as the dialysis session is shortened (solid bars, crude values; hatched bars, values adjusted by multiple logistic model). From EG Lowrie and NL Lew, *Am J Kidney Dis*, 1990 (64).



The more efficient dialyzers, permitting a shorter time for each dialysis session, may be responsible in part for the greater mortality rates for dialysis patients in the United States vs. Europe and Japan.

Despite its obvious clinical importance, the underlying mechanisms causing this episodic hypotension are poorly understood and the current interventions are not fully effective.

B. Postulated Mechanisms and Treatment.

1. Antihypertensive Medications as an Aggravating Factor.

2. Acetate as a Vasodilator.

In the 1960's, bicarbonate was used as the principal base in the dialysate. However, for technical reasons, acetate replaced bicarbonate as the principal base in the 1970's and 1980's. Acetate is a vasodilator, in part by its conversion to adenosine, and a negative inotrope (17). Dr. Henrich

and others have demonstrated that hypotension is more frequent with acetate dialysis than with bicarbonate dialysis (17). Thus, in the 1990's, bicarbonate again has become the preferred dialysate buffer in many centers.

3. The Importance of Hypovolemia and Plasma Osmolality.

As illustrated below, the normal hemodialysis procedure consists of both **ultrafiltration**, the isosmotic removal of volume, and **dialysis**, the removal of uremic toxins and electrolytes.

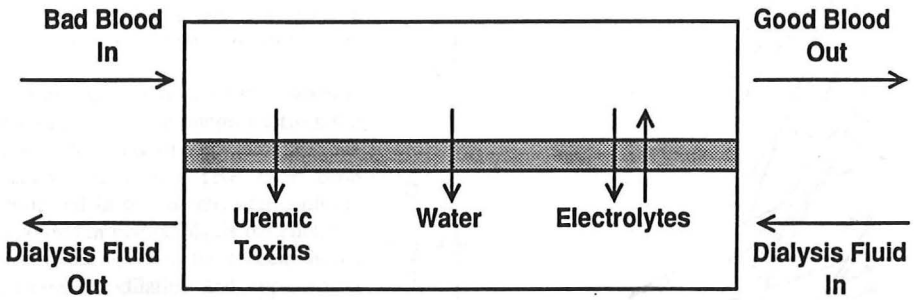


Figure 19. The dialysis principle.

With ultrafiltration alone, plasma osmolality remains stable, whereas with hemodialysis plasma osmolality decreases, creating an osmolar gradient favoring water to shift from the extracellular to intracellular compartment, thereby exacerbating the contraction in plasma volume induced by ultrafiltration alone. The importance of volume removal and plasma osmolality in causing dialysis-induced hypotension was first suggested by the observation that ultrafiltration alone (isosmotic removal of volume without removal of solute or toxins) seems to cause less hypotension than does removal of an equal amount of volume with the normal hemodialysis procedure (i.e., ultrafiltration plus dialysis) (65,66).

The work of Dr. Henrich and others in the 1980's (17,66) demonstrated that increasing dialysate sodium to > 135 mEq/l, which minimizes the decreases in plasma osmolarity during hemodialysis, is an effective strategy to reduce dialysis-induced hypotension without exacerbating hypertension during the interdialytic period.

Despite the switch to high-sodium, bicarbonate dialysis in the past decade, hypotension still remains a major problem in the hemodialysis unit, suggesting that additional pathophysiologic mechanisms must be involved. These include activation of vasodilator mechanisms and/or failure of vasoconstrictor mechanisms.

4. Dialysis-Induced Activation of Complement and Macrophage-Derived Cytokines as a Potential Cause of Peripheral Vasodilation and Hypotension During Hemodialysis.

Contact between blood and the dialysis membrane activates monocytes to release cytokines, including interleuken-1 (IL-1) and tumor necrosis factor (TNF) (67-71).

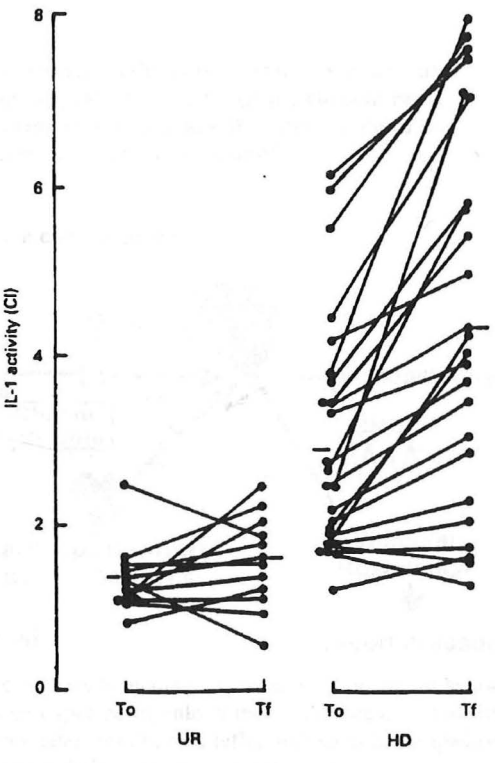


Figure 20. Changes in IL-1 activity from the start (T_o) to the finish (T_f) of a hemodialysis session. Uremic patients (UR) were studied during their very first session of hemodialysis. Hemodialysis patients (HD) were studied after six months of regular hemodialysis. From A Herbelin et al., *Kidney Intl*, 1990 (69).

In chronic hemodialysis patients, plasma IL-1 activity increases from the start to the end of a typical dialysis session. IL-1 and TNF have been implicated in the altered immunologic responses in hemodialysis patients, but these cytokines also have been shown to cause vasodilation and hypotension in experimental animals and therefore might possibly contribute to hypotension during hemodialysis (this has been termed the "interleuken hypothesis") (67,72). IL-1, for example, induces the production of prostacyclin and nitric oxide from vascular smooth muscle cells (67).

The degree of cytokine activation seems to be related to the dialyzer membrane being used: greatest with the "bio-incompatible" cellulose (Cuprophan) membranes and less with the more "bio-compatible" synthetic (polysuphone, polycarbonate, polyamide, and polyacrylonitrile) membranes (70). Activation of complement and cytokines is thought to mediate episodes of hypotension with chest pain and dyspnea during exposure to new cuprophane dialyzers (the "first-use syndrome"), but this effect dissipates when the dialyzers are reused (73).

At present, there is no evidence that hemodynamic stability is improved with the bio-compatible membranes and a causal relation between activation of vasodilator-cytokines and hemodialysis-induced hypotension has not been established.

5. Chronic Baroreceptor Impairment (Uremic Autonomic Neuropathy) as Cause of Dialysis-Induced Hypotension.

Another popular theory is that dialysis-induced hypotension is a manifestation of uremic autonomic neuropathy, a form of chronic autonomic insufficiency caused by uremic poisoning of the baroreceptors (18-23). This view is stated clearly in Sir Roger Bannister's *Textbook of Clinical Disorders of the Autonomic Nervous System* (Oxford, 1988) (18):

> **"The precise mechanism of the autonomic dysfunction remains unclear but, since efferent sympathetic function appears to be normal [in chronic renal failure], the most likely sites of primary damage are the baroreceptors or their afferent fibers or central nervous system connections."**

This concept is depicted schematically on the cartoon below.

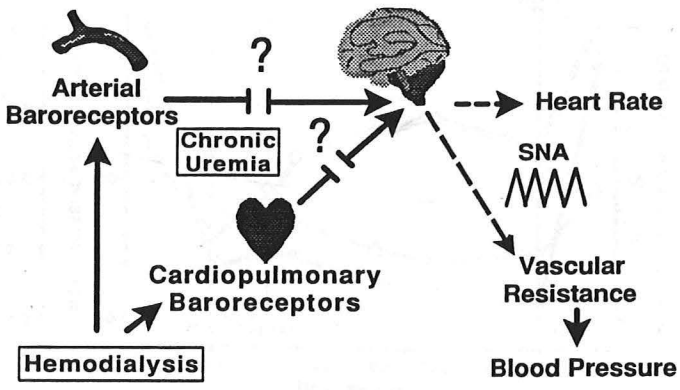


Figure 21. Postulated effects of chronic uremia on baroreflex control of heart rate and peripheral vascular resistance.

Under normal conditions, sympathetic neural outflow is under tonic restraint by baroreceptors in the aortic arch and carotid sinus as well as baroreceptors in the cardiopulmonary region. With the volume removal that accompanies hemodialysis, reductions in central venous pressure and arterial blood pressure would be expected to unload these baroreceptors and thus reduce their tonic restraint on the vasomotor center, resulting in reflex increases in sympathetic outflow to the heart and peripheral circulation to help maintain blood pressure.

Chronic exposure to uremic toxins is thought to poison the baroreceptors, leading in some patients to almost complete removal of their tonic inhibitory effects on sympathetic vasomotor outflow (18-23). According to this view, uremia-induced baroreceptor deafferentation causes central sympathetic outflow to be nearly maximal under basal conditions so that it could not possibly increase much further during the hypotensive stress of hemodialysis. However, the experimental support for this construct is indirect, relying mainly on plasma catecholamines and semi-quantitative bedside tests to assess sympathetic neural function.

Decreased blood pressure (e.g., with amyl nitrite or Valsalva maneuver) often triggers a blunted increase in heart rate in chronic hemodialysis patients (18-23), but the mechanism causing this abnormality and its functional significance remain controversial. There is evidence to suggest that uremic autonomic neuropathy is caused by an efferent, rather than an afferent, defect localized to the vagal innervation of the sinus node (74). Furthermore, a causal relationship between impaired baroreflexes and dialysis-induced hypotension has not been established, since abnormal heart rate responses to the Valsalva maneuver have been observed in hypotension-resistant, as well as hypotension-prone, dialysis patients (40).

One of the classic studies in this field examined systemic hemodynamic changes during hemodialysis in patients who were prone to repeated episodes of hypotension (21). In three patients, dialysis-induced hypotension was readily corrected with infusion of normal saline, but in eight other patients the hypotension was resistant to volume expansion.

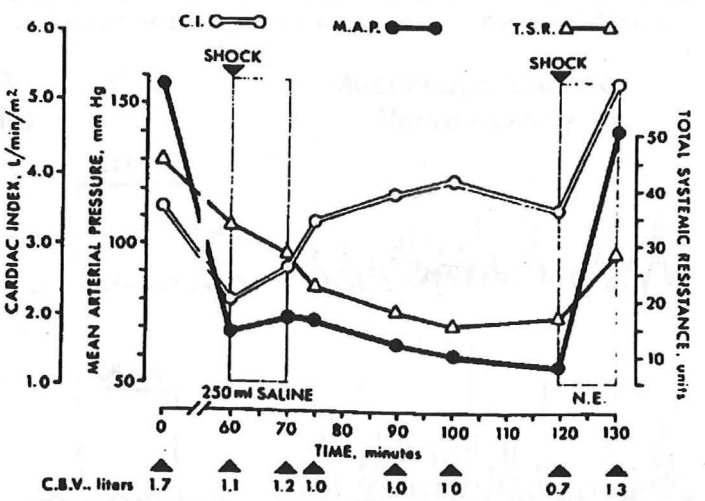


Figure 22. Changes in cardiac index (CI), mean arterial pressure (MAP), and total systemic resistance (TSR), measured during a session of hemodialysis in a patient with "autonomic insufficiency." From ES Kersch et al., *N Engl J Med*, 1974 (21).

After 60 minutes of hemodialysis, the patient's blood pressure falls dramatically and is not resuscitated by administration of 250 cc of normal saline but later is corrected with infusion of norepinephrine (N.E.). Because a large fall in blood pressure would be expected to trigger reflex tachycardia and vasoconstriction, the absence of vasoconstriction and tachycardia here were interpreted to suggest that baroreflex impairment is a major cause of hypotension during hemodialysis.

During the sharp fall in blood pressure, cardiac index falls, which could easily be explained by volume withdrawal. But note that total systemic vascular resistance not only does not increase but it actually falls far below the baseline level. I would interpret these data to indicate active vasodilation, which I cannot explain on the basis of a chronic poisoning of the baroreceptors. I believe that this is a very important point and I will come back to it later.

Dr. Rick Converse and colleagues in my lab recently performed a detailed analysis of baroreflex function in 16 hypotension-resistant and 7 hypotension-prone hemodialysis patients (75). "Hypotension-prone" patients were defined as those in whom a sudden, symptomatic decrease in mean arterial pressure of > 30 mmHg occurred during at least one-third of maintenance hemodialysis sessions. Patients with diabetes were excluded from the study because autonomic neuropathy is a well-known complication of diabetes mellitus (76). We used direct, rather than indirect, measurements of sympathetic nerve activity and several quantifiable reflex maneuvers which allowed us to test effects of chronic uremia on a number of specific reflexes, including arterial baroreflex control of heart rate and cardiopulmonary baroreflex control of vascular resistance. Each patient was studied twice: first in my lab during the inter-dialytic period and then in the clinical unit during actual sessions of maintenance hemodialysis. This allowed us to separate the autonomic effects of chronic uremia, which in our study were undetectable, from the acute autonomic effects of the hemodialysis procedure, which were profound.

To investigate the arterial baroreflex, we examined the increases in heart rate and sympathetic nerve activity produced by decreases in blood pressure during infusion of nitroprusside (77).

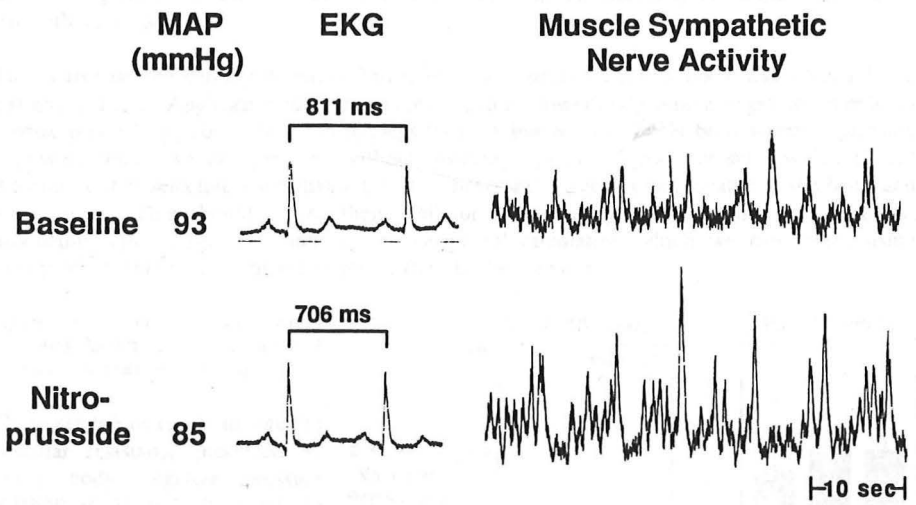


Figure 23. Baroreflex assessment with nitroprusside.

This record is from a dialysis patient in Dr. Toto's unit at Parkland Hospital. The record shows the patient's mean arterial pressure (MAP), electrocardiogram (EKG), and sympathetic neurogram at baseline and during infusion of a low dose of nitroprusside. Even though this patient routinely becomes severely hypotensive during hemodialysis, in my lab his arterial baroreceptors functioned normally: a fall in blood pressure of <10 mmHg triggered a brisk reduction in cardiac cycle length and a brisk increase in sympathetic traffic.

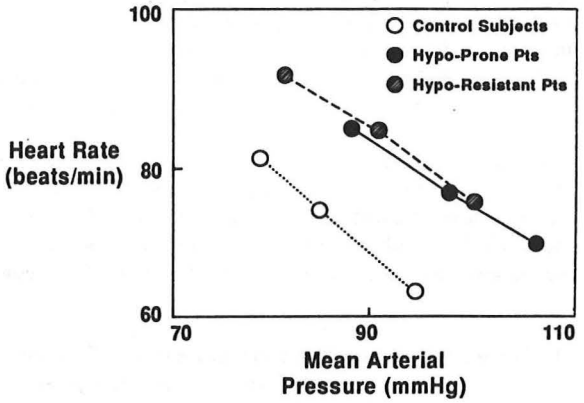


Figure 24. Normal arterial baroreflex control of heart rate in chronic dialysis patients (75).

These are summary data from those experiments in which heart rate is plotted as a function of blood pressure, which was decreased with nitroprusside and then increased with phenylephrine. Both groups of dialysis patients had elevated baseline blood pressures, producing an upward shift in lines. But the important point is that the slopes of these lines are equivalent to that in normotensive control subjects, indicating quantitatively normal baroreflex function.

To interrogate the cardiopulmonary baroreflex, each patient's lower body was placed in an airtight chamber. Application of negative pressure to the lower body simulates gravity: it reduces cardiac preload by pooling blood in the legs (50). A low level of lower body negative pressure decreases central venous pressure without lowering systemic blood pressure, which should therefore rather selectively deactivate the "low pressure" baroreceptors located in the heart and great veins. This should reduce their inhibitor effect on sympathetic vasomotor outflow, producing reflex vasoconstriction in the peripheral circulation which we can detect using plethysmographic measurements of blood flow in the forearm.

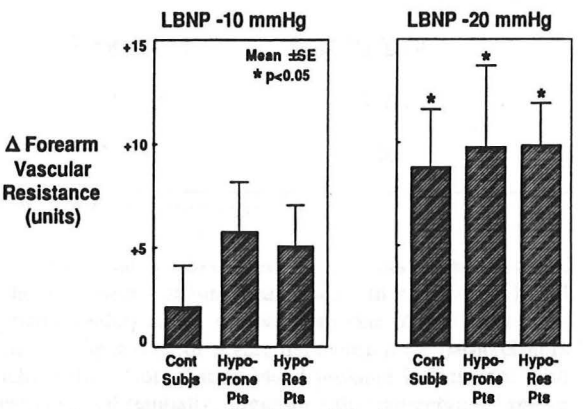


Figure 25. Normal cardiopulmonary baroreflex control of vascular resistance in chronic dialysis patients (75).

These are the increases in forearm vascular resistance produced by lower body negative pressure (LBNP) at -10 and -20 mmHg in the three groups of subjects. In the dialysis patients, cardiopulmonary baroreflex function was normal, since graded lower body negative pressure produced comparable graded increases in vascular resistance in all three groups, even in the patients with recurrent hypotension during hemodialysis.

In our non-diabetic hemodialysis patients, therefore, it would be very difficult to explain dialysis-induced hypotension on the basis of a chronic abnormality in either arterial or cardiopulmonary baroreceptors. These findings, however, do not exclude the possibility that in other groups of dialysis patients, such as those with diabetic autonomic neuropathy, impaired baroreflexes indeed may contribute to hypotension during hemodialysis.

Another possibility is that this episodic hypotension could be related to the hemodialysis procedure per se which could produce acute alterations in sympathetic neural function. Dialysis causes intra/extra-cellular shifts in cations such as sodium and potassium that are involved in the generation of nerve action potentials. Moderate changes in extracellular sodium and potassium concentrations in rats can have profound effects on the electrophysiologic properties of the baroreceptors (78).

Ultrafiltration can cause a marked contraction of plasma volume, which may trigger a seemingly paradoxical response in sympathetic nerve activity, as explained below.

6. Paradoxical Withdrawal of Reflex Vasoconstriction as A Cause of Hemodialysis-Induced Hypotension.

Hypotensive states generally are thought to cause reflex activation of the sympathetic nervous system, producing a compensatory tachycardia and vasoconstriction (77). However, there is increasing evidence that hypovolemic hypotension, as occurs with severe hemorrhage, can trigger a paradoxical inhibition of sympathetic vasomotor outflow producing bradycardia and peripheral vasodilation (79-84), an inappropriate vasodepressor reaction which would exacerbate the volume-dependent fall in blood pressure.

TABLE 3. Paradoxical Bradycardia During Hemorrhagic Shock.

	Presentation	After 5L Volume
Blood Pressure (mmHg)	81/55	111/72
Heart Rate (bpm)	73	102

Adapted from R Sander-Jensen et al., *British Med J*, 1986 (84).

These are the average blood pressures and heart rates of 20 consecutive patients presenting to the emergency room with hemorrhagic shock. These patients clearly were in shock with blood pressures of 81/55 mmHg. The surprising finding is the normal heart rate of 73. This is an inappropriately "normal" heart rate, since in the setting of severe hypotension the baroreceptors would be expected to cause reflex tachycardia. Note that as blood pressure is increased with volume resuscitation, heart rate also increases substantially, suggesting that correction of severe hypovolemia removed some inhibitory influence on sinus node function.

Such paradoxical relative bradycardia in the setting of hypovolemic hypotension also has been described during administration of nitrovasodilators and during upright tilt testing, the latter being used as a new proactive test for unexplained syncope (85-87). We therefore hypothesized that such a paradoxical vasodepressor reaction also might be triggered by the relative hypovolemia that accompanies hemodialysis. In other words, we wondered whether hemodialysis-induced hypotension might be caused by an acute, rather than chronic, form of autonomic insufficiency.

Several different mechanisms have been implicated in causing this paradoxical bradycardia and vasodilation during hypovolemic hypotension (88-93). Currently, the most popular theory is that this response is caused by an inhibitory reflex arising in the heart. In addition to being a pump, the heart is also a sensory organ, being richly innervated with sensory (or afferent) nerves (94,95). Many of these sensory nerves function as mechanoreceptors and thus signal the brain of changes in loading conditions and contractility of the ventricles (94). Their function is to inhibit sympathetic outflow. Because these sensory nerve impulses travel to the brain in discrete fibers within the vagus nerve, it is possible in animals to dissect out these individual nerve fibers and record their electrical activity (94,96). The results of those animal experiments advanced the following hypothesis.

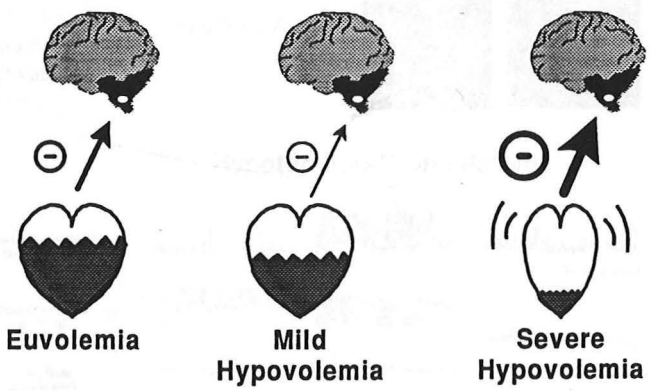
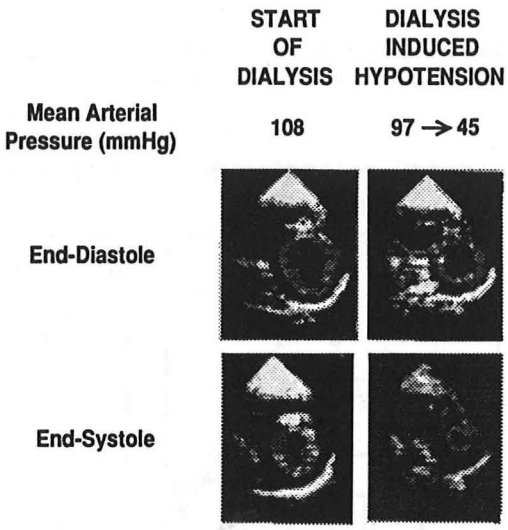


Figure 26. Cartoon illustrating the concept of paradoxical activation of inhibitory ventricular afferents during hypovolemic hypotension.

During euvolemia, these sensory nerves normally exert a tonic inhibitory influence (arrow) on sympathetic vasomotor outflow. During mild hypovolemia, this inhibitory influence is reduced. During severe hypovolemia, however, this inhibitory influence is not reduced further but rather increases paradoxically. The theory is that the receptive fields of these endings are deformed as the adrenergically stimulated heart contracts forcefully around an almost empty ventricular chamber (96).

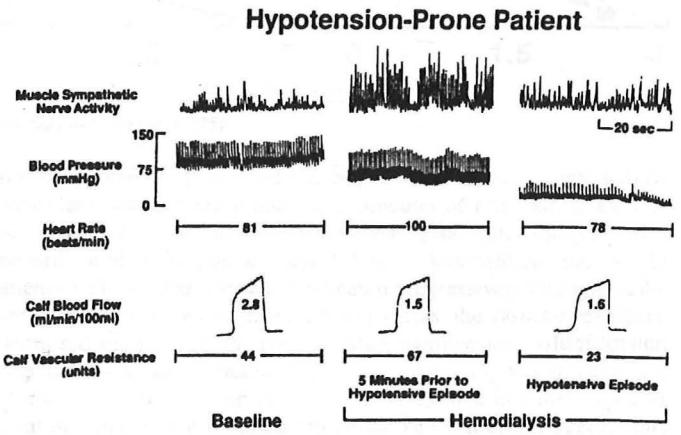
We hypothesized that mild hypovolemia might simulate non-hypotensive hemodialysis: unloading of inhibitory ventricular afferents causing reflex sympathetic activation. In contrast, severe hypovolemia might simulate hemodialysis-induced hypotension: paradoxical activation of inhibitory ventricular afferents causing reflex inhibition of sympathetic outflow resulting in bradycardia and peripheral vasodilation. To test this hypothesis, Dr. Paul Grayburn helped us perform echocardiographic measurements of left ventricular volumes during hemodialysis.

Figure 27. Left ventricular cavity obliteration during dialysis-induced hypotension (75).



These are short axis 2-D echocardiographic left ventricular end-diastolic and end-systolic frames from a hypotension-prone hemodialysis patient. At the start of dialysis, the patient's mean arterial pressure was 108 mmHg and after 2h of hemodialysis it drifted down to 97 mmHg (second column of frames). Shortly thereafter, his blood pressure fell precipitously to 45 mmHg and the patient became symptomatic. Note that the onset of severe hypotension was preceded in this patient by a small decrease in end-diastolic dimension but a marked decrease in end-systolic dimension, the latter approaching obliteration of the left ventricular cavity. This should be the setting for paradoxical activation of inhibitory left ventricular afferents.

Figure 28. Paradoxical withdrawal of sympathetic activation during dialysis-induced hypotension (75).



These are the neurocirculatory responses from the same patient. Prior to the onset of the severe hypotensive episode, the patients baroreceptors seem to function normally. A small decrease in blood pressure is accompanied by the appropriate reflex increases in sympathetic nerve activity, heart rate and peripheral vascular resistance. With the onset of severe hypotension, however, normal baroreflex function is replaced by the sudden appearance of an inappropriate vasodepressor reaction. With the additional fall in blood pressure, sympathetic activity, heart rate, and vascular resistance do not increase further but rather fall paradoxically back to or below baseline.

Shortly after the onset of the hypotension and loss of sympathetic activation, classic signs and symptoms of vasovagal syncope developed in the patient, including nausea, abdominal discomfort, diaphoresis, and giddiness.

To further examine the mechanism triggering this vasodepressor reaction, we performed additional experiments in which we dissected the normal hemodialysis procedure into its component parts, ultrafiltration alone and dialysis alone.

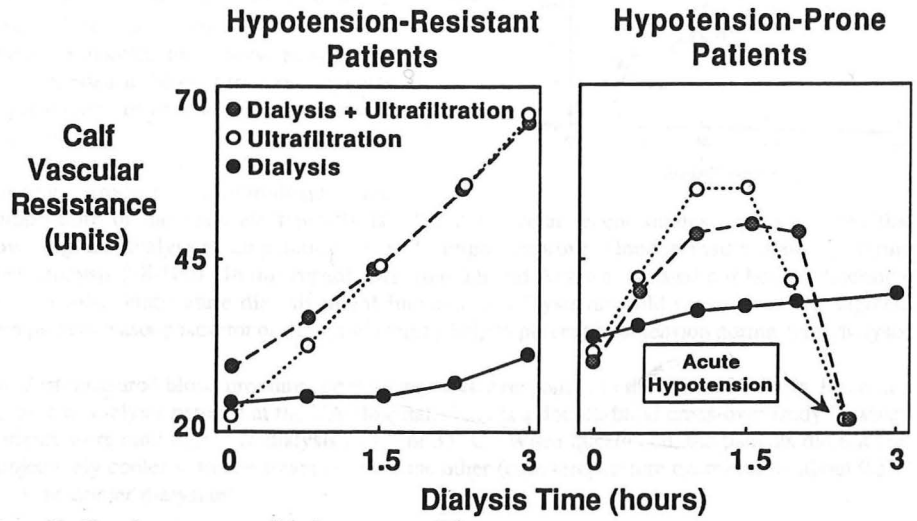


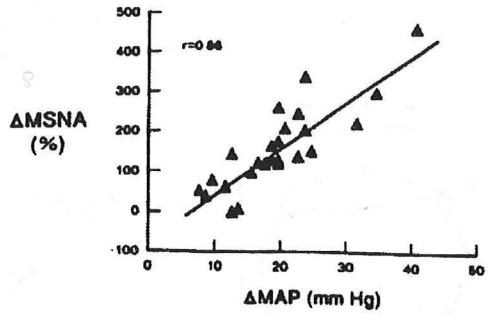
Figure 29. Vascular responses to dialysis maneuvers (75).

These are pooled data from two hypotension-prone and two hypotension-resistant hemodialysis patients. Changes in calf vascular resistance are plotted as a function of time during each of three separate hemodialysis maneuvers: the usual hemodialysis procedure (dialysis plus ultrafiltration), dialysis alone without ultrafiltration, and ultrafiltration alone without dialysis. In the hypotension-resistant patients, calf vascular resistance increased progressively throughout the usual hemodialysis procedure, whereas in the hypotension-prone patients, the vascular resistance increased at first and then decreased sharply with the onset of acute hypotension. Ultrafiltration reproduced both the increases and decreases in vascular resistance (including vasodilation and hypotension), while dialysis alone had no effect on calf vascular resistance in either group of patients. Thus, the withdrawal of volume indeed appears to be the key stimulus triggering this vasodepressor reaction, which in turn exacerbates the volume-dependent fall in blood pressure.

If paradoxical withdrawal of reflex vasoconstriction indeed is one important cause of hemodialysis-induced hypotension, we should be able to ameliorate the hypotension if we could either interrupt this vasodilator reflex pathway or counteract its effects by the activation of a

vasoconstrictor reflex pathway. For example, the cold pressor test, immersion of the hand in ice water, causes robust increases in sympathetic vasoconstrictor outflow (97).

Figure 30. Relation between increased mean arterial pressure (MAP) and muscle sympathetic nerve activity (MSNA) during the cold pressor test (RG Victor et al., *Hypertension*, 1987 (97).

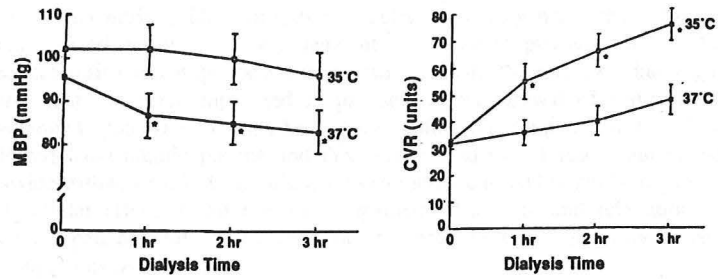


These data are from 25 normal subjects. The close correlation between the increases in sympathetic nerve activity and the increases in blood pressure suggests sympathetic mediation of the pressor response.

During routine hemodialysis, the temperature of the dialysate typically is 37°C but several recent studies have suggested that lowering the dialysate temperature to 35°C might improve blood pressure stability during hemodialysis (98-100). In this regard, Drs. Henrich and Agarwal enlisted our help to determine if the cooler temperature dialysis might function as a "systemic cold pressor test" to augment sympathetic vasoconstrictor outflow and thereby help to prevent hypotension during hemodialysis.

Dr. Jost measured blood pressure and vasoconstrictor responses in the calf in 20 of Dr. Henrich's "problem" dialysis patients at the VA Hospital. This is a double-blind cross-over study in which patients were randomized to dialysis at 37° or 35° C. When questioned, the patients did not feel subjectively cooler with one treatment than the other (core temperature decreases by about 0.5°C with the cooler dialysate).

Figure 31. Effects of dialysate temperature on blood pressure and vascular resistance. From R Agarwal et al., *J Am Soc Nephrol*, 1992 (101).



The left panel shows that blood pressure fell by an average of 20 mmHg with the normal temperature dialysis but remained elevated with the cooler temperature dialysis. The right panel shows that the increases in calf vascular resistance during hemodialysis were much greater with the cooler dialysate. Further studies are needed to determine if the cold dialysate also will prevent the severe episodes of hypotension in patients who are prone to paradoxical withdrawal of reflex vasoconstriction during warm hemodialysis.

7. Nitric Oxide as Neurotransmitter Causing Paradoxical Withdrawal of Sympathetic Outflow During Hypovolemic Hypotension.

Nitric oxide is present not only in vascular endothelium where it functions as an endothelium-dependent vasodilator but also is abundant in the peripheral and central nervous system where it functions as a neurotransmitter, having an inhibitory effect on sympathetic outflow (53,59-63).

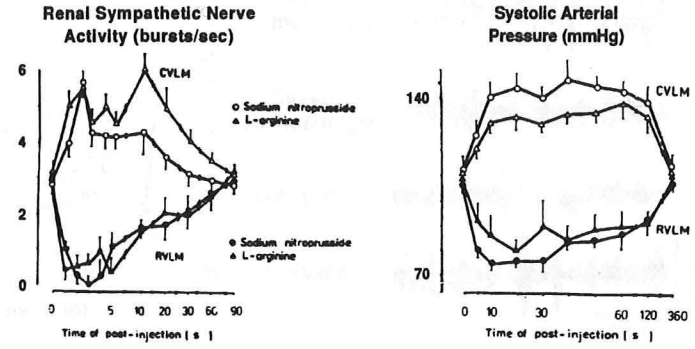


Figure 32. Changes in sympathetic nerve activity and blood pressure caused by selective microinjections of nitroprusside or L-arginine into either the rostral (RVLM) or the caudal (CVLM) ventral lateral medulla in the cat. From LN Shapoval et al., *Neuroscience Letters*, 1991 (63).

The rostral ventral lateral medulla contains excitatory sympathetic neurons and is the origin of sympathetic outflow from the brain stem, whereas the caudal ventral lateral medulla contains neurons that mainly inhibit sympathetic outflow (102,103). NO seems to be an inhibitory neurotransmitter in these key medullary vasomotor circuits, because ambient levels of renal sympathetic nerve activity and blood pressure in cats are decreased by microinjection of nitroprusside or L-arginine (i.e., increased NO production) into the RVLM but increased by their injection into the CVLM (63).

Recent evidence suggests that nitric oxide synthesis is accelerated during hemorrhage (by an unknown stimulus) and exacerbates the volume-dependent fall in blood pressure (104). We therefore hypothesized that nitric oxide might be a neurotransmitter in the inhibitory cardiac vagal afferent reflex pathway that has been implicated in paradoxical withdrawal of sympathetic outflow during hypovolemic hypotension. During hemodialysis, the circulating inhibitor of nitric oxide (ADMA) is cleared from uremic plasma and this should lead to a further gain in the function of the nitric oxide pathway (55). In addition, a given increase in NO might be expected to cause exaggerated cellular effects (inhibition of sympathetic discharge and relaxation of vascular smooth muscle) in patients with chronic renal failure because chronic inhibition of NO synthase leads to NO supersensitivity (105).

The principal investigators on this project are Troy Obregon, an MS-II, and Dr. Teresa Lyson, a postdoctoral fellow in my lab. We began by testing effects of nitric oxide synthesis on the reflex regulation of sympathetic nerve activity and blood pressure during severe hemorrhage in rats. According to our studies in the hemodialysis unit, hemorrhage should be a reasonable initial model of ultrafiltration and hemodialysis.

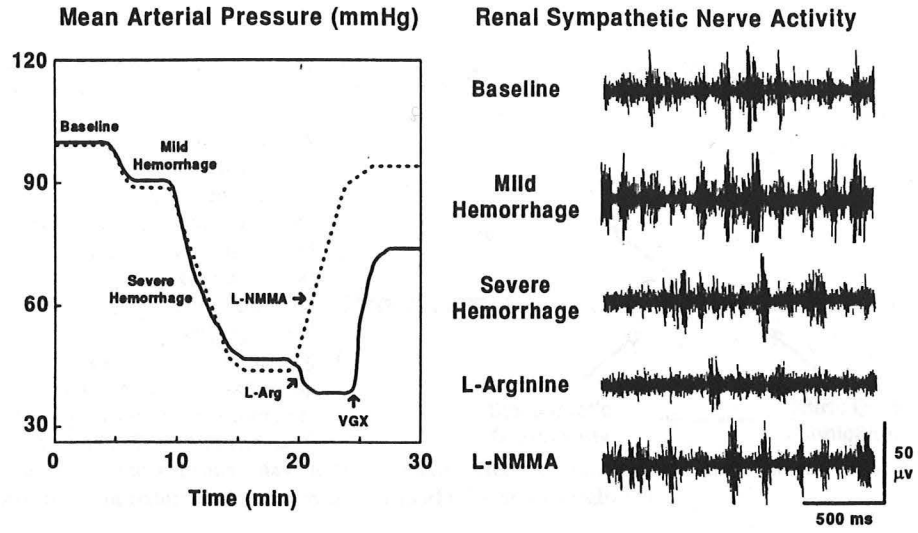
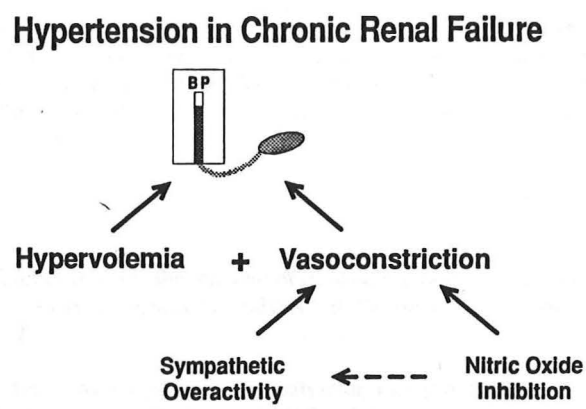


Figure 33. An illustrative experiment providing evidence that NO modulates decreases in blood pressure and sympathetic nerve activity during hemorrhagic shock. The left panel plots the changes in blood pressure as a function of time during the hemorrhage protocol. The right panel shows the recordings of sympathetic nerve activity at these different points in time. From TM Obregon et al, *FASEB J*, 1993, in press (106).

During mild hemorrhage, sympathetic activity increases, indicating normal baroreceptor function. During severe hemorrhage, however, the sympathetic activity does not increase further but rather decreases, resembling the inappropriate decrease in sympathetic activity during dialysis-induced hypotension. We then infused L-NMMA to inhibit NO synthesis or L-arginine to augment it.

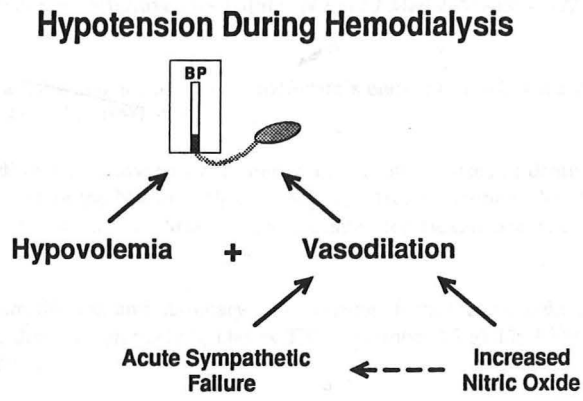
L-NMMA (dashed line) effectively reversed the large hemorrhage-induced decreases in sympathetic nerve activity and blood pressure, even though the volume of the infusate was trivial. We believe that NO is being synthesized at an accelerated rate during hemorrhage and is contributing to the decreases in sympathetic outflow and blood pressure. Thus, in subsequent experiments, the same dose of L-NMMA produced increases in blood pressure and sympathetic activity that were several times larger in the hemorrhage than in the non-hemorrhage state. Furthermore, hemorrhagic hypotension and sympathetic inhibition were exacerbated by L-arginine (solid line) and subsequently partially reversed by vagotomy, which interrupts the inhibitory cardiac afferents. If the vagotomy is performed first, subsequent administration of L-arginine has no effect on sympathetic activity and blood pressure, suggesting that NO may be a key neurotransmitter in the cardiac vagal afferent pathway mediating this inappropriate inhibitory neural response. That L-NMMA mimics the effect of vagotomy on blood pressure and sympathetic activity during hemorrhagic shock suggests that pharmacologic inhibition of NO synthase may be an effective treatment for hypovolemic hypotension, including hemodialysis-induced hypotension.

Figure 34. Hypertension in patients with chronic renal failure.



Although undoubtedly multifactorial, hypertension in chronic renal failure would appear to be caused primarily by hypervolemia *plus* increased vasomotor tone. Recent studies have focused attention on sympathetic overactivity and inhibition of nitric oxide as two important mechanisms contributing to the excessive vasoconstriction. A better scientific understanding of these basic mechanisms may lead to more effective antihypertensive treatment and a corresponding reduction in cardiovascular morbidity and mortality.

Figure 35. Hemodialysis - induced hypotension.



Although also multifactorial, hemodialysis-induced hypotension appears to be caused primarily by relative hypovolemia *plus* a sudden reduction in vasomotor tone. Recent studies have suggested that acute, paradoxical withdrawal of reflex sympathetic activation is one important cause of the abrupt reduction in vascular resistance and blood pressure. Further studies are needed to test the hypothesis that nitric oxide may function as a central neurotransmitter in causing this inappropriate sympathetic response. These considerations may lead to the development of more effective strategies to maintain vasomotor tone and blood pressure during hemodialysis.

According to some nephrologists, the heart exists mainly to perfuse the kidney, which in their view must be the more important organ (107). However, heart disease is unquestionably the main cause of death and disability in patients with chronic renal failure. Furthermore, the heart may well be the site of origin of an inhibitory neural reflex that is an important cause of hypotension during hemodialysis. Thus, for physicians caring for patients with chronic renal failure, it should be evident which is the more important organ.

ACKNOWLEDGEMENTS

I am indebted to Richard Cooley and Pernille G. Hansen for their expert research assistance and preparation of the illustrations; to Ms. Patricia Powell and Ms. Pamela Maass for secretarial assistance; to Drs. William Henrich, Jere H. Mitchell, R. Sanders Williams, Robert Star, and Donald W. Seldin for their thoughtful comments; and to Baxter Healthcare Corporation (Renal Division) for their extramural grant support.

REFERENCES

1. Abel JJ, Rowntree LG, and Turner BB. On the removal of diffusible substances from the circulating blood of living animals by means of dialysis. *J Pharmacal Exp Therap* January:51-54, 1914.

2. Kolff WJ, and Berk HT. De kunstmatige neir:een dialysator met groot oppervlak. *Nederlandske Tijdschrift van de Geneeskunde* 87:1684-1692, 1943.

3. Brescia MJ, Cimino JE, Appel K, and Hurwich BJ. Chronic hemodialysis using venipuncture and a surgically created arteriovenous fistula. *N Engl J Med* 275:1089-1092, 1966.

4. Eggers PW. Mortality rates among dialysis patients in medicare's end-stage renal disease program. *Am J Kid Dis* 15:414-421, 1990.

5. Decline in mortality for cardiovascular diseases and non-cardiovascular causes of death, United States, 1970 to 1984. From the National Heart, Lung, and Blood Institute. Vital Statistics of the United States. Rockville, MD, National Center for Health Statistics, 1986.

6. Hull AR, and Parker TF. Introduction and summary. Proceedings from the morbidity, mortality and prescription of dialysis symposium, Dallas TX, September 15 to 17, 1989. *Am J Kid Dis* 15:375-383, 1990.

7. Feduska NJ, Melzer JS, Amend WJC, Vincenti F, Tomlanovich SJ, Garovoy M, Husing R, and Salvatierra O. Cyclosporine provides better success rates for both higher- and lower-risk cadaveric kidney transplant recipients. *In*: Cyclosporine, Therapeutic Use in Transplantation, Kahan BD, ed. Grune & Stratton, Inc., Philadelphia, PD; pp102-109, 1988.

8. Fries D, Hiesse C, Santelli G, Gardin JP, Cantarovich M, Lanz O, Charpentier B, Paillard M, and Benoit G. Triple therapy with low-dose cyclosporine, azathioprine, and steroids: long-term results of a randomized study in cadaver donor renal transplantation. *In*:

Cyclosporine, Therapeutic Use in Transplantation, Kahan BD, ed. Grune & Stratton, Inc., Philadelphia, PD; pp130-135, 1988.

9. Lindner A, Charra B, Sherrard DJ, and Scribner BH. 1974. Accelerated atherosclerosis in prolonged maintenance hemodialysis. *N Engl J Med* 290:697-701, 1974.

10. Rostand SG, Brunzell JD, Cannon III RO, and Victor RG. Cardiovascular complications in renal failure. *J Am Soc Nephrol* 2:1053-1062, 1991.

11. Goldberg AP, Harter HR, Patsch W, Schechtman KB, Province M, Weerts C, Kuisk I, McCrate MM, and Schonfeld G. Racial differences in plasma high-density lipoproteins in patients receiving hemodialysis: a possible mechanism for accelerated atherosclerosis in white men. *N Engl J Med* 308:1245-1252, 1983.

12. Rostand SG, Kirk K, and Rutsky EA. Relationship of coronary risk factors to hemodialysis-associated ischemic heart disease. *Kid Int* 22:304-308, 1982.

13. Grundy SM. Management of hyperlipidemia. *Kid Int* 22:304-308, 1982.

14. Zucchelli P, Santoro AN, and Zuccala A. Genesis and control of hypertension in hemodialysis patients. *Sem Nephrol* 8:163-168, 1988.

15. Maher JF, and Schreiner GE. Hazards and complications of dialysis. *N Engl J Med* 273:370-377, 1965.

16. Henderson LW. Symptomatic hypotension during dialysis. *Kid Int* (Editorial Review) 17:571-576, 1980.

17. Henrich WL. Hemodynamic instability during hemodialysis. *Kid Int* 30:605-612, 1986.

18. McLeod JG. Autonomic dysfunction in peripheral nerve disease. *In:* Autonomic Failure. R. Bannister, ed. Oxford University Press. pp615-616, 1988.

19. Campese VM, Romoff MS, Levitan D, Lane K, and Massry SG. Mechanisms of autonomic nervous system dysfunction in uremia. *Kidney Int* 20:246-253, 1981.

20. Lilley JJ, Golden J, and Stone RA. 1976. Adrenergic regulation of blood pressure in chronic renal failure. *J Clin Invest* 57:1190-1200, 1976.

21. Kersh ES, Kronfield SJ, Unger A, Popper RW, Cantor S, and Cohn KS. Autonomic insufficiency in uremia as a cause of hemodialysis-induced hypotension. *N Engl J Med* 290:650-653, 1974.

22. Zoccali C, Ciccarelli M, and Maggiore Q. Defective reflex control of heart rate in dialysis patients: evidence for an afferent autonomic lesion. *Clin Sci* 63:285-292, 1982.

23. Henrich WL. Autonomic insufficiency. *Arch of Med* 142:339-344, 1982

24. Bommer J. Medical complications of the long-term dialysis patient. *In:* Oxford Textbook of Clinical Nephrology, Volume 2. Cameron S, Davison AM, Grünfeld J-P, Kerr D, and Ritz E, eds. Oxford University Press; Oxford, pp1436-1458, 1992.

25. Cheigh J, Bui D, Milite C, Tapia L, Sullivan J, Stenzel K, and Rubin A. How well is hypertension (H) controlled in hemodialysis patients. *J Am Soc Nephrol* 4:351, 1990 (abstract).

26. Whelton PK, and Klag MJ. Hypertension as a risk factor for renal disease. Review of clinical and epidemiological evidence. *Hypertension* 13:I19-I27, 1989.

27. Cressman MD, Heyka RJ, Paganin EP, O'Neil J, Skibinski CI, and Hoff HF. Lipoprotein(a) is an independent risk factor for cardiovascular disease in hemodialysis patients. *Circulation* 86:475-482, 1992.

28. Moliterno DJ, Lange RA, Meidell RS, Willard JE, Leffert CC, Boerwinkle EA, Gerard RD, Hobbs HH, and Hillis LD. Relation of plasma lipoprotein(a) to infarct artery patency in survivors of myocardial infarction. *Circulation*, 1992, in press.

29. Haire HM, Sherrard DJ, Scardapane D, Curtis FK, and Brunzel JD. Smoking, hypertension and mortality in a maintenance dialysis population. *Cardiovasc Med* 3:1163-1168, 1978.

30. Kaplan NM. Renal parenchymal hypertension. In Clincal Hypertension. Fifth Edition, Williams and Wilkins:Baltimore, pp. 283-302, 1990.

31. Zucchelli P, and Zuccala A. Control of blood pressure in patients on hemodialysis. *In:* Oxford Textbook of Clinical Nephrology, Volume 2. Cameron S, Davison AM, Grünfeld J-P, Kerr D, and Ritz E, eds. Oxford University Press:Oxford, pp1458-1467, 1992.

32. Schaefer RM, Leschke M, Strauer BE, and Heidland A. Blood rheology and hypertension in hemodialysis patients treated with erythropoietin. *Am J Nephrol* 8: 449-453,1988.

33. Schalekamp MA, Beevers DG, Briggs JD, Brown JJ, Davies DL, Fraser R, Lebel M, Lever AF, Medina A, Morton JJ, Robertson JIS, and Tree M. Hypertension in chronic renal failure. An abnormal relation between sodium and the renin-angiotensin system. *Am J Med* 55:379-390, 1973.

34. Recordati G, Moss NG, Genovesi S, and Rogenes P. Renal chemoreceptor. *J Autonomic Nerv Sys* 3:237-51, 1981.

35. DiBona GF. The function of the renal nerves. *Rev Physiol Biochem Pharmacal* 94:76-181, 1982.

36. Katholi RE. Renal nerves and hypertension: an update. *Federation Proc* 44:2846-2850, 1985.

37. Faber JE, and Brody MJ. Afferent renal nerve-dependent hypertension following acute renal artery stenosis in the conscious rat. *Circ Res* 57:676-688, 1985.

38. Katholi RE, Whitlow PL, Hageman GR, and Woods T. Intrarenal adenosine produces hypertension by activating the sympathetic nervous system via the renal nerves. *J Hypertension* 2:349-359, 1984.

39. Vallbo AB, Hagbarth K-E, Torebjörk HE, and Wallin BG. Somatosensory, proprioceptive, and sympathetic activity in human peripheral nerves. *Physiol Rev* 59:919-957, 1979.

40. Nies AS, Robertson D, and Stone WJ. Hemodialysis hypotension is not the result of uremic peripheral autonomic neuropathy. *J Lab Clin Med* 94:395-402, 1979.

41. Lake CR, Ziegler MG, Coleman MD, and Kopin IJ. Plasma levels of norepinephrine and dopamine-ß-hydroxylase in CRF patients treated with dialysis. *Cardiovasc Med* 4:1099-1111, 1979.

42. Corder CN, Sharma J, and McDonald RH Jr. Variable levels of plasma catecholamines and dopamine ß-hydroxylase in hemodialysis patients. *Nephron* 25:267-272, 1980.

43. Textor SC, Gavras H, Tifft CP, Bernard DB, Idelson B, and Brunner HR. Norepinephrine and renin activity in chronic renal failure. *Hypertension* 3:294-299, 1981.

44. Henrich WL, Katz FH, Molinoff PB, and Schrier RW. Competitive effects of hypokalemia and volume depletion on plasma renin activity, aldosterone and catecholamine concentrations in hemodialysis patients. *Kidney Int* 12:279-284, 1977.

45. Cuche J-L, Prinseau J, Selz F, Ruget G, and Baglin A. Plasma free, sulfo- and glucuro-conjugated catecholamines in uremic patients. *Kidney Int* 30:566-72, 1986.

46. Zoller RP, Mark AL, Abboud FM, Schmid PG, and Heistad DD. The role of low pressure baroreceptors in reflex vasoconstrictor responses in man. *J Clin Invest* 51:2967-2972, 1972.

47. Smogorzewski M, Campses VM, and Massry SG. Abnormal norepinephrine uptake and release in brain synaptosomes in chronic renal failure. *Kidney Int* 36:458-465, 1989.

48. Wallin BG, and Fagius J. The sympathetic nervous system in man - aspects derived from microelectrode recordings. *TINS* 9:63-67, 1986.

49. Converse RL, Jacobsen TN, Toto RD, Jost CMT, Cosentino F, Fouad-Tarazi F, and Victor RG. Sympathetic overactivity in patients with chronic renal failure. *N Engl J Med*, 1992, in press.

50. Mark AL, and Mancia G. Cardiopulmonary baroreflexes in humans. Section 2: The Cardiovascular System, Volume III. *In*: Handbook of Physiology, Shepherd JT, Abboud FM, eds. Bethesda MD, American Physiological Society, pp497-555, 1983.

51. Henrich WL. The Endothelium: A key regulator of vascular tone. *Am J Med Sci* 302:319-328, 1991.

52. Moncada S, Palmer RMJ, and Higgs EA. Nitric oxide: Physiology, pathophysiology, and pharmacology. *Pharmacal Rev* 43:109-142, 1991.

53. Moncada S. The L-arginine: nitric oxide pathway. The 1991 Ulf von Euler Lecture. *Acta Physiol Scand* 145:201-227.

54. Rees DD, Palmer RMJ, and Moncada S. Role of endothelium-derived nitric oxide in the regulation of blood pressure. *Proc Natl Acad Sci* 86:3375-3378, 1989.

55. Vallance P, Leone A, Calver A, Collier J, and Moncada S. Accumulation of an endogenous inhibitor of nitric oxide synthesis in chronic renal failure. *Lancet* 339:572-575, 1992.

56. Baylis C, Mitruka B, and Deng A. Chronic blockade of nitric oxide synthesis in the rat produces systemic hypertension and glomerular damage. *J Clin Invest* 90:278-281, 1992.

57. Arnal JF, Warin L, and Michel JB. Determinants of aortic cyclic guanosine monophosphate in hypertension induced by chronic inhibition of nitric oxide synthase. *J Clin Invest* 90:647-652, 1992.

58. Ribeiro MO, Antunes E, de Nucci G, Lovisolo SM, and Zatz R. Chronic inhibition of nitric oxide synthesis. *Hypertension* 20:298-303, 1992.

59. Shibuki K, and Okada D. Endogenous nitric oxide release required for long-term synaptic depression in the cerebellum. *Nature* 349:326-328, 1991.

60. Knowles RG, Palacios M, Palmer RMJ, and Moncada S. Formation of nitric oxide from L-arginine in the central nervous system: A transduction mechanism for stimulation of the soluble guanylate cyclase. *Proc Natl Acad Sci* 86:5159-5162, 1989.

61. Bredt DS, Hwang PM, and Snyder SH. Localization of nitric oxide synthase indicating synthase indicating a neural role for nitric oxide. *Nature* 347:768-770, 1990.

62. Sakuma I, Togashi H, Yoshioka M, Saito H, Yanagida M, Tamura M, Kobayashi T, Yasuda H, Gross SS, and Levi R. N^G-methyl-L-arginine, an inhibitor of L-arginine-derived nitric oxide synthesis, stimulates renal sympathetic nerve activity in vivo: A role for nitric oxide in the central regulation of sympathetic tone? *Circ Res* 70:607-611, 1992.

63. Shapoval LN, Sagach VF, and Pobegailo LS. Nitric oxide influences ventrolateral medullary mechanisms of vasomotor control in the cat. *Neuroscience Letters* 132: 47-50,1991.

64. Lowrie EG, and Lew NL. Death risk in hemodialysis patients: the predictive value of commonly measured variables and an evaluation of death rate differences between facilities. *Am J Kid Dis* 15:458-482, 1990.

65. Wehle B, Asaba H, Castenfors J, Furst P, Grain A, Gunnarsson B, Shaldon S, and Bergstrom J. The influence of dialysis fluid composition on the blood pressure response during dialysis. *Clin Nephrol* 10:62-66, 1978.

66. Henrich WL, Woodart TD, and McPhaull JJ Jr. The chronic efficacy and safety of high sodium dialysate: Double-blind cross-over study. *Am J Kidney Dis* 3:349-353, 1982.

67. Beasly D, and Benner BM. Role of nitric oxide in hemodialysis hypotension. *Kid Int* 42:S96-S100, 1992.

68. Dinarello CA, Koch KM, and Shaldon S. Interleukin-1 and its relevance in patients treated with hemodialysis. *Kid Int* 33(Suppl):S21-S26, 1988.

69. Herbelin A, Nguyen AT, Zingraff J, Urena P, and Descamps-Latscha B. Influence of uremia and hemodialysis on circulating interleukin-1 and tumor necrosis factor α. *Kid Int* 37:116-125, 1990.

70. Bingel M, Lonnemann G, Koch KM, Dinarello CA, and Shaldon S. Plasma interleukin-1 activity during hemodialysis: the influence of dialysis membranes. *Nephron* 50:273-276, 1988.

71. Haffner-Cavaillon N, Cavaillon J-M, Ciancioni C, Bacle F, Delons S, and Kazatchkine MD. In vivo induction of interleukin-1 during hemodialysis. *Kid Int* 35:1212-1218, 1989.

72. Dinarello CA, Okusawa S, and Gelfand JA. Interleukin-1 induces shock-like state in rabbits: synergism with tumor necrosis factor and the effect of ibuprofen. *Prog Clin Biol Res* 299:203-215, 1989.

73. Hakim RM, Breillatt J, Lazarus M, and Port FK. Complement activation and hypersensitivity reactions to dialysis membranes. *N Engl J Med* 311:878-882, 1984.

74. Nakashima Y, Fouad FM, Nakamoto S, Textor SC, Bravo E, and Tarazi RC. Localization of autonomic nervous system dysfunction in dialysis patients. *Am J Nephrol* 7:375-381, 1987.

75. Converse RL, Jacobsen TN, Fouad-Tarazi F, Obregon TM, Toto RD, and Victor RG. Paradoxical withdrawal of reflex vasoconstriction as a cause of hemodialysis-induced hypotension. *J Clin Invest*, in press, 1992.

76. Ewing DJ, Campbell IW, and Clarke BF. Assessment of cardiovascular effects in diabetic autonomic neuropathy and prognostic implications. *Ann Int Med* 92(Part 2):308-311, 1980.

77. Mark AL, and Mancia G. Arterial baroreflexes in humans. Section 2: The Cardiovascular System, Volume III. *In:* Handbook of Physiology, Shepherd JT, and Abboud FM, eds. Bethesda MD, American Physiological Society. pp755-785, 1983.

78. Brown AM. Receptors under pressure: An update on baroreceptors. *Circ Res* 46:1-10, 1980.

79. Skoog P, Mansson J, and Thorén P. Changes in renal sympathetic outflow during hypotensive hemorrhage in rats. *Acta Physiol Scand* 125:655-660, 1985.

80. Victor RG, Thorén P, Morgan DA, and Mark AL. Differential control of adrenal and renal sympathetic nerve activity during hemorrhagic hypotension in rats. *Circ Res* 64:686-694, 1989.

81. Morita H, and Vatner SF. Effects of hemorrhage on renal nerve activity in conscious dogs. *Circ Res* 57:788-793, 1985.

82. Victor RG, Jost CMT, and Converse RL Jr. Paroxysmal autonomic syncope. In: Disorders of the Autonomic Nervous System. Burnstock G, ed. Harwood Academic Publishers, London, England, in press, 1993

83. Secher NH, and Bie P. Bradycardia during reversible hemorrhagic shock--a forgotten observation? *Clin Physiol* 5:315-323, 1985.

84. Sander-Jensen R, Secher NH, Bie P, Warberg J, and Schwartz TW. Vagal slowing of the heart during hemorrhage: Observation from 20 consecutive hypotensive patients. *Br Med J (Clin Res)* 292:365-366, 1986

85. Wallin BG, and Sundlöf G. Sympathetic outflow to muscles during vasovagal syncope. *J Auton Nerv Syst* 6:287-291, 1982.

86. Scherrer U, Vissing SF, Morgan BJ, Hanson P, and Victor RG. Vasovagal syncope after infusion of a vasodilator in a heart-transplant recipient. *N Engl J Med* 322:602-604, 1990.

87. Almquist A, Goldenberg IF, Milstein S, Chen M-Y, Chen X, Hansen R, Gornick CC, and Benditt DG. Provocation of bradycardia and hypotension by isoproterenol and upright posture in patients with unexplained syncope. *N Engl J Med* 320:346-351, 1989.

88. Schadt JC, McKown MD, McKown DP, and Franklin D. Hemodynamic effects of hemorrhage and subsequent naloxone treatment in conscious rabbits. *Am J Physiol* 247:R497-R508, 1984.

89. Morita H, Nishida Y, Motochigawa H, Uemura N, Hosomi H, and Vatner SF. Opiate receptor-mediated decrease in renal nerve activity during hypotensive hemorrhage in conscious rabbits. *Circ Res* 63:165-172, 1988.

90. Smith ML, Carlson MD, Sheehan HM, and Thames MD. Naloxone does not prevent vasovagal syncope during simulated orthostasis in humans. *Physiologist* 34:238, (Abstract) 27.2, 1991.

91. Morgan DA, Thorén P, Wilczynski EA, Victor RG, and Mark AL. Serotonergic mechanisms mediate renal sympathoinhibition during severe hemorrhage in rats. *Am J Physiol* 255:H496-H502, 1988.

92. Peuler JD, Schmid PG, Morgan DA, and Mark AL. Inhibition of renal sympathetic activity and heart rate by vasopressin in hemorrhaged diabetes insipidus rats. *Am J Physiol* 258:H706-H712, 1990.

93. Landgren S. 1952. On the excitation mechanism of the carotid baroreceptors. *Acta Physiol Scand* 26:1-3462, 1952.

94. Bishop VS, Malliani A, and Thorén P. Cardiac mechanoreceptors. Section 2: The Cardiovascular System, Vol III. *In*: Handbook of Physiology, Shepherd JT, and Abboud FM, eds. American Physiological Society, Bethesda, MD; pp497-555, 1983.

95. Abboud FM. Ventricular syncope: Is the heart a sensory organ? *N Engl J Med* 320:390-392, 1989.

96. Öberg B, and Thorén P. Increased activity in left ventricular receptors during hemorrhage or occlusion of caval veins in the cat -a possible cause of the vasovagal reactions. *Acta Physiol Scand* 85:164-173, 1972.

97. Victor RG, Leimbach WN, Seals DR, Wallin BG, and Mark AL. Effects of the cold pressor test on muscle sympathetic nerve activity in humans. *Hypertension* 9:429-436, 1987.

98. Sherman RA, Rubin MP, Cody RP, and Eisinger RP. Amelioration of hemodialysis-associated hypotension by the use of cool dialysate. *Am J Kid Dis* 5:124-127, 1985.

99. Marcen R, Quereda C, Orofino L, Lamas S, Terual JL, Matexanz R, and Ortuno J. Hemodialysis with low temperature dialysate. *Nephron* 49:29-32, 1988.

100. Levy FL, Grayburn PA, Foulks CJ, Brickner ME, and Henrich WL. Improved left ventricular pressure and renal function during hypovolemic shock. *Am J Physiol* 261:F868-F872, 1991.

101. Agarwal R, Jost C, Khair-el-din T, Victor R, Grayburn P, and Henrich W. 35° dialysis increases peripheral resistance and improves hemodynamic stability in "problem" hemodialysis patients. *J Am Soc Nephol* 3:351, 1992.

102. Reis DJ, Ruggiero DA, and Morrison SF. The C1 area of the rostral ventrolateral medulla oblongata: a critical brainstem region for control of resting and reflex integration of arterial pressure. *Am J Hypertension* 2 (12, Pt 2):363S-374S, 1989.

103. Cravo SL, Morrison SF, and Reis DJ. Differentiation of two cardiovascular regions within caudal ventrolateral medulla. *Am J Physiol* 261: R985-994, 1991.

104. Lieberthal W, McGarry AE, Scheils J, and Valeri CR. Nitric oxide inhibition in rats improves blood pressure and renal function during hypovolemic shock. *Am J Physiol* 261:F868-F872, 1991.

105. Moncada S, Rees DD, Schulz R, and Palmer RMJ. Development and mechanism of a specific supersensitivity to nitrovasodilators after inhibition of vascular nitric oxide synthesis *in vivo*. *Proc Natl Acad Sci* 88:2166-2170, 1991.

106. Obregon TM, Lyson T, Ermel LD, Hansen PG, and Victor RG. Nitric oxide as a neurotransmitter mediating vagal afferent inhibition of sympathetic nerve activity during hemorrhagic shock. *FASEB J*, 1993, in press.

107. Alpern RJ. Renal and cardiovascular hypertrophy: Implications for the treatment of patients with hypertension, renal, and cardiac disease. UT Southwestern Medicine Grand Rounds, August 6, 1992.