THE EFFECTS OF RENAL FAILURE ON CARDIOVASCULAR HOMEOSTASIS

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I. Morbidity and Mortality from Cardiovascular Disease in Renal Failure

The adverse effects of renal insufficiency are distributed uniformly in the body. However, these effects have the most profound consequences on the cardiovascular system. Despite the improved medical management of patients with chronic renal failure and the real advances in dialytic and transplantation technology, a number of extra-renal complications continue to cause significant morbidity and mortality. Cardiovascular abnormalities are by far the most common and most serious abnormalities which attend renal insufficiency.

This review examines two closely related aspects of the effects of uremia on the cardiovascular system: hypertension and uremic cardiomyopathy. Despite the fact that the two conditions may result in a common set of clinical findings (e.g., heart failure), they really represent different aspects of the same problem: while hypertension is uniformly recognized for its critical importance in the high morbidity and mortality in uremia, the existance of a specific cardiomyopathy remains a fascinating, but elusive diagnosis. In some aspects, the reason that a specific uremic cardiomyopathy is doubted is because hypertension is so prevalent in uremic patients, making other pathogenic factors difficult to isolate. Both abnormalities are discussed from a pathophysiologic perspective, and a section on therapy of hypertension is included.

The primary cause of morbidity and mortality in patients with chronic renal failure (CRF) is atherosclerosis. Early studies by Linder et al (1) reported a sharp increase in the cause-specific mortality from cardiac problems beginning 4 years after the institution of dialysis. The death rate from myocardial infarction rose steeply after 6 years in this study. When these data are compared with the incidence of coronary artery disease in the Framingham study, young dialysis patients are seen to have a mortality rate of 2.5 times that reported for older men with severe levels of hypertension. As shown in Figure 1, after a few years on dialysis the probability of death from any cause parallels that from a cardiovascular death. Data collected from European centers indicate a similar pattern. Among 12,000 deaths occurring in patients on chronic dialysis programs through 1976, 58% were secondary to cardiovascular disease.

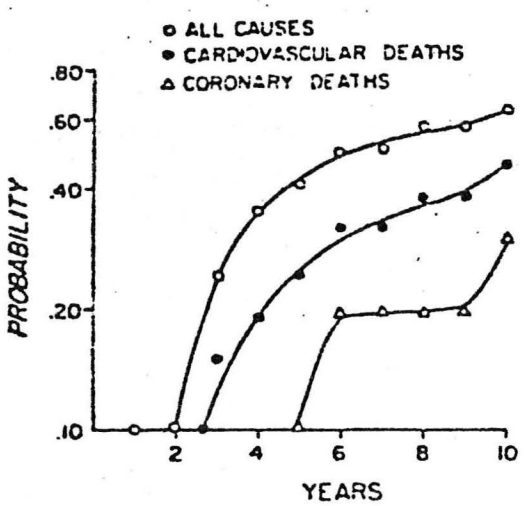
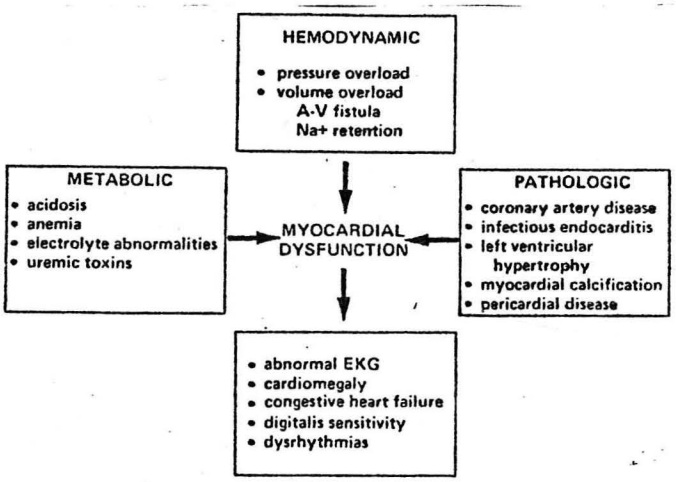


FIGURE 1: Life-table of mortality during maintenance hemodialysis. Mortality rates for all causes, for cardiovascular deaths and for coronary deaths are plotted against time. As shown, the probability of death from any cause parallels that of C-V death after several years on dialysis. (Reference 1).

There is no firm evidence that dialysis per se accelerates the development of vascular disease (2). As shown in Figure 2, a number of factors seem to produce myocardial dysfunction. Of these factors, the existance of hyper-

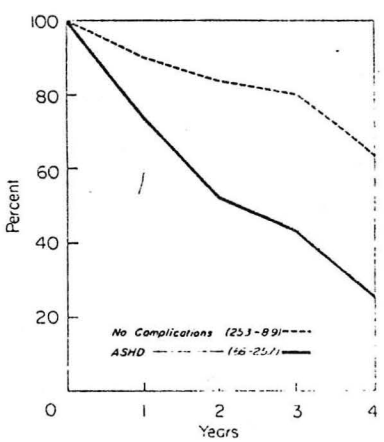


Factors causing myocardial dysfunction in patients with chronic renal disease.

FIGURE 2: The etiology of cardiovascular dysfunction in renal failure is often multifactorial.

tension is clearly most deleterious to the heart. Patients who were free of diabetes, underlying heart disease, and hypertension before entering dialysis programs were noted to have a low incidence of subsequent atherosclerotic complications. It is clear, therefore, that the cardiovascular status of the patient prior to entry into a dialysis program is a critical determinant for prognosis. As shown in Figure 3, striking differences in survival become apparent when this parameter is taken into consideration (3).

FIGURE 3: Cumulative poorer survival of chronic dialysis patients with a history of coronary artery heart-disease (ASHD) shown by the solid lines, as compared to patients without a history of ASHD (dashed lines). (Reference 3)



Hypertension is the most important variable which predisposes to the development of atherosclerosis in patients with CRF. In one recent study, the critical risk factors for subsequent morbidity due to atherosclerosis were age at entry and diastolic blood pressure (3). Another study (4) documented the poorer survival of hypertensive patients with CRF when compared to other etiologies of renal failure (Figure 4).

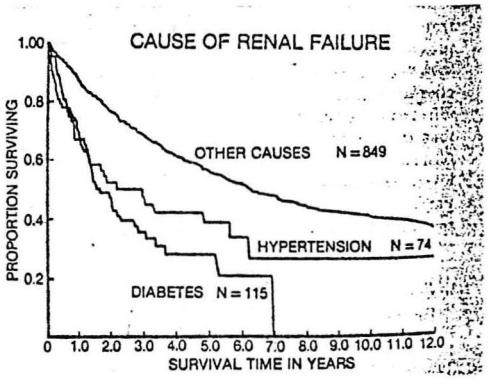


FIGURE 4: The probability of survival for 1038 patients, according to the cause of renal failure.

Estimates were obtained by using the method of Kaplan and Meier. Note the poorer survival in hypertensive and diabetic patients. (Reference 4).

Finally, hypertension also impacts negatively on the progression of renal disease due to several causes. This is strikingly illustrated in Figure 5 by

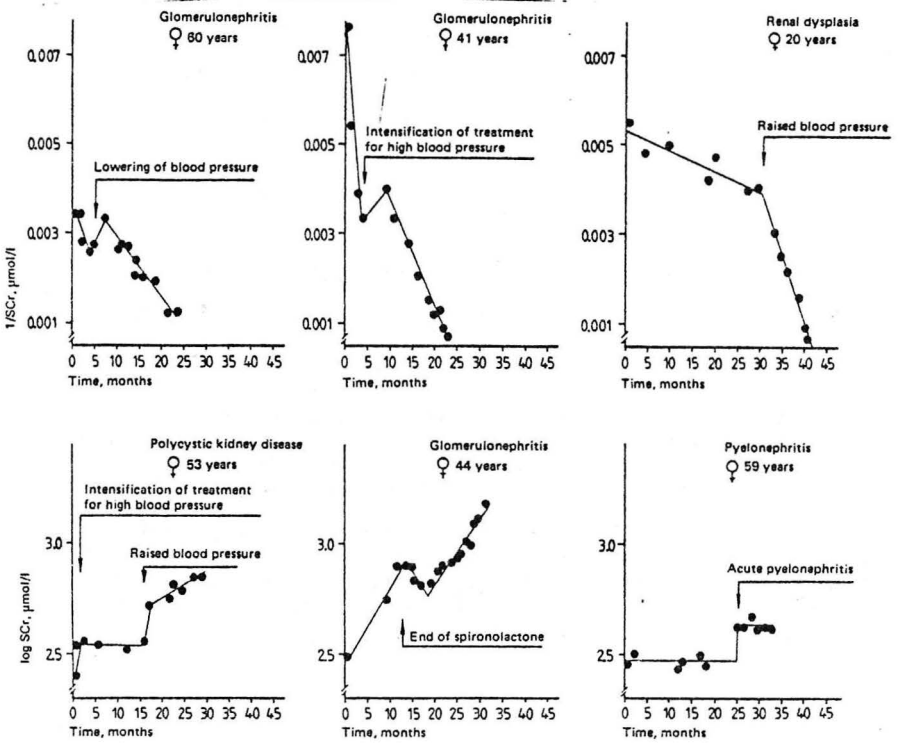


FIGURE 5: Deviations from the lines of progression in 6 patients. The most probable concurrent event affecting the progression is indicated. Poor BP control leads to striking declines in renal function. (Reference 5)

the observation of Oksa et al (5) who found a clear correlation between blood pressure control and the progression of renal disease. The control of blood pressure improved or stablized renal function when achieved.

II. Hypertension in Chronic Renal Failure

Hypertension and atherosclerotic heart disease is the most common form of cardiomyopathy in chronic renal failure. Between 80 and 85% of patients with CRF have an elevated blood pressure, so the problem occurs in the great majority of patients. Increased cardiac work, myocardial hypertrophy, increased myocardial oxygen requirements all occur in the setting of existant coronary artery disease and anemia. Left ventricular failure, angina pectoris, and cardiac arrythmias are frequent sequelae. A list of typical clinical features of heart failure in CRF is provided in Table 1.

Clinical Features of Congestive Heart Failure in Uremia

Symptoms/signs	Contributing factor[a]
Dyspnea	Anemia, acidosis
Orthopnea	Anemia, acidosis
Neck vein engorgement	Hypervolemia
Peripheral edema	Hypervolemia, hypoproteinemia
Cardiomegaly	Hypertension, coronary artery disease, hypervolemia, pericarditis
Gallop rhythm	Hypertension, coronary artery disease, hypervolemia
Pulmonary rales	Hypervolemia
Tachycardia	Anemia
Hepatomegaly	Hypervolemia
Pleural effusion	Hypervolemia, hypoproteinemia
Perihilar pulmonary congestion	Increased capillary permeability, decreased oncotic pressure, hypervolemia

[a] In addition to myocardial failure.

TABLE 1

Other frequent laboratory findings are provided in Table 2.

A. Pathogenesis of Hypertension in CRF

1. Volume and Peripheral Resistance

The pathophysiology of uremic hypertension has been classically divided into two patterns: 1) an increase in peripheral vascular resistance (PVR) associated with extracellular volume expansion (6); and 2) an increase in PVR associated with an increased activity of the renin angiotensin system (7-9).

Clearly, volume over-expansion characterizes the hemodynamics of CRF (10-12) for many patients. A classic observation was made by Vertes et al (6) who documented control of blood pressure in 35 of 40 patients with salt and water restriction and ultrafiltration dialysis alone (Figure 6). Today, most clinicians

Laboratory Findings in Cardiomyopathy Associated with Uremia[a]

	Acute renal failure	Uremia
Electrocardiogram	May be normal, or show tall T waves, prolonged S-T	Usually abnormal: left ventricular hypertrophy and strain, tall T waves, prolonged S-T, A-V block, nonspecific changes
Echocardiogram	Usually normal, or pericardial effusion	Usually abnormal: left ventricular dilatation, cardiomyopathy pattern, left ventricular hypertrophy, pericardial effusion, valvular calcifications, ejection fractions decreased
Chest x-ray		
Cardiomegaly	Less common	Common
Pericardial effusion	Usually absent	Frequent
Perihilar infiltrates	Uncommon	Common
Red cell mass	Normal	Always decreased
Plasma volume	Normal	Usually increased (50% or more)
Total blood volume	Normal	Normal
Exchangeable sodium	May be increased	Always increased
Plasma renin activity	Normal or increased	Normal or increased
A-V O_2 difference	Normal	Normal or high
Cardiac output	Normal or increased	Frequently increased
Stroke volume	Normal	Normal
Left ventricular end diastolic pressure	Normal	Usually increased
Left ventricular work	May be increased	Usually increased
Left ejection fraction	Normal	Frequently decreased
Stroke work	May be increased	Usually increased
Pulmonary mean pressure	Normal	Normal or borderline increased
Mean arterial pressure	May be increased	Usually increased
Total peripheral resistance	Normal	Usually increased
Circulation time	May be increased	Frequently increased

[a] A-V, arteriovenous.

Table 2

agree that rigorous control of volume will result in control of blood pressure in the majority (perhaps up to 75%) of patients with CRF. In addition, Cangiano

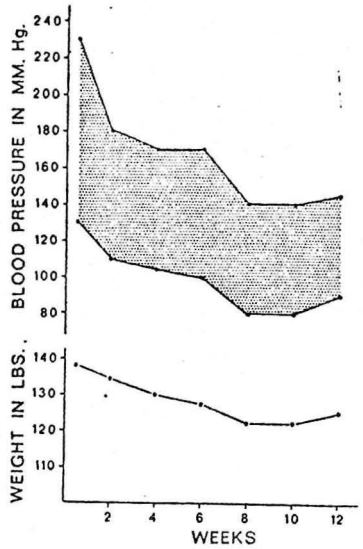


FIGURE 6: Blood pressure response to dry weight in a patient with chronic pyelonephritis. As weight (volume) declines (lower panel), blood pressure (upper panel) also falls. (Reference 6).

et al (13) have correlated the over-expansion of ECF with an increase in PVR (Figure 7).

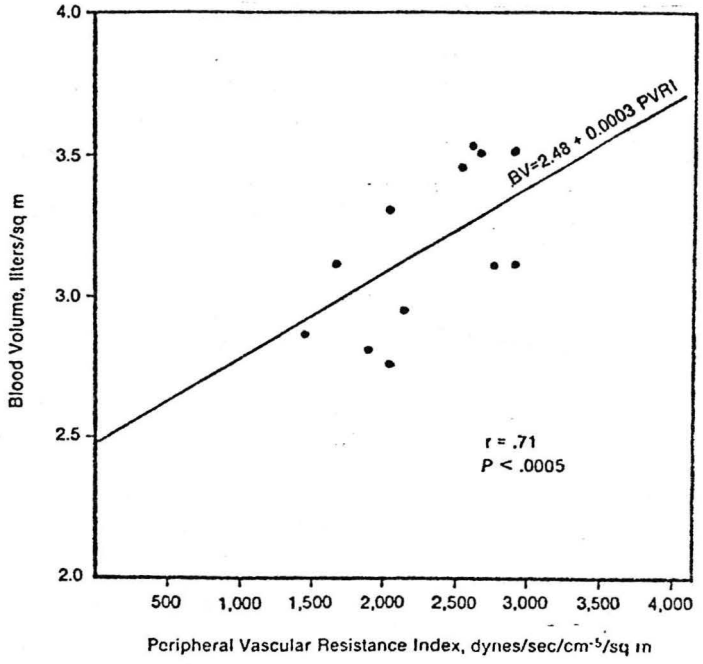


FIGURE 7: Relationship of PVR to BV in renal failure patients. (Reference 13)

2. Increase in Cardiac Output

Other hemodynamic characteristics of the patient with hypertension and CRF also exist. For example, Kim et al (7) have noted a high cardiac output in 75 normotensive and hypertensive uremic patients but an increase in PVR only in uremic subjects. This finding has led to the conclusion that an elevated PVR was primarily responsible for the increase in blood pressure in the hypertensive group. These findings were confirmed by Cangiano et al (13) who also documented a pattern of increased cardiac output, increased heart rate, and a normal stroke volume in patients with CRF. The authors proposed that the uremia of CRF and the presence of A-V fistulas in many patients contributed to the elevation in cardiac output. In support of these contentions are the results of Duke and Abelmann (14) who noted an elevated cardiac index in anemic patients with corrected elevation of the hematocrit. Similarly, Neff et al (15) measured a reduction in cardiac index following blood transfusions in anemic uremic patients. Finally, the presence of an A-V fistula may also contribute to the elevation of cardiac output in some uremic patients (16,17) (Figure 8). Despite these reports of an increase in cardiac output in hypertensive uremic subjects, the fact that normotensive uremic subjects have similar elevations of cardiac output make it unlikely that the elevation plays a major role in sustaining elevations of blood pressure. The difference in the normotensive and hypertensive patient population is the increase in PVR, which is favorably

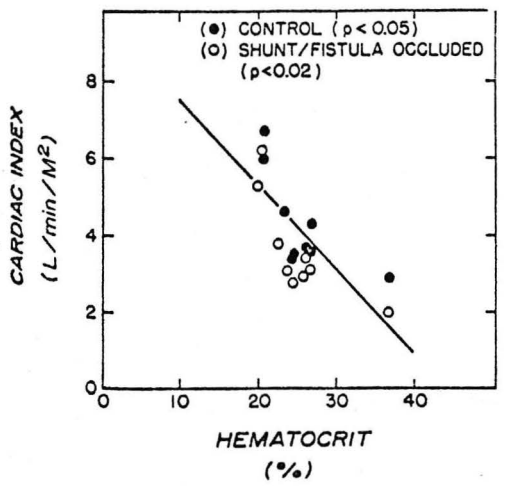


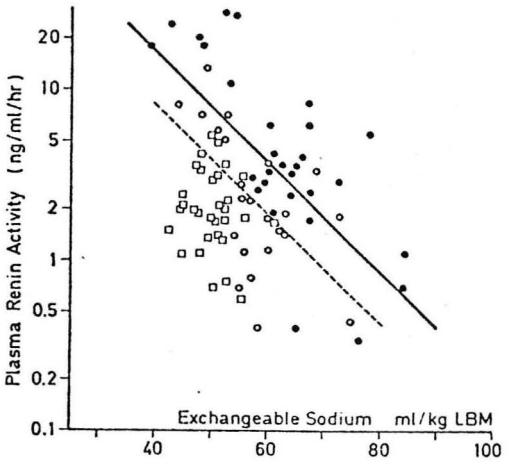
FIGURE 8: Inverse correlation between cardiac index and hematocrit was demonstrable before and after arteriovenous occlusion(s). (cardiac index control - 0.187 hematocrit + 9.11; cardiac index occlusion = -0.205 hematocrit + 8.91). (Reference 16).

reduced by volume control in most hypertensive subjects with CRF.

3. Renin-Angiotensin

An abnormal relationship may exist between the renin-angiotensin system and total exchangeable sodium. As shown in Figure 9, hypertension dialysis subjects have a marked elevation of PRA for the degree of volume expansion present.

FIGURE 9: Relationship between exchangeable body sodium and plasma renin activity in normal subjects and hemodialysis patients with normal or elevated blood pressure. For any given body sodium, plasma renin activity is on the average more than two times higher in hypertensive than in normotensive subjects.



	N=	r=	p<
□ Normal Subjects	31	-0.10	N.S.
Hemodialysis Patients			
○--- $\overline{BP}$ < 110 mmHg	23	-0.75	0.0025
●— $\overline{BP}$ ≥ 110 mmHg	29	-0.74	0.001

This elevation in renin-angiotensin may further contribute to an increase in PVR. A similar relationship was reported by Acosta, and is depicted in Figure 10.

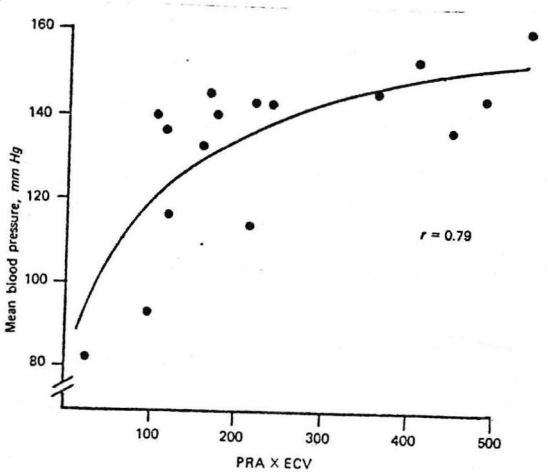


FIGURE 10: Relationship between mean blood pressure and the product of plasma renin activity and extracellular volume. The normal curve is significantly below the line depicted in the figure. (Reference 19).

In addition, the velocity of the renin substrate reaction is increased in uremic man (Figure 11). This finding indicates either an accelerator or lack of an inhibitor of this reaction in patients with terminal renal failure.

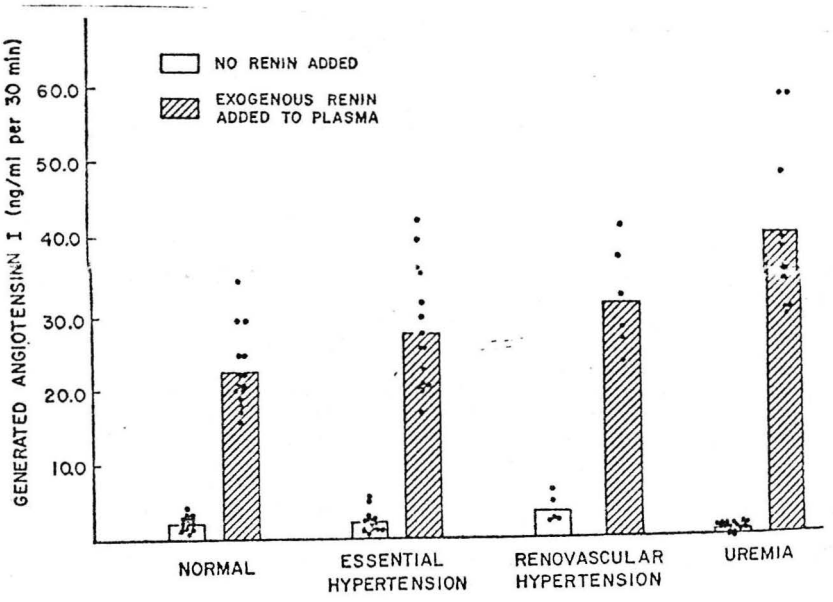


FIGURE 11: Generated angiotensin II in plasma of normal, hypertensive and uremic subjects during incubation for thirty minutes. The reaction velocity significantly increased in uremia.

Finally, one recent study indicates that plasma aldosterone may be increased even in the presence of a normal PRA (18).

It is clear, therefore, that the importance of the renin-angiotensin system, even in the primarily volume-dependent type of hypertension of CRF should not be underestimated. The aggregated studies suggest that an abnormal relationship in the sodium-volume-renin feedback mechanism exists in CRF. This leads to volume expansion and to inappropriately high renin levels (19).

Although volume control results in a favorable blood pressure response in the majority of uremic patients, a population of patients with an elevated PVR and hyperactive renin-angiotensin system also clearly exists. As noted by Del Greco et al (20), such patients are characterized by a normal cardiac output, a normal plasma volume, and an elevated PVR. These patients have been also characterized by an elevated PRA, although the interpretation of the PRA is sometimes difficult (20). Lifschitz et al (21) has tested the importance of circulating angiotensin II in the pathogenesis of hypertension in this group of hypertensive dialysis patients. Saralasin was shown to reduce blood pressure in 7 patients; 5 of the 7 patients ultmiately underwent nephrectomies with normalization of blood pressures (Figure 12).

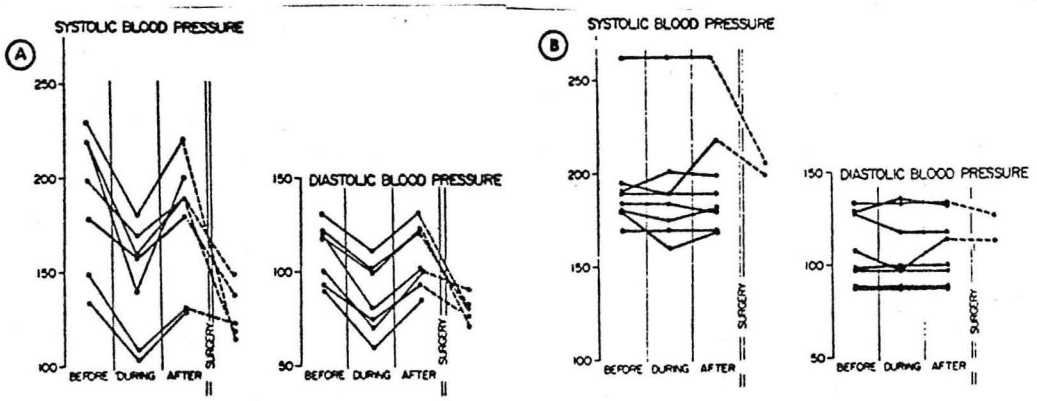


FIGURE 12: A: Systolic and diastolic blood pressure in seven patients considered responders before, during, and after the administration of saralasin (solid lines). Five patients subsequently had their kidneys removed, and the change in blood pressure 1 month later is indicated (dashed lines). B: Systolic and diastolic blood pressure in eight patients considered nonresponders before, during, and after the administration of saralasin (solid lines). Two patients subsequently had their kidneys removed, and their blood pressure 1 month later is indicated (dashed lines). (Reference 21)

Patients who responded to saralasin had PRA's which averaged 70 ng/ml/3 hr in contrast to the non-responders who averaged 21 ng/ml/3 hr. This pattern is consistant with data garnered by Weidman and Maxwell which shows that uncontrolled

hypertension in CRF is usually characterized by extremely high PRA's (Figure 13).

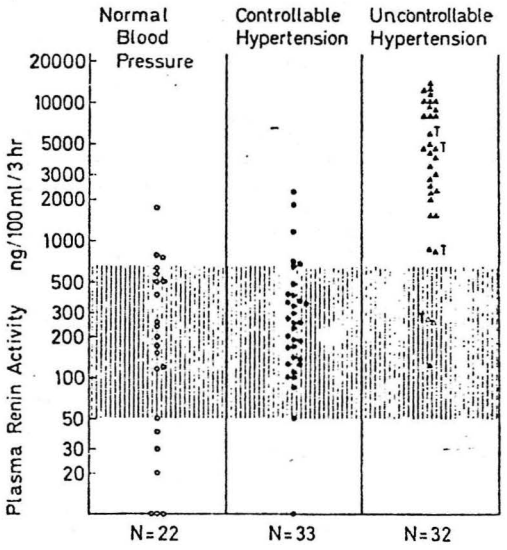


FIGURE 13: Basal renin activity levels in patients with terminal renal failure and normal blood pressure, controllable hypertension, or uncontrollable hypertension. Patients with uncontrollable BP's had the higher PRA's. (Reference 8)

Also of interest is the fact that captopril has been used with success in both dialysis patients and patients with moderate CRF (Figure 14).

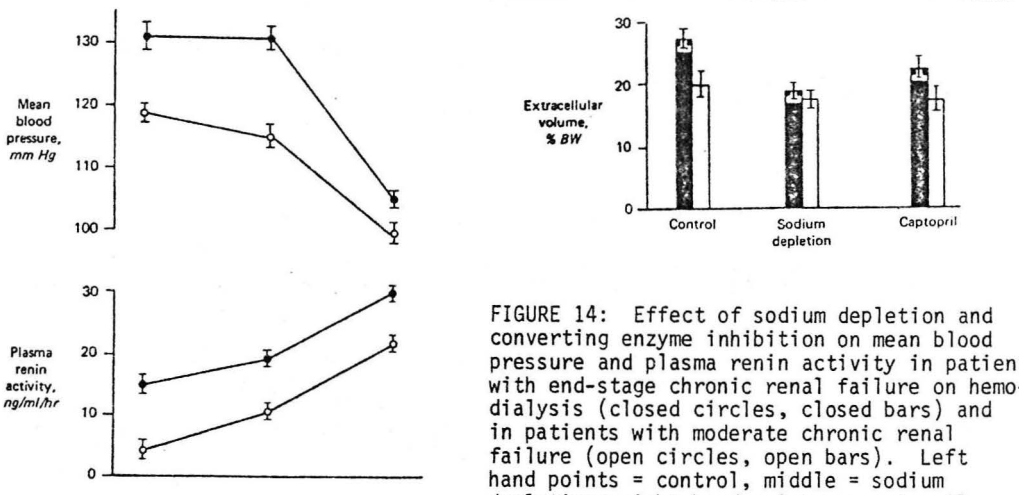


FIGURE 14: Effect of sodium depletion and converting enzyme inhibition on mean blood pressure and plasma renin activity in patients with end-stage chronic renal failure on hemodialysis (closed circles, closed bars) and in patients with moderate chronic renal failure (open circles, open bars). Left hand points = control, middle = sodium depletion; right hand points = captopril. (Reference 19).

Finally, it should be mentioned that the plasma concentrations of circulating catecholamines are also elevated in CRF and in dialysis patients. Patients with moderate CRF (Creatinine 2.4 mg/dl) were found to have supine (230 pg/ml) and upright (482 pg/ml) norepinephrine levels significantly greater than age-matched subjects without renal failure in one recent study (22). The possibility that these higher levels of norepinephrine may contribute to the elevated PVR in CRF hypertension was recently addressed by Buretta-Piccoli et al (23) who found that the threshold or pressor doses of norepinephrine decreased significantly in patients with renal failure (94 vs 134 ng/kg/min, respectively). Thus, these data provide evidence that these levels of norepinephrine may also contribute to the increased PVR in addition to the already mentioned expanded extra-cellular fluid volume and increased renin-angiotensin activity. Another consideration as a contributor to the increased PVR and hypertension in CRF is the fact that patients with CRF appear highly sensitive to the hypertensive effects of calcium. Although hypercalcemia is unusual in CRF, when present it represents a reversible cause of CRF. The enhanced sensitivity of the circulation to increments in calcium is depicted in Figure 15.

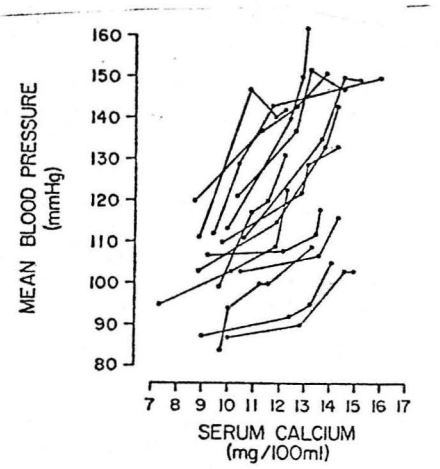


FIGURE 15: Relationship between total serum calcium concentration and blood pressure in renal failure patients.

B. Considerations in the Treatment of Hypertension in Uremia

Table 3 below lists several of the considerations which must be evaluated before a logical treatment plan can be individualized in the uremic, hypertensive patient.

The established factors have been considered previously in the hypertension section. It should be noted that patients with long-standing hypertension and renal failure may have abnormalities in the baroreflex limb of the autonomic arc; this leads to "de-afferentation" of the baroreceptor and a reflex increase in sympathetic tone (24,25). Such an increase may further contribute to an elevated PVR and cardiac output.

Table 3

PATHOGENIC FACTORS IN UREMIC HYPERTENSION

A. Established Factors
   Extracellular sodium
   Renin-angiotensin
   Aldosterone
   Calcium

B. Possible Factors
   Cardiovascular responsiveness
   Autonomic reflex arc and catecholamines

C. Hypothetical
   Vasodepressor prostaglandins or kinins

Given the described increment in ECF and its relationship to the increase in PVR which distinguishes hypertensive uremics from non-hypertensive uremics, the initial step in controlling blood pressure has involved volume reduction. In non-dialyzed patients with renal failure this goal is accomplished via diuretic administration and dietary sodium restriction. The use of furosemide is necessary with GFR's below 30 ml/min; metolazone may be used concomittantly to augment the natriuresis if necessary.

For dialyzed patients with hypertension, ultrafiltration (isotonic sodium and water loss via the dialyzer) controls the blood pressure in the majority of patients. Obviously, hypotension is a major problem in dialysis units when patients are too vigorously volume-depleted. This likely occurs because of a combination of factors; the volume depletion itself in patients with decreased cardiac reserve, the presence of autonomic insufficiency, the similtaneous decline in plasma osmolality which occurs on dialysis favoring intracellular water relocation, and, finally, the frequent use of sympatholytic anti-hypertensive drugs which blunt cardioaccelera-tory reflexes.

In patients with hypertension unresponsive to volume reduction, several choices are readily available. Table 4 depicts the current practice summarized from several

Table 4

Step 1
  A. Volume Reduction (ultrafiltration or furosemide ± metolazone)

Step 2
  A. β-Blockade
  B. Clonidine
  C. Methyldopa
  D. Calcium Antagonists

Step 3
  A. Hydralazine
  B. Prazosin

Step 4
  A. Minoxidil
  B. Captopril

sources. In patients with anginal syndromes as a prominent co-feature of hypertension, our practice is to utilize calcium β-blockers and antagonists as secondary therapies. If heart failure is co-existant, we avoid β-blockade and rely on clonidine and methydopa. Table 5 lists β-blockers presently available. Since most of our patients have renal function impairment, our preference is to use β-blockers metabolized by the liver (see Table 5) -

Drug	β_1-selective	Intrinsic sympathomimetic activity	Direct myocardial depression	Lipid solubility	Hepatic metabolism (%)	Significant activity of metabolites
Propranolol	-	-	+	High	99	Yes
Oxprenolol	-	+ +	+	Moderate	97	Probably not
Pindolol	-	+ + +	+	Moderate/low	60	No
Alprenolol	-	+	+	High	99	Yes
Timolol	-	-	-	Moderate	80	Yes
Sotalol	-	-	-	Low	40	No
Nadolol	-	-	-	Low	27	No
Acebutolol	+	+	+	Low	High	Yes
Metoprolol	+ +	-	-	Moderate	97	No
Atenolol	+ +	-	-	Low	< 10	No

Table 5

Some Properties of β-Blockers in Common Clinical Use

propranolol and metoprolol in particular. Table 6 is a guideline for β-blocker adjustment in renal insufficiency. Approximately 50% of males with creatinines $\geq$ 5 mg% are impotent, and methyldopa exascerbates this problem, limiting its utility. Hydralazine and (less frequently) prazosin have also been extremely valuable as antihypertensives. If a combination of these drugs fails, minoxidil therapy is nearly always effective when coupled with volume reduction. Captopril has been reported to be highly effective (14), although the side effect profile may be limiting with this drug.

One area of debate and interest which deserves particular comment is the long-term effects of β-blockade on renal function. Several reports have noted a 10-15% decline in both GFR and effective renal plasma flow (similar to RBF) in patients treated with propranolol (26-28). Most authors attributed this decline in kidney hemodynamics to the decline in cardiac output which accompanies the use of drugs. It is of interest, that in one report (28), depression of GFR and RBF persisted after discontinuation of propranolol. Another potential reason for the decline in GFR and RBF might be blockade of β_2 receptors (vasodilating function) with non-selective β-blockers (29). Early enthusiasm for nadolol as having a "sparing" effect on renal function (30) has wained considerably (31, 32).

Table 6

Drug	Half-life (h)		Dosage in renal failure GFR (ml/min)				Activity of metabolites which accumulate (%)	Plasma protein binding	Dialysability[a]
	normal renal function	uraemia	>50	35-50	15-35	<15 in renal failure			
Propranolol	2-4	2-3	Normal	Slight reduction	Slight reduction	Slight reduction	Yes	60-90	
Oxprenolol	2-3	2-3	Normal	Normal	Normal	Normal	Probably not	80	
Pindolol	3-4	3-4	Normal	Normal	Normal	Normal	No	40	
Alprenolol	2-3	2-3	Normal	Slight reduction	Slight reduction	Slight reduction	Yes	85	
Timolol	4-6	4	Normal	Slight reduction	Slight reduction	Slight reduction	Yes	Low	
Sotalol	13-17	42	Normal	Normal	50% dose	25% dose	—	No	Moderate
Nadolol	16-24	45	Normal	70% dose	50% dose	30% dose	—	25-30	High
Acebutolol	8[a]	>20[b]	Normal	70% dose	50% dose	30% dose	Yes	11-19	High
Metoprolol	2.5-4.5	2.5-4.5	Normal	Normal	Normal	Normal	Slight	12	High (metabolites)
Atenolol	6-9	127	Normal	Normal	50% dose	25% dose	—	6.16	High

Accordingly, the present available information suggests that β-blockade (selective and non-selective) may be expected to reduce GFR and RBF by 10-15%. Larger decrements in renal function may occur in patients with higher baseline GFR's and RBF's (31). In the great majority of patients, however, this reduction is minor, and must be weighed against the long-term benefits of blood pressure control. Finally, the question of persistance of these changes after therapy is discontinued is open at present.

III. Specific Uremic Cardiomyopathy

A. In vitro Studies

The ability of uremia to independently exert a negative influence on myocardial performance has been a much-debated, controversial topic in clinical medicine. Such a relationship between uremia and the heart seems plausible, given the ubiquitous effects of uremia on many organs. In particular, such basic abnormalities in cellular function as depressed activity of Na,K-ATPase, low cellular transmembrane potentials, and other derangements of intracellular composition accompany advancing renal failure (33,34). In 1822, Gaspard and Segalas independently noted that a cardiac death ensued if urine was infused into animals (35,36). Subsequently, the cardiotoxin in the infused urine was identified as potassium (37-39). As early as 1944, more sophisticated experiments utilizing the injection of uremic sera extracts into in vitro amphibian heart preparations were noted a decrease in contractility and an increase in arrhythmias (41). As shown in Table 7, the list of confounding variables which may affect heart function in uremia is huge; the problem has been to independently identify the importance of each factor.

Table 7

FACTORS POSSIBLY IMPLICATED IN THE MYOCARDIAL INVOLVEMENT OF THE UREMIC PATIENT

Systemic factors	Increase in peripheral resistance
	Arterial hypertension
	Decrease in peripheral resistance
	Anemia
	Arteriovenous fistula
	Fluid volume overload
	Hyporeninemia
	Involvement of the autonomous nervous system
	B_1 avitaminosis
	Augmentation of the pulmonary capillary permeability
Vascular factors	Coronary heart disease
	Atheromatosis (arterial hypertension, hyperlipidemia, increase of the phosphorus-calcium product)
	Anemia
	Permanent hypertension
"Metabolic," hormonal and other factors	Accumulation of uremic waste products
	Urea
	Creatinine
	Guanidinosuccinic acid
	Methylguanidine
	Other uremic toxins
	Accumulation of other substances or electrolytes
	Phenols
	Calcium, magnesium, potassium
	Phosphate
	Oxalate
	Cobalt
	Aluminum
	Acetate
	Hormonal and vitamin disturbances
	Hyperparathyroidism
	Catecholamine excess
	Avitaminosis
	Deficiency states and others
	Malnutrition
	Hypoxia
	Carnitine deficit
	Phosphorus deficit
	ATP deficit
	Iron deficit
	Cellular potassium depletion
	Decrease in Na-K-ATPase activity
	Viral contamination

The early experiments were followed by more recent in vitro work by Scheuer and Stezoski (42). These investigators utilized an isolated rat working heart system in which various concentrations of urea methyl guanidine, creatinine, and guanidinosuccinic acid were infused alone or in combination. Urea at 20, 10, and 2.5 mM all decreased the cardiac output response to increasing atrial pressure (Figure 16). A combination of urea 20 mM, creatinine 0.88 mM, and

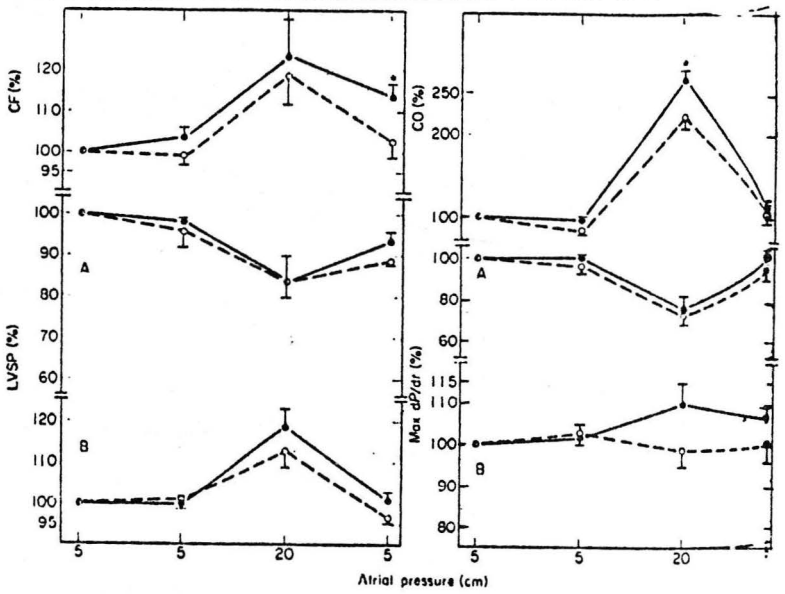
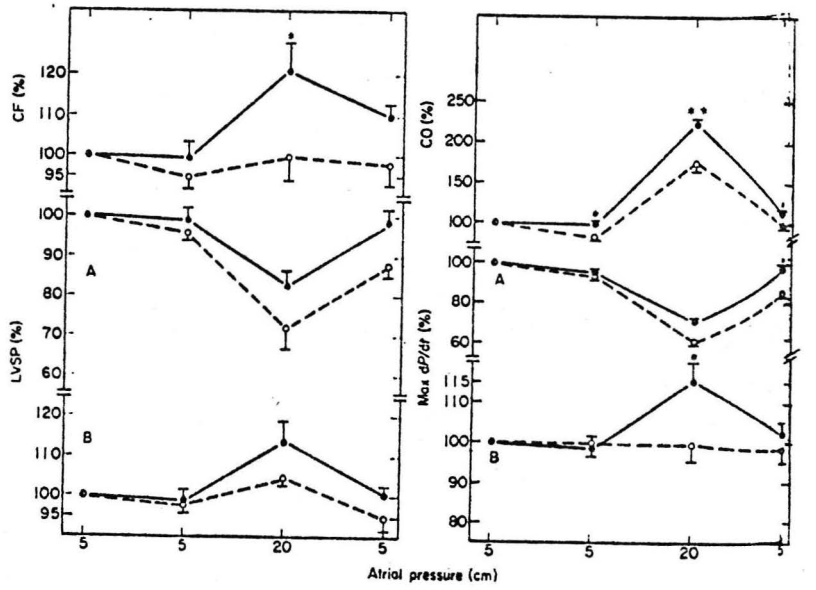


FIGURE 16: The effects of urea 20 mm (120 mg/100 ml) on cardiac dynamics. Perfusion during the initial and the final periods were in the absence of urea. Perfusion during the second and third periods was with urea for the experimental group. CF=coronary flow; CO=cardiac output; LVSP=left ventricular pressure; max dP/dt=maximum rate of left ventricular pressure rise. Panel A indicates LVSP and dP/dt during isovolumic beats, and panel B shows these variables during ejecting beats. Results are mean ± S.E. as percent of the initial 5 cm value. The number of hearts are shown in the parenthesis. *indicates $p<0.05$. (•) control 8; (o) urea, 11. Atrial pressures are in cm of perfusion medium, ventricular pressures are in mmHg. (Reference 42).

guanidinosuccinic acid 0.31 mM caused a depression in coronary flow, left ventricular pressure, and dP/dt; in addition, a rise in end diastolic pressure also occurred (Figure 17).

In addition to these studies in the isolated rat heart, isolated papillary muscle preparations have also been utilized. Lee and Downing (43) have studied the effects on phenol on developed tension (DT) and the maximal rate of tension development (max dT/dt) in samples obtained from piglets and cats. Phenol was

FIGURE 17: The effects of urea 20 mM, creatinine 0.88 mM, and guanidinosuccinic acid 0.31 mM on cardiac dynamics. The experimental design and format are the same as in Figure 16. ** indicates p<0.01 (•) control, 7; (o) uremic mixture, 8. Note difference in max dP/dt (lower left). (Reference 42)



selected for testing since it is known to accumulate in the plasma of uremic individuals and because of several known adverse effects of cellular function. For example, phenol is known to cause a marked increased in the permeability of lysosomal and mitochondrial membranes (44) in addition to causing reductions in ATP and DNA synthesis (45). Phenolic compounds are also recognized to uncouple oxidative phosphorylation in intact mitochondrial membranes (46). A dose dependent depression DT and dT/dt occurred at low phenol concentrations (< 12 mg%) in porcine moderator bands but not feline papillary muscles (Figure 18).

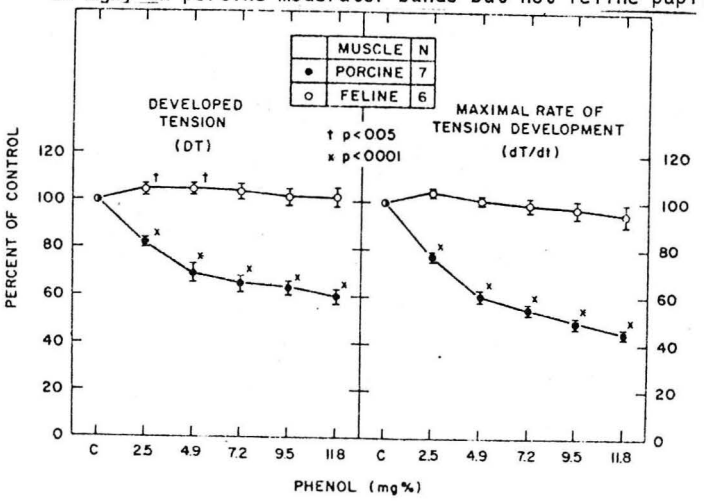


FIGURE 18: Dose-response curves for DT (left panel) and dT/dt (right panel) obtained from isolated porcine (closed circles) and feline (open circles) preparations showing effects of increasing phenol contractions. Vertical brackets indicate SE. Values for P refer to differences from initial control values (C). (Reference 43)

Higher concentrations of phenol did suppress feline papillary muscle DT and dT/dt, however (Figure 19).

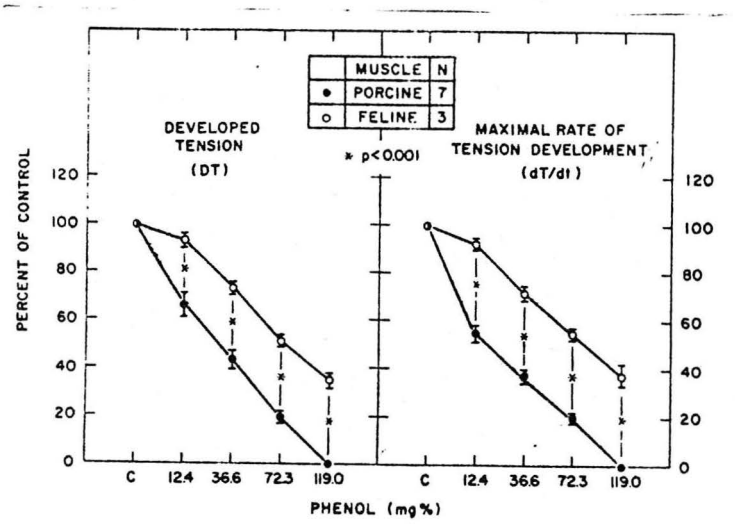
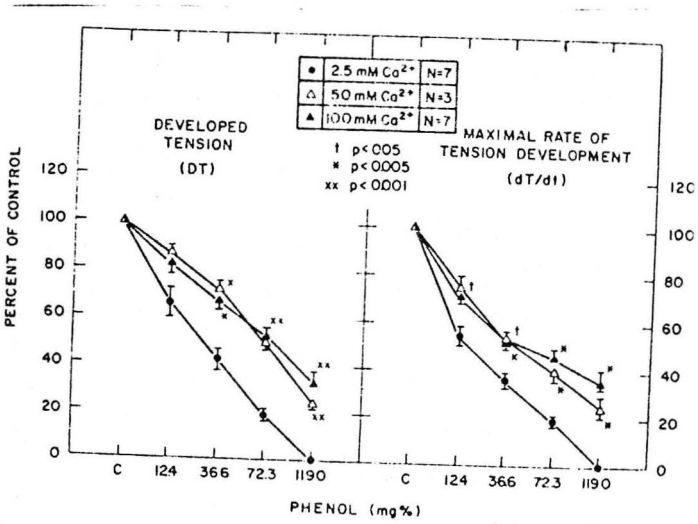


FIGURE 19: Dose-response curves for DT (left panel) and dT/dt (right panel) in isolated porcine (closed circles) and feline (open circles) muscle preparations using higher phenol concentrations range. Depression was significantly greater at all concentrations in pig, than in cat preparations. (Reference 43)

Of interest is the fact that an increase in calcium concentration in the bathing medium attenuated these negative inotropic effects (Figure 20).

FIGURE 20: Influence of external calcium concentration on the negative inotropic action of phenol in the isolated moderator band of the piglet. Vertical brackets indicate SE. Significance levels for differences at each phenol concentration compare 5.0 mM and 10.0 mM calcium with 2.5 mM concentrations. (Reference 43)



Finally, the addition of norepinephrine to the bathing medium also reduce the negative inotropic influence of phenol (Figure 21).

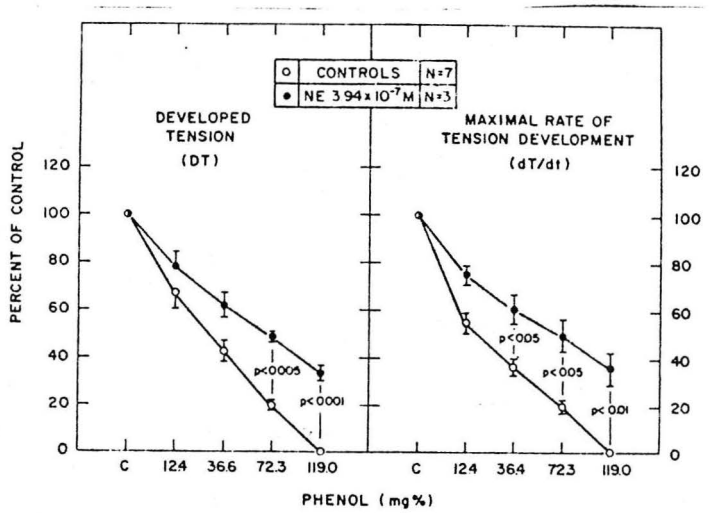


FIGURE 21: Influence of norepinephrine (NE) on the negative inotropic effects of phenol in the isolated moderator band of the piglet. Vertical brackets indicate SE. Contractile activity ceased at the highest concentration (open circles) but persisted in the presence of NE. (Reference 43)

The concentration of phenol in uremic humans is typically between 3-4%, a value less than most of the concentrations tested in the study. However, these experiments raise the possibility that phenol is able to induce a negative inotropic effect on isolated mammalian cardiac muscle. Further, an increase in extracellular calcium or the addition of norepinephrine were able to significantly attenuate this effect.

While most authors agree that left ventricular function is often abnormal in patients with renal failure, the convincing demonstration of a specific uremic cardiomyopathy in humans has not been achieved (47). An early observation by Bailey et al (48) suggested a low protein diet improved cardiac function in 4 patients with a syndrome consisting of a) cardiomegaly; b) gallop rhythm; c) high mean blood pressure; 4) pericarditis; and, e) arrythmias. However, the most dramatic improvement in these cases occurred after peritoneal dialysis was begun and blood pressure controlled. Hence, a clear association with uremic toxins was not made. In cases in which hypertension has not been present, but a dramatic reversal of cardiac function has been noted, a pericardial function rub has been present (49). In all of these reported cases, severe volume overload has also been a constant feature, and the institution of dialysis or successful transplantation has improved this parameter.

B. Parathormone as a Cardiotoxin

One intriguing possibility is that parathoromone is capable of acting as a direct cardiotoxin, independently of any changes in plasma calcium. Recent in vitro work by Drüeke's group has demonstrated a decrease in myocardial contractility in response to isoproterenol when parathormone is present (50-53) (Figure 22). In a recent study of 30 patients with advanced hyperparathyroidism,

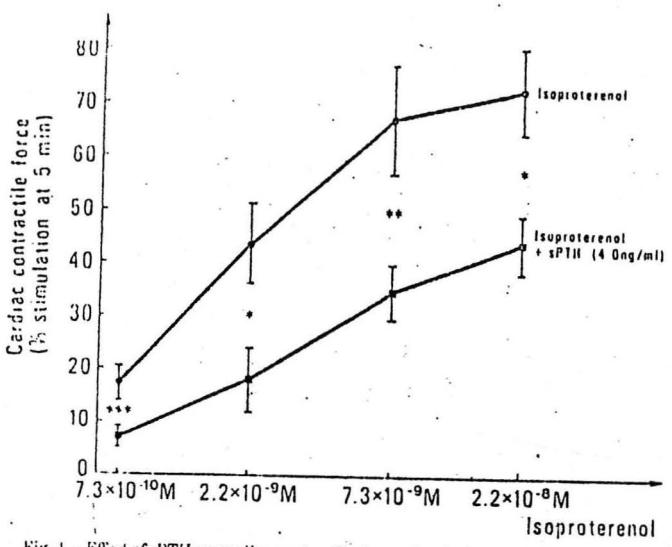


Fig. 1.—Effect of sPTH on cardiac contractile force stimulation produced by isoproterenol.

FIGURE 22: Effect of sPTH on cardiac contractile force stimulation produced by isoproterenol.

a series of non-invasive studies before and 1-2 weeks after parathyroidectomy were performed (54). Using both radionuclide angiocardiography and echocardiography, a significant increase in left ventricular ejection fraction was noted (see Tables 8 and 9 below). An augmented cardiac index and VCF (velocity of

Table 8
Radionuclide Left-Ventricular Performance & Blood-Volume Data Before & After Parathyroidectomy in 22 Patients

—	Heart rate (min^{-1})	Cardiac index ($ml.min^{-1}m^{-2}$)	LVEDV (ml)	LVESV (ml)	LVEF (%)	Blood-volume (ml)	Red-blood-cell space (ml)
Before parathyroidectomy	77·3±1·9	3623±198	152±7	77·5±6·8	50·6±2·7	4440±189	1100±107
After parathyroidectomy	80·9±1·7	3949±217	143±6	64·2±5·6	56·8±2·2	4380±251	1011±101
p*	NS	<0·05	<0·02	<0·005	<0·02	NS	NS

Results are mean ± SEM. NS = not significant.
* Student's paired *t* test.

Table 9
Echographic Left-Ventricular Performance Data Before & After Parathyroidectomy In 8 Patients

—	End-diastolic diameter (mm)	End-systolic diameter (mm)	Fibre shortening (%)	Ejection time (s)	Mean VCF	LVEDV (ml)	LVESV (ml)	LVEF (%)
Before parathyroidectomy	51·8±1·76	32·0±1·80	0·38±0·02	0·31±0·01	1·23±0·07	142±13·9	35·1±5·64	0·76±0·02
After parathyroidectomy	51·5±2·40	29·7±1·78	0·42±0·02	0·31±0·01	1·34±0·05	143±19·0	28·4±4·70	0·80±0·02
T*	18	1	1	4	1	17	1	1
p	NS	<0·05	<0·05	NS	<0·05	NS	<0·05	<0·05

Results are mean ± SEM.
*Wilcoxon's paired T test. NS=not significant.
VCF = Velocity of circumferential myocardial fibre shortening.

circumferential fiber shortening, an index of contractility) also significantly improved. Interestingly the improvements occurred despite a decline in plasma calcium concentration. These results were interpreted as showing a myocardial depressent effect of parathormone, either indirectly via intracellular calcium/phosphate change, via a direct effect.

The interaction between parathormone and myocardium has also been investigated by Massry's group (65). The workers found that both NH_2-terminal PTH and intact PTH produced an immediate and sustained signficiant rise in beat/min and earlier cellular death in rat heart cells grown in vitro. This effect was reversed if PTH was removed from the medium. The effect of intact PTH was greater than NH_2-PTH (Figure 23). The effect of PTH required calcium, was mimicked by calcium

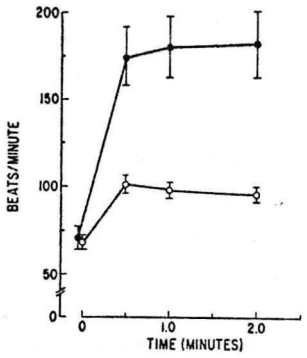
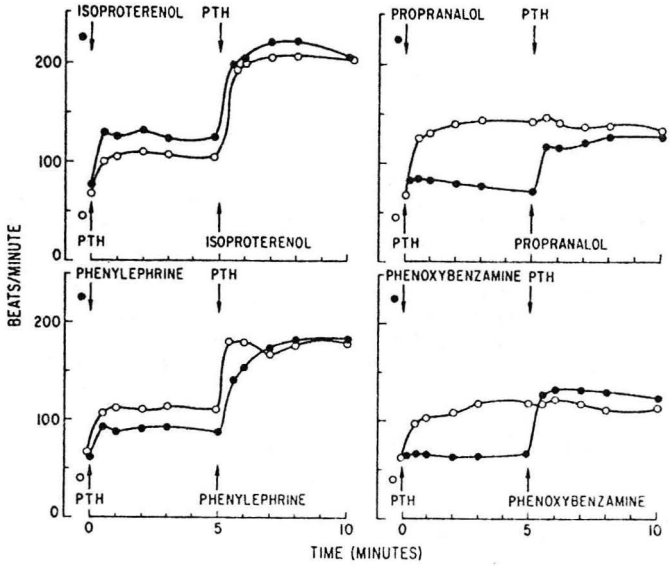


FIGURE 23: The effect of the intact molecule of PTH (1-84 PTH) and its amino-terminal fragment (1-34 PTH) on beating rates of heart cells in relation to time, after the addition of the hormone to medium containing the heart cells. • 1-84 PTH; o 1-34 PTH. (Reference 65)

ionophore, was prevented by verapamil, and was not abolished by α or β-adrenergic blockade. These relationships are shown in Figures 24 and 25. PTH action was

FIGURE 24: Representative studies depicting the interaction between PTH and α-(phenylephrine) and β-(isoproterenol) adrenergic agents and between PTH and α-(phenoxybenzamine) and β-(propranolol) adrenergic blockers and beating rates of heart cells. (Reference 65)



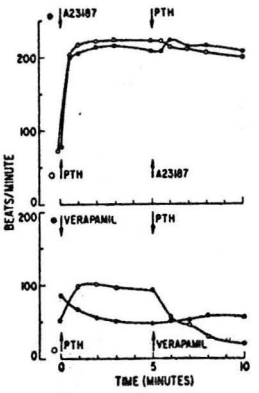
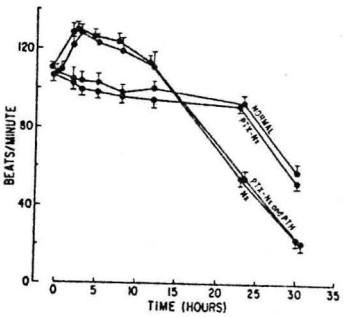


FIGURE 25: Representative studies on the interaction between PTH and calcium inophore A23187 (upper panel) and PTH and verapamil (lower panel) on the beating rates of heart cells. (Reference 65)

additive to α-adrenergic agonist and synergetic with a β-adrenergic agonist. Sera from uremic parathyroidectomized animals did not affect heart beats, but sera from uremic rats with intact parathyroid glands had similar effects to PTH alone (Figure 26). These observations were summarized as follows: 1) the

FIGURE 26: Representative experiment depicting the effect of sera from normal rats, nephrectomized (Nx) rats, parathyroidectomized-nephrectomized rats (PTX-NX), and PTX-NX rats treated with PTH (PTX-Nx and PTH). Each point represents the mean + SE of seven studies. (Reference 65)



heart cell is a target for PTH and may have PTH receptors; 2) PTH causes an increase in beating rate of heart cells and causes early death of cells; 3) PTH effect appears to be due to calcium entry into cells; 4) the locus of action through which PTH induces calcium entry is different from that for catecholamines; and 5) uremic sera have no effect unless they contain PTH. Thus, these investigations suggest that a major component of any uremic myocardiopathy must include PTH and that other accumulated toxins have no effect. These observations in vitro are congruent with Drüeke's clinical findings, however, ionized calcium declined in the patients after parathyroidectomy. Hence, for the observation to be correct, an increase in intracellular calcium would have to occur despite the decline in ionized calcium.

C. In Vivo Studies

Another approach to the question of the exist of a uremic cardiomyopathy is to examine the acute effects of hemodialysis on left ventricular function. One such study reported recently by Hung et al (55) was designed to assess the effects of dialysis in two groups of patients. Group A patients had a normal baseline ejection fraction whereas Group B patients had a low baseline ejection fraction. The patients were studied using radionuclide angiography to delineate changes in ejection fraction. The results of the study are summarized in Figure 27 below.

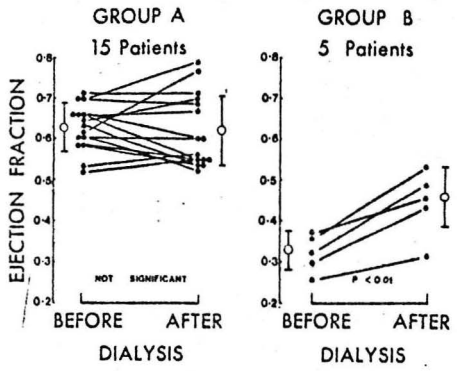


FIGURE 27: Ejection fraction before and after dialysis. Values are expressed as mean + 1 S.D. The P value in group B is of mean values. (Reference 55).

The conclusions from this study were that in patients with clinical signs of heart failure radionuclide angiography can separate patients with normal LV function from those with abnormal LV function. One issue not resolved by these studies is the effect of volume reduction per se, since the improvement in LV function from those with abnormal LV function in Group B patients occurred in the setting of weight removal on dialysis.

Another recent study using echocardiography reached a similar series of conclusions (56). Group 1 of this report consisted of patients with normal VCF's (velocity of circumferential fiber shortening, and index of myocardial contractility) before dialysis; Group 2 were patients with abnormally depressed VCF's. As shown in Figure 28 below, dialysis induced a significant fall in ventricular volumes in both groups of patients.

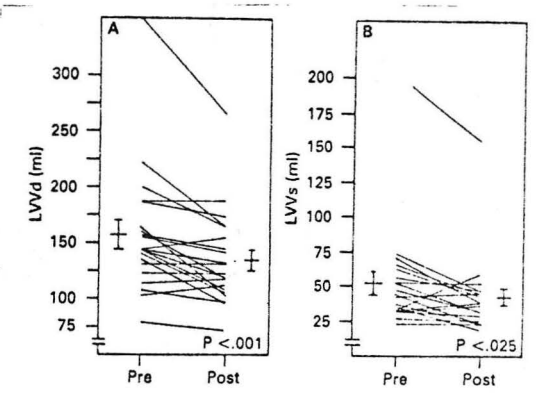


FIGURE 28: Influence of dialysis upon left ventricular volumes. Values for left ventricular end-diastolic (panel A) and left ventricular end-systolic (panel B) volumes are illustrated for pre and postdialysis periods. LVVd= left ventricular end-diastolic volume; LVVs=left ventricular end-systolic volume. (Reference 56)

However as depicted in Figure 29, a significant increase in VCF occurred in patients with a depressed VCF pre-dialysis (Group 2 patients)

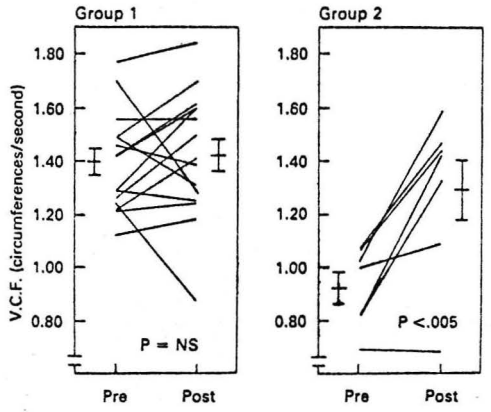
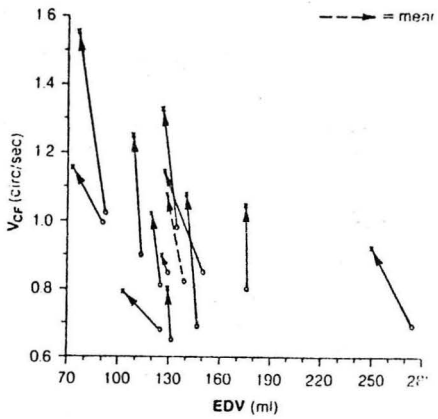


FIGURE 29: Influence of dialysis upon mean circumferential fiber shortening (VCF) is illustrated in Group 1 (15 patients with normal predialysis mean VCF) and Group 2 (7 patients with abnormal predialysis mean VCF) for pre-and post dialysis periods. (Reference 56)

A similar conclusion was reached by Fernando et al (57), who found an improvement in LV function (as determined by an increase in VCF) in volume depletion dialysis. (Figure 30, below).

FIGURE 30: Improved cardiac function, reflected by increased velocity of circumferential shortening (V_{cf}) was seen despite a fall in left ventricular end-diastolic volume (EDV) in each patient. (Reference 57)



The unanswered question in each of these studies was the independent contribution of volume removal to these improvements in LV function. This question had been left unresolved by several other good studies in the literature (58-62).

We recently attempted to anwer this question in a series of studies designed to separate the effects of volume from those dialysis (63,64). In the first of these studies, 5 stable patients without clinical evidence of coronary artery disease were evaluated with 2-D echocardiography before and after 3 dialysis procedures. Each patient was studied at 3 different cardiac filling volumes (pre-loads); Normal (supine), increased (head-down tilt), and decreased (produced by lower body negative pressure). Maneuver 1 was regular dialysis with volume loss (essentially a repeat of the prior studies); maneuver 2 consisted of volume loss only (no dialysis); and maneuver 3 consisted of dialysis, but no volume loss. The effects of these 3 maneuvers in LV function are depicted in Figures 31, 32, and 33 below.

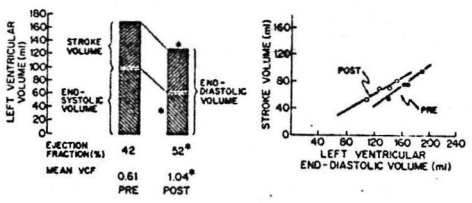
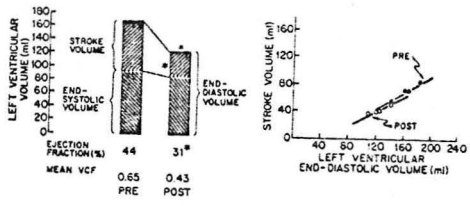


FIGURE 31: Regular dialysis with volume loss. A new ventricular function curve, but a loss of volume occurred. (Reference 63)

FIGURE 32: Volume loss only. No improvement in contractility; only a loss of volume. (Reference 63)



As noted previously, regular dialysis with volume removed was seen to improve VCF and ejection fraction despite significant decreases in cardiac filling volumes. As can be seen on the right of the figure, a new ventricular function curve was inscribed despite the reduction in filling volumes. When the effects of volume loss alone were tested in Maneuver 2 (Figure 32 above,) ventricular volumes were reduced, but VCF and ejection function were not increased; the ventricular function curve was unchanged.

Finally, when the effects of dialysis per se were tested in the final

maneuver in which no volume loss occurred (Figure 33 below), VCF and ejection fraction were markedly enhanced. Note that again a different LV function curve is described after dialysis. Thus dialysis was clearly associated with an improvement in the contractile state of the LV; the net effects of dialysis are the sum of the volume changes and these changes are LV contractility.

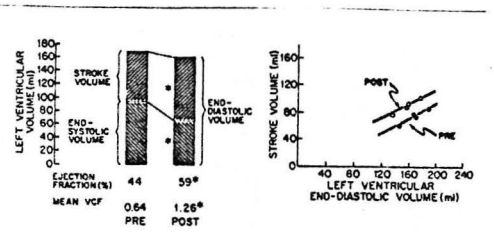


FIGURE 33: Dialysis but no volume loss. A significant increase in contractility, and new ventricular function curve results. (Reference 63)

A remaining obvious question is why did the improved contractile state occur? Among the most likely explanations are that dialysis reduces negative inotropic effects of uremia itself, an increase in ionized calcium occurs (a known effect of dialysis), or that an increase in the plasma bicarbonate concentration occurs (with a resultant improvement in pH and contractile state). To answer this question, another series of 3 dialysis maneuvers were performed in 8 stable dialysis patients. Special dialysis baths were prepared to examine these 3 variables; no volume was removed from the patients to eliminate the confounding effects of a reduction in LV volume. In the first dialysis maneuver, neither ionized calcium nor bicarbonate were allowed to increase, this test examined the effects of uremic toxin removal alone. In the second dialysis maneuver, ionized calcium increased, but bicarbonate was held constant. In the last maneuver, plasma bicarbonate concentration increased but ionized calcium did not. Changes in cardiac filling volumes are shown in Table 10 below, and VCF changes in Figure 34.

Table 10
(Reference 64)

CHANGES IN CARDIAC FILLING VOLUMES WITH EACH MANEUVER

		Maneuver 1		Maneuver 2		Maneuver 3	
		pre	post	pre	post	pre	post
End-Diastolic Volume (ml)	$\bar{x}$	158	157	161	152	157	154
	SE	7	7	8	8	7	6
	p	NS		<.02		NS	
End-Systolic Volume (ml)	$\bar{x}$	73	73	76	60	75	73
	SE	6	6	6	5	6	5
	p	NS		<.001		NS	
Stroke Volume (ml)	$\bar{x}$	85	85	84	92	82	81
	SE	5	5	6	7.3	5	4
	p	NS		<.05		NS	

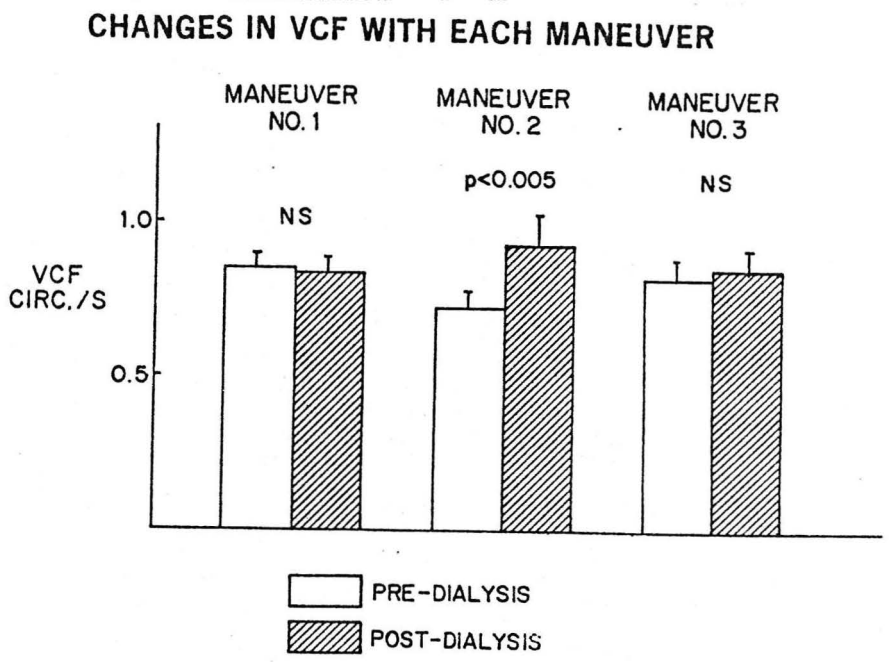


FIGURE 34: Only with an increase in ionized calcium concentration (Maneuver No. 2) did contractility improve. (Reference 64)

As can be appreciated, only when ionized calcium increased (from 4.4 to 5.4 mg/dl) did LV volumes decrease, stroke volume increase, and VCF increase. This result suggested that the rise in ionized calcium is a major key to the observed improvement in myocardial contractility. Whether or not this positive effect involves acute suppression of parathormone is open at present. These studies also provide evidence against a specific negative inotropic effect of a uremic toxin. However, it is possible a positive effect of dialysis alone might be seen in the setting of acute uremia or with more vigorous dialysis.

In summary, although dialysis clearly improves myocardial contractility in chronic uremia, the mechanism of improvement involves an increase in ionized calcium. The removal of uremic toxins (such as is accomplished in a single dialysis) does not have an independent improving effect. The role of PTH in this process is unclear at present, but *in vitro* work supports the hypothesis that PTH promotes an adverse cellular effect, again via changes in intracellular calcium concentration. Clinical studies in which the issue of PTH is the focus will help settle its importance. Additionally, studies of LV functions in acute uremic states are needed before a negative inotropic effect or uremia *per se* is excluded. Thus, while *in vitro* studies have provided evidence in animal of a clear-cut negative inotropic effects of toxins present in uremia, the demonstration of a specific uremic cardiomyopathy in humans has not been established.

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