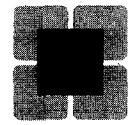

Cardiovascular disease in patients with chronic renal failure

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■ Most major medical centers are frequently involved in the care of patients with kidney disease. Currently available treatment modalities have prolonged patient survival and in most instances improved the quality of life. However, patients with chronic renal failure are prone to pericardial, myocardial, valvular, and coronary artery disease; 60% of deaths in patients undergoing chronic hemodialysis are the result of cardiovascular disease. This paper reviews the cardiovascular abnormalities common to patients with chronic renal failure.

□ INDEX TERMS: CARDIOVASCULAR DISEASES; KIDNEY FAILURE,CHRONIC □ CLEVE CLIN J MED 1988; 55:521–530

EFFECTIVE dialysis techniques and kidney transplantation have improved the long-term prognosis of patients with chronic renal disease. However, in patients undergoing dialysis, particularly chronic hemodialysis, cardiovascular disease develops with a higher incidence than the age-adjusted expected rate. Clinical observation and pathologic findings at autopsy indicate that the heart may be widely affected, with abnormalities of the pericardium, myocardium, valvular structures, and coronary vasculature.[1] Furthermore, cardiovascular mortality is significantly increased in patients with chronic renal failure.[2]

As an increasing number of patients with chronic renal failure become candidates for hemodialysis and kidney transplantation, factors contributing to the development and progression of cardiovascular disease will become increasingly important.

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ALTERATIONS IN NORMAL CARDIOVASCULAR PHYSIOLOGY

Patients with chronic renal failure develop a number of complex alterations in cardiovascular physiology as a result of their primary disease state and treatment. Chronic salt and water retention, anemia, hypertension, abnormalities of the neurocardiac regulatory system, and the creation of arteriovenous (AV) fistulae each contribute to this altered state.[3–7]

PERICARDIUM

Pericarditis

In the past, pericarditis was considered a "preterminal event" caused by urea, creatinine, and toxins that accumulated in the serum of patients with markedly reduced or absent renal function. It has become evident that pericarditis may develop in patients undergoing effective long-term hemodialysis in whom serum concentrations of nitrogenous by-products are relatively well controlled. However, modern dialysis techniques have indeed helped decrease the overall incidence of pericarditis in patients with chronic renal failure.[8–10]

The diagnosis of acute pericarditis can frequently be

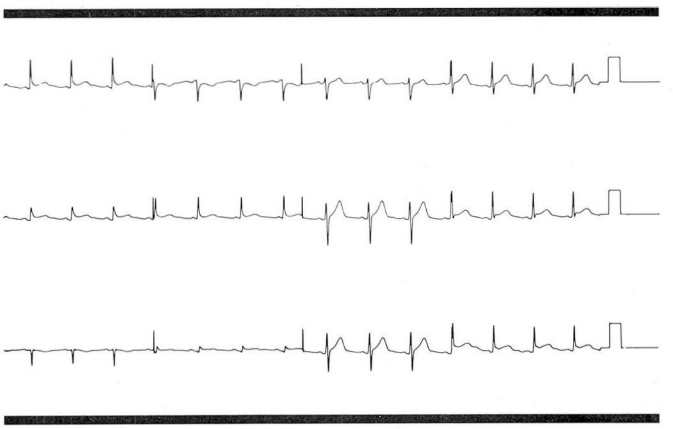


FIGURE 1. ECG tracing during acute pericarditis in a 49-year-old man with chronic glomerulonephritis and substernal chest pain of three days duration. Note diffuse "concave upward" ST segment elevation and PR segment depression.

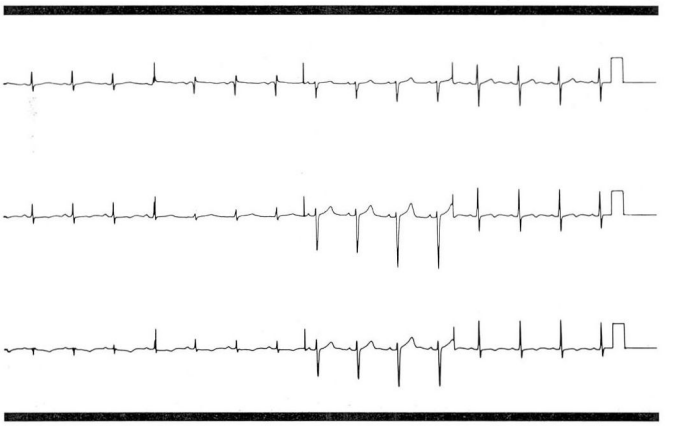


FIGURE 2. ECG tracing in pericarditis (subacute pattern) in the same patient as Figure 1, six weeks later. Symptoms have completely resolved; however, T wave inversions are present in leads II, III, aVF, V_5, and V_6.

made on the basis of historical and clinical information. A pericardial friction rub can be auscultated in up to 90% of cases.[8] Chest pain is a less common finding and may frequently be difficult to distinguish from the pain of myocardial ischemia. Large series indicate that up to 50% of patients with pericarditis are, in fact, asymptomatic.[8–11]

The increased incidence of pericarditis in patients with chronic renal failure, while well recognized, remains unexplained. However, it is clear that a linear relationship between the serum levels of nitrogenous byproducts and the development of pericarditis does *not* exist. The contribution of "uremic toxins" has been studied. Giovannetti et al[13] suggested that methylguanine, a low-molecular-weight substance ineffectively cleared in states of renal dysfunction, may be responsible. Others[14] have implicated "middle molecules." While the precipitation of uric acid within the pericardium has been postulated,[8] its actual presence has not been confirmed.[15,16]

Comty et al[17] were the first to suggest a relationship between parathyroid overactivity and pericarditis. Other investigators[8] have shown that patients in whom pericarditis develops have higher levels of parathyroid hormone (PTH), calcium, phosphorus, and calcium-phosphorus product than patients without pericarditis. Makó et al[18] studied 130 patients undergoing chronic intermittent hemodialysis. Marked bone abnormalities, as assessed by radiographic and densitometric methods, were observed more frequently in patients in whom pericarditis developed.

Outbreaks of viral pericarditis have been documented in patients undergoing chronic hemodialysis.[19] Whether cytomegalovirus, a common pathogen in this patient population, is capable of causing chronic, recurrent pericarditis remains to be determined. Sporadic cases of purulent pericarditis secondary to various bacteria (particularly *Staphylococcus aureus*), fungi, and atypical mycobacteria have been reported.[20,21]

The clinical recognition of polyserositis (pericarditis, pleuritis, and peritonitis) in a subset of patients with end-stage renal disease, together with the kidney's role in removing circulating immune complexes with antigen excess,[22,23] has led investigators to explore immune-mediated mechanisms of serosal inflammation. Twardowski et al[24] detected circulating immune complexes in 71 dialysis patients with chronic renal failure. Patients with pericarditis were more likely to have elevated serum titers.

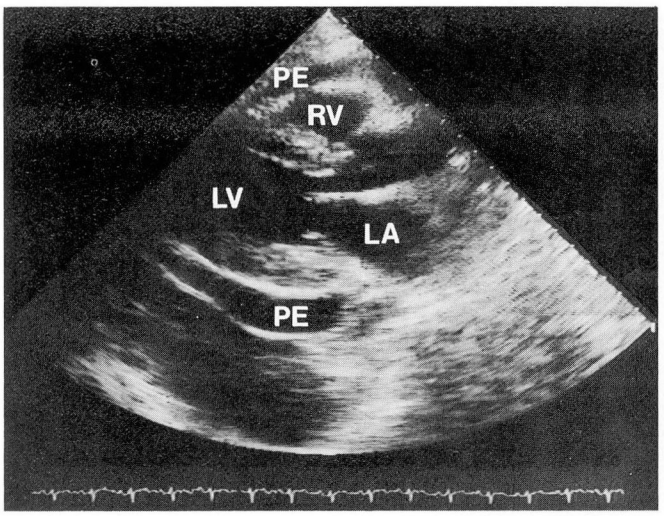
Hydralazine, diphenylhydantoin, procainamide, and minoxidil[25] have been responsible for cases of drug-induced pericarditis in this patient population.

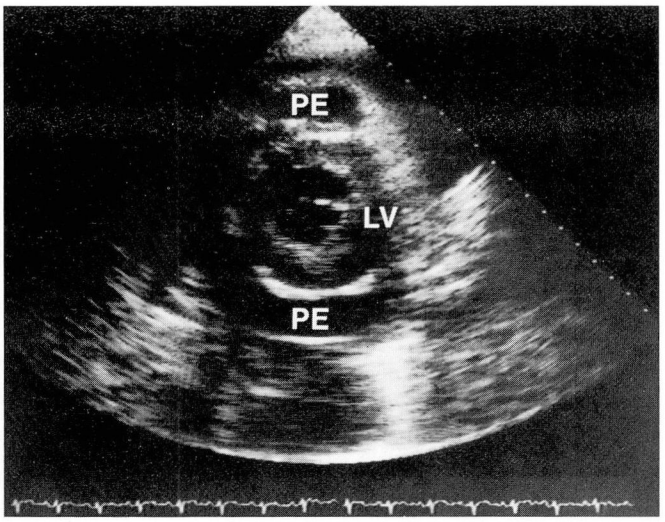
The characteristic electrocardiographic (ECG) abnormality observed in acute pericarditis is diffuse ST segment elevation. The ST segment is classically "concave upward," which helps distinguish it from the "convex upward" appearance in acute myocardial infarction (*Figure 1*). Nonspecific ST-T wave changes may be seen in resolving (subacute) pericarditis (*Figure 2*). However, on occasion the ECG may be entirely normal, particularly in cases of chronic pericarditis.

Treatment

Pericarditis developing in the early stages of newly diagnosed or inadequately treated renal failure is treated with dialysis. Most patients within this subgroup re-

A,B
C





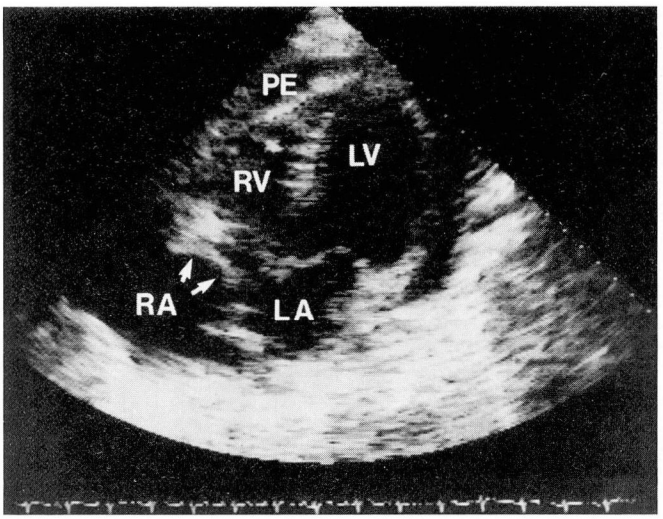


FIGURE 3A. Two-dimensional echocardiogram, parasternal long-axis (*PLA*) view, of a patient with a large pericardial effusion. Pericardial effusion (*PE*), left ventricle (*LV*), left atrium (*LA*), right ventricle (*RV*). FIGURE 3B.Pericardial effusion as seen in a short-axis (parasternal cross-sectional) view at the level of the mitral valve. FIGURE 3C. Pericardial tamponade: Apical four-chamber view showing collapse (arrows) of the right atrial free wall (*RA*) during diastole.

spond adequately within two weeks. Rarely, complete resolution requires up to two months.[8] Temporary peritoneal dialysis has been advocated by some authorities to avoid systemic heparinization and the risk of hemopericardium. However, most studies have shown hemodialysis with regional heparinization to be both safe and effective.[8]

In contrast to pericarditis occurring in the acute stages of renal failure, pericarditis in the setting of chronic intermittent dialysis responds poorly to intensification measures; reported series show an overall response rate of less than 50%.[8,10,26]

When dialysis alone is ineffective, anti-inflammatory agents such as indomethacin may be beneficial.[27] Corticosteroids may also be effective in relieving pericardial inflammation, however, caution must be observed when resorting to such therapy. Occasionally, drainage of pericardial fluid may be indicated as both a diagnostic and therapeutic measure.[28] Diagnostic pericardiocentesis is particularly warranted when a diagnosis of purulent pericarditis is being considered.

Cardiac tamponade

A feared complication of pericarditis is cardiac tamponade.[29,30] The primary causes of this condition in patients with chronic renal failure are serous pericarditis, hemorrhagic pericardial effusion, and collagenization of a pericardial exudate.[31] Regardless of the etiology, cardiac tamponade is a potentially life-threatening condition that must be recognized and treated appropriately (*Figure 3*).

Once the diagnosis of cardiac tamponade has been established, the hemodynamic and overall clinical status of the patient should dictate initial therapy. Patients with acute hemodynamic compromise should undergo emergent pericardiocentesis as a life-saving maneuver. However, patients who are able to maintain an adequate cardiac output may fare better with a definitive surgical drainage procedure.[32,33] Surgical drainage of the pericardium can be achieved by a number of techniques. Like pericardiocentesis, tube pericardiostomy is a temporary measure that may be life-saving. In addition, it is the treatment of choice for draining a purulent pericardial effusion. Creation of a "pericardial window" (partial pericardiectomy) through a left anterior thora-

TABLE 1
FACTORS IMPLICATED IN "UREMIC" CARDIOMYOPATHY

Metabolic
Catecholamine excess
ATP deficit
Carnitine deficiency (acquired)
Malnutrition
Uremic toxins
Urea
Creatinine
Phenols
"Middle molecules"
Endocrinologic
Hyperparathyroidism
Electrolytes
Calcium excess
Magnesium excess
Phosphorus excess
Systemic
Hypertension (chronic)
Anemia (chronic)
AV fistulae
Atherosclerosis
Autonomic insufficiency
Amyloidosis

cotomy allows complete removal of all pericardial fluid and allows digital fracture of pericardial adhesions as well.[32] Anterior phrenic to phrenic pericardiectomy via a median sternotomy is usually reserved for the treatment of patients with constrictive pericarditis.[31,32]

MYOCARDIUM

Patients with chronic renal failure frequently exhibit signs of myocardial dysfunction. Structural and functional abnormalities have been studied, both invasively and noninvasively, to define adaptive and maladaptive hemodynamic responses of the heart to chronic renal insufficiency. Drüeke et al[8] performed right- and left-sided heart catheterization on 10 patients with chronic renal failure. The mean patient age was 41.9 years and all had received maintenance hemodialysis for at least two years. Left ventricular dilatation and global dysfunction were commonly observed. Other investigators have noted similar findings in both symptomatic and asymptomatic patients.[34–38]

Systemic hypertension is common in this patient population. While it is well known that poorly controlled hypertension may result in a thickened, noncompliant left ventricle, its role in the development of abnormal systolic function remains undefined.[9]

Ikäheimo et al[39] performed M-mode and two-dimensional echocardiography on 41 patients undergoing

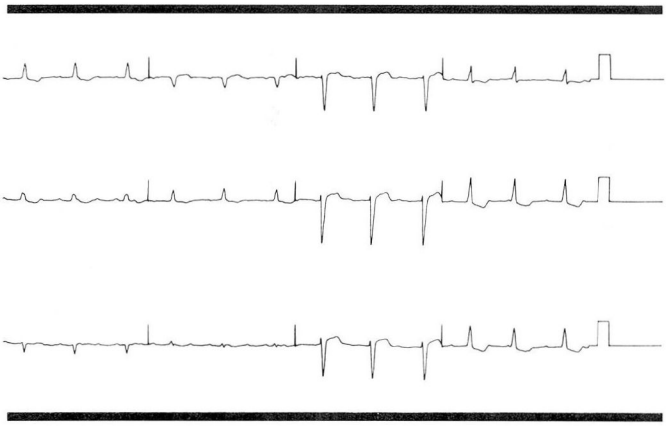


FIGURE 4. ECG in digitalis toxicity in a patient with chronic renal insufficiency. Atrial tachycardia with AV dissociation.

chronic intermittent hemodialysis; 31 patients were receiving treatment for systemic hypertension and the remaining 10 were normotensive. Although left ventricular wall thickness was increased in the hypertensive group, the overall left ventricular systolic function, as determined by percent fractional shortening, did not differ. Other investigators likewise have not been able to identify a direct correlation between systemic blood pressure and myocardial contractility.[40]

Uremic toxins

The search for a "uremic toxin" capable of suppressing myocardial function continues, with only indirect evidence to support its existence at the present time. Uraoka et al[41] divided patients with chronic renal failure into those with (Group I) and without (Group II) clinical evidence of circulatory congestion. There was no difference between groups in either plasma volume or thermodilution cardiac output. However, following hemodialysis, Group I patients were found to have a significant increase in cardiac output despite a similar decrease in plasma volume. While the author was quick to point out that a favorable shift on the Starling curve may explain this observation, a dialyzable myocardial suppressant could not be excluded. Vaziri and Prakash[42] observed similar findings.

A study by Nixon et al[43] provided further support for the presence of a "uremic toxin." Five hemodialysis patients with stable disease were studied echocardiographically before and after three separate dialysis regimens: hemodialysis with volume loss, ultrafiltration alone, and hemodialysis without volume loss. Hemodialysis with volume loss resulted in a decrease in both end-systolic and end-diastolic volumes without a

change in stroke volume. Ultrafiltration (pure volume loss) caused a decrease in end-diastolic volume and stroke volume, while hemodialysis without volume loss was shown to increase stroke volume, ejection fraction, and velocity of fractional shortening. Madsen et al[44] have shown a similar response to dialysis in the absence of significant left ventricular chamber enlargement. A number of potential toxins responsible for the myocardial dysfunction seen in patients with chronic renal failure have been investigated. Plasma catecholamine levels are increased in patients with end-stage renal disease with and without overt myocardial dysfunction.[45] Norepinephrine has been shown to cause myocardial necrosis under experimental conditions.[46,47] Miach et al[45] studied 22 hemodialysis patients with evidence of left ventricular dysfunction. Fractional shortening was found to correlate inversely with plasma catecholamine levels. Bernardi et al[49] observed a direct correlation between plasma norepinephrine levels and the presence of asymmetric septal hypertrophy.

Secondary hyperparathyroidism has been associated with the development of myocardial dysfunction. Hypercalcemia, hyperphosphatemia, and an elevated calcium-phosphorus product can cause metastatic calcification of the myocardium, which results in complete loss of myocardial cross-striations[50,51] and a global decrease in function.

A complete list of factors reported to affect myocardial function in patients with chronic renal failure is provided in *Table 1*.[52–55]

Conduction disturbances

Abnormalities involving the conduction system of the heart are not uncommon in patients with chronic renal failure, particularly those undergoing intermittent hemodialysis. Metastatic calcification frequently involves the conduction system and may present with high-grade atrioventricular (AV) block.[56] In addition, coronary artery disease is frequently seen in this patient population and may cause conduction disturbance either on a transient (ischemic) basis or permanently as a result of myocardial infarction. Atrophy and myocytolysis of the conduction system from long-standing extreme malnutrition[57] may rarely be a contributing factor.

Hyperkalemia has been reported to cause first-, second-, and third-degree AV block, intraventricular conduction delay, and intermittent Wolff-Parkinson-White syndrome.[58] Appropriate treatment of the hyperkalemia corrects the conduction abnormality unless an underlying problem persists.[56,59]

Arrhythmias

As with conduction disturbances, arrhythmias may result from intrinsic heart disease and/or metabolic derangements. Premature supraventricular and ventricular complexes are common.[60] Complex ventricular ectopy (multiform PVCs, couplets, and ventricular tachycardia) may also be seen on continuous, 24-hour Holter monitoring.[60] Vagal-mediated bradycardia has been reported in patients undergoing peritoneal dialysis.[61] Bradyarrhythmias may also be ischemic in origin or drug-related.[62]

Electrolyte abnormalities are frequently encountered in patients with impaired renal function, and dialysis may either accentuate pre-existing problems or create new ones via rapid fluctuation of serum electrolyte levels. Hypokalemia, with or without concomitant digitalis intoxication, can provoke an extensive array of rhythm disturbances including premature supraventricular complexes, atrial tachycardia with/without AV block, atrial fibrillation, atrial flutter, junctional tachycardia, premature ventricular contractions, ventricular tachycardia, and ventricular fibrillation (*Figure 4*). Severe hyperkalemia has been associated with ventricular standstill, ventricular tachycardia, and ventricular fibrillation. Hypercalcemia (>13.5 mg/dL) is capable of causing sinus bradycardia and sinus arrest in addition to potentiating the arrhythmogenic effects of hypokalemia and digitalis intoxication. Hypocalcemia, when severe (<6.0 mg/dL), may prolong ventricular repolarization sufficiently to predispose to ventricular tachycardia of the torsade de pointes variety.

Hypomagnesemia (<1.5 mg/dL) may cause premature ventricular complexes. On rare occasions, ventricular tachycardia or ventricular fibrillation is provoked, particularly in the setting of ischemia or digitalis intoxication.

ECG abnormalities

Electrocardiographic (ECG) changes in patients with chronic renal failure reflect both cardiac and metabolic abnormalities. ST and T wave changes may be observed with pericarditis, ischemia, myocardial infarction, and ventricular hypertrophy. Pathologic Q waves most commonly represent a previous transmural myocardial infarction. However, they may also be found in cases of end-stage dilated cardiomyopathy, marked left ventricular hypertrophy, obstructive cardiomyopathy, and rarely, in the setting of marked hyperkalemia.[63,64] Other ECG changes seen with hyperkalemia include peaked T waves (serum potassium, 5.5–7.5 mEq/L), absent P waves, ST segment depression, increased QRS duration,

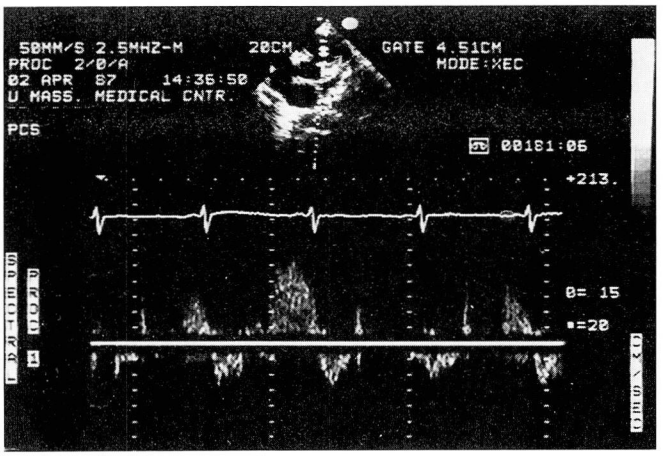


FIGURE 5. Pulsed Doppler echocardiogram at the level of the pulmonic valve showing pulmonic insufficiency. Sample volume is proximal to valve with diastolic blood flow toward the transducer.

and decreased R wave amplitude (7.5–10.0 mEq/L). Severe hyperkalemia (>10.0 mEq/L) may cause the classic "sine wave" pattern.[5] In clinical practice, treatment of hyperkalemia should be instituted upon its recognition. However, emergent reduction of serum potassium concentration is required for levels >7.5 mEq/L given the adverse effect on conduction and predisposition to lethal ventricular arrhythmias.

Hypokalemia (<3.0 mEq/L) is characterized by ST segment depression, T wave flattening, U wave prominence, and merging of the T and U waves simulating Q-T segment prolongation. Hypocalcemia may cause QTc prolongation, primarily due to lengthening of the ST segment. Hypomagnesemia may cause similar ECG alterations. Hypermagnesemia (>4.5 mg/dL) is characterized electrocardiographically by P-R and QRS prolongation. Similar changes may be observed in hypercalcemia with the addition of QTc shortening and T wave flattening.

ENDOCARDIUM

Valvular abnormalities

Autopsy studies involving patients with end-stage kidney disease frequently reveal mitral valve thickening and shortening of the chordae tendineae. The overall appearance is similar to that found in rheumatic valvular disease with the exception of commissural fusion.

Abrahams et al[65] reported calcification of the mitral apparatus (valve leaflets, anulus, chordae, and papillary muscles). Forman et al[66] analyzed biochemical, hemodynamic, and echocardiographic data in 168 patients with chronic renal failure undergoing intermittent hemodialysis. The overall incidence of mitral anular calcification was 9.5%, its presence directly correlating with serum calcium, phosphorus, and calcium-phosphorus product. Metastatic calcification of the mitral anulus from uncontrolled secondary hyperparathyroidism may cause progressive mitral stenosis and/or regurgitation.[67] Other cardiovascular complications associated with a calcified mitral anulus include endocarditis, arterial emboli, and variable degrees of atrioventricular (AV) conduction block.[68]

Chronic pulmonic insufficiency, while rarely of clinical significance, is frequently detected during Doppler echocardiographic evaluation. Many of these patients have a diastolic decrescendo murmur upon auscultation, which in the past was attributed to aortic insufficiency[69-72] (*Figure* 5).

Infective endocarditis

It has been recognized since the days of Sir William Osler[73] that valvular abnormalities predispose to infective endocarditis. In addition, certain bacterial organisms such as *Staphylococcus aureus* are capable of infecting previously undamaged valves.[74]

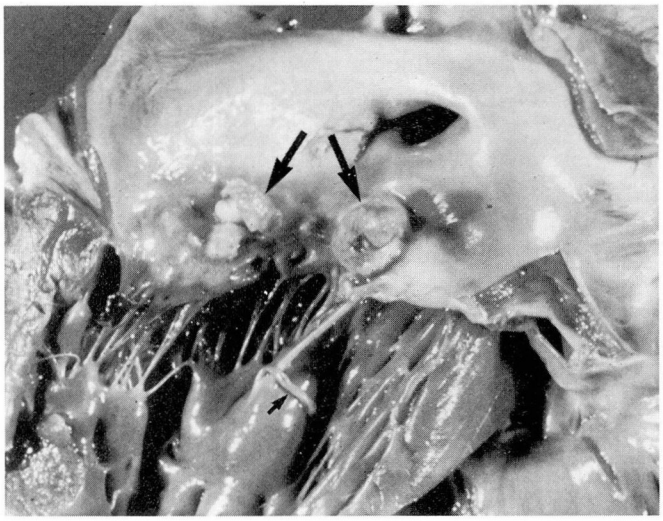
The overall incidence of infective endocarditis has increased over the past two decades. This increase has been attributed, in part, to an increase in the number of patients undergoing long-term maintenance hemodialysis.[75,76] It is known that patients with chronic renal failure have an increased susceptibility to infection,[77,78] and endocarditis is a recognized sequela[79,80] (*Figure* 6). Further, the "high output" state characteristic of long-standing renal insufficiency has been shown to cause valvular lesions that may serve as a nidus for infection.[81]

Clinicians must be aware that "textbook" signs and symptoms of infective endocarditis may be absent or masked in this subset of patients. Fever may not be present. Leukocytosis is frequently unimpressive. Sudden or progressive alteration in mental status and/or hemodynamic instability may be the only available clues to the diagnosis.

Coronary artery disease

Coronary heart disease (CHD) remains the chief cause of death in the United States and Western Europe.[82,83] The pathogenesis of atherosclerotic coronary artery disease has been intensely studied.[84–87]

Lindner et al[88] were the first group to investigate the incidence of CHD in patients with chronic renal failure. They studied a total of 39 patients over a 13-year period. Overall mortality was 56.4%; 61% of the deaths were cardiovascular and 57% were from acute myocardial infarction.



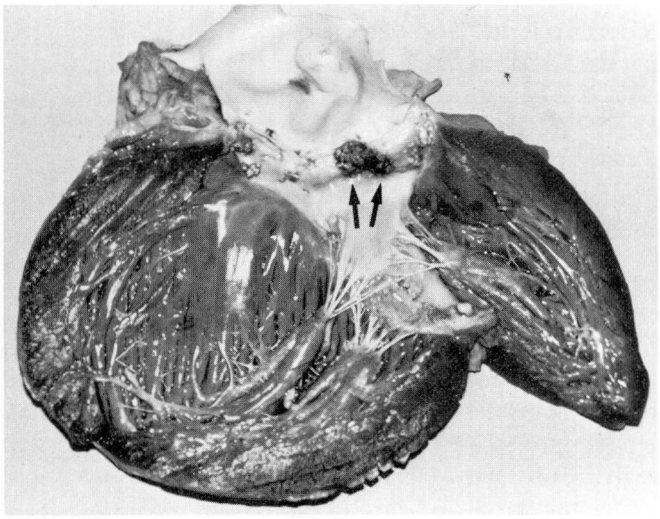


FIGURE 6A. *Streptococcus pneumoniae* endocarditis involving the anterior and posterior leaflets of the mitral valve (arrows). A ruptured chordae tendineae (small arrow) is also noted. FIGURE 6B. *Staphyloccus aureus* endocarditis of the aortic valve.

The National Dialysis Registry has recorded a gross annual death rate of 9% in patients with end-stage renal disease undergoing maintenance hemodialysis; the most common cause of death was CHD.[89]

Identifiable risk factors for the development of CHD in patients with chronic renal failure are similar to those in other patient populations and include: hypertension, tobacco abuse, hypercholesterolemia, hypertriglyceridemia, and glucose intolerance.[90–102] However, the potential role of calcium,[103] as well as other substances that may damage the vascular endothelium or sensitize it to the effects of blood pressure, lipoproteins, and tobacco, warrants further investigation.

Patients with limiting symptoms and/or critical coronary artery stenosis should be considered for angioplasty or coronary artery bypass grafting. Experience has clearly shown that successful surgical results can be obtained at acceptable risk despite earlier reports to the contrary.[104-110]

Cardiac complications during hemodialysis

Shifts in intravascular volume, osmotic equilibrium, peripheral vascular tone, and cardiac contractility occur during dialysis. As such, a well-orchestrated interaction involving the heart, peripheral vasculature, and autonomic nervous system is required to maintain hemodynamic stability.

Hypotension. A variable amount of intravascular volume (1–5 L) may be removed during hemodialysis. Compensatory responses to volume loss include increased peripheral vascular tone and increased plasma protein concentration, thereby enhancing interstitial fluid resorption. However, the removal of osmotically active solute (urea) during dialysis may prevent adequate interstitial-intravascular volume shifts. This mechanism is frequently encountered in clinical practice, particularly in patients with hemodynamically unstable disease who require dialysis; these patients tolerate ultrafiltration and hemofiltration better than hemodialysis.[111,112] Autonomic insufficiency may also contribute to hypotensive episodes by preventing a normal peripheral vasoconstrictor response to intravascular volume depletion.[113]

Myocardial ischemia. The hemodynamic stress of dialysis therapy renders patients with underlying CHD susceptible to myocardial ischemia.[114] Indeed, patients with exertional angina pectoris frequently have symptomatic myocardial ischemia during dialysis.[115] Although underlying coronary artery disease is the basis for most ischemic events, there is a subset of patients who experience angina despite angiographically normal coronary arteries. In these individuals, a combination of factors, including anemia, increased ventricular wall stress, and dialysis-related hypoxemia, may be responsible. Coronary arterial spasm has also been described in this setting.[115] The incidence of silent ischemia in this population may also be increased (R. Hendel, MD, personal communication) and is currently being investigated.

Arrhythmias: The following cardiac rhythm disturbances have been observed in patients undergoing hemodialysis: sinus tachycardia, atrial premature beats, supraventricular tachycardia (paroxysmal), atrial flutter, atrial fibrillation, ventricular premature beats, ventricu-

lar tachycardia, and ventricular fibrillation. Excluding patients with marked electrolyte disturbances, arrhythmias are encountered most frequently in patients with underlying structural heart disease and coronary artery disease.[116–118]

SUMMARY

Approximately 80,000 individuals are currently receiving chronic dialysis in the United States. An estimated 10,000 kidney transplantations will be performed in the upcoming year. Progress in this area will provide hope and promise for an increasing number of patients, but despite significant advances, a limiting factor still exists. Cardiovascular disease has emerged as the most common cause of death in patients with chronic renal failure. It is responsible for significant morbidity as well. All areas of the heart may be involved, including the pericardium, myocardium, endocardium, and coronary arteries. Therefore, continuing success in the care of patients with chronic kidney disease may depend on our ability to understand and prevent cardiovascular complications. Future investigations in cardiology and nephrology must vigorously pursue the complex and intricate relationship between the heart and kidneys.

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REFERENCES

1. Pahl NV, Vaziri ND, Gordon S, Tuero S. Cardiovascular pathology in dialysis patients with spinal cord injury. Artif Organs 1983; **7:**416–419.
2. Scharf S, Wexler J, Longnecker RE, Blaufox MD. Cardiovascular disease in patients on chronic hemodialytic therapy. Prog Cardiovasc Dis 1980; **22:**343–356.
3. O'Rourke RA, ed. The Heart and Renal Disease. New York, Churchill Livingstone, 1984.
4. Needleman P, Greenwald JE. Atriopeptin: a cardiac hormone intimately involved in fluid, electrolyte, and blood pressure homeostasis. N Engl J Med 1986; **314:**828–834.
5. Onesti G, Kim KE, Greco JA, et al. Blood pressure regulation in end-stage renal disease and anephric men. Circ Res 1975; **36(6 Suppl 1):**145–152.
6. Braunwald E, ed. Heart Disease: A Textbook of Cardiovascular Medicine. Philadelphia, WB Saunders, 1984, pp 1746–1762.
7. Braunwald E, Ross J Jr, Sonnenblick E. Mechanisms of Contraction of the Normal and Failing Heart. Boston, Little, Brown and Company, 1976.
8. Drüeke T, Le Pailleur C, Zingraff J, Jungers P. Uremic cardiomyopathy and pericarditis. Adv Nephrol 1980; **9:**33–70.
9. Bailey GL, Hampers CL, Hager EB, Merrill JP. Uremic pericarditis: clinical features and management. Circulation 1968; **38:**582–591.
10. Comty CM, Wathen R, Shapiro FL. Incidence, mortality and effects of treatment on uremic pericarditis. Presented at the Annual Meeting of the American Society of Nephrology, 1975.
11. Rostand SG, Rutsky EA. Cardiac disease in dialysis patients. [In] Nissenson AR, Fine RN, Gentile DE, eds. Clinical Dialysis. East Norwalk, CT, Appleton-Century-Crofts, 1984.
12. Yoshida K, Shina A, Asano Y, Hosoda S. Uremic pericardial effusion: detection and evaluation of uremic pericardial effusion by echocardiography. Clin Nephrol 1980; **13:**260–268.
13. Giovannetti S, Belestri PL, Barsotti G. Methylguanidine in uremia. Arch Intern Med 1973; **131:**709–713.
14. Bergström J, Fürst P. Uremic middle molecules. Clin Nephrol 1976; **5:**143–152.
15. Clarkson BA. Uric acid related to uremic symptoms. Proc Eur Dial Transplant Assoc 1976; **3:**3.
16. Marini PV, Hull AR. Uremic pericarditis: a review of incidence and management. Kidney Int 1975; **7:**S-163–S-166.
17. Comty CM, Cohen SL, Shapiro FL. Pericarditis in chronic uremia and its sequels. Ann Intern Med 1971; **75:**173–183.
18. Makó J, Szücs J, Gaizler G, Lengyel M, Mérei J. Study of the relationship between pericarditis and osteopathy in chronic haemodialysis. Int Urol Nephrol 1983; **15:**383–387.
19. Osanloo E, Shalhoub RJ, Cioffi RF, Parker RH. Viral pericarditis in patients receiving hemodialysis. Arch Intern Med 1979; **139:**301–303.
20. Makó J, Jansen J, Bognár B, Faragó A. Purulent pericarditis caused by *Staphylococcus aureus* in two patients undergoing haemodialysis. Int Urol Nephrol 1985; **17:**79–83.
21. Bacon ME, Whelan TV, Mahoney MD, Patel TG, Judson PL. Pericarditis due to *Mycobacterium kansasii* in a patient undergoing dialysis for chronic renal failure (letter). J Infect Dis 1985; **152:**846–847.
22. Hebert LA, Allhiser CL, Koethe SM. Some hemodynamic determinants of immune complex trapping by the kidney. Kidney Int 1978; **14:**452–465.
23. Simpson LO. Role of glomerular basement membrane thixotropy and influence of glomerular vascular pressure in the pathogenesis of immune complex-induced glomerulonephritis: a new hypothesis (edit). Nephron 1981; **27:**105–112.
24. Twardowski ZJ, Alpert MA, Gupta RC, Nolph KD, Madsen BT. Circulating immune complexes: possible toxins responsible for serositis (pericarditis, pleuritis, and peritonitis) in renal failure. Nephron 1983; **35:**190–195.
25. Zarate A, Gelfand MC, Horton JD, et al. Pericardial effusion associated with minoxidil therapy in dialyzed patients. Int J Artif Organs 1980; **3:**15–17.
26. Conners JP, Kleiger RE, Shaw RC, et al. The indications for pericardiectomy in the uremic pericardial effusion. Surgery 1976; **80:**689–694.
27. Minuth ANW, Nottebohm GA, Eknoyan G, Suki WN. Indomethacin treatment of pericarditis in chronic hemodialysis patients. Arch Intern Med 1975; **135:**807–810.
28. Spector D, Alfred H, Siedlecki M, Briefel G. A controlled study of the effect of indomethacin in uremic pericarditis. Kidney Int 1983; **24:**663–669.
29. Merikas G, Marketos S, Konstantanopoulos E. Uremic pericardial tamponade. Can Med Assoc J 1966; **95:**119–123.
30. Alexander J, Mehlman DJ, Talano JV. Cardiomegaly with chronic renal failure. Arch Intern Med 1984; **144:**101–103.
31. Baldwin JJ, Edwards JE. Uremic pericarditis as a cause of cardiac tamponade. Circulation 1976; **53:**896–901.
32. Frame JR, Lucas SK, Pederson JA, Elkins RC. Surgical treatment of pericarditis in the dialysis patient. Am J Surg 1983; **146:**800–803.
33. Singh S, Newmark K, Ishikawa I, Mitra S, Berman LB. Pericardiectomy in uremia. JAMA 1974; **228:**1132–1135.
34. Capelli JP, Kasparian H. Cardiac work demands and left ventricular function in end-stage renal disease. Ann Intern Med 1977; **86:**261–267.
35. D'Cruz IA, Bhatt GR, Cohen HC, Glick G. Echocardiographic detection of cardiac involvement in patients with chronic renal failure. Arch Intern Med 1978; **138:**720–724.
36. Trznadel K, Luciak M, Wyszogrodzka M. The left ventricular systolic

function after digoxin administration in patients with chronic renal failure. Clin Nephrol 1980; **13**:231–234.
37. Ikram H, Lynn KL, Bailey RR, Little PJ. Cardiovascular changes in chronic hemodialysis patients. Kidney Int 1983; **24**:371–376.
38. Renger A, Müller N, Jutzler GA, Bette L. Echocardiographic evaluation of left ventricular dimensions and function in chronic hemodialysis patients with cardiomegaly. Clin Nephrol 1984; **21**:164–168.
39. Ikäheimo N, Huttenen K, Takkunen J. Cardiac effects of chronic renal failure and hemodialysis treatment: hypertensive versus normotensive patients. Br Heart J 1981; **45**:710–716.
40. Cocci A, Mori R, Carosella L, et al. Echocardiographic aspects of cardiac hypertrophy and dilatation in normo and hypertensive hemodialyzed patients. Contrib Nephrol 1984; **41**:288–291.
41. Uraoka T, Sugimoto T, Inasaka T, et al. Changes of cardiac performance in renal failure. Jap Heart J 1975; **16**:489–499.
42. Vaziri ND, Prakash R. Echocardiographic evaluation of the effect of hemodialysis on cardiac size and function in patients with end-stage renal disease. Am J Med Sci 1979; **278**:201–206.
43. Nixon JV, Mitchell JH, McPhaul JJ Jr, Henrich WL. Effect of hemodialysis on left ventricular function: dissociation of changes in filling volume and in contractile state. J Clin Invest 1983; **71**:377–384.
44. Madsen BR, Alpert MA, Whitting RB, Van Stone J, Ahmad M, Kelly DL. Effect of hemodialysis on left ventricular performance: analysis of echocardiographic subsets. Am J Nephrol 1984; **4**:86–91.
45. Miach PJ, Louis WJ, Dawborn JK, Doyle AE. Plasma catecholamines in dialysed uremic patients (abst). Eur J Clin Invest 1977; **7**:245.
46. Szakács JE, Cannon A. L-norepinephrine myocarditis. Am J Clin Pathol 1958; **30**:425–434.
47. Factor SM, Sonnenblick EH. The pathogenesis of clinical and experimental congestive cardiomyopathies: recent concepts. Prog Cardiovasc Dis 1985; **27**:395–420.
48. Miach PJ, Dawborn JK, Louis WJ, McDonald IG. Left ventricular function in uremia: echocardiographic assessment in patients on maintenance dialysis. Clin Nephrol 1981; 15:259–263.
49. Bernardi D, Bernini L, Cini G, Ghione S, Bonechi I. Asymmetric septal hypertrophy and sympathetic overactivity in normotensive hemodialyzed patients. Am Heart J 1985; **109**:539–545.
50. Woodhouse MA, Burston J. Metastatic calcification of the myocardium. J Pathol 1969; **97**:733–736.
51. Arora KK, Lacey JP, Schacht RA, Martin DG, Gutch CF. Calcific cardiomyopathy in advanced renal failure. Arch Intern Med 1975; 135:603–605.
52. Mansell MA, Crowther A, Laker MF, Wing AJ. The effect of hyperacetatemia on cardiac output during regular hemodialysis. Clin Nephrol 1982; **18**:130–134.
53. Smythe PM, Swanepoel A, Campbell JAH. The heart in kwashiorkor. Br Med J 1962; **1**:67–73.
54. Shyamal S. A case of giant cell myocarditis associated with pyelonephritic hypertension and cardiorenal failure. J Indian Med Assoc 1968; **50**:154–159.
55. Von Bibra H, Castro L, Autenrieth G, McLeod A, Gurland HJ. The effects of arteriovenous shunts on cardiac function in renal dialysis patients—an echocardiographic evaluation. Clin Nephrol 1978; **9**:205–209.
56. Henderson RR, Santiago LM, Spring DA, Harrington AR. Metastatic myocardial calcification in chronic renal failure presenting as atrioventricular block. N Engl J Med 1971; **284**:1252–1253.
57. Sims BA. Conducting tissue of the heart in kwashiorkor. Br Heart J 1972; **34**:828–829.
58. Chait L, Mandel WJ. Wolff-Parkinson-White syndrome: alterations in ventricular activation induced by changes in serum potassium. Chest 1973; **64**:780–781.
59. Fazzini PF, Marchi F, Sodi A. Hyperkalemia in renal failure inducing atrio-ventricular block. G Ital Cardiol 1974; **4**:89–92.
60. deMello VR, Malone D, Thanavaro S, Kleiger RE, Kessler G, Oliver GC. Cardiac arrhythmias in end-stage renal disease. South Med J 1981; **74**:178–180.
61. Rutsky EA. Bradycardic rhythms during peritoneal dialysis. Arch Intern Med 1971; **128**:445–447.
62. Kim HG, Friedman HS. Procainamide-induced sinus node dysfunction in patients with chronic renal failure. Chest 1979; **76**:699–701.
63. Klein LW, Meller J. Hyperkalemia-induced pseudoinfarction pattern. Mt Sinai J Med 1983; **50**:428–431.
64. Arnsdorf MF. Electrocardiogram in hyperkalemia. Arch Intern Med 1976; **136**:1161–1163.
65. Abrahams C, D'Cruz I, Kathpalia S. Abnormalities in the mitral valve apparatus in patients undergoing long-term hemodialysis: autopsy and echocardiographic correlation. Arch Intern Med 1982; **142**:1796–1800.
66. Forman MB, Virmani R, Robertson RM, Stone WJ. Mitral annular calcification in chronic renal failure. Chest 1984; **85**:367–371.
67. Depace NL, Rohrer AH, Kotler MN, Brezin JH, Parry WH. Rapidly progressing, massive mitral annular calcification: occurrence in a patient with chronic renal failure. Arch Intern Med 1981; **141**:1663–1665.
68. Fulkerson PK, Beaver BM, Auseon JC, Graber HL. Calcification of the mitral annulus: etiology, clinical associations, complications and therapy. Am J Med 1979; **66**:967–977.
69. Storstein O, Örjavik O. Aortic insufficiency in chronic renal failure. Acta Med Scand 1978; **203**:175–180.
70. Alexander WD, Polak A. Early diastolic murmurs in end-stage renal failure. Br Heart J 1977; **39**:900–902.
71. Barratt LJ, Robinson MA, Whitford JA, Lawrence JR. The diastolic murmur of renal failure. N Engl J Med 1976; **295**:121–124.
72. Pérez JE, Smith CA, Meltzer VN. Pulmonic valve insufficiency: a common cause of transient diastolic murmurs in renal failure. Ann Intern Med 1985; **103**:497–502.
73. Osler W. Malignant endocarditis. Lancet 1885; **1**:505–508.
74. Becker RC, Di Bello P, Lucas FV. Bacterial tissue tropism: an in vitro model for the study of endocarditis. Cardiovasc Res 1987; **21**:813–820.
75. Freedman LR, Valone J Jr. Experimental infective endocarditis. Prog Cardiovasc Dis 1979; **22**:169–180.
76. Cross AS, Steigbigel RT. Infective endocarditis and access site infections in patients on hemodialysis. Medicine 1976; **55**:453–466.
77. Montgomerie JZ, Kalmanson GM, Guze LB. Renal failure and infection. Medicine 1968; **47**:1–32.
78. Dobkin JF, Miller MH, Steigbigel NH. Septicemia in patients on chronic hemodialysis. Ann Intern Med 1978; **88**:28–33.
79. Goodman J, Crews HD, Ginn HE, Koenig MG. Bacterial endocarditis as a possible complication of chronic hemodialysis. N Engl J Med 1969; **280**:876–877.
80. Turner HR, Taylor MR, Lockwood WR. *Branhamella catarrhalis* endocarditis in a patient receiving hemodialysis. South Med J 1985; **78**:1021–1022.
81. Lillehei CW, Bobb JRR, Visscher NB. The occurrence of endocarditis with valvular deformities in dogs with arteriovenous fistulae. Ann Surg 1950; **132**:577–590.
82. Report of the Working Group of Arteriosclerosis of the National Heart, Lung and Blood Institute, Vol.2, Washington DC, DHEW No. (NIH) 82-2035, 1981.
83. Ross R. The pathogenesis of atherosclerosis—an update. N Engl J Med 1986; **314**:488–500.
84. Stary HC. Evolution of atherosclerotic plaques in the coronary arteries of young adults. Arteriosclerosis 1983; **3**:471A.
85. McGill HC Jr. Persistent problems in the pathogenesis of atherosclerosis. Arteriosclerosis 1984; **4**:443–451.
86. Faggiotto A, Ross R. Studies of hypercholesterolemia in the nonhuman primate. II. Fatty streak conversion to fibrous plaque. Arteriosclerosis 1984; **4**:341–356.
87. Leslie CC, Musson RA, Henson PM. Production of growth factor activity for fibroblasts by human monocyte-derived macrophages. J Leukocyte Biol 1984; **36**:143–159.
88. Lindner A, Charra B, Sherrard DJ, Scribner BH. Accelerated atherosclerosis in prolonged maintenance hemodialysis. N Engl J Med 1974; **290**:697–701.
89. Burton BT, Krueger KK, Bryan FA Jr. National Registry of Long-Term Dialysis Patients. JAMA 1971; **218**:718–722.
90. Haas LB, Brunzell JD, Sherrard DJ. Atherosclerotic risk factors in a chronic dialysis population (abst). Kidney Int 1979; **16**:888.
91. Haire HM, Sherrard DJ, Scardapane D, Curtis FK, Brunzell JD. Smok-

ing, hypertension, and mortality in a maintenance dialysis population. Cardiovasc Med 1978; **3:**1163–1168.
92. Rostand SG, Kirk KA, Rutsky EA. Relationship of coronary risk factors to hemodialysis-associated ischemic heart disease. Kidney Int 1982; **22:**304–308.
93. Vincenti F, Amend WJ, Abele J, Feduska NJ, Salvatierra O Jr. The role of hypertension in hemodialysis-associated atherosclerosis. Am J Med 1980; **68:**363–369.
94. Sreepda Rao TK, Roxe DM, Laird NM, Santiago GC. Hemodynamic and cardiac correlates of different hemodialysis regimens: the National Cooperative Dialysis Study. Kidney Int 1983; **23(suppl 13):**S-89–S-94.
95. Burke JF Jr, Francos GC, Moore LL, Cho SY, Lasker N. Accelerated atherosclerosis in chronic-dialysis patients—another look. Nephron 1978; **21:**181–185.
96. Rostand SG, Gretes JC, Krik KA, Rutsky EA, Andreoli TE. Ischemic heart disease in patients with uremia undergoing maintenance hemodialysis. Kidney Int 1979; **16:**600–611.
97. Murase T, Cattran DC, Rubenstein B, Steiner G. Inhibition of lipoprotein lipase by uremic plasma, a possible cause of hypertriglyceridemia. Metabolism 1975; **24:**1279–1286.
98. Mordasini R, Frey F, Flury W, Klose G, Greten H. Selective deficiency of hepatic triglyceride lipase in uremic patients. N Engl J Med 1977; **297:**1362–1366.
99. Newman WP III, Freedman DS, Voors AW, et al. Relation of serum lipoprotein levels and systolic blood pressure to early atherosclerosis. N Engl J Med 1986; **314:**138–144.
100. Hamsten A, Wiman B, de Faire U, Blombäck N. Increased plasma levels of a rapid inhibitor of tissue plasminogen activator in young survivors of myocardial infarction. N Engl J Med 1985; **313:**1557–1563.
101. Bagdade JD, Albers JJ. Plasma high-density lipoprotein concentrations in chronic-hemodialysis and renal-transplant patients. N Engl J Med 1977; **296:**1436–1439.
102. Holme I, Enger SC, Helgeland A, et al. Risk factors and raised atherosclerotic lesions in coronary and cerebral arteries: statistical analysis from the Oslo study. Arteriosclerosis 1981; **1:**250–256.
103. Roberts WC, Waller BF. Effect of chronic hypercalcemia on the heart: an analysis of 18 necropsy patients. Am J Med 1981; **71:**371–384.
104. Sakurai H, Ackad A, Friedman HS, et al. Aorto-coronary bypass graft surgery in a patient on home dialysis. Clin Nephrol 1974; **2:**208–210.
105. Crawford FA Jr, Selby JH Jr, Bower JD, Lehan PH. Coronary revascularization in patients maintained on chronic hemodialysis. Circulation 1977; **56:**684–687,
106. Siegel MS, Norfleet EA, Gitelman HJ. Coronary artery bypass surgery in a patient receiving hemodialysis. Arch Intern Med 1977; **137:**83–84.
107. Francis GS, Sharma B, Collins AJ, Helseth HK, Comty CM. Coronary-artery surgery in patients with end-stage renal disease. Ann Intern Med 1980; **92:**499–503,
108. Cheng PC, Brown AH. Aortocoronary bypass surgery and chronic renal failure: Case report. NZ Med J 1978; **87:**319–320.
109. McGovern E, Rooney R, Neligan NC. Open heart surgery in patients receiving chronic hemodialysis. Thorax 1984; **39:**388–389.
110. Kuehnel E, Lundh H, Bennett W, Porter G. Aortocoronary bypass surgery in patients with end-stage renal disease. Trans Am Soc Artif Intern Organs 1976; **22:**14–21.
111. Rouby JJ, Rottembourg J, Durande J-P, et al. Hemodynamic changes induced by regular hemodialysis and sequential ultrafiltration hemodialysis: a comparative study. Kidney Int 1980; **17:**801–810.
112. Kinet J-P, Soyeur D, Balland N, Saint-Remy M, Collignon P, Godon J-P. Hemodynamic study of hypotension during hemodialysis. Kidney Int 1982; **21:**868–876.
113. Fouad FN, Tarazi RC, Bravo EL. Orthostatic hypotension: clinical experience with diagnostic tests. Cleve Clin Q 1985; 52:561–568.
114. Diskin CJ, Salzsieder KH, Solomon RJ, Carvalho JS, Trebbin WM. Electrocardiographic changes following dialysis. Nephron 1981; **27:**94–100.
115. Roig E, Betriu A, Casteñer A, Magriña J, Sanz G, Navarro-Lopez F. Disabling angina pectoris with normal coronary arteries in patients undergoing long-term hemodialysis. Am J Med 1981; **71:**431–434.
116. Wizemann V, Kramer W, Funke T, Schütterle G. Dialysis-induced cardiac arrhythmias: fact or fiction? Nephron 1985; **39:**356–360.
117. Ramirez G, Brueggemeyer CD, Newton JL. Cardiac arrhythmias on hemodialysis in chronic renal failure patients. Nephron 1984; **36:**212–218.
118. Kyriakidis N, Voudiclaris S, Kremastinos D, et al. Cardiac arrhythmias in chronic renal failure? Holter monitoring during dialysis and everyday activity at home. Nephron 1984; **38:**26–29.