

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

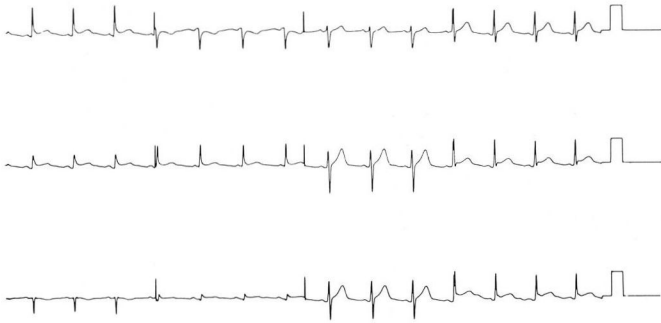


FIGURE 1. ECG tracing during acute pericarditis in a 49-year-old man with chronic glomerulonephritis and substernal chest pain of three days duration. Note diffuse “concave upward” ST segment elevation and PR segment depression.

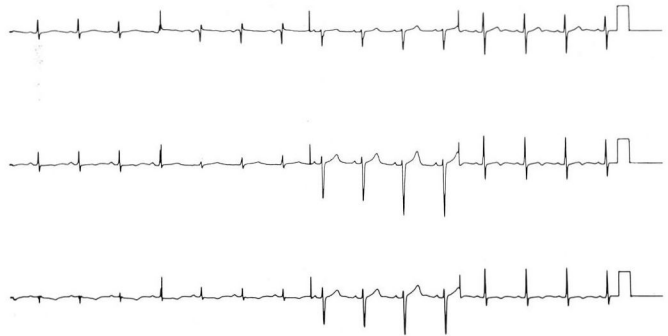


FIGURE 2. ECG tracing in pericarditis (subacute pattern) in the same patient as Figure 1, six weeks later. Symptoms have completely resolved; however, T wave inversions are present in leads II, III, aVF, V₅, and V₆.

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 by-products and the development of pericarditis does *not* exist. The contribution of “uremic toxins” has been studied. Giovannetti et al¹³ suggested that methylguanidine, a low-molecular-weight substance ineffectively cleared in states of renal dysfunction, may be responsible. Others¹⁴ 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 al¹⁷ were the first to suggest a relationship between parathyroid overactivity and pericarditis. Other investigators⁸ 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 al¹⁸ 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 al²⁴ 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 minoxidil²⁵ 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

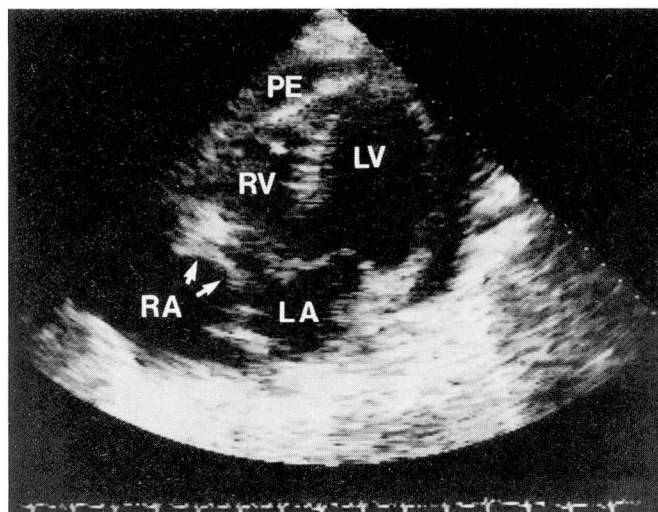
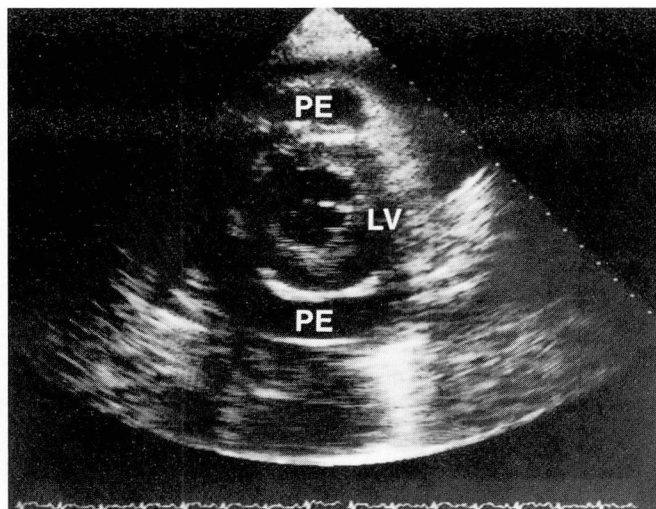
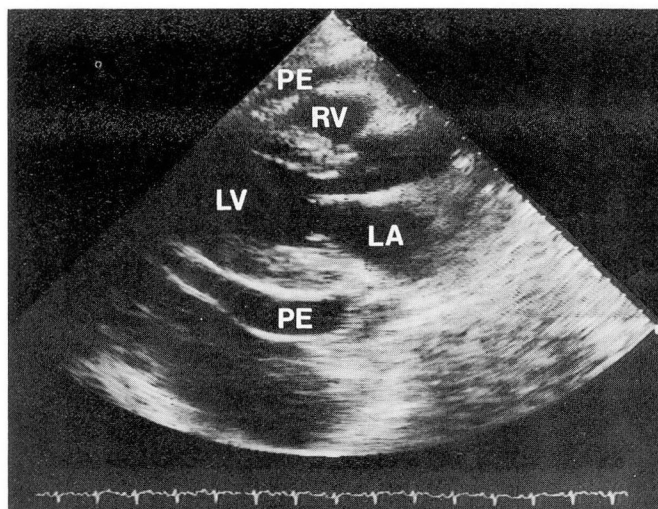


FIGURE 3A. Two-dimensional echocardiogram, parasternal long-axis (PLA) view, of a patient with a large pericardial effusion. Pericardial effusion (PE), left ventricle (LV), left atrium (LA), right ventricle (RV). FIGURE 3B. Pericardial effusion as seen in a short-axis (parasternal cross-sectional) view 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 per-

icardial 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 al⁸ 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 al³⁹ performed M-mode and two-dimensional echocardiography on 41 patients undergoing

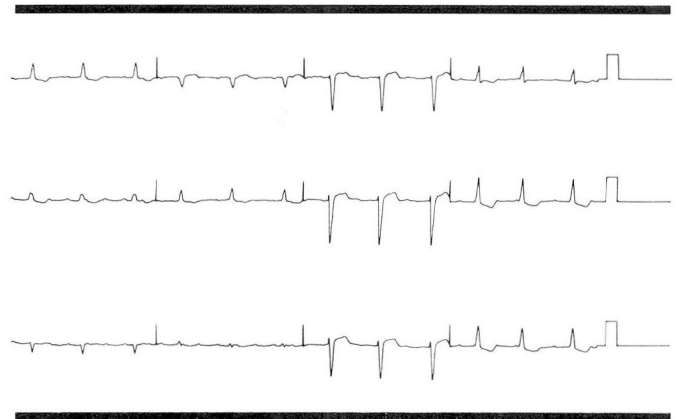


FIGURE 4. ECG in digitalis toxicity in a patient with chronic renal insufficiency. Atrial tachycardia with AV dissociation.

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 al⁴¹ 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 Prakash⁴² observed similar findings.

A study by Nixon et al⁴³ 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 al⁴⁴ 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 al⁴⁵ studied 22 hemodialysis patients with evidence of left ventricular dysfunction. Fractional shortening was found to correlate inversely with plasma catecholamine levels. Bernardi et al⁴⁹ 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 malnutrition⁵⁷ 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,

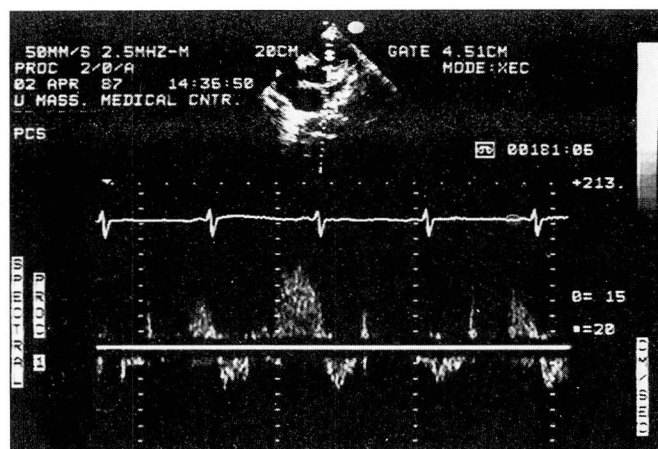


FIGURE 5. Pulsed Doppler echocardiogram at the level of the pulmonic valve showing pulmonic insufficiency. Sample volume is proximal to valve with diastolic blood flow toward the transducer.

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 al⁶⁵ reported calcification of the mitral apparatus (valve leaflets, anulus, chordae, and papillary muscles). Forman et al⁶⁶ analyzed biochemical, hemodynamic, and echocardiographic data in 168 patients with chronic renal failure undergoing intermittent he-

modialysis. 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 insufficiency⁶⁹⁻⁷² (Figure 5).

Infective endocarditis

It has been recognized since the days of Sir William Osler⁷³ 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 al⁸⁸ 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.

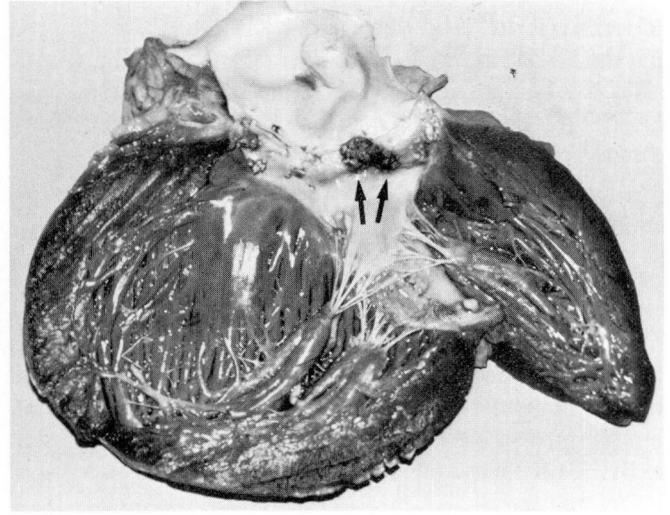
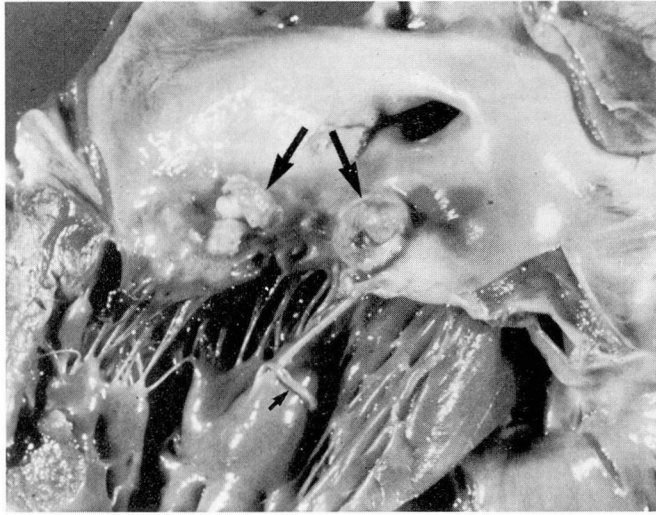


FIGURE 6A. *Streptococcus pneumoniae* endocarditis involving the anterior and posterior leaflets of the mitral valve (arrows). A ruptured chordae tendineae (small arrow) is also noted. FIGURE 6B. *Staphylococcus aureus* endocarditis of the aortic valve.

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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