



Coronary Artery Disease and Renal Failure

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4

ABSTRACT

Renal failure and coronary artery disease (CAD) are linked in a cause - effect relationship bi-directionally. Renal failure causes and exacerbates CAD and vice versa. When acute heart failure develops the kidney is always affected as renal perfusion is not supported and pre-renal ARF develops. In chronic setting as with chronic ischemic cardiomyopathy there is maximal efferent arteriolar vasoconstriction and further compensation is not possible. Hence any hypotension leads to a major decrease in glomerular filtration rate. The risk of death from cardiovascular events is several folds higher in the chronic kidney disease population than in the general population. Coronary artery disease and cardiac failure contribute to more than 50% mortality in these patients. Classical risk factors such as hypertension, diabetes, obesity, smoking, hypercholesterolemia etc. operate but renal failure adds some unique risk factors such as left ventricular hypertrophy, hyperhomocystinemia, inflammation, elevated calcium x phosphate product, endothelial dysfunction, and oxidant stress. Additional hemodynamic and metabolic risk factors operate in this subset of patients which make them more prone to CAD. Risk factor modification in the renal failure patients can make a marked difference in the prognosis. Recent data clearly support that application of proven cardiac interventions as in the general population give gratifying results in chronic kidney failure patients. The recent data clearly support the application of proven interventions in the general population.

INTRODUCTION

Although chronic uremia is not a conventional risk factor for coronary artery disease, the estimated prevalence of coronary artery disease in patients who are undergoing dialysis is much more than in the general population, in the range of 17 to 34 percent.¹ The rate of death from cardiovascular causes in patients undergoing dialysis is about 20 times greater than in the age-matched general population.² The figures are approximately the same for patients who undergo renal transplantation.³

Renal failure and coronary artery disease (CAD) are linked in a cause - effect relationship bi-directionally. Renal failure causes and exacerbates CAD and vice versa. Suffice it to say that the two coexist frequently enough to merit a high index of suspicion of one in the presence of the other.

CORONARY ARTERY DISEASE CAUSING RENAL FAILURE

Acute heart failure (AHF): In acute setting as in acute myocardial infarction with pump failure or in acute coronary syndrome with poor LV function or post-CABG surgery, when AHS develops the kidney is always affected as renal perfusion is not supported and pre-renal acute renal failure (ARF) develops. In fact, some degree of renal dysfunction is seen in about 30% of patient undergoing open heart surgery.

Post Cardiac Surgery

Acute renal failure usually after cardiac surgery can be divided into three types based on the severity.⁴

Type 1

That associated with acute peri-operative insult with rapid resolution. The rise in urea and creatinine typically peaks in 3-4 days but since there is no ongoing insult usually recovery is rapid over the next 7-8 days. It is possible in most cases to just observe the patient, ensure adequate intravascular filling, BP and cardiac output. It is often useful to give loop diuretics. This is helpful to avoid fluid overload, acidemia and hyperkalemia while the kidney recovers. One can usually avoid dialysis.

Type 2

Patients with continued hemodynamic instability and severe cardiovascular dysfunction will often be on intra-aortic balloon pump and ventilator with inotrope support. The renal failure is invariably prolonged and runs a course of 2-3 weeks in parallel with recovery of cardiac function. Such a patient must be rapidly identified and would require early continuous renal replacement therapy.

Type 3

In this ARF initially presents like the type 2 but instead of resolving is further complicated by renewed independent renal

insult such as severe sepsis. In such patients treatment must be early, aggressive and continuous. Diligent control of fluid overload, acidemia, electrolyte disorder, azotemia and nutrition is a must.

Chronic Ischemic Cardiomyopathy

In chronic setting as with chronic ischemic cardiomyopathy there is a very fragile state of physiological compensation that can be altered even by small changes in fluid status or medication. The major mechanism for preservation of GFR and filtration fraction involves a striking increase in efferent arteriolar resistance and intraglomerular hydrostatic pressure. Because of the maximal efferent vasoconstriction further compensation is not possible and any hypotension leads to major decrease in GFR. Neurohormonal responses are managed through the sympathetic system, renin-angiotensin-vasopressin and endothelin release. Thus misuse of diuretics and ACE inhibitors can land such a patient into ARF.

Then there are other scenarios where coronary artery disease causes or is associated with renal failure such as –

1. ARF in CABG for coronary blocks with independent effect of cardiopulmonary bypass.
2. Contrast-induced nephropathy in coronary angiography while investigating CAD.
3. Atheroembolic renal disease resulting from manipulations during cardiac interventions.
4. Drugs causing ARF used in the treatment of CAD as ACE inhibitors and ARBs in patients with associated renal artery stenosis.

RENAL FAILURE CAUSING CORONARY ARTERY DISEASE

The risk of death from cardiovascular events is several folds higher in this population than in the general population. There is a constant interplay between the vascular events and myocyte dysfunction – ultimately resulting in either manifest heart failure or a catastrophic ischemic event.

About 35% of CKD (chronic kidney disease) patients show clinical symptoms of heart failure before they become dialysis dependent.⁵ The probability of having MI or angina is 10% per year for dialysis patients and such patients have a 1 and 5-year mortality rates of 60% and 90%, respectively. Moreover in the diabetic subset, which forms 40% of all end-stage renal disease patients the incidence, clinical course, overall mortality and CV mortality is still worse. These figures bring out the enormity of CV disease in the spectrum of CKD disease. There has been a decrease in the mortality rates in the last decade.⁶

Atheromatous IHD

Coronary stenosis exhausts the coronary vasodilator reserve. Uremic milieu and comorbid conditions favour vascular wall damage. 15%⁵ to 73%⁷ of patients have CAD by the time they enter dialysis. The wide range in prevalence depends on whether patient is worked up for CAD only when he is symptomatic or is detected by screening. About 50% of CKD patients (especially diabetics) are asymptomatic.⁸ Both mechanical and humoral factors predispose to atheroma.

Tensile and shear site stress results in endothelial cell activation stimulating flow-sensitive cationic channels producing vasoactive and growth regulating factors. In addition, autocrine and endocrine factors come in to play in chronic uremia. These include dyslipidemia,⁹ platelet dysfunction with high growth prothrombotic factors,¹⁰ increased oxidant stress,¹¹ hyperhomocystenemia,¹² advanced glycation end-products,¹³ dysregulation between proinflammatory cytokines and their inhibitors.¹⁴ Inflammation in general and C reactive protein in particular may contribute to the pathogenesis of atherosclerosis. CRP levels have been shown to have a powerful predictive value for mortality in dialysis patient.¹⁵ Positive calcium and phosphate balance results in calcifications of the coronaries although its clinical significance in patients with CKD is unknown.

Risk factors for coronary artery disease in patients with renal failure

Vigorous treatment of modifiable cardiovascular risk factors has reduced cardiovascular risk in patients without ESRD. The extent to which such risk factor modification would alter cardiovascular risk in ESRD remains uncertain.

Left Ventricular Hypertrophy (LVH)

LVH is present in 75% of patients starting dialysis. It is an important risk factor for coronary heart disease in CKD patients. Concentric LVH is an adaptive response, initially beneficial, to chronic pressure load with addition of sarcomers in parallel. Hypertension, aortic stiffness, and aortic stenosis predispose to concentric LV hypertrophy. Eccentric hypertrophy is adaptation to chronic volume overload by addition of sarcomers in series. High cardiac output related to renal anemia, hypertension, volume overload, and the arteriovenous fistula (in patients on hemodialysis) predispose to eccentric LVH. Most ESRD patients have a hybrid form of LV hypertrophy. Stress induced gp 130- dependent ligands such as cardiotrophin bind to their receptor gp 130-LIF (leukemic inhibitory factor) promote sarcomers formation and block apoptosis. In the presence of gp 130 balance is shifted towards myocyte hypertrophy and in the absence to apoptosis causing heart failure. Unlike myocytes, fibroblasts proliferation causes increase in interstitial fibrosis. Uremia is an independent factor related to myocardial fibrosis in CKD, independent of hypertension, diabetes, dialysis etc.¹⁶ LV hypertrophy is commonly accompanied by LV diastolic dysfunction. LV systolic dysfunction is less common but when present is strongly associated with presence of IHD or sustained biomechanical stress.

Newer dialytic techniques, excellent control of hypertension and correction of renal anemia produce regression of LVH. Recent studies show that interventions that reduce LV mass index improve survival. A recent study by Zoccoli et al shows that progression of LVH is associated with increase in mortality and cardiovascular events in ESRD patients. Monitoring LVH by echocardiography may provide prognostic evidence and may be useful in preventing CAD. After renal transplant two-thirds had a significant regression of LVH despite the blood pressure remaining in the same range suggesting other uremic factors contribute to the same.

Hypertension (HTN)

About 70 to 80% of patients with CKD have hypertension in pre-dialysis period and the incidence increases as GFR falls. Increase in extracellular volume through salt and water retention is a primary determinant. However enhanced sympathetic activity, activated renin angiotensin system, and endothelial cell dysfunction also contribute. Despite strong evidence high blood pressure is an independent risk factor for cardiac events in CKD, low blood pressure is associated with a higher risk of death possibly due to confounding cardiac co-morbidity.¹⁷

Drug therapy, particularly angiotensin-converting enzyme inhibitors and beta-adrenergic receptor blockers is under-used in patients with ESRD and CHF.

Large arteries may be involved by arteriosclerosis in addition to arteriosclerosis. Aortic and mitral annular and leaflet calcifications causing vascular disease is actually far more frequent than previously recognised.¹⁸

Dyslipidemia

Approximately 50 to 70% patients on dialysis have dyslipidemia. As GFR falls triglyceride levels increase and HDL levels fall. As proteinuria increases total serum cholesterol and LDL cholesterol also increase. Few studies have examined the relation of dyslipidemia and cardiac outcomes in CKD patients. However low HDL, high LDL and total cholesterol are related to adverse cardiac outcome. High lipoprotein A found in renal failure patients also contributes to the cardiac morbidity.

Tobacco use

This is clearly related to progression of kidney disease and development of cardiovascular disease.

Diabetes

Diabetic patients have more widespread CAD than do age and sex-matched controls. Some have impaired LV function despite normal coronaries perhaps due to diabetic cardiomyopathy. Only 11% of diabetics had a normal echo dimensions compared to 25% of nondiabetics. LV size and function was a good predictor of survival.

Uremia Related Risk Factors

Additional risk factors operate in this subset of patients which make them more prone to CAD.

Hemodynamic risk factors

1. Anemia is associated with LVH and LV dilation as GFR falls below 50ml/min. It contributes to sensitivity but has not shown to be a risk factor for IHD.
2. Increased extracellular volume: In patients on CAPD, lower total sodium and water removal is independently associated with survival.
3. AV fistula and grafts predispose to LV volume overload
4. Type of dialysis modality induces unique risks.

Metabolic risk factors

1. Hypoalbuminemia is the most potent predictor of outcome in dialysis patients. It predisposes to cardiac failure and de novo coronary artery disease. It suggests a more marked inflammatory milieu and malnourishment especially in CAPD population.

2. Inflammation – CRP is an acute phase reactant and marker for inflammation and is directly related to cardiovascular events.
3. Hyperhomocysteinemia (HCT): In absence of inflammation higher HCT levels correlate with CAD as in general population. Lower HCT levels, in the presence of inflammation correlate more strongly with CAD in the dialysis population. This is the so called inverse epidemiological risk.
4. Others - Oxidative stress, abnormal divalent ion metabolism and pro-thrombotic factors have all been correlated with heart failure and CAD in CKD population.

Non-atheromatous IHD

About 25% dialysis patients with ischemia do not have critical CAD.¹⁹ Small vessel smooth muscle hypertrophy, endothelial abnormalities, and myocyte capillary mismatch have been reported in uraemic patients exposing the myocyte to the risk of hypoxia. The ischemic symptoms in these patients result from small vessel disease and LV hypertrophy.

MANAGEMENT

Diagnosis

ECG detects LVH, ST-T changes, myocardial infarction as in non-CKD cases. Limited exercise capacity may either mask or err in predicting ischemia in stress test.

Biochemical markers serial estimates of CPK and LDH when elevated reliably diagnose acute MI. The presence of either troponin T or troponin I can be used to diagnose acute ischemia.

Echocardiography provides a good non-invasive tool for assessment of LV structure and function. Dobutamine stress echo is a good screening tool in CKD patients. Its overall sensitivity and specificity for detection of CAD have been reported as 80-84%.

Nuclear scanning can be used to assess systolic function and reversible ischemia. Dahan and Foligis²⁰ showed a positive and negative predictive value of 41% and 91% respectively for coronary events using thallium scanning compared to coronary angiography.

Electron beam ultrafast CT (EBCT) relies on the principle that coronary artery calcification is a reliable surrogate for significant coronary atherosclerosis.²¹

Coronary angiography remains the gold standard for diagnosis of CAD.

Color Doppler, ankle-brachial index test, MR angiography and intravascular ultrasonography are frequently used for diagnosis.

The treatment of acute and stable angina is the same as for non-CKD patients. Risk factors should be managed aggressively in CKD patients (Table 1).

Pharmacotherapy

For those who have had an infarction beta-blocker should be prescribed as also ACE inhibitor for patients with LV dysfunction. Although the benefit of aspirin in non-uremic patient is substantial, the risk of complications, mainly bleeding, increases

Table 1

Interventions to Minimize Cardiovascular Disease Risk in Patients with Chronic Kidney Disease (Adapted from *The Kidney* by Brenner & Rector, 7th Ed. 2004)

Nonpharmacologic Interventions

Stop tobacco use

Minimize excess extracellular fluid to target blood pressure <130/80mmHg

Awareness and prevention of inflammation and hypoalbuminemia.

Dietary modification to target low density lipoprotein

Keep LDL cholesterol <100mg/dL

Renal transplantation when appropriate

Coronary revascularisation for secondary prevention of ischemic vascular disease

Pharmacologic interventions

Drug therapy to target blood pressure <130/80 mmHg

Epoetin and iron therapy to target hemoglobin concentration >110g/L (upper limits not clearly defined)

Treatment with HMG-CoA reductase inhibitor (statin) therapy to target low-density lipoprotein cholesterol < 100mg/dL

Treat abnormal divalent ion levels to target serum calcium 9.2-9.6 mg/dL, serum phosphate 2.5-5.5 mg/dL, and intact parathyroid hormone 100-200 pg/mL

Anti-platelet agents in patients with coronary disease, vascular disease or diabetes

Appropriate use of ACE inhibitors (or ARBs in predialysis patients) for treatment of proteinuria and arteriosclerosis

Use of ACE inhibitors and E-receptor antagonists in patients with known ischemic vascular disease.

as renal function declines. Hence use of aspirin for primary prevention is not recommended; however in acute ischemia the benefits may outweigh the risk.

Coronary revascularization

In asymptomatic disease there is no evidence to suggest that investigation and treatment of these patients results in improved mortality statistics. Post-infarction angiography is indicated if there is angina or ischemia during a stress test. The initial success rate for coronary angiography in CKD patients is 90%. Among haemodialysis patients the indoor mortality for coronary artery bypass grafting is 12.5% or four times higher than in general population. There is a consensus in favor of bypass surgery for left main or extensive triple vessel disease and in favour of angiography for single vessel disease. In view of propensity for restenosis after angioplasty CABG probably is the procedure of choice. However, there is a substantial reduction in restenosis rate while using sirolimus coated stent.²²

Eventhough cardiovascular disease is the leading cause of death in patients with CRF and end-stage renal disease (ESRD), ill-conceived notions have led to therapeutic nihilism as the predominant strategy in the management of cardiovascular disease in these populations. The recent data clearly support the application of proven interventions in the general population, such as angiotensin-converting enzyme inhibitors and statins to patients with CRF and ESRD. The advances in coronary stents and intracoronary irradiation have decreased the restenosis rates in renal failure patients. Coronary artery bypass with internal

mammary graft might be the procedure of choice for coronary revascularization in these patients. The role of screening for asymptomatic coronary disease is established as a pretransplant procedure, but it is unclear whether this will be applicable to all patients with ESRD. Future studies need to focus on unraveling the mechanisms by which uremia leads to increased cardiovascular events to design optimal management.

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