

The Heart and the Kidneys: a Close Link

Topoti Mukherjee*

Fellowship in Transplantation, University of Alberta, Canada

*Corresponding author: Topoti Mukherjee, Fellowship in Transplantation, University of Alberta, Canada, Tel: +91-9538811972; E-mail: drtopoti@gmail.com

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Introduction

The kidneys and the heart have a very intriguing and close relationship. It is now well established that kidney disease can trigger or aggravate heart disease; and conversely, heart disease has the ability to ravage the kidneys. While chronic kidney disease (CKD) patients are often terrified of having to go on dialysis (or a kidney transplant), the hard truth is that most will die of heart disease before their kidneys disintegrate to that point.

A common umbrella term “cardiorenal syndrome” is used to describe acute or chronic dysfunction of the heart or kidneys that can cause dysfunction in the other organ. Cardiorenal syndrome was classified by Ronco in 2008 into 5 types [1]:

1. Type I or acute cardiorenal syndrome: An abrupt worsening of cardiac function leading to acute kidney injury (AKI)
2. Type II or chronic cardiorenal syndrome: Chronic cardiac dysfunction leads to progressive renal dysfunction
3. Type III or acute renocardiac syndrome: An abrupt worsening of kidney function causes acute cardiac dysfunction
4. Type IV or chronic renocardiac syndrome: Chronic kidney dysfunction contributes to cardiac dysfunction
5. Type V or secondary cardiorenal syndrome: A systemic condition like Diabetes or Hypertension or Sepsis that causes both cardiac and renal dysfunction through independent mechanisms.

This review broadly has two parts. The first, on how cardiac failure affects the kidney (type II cardio renal syndrome). And the second, on how the heart is affected in kidney disease (type IV cardio renal syndrome).

Cardiac Failure and the Kidney

The kidney plays a vital role in salt and water retention that is found in heart failure. Heart failure represents an edematous state in which renal salt and water retention is observed despite an excess of total body sodium and water. Left ventricular systolic and/or diastolic dysfunction leads to this retention that in turn aggravates the heart failure.

Mechanism of edema and fluid retention in cardiac failure

The type of edema in cardiac failure represents an alteration in Starling forces in the capillary beds wherein the normal balance between tissue capillary and interstitial hydrostatic and colloid osmotic pressures is altered in favour of intravascular fluid escaping into the interstitial space. The transcapillary hydraulic pressure is influenced by a number of hemodynamic factors like systemic arterial and venous blood pressures, regional blood flow, resistances of the pre and post capillary sphincters. Other factors include the cardiac output,

intravascular volume, systemic vascular resistance. The right atrial or right ventricular preload is greatly modulated by changes in the intravascular volume, which is largely determined by the kidney, and alteration in venous capacitance.

There are certain compensatory mechanisms to offset the initial disturbances of cardiac failure. In low output cardiac failure, the initial adjustments happen both at the cardiac, renal and peripheral levels. There are increases in plasma volume, atrial and ventricular filling pressures, cardiac contractility, heart rate and peripheral vasoconstriction. The major renal compensation for a failing myocardium is retention of sodium and water, but later this also accounts for aggravating the symptoms of cardiac failure.

There are two theories to explain how the kidneys get involved. According to the “backward failure” theory, as the cardiac pump fails, there is a rise in the central venous pressure and the peripheral venous pressure, which causes the hydraulic pressure in the capillaries to exceed the opposing forces and leads to transudation of fluid from the intravascular compartment [2,3]. This loss of intravascular fluid volume signals the kidney to retain sodium and water in an attempt to restore the circulating volume to normal. On the other hand, the “forward failure” theory states that renal under-perfusion in the face of cardiac failure leads to decreased excretion of sodium and water [4]. Both the hypotheses could be assumed to be occurring simultaneously in the clinical scenario.

Hemodynamic and neurohumoral factors in cardiac failure

The effective arterial blood volume (EABV), when low, stimulates high pressure baroreceptors in the carotid sinus, aortic arch, left ventricle or the juxtaglomerular apparatus [5]. This can stimulate the renin angiotensin aldosterone system (RAAS) and can trigger the non-osmotic release of arginine vasopressin (AVP). There are also low pressure baroreceptors in the left atrium that are sensitive to small changes in distension of the atria [6]. In addition, there are cardiac, pulmonary and hepatic chemoreceptors which do have a role in the pathophysiology of cardiac failure and fluid retention.

The three major neurohumoral vasoconstrictor systems activated in response to arterial underfilling are the sympathetic nervous system, the RAAS and the non-osmotic release of AVP. Therapy is based on these mechanisms. Alpha blockade is associated with a significant natriuresis. Beta receptor blockade may decrease renin release and improve the neurohumoral milieu. Angiotensin, via activation of the angiotensin II (AT- II) receptors, enhances proximal tubular sodium reabsorption. There is a beneficial effect of angiotensin converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB) in heart failure. Patients with reduced LV systolic function benefit from ACEI or ARB. Patients with post myocardial infarction benefit from beta blockade. Aldosterone antagonists may be used for the same reason in addition to their role in ameliorating cardiac fibrosis. Recent

studies have also supported the role of V2 receptor antagonism to correct water retention and hyponatremia of heart failure.

There are other vasoconstrictor mechanisms like endothelin that may have an active role in heart failure. The endothelin antagonist bosentan has shown to be beneficial in animal experiments. The details of the pathophysiology are beyond the scope of this chapter.

The hemodynamic consequences on the kidney need a mention. The Glomerular Filtration Rate (GFR) is normal in mild heart failure and is reduced as the pump fails more and more. There is an increase in renal vascular resistance and decrease in renal blood flow. These changes are mediated by the neurohumoral mechanisms like AT-II, norepinephrine, vasopressin or other vasoconstrictors.

Cardiac Disease in Chronic Kidney Disease (CKD)

As mentioned above, patients with CKD are more likely to die from a cardiac cause before they reach End Stage Renal Disease (ESRD). As the GFR halves, the cardiac risk factor doubles and the risk for a cardiac death is almost three times.

Risk factors for cardiac disease in CKD could be classified as follows:

1. Traditional: Diabetes, hypertension, smoking, hyperlipidaemia and obesity
2. Uremia related: Inflammation, hyperfibrinogenemia, oxidative stress, hyperhomocysteinemia, divalent ion abnormalities, Asymmetric Dimethyl Arginine (ADMA)
3. Small vessel disease: Hypertension, diabetes, calcification, decreased capillary density.

The heart can be involved in CKD in the several ways. These include ischemic heart disease (IHD), arteriosclerosis, cardiomyopathy, valvular disease, congestive heart failure (CHF), arrhythmias, atrial fibrillation and sudden death. Many of these are exaggerated by dyselectrolytemias, increased ultrafiltration volumes during dialysis, divalent ion abnormalities, a low potassium or low calcium dialysate during haemodialysis.

Pathogenesis

The atherogenic risk increases particularly when the GFR falls below 30ml/min/1.73sq.mt. Renal failure can modify the atherogenic process at multiple levels. Concentric left ventricular hypertrophy (LVH) occurs because of LV pressure overload and eccentric LVH can occur from LV volume overload, arteriovenous fistula or anemia. LVH leads to systolic dysfunction over a period of time. LV diastolic dysfunction can lead to pulmonary edema. With diastolic dysfunction, there is an impaired ventricular relaxation and an exaggerated increase in LV end diastolic pressure. Therefore, a small excess of salt and water retention can rapidly lead to a large increase in LV end diastolic pressure and pulmonary edema. Dialysis patients have a 10% annual risk of developing pulmonary edema requiring hospitalization or ultrafiltration [7].

The initiating event in coronary artery disease is endothelial injury which may be precipitated by various triggers. The ensuing cascade of events leading to atherosclerosis remains the same as in the non CKD population. Endothelial denudation permits influx of lipoproteins and macrophages into the sub-intimal space. LDL cholesterol and other lipoproteins get oxidized which is chemotactic for macrophages. The

macrophages engulf the oxidized lipids which results in the formation of foam cells. Several profibrotic factors are stimulated and sub-occlusive thrombi are formed. These thrombi get organized over a period of time.

The factors that worsen the atherogenic process in CKD are several. Hypertension and volume overload may increase the stresses on the vascular wall and also create chronic inflammatory states that cause endothelial dysfunction. Hyper-homocysteinemia promotes endothelial activation and thrombosis. Hyperparathyroidism and divalent ion abnormalities may promote vascular calcification and medial hypertrophy.

An increased calcium phosphate product promotes vascular calcification. CKD is often complicated by an imbalance between the promoters and inhibitors of calcification. Fetuin A, which is an inhibitor of vascular calcification, is down regulated. Vascular smooth muscle cells undergo a chondrocyte like or osteoblast like phenotypic modification. These processes can trigger diffuse calcification of the media.

Aortic valve calcification is common in the dialysis population leading to aortic valve orifice stenosis. Mitral valve calcification is less common than aortic valve calcification but is known. Phosphate control is especially important from a cardio-protective point of view.

Asymmetric dimethyl arginine (ADMA) is a nitric oxide (NO) inhibitor which is increased in CKD. It inhibits the beneficial effects of NO on vasodilatation, arterial stiffening and endothelial function.

Treatment

Treatment is mainly focused on optimization of the CKD state. Maintenance of haemoglobin, calcium, phosphorus, parathyroid hormone (PTH), adequacy of dialysis; compliance with frequency of dialysis, blood tests and medications, all constitute cardio protective measures. Having a good nutritional status as assessed by dietary recall, serum albumin and subjective global assessment (SGA), among others contribute to the overall quality of life of dialysis patients. Avoiding high ultrafiltration volumes during haemodialysis and maintenance of a low inter dialytic weight gain are equally important. Maintenance of normal extracellular volume can cause regression of LVH and improved survival [8]. Patients with a poor LV systolic function do better with peritoneal dialysis. If haemodialysis is the on-going dialysis, nocturnal / daily dialysis may be beneficial for the heart [9].

Aspirin is beneficial in patients with CKD with cardiac disease and may confer protection to the patency of the arteriovenous fistula as well [10]. Statins are given as needed. The combination of statins and fibrates increases the muscle toxicity. Antioxidants and multivitamins are given to dialysis patients.

The role of other drugs is discussed in the section of pathophysiology. Anti-anginals can be given as needed. Calcium channel blockers and other anti-hypertensive can also be given.

Surgical revascularization (Coronary artery bypass grafting) may be done when indicated. The peri operative mortality of dialysis patients is higher than non CKD patients [11,12]. The role of stenting or angioplasty is controversial in CKD patients but may be individualized.

A routine annual cardiac evaluation in all patients with CKD is recommended. Periodic counselling about the optimization of the CKD state and reinforcing compliance remain the mainstay of therapy.

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