Heart failure in the patients with chronic kidney disease

Lisowska A, Musiał WJ

Department of Cardiology, Medical University of Białystok, Poland

Abstract

Heart failure is highly prevalent in the population with chronic kidney disease. Upon starting dialysis, 37% of patients will have had a previous episode of heart failure, doubling the risk of death. Both systolic and/or diastolic function may be impaired. 15% of patients starting dialysis therapy have systolic dysfunction of the left ventricle. The prevalence of diastolic dysfunction at dialysis inception is unknown, but is likely to be high. Either systolic or diastolic dysfunction can lead to clinically evident congestive heart failure. Hypertension and coronary heart disease are important causes of myocardial dysfunction in end-stage renal disease. Individuals with chronic kidney disease are at a very high risk for the development and progression of cardiovascular disease. The increased risk of cardiovascular disease is due to a higher prevalence of both traditional risk factors as well as nontraditional "uremia-related" risk factors. The prevalence of coronary artery disease (CAD) approaches 40% among patients starting dialysis. About 70 - 80% of these patients have hypertension. Anaemia is a known risk factor for left ventricular hypertrophy (LVH) and dilatation, heart failure and death. The diagnosis and treatment of heart failure in the patients with chronic kidney disease (CKD) are similar to that reccomended for patients without CKD. The potent drugs like ACE-I, AT-1 antagonists, β-receptor antagonists are the main tools in nowadays treatment of CHF. New therapeutic regiments using natriuretic peptides are being evaluated in clinical settings.

ADDRESS FOR CORRESPONDENCE:
Anna Lisowska M.D.
Department of Cardiology,
Medical University of Białystok,
ul. Skłodowskiej-Curie 24a
15-273 Białystok, Poland
e-mail: anlila@poczta.onet.pl

Received 5.05.2004 Accepted 11.06.2004

Key words: heart failure, chronic kidney disease, systolic dysfunction, diastolic dysfunction.

Introduction

The cardiovascular system is closely related to function of the kidneys. Renal insufficiency can affect cardiac performance leading to its failure which consequently worsens renal function. The fact, that impairment of one component of the cardio-renal system aggravates dysfunction of the other is clinically very important.

Heart failure (HF) is a specific term used to define the clinical syndrome when the heart is unable to pump enough blood to supply the metabolic needs of the body [1]. Subjects with myocardial failure can have symptomatic HF or asymptomatic ventricular dysfunction. Symptoms of exercise intolerance are typically assessed by the New York Heart Association (NYHA) functional classification.

About half of all deaths in end-stage renal disease (ESRD) patients are attributable to cardiac causes [2]. Heart failure and coronary heart disease (CHD) are highly prevalent in this population.

Epidemiology

Upon starting dialysis, 37% of patients will have had a previous episode of heart failure, doubling the risk of death [3]. The remaining patients will develop heart failure at a rate of about 10%/year [4]. Both systolic and/or diastolic function may be impaired. 15% of patients starting dialysis therapy have systolic dysfunction of the left ventricle [5]. The prevalence of diastolic dysfunction at dialysis inception is unknown, but is likely to be high [6]. Either systolic or diastolic dysfunction can lead to clinically evident congestive heart failure (CHF). Risk factors for new onset CHF include hypertension, older age, anaemia and coronary heart disease [7]. Hypertension and CHD are important causes of myocardial dysfunction in ESRD.

Coronary heart disease in patients with chronic kidney disease

Individuals with chronic kidney disease are at a high risk for the development and progression of cardiovascular disease [8]. The prevalence of CAD approaches 40% among patients starting dialysis. 22% of them have stable angina, while 18% will have suffered from a prior myocardial infarction. The symptoms of myocardial ischaemia in dialysis patients are the same as those observed in other groups, although silent ischaemia may be more common because of the higher prevalence of diabetics [2]. The increased risk of cardiovascular disease is due to a higher rate of both traditional as well as nontraditional "uremia-related" risk factors [9].

Most important traditional risk factors are: older age, male gender, hypertension, lipid abnormalities (increased level of total and LDL cholesterol, decreased level of HDL cholesterol), diabetes, smoking, physical inactivity, left ventricular hypertrophy, family history of cardiovascular disease.

For the nontraditional risk factors we account: albuminuria, anaemia, abnormal calcium/phosphate metabolism, hyperhomocysteinemia, extracellular fluid volume overload, oxidative stress, inflammation, malnutrition, thrombogenic factors.

CHD is usually the result of critical coronary artery disease, but in 27% of hemodialysis patients ischaemic symptoms are caused by other changes, like: small vessel disease (caused by hypertension, diabetes mellitus and calcium-phosphate deposition), reduced capillary density and abnormal myocyte bioenergetics [10]. LV hypertrophy predisposes to ischaemic symptoms by reducing coronary reserve.

The patology of CHD in patients with renal insufficiency is complex. It's important to note that, in uremic patients the atherosclerotic plaque is more calcified [11]. Morever not only epicardial arteries, but also small arterioles are involved in atherosclerosis. The left ventricular hypertrophy often coexists. In the beginning it is concentric, followed by excentric hypertrophy which leads to the dilatation of the left ventricle.

The coronary flow reserve is decreased [12]. Increased concentration of NO inhibitors due to decreased accessibility of nitric oxide is present [13]. Hypertrophy and hyperplasia of the coronary vessels further limit its dilatation ability [14]. Decreased amount of capillary vessels in myocardium impairs oxygen diffusion.

The following risk factors lead to cardiomyopathy in patients with chronic kidney disease:

- LV volume overload: salt and water overload, arteriovenous fistula, anaemia
- LV pressure overload: hypertension, aortic stenosis, arteriosclerosis.

Other causes are: hypoalbuminemia, small and large coronary vessel disease [15].

Hypertension in patients with chronic kidney disease (CKD)

About 70-80% of these patients have hypertension. The prevalence of high blood pressure increases as GFR declines [16]. Three out of four of patients starting dialysis have left ventricular hypertrophy (LVH) [17]. For dialysis patients, each 10 mmHg increment in blood pressure is associated with a 48% higher risk of LVH [18]. Risk factors for LVH apart from systolic blood pressure, include: anaemia, age and gender. Reducing blood pressure slows the rate of loss of renal function in CKD [6]. On the other hand NHANES III data suggest that in the majority of patients with renal insufficiency hypertension is poorly controlled. 2/3 of them had blood pressure > 140/90 mmHg. Only 11% individuals had adequate values.

Angiotensin converting enzyme inhibitors and angiotensin receptor blockers should be considered the preferred antihypertensive agents. Calcium channel blockers are recommended to be used only as a part of a multidrug regimen in combination with ACE inhibitors and angiotensin receptor blockers [8]. Usually multidrug therapy is needed. According to the standards, the uremic patients require more intensive treatment of high blood pressure (INC VI):

- individuals without proteinuria – less than 130/85 mmHg
- individuals with proteinuria (> 1 g/day) and/or diabetes it should be lower – 125/75 mmHg.

The optimal pressure values for dialysis patients is not clear, as low blood pressure has been associated with increased mortality in this group [19].

It is worth to note that, in the Hypertension Optimal Treatment (HOT) trial participants with elevated baseline serum creatinine were two- to threefold more likely to experience a major or fatal CVD events compared to subjects with normal serum creatinine levels [20]. The prognostic significance of serum creatinine levels was also reported in the Heart Outcomes Evaluation Protection Study (HOPE) [21].

Dyslipidemia in patients with chronic kidney disease (CKD)

The most important abnormalities of uremic dyslipidemia are: elevated levels of trigliceryde trigliceryde-rich particles (VLDL and IDL) and LDL-cholesterol, increased Lp(a) lipoprotein level, low concentration of HDL-cholesterol. Total cholesterol level can be normal, although this is not the rule [22]. The prevalence of dyslipidemia in CKD is associated with the level of GFR and the level of proteinuria [23].

The patients with CKD and hyperlipidemia should be treated according to the National Cholesterol Education Program (NCEP) guidelines [2]. The target LDL cholesterol level is ≤100 mg/dl. The HMG-CoA reductase inhibitors (statins) are the most effective drugs. Fibrates are also effective, but they are excreted by the kidney, that is why dosage reduction is required.

Anaemia in patients with CKD

Anaemia is a special risk factor in patients with CKD. This fact well recognized by nephrologists is often unrealised by other specialists, also cardiologists. It influences left ventricular hypertrophy (LVH) and dilatation, heart failure and death [24].

Anaemia with haemoglobin levels < 12 g/dl is present in more than half of patients with advanced heart failure. Its incidence increases with higher NYHA classes. Several observational studies have suggested that anaemia (haemoglobin levels 6 - 12 g/dl) is an independent predictor of mortality in dialysis patients [6]. It has been shown that haemoglobin normalization may prevent progressive LV dilatation in patients with normal cardiac volumes at baseline [25]. Results of recent studies indicated that partial or complete correction of anaemia with erythropoietin decreases the cardiac output and heart rate, and induces a partial regression of the LVH, principally in relation with decreased left ventricular end-diastolic diameter [26]. Foley et al. postulated, that normalization of haemoglobin in haemodialysis patients with asymptomatic cardiomyopathy prevented the development of further left ventricle dilation [25]. The Canadian Normalization of Hemoglobin study (haemodialysis patients with either LVH or LV dilatation randomly treated to hemoglobin levels of 10 or 13.5 g/dl) showed that normalization of haemoglobin led to clinically significant improvements in quality of life, while survival rate were similar in both target groups [6].

Hyperparathyroidism in patients with CKD

High level of parathyroid hormone is an important factor in the genesis of myocardial fibrosis [27]. Hyperparathyroidism is associated with LV hypertrophy. Some studies have shown improvement in left ventricular function and size after parathyroidectomy [6].

Diagnosis of heart failure in patients with CKD

The diagnosis consists of:

- symptoms of heart failure
- declinations in physical examination
- ECG
- chest X-ray
- echocardiogram.

Echocardiography is the most important tool for the diagnosis of CHF in CKD patients. Especially echocardiography in the patients starting dialysis revealed a variety of abnormalities. Most common was concentric LV hypertrophy found in 42% of patients, eccentric LV hypertrophy in 23%, isolated LV dilatation in 4% and systolic dysfunction in 16%. Only 16% had a normal echocardiogram [28]. Similar data (about 75% patients with LVH) showed USRDS (United States Renal Data System) [29].

However, LV volume fluctuates in haemodialysis patients. Therefore it is necessary to perform echocardiography at the patients "dry weight" – the day after dialysis. In patients with anaemia the increase in cardiac preload alters the pattern of Doppler signals that is used for the evaluation of diastolic function.

Treatment of heart failure in patients with CKD [2]

The data are lacking, because patients with significant renal impairment have been exluded from randomized studies. Few little trials indicated that ACE inhibitors and β-receptor antagonists improve outcomes also for patients with heart failure in the CKD and ESRD populations.

ACE Inhibitors are metabolized in kidneys, therefore their dose has to be adjusted according to the renal insufficiency. This, however, is not a problem in the case of the angiotensin II receptor type 1 (AT-1) antagonists, which are metabolized predominantly by liver. Nevertheless some of them, like valsartan, also require dose adjustments in advanced renal failure (GFR < 30 ml/min). A separate problem is the risk of hyperkalaemia and decrease of the glomerular filtration as the consequence of the inhibition of the renin-angiotensin-aldosterone system. According to the guidelines, serum levels of potassium and creatinine should be initially monitored every 4 weeks and at least twice a year on a regular basis. A discontinuation of the drug should be considered when serum potassium exceeds 5.5 mmol/L or creatinine increases more than 30% of the basal (pre-treatment) values [16].

There was one prospective placebo-controlled trial – 114 dialysis patients with dilated cardiomyopathy were randomized to receive either carvedilol or placebo in addition to standard therapy. All patients were followed up for two years. After two years, 51.7% of the patients died in the carvedilol group, compared with 73.2% in the placebo group ($p < 0.01$). These data suggest the use of carvedilol in all dialysis patients with chronic heart failure [30]. In such patients carvedilol has good kinetic characteristics – its hepatic metabolism does not require dose adjustments in case of impaired renal function.

Loop diuretics are complying in patients with symptoms of CHF in renal failure. Their effect will be attenuated in cases with advanced renal insufficiency, but not as severly as thiazide diuretics, which usually become ineffective with a GFR less than 30 ml/min. The effects of aldosterone antagonists are unpredictictable in patients with CKD – they can induce hyperkalemia, in combination with ACE inhibitors and β-receptor antagonists in the setting of reduced GFR.

It has been demonstrated that the use of diuretics alone, by reducing the effective plasma volume, results in further activation of the neurohormonal axis. The administration of diuretics rises activation of the renin-angiotensin-aldosterone system (RAAS). Multiple studies have shown that, when diuretics are used alone, one of their effects on the kidney is to significantly decrease glomerular filtration rate. Acute Decompensated Heart Failure National Registry (ADHERE) database indicates than more than 80% of patients are managed with diuretics. It makes sense when patients are congested. But it must be emphasized that diuretics are really a double-edged sword in heart failure. They activate neurohormones, they cause potassium loss, and they have detrimental effects on renal function.

It is worth to note that, aggressive therapy for advanced heart failure can aggravate renal dysfunction. Estimation creatinine clearance may predict this situation better than baseline creatinine levels.

Increased experience with natriuretic peptides suggests that their administration might facilitate diuresis with less compromise of renal function. Probably they can also limit the dilatation of the heart and maybe activation of pathways at a cellular and molecular level for cardiac remodeling.

Each of modern medications alone causes a significant reduction in mortality; but the cumulative risk reduction when combined therapy (ACE-I, β-receptor antagonists and aldosterone antagonists) is used brings a 66% risk reduction [31].

Digoxin is useful in patients with atrial fibrillation and heart failure, and it improves exercise tolerance in nonuremic patients with symptomatic LV systolic dysfunction. Digoxin should be considered for similar patients with CKD or ESRD.

Conclusions

More than one a third of patients starting dialysis have clinical symptoms of heart failure. On the other hand, congestive heart failure is a common and crucial contributor to the progression of chronic renal disease. If we can help prevent renal dysfunction in heart failure, we are likely to be much more successful in dealing clinically with such patients. Therefore close cooperation between cardiologists and nephrologists is needed. The potent new drugs like ACE-I, β-receptor antagonists and angiotensin receptor blockers are the main tools in nowadays treatment of CHF. New therapeutic regiments using natriuretic peptides are being evaluated in clinical settings.

References

1. Braunwald E. Heart Disease. W.B. Saunders Company. Philadelphia 2001, 635.
2. Murphy S. Management of heart failure and coronary artery disease in patients with chronic kidney disease. Seminars in Dialysis, 2003; 16: 165-72.
3. Foley R, Parfrey P, Hefferton D, Kent G, Murray D, Barre P. Advance prediction of early death in patients starting maintenance dialysis. Am J Kidney Dis, 1994; 23: 836-45.
4. Churchill D, Taylor D, Cook R, LaPlante P, Barre P, Cartier P, Fay W, Goldstein M, Jindal K, Mandin H. Canadian Hemodialysis Morbidity Study. Am J Kidney Dis, 1992; 19: 214-34.
5. Foley R, Parfrey P, Harnett J, Kent G, Martin C, Murray D, Barre P. Clinical end echocardiographic disease in patients starting end-stage renal disease therapy. Kidney Int, 1995; 47: 186-92.
6. Foley R. Clinical epidemiology of cardiac disease in dialysis patients: left ventricular hypertrophy, ischemic heart disease, and cardiac failure. Seminars in Dialysis, 2003; 16: 111-7.
7. Harnett J, Foley R, Kent G, Barre P, Murray D, Parfrey P. Congestive heart failure in dialysis patients: Prevalence, incidence, prognosis and risk factors. Kidney Int, 1995; 47: 884.
8. Uhlig K, Levey A, Sarnak M. Traditional cardiac risk factors in individuals with chronic kidney disease. Seminars in Dialysis, 2003; 16: 118-27.
9. Parfrey P, Foley R. The clinical epidemiology of cardiac disease in chronic renal failure. J Am Soc Nephrol, 1999; 10: 1606-15.
10. London G, Parfrey P. Cardiac disease in chronic uremia: pathogenesis. Ad Renal Replac Ther, 1997; 4:194-211.
11. Schwarz U, Buzello M, Ritz E, Stein G, Raabe G, Wiest G, Mall G, Amann K. Morphology of coronary atherosclerotic lesions in patients with end-stage renal failure. Nephrol Dial Transplant, 2000; 15: 218-23.
12. Amann K, Ritz E. Microvascular disease: The Cinderella of uraemic heart disease. Nephrol Dial Transplant, 2000; 15: 1493-503.
13. Kielstein J, Boger R, Bode-Boger S, Frolich J, Haller H, Ritz E, Fliser D. Marked increase of asymetric dimethylarginine in patients with incipient primary chronic renal disease. J Am Soc Nephrol, 2002; 13: 170-6.
14. Amann K, Wolf B, Nichols C, Tornig J, Schwarz U, Zeier M, Mall G, Ritz E. Aortic changes in experimental renal failure: hyperplasia or hypertrophy of smooth muscle cells? Hypertens, 1997; 29: 770-5.
15. Parfrey P. Cardiac disease in dialysis patients: diagnosis, burden of disease, prognosis, risk factors and management. Nephrol Dial Transplant, 2000; 15 (5): 58-68.
16. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Kidney Disease Outcome Quality Initiative. Am J Kidney Dis, 2002; 39: 1-246.
17. Levin A. Clinical epidemiology of cardiovascular disease in chronic kidney disease prior to dialysis. Seminars in Dialysis, 2003; 16: 101-5.
18. Foley R, Parfrey P, Hefferton D, Kent G, Murray D, Barre P. Impact of hypertension on cardiomyopathy, morbidity and mortality in end-stage renal disease. Kidney Int, 1996; 49: 1379-85.
19. Port F, Hulbert-Shearon T, Wolfe R, Bloembergen W, Golper T, Agodoa L, Young E. Predialysis blood pressure and mortality risk in a national sample of maintenance hemodialysis patients. Am J Kidney Dis, 1999; 33: 507-17.
20. Ruilope L, Salvetti A, Jamerson K, Hansson L, Warnold I, Wedel H, Zanchetti A. Renal function and intensive lowering of blood pressure in hypertensive participants of the hypertension optimal treatment (HOT) study. J Am Soc Nephrol, 2001; 12: 218-25.
21. Mann J, Gerstein H, Pogue J, Bosch J, Yusuf S. Renal insufficiency as a predictor of cardiovascular outcomes and the impact of ramipril: the HOPE randomized trial. Ann Intern Med, 2001; 134: 629--36.
22. Madore F. Uremia-related metabolic cardiac risk factors in chronic kidney disease. Seminars in Dialysis, 2003; 16: 148-56.
23. Sarnak M, Coronado B, Greene T, Wang S, Kusek J, Beck G, Levey A. Cardiovascular disease risk factors in chronic renal insufficiency. Clin Nephrol, 2002; 57: 327-35.
24. Foley R, Parfrey P, Harnett J, Kent G, Murray D, Barre P. The impact of anaemia on cardiomyopathy, morbidity and mortality in end stage renal disease. Am J Kidney Dis, 1996; 28: 53-61.
25. Foley R, Parfrey P, Morgan J, Barre P, Campbell P, Cartier P, Coyle D, Fine A, Handa P, Kingma I, Lau C, Levin A, Mendelssohn D, Muirhead N, Murphy B, Plante R, Posen G, Wells G. Effect of hemoglobin levels in hemodialysis patients with asymptomatic cardiomyopathy. Kidney Int, 2000; 58: 1325-35.
26. London G. Cardiovascular disease in chronic renal failure: pathophysiologic aspects. Seminars in Dialysis, 2003; 16: 85-94.
27. Amann K, Ritz E, Wiest G, Klaus G, Mall G. A role of parathyroid hormone for the activation of cardiac fibroblasts in uremia. J Am Soc Nephrol, 1994; 4: 1814-9.
28. Parfrey P, Foley R, Harnett J, Kent G, Murray D, Barre P. The outcome and risk factors for left ventricular disorders in chronic uremia. Nephrol Dial Transpl, 1996; 11: 1277-85.
29. Foley R, Herzog C, Collins A. Blood pressure and long-term mortality in United States hemodialysis patients: USRDS Waves 3 and 4 study. Kidney Int, 2002; 62: 1784-90.
30. Cice G, Ferrara L, D'Andrea A, D'Isa S, Di Benedetto A, Cittadini A, Russo P, Golino P, Calabro R. Carvedilol increases two-year survival in dialysis patients with dilated cardiomyopathy. JACC, 2003; 41: 1438-44.
31. Fonarow G. Heart failure: recent advances in prevention and treatment. Rev Cardiovasc Med, 2000; 1: 25-33.