Optimising care at the cardio-renal interface

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Introduction

The increasing numbers of patients with co-existent cardiovascular and renal disease calls for a closer association between the two specialties. It is well known that the adjusted rates of death or hospitalisation due to cardiovascular causes increase as estimated glomerular filtration rate (eGFR) falls1 and the majority of patients with impaired renal function commonly die from cardiovascular disease (CVD) prior to requiring renal replacement therapy (RRT). Deaths from CVD account for 34% of all-cause mortality in the RRT population in the UK with the relative risk of death on RRT being 30 times at age 30 and three times at age 80. Conversely the presence of reduced renal function in CVD or congestive heart failure (CHF) is in itself an independent predictor of adverse prognosis.

Inflammation as a cardiovascular risk factor

The plenary lecture focused on inflammation as a vascular risk factor. The loss of endothelium-dependent dilatation in the systemic arteries occurs in the preclinical phase of vascular disease2 with local haemodynamic shear stresses,3 collagen turnover4 and C-reactive protein (CRP) all playing a role in the pathogenesis of early atherosclerosis. Atherosclerosis can thus be considered an inflammatory condition initiated by endothelial dysfunction via exposure to risk factors, driven by lipid accumulation into monocyte/macrophage lineage cells. Ongoing inflammation, immune activation and cellular migration and proliferation promote progression and destabilisation of atherosclerotic plaque. Inflammation is not specific to a single organ and as such may partly explain some of the pathophysiological interactions that occur between different organ systems, such as the heart and kidney.

Relationship between cardiovascular and renal disease

CVD and chronic kidney disease (CKD) have a number of shared risk factors (dyslipidaemia, hypertension, diabetes, smoking, genetics, etc). The development of CVD in patients with CKD is also driven by a number of pathophysiological processes which include elevated parathyroid hormone, elevated calcium-phosphate product, chronic inflammation, neurohormonal activation, anaemia, duration of dialysis and so on.

Emerging interest is seen in the relationship between phosphate levels and CVD. While higher serum phosphorus levels are associated with an increased CVD risk in individuals free of CKD and CVD in the community,6 recent reports suggest that phosphate in the ‘high’ normal range is a cardiovascular risk in the general population. Tonelli and colleagues demonstrated a graded independent relation between higher levels of serum phosphate and the risk of death and cardiovascular events in people with prior myocardial infarction, most of whom had serum phosphate levels within the normal range.7 More recently data analysed from the CARDIA study (Coronary Artery Risk Development in Young Adults)8 showed that phosphate levels were significantly associated with the category of coronary artery calcium level and higher serum phosphorus levels, even within the normal range, may be a risk factor for coronary artery atherosclerosis in healthy young adults.

Chronic kidney disease in chronic heart failure

Many patients with CHF exhibit significantly impaired renal function and pose a therapeutic challenge for the physician. Acute kidney injury (AKI) defined as an increase in serum creatinine >26 micromol/l (0.3 mg/dl) is common in decompensated heart failure with prevalence as high as 25%. The pathophysiologic mechanisms involve haemodynamic factors, activation of the renal angiotensin system (RAS), inflammation and anaemia among others. The historical belief is that reduced cardiac output (COP) leads to reduced renal perfusion. Systemic and intrarenal responses are directed to retain fluid and restore COP, and therefore the circulating volume increases. Eventually the neurohumoral responses fail to normalise COP and renal blood flow and the GFR decreases. Recent data highlight the role of elevated right atrial pressures in worsening renal function; hence treatment should focus not only on improvement of renal perfusion, but also on decreasing venous congestion.9

Atherosclerotic renovascular disease and CVD often coexist due to shared risk factors, with an incidence much higher than assumed. These patients exhibit a high prevalence of cardiac morphologic and functional abnormalities at early stages of renal dysfunction and early identification of such patients may permit risk factor modification.10

Impact of haemodialysis on cardiovascular status

Left ventricular hypertrophy, systolic dysfunction, hypotension during haemodialysis and fluid/electrolyte shifts during haemodialysis all contribute to the excess cardiovascular (CV) risk in this group of patients.11 Studies have shown that the
degree of blood pressure reduction, ultrafiltration volume, age and troponin T levels are associated with the development of significant regional wall motion abnormalities (cardiac stunning) in haemodialysis. It is believed that this in turn leads to myocardial hibernation, increased levels of N-terminal prohormone brain natriuretic peptide (NT-pro BNP), ventricular arrhythmias and reduction in overall systolic function. Improved haemodynamic stability of biofeedback dialysis and cooling of the dialysate are possible targets for intervention.

Challenges in treatment

Diuretic resistance

Diuretic resistance or oedema despite adequate diuretic therapy is increasingly encountered in clinical practice and high diuretic requirements in CHF suggest a poor prognosis. Contributors to diuretic resistance include poor adherence to drugs, excessive dietary sodium intake, drug interactions (eg nonsteroidal anti-inflammatory drugs, including topical preparations), CKD, worsening cardiac function/arrhythmia and co-morbidities (eg infection).

Management should involve sodium and fluid restriction (<100 mmol and 1.5 l/day respectively). The dose of diuretics may need to be increased, agents switched or the route of administration varied to improve bioavailability. A continuous infusion may need to be increased, agents switched or the route of administration. Loop and thiazide diuretics for sequential nephron blockade. Other agents are under evaluation and include nesiritide (synthetic human BNP), a vasodilator with weak diuretic effect, vasopressor receptor antagonists (vaptans), currently only licensed for the treatment of hyponatremia in patients with syndrome of inappropriate antidiuretic hormone hypersecretion and adenosine receptor antagonists.

Anaemia

Anaemia is very common in patients with CHF and its successful treatment with erythropoietin or iv iron, is associated with a significant improvement in cardiac function, functional class, renal function and in a marked fall in the need for diuretics and hospitalisation. Other agents are under evaluation and include nesiritide (synthetic human BNP), a vasodilator with weak diuretic effect, vasopressor receptor antagonists (vaptans), currently only licensed for the treatment of hyponatremia in patients with syndrome of inappropriate antidiuretic hormone hypersecretion and adenosine receptor antagonists.

Sudden cardiac death

The risk of sudden cardiac death (SCD) in dialysis patients is estimated to be 7% per year. Arrhythmias in CKD are due to several closely interlinked factors like electrolyte disturbances, inflammation (pericarditis/myocarditis), uraemia (which promotes interstitial fibrosis) and repolarisation abnormalities. These commonly occur in the background of cardiac structural abnormalities such as left ventricular hypertrophy. Studies are required to evaluate the arrhythmia burden and the potential role of implantable cardioverter defibrillators (ICDs) in the CKD population. The ongoing ICD2 trial and CRASH ILR studies will hopefully give further insight.

Although a 42% reduction in risk of death has been demonstrated with the implantation of ICDs in a dialysis population (1996 to 2001) with prior ventricular fibrillation/ cardiac arrest, the presence of CKD prior to ICD implantation is independently associated with increased mortality. The risk is proportional to the degree of renal dysfunction present. ICD implantation in this population is itself challenging with the
increased complication rate (problems with vascular access, anticoagulation, platelet function, infection risk), as well as refractory arrhythmias due to electrolyte imbalance and enhanced sympathetic activation.\textsuperscript{19} Deciding on the most rational form of treatment can therefore be difficult. Guidance has been suggested with the development of a decision analysis model used by Amin and colleagues.\textsuperscript{20} This demonstrated that has been suggested with the development of a decision analysis rational form of treatment can therefore be difficult. Guidance has been suggested with the development of a decision analysis model used by Amin and colleagues.\textsuperscript{20} This demonstrated that those CKD patients that currently meet the criteria for primary prevention ICD, benefit was determined by stage of kidney disease and patient’s age. ICD implantation is favoured at ages $<80$ for stage 3, ages $<75$ for stage 4, and ages $<65$ for stage 5.

**Cardio-renal disease in primary care**

While the aetiology of renal disease has changed over the years with a growing incidence of end-stage renal disease (ESRD) due to hypertensive, renovascular disease and type 2 diabetes mellitus, there may be a ray of hope on the population level in the form of reno-protective interventions. Screening programmes (including evaluation of microalbuminuria) will be crucial in the early identification of patients at risk for development of ESRD.\textsuperscript{3} The National Institute for Health and Clinical Excellence (NICE) guidelines on CKD published in September 2008 and the recent Quality and Outcomes Framework (QOF) modifications for CKD (to underline the importance of detection and appropriate management of patients with coexisting proteinuria and hypertension) are steps in the right direction. A single centre audit published by the Renal Association in April 2009 showed that the introduction of CKD referral guidelines by NICE was associated with a 50% reduction in dialysis ‘crash landings’. The conference speakers, however, pointed out that for CVD the rate of improvement following the QOF scheme has not been as encouraging. There is thus the need to bring more clinical leadership into CVD management in primary care and ensure better integration between primary, community and secondary care.

**UK cardio-renal trials group**

The recent formation of clinical specialty groups (CSG) as recommended by Kidney Research UK, Renal Association and UK-Renal Research Consortium will hopefully encourage collaborative UK research. Each group consisting of eight to 12 researchers with particular interest in the subspecialty area would consider funding opportunities and take a lead in developing studies aimed at filling existing major evidence gaps. The cardio-renal disease CSG, in particular, aims to bring the two specialties closer and instigate studies in areas of common interest. Following the first cardio-renal CSG meeting in July 2009, studies in development include epidemiological investigations of sudden cardiac death in dialysis patients, peritoneal dialysis for treatment of severe heart failure and investigation of cardiac structural and functional changes in nephrectomised patients.

**Conclusion**

As we gain new insight into the complex associations between CVD and CKD, it is the need of the hour that the individual specialties at primary, secondary and tertiary care work in unison to enhance understanding and identification of at-risk patients. This would help us deliver better treatment and work towards stemming the growing burden of cardiac-renal disease.

**Further information**

Information regarding future meetings can be obtained from the Cardio-renal Forum website: www.cardiorenalforum.com

**References**

16 Silverberg DS, Wexler D, Blum M et al. The use of subcutaneous erythropoietin and intravenous iron for the treatment of the anemia of severe, resistant congestive heart failure improves cardiac and renal function and functional cardiac class, and markedly reduces hospitalizations. *J Am Coll Cardiol* 2000;35:1737–44.


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