Acute kidney injury in patients with decompensated heart failure

Decompensated heart failure is one of the leading causes of acute hospital admission in the UK. Worsening renal function, essentially reflecting acute kidney injury, is frequently encountered in such patients and is associated with significantly worse outcome. Recognition and appropriate management of such patients is vital.

This article outlines the challenging problem of managing acute kidney injury in patients with decompensated heart failure. It provides insight into the complex pathophysiological interplay between cardiac and renal function, gives an overview of standard and novel approaches to treatment of these patients and highlights difficulties encountered.

Definition of the cardiorenal syndrome

The exact definition of cardiorenal syndrome is debated. It has generally been used to describe declining renal function in the setting of advanced heart failure (Francis 2006; Ronco et al, 2008). Some authors have expanded upon this to define it as the spiral of worsening heart failure and acute kidney injury that leads to diuretic resistance, volume overload and worsening heart failure (Geisberg and Butler, 2006). It is a serious and frequent problem with up to 45% of patients hospitalized with decompensated heart failure developing worsening renal function (Kimmenade et al, 2007). Multiple studies have concluded that deterioration of renal function in patients with decompensated heart failure is an independent poor prognostic marker.

Cardiorenal or renocardiac syndrome?

During the last decade much attention and research has focused on the dramatically increased risk of cardiac disease in patients with chronic kidney disease. In a large American epidemiological study, Go et al (2004) evaluated data from the Kaiser Permanente health-care registry between 1996 and 2000 (n=1 120 295). Reduction in estimated glomerular filtration rate (eGFR) was found to be an independent and progressively increasing risk factor for death, cardiovascular events and hospitalization.

Patients with chronic kidney disease are much more likely to suffer from cardiovascular events including sudden cardiac death than to eventually require renal replacement therapy (Sosnov et al, 2006). This is nowhere more apparent than in patients with atherosclerotic renal vascular disease who are five times more likely to die from cardiovascular disease than to require renal replacement therapy (Kalra et al, 2005).

Impaired renal function (either acute kidney injury or chronic kidney disease) is a major predictor of adverse outcomes in patients with cardiovascular disease. A key question is whether these associations merely reflect advanced disease and co-morbidity per se or whether an impairment of physiology in one system directly contributes to disease progression in the other.

Since individuals with chronic kidney disease have a much greater risk of morbidity and mortality as a result of cardiovascular events, management of cardiovascular risk factors should be a key element of their management; however, randomized control data are lacking in the chronic kidney disease population, in part because patients with impaired renal function have traditionally been excluded from large cardiovascular trials. This review will now focus on acute kidney injury in patients hospitalized for decompensated heart failure.

Renal function as an independent prognostic indicator in decompensated heart failure

Worsening renal function, a term used synonymously here with acute kidney injury, in patients hospitalized with decompensated heart failure is increasingly recognized as a significant problem and also a potential barrier to delivery of desired treatment. Studies have reported poor clinical outcomes in patients who develop acute kidney injury when hospitalized for decompensated heart failure (Cowie et al, 2004). Renal insufficiency, both pre-existing (chronic kidney disease) and new onset (acute kidney injury), is associated with an increased risk of death (Geisberg and Butler, 2006), both during and post-hospital stay, and increased duration of hospital admission (Cowie et al, 2004). Actual worsening of renal function (acute kidney injury), as opposed to degree of baseline renal impairment (chronic kidney disease), seems to be a stronger predictor for adverse outcome (Shlipak and Massie, 2004).

Cowie et al (2004) conducted the POSH trial (Prospective outcomes study in heart failure) looking at 299 patients aged >20 years, across eight European countries admitted to hospital with decompensated heart

Dr Natalie L Borman *is Renal Registrar in the Wessex Renal Unit, Queen Alexandra Hospital, Cosham, Hampshire,* **Dr Philip A Kalra** *is Consultant Nephrologist in the Department of Renal Medicine, Salford Royal Hospital and* **Dr Paul R Kalra** *is Consultant Cardiologist in the Department of Cardiology, Portsmouth Hospitals NHS Trust, Queen Alexandra Hospital, Cosham, Hampshire PO6 3LY*

Correspondence to: Dr PR Kalra

failure between October 2001 and November 2002, with 6 months' follow up. They found that 33% (95% confidence interval (CI) 27–38%) of patients developed acute kidney injury (which they described as 'worsening renal function') as defined by an increase in serum creatinine of >26 μmol/litre* (0.3 mg/dl) from baseline during their hospital admission with a mean time to development of acute kidney injury of 4 days (90% range 1–12 days). Mortality was higher in the acute kidney injury group during admission (12% *vs* 2% in those without acute kidney injury), rising to 15% by 30 days and 28% in total by 6 months, compared to 5 and 18% respectively in patients without acute kidney injury. However, the increased mortality in the acute kidney injury group was in part confounded by major events such as sepsis and intensive care unit admission, and the results were not statistically significant. The length of hospital stay was also significantly longer in patients who developed acute kidney injury at 13 days (90% range 4.9–44 days) *vs* 9 days in patients without acute kidney injury (90% range 4–31.2 days) (P<0.001).

The ADHERE registry collected data on more than 100 000 patients across 275 hospitals in the USA. It provides a comprehensive data set of unselected hospitalized patients with heart failure, unlike most clinical trials which have often excluded elderly patients and those with chronic kidney disease. Heywood (2004) specifically analysed patients from the ADHERE registry with the cardiorenal syndrome. Impaired eGFR was a strong predictor of mortality, being more predictive than ejection fraction in decompensated heart failure. Even a moderate rise in creatinine (>0.3 mg/dl) in hospitalized patients predicted an increased risk of death and prolonged hospitalization. The study confirmed that pre-existing chronic kidney disease is also a predictor of worse outcome and mortality. Individuals with pre-existing renal impairment were far more likely to suffer acute kidney injury in the setting of decompensated heart failure and had the poorest prognosis, regardless of their systolic function. Overall mortality was 4.8% when creatinine >2 mg/dl *vs* 2.3% when creatinine <2 mg/dl in patients with preserved systolic function. This rose to 8.4% when creatinine >2 mg/dl but remained similar at 2.9% with creatinine <2 mg/dl in those with reduced systolic function. When adjusted for other variables this gave an odds ratio of 2.45 (95% CI 2.07–2.92) in the group with preserved systolic function and 2.72 (95% CI 2.35–3.14) in the group with reduced systolic function, both of which were statistically significant (Yancy et al, 2006).

An increasing body of evidence has consistently shown that renal impairment and acute kidney injury in heart failure are strong and independent predictors of poor outcome and prognosis. Even a relatively small decline in renal function, that might be overlooked or dismissed in clinical practice, is of great significance in these patients (Smith et al, 2003).

Table 1 (p. 271) summarizes the major studies that have evaluated the impact of renal function on outcomes in patients with decompensated heart failure.

Pathophysiological mechanisms

Haemodynamic

The traditional theory of the pathophysiological mechanism of the cardiorenal syndrome concentrates on impaired renal function as a direct consequence of decreased renal perfusion as a result of reduced cardiac output. This derives from the understanding that the integrity of the arterial circulation, as determined by cardiac output and peripheral arterial resistance, is the primary determinant of renal sodium and water excretion (Schrier and Abraham, 1999; Zannad et al, 2006). Hence reduction in cardiac output stimulates systemic and intrarenal responses to retain fluid and restore cardiac output at an increased circulatory volume. As cardiac output continues to diminish, renal blood flow becomes impaired which activates complex responses that further decrease renal function but fail to normalize cardiac output (Stevenson et al, 2005).

However, the pathophysiology is far more complicated than this. A number of studies have shown little or no correlation between low ejection fraction and worsening renal function (Geisberg and Butler, 2006), suggesting that renal hypoperfusion consequent upon reduced cardiac output cannot be the only mechanism for the development of cardiorenal syndrome.

Intravascular hypovolaemia, especially in the context of diuretic use, has also been considered as a contributory factor in the development of cardiorenal syndrome. While Forman et al (2004) found that patients who develop cardiorenal syndrome were more likely to be clinically fluid overloaded than deplete on admission to hospital, patients can develop intravascular fluid depletion despite total body fluid overload with intravenous diuretics. Careful and repeated assessment of fluid status is therefore vital in all patients.

Damman et al (2007) highlighted the importance of venous congestion in the pathogenesis of cardiorenal syndrome, by finding that an increase in right atrial pressure was a significant independent predictor for the development of renal dysfunction in patients with decompensated heart failure. This appears to remain significant even when adjusted for renal blood flow (Dries et al, 2000). As renal perfusion will be influenced by the pressure gradient across the kidney it will be reduced not only when there is a reduction in mean arterial pressure but also when renal venous pressure is elevated (such as in patients with 'congestion' and elevated right atrial pressure). In decompensated heart failure both of these abnormalities commonly co-exist.

*Conversion factor for creatinine 1 mg/dl= 88 μmol/litre

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Atheromatous renal vascular disease can be identified in about a third of elderly patients who present with heart failure (MacDowall et al, 1998). Although renal artery stenosis is likely to be functionally and clinically insignificant in most of these patients (Cheung et al, 2005), in a small sub-group renal artery stenosis is a major contributor to patient morbidity. The syndrome of sudden onset or 'flash' pulmonary oedema is well described, patients typically having chronic kidney disease, hypertension, no overt coronary lesions and bilateral significant renal artery stenosis. However, there is increasing interest in the co-existence of atheromatous renal vascular disease with chronic heart failure (de Silva et al, 2005), not only because of the implications for renin–angiotensin–aldosterone system blockade but also because the kidney with renal artery stenosis is less likely to be able to respond with an appropriate natriuresis when conventional diuretic therapy is used to treat these patients.

Table 1. Clinical trials and studies detailing the prognostic implications of worsening renal function in decompensated heart failure

Study	No of patients	Patient characteristics	Measure of renal function	Outcome	Main results
Hillege et al (2000), clinical trial	1906	Patients aged 18–80 years enrolled in a survival study (PRIME II), in 13 European countries	Baseline eGFR <44 ml/min/1.73m² *vs* >76 ml/min/1.73m²	↑ mortality with eGFR <44 ml/min/1.73m² (relative risk 2.85, *P*<0.001) *vs* eGFR >76 ml/min/1.73m² left ventricular ejection fraction only modest predictor (*P*=0.053)	↓eGFR found to be strong and independent risk factor for poor outcome and mortality in decompensated heart failure
Ismailov et al (2007), retrospective cohort data analysis	4350	Patients hospitalized in the Worcester metropolitan area (USA) with acute heart failure between 1995 and 2000	eGFR grouped to: >60, 45–59, 30–44, <30 ml/min/1.73m²	Adjusted hazard ratio for mortality: eGFR (ml/min/1.73m²) — In hospital — 1 year >60 — 1.0 — 1.0 45–59 — 1.66 — 1.74 30–44 — 1.46 — 1.74 <30 — 1.88 — 2.29	eGFR of <60 ml/min/1.73m² was associated with a significantly higher mortality during hospital admission for decompensated heart failure and in the year following admission
Hillege et al (2006), analysis of data from CHARM study	2743	Patients with heart failure enrolled in the CHARM study with baseline serum creatinine assessment at enrolment	Baseline eGFR >60, 45–60, <45 ml/min/1.73m²	Hazard ratio for death, hospitalization and all causes mortality eGFR >60 ml/min/1.73m² = 1.0, eGFR 45–60 ml/min/1.73m² = 1.54, eGFR <45 ml/min/1.73m² = 1.86	Left ventricular ejection fraction and eGFR at baseline were independent prognostic markers. Lower eGFR = worse prognosis
Cowie et al (2004), prospective study (POSH)	299	Patients over age of 20 years, hospitalized for decompensated heart failure, across eight European countries	Baseline eGFR Change in creatinine WRF ≥ 26 μmol/litre increase	↑ mortality in WRF group *vs* non-WRF (nWRF) group. 12% during admission *vs* 2% in nWRF, 15% by 30 days in WRF *vs* 5% in nWRF, 28% in total by 6 months in WRF *vs* 8% in nWRF group, hospital stay significantly longer (≈ 4 days) in WRF 13 days *vs* 9 days in nWRF	WRF in patients hospitalized for decompensated heart failure leads to ↑ mortality during admission, at 30 days and 6 months post discharge, WRF ↑ duration of hospital stay
Forman et al (2004), retrospective cohort	1004	Patients hospitalized with a primary diagnosis of heart failure	Serum creatinine (mg/dl)	27% had WRF (increase >0.3 mg/dl). Patients who developed WRF (compared to no WRF) had: sevenfold ↑ death, twofold ↑complications, threefold↑ stay>10 days	Small ↑ in serum creatinine associated with adverse prognosis irrespective of the baseline or peak serum creatinine
Gottlieb et al (2002), retrospective cohort	1002	Patients hospitalized for decompensated heart failure	Serum creatinine (mg/dl)	72% had an ↑ creatinine	20% had ↑ >0.5 mg/dl, ↑ of 0.1 mg/dl associated with worse outcome and prolonged hospital stay
Dries et al (2000), retrospective analysis of SOLVD trial	4228	Patients enrolled into the SOLVD trial	Baseline creatinine (mg/dl) and eGFR: eGFR <60 ml/min/1.73m² or eGFR >60 ml/min/1.73m²	Moderate renal insufficiency in patients with heart failure (defined as eGFR <60) associated with ↑ risk of all causes of mortality relative risk = 1.41 (compared to 1.0 in eGFR >60) ↑ risk of death or hospitalization for heart failure relative risk = 1.33	Moderate renal insufficiency in patients with heart failure is associated with increased risk of all causes of mortality and heart failure progression
ADHERE registry	100 000	Data collection on patients admitted to hospital with decompensated heart failure, across 270 hospitals in North America	eGFR at baseline (ml/min/1.73m²) Change in creatinine mg/dl	30% of patients experienced > 20% ↑ in creatinine during admission >25% ↑ creatinine = specific marker for poor prognosis, worse eGFR at admission =↑ mortality and length of hospital stay (4.1 days with eGFR >90 ml/min/1.73m² *vs* 7 days <40 ml/min/1.73m²)	Worse eGFR at admission = ↑ mortality and length of hospital stay, small change in creatinine (>0.3 mg/dl) adverse prognostic indicator in patients hospitalized for decompensated heart failure WRF also associated with ↑ length of hospital stay

eGFR = estimated glomerular filtration rate; WRF = worsening renal function

Activation of renin–angiotensin–aldosterone system

The activation of the renin–angiotensin–aldosterone system secondary to low renal perfusion pressure or blood flow is a protective physiological mechanism that attempts to prevent under-perfusion of vital organs such as the kidney (Bongartz et al, 2005).

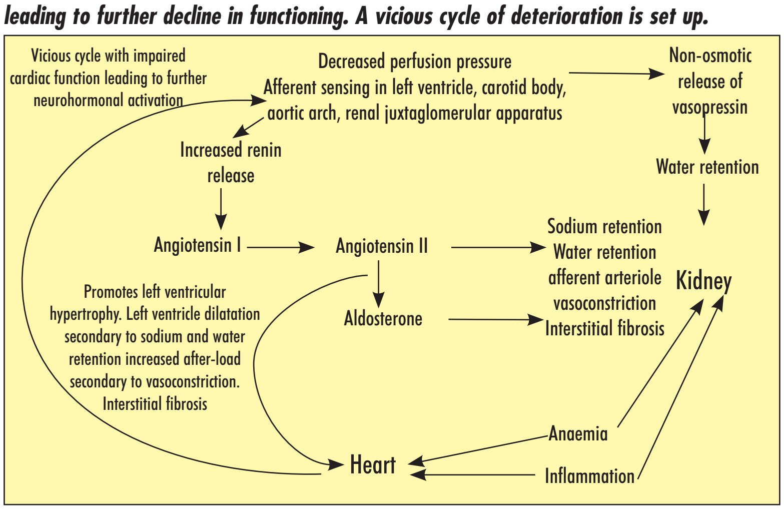
In heart failure activation of the renin–angiotensin–aldosterone system leads to sodium and water retention as a result of the actions of angiotensin II and aldosterone. Initially this may preserve central aortic pressure but continued activation leads to adverse haemodynamic effects on the vasculature, heart and kidney. For example, chronic sodium and water retention lead to left ventricular dilatation and increased afterload. Direct unfavourable effects of these neurohormones are seen on the kidney (intraglomerular hypertension and intrarenal fibrosis) and heart (myocardial cellular hypertrophy and interstitial fibrosis) (Hillege et al, 2000). Hence prolonged activation of the renin–angiotensin–aldosterone system leads to both worsening renal function, with a reduction in renal blood flow and eGFR (Bongartz et al, 2005), and worsening cardiac function with increased myocardial oxygen demand, myocardial ischaemia, impaired contractility and arrhythmogenesis.

Inflammatory immune activation

Chronic heart failure and advanced chronic kidney disease share pathophysiological similarities in terms of neurohormonal activation and inflammatory immune activation. In patients with chronic heart failure inflammatory cytokines such as tumour necrosis factor and interleukin-6 are independent predictors of adverse outcome (Anker et al, 2002), and they may contribute to progression of the clinical syndrome. It has been hypothesized that in decompensated heart failure gut wall oedema (secondary to elevated right atrial pressure) facilitates translocation of bacterial endotoxin (lipopolysaccharide) (Niebauer et al, 1999). The net result is inflammatory cytokine activation, which may in turn adversely impact on cardiac and renal function.

Interactions between the heart, kidneys, renin–angiotensin–aldosterone system, sympathetic nervous system, endothelium and immune system occur via intricate feedback loops (Geisberg and Butler, 2006) (*Figure 1*). Disruption or imbalance in this system can lead to deterioration in both cardiac and renal function. Hence any number of factors may contribute to acute kidney injury and cardiorenal syndrome and it is highly plausible that for any one patient a number of mechanisms may be at play.

Figure 1. A simplified overview of the complex interplay between afferent sensing mechanisms, neurohormonal systems and the kidney and heart. A decrease in arterial perfusion pressure leads to activation of the renin–angiotensin–aldosterone and sympathetic nervous (not shown) systems, together with non-osmotic release of vasopressin. The net result is volume expansion secondary to sodium and water retention and peripheral vasoconstriction, increasing in both pre- and after-load. Angiotensin II and aldosterone have direct deleterious effects on myocardial and renal structure and function. Other factors commonly seen in heart failure or chronic kidney disease, such as anaemia and inflammation, may adversely affect the kidney and heart leading to further decline in functioning. A vicious cycle of deterioration is set up.



Risk factors for development of cardiorenal syndrome

Advanced age, diabetes, pulmonary oedema on chest X-ray on admission (Cowie et al, 2004), co-morbid vascular disease, higher level of baseline urea (Heywood, 2004), hypertension and lower systolic blood pressure on admission (SOLVD Investigators, 1991) have all been associated with increased risk of developing cardiorenal syndrome. There have been inconsistent findings in relation to ejection fraction with studies such as SOLVD suggesting a link between poor ejection fraction and increased risk of acute kidney injury in decompensated cardiac failure, while others have shown no association (Geisberg and Butler, 2006).

Pre-existing renal impairment

Pre-existing renal impairment (chronic kidney disease) is associated with progressive heart failure. There are several plausible pathophysiological reasons to account for this:

- A number of aetiological factors are common to both renal and cardiac disease such as diabetes and hypertension and hence renal impairment may reflect a greater burden of co-existing disease (Dries et al, 2000)
- Renal dysfunction may also be a marker of general vascular disease, with atherosclerosis present both within the kidney and the heart
- Patients with renal impairment are commonly anaemic. Low haemoglobin may directly impact on cardiac dysfunction and renal dysfunction thereby contributing to a vicious cycle of deterioration in both organ systems (Kalra et al, 2003; Iaina et al, 2007)
- Impaired renal function may also be seen as a direct reflection of an impaired haemodynamic status that relates to the severity of the underlying cardiac disease (Hillege et al, 2006)
- Impaired renal function via activation of neurohormonal systems (as described above) contributes to further cardiac dysfunction.

For many patients with heart failure the development and progression of renal dysfunction is the result of a combination of these factors (*Figure 1*). From a pathophysiological perspective, no matter what the aetiology, it is highly likely that advancing renal function leads to worsening cardiac function, and vice versa.

Treatment options

Treatment of patients with acute kidney injury in the setting of decompensated heart failure is challenging. Most heart failure trials excluded patients with marked renal impairment, resulting in a lack of evidence to guide best practice in the management of patients with renal impairment and heart failure. *Table 2* suggests a management approach for patients with cardiorenal syndrome.

Diuretics

Diuretics remain the mainstay of treatment in decompensated heart failure. Many studies found that, even when adjusting for confounding variables, higher doses of diuretics were independently associated with increased risk of death. However, it is likely that this is because sicker patients receive the highest doses of diuretic (Geisberg and Butler, 2006). A number of studies have also shown aggressive diuresis to be associated with worsening renal function (Shlipak and Massie, 2004).

Oral diuretics often have variable absorption secondary to gut oedema. This may be a contributory factor in the development of diuretic resistance which is usually seen in combination, but not exclusively, with cardiorenal syndrome. The net result is continued sodium and water retention and consequent increased cardiac filling pressure, progressive ventricular dilation and hyponatraemia (De Silva et al, 2005). In general, intravenous diuretics are needed in decompensated heart failure. These are more effective when given via slow continuous infusions than in bolus (Francis, 2006; Geisberg and Butler, 2006). The aim is to promote gradual diuresis, thereby allowing time for fluid in the periphery to move from the extravascular to intravascular space and avoid significant drops in renal perfusion (i.e. avoiding intravascular depletion).

Patients with renal impairment often develop diuretic resistance; various pathophysiological mechanisms contribute to this but detailed discussion is beyond the scope of this article (reviewed by Geisberg and Butler, 2006). An option here is to co-administer a thiazide diuretic which may provide synergistic benefit by ensuring that sodium reabsorption is inhibited at multiple sites within the nephron (i.e. loop of Henle and distal tubule).

Angiotensin-converting enzyme inhibitors and/or angiotensin receptor blockers

Treatment with angiotensin-converting enzyme inhibitors has a survival benefit in patients with heart failure (SOLVD Investigators, 1991; Cowie et al, 2004). Creatinine levels often rise after the initiation of angiotensin-converting enzyme inhibitors in decompensated heart failure, especially with pre-existing renal impairment (Shlipak and Massie, 2004). However, patients with renal impairment may derive greater benefit from angiotensin-converting enzyme inhibitors as they are at higher absolute mortality risk. It is the authors' opinion that for many such patients a moderate deterioration of renal function, allowing up to a 20% increase in creatinine, should be tolerated.

The CONSENSUS Study Group (1987) showed that patients were more likely to have a creatinine rise after initiation of an angiotensin-converting enzyme inhibitor if they had pre-existing renal impairment or severe heart failure. Most patients had a 10–15% increase in creatinine within 3 weeks of starting enalapril, irrespective of their baseline creatinine. Serum creatinine then tended to settle at this or an improved level over the subsequent months, despite continuation of enalapril.

Initiation of angiotensin-converting enzyme inhibitor or angiotensin receptor blocker therapy should be carried out when patients are as stable and well hydrated (i.e. intravascular volume optimized) as possible; use of other nephrotoxic drugs such as non-steroidal anti-inflammatory drugs should be avoided. Initiation of angiotensin-converting enzyme inhibitors in the setting of declining renal function and decompensated heart failure is not generally recommended. The majority of patients will most likely already be receiving such therapy. The temptation for the clinician is to discontinue angiotensin-converting enzyme inhibitor or angiotensin receptor blocker therapy in view of any developing acute kidney injury. Ideally these should be maintained wherever possible, provided renal function does not steadily decline or severe hyperkalaemia (potassium >6.0 mmol/litre) does not supervene.

A small subgroup of patients with very low blood pressure may require temporary reduction in beta-blockers or angiotensin-converting enzyme inhibitors (other antihypertensive agents such as calcium-channel blockers should be stopped first) during major exacerbations, with the aim of increasing mean arterial pressure and renal perfusion with consequent improved diuresis. Once the patient has been stabilized these should be re-introduced or uptitrated.

Table 2. Suggested management of cardiorenal syndrome in clinical practice
Avoid or discontinue all nephrotoxic drugs such as non-steroidal anti-inflammatory drugs
If blood pressure is low (systolic <100 mmHg) reduce or stop other 'non-specific' antihypertensive drugs, e.g. calcium-channel antagonists, nitrates
Try to continue angiotensin-converting enzyme inhibitors and beta-blockers
Give intravenous diuretics via a continuous infusion
Co-administer a thiazide diuretic if renal function allows and especially if diuresis is inadequate
In extreme cases with accelerated worsening renal function and low blood pressure (systolic <90 mmHg) temporary reduction or discontinuation of angiotensin-converting enzyme inhibitors or beta-blockers may be necessary
Other treatments such as haemofiltration may be considered
Potential novel therapies include treatment of anaemia (erythropoietin and intravenous iron), vasopressin receptor antagonists, adenosine receptor antagonists

Other treatments

While beta-blocker therapy has dramatically improved the prognosis for patients with chronic heart failure, it should not be started in acute decompensated heart failure. The COPERNICUS study (Packer et al, 2002) showed the benefits of beta-blockers in severe heart failure, but intravenous therapies were discontinued in all patients in this study for >48 hours before introduction of beta-blockers.

Spirinolactone is of prognostic and symptomatic benefit in advanced heart failure (Pitt et al, 1999). Its use poses a particular problem of hyperkalaemia in acute kidney injury and patients with pre-existing chronic kidney disease, especially when used in conjunction with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. However, in the authors' opinion these agents should not be routinely stopped in cardiorenal syndrome unless severe hyperkalaemia (potassium >6.0 mmol/litre) ensues, and even this can often be offset by optimization of other diuretic therapy and appropriate dietary modifications.

Novel therapies

Arginine vasopressin secretion from the pituitary gland may be increased by low blood pressure in heart failure (Kalra et al, 2001). It has a regulatory effect on aquaporin-2 activity in the collecting duct of the kidney. It determines the water permeability of the collecting duct and hence is associated with decreased diuresis; excess arginine vasopressin therefore leads to free water retention and hyponatraemia. Blocking the vasopressin receptor has potential appeal in heart failure, with increased free-water diuresis and associated retention of electrolytes improving congestion and hyponatraemia (Geisberg and Butler, 2006). Hence, vasopressin receptor antagonists are a promising option for the future. In the ADHERE registry 5% of patients with decompensated heart failure had severe hyponatraemia with sodium <130 mmol/litre (a larger number had milder degrees of hyponatraemia). In the EVEREST study 4133 patients with decompensated heart failure were randomized to conventional therapy and tolvaptan (vasopressin antagonist) or placebo. There was no difference in mortality at 60 days, but tolvaptan was associated with improved weight loss and patient symptoms (Gheorghiade et al, 2005; Cavalcante et al, 2008).

Adenosine receptor antagonists are also currently under investigation. Patients with heart failure have high plasma adenosine levels. Adenosine can lower renal cortical blood flow, restricting the diuretic response to traditional diuretic agents. Blocking the adenosine receptor improves diuresis without adversely affecting the eGFR (Cotter et al, 2008). The results of large scale outcome studies are awaited.

Haemofiltration as an alternative to diuretic therapy has many theoretical advantages in patients with severe decompensated heart failure. These include removal of isotonic fluid directly from the intravascular space and also the beneficial removal of cytokines. Small scale clinical studies have not demonstrated consistent improvement in outcomes or renal function (Francis, 2006). Costanzo et al (2007) conducted the largest study to date comparing ultrafiltration and standard intravenous diuretic therapy for hypervolaemic heart failure patients. They randomized 200 patients hospitalized with heart failure to either ultrafiltration or intravenous diuretic, and looked at weight loss and dyspnoea assessment at 48 hours after randomization, net fluid loss at 48 hours, functional capacity and readmission to hospital with heart failure. At 48 hours weight loss and net fluid loss were greater in the ultrafiltration group (P=0.001), and rehospitalization for heart failure was also lower (P=0.022). However, there was no significant difference in dyspnoea scores, serum creatinine levels or death.

Peritoneal dialysis has been used in patients with refractory heart failure. The largest trial to date was a single centred, prospective non-randomized study of 20 patients between 2000 and 2003 (Gotloib et al, 2005). Patients received three 8-hour sessions of automated peritoneal dialysis a week with a mean ultrafiltration rate of 2102 ml/session (95% CI 2009–2195 ml/session). They reported a subsequent improvement in the patients' clinical condition and fluid balance, and a reduction in mortality and in hospitalization, but these results were not statistically significant. Other case series have also suggested improvement in patients' clinical condition and fluid status but these are limited by very small numbers (Kagan and Rapoport, 2005). The rationale is that peritoneal dialysis provides a slow continuous removal of fluid, resulting in a reduction in plasma volume, an improvement in hyponatraemia and a reduction in capillary wedge pressure. No overall improvements in cardiac function have been shown, but there are reports of improved diuretic responsiveness (Mehrotra and Khanna, 2001). There are, however, no specific trials looking at its use in the cardiorenal syndrome.

Conclusions

The cardiorenal syndrome is commonly encountered in hospital practice. Traditionally acute kidney injury has been attributed to poor cardiac output or pre-renal failure as a result of excess diuretic use. Accumulating evidence suggests that the mechanisms are much more complex. Acute kidney injury in patients hospitalized for decompensated heart failure is a poor prognostic indicator associated with increased patient mortality and longer duration of hospital stay. Traditional heart failure treatments which have proven efficacy and survival benefit should not be withheld in these patients. Treatment with angiotensin-converting enzyme inhibitors should be maintained, albeit with greater care, monitoring and appropriate dose alterations. Further research and the development of new therapeutic options is needed to provide a brighter future for this high-risk group of patients. **BJHM**

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KEY POINTS

- Acute kidney injury is commonly encountered in patients admitted to hospital with decompensated heart failure (previously referred to as worsening renal function).
- Acute kidney injury is an independent poor prognostic indicator in decompensated heart failure.
- These patients present a major clinical management challenge.
- Randomized controlled trial data for treatment of patients with decompensated heart failure and cardiorenal syndrome are notably lacking.
- In patients with decompensated heart failure, initial treatment with intravenous diuretics, often via continuous infusion, is generally required.
- Continuation of angiotensin-converting enzyme inhibitors, except in extreme cases, is highly preferable.
- Novel therapies are currently under investigation and these may be key to future improved management of these high-risk patients.