Renal replacement therapy for heart failure patients: in whom, when and which therapy to use?

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It has long been recognized that chronic or acute heart failure can lead to initiation or progression of renal dysfunction or insufficiency. More recently, it has been shown that the cross-talk is bi-directional and that primary renal dysfunction or insufficiency represents an independent cardiovascular risk factor. This bi-directional cross-talk between the heart and kidneys was defined as ‘the cardiorenal syndrome’ (CRS). CRS is associated with different clinical conditions and heart–kidney disorders and varies according to the initiating factor of the syndrome. In a recent state-of-the-art paper, Ronco et al. [1] proposed a new classification of CRS that includes five subtypes based on the primary cardiac or renal dysfunction as well as the acute or chronic clinical evolution. Acute CRS was categorized into type 1, characterized by rapid worsening of cardiac function leading to acute kidney injury or type 3, which is an acute renovascular syndrome characterized by primary abrupt worsening of kidney function leading to acute cardiac dysfunction. Chronic CRS was classified into type 2, characterized by chronic heart dysfunction and failure causing progressive deterioration of kidney function, and type 4, which includes a chronic renovascular syndrome characterized by primary chronic kidney disease (CKD) followed by cardiac and vascular complications. A secondary type 5 CRS was defined as combined cardiac and renal dysfunction secondary to systemic diseases or to multi-organ failure.

From the clinical and therapeutic point of view, practicing nephrologists most frequently observe the chronic CRS types in patients having renal disorders due to or associated with severe primary cardiac dysfunction.

Chronic heart failure and renal disorders

The kidney is an integrated component of the cardiovascular system. Cardiovascular dysfunction or failure can disturb renal function leading to acute or chronic renal failure, and in turn, the functions of the heart and blood vessels are closely linked to those of the kidney. Decreased renal function is highly prevalent among patients with chronic heart failure (CHF). The development of cardiac failure induces a series of pathophysiological changes that affect renal function, which can subsequently contribute to the pathophysiology of CHF and to a worsening of clinical manifestations. The degree of renal involvement is particularly important in patients with CHF characterized by low-cardiac output. The most characteristic alteration is a reduction in renal blood flow, a direct consequence of reduced cardiac output [2]. Renal blood flow normally represents 15–20% (600 ml/min/m²) of cardiac output and is very sensitive to changes in systemic flow. Decreases in cardiac output induce a redistribution of flow, and renal vasoconstriction is a characteristic consequence. Renal vasoconstriction involves both pre- and post-glomerular arterioles but with an enhanced constriction in the efferent arteriole. This adaptation maintains GFR within the normal range and is characterized by an increased filtration fraction. These systemic and local adaptations result from an activation of a number of systemic and local hormonal and humoral regulatory systems, such as the sympathetic nervous system, the renin–angiotensin–aldosterone axis, arginine vasopressin, atrial and brain natriuretic peptides, nitric oxide, prostaglandins, endothelin and other systems. One characteristic observed during the progression of CHF is an increased activation of vasoconstrictor systems that overwhelm the activity of vasodilators. The consequences of these neurohumoral responses are reduced excretions of salt, water and metabolic products (increased blood urea or creatinine) and the urinary loss of potassium and magnesium; all of these factors, in turn, directly affect cardiac dysfunction [3]. In addition to the haemodynamic effects associated with hypoperfusion of the kidneys, chronic activation of vasoconstrictor systems may directly affect the structure and remodelling of the heart, vessels and the kidneys. This is characteristic of angiotensin II and aldosterone, which promote vascular remodelling, tissue fibrosis, oxidative stress and inflammation.

In extremely advanced stages of CHF, patients show substantially reduced renal blood flow, depressed glomerular filtration, low urine output, refractory oedema and renal failure. These conditions are frequently exacerbated by therapy that add to the progression and worsening of renal function, which is a factor associated with poor outcomes. The management of combined CHF and CKD is difficult, and in the presence of refractory oedema and volume overload, renal replacement therapy (RRT) may provide an alternative [4]. Although short-term RRT is normally used, chronic RRT (frequently deferred for serious comorbid...
conditions) may provide a definitive therapeutic strategy in patients with irreversible renal failure. The incidence of chronic RRT in CHF patients is not well documented, and its impact on outcomes in the general CHF population has not been clearly documented.

In the current issue of this journal, Liang et al. [5] attempted to provide some of this information. The authors studied the rate of RRT and its impact on mortality in a large cohort of patients admitted for heart failure (HF) in the MAYO clinic. The major finding was that cardiac characteristics appeared not to influence the need for RRT (mainly haemodialysis during the 16-year follow-up). From a cardiological point of view, these results are disappointing: with or without systolic dysfunction (assessed in 76% of the global cohort with echo), heart characteristics did not play a role in the incidence of RRT. A history of coronary artery disease, which was higher in patients who subsequently required RRT (65% versus 57%, \(P = 0.0002\)), was not linked to RRT in multiple regression analysis. Instead, diabetes, anaemia and young age (the latter was probably linked to the retrospective design of the study) significantly predicted progression to RRT. Atrial fibrillation, which probably alters cardiac output (and subsequently renal blood flow) more than true left ventricular function, was at a lower prevalence in patients requiring RRT (25% versus 34%, \(P = 0.0039\)), and was not predictive of progression to RRT. The need for RRT was strongly associated with diabetes (61% of RRT patients versus 32% without, \(P < 0.0001\)) and probably with hypertension (but masked by the impact of diabetes in multiple regression analysis). Anaemia, which is probably the consequence of renal failure, exerts its own deleterious effects that have been well studied in HF populations [6,7]. Importantly, in Liang et al. [5], 97% of the patients were Caucasian. Although this provided a certain homogeneity in the data, which were based on a cohort study, this patient group was far different from the general HF population. A prevalence of diabetes was also observed in this global population requiring admission due to an HF event. These epidemiological problems may limit the applicability of the present findings to the entire hospitalized HF population.

After full adjustment, use of RRT was not associated with a decrease in mortality, while unadjusted survival was lower in this group. As this was a cohort-based retrospective study, it appears that RRT was given to younger patients having greater illness due to diabetes, anaemia and worsening of renal disease. Finally, RRT improved survival in these patients in spite of a lower life expectancy at baseline. In addition, RRT was offered to an increasing number of diseased patients during the latter part of the study. This study had many limitations, which included its retrospective nature, registry crossing and a limited access to data showing the natural evolution of HF after initial hospitalization that created a limited ability to adjust for medications and risk factors associated with CKD (nutrition, anaemia, mineral metabolism). As stressed by the authors in their conclusion, a further controlled study should define the appropriate clinical setting in which RRT should be used.

In conclusion, the methodology in the study by Liang and co-workers provides both an interesting focus and a new concept for studying the cardiorenal syndrome; however, the cross-linked methodology between two independent registries reminds us that new concepts must be based on a robust prospective study. Unexpectedly, the data showed that cardiac events related to HF or altered ventricular function were not determinants for a future need for dialysis. They nevertheless show that diabetes remains a strong deleterious disease for renal function. Although RRT is a well-established tool for refractory oedema and volume overload with major HF, the study by Liang et al. did not confirm an advantage of this strategy in the clinical setting of the MAYO clinic during the second half of the study. Recent and efficient pharmacological strategies for treatment of HF, including ACEI and beta blockers, probably reduced the need for RRT in this observational cohort and may have improved survival; however, this was not documented in the study. Finally, Liang et al. demonstrated that RRT improved the survival of mainly young diabetic patients. Because HF did not influence the need for RRT in this population, it is interesting that HF and its sequelae did not amplify the normally shortened life expectancy usually observed in patients requiring this survival technique. As mentioned by Liang and co-workers, further prospective studies are greatly needed to clarify these points.

Conflict of interest statement. None declared.


References


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