Cardio-renal failure: an emerging clinical entity

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Background and definition

The progressive ageing of the population, the extensive application of cardiac interventional procedures and the improved prognosis of diseases with a so far dismal outcome have generated several predictable corollaries. Of remarkable importance is the rising number of ‘survivors’ who have combined heart and kidney failure [1,2]. More specifically, we do not refer to the severe cardiovascular disease accompanying chronic renal failure, nor to the so-called ‘kidney in heart failure’, a concept which assumes normally functioning kidneys facing a failing heart. Instead, we draw attention to the fragile equilibrium between simultaneously and often seriously compromised renal and cardiac function. Let us define this condition as cardio-renal failure.

By definition, cardio-renal failure is more than renal failure and more than heart failure (HF) alone; therefore, its management may require strategies different from those for the two entities considered separately. The view presented herein is based on traditional concepts, personal observations and an oriented reading of the literature.

Epidemiology

Patients with cardio-renal failure are a group of potentially high resource expenditure, as the cost of HF alone has been estimated to amount to ~2% of the total health budget. Of these expenses, 70% are due to hospital readmissions [3]. Furthermore, cardio-renal failure may be a critical factor in the 50% mortality within 3 years of diagnosis of Europeans older than 75 years with HF [4].

Knowing the real prevalence of cardio-renal failure is not an easy task; in fact, it does not readily result from estimations in restricted inclusion trials. In the HF setting, trials involving large cohorts of aged or multimorbid patients are presently underway [5]. In this sense, large-scale studies such as HOPE [6] and HOT [7] have confirmed the frequent association between renal insufficiency and worsening of cardiovascular disease [8,9]. Also, renal failure is associated with increased cardiovascular mortality in HF patients, attaining up to 1% per each 1 ml/min decrease in creatinine clearance (CrCl) [5,10–13]. Recent data applicable to cardio-renal failure prevalence allow one to estimate that >50% of the population with HF has a CrCl <60 ml/min, including patients with a plasma creatinine below 2 mg/dl. Hidden renal failure may help to explain the unfavourable renal outcome of a number of patients with cardiac disease.

Pathophysiological considerations

The normal response to haemorrhage or hypotension is a stimulation of the renin–angiotensin–aldosterone system (RAAS) and the sympathetic nervous system. This response is not designed to defend the organism against HF or renal failure, but to preserve it from water and salt depletion. With volume reduction, the RAAS becomes activated in a progressive manner, namely increased proximal tubular reabsorption at $10^{-13}$ M angiotensin (ANG) II, efferent arteriole constriction at $10^{-12}$ M ANG II, and afferent arteriole constriction, central nervous system activation, systemic vasoconstriction and increased myocardial contractility between $10^{-11}$ and $10^{-10}$ M ANG II.

In HF, a neurohumoral sympathetic response and an endothelin response [ET1(A), ET1(B) and ET2] occur even earlier than the RAAS response. Blood ET-1 has been correlated with the severity and mortality of HF. Data obtained in animal models suggest that the endothelins have a relevant haemodynamic role that leads to systolic ventricular dysfunction [14].

In normal circumstances, the fluid content of a healthy organism has no major oscillations, and an efficient compensation exists for volume gain and
losses. In contrast, in the cardio-renal failure setting, the avoidance of pendular phases of overfilled-decompensated and emptied-overtreated states becomes of great importance. Maintaining the stimulation of the pressor systems as normal as possible, as well as normal/high levels of brain and atrial natriuretic peptides, is a major practical objective. In this regard, the natriuretic peptides have effects opposite to the RAAS and the adrenergic system. They decrease intrarenal vascular resistance, sodium reabsorption and tubular ATP consumption, diminish thirst and salt appetite, and improve myocardial contractility.

Management

A main initial difficulty resides in recognizing the presence of cardio-renal failure. In fact, a reduced nephron reserve may be concealed by near normal values of plasma creatinine [15]. Deranged renal function is an underappreciated prognostic factor in HF, and renal failure is frequently viewed as a relative contraindication to proven, efficacious therapies [5].

The management of cardio-renal failure patients is an intellectually demanding process. It requires an in-depth understanding of the particular renal, haemodynamic and internal milieu conditions of the patient to be treated (Figure 1). This should lead to the design of a specific, carefully tailored therapy which emphasizes the particular equilibrium of each individual patient. Management should be directed towards realistic objectives, aimed to preserve the best possible balance, rather than pursuing the entire normalization of parameters, e.g. some degree of peripheral oedema might be tolerated.

Recurrent complications should be prevented, using a close and individualized follow-up. The early recognition of impending complications or decompensations does not require a sophisticated work-up and can be achieved by simple tools, including basic routine physical examination, body weight and blood pressure monitoring, and the measurement of blood and urine urea and electrolyte concentration. Also, it is important to recognize minimal risk factors, such as minor changes in dietary salt intake, or diarrhoea, which may be irrelevant in other individuals, but critically important in cardio-renal failure patients.

Particular therapeutic issues

Drugs that have demonstrated their utility in HF, e.g. angiotensin-converting enzyme inhibitors (ACEIs), β-blockers or spironolactone, are rather underused in cardio-renal failure. Recent studies, however, suggest that their value in cardio-renal failure is at least equivalent to that observed in isolated HF [5]. In the case of ACEIs, it has been shown that early increases (<2 months) of plasma creatinine in cardio-renal failure patients may actually be a marker of lower risk of renal function worsening in the long run [16]. In cardio-renal failure patients, an extremely cautious introduction or reintroduction of ACEIs is advisable, starting with small doses, e.g. as low as 6.25 mg of captopril or 2 mg of enalapril daily.

The protective effects of β-blockers can be extended to patients with cardio-renal failure, although the

Fig. 1. The fragile equilibrium between factors predisposing to and protecting from cardio-renal failure. Frequent complications are shown in the grey box. ‘Flood’ pulmonary oedema refers to extremely acute pulmonary oedema, akin to the ‘flash’ pulmonary oedema of bilateral renal artery stenosis. RAAS = renin-angiotensin-aldosterone system; SNS = sympathetic nervous system; AVP = arginine vasopressin.
possibility of increasing the risk of hyperkalaemia should be taken into account (see below).

When using diuretics, a new balance can be reached at the expense of maintaining effective circulating volume at a nearly depleted level; this determines a deficient adaptation to volume variations and stimulates the RAAS and adrenergic drive [17,18]. Of interest, both pressor systems synergize with a third one, namely, arginine vasopressin (AVP), in an attempt to preserve arterial pressure in the setting of pump failure and diminished fluid content; however, the three systems probably are also synergistic in their deleterious cardiac and renal effects [19,20]. A readily appraisable clinical marker of this interaction is the presence of hyponatraemia, a common feature in advanced HF, whose occurrence is facilitated in cardio-renal failure.

In contrast to diuretics, when treatment focuses on RAAS inhibition or vasodilation goals, the renal perfusion pressure may diminish to critical values, thereby inducing a decrease in salt and fluid elimination, with an aggravation of extracellular fluid retention, and the precipitation of severe forms of pulmonary oedema [21].

The development of new families of drugs may significantly affect the therapy of cardio-renal failure. For example, the use of endopeptidase inhibitors improves haemodynamics, but at the price of RAAS stimulation and sodium retention; this can be potentially troublesome in cardio-renal failure. The combination of endopeptidase inhibitors and ACEIs does not appear to resolve these shortcomings. With regards to ET-1 antagonists, to our knowledge, no experience is available in patients with cardio-renal failure.

**Cardio-renal failure, aldosterone blockade and hyperkalaemia**

Even though cardio-renal failure may be a ploughed field for both cardiac and renal pro-fibrogenic effects of aldosterone, it is also a high risk situation for developing the potential complications of aldosterone inhibitors. Indeed, a combination of ACEIs and spironolactone should be considered with caution and monitored closely in patients with cardio-renal failure [22].

Hyperkalaemia can be the leading complication in the therapy of individuals with cardio-renal failure. Patients with a serum creatinine $>1.5\,\text{mg/dl}$ who are on ACEI treatment may have a markedly higher risk of developing hyperkalaemia due to impaired potassium elimination. HF by itself increases the risk of hyperkalaemia by $\sim 3$ times [23]. This risk in patients with HF has increased on the stream of the Randomized Aldactone Evaluation Study [24]. It seems that physicians may not monitor closely enough the serum potassium levels in these patients and may use spironolactone doses higher than $25\,\text{mg/day}$; furthermore, they may neglect baseline attributes that predispose patients to hyperkalaemia, specially renal failure and diabetes mellitus, and may overlook the impairment of renal function that develops during therapy [25]. No degree of insistence on this particular issue is sufficient in patients with cardio-renal failure. Plasma potassium should be monitored frequently; also, the measurement of urinary potassium can be of great help in the follow-up of cardio-renal failure patients, as a harbinger of changes in the capability for potassium excretion.

**Three relevant therapeutic aspects**

The role of anaemia is a particularly important issue in the scenario of cardio-renal failure. Recent studies have established that both renal failure and anaemia are independent risk factors for mortality in HF [26,27], even when renal failure is defined by a plasma creatinine of no more than $1.4\,\text{mg/dl}$. In the series of McClellan et al., the mortality observed at 12 months in individuals with HF, with or without anaemia, was of $44.9$ and $31.9\%$, respectively [26]. Several pathogenic factors have been contemplated in this context [28], e.g. increased blood losses, inflammation or decreased erythropoietin (EPO) production or effect. Since EPO treatment has been introduced as a new approach to the global care of HF, it is important to determine the optimal target for haemoglobin values. While in such patients, the correction of anaemia improves symptoms and contributes to cardiac remodelling, negative effects may perhaps occur if near normal values of haemoglobin are reached [29].

An additional point to be kept in mind about cardio-renal failure is the possible co-existence of bilateral renal artery stenosis. A survey in elderly patients presenting with HF showed unilateral renovascular disease in $26\%$ and bilateral renovascular disease in $8\%$. This makes the inclusion of a Doppler ultrasound advisable in the diagnostic work-up of cardio-renal failure patients. However, the benefits of renal revascularization procedures in cardio-renal failure may be more obvious for the cardiac than the renal component, and may be confined almost exclusively to patients with critical lesions [21]. The earlier the diagnosis of renovascular disease is made, the more valuable the results which can be obtained.

A special note should be issued on the promising utility of ultrafiltration techniques in the acute and chronic management of cardio-renal failure [30]. Ultrafiltration has been successfully employed in re-positioning these patients towards a more suitable point on the Frank–Starling curve, and may be a life-saving procedure in the case of diuretic failure.

**Conclusion**

Cardio-renal failure should be recognized as a specific entity. Medical expertise in finding the optimal point
of equilibrium is the key element in its management. Further experience needs to be accumulated to define more completely the clinical profile and therapeutic needs of these patients with a very complex disease.

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