Cardiorenal syndrome—current understanding and future perspectives

Branko Braam, Jaap A. Joles, Amir H. Danishwar and Carlo A. Gaillard

Abstract | Combined cardiac and renal dysfunction has gained considerable attention. Hypotheses about its pathogenesis have been formulated, albeit based on a relatively small body of experimental studies, and a clinical classification system has been proposed. Cardiorenal syndrome, as presently defined, comprises a heterogeneous group of acute and chronic clinical conditions, in which the failure of one organ (heart or kidney) initiates or aggravates failure of the other. This conceptual framework, however, has two major drawbacks: the first is that, despite worldwide interest, universally accepted definitions of cardiorenal syndrome are lacking and characterization of heart and kidney failure is not uniform. This lack of consistency hampers experimental studies on mechanisms of the disease. The second is that, although progress has been made in developing hypotheses for the pathogenesis of cardiorenal syndrome, these initiatives are at an impasse. No hierarchy has been identified in the myriad of haemodynamic and non-haemodynamic factors mediating cardiorenal syndrome. This Review discusses current understanding of cardiorenal syndrome and provides a roadmap for further studies in this field. Ultimately, discussion of the definition and characterization issues and of the lack of organization among pathogenetic factors is hoped to contribute to further advancement of this complex field.

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Introduction

Cardiorenal syndrome encompasses conditions in which failure of either the heart or the kidney leads to, or accelerates, failure of the other organ.[1] Combined heart and kidney dysfunction is very heterogeneous in its clinical presentation, although forms of cardiorenal syndrome associated with combined heart and renal failure confer extremely high morbidity and mortality.[1–4] Cardiorenal interactions have received substantial attention in the past decade. Nevertheless, two important prerequisites for further development of the concept have not yet been met: a precise definition of cardiorenal syndrome and a mechanistic framework that facilitates the design of clinical and experimental studies. Nevertheless, a clinical classification system has been designed, based on the order in which organs are affected and the time frame (acute versus chronic).[3] In the absence of any mechanistic alternative, this classification has been widely adopted.

Interactions between cardiac and renal function have traditionally been explained by haemodynamic factors.[5–8] Initial observations about renal venous pressure and, subsequently, the haemodynamic model proposed by Guyton, explain combined heart and renal failure in terms of interactions between cardiac filling and contractility, renal function, blood pressure, and blood and extracellular fluid volumes.[9] However, structural damage to both the heart and the kidney has been reported in patients with cardiorenal syndrome, which cannot easily be explained by haemodynamic factors alone.[10–14] Our research group consequently introduced the concept of cardiorenal connectors[1]—factors that are modulated by either heart or kidney failure, affect both organs, interact, and are associated with functional or structural, renal or cardiac consequences. Despite the attractiveness of this concept, conclusive identification of cardiorenal connectors is difficult and, specifically, a hierarchy among such factors is hard to define.

Deciphering of interactions between the heart and kidney is currently in its infancy. Thus, this Review focuses on two major conceptual issues that have emerged in the cardiorenal field: the difficulty of precisely defining disease entities that consist of combined cardiac and renal failure; and the current status of the hypothetical framework for cardiorenal syndrome. We also highlight issues regarding hierarchical organization of potential pathogenetic factors and the existence of a final common pathway to cardiorenal syndrome.

Definition of cardiorenal syndrome

The definition of the cardiorenal syndrome has developed over time (Box 1). Any definition should address key dimensions of the cardiorenal interaction: first, the primary failing organ, second, the interaction being unidirectional or bidirectional, third, the nature of the disease affecting the organs, fourth, the pathophysiological mechanism (haemodynamic versus nonhaemodynamic) and, finally, the time course of development of the interaction (acute versus chronic). None of the current definitions at this time addresses all of the dimensions.

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Competing interests
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Key points

- Interactions between the heart and kidney form the basis of cardiorenal syndrome, which is a heterogeneous and complex clinical entity associated with substantial morbidity and mortality
- Precise clinical characterization and classification of cardiorenal syndrome has not yet been performed
- The factors that mediate connections between the heart and the kidney and their complex interactions must be clarified *in vitro* and in experimental models before clinical applications are sought
- Iron metabolism and erythrocyte turnover are likely to be central to the pathophysiology of cardiorenal syndrome

Box 1 | Evolving definitions of cardiorenal syndrome

- 2004: The frequent presentation of combined cardiac and renal dysfunction[104]
- 2004: The presence or development of renal dysfunction in patients with heart failure[105]
- 2006: Severe cardiorenal syndrome is a pathophysiological condition in which combined cardiac and renal dysfunction amplifies progression of failure of the individual organs[1]
- 2008: Cardiorenal syndrome is a pathophysiological disorder in which acute or chronic dysfunction of one organ may induce acute or chronic dysfunction in the other[3]
- 2010: Each dysfunctional organ has the ability to initiate and perpetuate disease in the other organ through common haemodynamic, neurohormonal, and immunological and/or biochemical feedback pathways[16]

In the absence of clear mechanistic understanding, "a clinical-descriptive definition is the only possibility, and should be regarded as a temporary, operational, expedient" (Figure 1).[15] As a clinical expedient, the definitions by Bongartz *et al.*[1] published in 2005 and by Bock *et al.*[16] published in 2010 might be the most theoretically appealing; however, the operational definition described by Ronco *et al.*[3] in 2008 is likely the most practical in the clinic. Without a universally accepted definition, each study of cardiorenal syndrome should be explicit about what the definition for cardiorenal syndrome is for that study and each of the five 'dimensions' listed above should be defined and addressed. To achieve these overarching descriptions, it is problematic that nephrologists and cardiologists use different definitions of acute kidney injury (AKI, as used by nephrologists), also referred to as worsening of renal function (WRF, as used by cardiologists). Furthermore, when defining a cardiorenal condition, the damage to each individual organ should be graded. This specification might seem trivial; however, we have no generally accepted biomarker for the detection of early AKI and clinical grading of the severity of heart failure remains extremely complex, even in animal experiments.[17]

Classification of heart and kidney failure

Clinical classification of a disease serves a number of different purposes[18]. First, it can serve to create labels to establish clear communication about a clinical entity. This clarity would also enable quantification of the disease via measures of prevalence and incidence. Classification can also be used for the analysis of aetiologies and prediction of outcome. A good example in the cardiorenal field is how classification of patients with heart failure and elevated versus normal central venous pressure has led to the clinical recognition of the link between central venous pressure and renal function impairment in patients with heart failure.[19–21] Second, the method of classification can be based on temporal patterns (acute versus chronic, reversible versus irreversible), on simultaneous occurrence of signs and symptoms (that is, symptoms that define syndromes) and on particular diagnoses. Third, when disease mechanisms are well understood, classification can be based on structural and/or functional analysis. A recent proposal for cardiorenal syndrome based on this premise is an excellent first step towards such a functional classification.[22] Finally, a good classification is based on unambiguous and measurable criteria

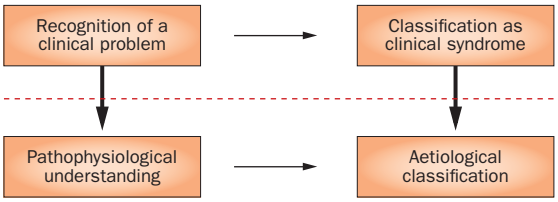

Figure 1 | Evolution in the understanding of a clinical condition. Initial recognition of a clinical condition typically leads to its characterization as a syndrome with a heterogeneous presentation. However, a mechanistic understanding of the basis of the condition is necessary to provide an aetiological classification. In the case of cardiorenal syndrome, the absence of mechanistic understanding (dashed line) presents a substantial obstacle to development of a useful and consistent classification scheme.

that are discriminatory in terms of clearly defining the disease and, preferably, map to disease mechanisms and therapeutic options for a given patient.

The few currently available classifications of cardiorenal syndrome do not comply with such requirements for a valid classification (Box 2). In the acute setting, there is no agreement among cardiologists, intensivists and nephrologists with respect to the diagnosis of worsening of renal function, that is AKI. Worsening of renal function in the context of heart failure has been diagnosed by an absolute change in serum creatinine levels,[4,20] or a change in plasma creatinine levels of >20%.[23] The RIFLE criteria (acronym indicating Risk of renal dysfunction, Injury to the kidney, Failure of kidney function, Loss of kidney function, and End-stage kidney disease) use a multilevel classification, and incorporate urine flow as parameter of renal function.[24] The rate of decline in renal function is considered by criteria used by the AKI Network,[25] but not by the other criteria.

To illustrate how easily a classification can become ambiguous, the aetiology and recognition of groups two (chronic cardiorenal syndrome) and four (chronic renocardiac syndrome) of the Acute Dialysis Quality Initiative (ADQI) cardiorenal syndrome classification should be considered.[26] If the patient is first diagnosed with CKD, cardiac investigations would likely follow and

Box 2 | Classification of cardiorenal interactions

Why classify?
- Labelling and communication
- Quantification (prevalence and incidence)
- Analyses of aetiology
- Prediction of prognosis

How to classify?
- Temporal patterns (acute versus chronic, reversible versus irreversible)
- Diagnoses or syndromes
- Mechanisms
- Structural features
- Functional features

What makes a classification useful?*
- Measurable criteria
- Unambiguous
- Discriminatory
- Highlights mechanisms
- Drives therapy

*None of these items has been fulfilled for cardiorenal syndrome.

Box 3 | Clinical presentation of cardiorenal interactions

The clinical presentations below might provide information about cardiorenal interactions.

Acute renocardiac
- Living kidney donor*
- Kidney transplant recipient*
- Acute renal failure*
- Acute interstitial nephritis
- Urinary tract obstruction

Acute cardiorenal
- Acute myocardial infarction (without important haemodynamic consequences*)
- Heart transplant*
- Acute heart failure (acute cardiomyopathy)*

Chronic renocardiac
- Chronic kidney disease*

Chronic cardiorenal
- Chronic heart failure*

*Not caused by a systemic haemodynamic event, not caused by a major systemic event (for example autoimmune disease), not associated with major haemodynamic consequences, and not associated with significant volume retention.

could reveal heart failure, and vice versa. This situation has been recognized by the ADQI group.[27] Clinical situations that could provide data for the compilation of a robust classification of CRS occur in critical care, nephrology and cardiology settings, and a combined effort might be required to achieve this goal (Box 3).

Coupling between the heart and kidneys

Haemodynamic factors

In 1931, an association between increased renal venous pressure and reduced renal blood flow was reported in dogs.[8] In 1956, the consequences of an increase in renal venous pressure for peritubular capillary and intratubular pressure were assessed in rats.[28] A slight increase in renal venous pressure (0–15 mmHg) had little effect on either peritubular capillary or intratubular pressures; however, further increases caused linear increases in both these parameters. The transmission of increased renal venous pressure to increased intratubular pressure is important, since every 1 mmHg increase in intratubular pressure directly reduces net ultrafiltration pressure—which is normally only ~20 mmHg[29]—thereby decreasing glomerular filtration rate (GFR). Importantly, this physiological principle resurfaced when several different studies established a relationship between central venous pressure and renal blood flow in patients with heart failure.[19]

Subsequent work, drawing together the understanding of systemic haemodynamics, pressure-natriuresis and the phenomenon of total-body autoregulation, explained physiological cardiorenal interactions in terms of extracellular fluid volume homeostasis and blood pressure control.[9] This conceptual framework is now widely accepted. A direct consequence of this model is that heart failure induces a decline in cardiac output and arterial blood pressure that activates the sympathetic nervous system (SNS) and the renin–angiotensin system (RAS).[30,31] This activation leads to volume expansion which, in turn, restores renal perfusion.[30,31] Interestingly, these haemodynamic factors provide bidirectional coupling in patients with heart failure, such that the renal failure induced by heart failure leads to sodium and water retention, further aggravating heart failure, and potentially further decreasing arterial pressure and elevating renal venous pressure. This bidirectional coupling is quite profoundly illustrated in patients with untreated heart failure, who show large increases in extracellular fluid and plasma volumes.[32] Indeed, drugs that reverse this vicious cycle (such as inhibitors of the RAS, β-blockers, digoxin, nitrates, aldosterone inhibitors and loop diuretics) are successfully used as therapeutic agents in patients with heart failure. However, this therapeutic approach is not successful in a number of conditions, suggesting that other underlying disturbances have a role.[33] A detailed discussion of all haemodynamic factors that could potentially drive heart and/or kidney failure is beyond the scope of this Review, and such information can be found elsewhere.[34,35] The reader should note, however, that information about renal haemodynamics and segmental sodium handling in patients with combined heart and renal failure is extremely limited.

Nonhaemodynamic factors

Our research group initially proposed that several cardiorenal connectors—the RAS, SNS, inflammation, and the balance between nitric oxide (NO) and reactive oxygen species (ROS)—underpin all nonhaemodynamic cardiorenal interactions.[1] This hypothesis forms an extension to the haemodynamic model of cardiorenal interaction, but does not replace it. However, for each of these factors, interactions have been described with all the other factors, which make this concept quite complicated.

The RAS can be considered a prototypical cardiorenal connector, since it fulfils the prerequisite of a bidirectional response and is induced by both heart failure and by renal failure. Renin release is triggered by decreased renal artery pressure,[36] increased renal venous pressure,[37,38] decreased delivery of sodium to the distal nephron[39] and increased

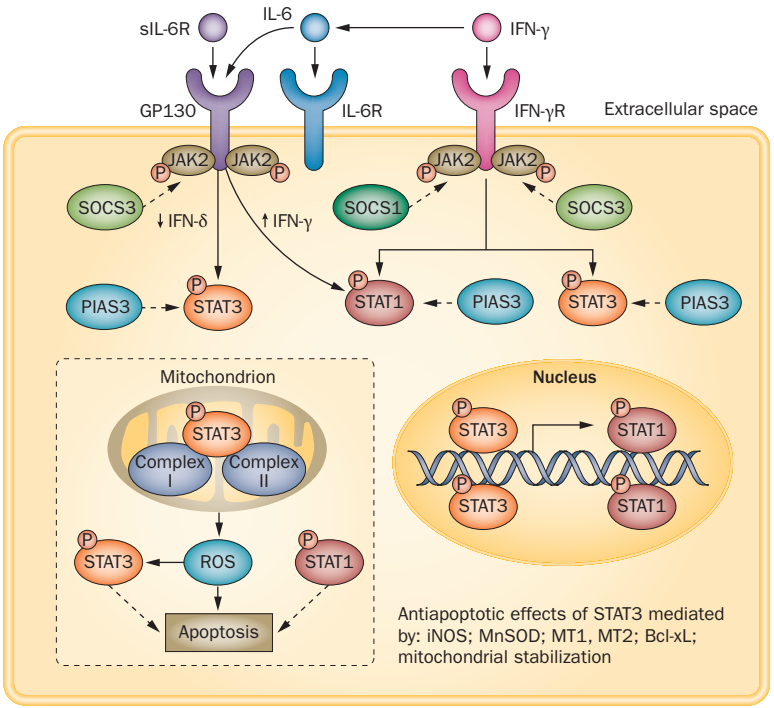

Figure 2 | IL-6 is one of the many factors implicated in cardiorenal interactions. Complex interactions occur between IL-6 and other cardiorenal connectors at various levels: signalling pathways, transcriptional regulation, and in mitochondria. Abbreviations: Bcl-xL, Bcl2 antagonist of cell death; IFN, interferon; IFN-γR, IFN-γ receptor; IL, interleukin; IL-6R, IL-6 receptor; iNOS, inducible nitric oxide synthase; JAK2, tyrosine-protein kinase JAK2; MnSOD, superoxide dismutase; MT, metallothionein; PIAS3, E3 SUMO-protein ligase; ROS, reactive oxygen species; sIL-6R, soluble IL-6R; SOCS, suppressor of cytokine signalling; STAT, signal transducer and activator of transcription.

activity of the SNS,[36] which all occur in heart failure and/or CKD. Activation of the RAS is associated with myocardial remodelling[40] and fibrosis.[41] These structural consequences of RAS activation seem to happen in conjunction with activation of other cardiorenal connectors. Angiotensin II-induced ROS production by NADPH oxidase is present in patients with cardiorenal syndrome and is implicated in inflammation. Angiotensin II stimulates proinflammatory cells through their type-1 angiotensin II receptors as part of the physiological response to stress (reviewed elsewhere[42]). Moreover, the RAS and SNS are tightly coupled.[43]

A critical look at the RAS in the context of clinical cardiorenal syndrome reveals that inhibition of the RAS is associated with improved outcomes in patients with heart failure, many of whom also have CKD. By contrast, whether RAS inhibitors can prevent AKI (or worsening of renal function) in patients during acute heart failure is not known. In fact, RAS inhibitors are frequently discontinued in such patients, since they are held to be responsible for the deterioration of renal function, which might not be true. Nevertheless, some arguments and data suggest that, for instance, aggressive diuresis would have increased efficacy during RAS inhibition.[35,44] Data on the effects of RAS inhibition on renal haemodynamic and excretory function or on cardiac function in experimental models of cardiorenal syndrome are absent.

The SNS, similarly to the RAS, also fulfils the prerequisites of bidirectional cardiorenal coupling and activation in both heart failure and CKD.[45–47] Again, multiple connections link the SNS with other cardiorenal connectors. Despite the availability of many drugs that target the RAS or the SNS, the consequences of dual inhibition of these systems in experimental models of combined heart and renal failure have not been investigated, and no robust clinical trials have tested whether any of the clinical presentations of cardiorenal syndrome can be prevented by such treatment. Of note, more than 10 studies of selective renal denervation are ongoing in patients with heart failure,[48] and their results are expected to provide detailed insight into the complex role of renal nerves in cardiorenal syndrome.

The last two connectors are of an even higher complexity: the balance between NO and ROS, and inflammation. NO and ROS are both involved in renal sodium handling, systemic haemodynamics[49] and renal haemodynamics,[50–54] generally in opposing ways. Moreover, the balance between NO and ROS has complex consequences for the regulation of cardiac function.[55] Both renal failure and heart failure are associated with decreased NO bioavailability and pro-oxidant status,[56,57] which in turn can lead to aggravation of renal failure and heart failure.[58] Treatment with a tolerance-free NO donor in a model of established renocardiac failure improved both renal and cardiac function.[59] However, convincing evidence that antioxidant therapy is effective at reducing cardiovascular events and/or renal disease progression in either CKD[60] or heart failure[61,62] is lacking, although discussion on this issue is ongoing.[63]

A complex cardiorenal connector: IL-6

The concept of cardiorenal connectors is hampered by a notable lack of insight into the hierarchy between the identified factors, owing to their complex molecular and cellular interactions. We will discuss the cellular actions of interleukin-6 (IL-6) in some detail to illustrate the drawbacks of this lack of knowledge about cardiorenal interactions. IL-6 is a pleiotropic cytokine that signals via the tyrosine-protein kinase JAK2 and signal transducer and activator of transcription 3 (STAT3). Throughout its signalling and effector pathways, complex interactions are documented at the level of receptor binding, postreceptor signalling and through mechanisms that modulate IL-6-induced gene transcription.[64]

The main IL-6 signalling pathway, which acts via STAT3 in the nucleus (reviewed elsewhere[65–67]), modulates the transcription of genes linked to the cell cycle, inflammation, apoptosis, cytokine signalling and lipid metabolism (Figure 2).[68] A first indicator of the complexity of IL-6 signalling is that STAT3 has also been found in the mitochondria of mouse heart, kidneys, liver, brain and splenocytes,[69] where it interacts with the electron transport chain. STAT activity is regulated by various protein tyrosine phosphatases, including suppressors of cytokine signalling (SOCS).[70–73] SOCS3 is a strong negative regulator of IL-6 signalling;[74] however, SOCS3 production and feedback inhibition is not necessarily specific to IL-6,

which can lead to cross-inhibition of other signals.[70,74] Furthermore, IL-6 interacts in multiple ways with other cardiorenal connectors, although these interactions have not been fully characterized. For example, angiotensin II alone[75] or a combination of tumour necrosis factor (TNF) and interferon gamma (IFN-γ)[76] both stimulate the production of IL-6 by monocytes. However, IFN-γ treatment (without TNF) upregulates the expression of IL-6 receptor mRNA and increases IL-6 binding to this receptor on the cell surface, whereas IL-6 combined with TNF treatment downregulates both IL-6 receptor mRNA and IL-6 receptor binding in monocytes.[76] Finally, the effects of IL-6 might not be identical under all circumstances. For instance, its antiapoptotic effects are modulated by other cytokines.[77–79] IFN-γ mainly promotes inflammation and apoptosis,[80] but notably also diverts IL-6 signalling to the STAT1 pathway rather than the 'main' STAT3 pathway, thereby dampening the antiapoptotic effects of IL-6.

Taken together, signalling downstream of the IL-6 receptor involves not only transcription-factor-related signalling to the nucleus, but also actions on the mitochondria. These responses strongly depend on the prevailing environmental conditions, formed by interactions with other cardiorenal connectors. Simple blockade of either IL-6 receptors or IL-6 signalling will, therefore, lead to unpredictable responses, and clinical trials of these approaches seem premature. Novel analytical methods, such as those based on systems biology, are probably needed to unravel the contributions of specific factors and cardiorenal connectors to clinically relevant outcomes.

The search for a master switch

Anaemia, as well as being highly prevalent in patients with chronic heart failure or CKD, is thought to convey an elevated risk of hospital admission for decompensated heart failure and of cardiovascular events and death in patients with CKD.[81] These observations led to the proposal that heart failure, CKD and anaemia interact such that the presence of one factor causes or exacerbates the other factors, termed cardiorenal anaemia syndrome.[82,83] Conversely, treatment of anaemia could improve outcome in patients with heart failure or CKD. Indeed, a large number of observations in experimental models of cardiorenal anaemia syndrome suggested that treatment of anaemia with erythropoiesis-stimulating agents has beneficial effects on both cardiac and renal function. The biological actions of erythropoietin on cardiorenal connectors are beyond the scope of this article, but have been reviewed elsewhere.[84,85]

In direct contrast to the positive preclinical findings, three major trials of this approach in patients with anaemia and CKD who were not on dialysis (CREATE,[86] CHOIR[87] and TREAT[88]) all reported negative results. Despite normalization of haemoglobin levels, treatment with erythropoiesis-stimulating agents did not reduce cardiovascular events, renal damage or mortality in these patients.[86-88] Moreover, a trend towards an increased risk of stroke was noted in TREAT.[88] *Post-hoc* analyses of the TREAT[85] and CHOIR[86] data indicated that, in particular, patients who received the highest doses of erythropoiesis-stimulating agents also had the lowest haemoglobin response, which seemed to account for the overall negative outcome; however, these studies were not designed to separate poor and good responders. The RED-HF trial compared the effects of darbepoietin alfa against placebo in over 2,000 patients with heart failure, and found no benefit (in terms of improved outcomes) for correction of anaemia with erythropoietin;[89] again a higher incidence of stroke was reported as well as more thromboembolic events in the active-treatment group. Multiple mechanisms could explain the absence of any positive effect of treatment with erythropoiesis-stimulating agents in patients with heart failure, such as increased blood viscosity, increased locoregional levels of endothelin-1[90] or components of the RAS,[91] and decreased antithrombotic activity.[92] Such responses to these agents might counteract any positive effects of the treatment.[93]

Despite observations that anaemia worsens the cardiovascular outcomes of patients with CKD and heart failure, partial or complete correction of anaemia using erythropoiesis-stimulating agents clearly does not reverse this increased risk. However, these findings do show that haemoglobin level *per se* is not the master switch (if such a switch exists) in the network of cardiorenal connectors. Yet, in our opinion, the mechanism driving anaemia remains of major interest to both the basic scientist and the clinician involved in cardiorenal syndrome.[94] In an attempt to elucidate the actions of erythropoietin and iron in more detail in patients with chronic combined heart and kidney disease and mild anaemia, our research group investigated short-term (2 weeks) and long-term (6 months) responses to low, fixed doses of erythropoiesis-stimulating agents. Our study (EPOCARES)[95] was designed so that the effects of erythropoiesis-stimulating agent that are not mediated by haemoglobin level could be evaluated, and distinguished from their haematopoietic effects by using a short treatment on the one hand and by keeping haemoglobin in one treatment group chronically at baseline by repeated phlebotomies on the other hand. A number of observations in this study point towards iron metabolism and erythrocyte turnover as a potentially important pathway in cardiorenal syndrome.[96–98] These findings are in keeping with those of studies on iron deficiency in heart failure and CKD.[99]

Owing to the negative results of studies based on normalization of haemoglobin levels using erythropoiesis-stimulating agents, anaemia management in patients with heart failure has shifted towards intravenous iron treatment. This change has been driven by studies demonstrating the beneficial effects of correcting iron deficiency with ferric carboxymaltose on quality of life, symptoms and functional capacity in patients with chronic heart failure,[100] and by publication of new KDIGO (Kidney Disease: Improving Global Outcomes) guidelines.[101] Unfortunately, these clinical investigations are not backed up by experimental studies in heart failure and CKD and understanding of the effects of iron administration on renal function and cardiomyocyte function remains limited. That being said, large trials to evaluate renal and

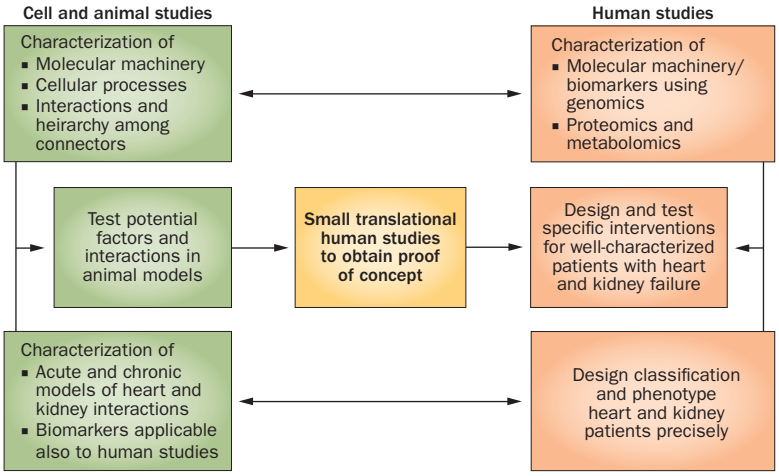

Figure 3 | Proposed 'roadmap' for future studies of cardiorenal syndrome. Small translational studies in well-characterized patients are central to this scheme, to serve as a link between experimental models, cell culture studies and human pathophysiology. A data-driven discussion in the literature might then facilitate a systems biology approach, which in turn could function as a solid basis for further clinical trials.

cardiac outcomes in patients with well-characterized cardiorenal syndrome are still awaited.

Models of cardiorenal syndromes

Given that a number of pathophysiological factors could drive the initiation and progression of cardiorenal syndrome, correcting or blocking some of the cardiorenal connectors seems a logical approach. Nevertheless, the information regarding interventions that target cardiorenal connectors is incomplete and/or conflicting. The complexity of these interactions is already clear from the above-described actions of IL-6, and the clinical observations about erythropoiesis-stimulating treatment of patients with cardiorenal anaemia syndrome. A few considerations with respect to RAS inhibition further illustrate this point.

Patients with CKD, heart failure or both respond differently to RAS blockade. Thus, these patients clearly do not all have the same renal and cardiac receptor density and sensitivity. Such differences will determine their renal and cardiac, functional and structural responses to the prevailing (local) levels of angiotensin II and other components of the RAS (such as angiotensin 1–7). For example, if angiotensin II strongly constricts the postglomerular vasculature in an individual, blockade of this factor's actions would induce a decrease in GFR with potential further deterioration of cardiorenal syndrome as a consequence. However, if vasoconstriction is preferentially preglomerular, RAS blockade could ameliorate the renal dysfunction, and potentially also renal ischaemia. Information about factors that predict the benefit or harm of RAS inhibitors (which are often administered in combination with diuretics) on renal excretory function is lacking. In this respect, one important approach might be study of the interaction of RAS with concomitant changes in other cardiorenal connectors.[102] However, the complexity of such interactions probably requires a systems biology approach, rather than a factor-by-factor analysis.

Future perspectives

A thorough consideration of the complex interactions between the heart and the kidney in disease is now required: the first step is to reach a consensus about useful theoretical and clinically practical definitions of cardiorenal syndrome; the next is to reach consensus about a useful classification of cardiorenal syndrome, which would enable subgroups of patients to be characterized and phenotypes to be linked to disease mechanisms (Figure 1). The haemodynamic and nonhaemodynamic abnormalities in patients with combined heart and kidney failure then need to be accurately phenotyped; finally, the molecular, cellular, and pathophysiological roles of individual factors involved in these interactions need to be studied in well-defined cell culture and animal models (Figure 3).

Crucially, future analyses of cardiorenal interactions should not focus on clinical outcomes in large studies, since such studies perpetuate the false assumption that the population of patients with cardiorenal syndrome is homogeneous. An example is provided by the PROTECT trial,[103] which was partly based on the asssumption that inappropriate activation of tubuloglomerular feedback (a component of renal autoregulation) was involved in the reduction of GFR in patients with heart failure. More than 2,000 patients were enrolled in the study, which compared the effects of an adenosine A1 receptor antagonist that inhibits tubuloglomerular feedback to placebo.[103] Unfortunately, we are currently unsure whether and to what extent tubuloglomerular feedback is activated in all patients with heart failure, and this potentially useful therapy might have been abandoned prematurely. Similarly, no reasons exist to assume that manipulating endogenous factors in the internal environment would cause homogeneous responses in the different cell types involved in the development of cardiorenal damage.

Conclusions

Heart and kidney interactions are complex and the subject of immense clinical and scientific interest and debate. In this Review, we argue that without consensus on definitions and classification, clinicians will not be able to precisely phenotype the various forms of cardiorenal syndrome. Such phenotyping, in turn, forms the basis for *in vitro* and animal studies, as well as small translational studies in patients. The Babylonian confusion that currently exists can then evolve into a classification of the disease and its treatment that has a sound mechanistic basis.

Review criteria

For this review we used PubMed as our main source of information. Search terms varied per subtopic. All articles identified were English-language, full-text or review papers. We also searched the reference lists of identified articles for further relevant papers.

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