Cardiorenal Syndromes: Definition and Classification

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Abstract
To include the vast array of interrelated derangements, and to stress the bidirectional nature of the heart-kidney interactions, the classification of the cardiorenal syndrome (CRS) includes today five subtypes whose etymology reflects the primary and secondary pathology, the time-frame and simultaneous cardiac and renal codysfunction secondary to systemic disease. The CRS can be generally defined as a pathophysiologic disorder of the heart and kidneys, whereby acute or chronic dysfunction in one organ may induce acute or chronic dysfunction in the other organ. Type 1 CRS reflects an abrupt worsening of cardiac function (e.g. acute cardiogenic shock or decompensated congestive heart failure) leading to acute kidney injury. Type 2 CRS describes chronic abnormalities in cardiac function (e.g. chronic congestive heart failure) causing progressive and permanent chronic kidney disease. Type 3 CRS consists in an abrupt worsening of renal function (e.g. acute kidney ischemia or glomerulonephritis) causing acute cardiac disorder (e.g. heart failure, arrhythmia, ischemia). Type 4 CRS describes a state of chronic kidney disease (e.g. chronic glomerular disease) contributing to decreased cardiac function, cardiac hypertrophy and/or increased risk of adverse cardiovascular events. Type 5 CRS reflects a systemic condition (e.g. diabetes mellitus, sepsis) causing both cardiac and renal dysfunction. The identification of patients and the pathophysiological mechanisms underlying each syndrome subtype will help to understand clinical disorders and to design future clinical trials.

Introduction
Cardiac disease is often associated with worsening renal function and vice versa. The coexistence of cardiac and renal disease significantly increases mortality, morbidity, and the complexity and cost of care [1, 2]. Syndromes describing the interaction between the heart and the kidney are recognized, but have never
been clearly defined and classified. Several different definitions have been proposed [1, 3–8] with limited understanding of epidemiology, diagnostic criteria, prevention and treatment.

In response to these issues, a consensus conference was organized under the auspices of the Acute Dialysis Quality Initiative (ADQI) by bringing together key opinion leaders and experts in the fields of nephrology, critical care, cardiac surgery, cardiology and epidemiology. A consensus definition and classification system for the cardiorenal syndromes (CRS) was reached [9].

**Methodology and ADQI Process**

The ADQI process was applied using previously described methodology [10]. In brief, the ADQI methodology comprises a systematic search for evidence with review and evaluation of relevant literature, establishment of clinical and physiologic outcomes for comparison of different treatments, description of current practice and analysis of areas in which evidence is lacking and future research is required. A full description of the used methodology can be found in the official ADQI website www.ADQI.net.

Three key questions regarding definition and classification were identified by the entire ADQI group, and a subgroup deliberated on these questions, bringing forth recommendations to the group as a whole.

1. Is there a need for an overall definition of the clinical syndromes derived from cardiac and renal interactions?

<table>
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<th>Table 1. Definition and classification of the CRS</th>
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<td><strong>CRS general definition:</strong></td>
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Results

There was unanimous agreement that a consensus definition was needed for the CRS. It was perceived that the existing literature was inconsistent or lacking, that disciplines tended to be organ centered, and that the bidirectional nature of these syndromes was poorly appreciated. A new definition would provide a common platform for multidisciplinary approaches. It was agreed that a large umbrella term be preferred, using the plural, to indicate the presence of multiple syndromes. Subtypes would recognize the primary organ dysfunction (cardiac versus renal) as well as the acute versus chronic nature of the condition. Both organs must have or develop structural or functional abnormalities. An additional subtype was desired to capture systemic conditions that affect both organs simultaneously [3–9].

Consensus Definition and Classification

CRS were defined as ‘disorders of the heart and kidneys whereby acute or chronic dysfunction in one organ may induce acute or chronic dysfunction of the other’. Five subtypes of the syndromes were identified and defined as reported in table 1.

Acute Cardiorenal Syndrome (Type 1)
This appears to be a syndrome of worsening renal function that frequently complicates hospitalized patients with acute decompensated heart failure and acute coronary syndrome. Many previous attempts to define ‘cardiorenal syndrome’ correspond to this subtype. This entity has specific epidemiology, pathogenesis, treatment and prevention strategies. In the US, over one million patients are hospitalized each year with acute decompensated heart failure, and it is estimated that 27 to nearly 40% of these patients will develop acute kidney injury as defined by an increase in serum creatinine of at least 0.3 mg/dl [2, 11]. Those who experience worsening renal function have a higher mortality and morbidity, and increased length of hospitalization.

Chronic Cardiorenal Syndrome (Type 2)
This subtype is a separate entity from acute CRS as it indicates a more chronic state of kidney disease complicating chronic heart disease. This is an extremely common problem. For instance, in patients hospitalized with congestive heart failure, approximately 63% meet the K/DOQI definition [12] of stage 3–5.
chronic kidney disease, representing an estimated glomerular filtration rate <60 ml/min/1.73m² [13].

**Acute Renocardiac Syndrome (Type 3)**

Although acute kidney injury is recognized as an important cause of acute heart disorder, the pathophysiological mechanisms likely go beyond simple volume overload and hypertension, and the recent consensus definition for acute kidney injury [14] will aid in the investigation and analysis of epidemiologic data. The incidence and prevalence of this syndrome are currently unknown; however, the development of new biomarkers, and the study of prevention and management strategies in acute kidney injury following radiocontrast or cardiac surgery, for example, will increase our knowledge of this syndrome.

**Chronic Renocardiac Syndrome (Type 4)**

A large body of evidence has accumulated demonstrating the graded and independent association between level of chronic kidney disease and adverse cardiac outcomes. In a recent meta-analysis, an exponential relation between the severity of renal dysfunction and the risk for all-cause mortality was described. Compared with a ‘normal’ glomerular filtration rate of 100 ml/min, the adjusted relative odds for death associated with glomerular filtration rate of 80, 60, and 40 ml/min were 1.9, 2.6, and 4.4, respectively [15]. Overall mortality was driven by excess cardiovascular deaths, which constituted over 50% of the total mortality.

**Secondary Cardiorenal Syndromes (Type 5)**

Although this subtype does not have a primary and secondary organ dysfunction, situations do arise where both organs simultaneously are targeted by systemic illnesses, either acute or chronic. Examples include sepsis, systemic lupus erythematosus, amyloidosis and diabetes mellitus.

Many patients may populate or move between subtypes during the course of their disease describing the possibility that a vicious circle is instituted when heart and kidney present simultaneous or combined dysfunction (fig. 1) [16]. The classification was not meant to fix patients into one immovable category. The group discussed and considered further subclassification, to include situations of transient or reversible dysfunction, slowly or acutely progressive versus stable disease, however chose a more parsimonious and simple scheme for this iteration.

**Conclusions**

Through the ADQI consensus on CRS, other processes will now be facilitated, including a better or clearer understanding of the epidemiology of these
conditions, opportunities for early diagnosis through biomarkers, the development of preventive strategies and application of evidence-based management strategies (where available). The application of these consensus definitions will also allow the identification of gaps in the literature, and provide direction for future research including clinical trials.

This classification indeed represents a tool to promote new interaction between cardiology and nephrology in the attempt to build a new pathway of collaboration and a new holistic approach to patients suffering from combined heart and kidney disorders.

References


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