Definition and classification of Cardio-Renal Syndromes: workgroup statements from the 7th ADQI Consensus Conference

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Introduction

Both cardiac and renal diseases are extremely common in the population and frequently coexist. Cardiac disease is often associated with worsening renal function and vice versa. The coexistence of cardiac and renal disease significantly increases mortality, morbidity and 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] but none have been published as a result of a consensus process. As a result of the lack of consensus definition and classification, there is limited appreciation of its epidemiology, no standardized diagnostic criteria and no uniform approaches to prevention and treatment. Furthermore, treatment is often fragmented, single organ centred, with perceived competing priorities and specialty care is not necessarily integrated amongst relevant specialties. As a result, timing and appropriateness of care may suffer. 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 meeting was held in Venice, Italy from September 3 to 6, 2008. In this manuscript, we present the consensus document and the methodology by which a consensus definition and classification system for Cardio-Renal Syndromes was reached [9].

Methods

Rationale

The group recognized that an overall definition was needed to recognize the coexistence of cardiac and renal disorders. Classification of subtypes was required to recognize the primacy of one organ leading to dysfunction in the other and to identify, if possible, the time course of this interaction. The group also considered that, by analogy with other conditions in medicine, a classification system for Cardio-Renal Syndromes would prove useful for epidemiological studies, identification of target populations for intervention, development of targeted diagnostic tools, prevention and management of the syndromes and promotion of effective communication and collaboration among investigators and clinicians from multiple disciplines. The group believed that this process would help in furthering education and awareness in this field. The group was also aware that significant knowledge gaps exist and considered that definition and classification would help promote a research agenda.

ADQI process

The ADQI process was applied using previously described methodology [10] to identify key opinion leaders in this field and appropriate topics for consensus. 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.

ADQI activities are divided into a pre-conference, conference and post-conference phase. During the pre-conference phase, topics are selected and work groups are assembled. Each group identifies key questions, conducts a systematic literature search and generates a bibliography of key studies. Literature review is applied using key terms relevant to the topic and electronic reference libraries with focus on human studies. During the conference, work groups assemble in breakout sessions, as well as plenary sessions where their findings are presented, debated and refined. A series of summary statements are then developed and final versions are agreed upon by the entire group. Post-conference, reports are produced from each working group and posted on the ADQI website (http://www.ADQI.net) and mailed to each participant for comment and revision. Final reports are summarized into a final conference document.

Informed by previous publication records, the Steering Committee of ADQI VII assembled a diverse panel representing multiple relevant disciplines from a variety of countries and scientific societies. Experts were selected on the basis of previous contribution to the literature in this field and invited by an organizing committee. Funding for the meeting was provided in the form of an unrestricted grant by the non-profit organization Associazione Amici del Rene di Vicenza (http://www.aarvi.org). From this larger group, a smaller working group was identified to examine the topic of definition and classification of clinical syndromes affecting both the heart and the kidneys. ADQI represents a non-profit association with an elected rotating board and a website supported by the University of Pittsburgh Medical Centre and San Bortolo Hospital. ADQI does not endorse specific guidelines. It reviews the literature and provides expert-based statements and interpretation of current knowledge for use by clinicians according to professional judgment.

Key questions

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?
2. What should be the principles of such a definition system?
3. How should they be defined and classified?

Results

Need for consensus definition

There was unanimous agreement that a consensus definition was needed for Cardio-Renal Syndromes. It was perceived that the existing literature was inconsistent or lacking, that disciplines tended to be organ centred and that the bidirectional nature of these syndromes was poorly appreciated. A new definition would provide a common platform for multidisciplinary approaches.

Principles of definition and classification

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. Definitions should include and respect, where possible, existing and accepted criteria as published by national and international societies. Abbreviations would be useful in providing a shorthand way of communicating information in manuscripts, data collection and presentations.

Consensus definition and classification

The consensus definition and classification of subtypes (Table 1) followed 3 days of deliberation amongst 30 attendees [9]. Proposed definitions in the literature were considered, and a recently published article [3] was chosen as an important source document to serve as a template. Following extensive discussion and modification of this proposed classification system, an unanimous agreement was reached.

The umbrella term Cardio-Renal Syndromes (CRS) was 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 follows:

1. Acute Cardio-Renal Syndrome (Type 1): an acute worsening of cardiac function leading to renal dysfunction;
2. Chronic Cardio-Renal Syndrome (Type 2): chronic abnormalities in cardiac function leading to renal dysfunction;
3. Acute Reno-Cardiac Syndrome (Type 3): an acute worsening of renal function causing cardiac dysfunction;
4. Chronic Reno-Cardiac Syndrome (Type 4): chronic abnormalities in renal function leading to cardiac disease;
5. Secondary Cardio-Renal Syndromes (Type 5): systemic conditions causing simultaneous dysfunction of the heart and kidney.

Discussion

We have established, through a previously described consensus process, a definition and classification system for the Cardio-Renal Syndromes [9]. The umbrella term highlights the fact that multiple syndromes exist, are readily clinically identifiable and represent specific types of interactions between the heart and the kidney, and vice versa, during disease states. The term Cardio-Renal Syndromes was derived with a conscious effort to account for the following factors: the need to indicate bidirectional interaction between the heart and the kidney and the fact that different subgroups arise because of the primary process involving either the heart or the kidney and affecting the other. The plural term ‘syndromes’ was chosen to emphasize the multiplicity of relationships as outlined previously. We considered a novel term such as ‘Heart–Kidney Interaction Syndrome’; however, we recognized that the term ‘cardiorenal syndrome’ was already established in the medical lexicon, notwithstanding the lack of a formal definition. Accordingly, to avoid confusion, we chose to preserve this terminology as the umbrella term, while modifying it to account for the plurality of conditions. Furthermore, we capitalized ‘Cardio’ and ‘Renal’ and hyphenated the term to respect the equal importance of both organ systems in the disorder and to highlight bidirectionality. Finally, in the subtypes, we ordered ‘Cardio’ and ‘Renal’ to indicate the primacy of the organ dysfunction leading to the discrete syndrome. The potential utility of this classification is to establish a framework of reference for communication and comparison of data from different studies and for focusing further research toward specific groups of patients.

Acute Cardio-Renal Syndrome (Type 1)

- This appears to be a discrete 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 1 million patients are hospitalized each year with acute decompensated heart failure, and estimates ranging from 27 to nearly 40% of these patients will develop acute kidney injury (AKI) as defined by an increase in serum creatinine of 0.3 mg/dL [2,11]. Those who experience worsening renal function have a higher mortality and morbidity and increased length of hospitalization.

Chronic Cardio-Renal 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 (CKD), representing an estimated glomerular filtration rate < 60 mL/min/1.73 m² [13].
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Acute Reno-Cardiac Syndrome (Type 3)

- Although AKI 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 AKI [14] will aid in the investigation and analysis of epidemiologic data. The incidence and prevalence of this syndrome are currently unknown but multiple case reports and clinical experience indicate that, in AKI, the heart can develop dysfunction and complications which are predominately secondary to the kidney injury. Its presence requires the clinical development of AKI as the primary event in a temporal sense, which is then followed by cardiac complications (e.g. hyperkalaemic arrhythmias, fluid overload induced by oliguria or anuria, pericarditis from delayed treatment of severe AKI) all attributable to its presence. In addition, the development of new biomarkers and the study of prevention and management strategies in AKI following radiocontrast or cardiac surgery, for example, should increase our knowledge of how AKI can induce changes in cardiac function. In addition, its definition should allow the specific investigation of how many patients with AKI develop cardiac-specific complications (arrhythmias, pulmonary oedema, infarction) which are attributable to it. This has not yet been investigated.

Chronic Reno-Cardiac Syndrome (Type 4)

- A large body of evidence has accumulated demonstrating the graded and independent association between level of CKD 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. This group is not intended to classify all patients with CKD as having a cardiorenal syndrome. Such CKD patients must have evidence of cardiac disease that cannot be attributed to other conditions and where CKD is considered on the basis of history, physical examination and investigations to have contributed to cardiac disease.

Secondary Cardio-Renal Syndromes (Type 5)

- Although this subtype does not have a primary and secondary organ dysfunction, situations do arise where both organs are simultaneously targeted by systemic illnesses, either acute or chronic. Examples include sepsis, systemic lupus erythematosus, amyloidosis and diabetes mellitus. The importance and usefulness of defining this syndrome is to allow future investigations of how often there is combined acute kidney and heart dysfunction in patients with some of the above conditions and to facilitate investigations of new diagnostic and interventional strategies which can identify and address common pathways to organ injury. It is acknowledged that this is a controversial addition to the classification and it was widely debated during the consensus conference. Despite its potential heterogeneity, the group considered that the simultaneous presence of kidney and heart disease created a ‘syndrome’ where, on the basis of known pathophysiology, injury to one organ, was likely to, in part, contribute to injury to the other. The group considered that appreciation of such possible interactions may foster the understanding that, under such circumstances, in order to improve the function of the kidney, attention should not be solely directed to it but also focus on how the heart might contribute to it (and vice versa).

The ADQI working group recognized that many patients may populate or move between subtypes during the course of their disease. 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 and slowly or acutely progressive versus stable disease; however, they chose a more parsimonious and simple scheme for this iteration.

Through the ADQI consensus on Cardio-Renal Syndromes, 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 and interventional 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.

Conflict of interest statement. None declared.

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