A Call to Action to Develop Integrated Curricula in Cardiorenal Medicine

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With the adoption of the new definition and classification of cardiorenal syndrome (CRS) and its relevant subtypes, much attention has been placed on elucidating the mechanisms of heart and kidney interactions. The pathophysiologic pathways are of great interest by which acute heart failure may result in acute kidney injury (AKI; type 1), chronic heart failure accelerates the progression of chronic kidney disease (CKD; type 2), AKI provokes cardiac events (type 3), and CKD increases the risk and severity of cardiovascular disease (type 4). A remarkable interest has also been placed on the acute and chronic systemic conditions, such as sepsis and diabetes, that simultaneously affect heart and kidney function (type 5). Furthermore, the physiology of acute and chronic heart-kidney crosstalk is drawing attention to hemodynamics (fluids, pressures, flows, resistances, perfusion), physiochemical (electrolytes, pH, toxins) and biologic (inflammation, immune system activation, neurohormonal signals) processes. Common clinical scenarios call for recognition, knowledge, and skill in managing CRS. There is a clear need for medical and surgical specialists who are well versed in the pathophysiology and clinical manifestations that arise in the setting of CRS. With this editorial, we make a call to action to encourage universities, medical schools, and teaching hospitals to create a core curriculum for cardiorenal medicine to better equip the physicians of the future for these common, serious, and frequently fatal syndromes.

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For many years, increasing efforts have been made to manage patients with simultaneous heart and kidney dysfunction, as evidenced by a rising number of clinical investigations and publications concerning cardiorenal syndrome (CRS).[1,2] However, very little progress has been made in managing patients with heart or kidney disease with specific attention to preserving the integrity of the cardiorenal axis and the surviving function of both organs.[3,4] For example, patients with acute heart failure (AHF) often have worsening renal function, such as during the course of intravenous diuretic treatment, due to delayed plasma refill and possibly acute kidney injury (AKI).[5] Whether the setting is AHF or any other illness requiring hospitalization, studies suggest that AKI—according to virtually any definition—is associated with increased risks for prolonged hospitalization, need for intensive care unit services, renal replacement therapy, progression of kidney disease, cardiovascular events, rehospitalization, and death.[6] In 2008, a systematic approach to heart and kidney interactions was published in the *Journal of the American College of Cardiology,*[7] immediately followed by a consensus statement by the Acute Dialysis Quality Initiative published in the *European Heart Journal,*[8] to bring the issue of CRS to a focal point among experts in cardiology, nephrology, and critical care.

The first step was to create and drive consensus on definitions of and classification of CRS in common clinical scenarios, with the recognition that the process of organ injury or dysfunction leading to injury or dysfunction of the other organ could be unidirectional, bidirectional, or interactive.[9] The consequent adoption of the new definition/classification of CRS led to significant efforts to elucidate pathophysiologic mechanisms and to describe the clinical consequences of each subtype.[10] Thus, specific features have been analyzed: AKI following AHF (type 1),[11] chronic kidney disease (CKD) induced by chronic heart failure (CHF; type 2),[12] acute myocardial dysfunction in the context of AKI (type 3),[13] and high incidence of cardiovascular events in patients with CKD on hemodialysis (type 4).[14] A remarkable interest has also been placed on simultaneous, overwhelming systemic conditions causing fulminant failure of both organs, for example, in the setting of burns, sepsis, and rhabdomyolysis (type 5).[15]

A critical feature to most analyses has been the status of both intravascular and extravascular volume. A reasonable conclusion that appears to be generalizable is that, in the setting of both acute and chronic CRS (as compared with the normal renal state), there is a narrowed therapeutic window for volume management. This means that a patient at risk for or with CRS has hazards of relative volume depletion including hypotension and hypoperfusion. Conversely, there appears to be little tolerance for volume overload; the consequences range from peripheral edema, which is nearly universal in hospitalized patients, to pulmonary edema and respiratory failure resulting in the need for diuresis, mechanical ventilation, and death.[16] An important recent understanding is that the kidneys are exquisitely sensitive to this volume spectrum. Additionally, the kidneys are the most sensitive organ to hypotension and are most likely to sustain damage with hypotension than any other organ system.[17] Although hypotension and volume depletion are well recognized determinants of prerenal azotemia and AKI, it has been recently appreciated that volume overload can result in renal congestion and a similar manifestation of AKI. With regard to physiochemical stressors, it is becoming increasingly recognized that both early detection and management of lactic acidosis, electrolyte disturbances, and organ toxicities (including nephrotoxic pharmacologic agents and iodinated contrast) can make meaningful differences in the outcomes of cardiorenal patients.[18] Finally, pathobiologic mechanisms involving innate immunity, inflammation, and neurohormonal response have also been highlighted in the bidirectional nature of heart-kidney crosstalk.[19,20] It is well recognized that, in the setting of critical illness, even in the absence of hypotension or marked electrolyte disturbances, both the heart and the kidney can manifest evidence of damage with elevations of cardiac troponin and novel markers of AKI.[21] For each mechanism and its resultant clinical syndrome, specific knowledge and skills are required to avoid harmful interventions and to provide the optimal supportive therapy to enable recovery. The need for a specialist in cardiorenal medicine is emerging for optimal patient care of the patients at greatest need in order to reduce the burden of serious sequelae, including the need for dialysis, permanent disability due to heart or kidney impairment, and death.

With this editorial, we are making a call to action to encourage universities, medical schools, and teaching hospitals to create a core curriculum for cardiorenal medicine as has been done for critical care nephrology, cardiac critical care, and other disciplines that bridge the knowledge and skills between fields of cardiology and nephrology (Figure 1).[22,23]

Cardiorenal Syndrome Type 1

This condition occurs across the entire spectrum of hemodynamic

subsets of AHF.[24] Commonly, a state of relatively low cardiac output or impaired forward perfusion are determinants of the rise in serum creatinine and blood urea nitrogen, and the reduction in urine output after intravenous diuretics.[8] Conversely, effective perfusion to the kidneys could be impaired due to renal congestion, venous hypertension, or right ventricular dysfunction. Diastolic dysfunction and acute heart decompensation may represent additional risk factors and precipitating events leading to decreased kidney perfusion. The underlying pathophysiology is complex and involves oxidative stress dysfunctional cell signaling; therefore, there is hope for future therapies.[25,26] In this syndrome, there is a need to coordinate the balance between optimizing hemodynamics and decongesting the kidneys within an appropriate timeline.[27] Development of novel therapies has been hampered by "short-termism" among pharmaceutical sponsors and investigators, as evidenced by the uniform failure of agents given for only 48 hours.[28] The acute and extended use of drugs and strategies should be considered as a way forward. A combined strategy should be undertaken to achieve organ function recovery and symptom relief with maintenance or improvement in renal filtration function. Concerted efforts by cardiologists, nephrologists, and critical care specialists are needed to identify specific phenotypes of CRS type 1, and then design management strategies for that phenotype to maximize both cardiac and renal outcomes.[29]

Cardiorenal Syndrome Type 2

CHF is one of the most common cardiovascular conditions, with ischemic heart disease contributing to two-thirds of those with reduced left ventricular (LV) function and to approximately one-half of those with preserved LV function.[30] The majority of patients have long-standing antecedent hypertension with ostensibly normal renal filtration function but subclinical kidney disease, and an impaired renal functional reserve. This means, in the setting of stress or load of any type, the kidneys have a reduced ability to adapt and manage a filtered load of solute and are at risk of creating volume overload and azotemia.[9] Small episodes of acute decompensation or superimposed ischemic events may unveil a latent CKD and cause further damage in a highly susceptible kidney, leading to a rise in serum creatinine and proteinuria, and CKD progression.[31] In these patients, it is quintessential to coordinate a treatment that combines the clinical demand of neurohormonal modulation, maintenance of diuresis, control of blood pressure, management of potassium and acid base, and maintenance of adequate body hydration. In particular, the use of diuretics and disease-modifying drugs for heart failure should be carefully titrated with a multidisciplinary approach based on the criteria of precision and personalized medicine.

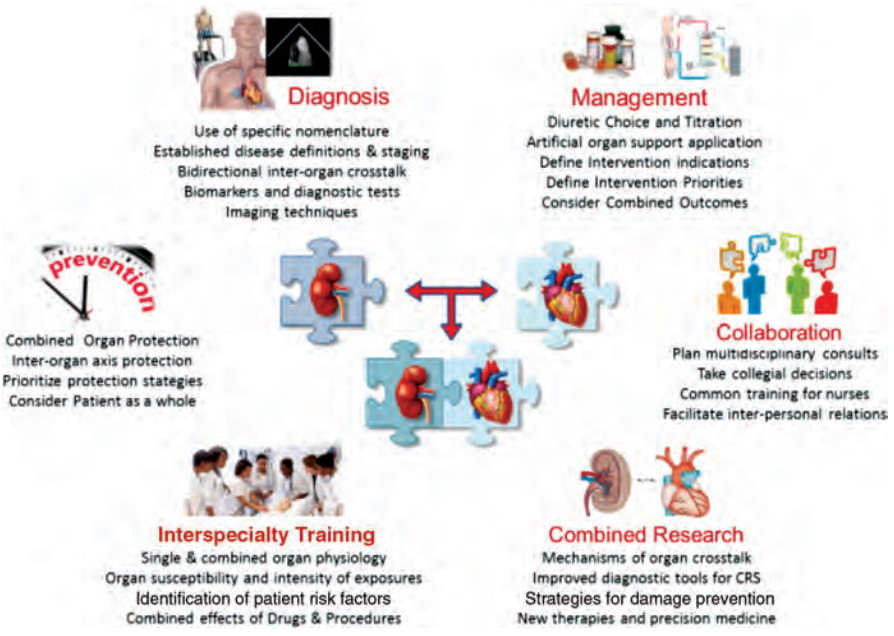

Figure 1. Conditions and opportunities for common intervention and collaboration between cardiologists and nephrologists in patients with combined disorders of the heart and kidney. The pieces of the puzzle may come together due to a combined effort of interdisciplinary training, common research, and strong commitment to collaboration. Multiple areas from pathophysiology to diagnosis, prevention, and treatment represent the ideal arena for this future exercise, hopefully leading to a true discipline of cardiorenal medicine. CRS, cardiorenal syndrome.

Cardiorenal Syndrome Type 3

For many years, AKI was considered an isolated entity to be managed with the intent to replace renal function, and to maintain fluid and solute balance in patients at risk for severe pathophysiologic derangements.[32] Today, AKI is perceived as a syndrome with evident consequences on distant organ function.[10] Among these, the renocardiac effects mediated through physical, chemical, and immunologic signals, may result in severe myocardial dysfunction.[33] Not only should acid-base and electrolyte levels be carefully

managed, but fluid balance and blood pressure should also be controlled in patients with AKI. In patients undergoing renal replacement therapy for severe oliguria and uremia, these tasks should be accomplished via different extracorporeal techniques, whose prescription and delivery must be accurate and carefully executed using an accepted nomenclature.[34] The experience of the nephrologist is paramount in establishing the scope and goals of diuretic and extracorporeal therapy. The prescription and delivery of renal treatments should be aimed at physiologic targets covering the magnitude and timing of the desired changes in volume in relation to the response in right and left ventricular function. In this endeavor, the combined effort of the nephrologist and cardiologist in the care of the critically ill patient is the winning strategy.

Cardiorenal Syndrome Type 4

The effects of CKD on the "four corners of cardiovascular disease," including atherosclerosis, myocardial disease, arrhythmias, and valvular disease, are well known.[35] Every patient with CKD and end-stage renal disease (ESRD) is almost inevitably a cardiac patient with several comorbid complications.[36] With regard to kidney function, the main task is the reduction of CKD progression by control of intraglomerular hemodynamic and hyperfiltration, limitation of protein and salt intake, neurohormonal modulation, and control of blood pressure.[37] Recent evidence has pointed out that chronic inflammation, anemia, and metabolic alterations typical of uremia (eg, hyperuricemia),[38,39] even in its early stages, may influence the rate of vascular calcification, myocardial fibrosis, aortic and mitral calcification, and the propensity for atrial and ventricular arrhythmias.[40,41] In patients with this syndrome, there appear to be opportunities to improve micronutrient status, with the goal of reducing frailty and complications over time.[42,43] We suggest that every CKD patient be regularly followed by both a nephrologist and a cardiologist with mutual interests in cardiorenal medicine.[44] Particular attention should be paid to detection and management of asymptomatic LV dysfunction, atrial fibrillation, and valvular disease, with an eye on the risk for bacterial endocarditis.[45,46] Assessment of functional classification is important for nephrologists in patients with ESRD in order to communicate effectively with heart failure specialists.[47] The message is clear: CKD and ESRD are signals for cardiovascular care, as are congenital heart disease, severe dyslipidemia, or a family history of premature cardiovascular disease.[48] Additionally, there are considerable opportunities to collaborate on the mode of dialysis in order to optimize cardiovascular outcomes.[49] For example, patients appropriately selected for short-term, daily home hemodialysis have been found to have significantly lower rates of heart failure hospitalizations; however, this is balanced against a higher risk of infection.[50]

Cardiorenal Syndrome Type 5

Simultaneous heart and kidney dysfunction may result from systemic disorders such as sepsis from burns, or other fulminant syndromes.[12] These conditions may affect each organ through common mechanisms (eg, endotoxin), but also through disease- or pathogen-associated molecular patterns.[51,52] Specialists in the field of cardiology and nephrology can successfully collaborate to identify simultaneous cardiac and renal dysfunction in the setting of multiorgan system failure. Specialty-driven decisions may contribute to modifying the course or mitigating the effects of the primary disease on a single organ, including inotropic support, renal replacement therapy, and extracorporeal oxygenation. Interpretation of laboratory testing and decisions to perform diagnostic procedures or specific therapies require coordinated evaluation of each single case.[53] Optimal strategies defined for type 5 CRS will be paramount to improving the outcomes of these dire cases.

Unmet Clinical Needs

Heart and kidney interactions are bidirectional and time dependent.[10] It is evident from what has been described above, that it is misleading and even dangerous to manage a single organ dysfunction without considering the secondary organ in the cardiorenal axis. It is worthless to consider the primary organ involvement and the origin of the syndrome without considering the vicious circle that may ensue once both organs are affected.

Today, the cardiologist primarily manages CRS types 1 and 2, whereas the nephrologist primarily treats types 3 and 4. There is no concerted effort for the prevention of CRS at the individual or institutional level.[54] Very little interaction is institutionally defined, and occasional interdisciplinary activity may take place based on consultation, which often comes too late in patient care.[55] There is no uniform utilization of novel biomarkers to phenotypically classify and manage

patients.[53,56,57] A multidisciplinary approach to managing CRS is lacking, and patients are suffering from partial or restricted care due to a narrow medical perspective of the primary specialty.[58] We make a call to action for specialists of different disciplines, namely cardiology and nephrology, to collaborate and to share information and knowledge concerning the critically ill patient, both at the bedside and in the classroom, to provide a platform for this increasingly ill and expanding population.[59]

Educational Proposal

We make a special call for specialists from both fields to work side by side to achieve optimal care for every cardiorenal patient. Major changes have occurred in the practice of medicine in the past 20 years. AKI and CKD increase cardiovascular risk; this understanding has evolved significantly in recent years. At the same time, the understanding of the importance of preserving renal function and protecting the kidney during cardiac operations and acute cardiac events has also increased significantly (Figure 2). A particularly striking development is the increase in overlapping literature in cardiology and nephrology regarding CRS and heart- and kidney-associated disorders. Initially sustained by passionate specialists interested in cooperation between the two fields, cardiorenal medicine is now a discipline whose time has come.

There have been barriers to collaboration, however. Historically, the customary training in cardiology never focused on areas outside of heart disease. Some institutions have branched their departments of cardiology from their departments of internal medicine, further increasing the distance, both clinically and intellectually, of cardiologists from the other specialties. The same is true for nephrology, although a more comprehensive education has always been part of this specialty as a branch of internal medicine, because of the impact of systemic disease on the kidneys.[60] Thus, physicians in postgraduate medical education were oriented to a specialty rather than to patient problems.[60] This sectorial education often resulted in an adversarial "us versus them" mentality. Thus, specialists are often consulted for a procedure (eg, cardiac catheterization or initiation of dialysis) with little collaboration addressing the cardiorenal health of the patient.[61] In addition, complex syndromes encompassing heart and kidney disorders require the application of intricate knowledge and familiarity with hemodynamic assessment, skilled use of the clinical laboratory, pharmacology, and the use of invasive procedures.[62] This "package" seldom exists in a single physician or practice. The result is that such specialists often clash and provide only partial consultation and limited vision of therapeutic strategies, fueling the fire of antagonism rather than cooperation. A second cause for a delayed interdisciplinary collaboration may reside in the desire to maintain control of acute patients while chronic or terminal patients are "left to the others." This may be different in a full-coverage social security system versus a private practice and insurance-based for-profit environment. The truth is that a combined path of diagnosis and care can only come from a multidisciplinary approach in which cardiologists and nephrologists cooperate mutually and respectfully. It may be true that one specialist has advanced knowledge and skills concerning certain pathophysiologic disorders (eg, acute coronary syndrome) whereas the other is the expert in a given therapy (eg, hemodialysis). However, neither specialist is fully competent to manage a patient in whom organ crosstalk is continuous and even amplified by an ever-changing clinical profile. Control of patient care defines power within the medical structure for the individual physician and his or her practice or department. In the pursuit of higher standing in

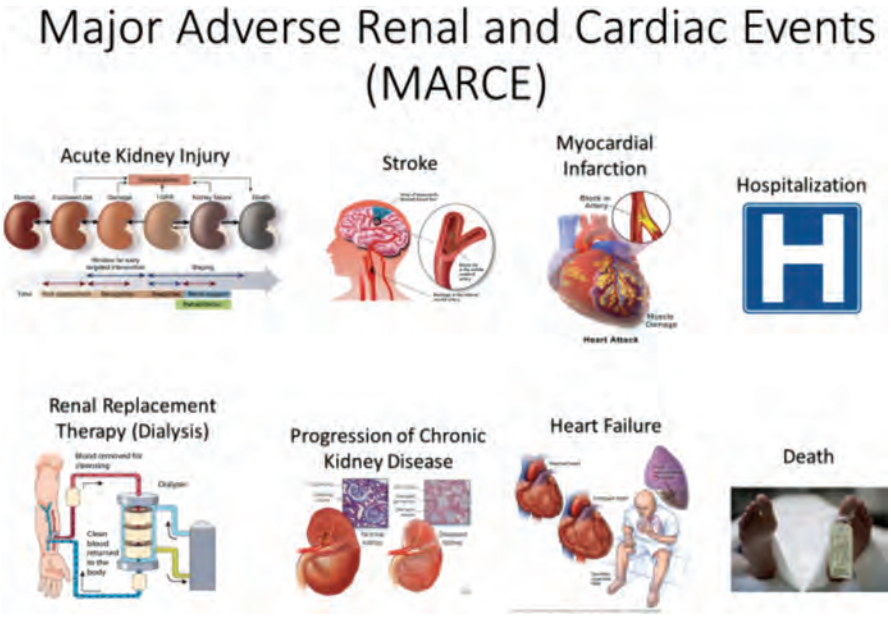

Figure 2. Major adverse renal and cardiac events (MARCE) are strongly associated with acute kidney injury and raise the possibility that strategies that reduce acute kidney injury may translate into improved clinical outcomes, as measured by time to first MARCE event in clinical trials.

the medical community, specialists clash instead of cooperate. There are important and obvious clinical reasons for collaborative care. Patients with combined heart and renal failure are complex and difficult to manage, and the secondary dysfunction of one organ may affect outcomes and results of treatments of the primary organ. This is the case in patients undergoing interventional procedures or cardiac surgery. In fact, the occurrence of AKI strongly influences the clinical course and often dominates outcomes (intensive care unit length of stay, general care, need of dialysis, rehospitalization, and death). An additional consideration is the need to allocate resources appropriately, with recognition of terminal patients for whom both the cardiologist and nephrologist can jointly convey a terminal prognosis to the patient and family members. A combined-care model of specialists can re-evaluate the use of drugs such as inotropic agents, vasopressors, diuretics, and renin-angiotensin system inhibitors, anticoagulants, lipid-lowering therapy, and agents to modify electrolytes (eg, bicarbonate, phosphate binders, calcium). New perspectives can be developed to help revise criteria for extracorporeal therapy and mechanical ultrafiltration in patients with CRS.

Common goals should be established for both organ protection and prevention of CRS, while maximum attention and a combined effort should be given to maximizing all chances for organ and patient recovery. There should be no financial penalties for physicians who participate in paired consultation and comanagement.[63]

This area undoubtedly needs focused attention, and effort should be given to the structure of training and research, clinical application, and creativity.[64] We propose an innovative educational program to enhance the curricula in both cardiology and nephrology training:

1. Nephrology fellows should spend at least 6 months in a cardiology department learning the approach to the cardiac patient and the point of view of the paired specialty, providing answers to problems that currently seem insoluble, including the management of heart failure, hemodynamic assessment, electrocardiography, and noninvasive imaging. Particular emphasis should be placed on the detection and management of arrhythmias, as well as noninvasive imaging of the hemodialysis patient, who is often remote from cardiovascular care.

2. Cardiology fellows who intend to take an active role in the management of patients with AHF and CHF at high risk to develop CRS should spend at least 6 months in a nephrology department learning indication, prescription, and delivery of extracorporeal support therapies. The cardiology fellow should acquire competency in indications, initiation, and delivery of continuous renal replacement therapy for the cardiac patient with kidney problems. A special training program should be created for this purpose.[65]

3. In large institutions, it is desirable to develop fully combined programs, resulting in board certification in both cardiology and nephrology. Fellowship status in aligned organizations such as the Cardiorenal Society of America is encouraged.[66]

4. All tertiary institutions should have a task force allocated to the combined management of CRS and seek quality improvement and research opportunities in cardiorenal medicine.

5. Large institutions should encourage faculty in cardiology and nephrology to develop career focus areas on cardiorenal medicine, with research platforms in basic, translational, preclinical, and clinical studies. Participation and leadership in multidisciplinary courses such as the annual International Vicenza Course in Critical Care Nephrology, the Cardiorenal Society of America Annual Meeting, and the Acute Dialysis Quality Initiative series of meetings should be strongly encouraged for cardiorenal faculty with support from department chairs.[48,67,68]

Conclusions

Cardiologists and nephrologists should form a new union of cardiorenal medicine, as was the case decades ago. This pivotal branch of internal medicine deals with the most critically ill patients in our hospitals and clinics. Formal collaboration is a necessity.

Our views may be criticized as being overly ambitious and out of proportion to the significance of renal disease in the cardiology world, and vice versa. It is clear that renal disease is the most important predictor of cardiovascular outcomes in all areas of cardiology, and that cardiovascular disease is the leading cause of death in patients with kidney disease. Barriers to collaboration must be overcome. We need a new generation of cardiorenal physicians with an avant-garde approach to the screening, detection, diagnosis, prognosis, and management of CRS. With these enthusiastic words, we pledge our professional efforts to realize these aspirations and call on each of you to play a role in the evolution of this specialty. ■

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