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Epidemiology, pathophysiology, clinical characteristics and management of childhood cardiorenal syndrome

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Abstract

Cardiorenal syndrome (CRS) is a new term recently introduced to describe the acute or chronic comorbid state of the heart and kidney that has been long known and frequently managed in very sick individuals. The tight and delicate coordination of physiological functions among organ systems in the human body makes dysfunction in one to lead to malfunction of one or more other organ systems. CRS is a universal very common morbidity in the critically ill, with a high mortality rate that has received very little research attention in children. Simultaneous management of heart and renal failures in CRS is quite challenging; the therapeutic choice made for one organ must not jeopardize the other. This paper reviews the epidemiology, pathophysiology, clinical characteristics and management of acute and chronic CRS in children.

Key words: Acute kidney injury; Congestive heart failure; Chronic kidney disease; Ultrafiltration

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INTRODUCTION

The tight and delicate coordination of physiological functions among organ systems in the human body is such that a dysfunction in one could lead to malfunction of one or more organ systems. Cardiorenal syndrome (CRS) is a new term recently introduced to describe the heart and kidney comorbid state that has been long known and frequently managed in very sick individuals. It is a disorder of the heart and kidneys whereby acute or chronic dysfunction in one organ induces acute or chronic dysfunction of the other[1,2]. The 7th Acute Dialysis Quality Initiative Workgroup recently standardized the classification of CRS into five distinct clinical types[1,2]. These are namely: Acute CRS (CRS Type 1 or CRS-1) - acute worsening of heart function leading to acute kidney injury (AKI) and/or dysfunction; chronic CRS (CRS Type 2 or CRS-2) - chronic abnormalities in heart function leading to kidney injury and/or dysfunction; acute renocardiac syndrome (CRS Type 3 or CRS-3) - acute worsening of kidney function leading to heart injury and/or dysfunction; chronic renocardiac syndrome (CRS Type 4 or CRS-4) - chronic kidney disease leading to heart injury, disease and/or dysfunction; and secondary CRS (CRS Type 5 or CRS-5) - systemic conditions leading to simultaneous acute or chronic injury and/or dysfunction of heart and kidney. Acute decompensated heart failure (ADHF), defined as new onset or acute exacerbation of heart failure (HF) with signs or symptoms requiring hos-

pitalization and inpatient treatment, has been associated with AKI in hospitalized children, prolonged hospitalization and in-hospital death, or the need for mechanical circulatory assistance[3]. Congestive HF (CHF) is a very serious morbidity that has been frequently associated with an increased need for acute dialysis and death in childhood AKI[4]. Children with mild or moderate chronic renal insufficiency (CRI) were associated with left ventricular hypertrophy (LVH) that progressed as renal function deteriorated[5]. Increased left ventricular mass index, indicating LVH, occurred in a third of children with mild to moderate CRI in some studies[6-8]. Risk factors for cardiovascular disease (CVD) in childhood chronic kidney disease (CKD) as reviewed by Mitsnefes *et al*[5] include: hypertension, anemia, dyslipidemia, hyperparathyroidism, hypoalbuminemia, increased C-reactive proteins level and hyperhomocysteinemia.

CRS is a very common disorder with a high mortality rate in children that has received very little original research attention[3,9]. This paper reviews the epidemiology, pathophysiology, clinical characteristics and management of acute and chronic CRS in children.

EPIDEMIOLOGY

Currently, the incidence of CRS in children is unknown as very little work has been done in this area, in spite of the fact that HF is a common comorbidity in renal failure. To date, there have been only three publications on childhood CRS in the medical literature. Two are original reports[3,9] while one is a review article[10]. A review of the various publications in which HF was a complication of acute or chronic renal dysfunction and vice versa revealed that CRS prevalence could range between 3.0% and 52.0%[3,4,9,11-19].

CRS-1

HF in children is a progressive clinical and pathophysiological syndrome caused by cardiovascular and non-cardiovascular abnormalities that result in characteristic signs and symptoms, including edema, respiratory distress, growth failure and exercise intolerance, and accompanied by circulatory, neurohormonal and molecular derangements[20]. The AKI in this CRS type may be a sequel to renal ischemia following low cardiac output or renal congestion as a result of volume overload HF. Classes Ⅲ and Ⅳ HF (based on modified Ross HF classification for children[20]) are more likely to be associated with renal dysfunction than classes I and Ⅱ HF. In a study by Price *et al*[3], the median age of children at admission was 10 years (0.1-20.3), while the male: female ratio was 1.3. Reports show that CHF leading to CRS-1 is a common complication of cardiopulmonary bypass (CPB) surgery. The prevalence rate of CRS-1 following CPB surgery ranged between 5% and 52% in various studies[12-14,19,21]. Congestive anemic HF was identified as a risk factor for hospital- acquired AKI in 30.43% of Nigerian children[22], while Price *et al*[3] showed that AKI, which they referred to as acute worsening of renal function (WRF), occurred in 35 of 73 (48%) American children hospitalized for ADHF. Dilated cardiomyopathy (52%), cyanotic congenital heart disease (14%), myocarditis (12%), acute graft rejection (12%) and ischemic cardiomyopathy (10%) caused ADHF that led to AKI in the American children. AKI was not only independently associated with in-hospital death or the need for mechanical circulatory support [odds ratio (OR) 10.2; 95% CI: 1.7- 61.2, $P = 0.011$], but it was also significantly associated with longer observed length of stay ($P < 0.03$). Fifteen of 35 (43%) patient hospitalizations in which AKI occurred resulted in death or the need for mechanical circulatory support[3]. HF was a significant risk factor for mortality among Thai children with CPB surgery associated AKI (OR, 8.7; 95% CI: 3.0-25.3, $P = 0.0001$). The mortality rate was 53.9%[13].

CRS-2

Although CRS-2 has rarely been reported in children, cardiac conditions capable of precipitating a CRS-2 in children include left-to-right shunting (due to ventricular septal defect and patent ductus arteriosus) and atrioventricular or semilunar valve insufficiency (due to aortic regurgitation in bi-commissural aortic valve or pulmonary regurgitation after repair of tetralogy of Fallot). All of these will cause CHF due to volume overload. On the other hand, CHF due to pressure overload may be secondary to severe aortic stenosis, aortic coarctation or severe pulmonary stenosis. The child with a structurally normal heart may also develop CHF following a primary dilated cardiomyopathy, ischemic, toxic, infectious, infiltrative or lupus cardiomyopathy. A number of causes of CHF in childhood CRS-1 may in fact become persistently progressive, leading to CRS-2. Postoperatively, transient or chronic CHF may complicate CPB surgery for a congenital heart disease in both children and adults[23-27]. Examples of the latter include right HF due to residual right ventricular outflow tract obstruction, volume overload from pulmonary insufficiency following repair of tetralogy of Fallot, and systemic ventricular dysfunction or elevated venous pressures in single ventricle physiology, leading to low cardiac output[28-32] and subsequent chronic renal dysfunction.

CRS-3

Acute HF following AKI typifies CRS-3. AKI is an abrupt clinical and/or laboratory manifestation of kidney dysfunction, usually within 48 h of bilateral kidney insult of any kind. Using serum creatinine (Scr) as a marker, the AKI network group used an increase in Scr level from the baseline within 48 h of bilateral kidney insult by at least 0.3 mg/dL (≥ 26.4 μmol/L) or a 50% (1.5-fold) increase or more as diagnostic of AKI[33]. Scr alone is an inadequate marker of AKI, as injury would have been far advanced before detection[22]. Chertow *et al*[34] showed a slight rise in Scr level as low as 0.3 mg/dL (26.5 μmol/L) to be significantly associated with kidney damage, high morbidity and mortality from AKI, indicating the need

Table 1 Some clinical and non-clinical features of cardiorenal syndrome

Heart failure	Renal failure
Difficulty in breathing; grunting respiration	Reduced daily urine output
Prolonged feeding time in infants	Facial puffiness
Tiredness	Acidotic breathing
Tachypnea	Drowsiness due to uremia
Tachycardia	Ascites/pitting bipedal edema
Raised jugular venous pressure	Pallor
Displaced apex beat	Hypertension when fluid overloaded or renal failure is due to either acute glomerulonephritis, Burkitt's lymphoma nephropathy or CKD
Heart murmurs	Bleeding diathesis
Galloping cardiac rhythm	Seizures
Bilateral basal crepitations	Failure-to-thrive in CKD
Tender hepatomegaly	Hyponatremia, hyperkalemia, metabolic acidosis, hypocalcemia, hyperhosphatemia, hyperuricemia, azotemia, hypercreatinemia, high fractional sodium excretion, reduced GFR; Ca × $PO4^{-3}$ product is elevated in late CKD stages and in those receiving calcium and vitamin D_3 supplements and regular dialysis
Pitting bipedal edema in older children with chronic heart failure; usually a late manifestation	Dyslipidemia and proteinuria especially in CKD; reduced plasma level of vitamin D_3; elevated parathyroid hormone. Low circulating level of erythropoietin
Increased cardiothoracic ratio on chest X-ray (> 60% in under fives and > 55% in older children)	Kidneys may be slightly enlarged in AKI or grossly enlarged in infantile polycystic kidney disease on ultrasound or shrunken in size in other forms of CKD. Radiological evidence of vascular calcification may be present
Electrocardiographical evidence of left ventricular hypertrophy	Biomarkers of kidney injury
	Plasma NGAL, plasma cystatin C, urine NGAL, urine interleukin-18, urine kidney injury molecule-1 and urine liver fatty acid-binding protein (rises within 4 h of injury) levels are elevated few hours after kidney injury
Echocardiographical evidence of heart failure like increased left ventricular mass index (> 38 g/$m^{2.7}$), reduced ejection fraction (normal: 64%-83%) and reduced shortening fraction (normal: > 30%)	
Biomarkers of cardiac injury	
Troponin, creatine kinase myocardial band and natriuretic peptides are elevated	

NGAL: Neutrophil gelatinase-associated lipocalin; CKD: Chronic kidney disease; GFR: Glomerular filtration rate; AKI: Acute kidney injury.

for early diagnosis that is presently not possible with Scr. Early AKI diagnosis and treatment should be expected to prevent morbidity like CRS. Plasma and urinary biological markers of AKI[35,36] show some promise with regards to diagnosing AKI within few hours of bilateral kidney insult (Table 1). These are, however, still in their experimental and research stages. Usually, AKI is a reversible clinical state in which normal functions of both organs are expected to occur following treatment and recovery from the renal insult. CRS data from Nigeria in which the male to female ratio was 1.24, revealed the median age for both CRS-3 and CRS-5 to be 4.0 years (0.3-14.5) with 70.21% of the children being less than 6 years of age[9]. In that study, the CRS-3 prevalence rate was 21.3%. The etiologies were acute glomerulonephritis (AGN, 70.0%), captopril (10.0%), frusemide (10.0%) and hypovolemic shock due to gastroenteritis (10.0%). Bailey *et al*[11] reported that 45% of their AKI patients subsequently developed cardiac dysfunction or cardiac arrest as a complication. The overall mortality was 11 times higher in patients with than in those without AKI (27.3% *vs* 2.4%, $P < 0.001$)[11]. We had earlier reported a 25% prevalence rate for CHF in children with AKI. CHF was a major indication for acute dialysis in that report[4]. Similarly, CRS occurred in 31.03% of Nigerian children with AGN[17]. Recently, the cumulative mortality rate for CRS-3 in our unit was 87.5%[9]. This high mortality rate was attributed to AGN, which the majority of patients had. AGN was significantly associated with a very low survival rate in the study. CRS due to etiologies other than AGN was significantly less associated with mortality compared with CRS due to AGN (40.4% *vs* 78.6%; HR: 0.544; 95% CI: 0.322-0.919, $P = 0.023$). Figure 1 demonstrates the significance of etiology on CRS outcome as patients with CRS-5 survived well than those with CRS-3 (HR: 0.479, 95% CI: 0.299-0.768)[9].

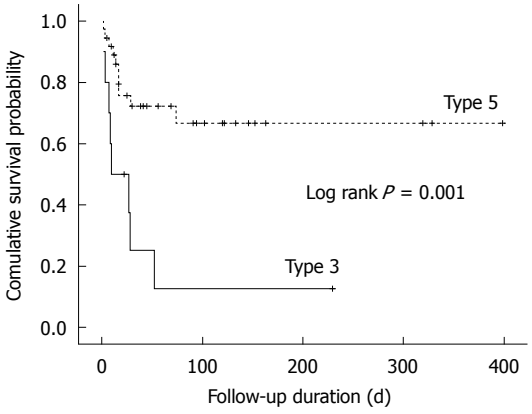

Figure 1 Kaplan -Meier survival curves showing significantly better survival in Type 5 compared to Type 3 cardiorenal syndrome (72.3% *vs* 12.5%). Figure reproduced from reference number 9 with permission.

CRS-4

This is a clinical syndrome in which a CKD, irrespective of etiology, leads to chronic HF or dysfunction. The National Kidney Foundation/Kidney Disease and Outcome Quality Initiative defined CKD as a bilateral kidney injury and/or impaired kidney function of at least 3 mo duration[37]. Kidney injury refers to the presence of microalbuminuria or overt proteinuria or abnormal urine sediment such as red blood cell (RBC), RBC casts, white blood cell (WBC), WBC casts, cellular casts, granular casts, oval fat bodies, fatty casts or free fats. Impaired kidney function is defined as a glomerular filtration rate (GFR) of 60 mL/min/1.73 m^2 or less[37]. Perturbed kidney function in CKD is frequently associated with multi-organ systems dysfunction which may occur sequentially or simultaneously as kidney function deteriorates progressively. Cardiovascular malfunction is a common comorbidity in CKD with a high prevalence of CVD associated deaths. Cardiac involvement in CKD is more often than not multi-factorial. Hypertension, malnutrition, uremia, sodium/water retention, regular dialysis, anemia, dyslipidemia and abnormal calcium-phosphorous metabolism are some of these factors. Both concentric and eccentric LVH consistent with the combined pressure and volume overload have been reported in children with mild to moderate chronic renal failure (CRF)[7,8]. Reduced left ventricular (LV) functional reserve during exercise has been observed in regularly dialyzing children with CRI, notwithstanding a normal resting LV function[7]. Concentric LVH occurs frequently because of left ventricular pressure overload caused by hypertension, arteriosclerosis and sometimes aortic stenosis, while eccentric LVH results from left ventricular volume overload associated with hypervolemia, arterio-venous fistula and anemia[38]. In patients starting dialysis, left ventricular growth occurs[39], although it regresses following renal transplantation[40]. While LVH can progress to left ventricular systolic dysfunction through progressive myocyte loss, LV diastolic dysfunction resulting from LVH frequently results in symptomatic pulmonary edema[41]. In Nigeria, cardiac dysfunction was found in 25% of pediatric patients with CRF[15] while 31% of incident pediatric patients in the US, who started chronic dialysis between 1991 and 1996, developed CVD[16]. Mortality from CKD associated CVD is very high, ranging between 23 and 45%[42-46]. Cerebrovascular accident (58%), CHF (15.4%), myocardial infarction (11.54%) and cardiac arrest (7.7%) were the most common causes of cardiac death among Dutch children with CKD[44]. The survival of children with CKD in the U.S. remains low; lifespan is 40-60 years less for children on dialysis and about 20-25 years less for transplant patients than that of an age and race-matched US population[47,48]. Development of accelerated ischemic heart disease and premature dilated cardiomyopathy were thought to be responsible for this. Similar analysis of long-term survival from the Australia and New Zealand Dialysis and Transplant Registry of all children and adolescents who were under 20 years of age when renal replacement therapy (RRT) commenced, showed mortality rates were 30 times higher than in the age-matched general population. CVD was the most common cause of death (45%)[46].

CRS-5

In CRS-5, acute or chronic failure or dysfunction of both the heart and the kidneys occur simultaneously as sequelae of a severe acute or chronic systemic illness. In an earlier report, simultaneous failure of both organs occurred in 36.4% of Nigerian children with systemic lupus erythematosus[18]. One of the two original publications to date on childhood CRS reported a 78.7% prevalence rate for CRS-5[9]. Malaria-associated hemoglobinuria (54.05%), septicemia (29.73%), lupus nephritis (8.11%), tumor lysis syndrome due to Burkitt's lymphoma (5.41%) and acute lymphoblastic leukemia (2.70%) were the etiologies in that study. Compared to CRS-3, children with CRS-5 survived better (HR: 0.479, 95% CI: 0.299-0.768, Figure 1). The better outcome in CRS-5 alluded to the majority of the patients having had malaria-associated hemoglobinuria that was significantly associated with the highest survival rate (81.4%), compared to CRS-3 in which majority of the patients had AGN that was significantly associated with a very low survival rate (21.4%, $P = 0.014$). A mortality rate of 27.7% was associated with CRS-5 in that study. The cumulative CRS-specific mortality rate for the study was 45.7% (CRS-3 and CRS-5 combined).

MECHANISMS, PATHOLOGY AND CLINICAL MANIFESTATIONS OF CRS

Acute CRS (CRS-1, CRS-3 and acute CRS-5)

A sudden decrease in cardiac stroke volume and cardiac output, regardless of whether symptomatic hypotension is present, can cause a decrease in renal arterial filling and perfusion, thus reducing the GFR. This reduction could cause AKI secondary to ischemic pre-renal acute tubular necrosis (CRS-1)[49,50]. Reduced renal perfusion activates the renin-angiotensin-aldosterone-system (RAAS). Upon RAAS activation, angiotensin Ⅱ (ANG Ⅱ) stimulates endothelin-1 (ET-1) expression in the kidney, a very strong pro-inflammatory and pro-fibrotic vasoconstrictor peptide. ET-1 reduces renal blood flow and GFR and, when over-expressed, might precipitate AKI and/or pre-renal ischemic acute tubular necrosis during acute heart dysfunction[51]. Irrespective of the etiology of AKI, impaired glomerular filtration (due to many factors) leads to circulatory congestion which, when associated with sodium and water retention and hypertension, as is often the case with AGN, could lead to CHF. As stated above, 70.0% of the cases of CRS-3 were caused by AGN[9].

Chronic CRS (CRS-2, CRS-4 and chronic CRS-5)

In CRS-2, chronic HF from any cause leads to persistently low cardiac output and circulatory blood volume with persistently reduced renal blood flow and resultant chronic renal damage brought about by the pro-

inflammatory and pro-fibrotic activity of activated RAAS, described in detail below for CRS-4. A number of pathological processes are involved in the development of CKD. Proteinuric kidney damage is one such pathological process. Proteinuria is an important marker of CKD that provokes intense and persistent inflammatory reaction through simultaneous vasoactive and pro-inflammatory signaling that ultimately causes irreversible kidney damage, leading to abnormal kidney function and serious morbidities in other organ systems such as CRS-4 when the CVS is involved.

Vasoactive signaling involves production of ANG Ⅱ, aldosterone and ET-1, leading to increased production of transforming growth factor-β (TGF-β), tissue inhibitor metalloproteinase-1 (TIMP-1) and -2 (TIMP-2) and plasminogen activator inhibitor-1 (PAI-1). Increased production of TGF-β results in increased fibroblast proliferation, collagen and matrix proteins formation with resultant tissue fibrosis both within the glomerulus and renal tubulointerstitium. TIMP-1, TIMP-2 and PAI-1 complicate the process further by inhibiting the tissue protease enzyme activity, thereby inhibiting matrix protein and collagen degradation, thus further promoting matrix deposition, fibrosis and kidney damage. ANG Ⅱ, aldosterone, and ET-1 are also independently associated with glomerular hypertrophy, hyperfiltration and intraglomerular hypertension, leading to proteinuria and further kidney damage[52].

Pro-inflammatory signaling similarly results in increased collagen and matrix protein formation, causing tissue fibrosis through increased production of the pro-inflammatory mediators, namely monocyte/macrophage chemoattractant protein-1, interleukin-8, nuclear factor κB and regulated upon activation, normal T-cell expressed and secreted; these pro - inflammatory mediators stimulate the production of TGF-β that enhances tissue fibrosis, as described earlier. The consequences of fibrosis are tubulointerstitial hypoxia and reduced nephron mass with intraglomerular hypertension; the latter results in increased glomerular filtration pressure and worsening of the proteinuria, as well as a vicious cycle of proteinuria and fibrosis[52].

The cardiovascular complications of chronic kidney damage include myocardial ischemia, hypertension, LVH and CHF. CKD-associated hypertension develops by a large variety of pathophysiological mechanisms. Fluid overload and RAAS activation have long been recognized as crucial pathophysiological pathways but sympathetic hyperactivation, endothelial dysfunction and chronic hyperparathyroidism have more recently been identified as important factors contributing to CKD-associated hypertension[53]. Two parallel processes are involved in the development of CVD in CKD patients. The first is cardiac remodeling leading to LVH as a response to either mechanical or hemodynamic overload. Two different patterns of LV remodeling can produce increase in LV mass (LVM). The patterns of sarcomere formation induced by pressure or volume overload are distinct. Pressure-induced concentric LVH is characterized by a parallel addition of sarcomeres, resulting in the increase of cross-sectional area and diameter of the myocytes. Increase in LVM in this case is obtained by a marked increase in wall thickness with a less evident increase in the LV cavity that yields an elevated relative wall thickness and concentric LVH. From the physiological view, increased systolic blood pressure and pulse pressure, due to increased peripheral resistance and arterial stiffness, are the principal factors opposing LV ejection and leading to an increased LV workload and concentric LVH[54]. An increase in LVM can also be obtained by an increase in the LV cavity with a symmetric increase in wall thickness to maintain the ratio between the wall thickness and normal LV transversal radius (relative wall thickness), producing eccentric LVH. In this case, the addition of sarcomeres occurs mainly in series resulting in longitudinal cell growth. In the transition to maladaptive LVH, LV dilatation becomes disproportional to wall thickness, with myocytes elongated without an increase in diameter[54]. In children, hypertension is one of the most common sequelae of CKD[55]. Anemia is also a highly prevalent comorbidity in both AKI[4,56-58] and CKD. It has been associated with increased severity of CHF, increased hospitalization, worse cardiac function and functional class, the need for higher doses of diuretics, progressive WRF and reduced quality of life[59]. Anemia occurred in 91.5% of our CRS patients with an anemia-specific mortality rate of 38.6%[9]. Anemia lowers the blood pressure as a result of peripheral vasodilatation due to anemia-associated tissue hypoxia. Reduced blood pressure stimulates increased sympathetic activity with attendant tachycardia and increased stroke volume. The latter leads to reduced renal blood flow, increased RAAS activity and anti-diuretic hormone production leading to salt and water retention. The effect of this is increased plasma volume, ventricular diameter and brain natriuretic peptide. The final outcome is ventricular dilation and hypertrophy with eventual myocardial cell death, fibrosis and CHF[60]. The child with CRS usually manifests with both features of heart and kidney failure, either sequentially depending on which organ was affected first or simultaneously when the two organs are injured at the same time, as it occurs in Type 5 CRS. These manifestations are summarized in Table 1.

THERAPEUTIC CONSIDERATIONS IN CRS

Simultaneous treatment of both heart and kidney failure, as is the case with CRS, requires sound understanding of the mechanisms, pathology and the hemodynamic changes that brought about the syndrome if unwanted complications associated with therapeutic indiscretion are to be avoided. This is not usually an easy task as many competing pathological factors must be considered for effective management and desired outcome. Treatment of HF requires that the myocardial contractility be increased, hyper-reninemia and associated sympathetic nervous system hyperactivity and the tachycardia be aborted

for a better outcome. Furthermore, there is the need for improved oxygenation of the cardiomyocytes for effective myocardial function. Digoxin is a popular positive inotropic agent that is used globally to achieve these objectives in pressure overload HF without any significant negative impact on kidney functions. It is rarely of any benefit in volume overload HF that requires a loop diuretic for rapid pulmonary and circulatory decongestion. Other positive inotropes that have been used in CRS with the objective of improving myocardial contraction in children hospitalized for ADHF include milrinone (78%), dopamine (38%), epinephrine (13%) and dobutamine (3%)[3]. Negative inotropes like β and calcium channel blockers are better avoided in CRS (with or without hypertension) because they are likely to do more harm than good.

Loop diuretics, namely frusemide, ethacrynic acid and bumetanide, are strongly plasma bound and are therefore actively secreted into the renal tubule by the organic anion transporter; they normally bind to the sodium potassium chloride co-transporter channel 2 (NKCC2) in the thick ascending limb of the loop of Henle where they inhibit sodium, potassium and chloride reabsorption, causing diuresis and loss of these electrolytes. Long-term use of these diuretics, however, may become counterproductive as the distal tubule becomes hypertrophied owing to the constant heavy load of solutes (sodium, potassium and chloride) delivered to it for reabsorption as result of the NKCC2 inhibition, causing sodium and water retention that was primarily meant to be prevented with the loop diuretics (loop diuretic resistance). Blocking the sodium chloride co-transporter (NCC) channel in the distal tubule using a thiazide diuretic (serial nephron blockade) may be beneficial if this situation arises. A small study reported significant improvements in urinary volume and sodium excretion following frusemide and metolazone (a thiazide-related diuretic) combination treatment in non-CRI children with frusemide-resistant edema[61]. Relieving congestion and volume overload, which is critical to survival in CHF and pulmonary edema, may be difficult to achieve alone with diuretics in the setting of severe CRS in which anyone of stage 3 AKI (severe oliguria or anuria), stage 4 CKD, end-stage renal disease (ESRD), class Ⅲ or Ⅳ HF is a component. It is in this clinical setting that ultrafiltration (UF) becomes the ultimate therapeutic goal if mortality is to be prevented. Studies have shown that UF could be performed safely in HF patients with significant relief of pulmonary congestion and volume overload[62-65]. In CRS patients with extremely low left ventricular shortening and ejection fractions, gradual removal of both fluid and solutes by continuous RRT (CRRT), like continuous venovenous hemofiltration or hemodialfiltration, becomes imperative if serious hemodynamic instability and death are to be avoided. Although CRRT is frequently indicated for AKI, it can also be used temporarily in patients with acute-on-chronic renal failure with pulmonary edema or severe CHF (class Ⅲ or Ⅳ HF) when hemodialysis (HD) cannot be tolerated. The functions the kidneys perform in 168 h/wk are what HD will do in 12 h/wk, thus imposing enormous stress on the heart leading to LVH over time or worsening of existing LVH and cardiac dysfunction. Patients treated with CRRT can be switched over to intracorporeal diffusive and convective therapy like continuous ambulatory or cycling peritoneal dialysis (CAPD/CCPD) when stable to protect the heart from the stress of HD. Some studies have shown improvements in altered cardiac geometry and functions as well as lack of progression of LVH in ESRD patients treated with CAPD[66,67], while others showed no improvement[68,69]. Lack of improvement in the latter was ascribed to high cardiac output[68] and inadequate control of hypertension in the patients[68, 69].

Adenosine is released endogenously from the macula densa in the injured kidney, causing vasoconstriction of the renal afferent arteriole *via* the adenosine A1-receptor as well as vasodilatation of the renal efferent arteriole *via* the adenosine A2-receptor. These actions lead to reduction in the renal blood flow and glomerular perfusion pressure, resulting in ischemic kidney injury[70]. Treatment with an adenosine A1-receptor antagonist like aminophylline may therefore be beneficial in CRS for the following reasons. One, it will improve breathing by dilating the bronchioles, thus increasing oxygen delivery to the lungs and ultimately to body tissues; two, it will promote diuresis by blocking the adenosine A1-receptor thereby reducing congestion and circulatory overload. Aminophylline therapy has been significantly associated with improved urine flow rate and decreased need for dialysis but not survival in children with acute oligoanuric AKI[71].

Studies have shown ANG Ⅱ[72] and aldosterone[73] to be independently associated with inflammatory kidney damage through promotion of adhesion molecules, pro-inflammatory mediator expression, cellular growth/proliferation, endothelial cell dysfunction, extracellular matrix and fibrosis. Clinical trials of angiotensin converting enzyme inhibitor (ACEi) and spironolactone (a mineralocorticoid receptor blocker or aldosterone antagonist) have been associated with clinical improvement and retardation of renal disease progression[72]. All of these pro-inflammatory properties of ANG Ⅱ and aldosterone are also active in the heart, causing progressive heart disease and HF. ACEi, ANG Ⅱ receptor-1 blocker (ARB) and spironolactone are now increasingly used in children to treat hypertension, altered cardiac geometry (LVH), HF, proteinuric and non-proteinuric CKD and to abort all of the inflammatory properties of escalated RAAS activity that are seen in both CHF and CKD[3,53,74-78]. It is, however, important to note that AKI may complicate ACEi therapy when renal perfusion is compromised[79]. In CHF, the renal perfusion pressure is low and the GFR is highly ANG Ⅱ driven; therefore, the use of ACEi/ARB when CHF is severe could further worsen the renal failure, thereby increasing morbidity and mortality from CRS. Therefore, in the clinical setting of CRS, patients treated with an ACEi or ARB should be carefully monitored for evidence of AKI by checking their urine output and Scr level regu-

larly. An acute rise in Scr by at least 0.3 mg/dL or 50% increase from baseline or a urine output < 0.5 mL/kg per hour for 6 or more hours should warrant immediate drug withdrawal. Serum potassium level should equally be monitored in such patients for early detection of hyperkalemia. Some conditions in which use of ACEi or ARB in CRS may not be advisable will include CRS: (1) with severe CHF (Class Ⅲ and Ⅳ HF); (2) with severe CHF on diuretics; (3) on non-steroidal anti-inflammatory drugs or calcineurin inhibitors (cyclosporine A or tarcrolimus), irrespective of CHF severity; and (4) with mean arterial pressure < 60 mmHg, irrespective of CHF class. In these conditions, treatment with spironolactone (for its anti-sodium/water retention, anti-renal and -myocardial fibrotic properties) in addition to loop diuretics, digoxin (in pressure overload CHF) and other safe therapeutic measures like CRRT may be helpful. However, in CRS patients with ESRD, it appears that drug treatment emphasis will shift to the HF while the ESRD is managed accordingly with regular dialysis until a kidney transplant is feasible. In the latter category of patients, there is no further fear of a worsening renal function. Treatment with either ACEi or ARB for better cardiovascular outcome should not, therefore, be inhibited unless they are reasonably contraindicated.

CONCLUSION

There is the need for collaborative work on childhood CRS between pediatric cardiologists and nephrologists to better understand the syndrome so that a well coordinated therapeutic program can be developed for universal application. Simultaneous management of heart and renal failure in CRS is quite challenging; the therapeutic choice made for one organ must not jeopardize the other.

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