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Review

Renal dysfunction in adults with congenital heart defects

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ABSTRACT

Congenital heart disease (CHD), with its worldwide incidence of 1% in live births, is the most common inborn defect. Due to enormous advances in pediatric cardiology, congenital heart surgery, interventional cardiology, intensive care, and diagnostic imaging the number of adults with congenital heart disease (ACHD) is rapidly rising: the number of ACHD patients now exceeds the number of children and adolescents with congenial heart disease. As ACHD patients are getting older, not only complications of their underlying congenital heart defect such as valve diseases, valve complications, arrhythmias, and heart failure but also acquired cardiovascular and non-cardiovascular co-morbidities such as coronary artery disease, lung disease, liver disease, or chronic kidney disease, are becoming equally important for the outcome of this population. ACHD patients exhibit a 3-fold higher mortality in the presence of chronic kidney disease. This article reviews the mechanism of cardio-renal syndrome in ACHD patients and introduces some clinical implications for their assessment.

1. Introduction

Increasing life expectancy during the last several decades has led to increasing risk of aging-related diseases. The normal process of aging is associated with progressive deterioration in structure and function of all organs. This aging process or pathobiological and pathophysiological derangement also affects the vasculature, heart, and kidneys and contributes to the development of cardiovascular disease (CVD), including coronary artery disease (CAD). This condition can lead to myocardial ischemia/myocardial infarction and usually ends up in heart failure (HF). Modifiable cardiovascular risk factors can be prevented or treated, such as overweight/obesity, high blood pressure, high cholesterol, tobacco use, sedentary life style, and diabetes.

Cardiovascular disease is the leading cause of death globally. The 2010 Global Burdon of Disease study estimated that CVD caused almost 30% of all deaths [1]. CVD is responsible for over 4 million deaths in Europe and more than 600,000 deaths in the United States every year [2]. Renal dysfunction in patients with acquired cardiovascular disease and heart failure is a marker of cardiovascular events and death and, hence, an ominous prognostic sign [3–7]. Renal dysfunction is common in patients with HF and is associated with high morbidity and mortality. There is evidence that cardiac dysfunction may cause renal dysfunction, and vice versa [8]. Chronic kidney disease is present in 30–40% of the patients with HF with a greater prevalence in those with more severe symptoms [9–11].

The diagnosis and successful management of congenital heart disease (CHD) represents one of the greatest triumphs of cardiovascular medicine and surgery in the 20th century. Consequently, the number of adults with CHD (ACHD) has grown rapidly and now exceeds the number of children and adolescents with congenial heart disease; congenital heart disease is no longer a paediatric disease [12]. Extrapolating the Quebec data to a Canadian population of 34 million people, there are approximately 166,000 adults and 90,700 children with congenital heart disease in 2010; the adult population in the United States comprises approximately 1.5 million ACHD patients in the year 2010 [12,13].

The care of ACHD patients implies major challenges, which include a large number of anatomic malformations and pathophysiologies of varying severities, at various stages of their natural and "unnatural" history and with different degree of anatomic and/or physiologic repair. Approximately one-third of these patients are considered to have "simple" CHD but the majority, such as those with cyanotic heart disease, have lesions of greater complexity [14].

As ACHD patients age, not only complications of their underlying congenital heart defect such as valve diseases, valve complications, arrhythmias, and HF but also acquired cardiovascular and non-cardiovascular co-morbidities such as CAD, lung disease, liver disease, or chronic kidney disease (CKD) are becoming equally important for the outcome of this population [15,16].

Precise and elegant interaction between kidney and heart is critical for maintenance of vascular tone, blood volume, blood pressure, and

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hemodynamic stability. The complex interrelation between the kidneys and the heart has been termed the cardio-renal syndrome (CRS) [17]. Pathophysiological mechanisms indicating the involvement of cardiovascular and renal functions in the manifestation of CRS are complex and have not yet been fully elucidated.

In patients with HF for instance, the impairment of systolic and/or diastolic blood pressure leads to decreased cardiac output, stroke volume, and circulating volume [18]. The decrease in arterial circulating blood stimulates arterial baroreceptors and causes neurohormonal activation. This leads to production of compensatory mechanisms to cope with relative hypovolemia and altered tissue perfusion [19,20].

These compensatory mechanisms include activation of renin–angiotensin–aldosterone system (RAAS), the sympathetic nervous system (SNS), endothelin system, natriuretic peptides, and cytokines [21,22]. Under normal conditions, these mechanisms act unanimously in maintaining vascular tone and normalizing cardiac output. However, in patients with HF, the same mechanisms perpetuate in vicious cycles as contributors for progression of chronic renal hypoxia, inflammation, and oxidative stress, which alone can alter cardiac and renal structure and function [23].

Similar neurohormonal derangements have been demonstrated in adult patients with various CHD [22,24–26]. In the ACHD population, the development of HF is usually a chronic process with a long asymptomatic period despite overt ventricular dysfunction and decreased measured functional capacity. Many seem to have adapted to their chronic HF symptoms and insidious limitations in exercise capacity, with exercise intolerance being almost universal and progressive in this cohort [27,28].

The data collected from several observational studies and clinical trials indicate that acute or chronic acquired cardiac disease can directly contribute to acute or chronic worsening kidney function and vice versa [29]. This interaction is not well studied in patients with congenital heart defects, and particularly, the literature indicating the role of CRS in ACHD is limited.

This article aims to give some insights into CRS in ACHD patients by reviewing published papers in the field of congenital heart defects and introducing some clinical implications for their assessment.

2. Cardio-Renal Syndrome

In 2004, a working group of investigators at the National Heart, Lung, and Blood Institute defined for the first time the CRS as a state in which therapy to relieve HF symptoms is limited by further worsening renal function [30]. In 2008, a consensus conference on CRS in Venice, Italy, identified and classified five subtypes of CRS (see also Fig. 1) [31]. The terms CRS and reno-cardial syndrome (RCS) indicate that each dysfunctional organ has the ability to initiate and perpetuate disease in the other organ. However, this is more complex than kidney dysfunction in HF being a direct consequence of altered renal blood flow due to reduced ventricular systolic function. There are other conditions contributing to this complex syndrome such as increased central venous pressure, anemia, cyanosis, neurohormonal elaboration, oxidative stress, and renal sympathetic activity [32].

2.1. Type I (acute CRS)

Any patient with any kind of congenital heart defect of simple, moderate, or great complexity is at risk for acute worsening of heart function with impaired cardiac output and subsequent acute kidney injury and/or dysfunction. Children or adults with congenital heart disease of moderate or great complexity who undergo congenital heart surgery or a catheter-based intervention are particularly vulnerable for acute renal injury in the periprocedural period. Kidney injury can be transient or permanent.

2.2. Type II (chronic CRS)

Any chronic abnormalities in heart function can lead to kidney injury and/or dysfunction (e.g., in CHD, chronic HF, atrial fibrillation, and chronic ischemic heart disease). Patients with a univentricular circulation including unrepaired, cyanotic patients, and patients palliated with a Fontan physiology meet all pathophysiological mechanisms to develop chronic renal insufficiency as discussed below. Patients with a history of heart failure, patients with ventricular dysfunction, and those with a subaortic right ventricle in particular are populations who can be or are in a chronic low cardiac output state, with neurohormal activation, and then at risk for chronic subclinical or clinical renal insufficiency. Many of these patients present with more than one pathophysiological and pathobiological mechanism (as discussed below), which maintain a vicious cycle and cumulate the risks to develop chronic kidney dysfunction.

2.3. Type III (acute reno-cardiac syndrome, RCS)

Diagnostic procedures (e.g., application of contrast material for cardiac CT, MRI, angiograms), nephrotoxic agents (e.g., aminoglycosides, non-steroidal anti-inflammatory drugs, ACE inhibitors, or angiotensin receptor blockers), vasoconstrictors (inotropes), or hypovolemia (e.g., overdiuresis with diuretics, dehydration due to diarrhea or inadequate fluid intake) can cause acute worsening of a preexisting sublinical or clinical kidney dysfunction, with secondary acute negative impact on cardiovascular function, which can resolve or transition to type IV (chronic RCS). However, any other chronic kidney disease, which is less common in ACHD patients, can lead to heart injury and/or dysfunction (in diabetes mellitus, polycystic kidneys, and glomerulonephritis)

2.4. Type V (secondary CRS)

Systemic conditions leading to simultaneous injury and/or dysfunction of heart and kidney (in systemic lupus erythematosus and amyloidosis). Systemic infections (sepsis) can have a negative impact on cardiorenal interaction with an insult to both cardiovascular and kidney function and cause or worsen a preexisting, subclicinal cardiovascular dysfunction kidney dysfunction. Nephrotoxic and cardiotoxic agents can exacerbate the cumulate the toxic effect on the heart and the kidneys

Morgan et al.'s review of CKD in adult CHD patients concludes patients should be recognized as at risk of developing CKD due to not only pathophysiological factors of CHD, such as cardiac volume overload, but also extrinsic factors, such as cardiopulmonary bypass during surgery [33]. Acute kidney injury (AKI) is common after cardiac surgery, and it has been demonstrated that cardiopulmonary bypass time in pediatric CHD patients undergoing cardiac surgery is independently associated with the development of AKI [34–36].

Although AKI has been shown to be a significant risk factor for stages 4 and 5 CKD after cardiac surgery in the general adult population, the AKD–CKD relationship and its long-term characteristics have not been adequately studied in ACHD patients [37]. This is a concern as the prevalence of CKD is higher in the ACHD population than in the normal population, and the added complexity of their conditions may affect ACHD patients' susceptibility to CKD [33,38]. To our knowledge, there are only 2 studies that measured long-term changes in renal function of neonatal and pediatric CHD patients requiring dialysis after cardiac surgery (all others are short-term). In the earlier study, 3 out of 11 survivors showed abnormal renal function after a mean follow-up period of 3.4 years [39]. In the more recent study, patients that survived the postoperative period did not show adverse renal outcomes 5.5 median years at follow-up [40]. However, both studies have weaknesses in their methodology, such as not measuring albumin/creatinine ratios, and authors caution that seemingly full recovery of renal function cannot