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Review

Left ventricular mass and cardiac function in pediatric dialysis patients

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ABSTRACT

Cardiovascular disease is a major determinant of morbidity and may impact on life expectancy of children with chronic kidney disease. Myocardial disease in children requiring renal replacement therapy in the form of dialysis is distinct from atherosclerosis commonly found in the adult population. Left ventricular hypertrophy associated with diastolic dysfunction and to a lesser extent by systolic dysfunction is the most common manifestation. Most patients remain asymptomatic whereas some may develop congestive heart failure. Abnormalities in cardiac structure and function are usually detected by echocardiogram, although in recent years the use of cardiac magnetic resonance imaging emerges as a potential alternative. The pathophysiological mechanisms underlying cardiac disease are complex and an attempt has been made to dissect the main risk factors. Given the high incidence of cardiac disease among children with end-stage kidney disease mandates timely diagnosis of this condition and underscores the need to identify risk factors which are amenable to preventive or interventional measures. Kidney transplantation may significantly improve the cardiac status.

1. Introduction

Cardiovascular disease is a major determinant of morbidity and may impact on life expectancy, not only in adults, but also in children with chronic kidney disease (CKD). Traditionally, it has been perceived that the cardiovascular disease in this context is an augmented and accelerated form of the widely known atherosclerotic process. However, during the last two decades, studies have shown that it entails a distinct pathophysiological process which differs in various aspects including risk factors, anatomical site and histologic findings resulting in different symptoms, deserving distinct therapeutic approaches which will determine its unique prognosis. Interventional trials, such as the use of statins, assuming that these patients had atherosclerosis, failed to show distinct benefit in children with CKD and therefore are not universally recommended [1].

2. Epidemiology

Myocardial disease in children with end-stage kidney disease (ESKD) is commonly manifested as left ventricular hypertrophy (LVH), often associated with diastolic dysfunction and to a lesser extent by systolic dysfunction [2]. Differences in the reported incidence of cardiac disease among the pediatric dialysis population may stem from variability in the diagnostic test used. In a cross-sectional analysis of 656 children on hemodialysis, only 69% were tested for cardiac disease [3]. Sixty percent were evaluated by chest radiography, 35% by echocardiography and 33% by ECG [3]. Left ventricular hypertrophy/enlargement was diagnosed by echocardiography in 72%, by chest X-ray in 20% and by ECG in 15% of patients tested. In recent years, the vast majority of studies used echocardiography for the evaluation of cardiac structure and function in the context of ESKD. The exact methodology and analysis of the data may have varied between researchers, thus influencing the interpretation of the results. Additional confounders which may bias the estimation of the true incidence of LVH among children with ESKD include the sample size and the precise definition of LVH used. As a result, an incidence varying between 30% and 82% has been established in various reports [4,5]. Furthermore, it was argued that echocardiography, compared to cardiac magnetic resonance, may over-estimate the prevalence of LVH [6].

Cardiac calcifications, assessed by ultrafast gated CT and quantified by the Agatston score, are more prevalent among children treated with hemodialysis compared to peritoneal dialysis and may be attributed, at least in part, to older age and worse control of mineral balance in the former group [7].

The leading cause of mortality in children with ESKD receiving renal replacement therapy (RRT), including chronic dialysis or kidney transplantation, is cardiovascular disease, accounting for 22.5% of deaths in this population [8]. This cohort included patients who reached ESKD in childhood and died before the end of their third decade of life. Percentage of cardiac deaths varied with age: the highest incidence was noted among infants and toddlers as well as young adults. Also, black

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patients were more likely to die of cardiac etiology. The main flaw of this retrospective study is that the data were derived from death certificates that commonly defined the immediate cause of death as "cardiac arrest". As cardiac arrest may often be a final common pathway to various processes, this may have skewed the results and overestimated the true incidence of cardiac-related deaths, A comprehensive study suggested that cardiovascular-related diseases are the main cause of death (overall 41%) in a cohort of children with early-onset ESKD (0–14 years of age) [9]. It is truly alarming that 3 patients died of myocardial infarction during their 3rd–4th decades of life. However, thorough analysis of the diagnoses presumably leading to death, includes clinical situations which may be attributable, at least partly, to hypertension, electrolyte imbalance and fluid overload and not necessarily to myocardial disease, per se. These include cerebrovascular events, cardiac arrest, congestive heart failure and dissection of the aorta. Of note, the high death rate declined by 50% from the decades of 1972–1981 to 1982–1992 and the cardiovascular-related mortality decreased even further, by 61% [9].

3. Clinical Manifestations

Left ventricular hypertrophy is prevalent among children with CKD and often associated with diastolic dysfunction. Nevertheless, most patients remain asymptomatic (personal observation). The most common clinical manifestation is congestive heart failure (CHF). This is in contrast to the adult CKD population, in whom cardiac disease is often symptomatic manifesting as myocardial infarction or CHF. This underscores the fact that in the pediatric age group, CKD-associated cardiac disease is not caused by an underlying cardiovascular disease mechanism such as atherosclerosis.

4. Diagnostic Tools for Cardiac Dysfunction

Imaging tests are the most important tool used today to diagnose cardiac involvement in the context of pediatric CKD. The aim is timely diagnosis that will enable prevention measures to be taken. Newly emerging biomarkers may play a significant role in the future.

4.1. Left Ventricular Mass

4.1.1. Echocardiogram

Echocardiography is the most important tool for measurement of cardiac structure, size and function. The American Society of Echocardiography (ASE) guidelines for pediatric echocardiogram include the following: recommendations for the measurement of LV size using two-dimensional (2D) linear measurement of short axis diameters and wall thickness as well as 2D and M-mode volumetric assessment of LV mass [10]. LV mass can be estimated by measurement of septal and LV free wall thickness and the LV diastolic dimensions on M mode, assuming normal LV shape. In clinical practice, many pediatric cardiologists rely on z-scores of the thickness of the LV posterior wall (LVPW) and/or interventricular septum (IVS) alone to determine LVH [11]. These measurements bear some flaws: in the presence of LV dilatation, wall thickness may be within normal limit despite hypertrophy, as depicted in the Fig. 1. Moreover, the way to index LV mass to body size in infants and children is not entirely settled. The American Academy of Pediatrics (AAP) recommends the use of LV mass indexed to height to the 2.7th power ($LVMI^{2.7}$) in $g/m^{2.7}$ to diagnose LVH. This report recommends the use of $LVMI^{2.7} > 51\ g/m^{2.7}$ (>99th % for adults and children) as a cut-off point for the diagnosis of LVH [12]. This calculation is aimed at indexing LV mass to lean body weight, as adult data suggest that this indexing method eliminates the effect of obesity (that increases body surface area) on the calculation. This concept may be questioned, as the increase in cardiac mass with increasing in body mass may be physiologic and does not necessarily represent cardiac pathology. Age-specific reference values for $LVMI^{2.7}$ have been developed [13]. However, in this large study, the indexed LV mass leveled only in children older than 9 years of age [13]. This phenomenon can be explained by the fact that if the height, which is the denominator, is <1 m (around age 4), the 2.7 power is even smaller which will result in a high figure. Between birth and 12 years of age, the average BSA increases 5.8-fold, while height to 2.7 power increases 156-fold. Thus the resultant indexed LV mass 95th percentile is 80 $g/m^{2.7}$ compared to 40 $g/m^{2.7}$ at age 9. Interestingly, in the study by Khoury et al. children whose weight was >85th percentile were excluded. Recently, Mirchandani et al. [14] compared wall thickness measurements with $LVMI^{2.7}$ age-specific reference criteria, and found that fewer than half of the patients with LVH by $LVMI^{2.7}$ were diagnosed as LVH by wall thickness criteria. This apparent discrepancy should be settled with a gold standard method like magnetic resonance imaging (MRI). Another interesting approach is indexing LV mass to reference values of children of the same height rather than the same age. As many CKD children have growth retardation, referencing to age-matched healthy children with normal height may not be accurate. Matching for height age rather than chronological age provides an approximative solution to this problem [15]. The threshold for clinically significant hypertrophy should be determined. The newly developed 3D echocardiogram may improve the accuracy of mass measurement. Laser et al. [16] described a very good correlation between real time 3D echocardiography and cardiac MRI in children, with slight overestimation of LV mass by 3D echo. They studied a group of 332 infants and children, and found that LV mass correlated with age, weight, height and body surface area. In children aged 7 to 18, gender difference was also noted. In a recent multicenter study enrolling 272 CKD children aged 6–17 years, compared to 61 age-matched controls, LV mass was determined by wall thickness and LV diameter [17]. LVH was present in 57% of CKD patients but also in 7% of control subjects, suggesting oversensitive criteria for LVH.

4.1.2. Cardiac MRI

Cardiac magnetic resonance imaging (CMRI) is widely considered to be the "gold standard" technique for the assessment of LV dimensions because it accurately defines mass, volume, and pattern of LVH (concentric, eccentric, or asymmetric) independently of geometric assumptions used in echocardiography. In addition CMRI can provide important information on systolic function and possibly cardiac fibrosis. However, the use of CMRI is limited by its lower availability and higher cost compared to echocardiogram [18]. CMRI LV mass is indexed to BSA. Compared to CMRI, M-mode echocardiography overestimates left ventricular mass in ESKD. The disparity between the two methods has also been demonstrated in other patient populations, such as individuals with LVH secondary to either hypertension or aortic stenosis. Conversely, in one large study of healthy army recruits, echocardiography consistently underestimated LV mass compared to CMR by a mean of 14.3 g [6].

Data derived from CMRI in pediatric CKD patients is scarce, but shows similar results to those obtained in adults [19]. Reference values for LV volume and mass in children 4–10 years of age have been published as

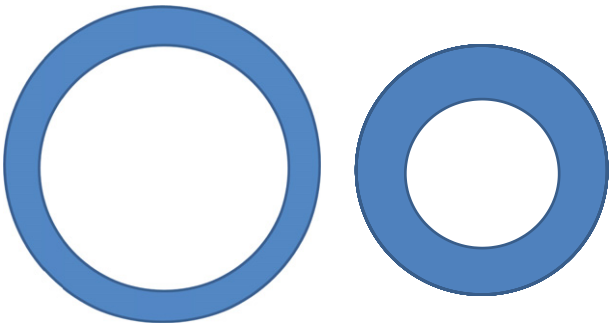

Fig. 1. Demonstration of pre (left) and post (right) parasternal short axis views of the same heart. Wall thickness increases with volume depletion, while mass remains the same.