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Review

How to estimate glomerular filtration rate (GFR) in pediatric cardiac patients

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ABSTRACT

The management of pediatric patients with congenital heart disease and pediatric heart transplant recipients has become complex. One of the issues a pediatric cardiologist has to be mindful about is renal function, which is often impaired in these patients due to a variety of causes. There is consensus that glomerular filtration rate (GFR) is the best surrogate marker for renal function. Inulin clearance is the gold standard method for measurement of GFR, but it is invasive, cumbersome and requires bladder catheterization in smaller children. Nuclear medicine methods replaced the measurement of inulin clearance, but these methods are poorly standardized, not evaluated using appropriate two-compartmental models and have several drawbacks, including inaccuracy due to plasma protein binding or exposure to radiation. The most widely used endogenous marker of GFR, serum creatinine, is afflicted by multiple shortcomings, particularly in pediatric cardiology patients with congenital heart disease or cardiomyopathy. Creatinine is affected by dietary intake, nutritional status and muscle mass, which are often altered in these patients. Small molecular weight proteins such cystatin C may be the most promising endogenous alternatives.

1. Introduction

Renal injury is common among pediatric cardiac patients, especially those with heart failure [1]. In addition to the renal injury that may result from poor cardiac function itself, many heart failure therapies, including diuretics, vasoactive medications, and angiotensin converting enzyme (ACE) inhibitors, have known deleterious effects on renal function, especially in the setting of poor cardiac output or hypovolemia. Single-center cohort studies of pediatric heart transplant recipients report a range of pretransplant renal dysfunction of 31.7%, and up to 13% of survivors after 15 years reach ESRD [2]. UNOS data from 2000 to 2010 report rates of renal failure requiring dialysis in the post-operative period of 5% [3]. Recent data from the Pediatric Cardiomyopathy Registry found that 62% of patients with dilated cardiomyopathy had an abnormally low estimated glomerular filtration rate for age (<90 mL/min/1.73 m^2) [4].

Decreased GFR is a major predictor of outcome in patients with heart failure [5]. This has been abundantly demonstrated in adult cardiac patients. However, data in children are comparatively scarce, but nevertheless compelling. Recent data linked cardiorenal syndrome with a 2.4-fold incidence of death over 5 years among 93 pediatric dilated cardiomyopathy patients [6]. Cystatin C, an alternative marker for the measurement of GFR, is positively correlated with the ratio of N-terminal pro-brain natriuretic peptide to brain natriuretic peptide levels in children, which are increasingly utilized as biomarkers of chronicity and severity of heart failure [7]. Production of N-terminal pro-brain natriuretic peptide (NT) and BNP is equimolar. Although NT clearance occurs only in the kidneys, BNP clearance occurs in the kidneys and other organs. Hence, the ratio should be used [7]. Worsening renal function was also associated with worse clinical outcome after surgery for congenital heart disease (average 7.2 days longer stay in the intensive care unit, 10.4 days longer stay in hospital), even after controlling for age and operative factors [8]. Increasing severity of renal dysfunction while on the cardiac transplant waitlist is associated with increasing risk of death in the immediate post-transplant period (2-fold risk with mild pre-transplant renal dysfunction, 3.6-fold risk with severe pre-transplant renal dysfunction) [2]. In UNOS data for all pediatric heart transplant recipients between 2000 and 2010 ($n = 3562$), patients who required dialysis for renal failure in the immediate post-operative period had a 9-fold risk of death in the first year post-transplant [3]. Data in adults with congenital heart disease clearly

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demonstrate that deranged physiology is not limited to the heart, but also affects the kidneys, with a clear effect of renal impairment on clinical outcomes in addition to that due to functional class and systemic ventricular function [9]: mortality in the affected patients was 3-fold higher [9].

The causes of chronic kidney disease (CKD) in heart transplant recipients are multifactorial [10,11]:

- Pre-transplant renal dysfunction, especially cardio-renal syndrome
- Pre-transplant hypoxic episodes and peri-operative renal injury
- Immunosuppressant nephrotoxicity
- Hypertension, dyslipidemia and diabetes mellitus

In a large study ($n = 69{,}321$) of non-renal solid organ transplant recipients, largely adult, 16.5% developed CKD stage IV or higher (defined as a GFR <30 mL/min/1.73 m^2) at a median of 35 months after transplantation [9]. In the heart transplant subgroup, the prevalence of stage IV-V CKD was 6.9%. According to ISHLT data from the 2014 registry report, the need for renal replacement therapy ranged from 5% to 13% depending on the age group by 13 years post-heart transplant [12,13]. Major risk factors included renal dysfunction prior to transplant and the need for post-operative renal replacement therapy [12,13]. Although pediatric data are scarce, a recent systematic review demonstrated an even higher prevalence of CKD in children: 22.7%–40% of pediatric heart or heart-lung transplant recipients had mild and 6.8%–46% had severe CKD [14].

Renal dysfunction is common among pediatric cardiac patients. As such, its accurate detection is of critical importance to pediatric cardiologists. This review provides a summary of the best current knowledge on assessing renal function in children and adolescents with heart disease, and also provides the basis for involvement of pediatric nephrologists in the case of abnormal GFR.

2. Renal Function Should Be Monitored as GFR

As outlined above, renal function cannot be measured directly. Renal clearance of solutes and toxins is considered to be the best index of renal function in health and disease [15,16]. The year 1773 marked the beginning of efforts to quantify renal function with the quantitation of serum urea [17]. Moller introduced the concept of urea clearance as a measure of renal function in 1928–1930. He defined clearance as “the volume of blood that a one minute's excretion of urine suffices to completely clear of urea” [18–21]. Shortly thereafter, Homer Smith refined the GFR measurement with the introduction of “inulin clearance” in 1933 [22]. Today, GFR is considered to be the most useful markers of renal function, [23,24] with inulin clearances set as the gold standard for its measurement [25].

The ideal GFR marker must have stable concentration in the plasma and must be physiologically inert, cleared only by the kidney, and freely filtered at the glomerulus, [26] without reabsorption or secretion by the tubules. While the gold standard for the measurement of GFR is inulin clearance [25], very few centers, such as the Karolinska Institute in Stockholm, currently perform this on a routine basis [27,28], as there are several significant limitations to the procedure. There is only one supplier left in the world who provides Inutest®, and at a prohibitive cost. A detailed review on the methods of measuring renal function was published recently by our group [29].

3. GFR Measurement Using Radiolabeled Isotopes or Cold Iohexol

Nuclear medicine techniques replaced inulin clearance in the 1970s. For a comprehensive explanation of various methods, please see our extensive review [29]. The most commonly used tracers are summarized in Table 1.

Table 1
Commonly used exogenous markers of glomerular filtration rate (GFR). All except iohexol are radiolabeled.

GFR compound	Location where the test is commonly used	Plasma protein binding
^{51}Cr-ethylenediamine tetra-acetic acid (EDTA) clearance [31]	Europe	12.2% [32]
^{99}Tc-diethylenetriamine penta-acetic acid (DTPA) [33]	Most of the world except Europe	11.0% [32]
^{125}I-iothalamate [34]	US	9.6% [32]
Cold iohexol [35,36]	North America	2.0% [37]

These methods typically involve the injection of radiolabeled pharmaceuticals that are predominantly cleared by glomerular filtration, and requires insertion of a second IV cannula for timed blood samples. The GFR is calculated from the plasma disappearance of the agent. Iohexol is theoretically superior to other exogenous markers because of its low plasma protein binding: the higher the plasma protein binding, the larger the proportion of an agent's clearance that is contributed by tubular secretion, leading to greater overestimation of GFR. In practice, however, accuracy of iohexol GFR estimates demonstrate considerable scatter [30]. Clinical studies comparing inulin clearance with nuclear medicine scans favor ^{51}Cr EDTA, which showed the least bias and best agreement in both transplant and non-transplant patients. However, these studies have not typically been performed in children with congenital heart disease, but rather in adult and pediatric renal patients [29]. In addition, ^{51}Cr EDTA is not available in North America. Significant limitations apply with each of these methods if extravasation occurs, if samples are drawn before the infused substance reaches equilibrium with the entire extracellular volume, or if analysis methods do not include a two-compartment model [29]. Proper pharmacokinetic non-linear two-compartmental models with exact time points are rarely employed, which is a significant source of error for these methods [29].

4. Renal Development in Childhood

Developmental changes during childhood have a significant effect on the determination of GFR. This age dependency is most marked in the first 18–24 months, but even thereafter, absolute GFR constantly changes with height due to glomerular growth. GFR is therefore normalized to body surface area.

GFR is particularly difficult to estimate in infancy. While all nephrons are terminally differentiated at 36 weeks gestation [38], only the juxtaglomerular glomeruli are used immediately after birth. Neonatal GFR and effective renal plasma flow (ERPF) are low, both in term and in preterm infants [39]. The low GFR of a newborn, attributable to a delicate balance between vasoconstrictive and vasodilatory forces at work on the renal vasculature, resulting in ongoing high vascular resistance, limits the postnatal adaptation of renal function to endogenous and exogenous stress [40,41]. GFR is especially low in premature infants [38]. Systemic vascular resistance decreases markedly after birth, causing redistribution of blood flow, which may contribute to the low neonatal blood flow to the kidneys. Low ERPF and GFR contribute to the altered pharmacokinetics of drugs excreted by the kidney in the newborn [42]. There is continuous recruitment of additional glomeruli until 18–24 months of age [43,44]. For an in depth review of the adaptation of renal function in infancy, please see our recent review [45].

In the first year of life, and during puberty, there are periods of rapid increase in muscle mass during growth spurts, requiring special considerations for the calculation of GFR [46], especially in adolescent males [47]. The most important determinant of GFR is height, which, when taken into account, led to the widely used Schwartz formula [48], a pediatric GFR estimation model based on the height/creatinine ratio. In its most recent iteration, known as the updated Schwartz formula, the accuracy is much improved,