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Original Article

Assessment of Radiocontrast Nephropathy after Cardiac Catheterization in Infants and Children with Congenital Heart Diseases

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ABSTRACT

Background: Increasing numbers of patients are exposed to contrast medium (CM) during cardiac catheterization procedures. Radiocontrast use in all branches of medicine is reported to be the third most common cause of new onset renal failure in hospital patients.

Objectives: To assess renal dysfunction induced by use of contrast media (CM) in infants and children with congenital heart disease (CHD) undergoing cardiac catheterization.

Methods: Serum Creatinine (Cr), corrected creatinine clearance (c.CrCl.), serum Beta 2 microglobulin (β_2MG), urinary retinol binding protein (uRBP), fractional excretion of sodium (FENa), and urine to serum osmolality ratio (u/sOSM) were measured in 19 patients with congenital cyanotic heart diseases (CCHD) and 26 patients with congenital acyanotic heart diseases (CAHD) 24 hours before and 72 hours after cardiac catheterization using low osmolar nonionic CM. Patients were compared to 31 healthy controls of matched age and sex.

Results: Before cardiac catheterization, there was no significant difference in the studied parameters between CCHD and CAHD patients when compared either to each other or to the healthy controls. Only u/s OSM ratio was significantly reduced in CCHD patients when compared to CAHD ($p = 0.02$) or controls ($p = 0.01$). After cardiac catheterization, all patients showed significant reduction of their c.CrCl, u/s OSM ($p < 0.001$ & 0.002 respectively) and a significant increase of β_2MG, uRBP & FENa ($p < 0.001$, 0.002 and 0.003 respectively) and a non-significant change of Cr ($p = 0.23$). Both before and after cardiac catheterization; c.CrCl correlated more significantly with β_2MG ($r = -0.65$ & -0.79, $p = 0.001$ & 0.005 respectively) rather than with Cr ($r = -0.41$ & -0.52, $p = 0.02$ & 0.01; respectively). Out of the studied 45 patients, only 3 patients matched the definition of CM nephropathy despite the significant changes in different renal parameters.

Conclusions: Children with CHD develop significant defects in glomerular and tubular parameters after CM use despite the fact that their Cr may not increase. Revision of the currently used definition of CM nephropathy may be required.

INTRODUCTION

Cardiovascular disease, dysfunction, and failure can disturb renal function, occasionally to the point of evoking acute or chronic renal failure (CRF), which, in turn, causes further deterioration of the cardiovascular condition[1]. The incidence of nephropathy among patients with congenital cyanotic heart diseases (CCHD) is about 30%[2]. Increasing numbers of patients are exposed to contrast medium (CM) during cardiac catheterization procedures. Radiocontrast use in all branches of medicine is reported to be the third most common cause of new onset renal failure in hospital patients[3]. CM nephropathy is defined as an

impairment in renal function (increase of serum creatinine by more than 25% that occurs within 3 days following IV administration of CM in the absence of another alternative etiology)[4]. High osmolar contrast media (HOCM) are more nephrotoxic than low osmolar contrast media (LOCM) particularly in patients with pre-existing renal impairment[4]. Serum creatinine (Cr) is a crude marker of GFR[5]. Serum Beta2 microglobulin (β_2MG) is a good endogenous marker of GFR, better than Cr with declining renal function. Serum β_2MG increases more than and before serum Cr[6]. Retionol-binding protein (RBP) is a low molecular mass protein easily filtered in renal glomeruli and very efficiently reabsorbed by proximal tubules. In tubular dysfunction, high concentrations of RBP are found in urine[7].

AIM OF THE WORK

To assess renal dysfunction induced by use of CM in infants and children with congenital heart diseases undergoing cardiac catherization.

SUBJECTS AND METHODS

This study included 45 infants and children with different congenital heart diseases (CHD) (23 males and 22 females) with their ages ranging from 6 months up to 10 years (median = 3.1, IQR = 0.8-7.7 years). They were recruited consecutively from patients admitted for cardiac catheterization in the Pediatric Cardiology Unit (PCU), Mansoura University Children's Hospital (MUCH). The study included nineteen patients with CCHD (13 males and 6 females) with their ages ranging from 6 months up to 8 years, (median = 2.8, IQR = 1-6.5 years) and twenty-six patients with congenital acyanotic heart diseases (CAHD) (10 males and 16 females) with their ages ranging from 6 months up to 10 years (median = 2.33, IQR = 0.75-8 years). CHD was correctly diagnosed in all patients by thorough history & physical examination, assessment of arterial blood gases oxygen saturation, plain X-ray chest, 12 leads ECG, echocardiography, and cardiac catheterization. Before the study, patients having elevated serum Cr levels, history of intake of nephrotoxic drugs or volume loss within 2 weeks from sampling were excluded. Moreover; patients with radiological evidence of obstructive uropathy were similarly excluded. All patients were subjected to cardiac catheterization; 36 patients underwent diagnostic cardiac catheterization and 9 patients underwent interventional cardiac catheterization in the form of balloon pulmonary valvuloplasty, using the low osmolar nonionic contrast medium iopromide [Ultravist 150 (Shering, Germany), 0.31 gm/ml] in a total dose not exceeding 6 ml/kg (average dose of 3.94 $\pm$ 1.03 and 2.05 $\pm$ 0.33 ml/kg; respectively)[8]. All patients were generally anaesthetized using halothane. Before catheterization, patients were overnight fasted. Adequate hydration was ensured by giving maintenance IV fluids (< 20 kg; Dextrose 5% 1/3 Isotonic Saline, > 20 kg; Dextrose 5% ½ Isotonic Saline) in a rate of 4 ml/kg/hours for the first 10 kg of body weight; plus 2 ml/kg/hour for the second 10 kg and 6 ml/kg/hour plus 1 ml/kg/hour for patients weighing more than 20 kg. Medications as diuretics, captopril and propranolol were

stopped 6 hours before catheterization but diagoxin was stopped 24 hours before the procedure.

Sera were obtained from all patients (No. = 45) 24 hours before and again 72 hours after cardiac catheterization. Serum was frozen and stored at -20°C until the time of assay. Stored serum was used to assay serum Cr[9] and serum β_2MG by enzyme immuno assay (ORGENTEC Diagnostika GmbH, Germany). This kit contains microplates coated with highly purified anti-human β_2MG antibodies. A reaction between these antibodies and β_2MG in patient samples occurs in 3 phases; pipetting of samples into wells, pipetting of anti β_2MG horse radish peroxidate conjugate solution, and pipetting of a chromogen substrate solution containing TMB. The amount of color is directly proportional to the amount of β_2MG present in the sample. The optical density is read with a microplate reader with a 450 nm filter. The β_2MG concentration of patient specimen is determined from the standard curve using a lin-log coordinates curve[10].

Twenty four hour urine was accurately collected 24 hour before and again 72 hours after cardiac catheterization. Corrected creatinine clearance (c.CrCl) was measured in the studied patients using the following equation:

$$\text{c.CrCl. } (ml/min/1.73m^2) = \frac{(U \times V/P) \times 1.73/BSA}{1440}$$

Where: U (mg/dL) = urinary Cr concentration, V (ml/min) = total urine volume (ml) divided by the duration of urine collection (min) = 1440 minute, P (mg/dL) = serum Cr, and BSA (m^2) = body surface area[11].

Urinary RBP (uRBP) was assayed by Enzyme linked Immunosorbant assay (ELISA) technique using Immudiagnostic KAG Kit; Germany. Urine was adjusted to pH of 6-8 with 1 N Na OH and stored at -20°C till the time of assay. The assay procedure depends on the binding of RBP in the sample with polyclonal rabbit antibodies against RBP. The quantification of bound RBP is carried out by adding an enzyme labelled antibody, which also binds RBP. The amount of converted substrate is directly proportional to the amount of bound RBP and is determined at a 450 nm using ELISA reader[12]. Urine to serum osmolality ratio (u/s OSM) was calculated by an osmometer (osmomat 030, Germany). Sodium assay in serum and urine was done by an electrolyte auto analyzer (AVL 984-S, AVL List GmbH Medizintechnik, Austria). Fractional excretion of Na (FENa) was calculated from the following equation:

$$FEN = \frac{UNa / PNa}{UCr / PCr} \times 100\%$$

UNa = Urinary sodium (mEq/L), UCr = urinary creatinine (mg/dL), PNa = serum sodium (mEq/L) and PCr = serum creatinine (mg/dL)[13].

Thirty one healthy controls of matched age and sex were used for the comparison process.

Statistical Methods:

The data of the study were analysed by the SPSS (Statistical Package for the Social Sciences) under Windows (version 10). Data were found to have non parametric distribution by Kolmogorov Smirnov test. Data were expressed as median and inter-quartile range (IQR). Tests used included Mann-Whitney U test, Wilcoxon-signed

ranks test, and spearman correlation test. A p value < 0.05 was considered significant.

RESULTS

- Before cardiac catheterization, there was no significant difference in the studied parameters between CCHD and CAHD patients when compared either to each other or to the healthy controls. Only u/s OSM ratio was significantly reduced in CCHD patients when compared to CAHD (p = 0.02) or controls (p = 0.01), Tables (1 & 2).
- After cardiac catheterization, patients with CHD showed significant reduction of their c.CrCl., u/s OSM (p < 0.001 & 0.002 respectively) and a significant increase of B_2MG, uRBP & FENa (p < 0.001, 0.002 and 0.003 respectively) and a non significant change of serum Cr (p = 0.23); Table (3). Both before and after cardiac catheterization; c.CrCl. correlated more significantly with β_2MG (r = -0.65 & -0.79, p = 0.001 & 0.005; respectively) rather with serum Cr (r = -0.41 & 0.52, p = 0.02 & 0.01; respectively), Table (4).
- Out of the studied 45 patients, only 3 patients had their post catheterization serum Cr elevated by more than 25% of the basal levels representing an incidence of only 6.6% of CM nephropathy.

Table 1: Comparison of the studied parameters in patients versus controls before cardiac catheterization*

Parameter	CCHD (No. = 19)	CAHD (No. = 26)	Controls (No. = 25)	P1	P2	P3
Cr (mg/dl)	0.5 (0.45-0.56)	0.55 (0.47-0.58)	0.5 (0.47-0.58)	0.060	0.35	0.293
c.CrCl. (ml/min/1.73m^2)	119.80 (107.12-152.75)	123.35 (107.52-130.22)	120.80 (98.8-136.42)	0.161	0.639	0.533
β_2MG (µg/ml)	1.7 (1.5-1.9)	1.4 (1.1-1.6)	1.30 (0.9-1.5)	0.070	0.556	0.090

* Mann-Whitney Test, values expressed as median and IQR
P1 = CCHD verus controls
P2 = CAHD verus controls
P3 = CCHD verus CAHD

Table 2: Comparison of the studied parameters in patients versus controls before cardiac catheterization*

Parameter	CCHD (No. = 19)	CAHD (No. = 26)	Controls (No. = 25)	P1	P2	P3
uRBP (mg/l)	0.31 (0.23-0.34)	0.29 (0.25-0.31)	0.29 (0.25-0.33)	0.429	0.347	0.305
FENa (%)	0.93 (0.90-1.09)	1.08 (0.92-1.21)	1 (0.86-1.12)	0.838	0.305	0.142
u/sOSM	1.2 (1.1-1.6)	1.6 (1.50-2.4)	1.8 (1.4-2.43)	0.01	0.15	0.02

* Mann-Whitney Test, values expressed as median and IQR
P1 = CCHD verus controls
P2 = CAHD verus controls
P3 = CCHD verus CAHD

Table 3: Comparison of the studied parameters in patients before and after cardiac catheterization (No. = 45)*

Parameter	+ve Ranks (Before < After)	-ve Ranks (Before > After)	Ties (Before = After)	p
Cr	21	24	0	0.23
c.CrCl.	5	40	0	< 0.001
B_2MG	37	3	5	< 0.001
uRBP	34	10	1	0.002
FENa	36	8	1	0.003
u/s OSM	12	32	1	0.002

* Wilcoxon-Signed ranks test

Table 4: Correlation between c.CrCl. and Serum Cr & B_2MG in patients before and after cardiac catheterization*

	c.CrCl.			
	Before (No. = 45)		After (No. = 45)	
	r	p	r	p
Cr	- 0.41	0.02	- 0.52	0.01
B_2MG	- 0.65	0.001	- 0.79	0.005

* Spearman correlation

DISCUSSION

In the current study, there was no significant difference in the studied parameters between CCHD, CAHD and controls before cardiac catheterization. Only u/s OSM was significantly reduced in CCHD in comparison to CAHD and controls indicating defective distal tubular function. Renal abnormalities have been previously described in patients with CCHD. These abnormalities varied from isolated pathological proteinuria[14], reduced creatinine clearance & elevated serum β_2MG[15], and elevated urinary NAG[16]. This nephropathy has been attributed to be caused by the effect of hypoxaemia and subsequent polycythaemia in these patients[1]. The appearance of these renal abnormalities depends on the duration of cyanotic heart disease as it was found that proteinuria appears relatively early in the course of the disease, while reduced GFR and elevated β_2MG need a relatively longer time to appear[14]. Our results are in harmony with previously mentioned studies, but interestingly, distal tubular dysfunction has not been previously reported-up to our knowledge-in cyanotic heart children.

After cardiac catheterization and CM administration children whether cyanotic or acyanotic showed evidence of nephropathy. Glomerular dysfunction was evidenced by significant reduction of c.CrCl. and significant increase in β_2MG. Interestingly, serum Cr did not show any significant change. Similar results have been reported in adult patients receiving ionic CM diatrizoate melgumine[17]. The current study also revealed a more significant correlation between GFR and β_2MG rather than that with Cr both before and after cardiac catheterization.

Iodinated CM, whether of high, low or iso-osmolality, can induce acute functional changes in the kidney characterized by an increase in the renal vascular resistance (RVR) together with a decrease in the GFR and sodium reabsorption[18]. These acute changes resolve within few hours, followed 24 hours later by a decline in renal function, which can last for several days. The actual mechanisms which link the two phases remain unclear, but interference with the initial responses is protective against the delayed renal dysfunction[19].

It has been suggested that the

development of CM nephropathy is affected by changes in renal hemodynamics because of the effects of the CM on the action of many substances, including increased activity of renal vasoconstrictors (vasopressin, angiotensin II, dopamine-1, endothelin and adenosine) and decreased activity of renal vasodilators (nitric oxide and prostaglandin)[20,21]. Other factors that may decrease renal blood flow include increased viscosity of CM[22] and increased erythrocyte aggregation induced by contrast media, which result in diminished oxygen delivery[23]. Moreover, contrast media have been found to reduce antioxidant enzyme activity in the rat kidney, and direct cytotoxic effects mediated by oxygen free radicals have been found in canine and rat models of contrast-medium nephropathy[24,25].

It is well known that GFR provides the overall estimate of renal function. The urinary clearance of exogenous substance is accepted as the gold standard for estimation of GFR. However, because of the cost and inconvenience, serum Cr and creatinine clearance are the most widely used measures of renal function. The measurement of c.CrCl. involves a timed collection of urine, measurement of its volume and determination of creatinine concentration in the urine and sera[26].

The reported ratio of c.CrCl. to GFR increases with decreasing GFR to 1.7 at a GFR of 20 ml/min[27], when GFR is moderately impaired or normal, however, and urine collection errors were reduced c.CrCl. was nearly equal to GFR, with a ratio of c.CrCl. to GFR of 1.15[27]. In our, study, all patients were hospitalized, and urine collections were carefully monitored and done by trained personnel. Thus we can assure that the measured c.CrCl. in our cases reflects the actual GFR of these patients to a large degree.

Serum Cr is of limited value in early detection of renal insufficiency because it is well established that its concentration does not change significantly until c.CrCl. is < 70 ml/min/1.73m^2 or inulin clearance is < 50 ml/min/1.73m^2. Several low molecular weight proteins have been studied as candidate markers of GFR such as serum β_2MG[28]. With declining renal function serum β_2MG increases more & before serum Cr[29].

In all the studied patients, prerenal causes of renal impairment were excluded; all of the patients were normotensive, none of them had volume losses two weeks before sampling. None of the patients had clinical manifestations suggestive of sepsis. Obstruction of the urinary tract and renal malformations were excluded in all the studied patients by performing renal ultrasonography. No patient received nephrotoxic medications for at least 3 months before the study. No anesthetic complications occurred during cardiac catheterization as asphyxia or hypotension. The dose of ionizing radiation, to which the patients were exposed, were at the diagnostic level which is harmless with no effect on renal functions[30]. As we excluded other possible causes of renal impairment; we can assure that the renal dysfunction in our cases is mostly due to the nephrotoxic effect of the CM used.

In the present study, renal tubular dysfunction was manifest in patients after CM administration. Tubular dysfunction

was evidenced by a significant increase of both FENa, uRBP, and decreased u/s OSM ratio. Pathological changes induced by CM (e.g. epithelial cell vacuolization, interstitial inflammation and cellular necrosis) suggest a direct toxic effect of contrast media on renal tubular epithelial cells[25] that is independent of hypoxia and may be related to hyperosmolality of the contrast agent[31]. Apoptosis is also involved as a result of cellular injury[25]. uRBP has been reported to be the most appropriate test for early detection of proximal tubular dysfunction[32]. RBP is a low molecular weight protein synthesized by the liver. It occurs in serum complexed with pre-albumin and retinol. Once retinol has been delivered to the target cells, RBP rapidly dissociates from pre-albumin and is then freely filtered at the glomerulus, reabsorbed by proximal convoluted tubulars (PCT), catabolized and the constituents amino acids returned to circulation[33]. The major part of uRBP is free (not bound to pre-albumin) even in patients with massive glomerular proteinuria[34]. Recovery of uRBP from highly proteinuric urine is unimpaired[35]. Although uRBP have been found to be a useful marker for detection of PCT dysfunction in a variety of diseases[34], the current study is the first report, up to our knowledge, of its efficacy in detecting PCT in children after CM administration.

The urine concentrating ability is a very sensitive index of tubular function. In acute tubular necrosis, the ability to concentrate the urine may be lost 24-48 hours before serum creatinine or BUN starts to increase[35]. The renal medulla is uniquely susceptible to ischemic injury, and contrast media may cause medullar hypoxia by shunting blood flow to the renal cortex[36,37]. In the current study decreased u/s OSM suggests impaired concentrating capacity due to CM use. This effect may be due to either directcytotoxic effect of used CM on renal tubular cells or due to medullary injury secondary to ischaemia or both.

CM nephropathy is defined as impairment of renal function occurring usually within 48 hours after administration of CM[38]. It is manifested by a relative increase of at least 25% over the baseline value[39,40] in the absence of another cause. Because creatinine levels typically peak 3 days after administration of contrast media[41], this definition may overlook a large group of patients in whom nephropathy develops up to a week after administration of contrast media. Interestingly in the current study, only 3 (6.6%) patients matched the criteria of CMN. This finding despite the significant glomerular and tubular defects found-may indicate a need to revise the currently used definition of CM nephropathy and to evaluate the possibility of including other renal parameters in this definition.

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