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Renal function after percutaneous coronary interventions depending on the type of hydration

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ABSTRACT

Purpose: The aim of our study was to evaluate renal function assessed by serum creatinine as well as novel biomarkers in 142 patients with stable coronary heart disease and normal serum creatinine undergoing percutaneous coronary interventions (PCI) depending on the type of hydration: physiological saline vs. sodium bicarbonate (1:1 randomization).

Materials and Methods: Serum and urinary NGAL were evaluated before and after 8-12, and 24 hours after PCI. Serum cystatin C, serum creatinine, estimated glomerular filtration rate using different formulae were assessed before PCI, and 24 hours after the procedure.

Results: Only 2 patients (2.8%) from the saline-hydrated group fulfilled the criteria for CI-AKI. In patients hydrated with sodium bicarbonate serum creatinine declined significantly ($p<0.01$). In patients hydrated with sodium bicarbonate a significant fall in serum NGAL after 8-12 hours was found. In sodium bicarbonate group cystatin C decreased non significantly after 8-12 hours, then returned to the baseline values.

In patients hydrated with physiological saline serum NGAL before PCI and after 24 hours correlated positively with cystatin C and eGFR by CKD-EPI. In patients hydrated with sodium bicarbonate baseline serum NGAL correlated with NGAL baseline cystatin C and eGFR by CKD-EPI, similarly serum NGAL after 24 hours correlated with cystatin C.

Conclusion: We suggest to rather use sodium bicarbonate in a hydration protocol in patients undergoing PCI. However, the value of NGAL in this setting remains to be elucidated and volume expansion remain the unquestionable prevention methods of CI-AKI.

Key words: Cystatin C, NGAL, kidney function, PCI, hydration

INTRODUCTION

Approximately 5 billion doses of contrast agents are annually used in the US. The administration of contrast media can lead to a usually reversible form of acute kidney injury (AKI) called contrast-induced nephropathy that begins soon after the contrast is administered [1-7]. Most commonly, contrast-induced nephropathy (nowadays contrast-induced acute kidney injury CI-AKI) is defined as an acute impairment of renal function manifested by an absolute increase in serum creatinine of at least 0.5 mg/dL or by relative increase by at least 25% from the baseline levels [2,8,9]. Peak creatinine typically occurs 3 to 5 days after contrast administration and returns to baseline (or a new baseline) in 1 to 3 weeks [2]. Renal failure is nonoliguric for the vast majority of patients. In almost all cases, the decline in renal function

is mild and transient. AKI may also occur after primary angioplasty. The most common causes are hemodynamic instability, radiocontrast toxicity, and atheroembolism. This variability results from differences in the presence or absence of risk factors (primarily chronic kidney disease - CKD), definition of CI-AKI, amount and type of agent administered, prospective or retrospective design, the exact radiologic procedure, and whether other causes of AKI unrelated to contrast media were excluded (e.g. atheroemboli during arteriography) [10]. In comparison to percutaneous coronary interventions (PCI), the risk of contrast-induced nephropathy is low following intravenous contrast administration, even in patients with CKD [11]. Since interventional cardiologists are being asked more frequently to perform PCI on an increasing numbers of patients with significant co-morbidities such as CKD and/or diabetes, contrast nephropathy is a potentially serious complication of PCI [2]. The most important issue is prophylaxis, however, there are still many unresolved questions concerning the type, volume, duration of hydration, type of contrast agents etc. Merten et al. [12] demonstrated in their study that hydration with sodium bicarbonate was better than with physiological saline. Up to now, intravenous volume load is the only reasonably proven and widely accepted prophylaxis for CI-AKI after contrast media application [13-15]. Many new biomarkers of CIN were studied, and some of them seemed promising as NGAL [16,17]. The "window of opportunity" is narrow in contrast-induced nephropathy and time is limited to introduce proper treatment after initiating insult, particularly when patients are discharged within 24 – 48 hours after the procedure. Therefore, there is an extensive search for potential early markers for AKI and nephrotoxicity as well as assessment of kidney function [18], especially in the upcoming setting of short-time hospitalizations for coronary angiographies and interventions. As we presented previously, in high-risk population, awareness of potential complications resulted in better standard care and even lower creatinine after PCI [19]. We also reported that prevalence of CKD is relatively high in patients with normal serum creatinine [20], particularly in the elderly [21].

Taking all these data into consideration the aim of the study was to evaluate renal function assessed by serum creatinine as well as novel biomarkers in patients with stable coronary heart disease and normal serum creatinine (i.e. low-risk) undergoing PCI depending on the type of hydration: physiological saline versus sodium bicarbonate.

PATIENTS AND METHODS

The study included 142 patients, i.e. 71 patients hydrated with physiological saline compared to 71 patients hydrated with sodium bicarbonate with normal serum creatinine undergoing PCI to stable angina (II/III class according to CCS). Patients were randomly assigned to each group. The whole group included 91 males (63.2%), the mean age was 64.23±9.82 years.

We excluded patients with preexisting CKD (more than 1.5 mg/dL in males and less than 1.2 mg/dL in females). None of the patients investigated had received nephrotoxic drugs at least 1 week before and during the study period. In all the patients, 24 hours before PCI all the nephrotoxic drugs (NSAIDs, diuretics, biguanidine derivatives in diabetic patients) were withdrawn and ACE inhibitors were either withdrawn (when blood pressure permitted) or halved 24 hours before the procedure. All the patients were informed about the aim of the study and gave their consent. The protocol of the study was approved by the local Ethics Committee of the Medical University of Bialystok (Poland). All the patients admitted to the Department of Invasive Cardiology were given 2 liters of hydration within 24 hours periprocedurally. It was a randomization, 1:1 neither patients nor physicians know the hydration regimen.

The hydration protocol included two groups and was as follows: hydration with either physiological saline (154 mEq/L NaCl which is equivalent to 0.9% isotonic saline) or sodium bicarbonate (154 mEq/L $NaHCO_3$ in 5% dextrose) 1 hour before PCI as an infusion of 3mL/kg/h and 6 hours after PCI as an infusion of 1mL/kg/h. CI-AKI was defined as a rise in serum creatinine by >0.5mg/dL or as a relative increase by ≥25% or fall in eGFR by >25%.

Iso-osmolal contrast agent (iodixanol) was used in all the studied patients. Serum and urinary NGAL, serum cystatin C were evaluated at admission, i.e. before, and after 8-12, and 24 hours after PCI, while serum creatinine was assessed at admission and 24 hours after the procedure. Hemoglobin, hematocrit, cholesterol, creatinine, were studied at admission. We assessed kidney function according to the simplified MDRD equation [22], CKD-EPI equation [23], Cockcroft-Gault formula [24] and Cockcroft-Gault formula adjusted to lean body mass (lean body mass=[0.9x(height [cm]-152)]+(50 for males or 45.5 for females).

NGAL was evaluated using commercially available ELISA kit from Bioporto (Gentofte, Denmark). All tests were performed according to manufacturer's instructions by the same person. Serum cystatin C was measured using commercially available kits from BioVendor, Modrice, Czech Republic.

Data given were analyzed using Statistica 8.0 PL. ANOVA or Kruskall-Wallis ANOVA for repeated measurements were used in statistical analysis with $p<0.05$ considered statistically significant, when appropriate.

RESULTS

Baseline clinical and biochemical characteristics is given in *Tab. 1*. In a group hydrated with physiological saline, mean serum creatinine after 24 hours was 0.99 mg/dL and

it was 0.01±0.18mg/dL higher than the baseline values. A rise in serum creatinine after 24 hours was found in 53.6% and a decrease in 44.6%. In patients hydrated with sodium bicarbonate, serum creatinine declined from 1.01mg/dL to 0.96 mg/dL (p<0.01). A rise in serum creatinine after 24 hours was found in 31.8% and a decrease in 62.1%. Changes in eGFR in both groups are presented in *Tab. 2*. Changes in serum and urinary NGAL as well as in serum cystatin C are given in *Tab. 3*.

In patients hydrated with physiological saline, serum NGAL before PCI correlated positively with cystatin C (r=0.36, p<0.01) and eGFR by CKD-EPI (r=-0.79, p<0.001), similarly serum NGAL after 24 hours correlated with cystatin C (r=0.35, p<0.01) and eGFR by CKD-EPI (r=-0.55, p<0.001). In patients hydrated with sodium bicarbonate, baseline serum NGAL correlated with NGAL baseline cystatin C (r=0.45, p<0.001) and eGFR by CKD-EPI (r=-0.39, p<0.001), similarly serum NGAL after 24 hours correlated with cystatin C (r=0.48, p<0.001).

Only 2 patients (2.8%) from the saline-hydrated group fulfilled the criteria for CI-AKI, no patients from the sodium bicarbonate hydrated group suffered from CI-AKI, the

Table 1. **Baseline clinical and biochemical characteristics in the 2 studied groups.**

		total (n=142)	Group with NaCl (n=71)	Group with NaHCO3 (n=71)
Age (years)		64.23±9.82	63.27±9.71	65.18±9.91
Prevalence of hypertension (n, %)			67 (94.4%)	59 (83.1%)*
Prevalence of glucose intolerance (n, %)			23 (32.4%)	19 (26.8%)
BMI (kg/m^2)			28.99±4.51	28.8±4.39
Cholesterol (mg/Dl)			169.79±39.44	157.45±37.5
Creatinine (mg/dL)		0.99±0.20	0.97±0.19	1.01±0.22
NGAL serum (ng/dl)		59.8 (49.2; 76.4)	58.8 (48.0; 73.6)	60.4 (50.8; 78.2)
NGAL urine (ng/dl)		9.8 (5.6; 18.6)	9.5 (5.5; 16.7)	9.95 (6.1; 21.5)
cystatin C serum (mg/L)		0.98 (0.80; 1.21)	0.93 (0.74; 1.14)	1.02 (0.86; 1.35)**
eGFR	MDRD (ml/min/1.73m^2)	75.75±16.67	76.78±16.53	75.75±16.79
	Cockcroft-Gault (ml/min)	84.33±28.39	87.51±27.86	85.12±28.38
	CKD-EPI (ml/min/1.73m^2)	75.26±17.89	76.87±18.05	75.26±18.03
	Cockcroft-Gault (LBM) (ml/min)	65.45±20.20	66.66±20.1	66.09±20.20
PCI time (min)		55.56±26.60	55.35±28.23	55.77±25.07
Contrast volume (ml)		156.30±82.54	152.39±73.01	160.21±91.45

**p<0.05, p<0.01 group I vs. II;*
Data given are means ± SD, or medians and interquartile ranges.

Table 2. **eGFR (MDRD, CKD-EPI)/creatinine clearance (Cockcroft-Gault) in patients undergoing PCI depending on the type of hydration.**

eGFR	0 baseline	after 24 h	delta GFR (0-24)
NaCl group			
MDRD ml/min/1.73m^2	75.53±16.18	75.54±15.74	-0.0018±10.81
Cockcroft-Gault ml/min	83.72±25.93	83.67±25.18	0.0530±10.40
CKD-EPI ml/min/1.73m^2	75.43±17.48	75.26±16.52	0.1781±10.67
Cockcroft-Gault (LBM) ml/min	65.32±19.70	64.99±17.84	0.3317±8.06
NaHCO$_3$ group			
MDRD ml/min/1.73m^2	75.77±16.23	80.55±21.87*	-4.7868±18.75
Cockcroft-Gault ml/min	84.76±27.93	88.46±27.57*	-3.6984±13.10
CKD-EPI ml/min/1.73m^2	75.17±17.38	78.48±17.08*	-3.3022±10.98
Cockcroft-Gault (LBM) ml/min	66.01±19.74	69.37±22.14	-3.3572±14.32

**p<0.05 before vs. after 24 hours;*
Data given are means ± SD, or medians and interquartile ranges.

Table 3. **NGAL and cystatin C depending on the type of hydration.**

	baseline 0	after 8-12 h	after 24 h
NaCl group			
NGAL serum(ng/dl)	58.8 (48.0; 73.6)	58.8 (45.2; 67.6)	59.2 (51.4; 74.8)
NGAL urine (ng/dl)	9.5 (5.5; 16.7)	9.6 (4.5; 19.8)	10.8 (6.7; 24.5)*
cystatin C serum (mg/L)	0.93 (0.74; 1.14)	0.92 (0.72; 1.19)	0.99 (0.80; 1.25)
$NaHCO_3$ group			
NGAL serum(ng/dl)	60.4 (50.8; 78.2)	58.6 (48.4; 69.8)*	59.0 (50.6; 71.8)
NGAL urine (ng/dl)	9.95 (6.1; 21.5)	8.65 (5.4; 18.1)	10.55 (5.55; 22.7)
cystatin C serum (mg/L)	1.02 (0.86; 1.35)	0.97 (0.75; 1.24)	1.02 (0.88; 1.29)

**p<0.05 vs. baseline*

difference on the prevalence of CI-AKI between groups was statistically significant ($p<0.05$).

DISCUSSION

In our study, we found a low, but significantly higher prevalence of CI-AKI in patients hydrated with physiological saline over patients hydrated with sodium bicarbonate with normal serum creatinine. At least 5% of patients who undergo cardiac catheterization experience a transient rise in the plasma creatinine concentration of more than 1.0 mg/dL (88 µmol/L) due to contrast-induced renal dysfunction [6]. The risk is negligible with normal renal function, even if the patient is diabetic, whereas it exceeds 50% particularly in patients with diabetic nephropathy [6]. Therefore, we chose a low-risk population and searched for a new biomarker of kidney dysfunction following contrast administration, bearing in mind that CI-AKI was the third leading cause of hospital-acquired AKI and optimal therapy to prevent this complication remained uncertain [3].

In our study on low risk patients, the real prevalence of CI-AKI was low. It could be due to the fact that our patients were really at low risk, with normal serum creatinine at baseline, low comorbidities, with stable angina, undergoing elective coronary angiography. As shown previously, comorbidities such as diabetes, CKD, risk factor control and adherence to treatment are important risk factors for cardiovascular complications [25-28]. El-Hajjar et al. [28] and Aquiar-Souto et al. [29] found similarly low prevalence of CI-AKI in their low risk patients.

So far, there are only a few studies comparing various types of hydration. In vast majority of randomized controlled trials physiological saline infusion was used for volume expansion, whereas in other trials half-isotonic saline (0.45%) or sodium bicarbonate at higher volumes were administered. It seems that the benefit in these studies was rather due to volume expansion than to pharmacologic effect of a specific type of infusion. Both trials with sodium bicarbonate were terminated prematurely [12,30] and it was a matter of criticism. Moreover, there is still controversy concerning the type, amount, route and duration of volume administration. Comparisons between trials are very difficult or even impossible due to wide variations in hydration protocols among relevant randomized trials [31]. In addition, most studies also lacked statistical power, used different contrast agents, different definitions of contrast nephropathy or allowed for additional prophylactic measures, such as N-acetylcysteine or sodium bicarbonate in a varying percentage of their patients [32-40].

Maioli et al. [41] assessed the prevalence of contrast nephropathy in 502 patients with GFR below 60 ml/min. All of the patients were given N-acetylcysteine and iodixanol as contrast agents. They were hydrated with either physiological saline or sodium bicarbonate. They found similar prevalence of contrast nephropathy, however, this „negative" trial may have significant clinical implications to enhance frequency of hydration with sodium bicarbonate. It is more acceptable and more cost-effective to administer patients with 7-hours infusion of sodium bicarbonate than 24-hours infusion with physiological saline. On the other hand, Tomura et al. [42] reported that extra 20mEq sodium bicarbonate bolus 5 minutes before contrast agent administration decreased the incidence of contrast nephropathy were hydrated for 12 hours before and after the procedure. In the recent study by Klima et al. [43], patients were randomized to receive intravenous volume supplementation with either (A) sodium chloride 0.9% 1 mL/kg/h for at least 12h prior and after the procedure, (B) sodium bicarbonate (166 mEq/L) 3 mL/kg for 1h before and 1 mL/kg/h for 6h after the procedure or (C) sodium bicarbonate (166 mEq/L) 3 mL/kg over 20min before the procedure plus sodium bicarbonate orally (500 mg per 10 kg). They found that the incidence of contrast-induced nephropathy was significantly lower in Group A (1%) vs. Group B (9%, P=0.02) and similar between Groups B and C (10%, P=0.9). They concluded that 24-hours hydration with physiological

saline is superior to sodium bicarbonate, however, a short-term regimen with sodium bicarbonate is non-inferior to a 7 h regimen. In real life scenario, economy plays a crucial role, and in elective PCI, hydration could be given just before and after the procedure, but not 24 hours before. Therefore from clinical perspective we look for the optimal prophylaxis for CI-AKI taking into consideration logistic, economy and current standard care.

Due to all these inconsistencies, we designed the study to compare kidney function using novel biomarkers and two types of hydration. According to our knowledge, there is one study assessing the effect of early intervention by volume expansion in patients with increasing urinary NGAL levels 4-6 hours following contrast agent application [44]. In our study, we found a fall in serum NGAL in patients hydrated with sodium bicarbonate, whereas changes in urinary NGAL in both groups were not statistically significant. Serum cystatin C did not change significantly in patients hydrated with 0.9% NaCl whereas in patients hydrated with sodium bicarbonate it decreased significantly. Prevalence of CI-AKI was significantly higher, although still low, in patients administered physiological saline. We did not neglect cystatin C, however, as shown previously by Herget-Rosenthal et al. [45], cystatin C rises as early as after 1 day, whereas we looked for much earlier markers, since the vast majority of patients are discharged from the hospital within 24 hours after PCI.

On the basis of our findings, we suggest to rather use sodium bicarbonate in a hydration protocol in patients undergoing PCI. Metabolic acidosis is one of the most commonly encountered complications of CKD [46]. Clinical practice guidelines in nephrology recommend initiation of alkali therapy when the serum bicarbonate level is <22 mEq/l to prevent or treat complications of metabolic acidosis [47]. Alkali therapy is associated with an improvement in kidney function, which may afford a long-term benefit in delaying the progression of CKD [48]. Therefore, we would take into consideration that in patients with CKD, bicarbonate might offer additional benefit, to overcome or attenuate acid-balance disturbances.

CONCLUSIONS

The value of NGAL in low risk patients undergoing PCI, depending on different hydration regimens, needs to be explained while the volume expansion remains the unquestionable prevention method of CI-AKI. The question of hydration type is still unanswered, however, we suggest to rather use sodium bicarbonate in a hydration protocol in patients undergoing PCI.

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