Original Paper

Antithrombin III is a Novel Predictor for Contrast Induced Nephropathy After Coronary Angiography

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Key Words

Antithrombin III • Contrast induced nephropathy • Predictor • Coronary angiography

Abstract

Background/Aims: Antithrombin III (ATIII) is an important endogenous anticoagulant and has strong anti-inflammatory properties. Low ATIII activity is considered to be a predictor of poor outcomes in several conditions, including acute kidney injury after cardiac surgery. However, the association between the ATIII level and the occurrence of contrast induced nephropathy (CIN) has not been elucidated. In this study, our aim was to identify the potential predictive value of ATIII for CIN. **Methods:** We enrolled a total of 460 patients who underwent coronary angiography (CAG) from January 2015 to December 2016 in coronary care units (CCU). ATIII activity in plasma collected before CAG was measured and <75% was considered low activity according to reference values. A cross-sectional study on CIN after CAG was conducted and the risk factors were analyzed. CIN was diagnosed according to the KDIGO guideline. **Results:** Of these 460 patients undergoing CAG, 125 (27.17%) progressed to CIN. The incidence of CIN was significantly higher in patients with low ATIII activity compared to patients with normal ATIII activity (Pearson's chi-squared test $P=0.002$). As ATIII activity declined, the prevalence of CIN progressively increased, with the highest value (58.8%) in patients with an ATIII activity <60%. Moreover, the ATIII activity was significantly lower in CIN patients than in non-CIN patients ($84.43 \pm 16.3\%$ vs. $92.14 \pm 13.94\%$, $P<0.001$). After multivariable analysis, ATIII activity <75% remained a significant independent predictor of CIN (OR 2.207, 95%CI [1.29–3.777];

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P=0.004) as well as baseline serum creatinine (OR 1.009, 95%CI [1.001-1.016]; P=0.026).

Conclusions: Patients with low ATIII activity had a higher risk of developing CIN after CAG. The initial ATIII activity may be a novel independent predictor for CIN.

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Published by S. Karger AG, Basel

Introduction

Contrast-induced nephropathy (CIN) is an iatrogenic kidney injury secondary to the administration of contrast media for angiography. Despite technological advances, CIN is still ranked third in hospital acquired acute renal failure, while dehydration is ranked first followed by nephrotoxic drugs [1]. CIN incidence varies widely depending on patient conditions, concomitant risks factors, and even different diagnostic criteria. The incidence of CIN in one report was 0.6%-2.3% in the general population, while the incidence increases to 50% or more in patients with multiple risk factors [2, 3].

Pre-existent renal insufficiency may be the most important risk factor for CIN. Diabetes mellitus, low effective circulatory volume, older age, and heart failure are also classic risk factors [2, 4, 5]. While serum creatinine (SCr) has been widely used to evaluate CIN, there are many criticisms of this marker including its loose correlation to eGFR [6-8], its susceptibility to patient conditions (such as trauma, muscle mass, liver disease, age and immobilization) [6] as well as its failure to reflect early or slight changes in renal function [9, 10]. As a result, many clinical studies have been conducted in attempt to identify biomarkers of early CIN diagnosis. Recently, several novel renal biomarkers have been proposed to specifically predict early CIN, including neutrophil gelatinase-associated lipocalin (NGAL), cystatin C, liver fatty acid-binding protein, kidney injury marker 1 (KIM-1), interleukin 18 (IL-18) and N-Acetyl-β-(D)-Glucosaminidase (NAG) [11-16].

Antithrombin III (ATIII), encoded by the gene SerpinC1 and produced by the liver, is a serine protease inhibitor in the coagulation cascade. ATIII combines with thrombin factors VIIa, IXa, Xa, and XIa to exert influence on the anticoagulant process, which can be significantly accelerated by heparin-like substances [17]. In addition, ATIII has powerful anti-inflammatory properties, which are independent of its anticoagulant action [18, 19]. Administration of exogenous ATIII has been reported to exhibit protective effects against liver, lung, kidney and myocardial injury [20-23], while insufficiency of endogenous ATIII exacerbates renal ischemia/reperfusion injury in rats [24].

Despite the clinical value of exogenous ATIII administration for some critical illnesses such as severe sepsis or disseminated intravascular coagulation (DIC) [25-27], knowledge on the predictive value of ATIII activity is comparatively rare. Previously, it was reported that the initial ATIII level was highly predictive of patient mortality from septic shock and ATIII activity under 50% had the best sensitivity and specificity [28]. Additionally, low levels of postoperative ATIII are associated with poor outcomes in cardiac surgery and are predictive of prolonged ICU stay [29]. Our previous work confirmed that patients with low ATIII activity exhibit a higher risk for developing acute kidney injury (AKI) after cardiac surgery [24]. Recently, we demonstrated that exogenous ATIII administration *in vivo* attenuates CIN through inhibiting inflammation, oxidative stress, and apoptosis and through improving renal blood flow [30]. However, it is unknown whether low ATIII activity increases the susceptibility to CIN. The aim of this study is to investigate the association between initial ATIII level and the occurrence of CIN, and to evaluate the potential predictive value of ATIII.

Materials and Methods

We recruited a total of 460 patients who underwent coronary angiography (CAG) from January 2015 to December 2016 in coronary care units of Shanghai Jiao Tong University Affiliated Sixth People's Hospital, the First Affiliated Hospital of Harbin Medical University, Shanghai Eighth People's Hospital, and Shaoxing University Affiliated Hospital. ATIII activity in plasma collected before CAG was measured as reported previously [24]. According to the reference values, the normal ATIII activity ranged from 75 to 125%, whereas <75% was recognized as low activity.

CIN was diagnosed according to the KDIGO guideline, which was the latest criteria published in 2012. CIN was defined as any of the following: an increase in SCr by ≥ 0.3 mg/dl (≥ 26.5 μ mol/l) within 48 hours; or an increase in SCr to ≥ 1.5 times baseline, which is known or presumed to have occurred within the prior 7 days; or urine volume <0.5 ml/kg/h for 6 hours [31]. The exclusion criteria were as follows: occurrence of heart failure before or after CAG; renal toxic medicine intake; hepatic diseases; baseline eGFR <30 ml/min; malignant tumors. Patients were divided into two groups according to ATIII activity: a normal ATIII group and a low ATIII group. For analysis of risk factors of CIN, the different cases were classified into two groups once again according to the occurrence of CIN: a CIN group and a non-CIN group. The present study was approved by the Ethics Committees of the participating institutions.

Statistical analysis

SPSS (Ver 19.0, Chicago, IL) was employed to perform data analysis. Values are expressed as the mean $\pm$ SD or as the number of patients (percentage). Student's t-test was used to analyze the measurement data while the Chi-Square Goodness-of-Fit test was adopted for categorical comparison. Logistic regression analysis was applied to estimate odds ratio (OR) of associated risk factors for CIN. A P value <0.05 was considered significant. For the multiple comparisons of rates, the statistical significance level was adjusted according to the Bonferroni correction.

Results

Patients with low activity of ATIII were predisposed to developing CIN

The study population consisted of 460 patients receiving coronary angiography with a mean age of 65.09 ± 12.24 years, and 364 (79.1%) were men. The prevalence of CIN was 27.17% (125/460) based on the KDIGO guideline. Of the 71 cases with low ATIII activities, 30 (42.3%) patients developed acute kidney injury after CAG. In the group of patients with normal ATIII activities, there were 95 (24.4%) patients suffering from CIN. The incidence of CIN was significantly higher in patients with low ATIII activity (Pearson's chi-squared test $P=0.002$). However, no differences in gender, age, preoperative proteinuria, fibrinogen degradation product (FDP), D-dimer, fibrinogen, baseline serum creatinine, blood urea nitrogen and uric acid were observed between the normal ATIII group and the low ATIII group. (Table 1)

In order to further clarify the relationship between ATIII activity and the occurrence of CIN, we classified ATIII activity into four grades: <60%, 60–<75%, 75–<90%, $\geq 90\%$, and then made multiple comparisons on the CIN incidence of each grade. For the multiple comparisons of rates, the statistical significance level was adjusted according to the Bonferroni correction. Specifically, a P value <0.0083 was considered significant after adjusted:

$$[\alpha'] = \frac{\alpha}{k \times (k-1)/2} = \frac{0.05}{4 \times (4-1)/2} = 0.0083,$$

therein, “k” referred to the number of groups (a total of 4 groups in this study), “ α ” referred to the statistical significance level (commonly using a P value threshold of 0.05), and “ α' ” referred to the adjusted statistical significance level]. As shown in Fig. 1, the prevalence of CIN progressed as ATIII activity decreased. Only 19.2% patients with ATIII activity $\geq 90\%$ developed CIN. In contrast, the incidence of CIN was the highest (58.8%) in patients with

Table 1. Incidence of contrast induced nephropathy in patients with normal or low ATIII activity. Abbreviations: ATIII, antithrombin III; CIN, contrast induced nephropathy; FDP, fibrinogen degradation product; SCr, serum creatinine; BUN, blood urea nitrogen; UA, uric acid

Variables	Normal AT III (n = 389)	Low AT III (n = 71)	P
Gender (male/female)	308/83	58/13	0.564
Age (years)	64.27 ± 12.04	66.15 ± 12.48	0.23
Preoperative proteinuria, n (%)	47 (12.1%)	12 (16.9%)	0.264
CIN, n (%)	95 (24.4%)	30 (42.3%)	0.002
ATIII activity (%)	94.59 ± 10.7	65.13 ± 9.88	<0.001
FDP (mg/l)	3.43 ± 2.71	6.15 ± 19.47	0.244
D-dimer (mg/l)	0.59 ± 0.89	1.62 ± 5.43	0.117
Fibrinogen (g/l)	2.74 ± 0.57	2.74 ± 0.78	0.996
Baseline SCr (μmol/l)	75.64 ± 27.15	71.69 ± 19.7	0.242
BUN (mmol/l)	5.8 ± 1.92	6.08 ± 1.86	0.245
UA (μmol/l)	352.18 ± 99.17	328.01 ± 94.96	0.058

ATIII activity <60%. Patients with ATIII activity 60–<75% and 75–<90% also had significantly higher CIN incidence than patients with ATIII activity ≥90% (P=0.004 and P=0.001, respectively).

ATIII activity is an independent predictor for CIN

To analyze predisposing factors for CIN, all the patients were classified into two groups again, namely, the non-CIN group and the CIN group. A total of 125 (27.17%) patients were enrolled in the CIN group with the average age of 66.58 years and a gender ratio (male/female) of 106/19. In the group of patients without CIN, there were 335 individuals with the average age of 64.53 years and a gender ratio of 258/77. As shown in Table 2, the activity of ATIII was significantly

lower in CIN patients than that in non-CIN ones (84.43 ± 16.3% vs. 92.14 ± 13.94%, P<0.001). The baseline serum creatinine level was 79.3 ± 32.18 μmol/l in the CIN group, which was significantly higher than that in non-CIN group (P=0.033). Additionally, patients developing CIN had significantly lower albumin and serum sodium levels as well as significantly higher blood glucose and peak serum creatinine levels during hospitalization than those in whom CIN did not occur. However, there were no significant differences in age, gender, preoperative proteinuria, red blood cell count, hemoglobin, serum potassium, serum chlorine, diabetes mellitus, fibrinogen degradation product (FDP), D-dimer, fibrinogen, blood urea nitrogen and uric acid between two groups.

Univariate logistic regression indicated that albumin, serum sodium, blood glucose, baseline serum creatinine and ATIII activity <75% were all highly associated with the occurrence of CIN (Table 3). After adjustments for other risk variables in a multivariable regression model, ATIII activity <75% remained a significant independent predictor of CIN (OR 2.207, 95%CI [1.29–3.777]; P=0.004) as well as baseline serum creatinine (OR 1.009, 95%CI [1.001–1.016]; P=0.026) (Table 4).

Fig. 1. The incidence of contrast induced nephropathy increased as the ATIII activity decreased. Abbreviations: CIN, contrast induced nephropathy. # P<0.01.

Table 2. Baseline clinical characteristics between the non-CIN and CIN group. Abbreviations: ATIII, antithrombin III; CIN, contrast induced nephropathy; FDP, fibrinogen degradation product; SCr, serum creatinine; BUN, blood urea nitrogen; UA, uric acid

Variables	Non-CIN (n=335)	CIN (n=125)	P
Gender(male/female)	258/77	106/19	0.068
Age(years)	64.53±11.22	66.58±14.58	0.158
Preoperative proteinuria,n(%)	38(11.3%)	21(16.8%)	0.119
Red blood cell(10 ⁹ /l)	4.68±0.63	4.58±0.75	0.165
Hemoglobin(g/l)	139.01±17.73	135.65±28.86	0.225
Albumin(g/l)	39.49±5.39	38.06±6.43	0.017
Serum potassium(mmol/l)	4.01±0.44	4±0.49	0.726
Serum sodium(mmol/l)	141.1±3.21	139.8±7.4	0.008
Serum chlorine(mmol/l)	103.71±23.04	105.01±23.44	0.593
Blood glucose(mmol/l)	7.39±3	8.25±3.46	0.009
Diabetes mellitus, n(%)	86(25.7%)	33(26.4%)	0.874
ATIII activity(%)	92.14±13.94	84.43±16.3	<0.001
FDP(mg/l)	3.92±9.33	3.65±2.51	0.745
D-dimer(mg/l)	0.73±2.54	0.82±1.5	0.703
Fibrinogen(g/l)	2.74±0.6	2.72±0.57	0.827
Baseline SCr(μmol/l)	73.44±23.39	79.3±32.18	0.033
BUN(mmol/l)	5.83±1.96	5.86±1.8	0.863
UA(μmol/l)	345.33±99.35	356.81±97.27	0.268
Peak SCr during hospitalization(μmol/l)	85.94±24.4	140.8±63.31	<0.001

Table 3. Risk factors for contrast induced nephropathy by univariate logistic regression analysis. Abbreviations: ATIII, antithrombin III; CIN, contrast induced nephropathy; FDP, fibrinogen degradation product; SCr, serum creatinine; BUN, blood urea nitrogen; UA, uric acid; OR=odds ratio; CI=confidence interval

Variables	OR	95%CI	P
Gender	0.601	0.346-1.042	P=0.07
Age	1.014	0.997-1.031	P=0.112
Preoperative proteinuria	1.578	0.886-2.813	P=0.122
Red blood cell	0.801	0.586-1.096	P=0.166
Hemoglobin	0.993	0.984-1.002	P=0.137
Albumin	0.955	0.919-0.992	P=0.018
Serum potassium	0.921	0.584-1.455	P=0.725
Serum sodium	0.937	0.885-0.992	P=0.026
Serum chlorine	1.002	0.994-1.01	P=0.602
Blood glucose	1.083	1.019-1.152	P=0.011
Diabetes mellitus	1.039	0.651-1.657	P=0.874
ATIII activity	0.966	0.952-0.98	P<0.001
ATIII activity<75%	2.264	1.34-3.827	P=0.002
FDP	0.995	0.964-1.027	P=0.75
D-dimer	1.016	0.936-1.102	P=0.706
Fibrinogen	0.962	0.68-1.362	P=0.827
Baseline SCr	1.008	1.001-1.015	P=0.039
BUN	1.009	0.907-1.123	P=0.862
UA	1.001	0.999-1.003	P=0.268

Table 4. Risk factors for contrast induced nephropathy by multivariate logistic regression analysis. Abbreviations: ATIII, antithrombin III; CIN, contrast induced nephropathy; SCr, serum creatinine; OR=odds ratio; CI=confidence interval. * Adjusted for age, gender, albumin, blood glucose, serum sodium, ATIII activity<75% and baseline SCr.

Variables	B	SE	Wald	P	OR	95%CI
ATIII activity<75%*	0.792	0.274	8.343	0.004	2.207	1.29-3.777
Baseline SCr	0.009	0.004	4.958	0.026	1.009	1.001-1.016

Discussion

This study revealed the predictive value of endogenous ATIII activity in the development of CIN. Patients with low ATIII activity were predisposed to developing CIN after coronary angiography. As a common iatrogenic acute kidney injury, CIN immensely increases medical expenses, length of stay, and hospital mortality [32]. The incidence of CIN varies widely in the literature, partly due to differences in diagnostic criteria. Although there has been no consensus on the optimal definition of CIN, the most commonly used definition provided by ESUR Contrast Media Safety Committee is a 25% relative increase or 0.5mg/dl (44μmol/l) absolute increase in serum creatinine, assessed within 3 days after the procedure [33, 34].

However, a variety of questions and criticisms on this definition arise. It was reported that the relative definition was over-sensitive leading to false positives while the absolute definition led to false negatives [35]. Other criticisms include the absence of any functional assessment such as urinary output [7] and the short observation time, based on the evidence suggesting the peak increase of SCr could occur at 5 days rather than 3 days [31]. Recently, the KDIGO Clinical Practice Guideline redefined CIN based on changes in SCr level and on urinary output. The KDIGO definition, combining a higher relative and a lower absolute increase in SCr as well as extending the observation time up to 7 days, has been widely used in many clinical trials [36-38].

In this study, we chose to apply the KDIGO criteria to our population. The incidence of CIN after CAG was 27.17%, which was higher than that reported in other literature [35, 37, 39]. However, it is hard to compare incidences in these studies due to distinct criteria being adopted as well as special population being enrolled. The higher prevalence in our study may be due to the fact that patients receiving coronary angiography in CCU were always concomitant with cardiovascular complications or organ dysfunction, some of which might be the risk factors for CIN, leading to patients with high risks accounting for a comparatively large proportion in our study.

ATIII, encoded by the gene SerpinC1 and synthesized in the liver, is not only a serine protease inhibitor in the coagulation cascade but also possesses anti-inflammatory properties [24]. Our recent study showed that patients with low ATIII activities presented a high risk for developing AKI after cardiac surgery and endogenous ATIII insufficiency exacerbated renal ischemia/reperfusion injury in rats [24]. However, administration of exogenous ATIII could protect from CIN through anti-inflammatory and antioxidant effects as well as improved renal blood flow [30]. In this study, we found that patients with low activity of ATIII had an approximately 2.2-fold greater chance of developing CIN after coronary angiography than the normal group. Meanwhile, we have revealed a predictive value of endogenous ATIII activity in CIN development, suggesting that it would be clinically valuable to identify patients with low ATIII activities before administration of contrast media.

Additionally, this study highlighted the need for monitoring kidney function more closely and taking precautions to prevent or alleviate the development of CIN in these patients. Indeed, the predictive value of ATIII has gradually attracted attention, despite the fact that relevant studies are comparatively limited. Previously, it was reported that a low level of initial ATIII was highly associated with poor outcomes in several conditions and had been identified as an important prognostic indicator [28, 40, 41], providing new insights into the role of ATIII beyond its anticoagulant effects. However, the association between ATIII and the occurrence of CIN was unknown. To our knowledge, this is the first study that investigates the predictive value of ATIII in the development of CIN.

The pathophysiological mechanisms, by which low plasma ATIII activity correlates with CIN, are still unclear. One possible underlying mechanism may be the reduction in renal blood flow during ATIII deficiency. Prolonged vasoconstriction with a reduction of hemoperfusion occurs after contrast medium administration due to changes in calcium influx, increases

in adenosine and endothelin, as well as impaired nitric oxide production [42]. However, a majority of individuals fail to develop CIN, partly due to other protective factors contributing to self-defense and self-repair.

ATIII, a natural beneficial material, can stimulate endothelial cell to release prostaglandin I_2 (PGI_2), which has been considered a powerful vasodilator [43]. PGI_2 is known to regulate renal cortical blood flow and protect against renal failure [24]. Therefore, low ATIII activity may exert adverse influence on microcirculatory haemodynamics. ATIII deficiency is associated with hypercoagulability, microembolism, and with increased blood viscosity, eventually aggravating renal ischemic and hypoxia injury.

Another possible mechanism may be enhanced inflammatory response during ATIII deficiency. In addition to its anticoagulation properties, ATIII exhibits powerful anti-inflammatory effects in part by suppressing leukocyte recruitment, nuclear factor- κ B pathways activation and cytokine production [24, 43]. Therefore, under low ATIII conditions, intra-renal inflammation following contrast medium administration may increase due to oxidative stress or hypoxia [44-47]. However, the above explanations are speculative and the detailed molecular mechanisms involved in the adverse effects of ATIII deficiency on CIN should be further investigated.

The detrimental influence of low ATIII activity has suggested the need for supplementary therapies in patients with ATIII deficiency before administration of contrast medium. However, ATIII substitution has been previously subjected to a variety of questions and debates. It was reported that ATIII supplementation exhibited beneficial effects on organ function [48], protected against development of venous thromboembolism [49], and decreased mortality [49, 50] in patients with sepsis. Nevertheless, several meta-analyses have shown no significant beneficial effect of ATIII substitution on mortality in critically ill patients, whereas ATIII increased the risk of bleeding, especially in patients receiving concomitant heparin [51-53].

Indeed, some points on this issue merit attention. Firstly, a majority of trials provided clinical data and made the conclusions based on a small sample size, inevitably reducing power and increasing the risk of erroneous conclusions. Therefore, much larger randomized controlled trials (RCT) of ATIII replacement are needed to investigate its actual efficacy and harmful effects. Secondly, we should be discreet about concomitant use of heparin. Heparin can not only overwhelmingly accelerate the anticoagulant effect of ATIII, but competitively prevent ATIII from interacting with the endothelial cellular receptors, eventually reducing ATIII's anti-inflammatory properties, weakening vascular protection, and increasing the risk of bleeding [51]. Thirdly, randomized controlled trials are required to verify the clinical value of ATIII supplementation before contrast medium administration in protecting patients with low ATIII activities from developing CIN. Finally, in order to fully exert ATIII's anti-inflammatory effects and regulation of renal microcirculatory haemodynamics, the dose of ATIII should be reconsidered and redefined instead of the dose used in sepsis or DIC if ATIII is applied for protecting against CIN.

In this study, we also revealed that baseline serum creatinine was an independent risk factor for CIN, which was highly supported by other studies [2, 54-57]. The CIN Consensus Working Panel stated that the risk of CIN was increased when the baseline SCr is $\geq 114.9 \mu\text{mol/l}$ in men and $\geq 88.4 \mu\text{mol/l}$ in women [55]. Hence, we should pay more attention to patients with high baseline SCr and special precautions should be taken in these individuals.

Several limitations still exist in our study. Firstly, the number of enrolled patients is relative small, especially of the ones with low ATIII activities. Therefore, a retrospective analysis with a larger population is needed to reveal the clinical value of initial ATIII in CIN more accurately. Secondly, the current study didn't investigate the association between initial ATIII activities and short-term or long-term prognostic implications of CIN, including

in-hospital mortality, 1 and 5-year mortality, chronic kidney diseases and requiring dialysis [58]. Further follow-up studies should be carried on to reveal the predictive value of ATIII in long term outcome of CIN.

Conclusions

Patients with low ATIII activity presented a higher risk of developing CIN after CAG. The initial ATIII activity was an independent predictor for CIN. Hence, it would be clinically valuable to pay more attention to patients with low ATIII activity before contrast media administration as well as take precautions to prevent or alleviate the development of CIN in these patients.

Disclosure Statement

The authors declare no conflicts of interests.

Acknowledgements

This work was sponsored by the National Natural Science Foundation of China (81570603 and 81770741), the Health and Family Planning Commission of Shanghai Xuhui District (SHXH201605) and Shanghai Pujiang Talent Projects (15PJ1406700). Thanks to Dr. Anna Williams of Medical College of Wisconsin for language editing.

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