Original Paper

Contrast-Induced Nephropathy Is Less Common in Patients with Good Coronary Collateral Circulation

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Abstract

Background/Aims: Contrast-induced nephropathy (CIN) is a typically reversible type of acute renal failure that develops after exposure to contrast agents; underlying endothelial dysfunction is thought to be an important risk factor for CIN. Although the mechanism of coronary collateral circulation (CCC) is not fully understood, a pivotal role of the endothelium has been reported in many studies. The aim of this study was to investigate whether there is a relationship between CCC and CIN. ***Methods:*** Patients with at least one occluded major coronary artery and blood creatinine analyses performed before and on the second day after angiography were included in the study. CIN was defined as a 25% or greater elevation of creatinine on the second day after exposure to the contrast agent. Collateral grading was performed according to the Rentrop classification. Patients were grouped according to whether they developed CIN or not, i.e., CIN(–) and CIN(+) group. ***Results:*** A total of 214 patients who met the inclusion criteria were included in the study. CIN was diagnosed in 43 patients (20.1%) in the study population. Good CCC was identified in 112 patients (65.5%) in the CIN(–) group, whereas it was identified in 13 patients (30.2%) in the CIN(+) group. In the CIN(–) group, good CCC was significantly more frequent ($p < 0.001$). Furthermore, collateral circulation was an independent predictor of CIN. ***Conclusion:*** Good collateral circulation was associated with a lower frequency of CIN, and poor collateral circulation was an independent predictor of CIN.

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Introduction

Contrast-induced nephropathy (CIN) is a typically reversible type of acute renal failure that develops after exposure to contrast agents. Different studies have reported that the frequency of CIN ranges from approximately 3.3 to 16.6% in patients undergoing coronary invasive procedures [1–3]; however, this rate increases to 50% in high-risk patients [4]. CIN extends the length of hospital stays and increases mortality and morbidity [5, 6]. Although the pathophysiology of CIN has not been fully revealed, the direct toxic effects of contrast agents on renal tubular cells and the deterioration of vasoconstriction/vasodilation balance are implicated in the development of CIN. The balance of vasodilation/vasoconstriction has been reported to deteriorate because of underlying endothelial dysfunction, and susceptibility to contrast agents is increased in patients with diabetes, hypertension, atherosclerosis, and heart failure [7–11].

Numerous collateral vessels connect major coronary arteries in the healthy human heart [12]. Coronary collateral circulation (CCC) represents an alternative source of blood to ischemic areas in the case of obstruction in the coronary arteries. Although advances in molecular biology and genetics have provided insights into the mechanism underlying collateral development, the exact mechanism is not fully understood. The role of the endothelium in coronary collateral development has been emphasized, and many clinical and experimental studies have shown that a strong and functional endothelium plays an important role [13–15].

The endothelium plays a key role in the development of CCC as well as the formation of CIN. Therefore, we designed this study to determine the relationship between these two entities to provide insights into the pathophysiology of these two conditions, for which the exact mechanisms are unknown. The aim of this study was to determine the relationship between CCC and CIN, and we hypothesized that CIN frequency should be lower in patients with good CCC.

Methods

Patients who underwent coronary angiography between January 2012 and May 2016 were retrospectively evaluated. Patient information was obtained from their electronic records.

Inclusion and Exclusion Criteria

The inclusion criteria for the study were as follows: (1) patients who had undergone diagnostic coronary angiography; (2) patients with at least one completely occluded major coronary artery determined by coronary angiography in the proximal or middle section; (3) patients whose creatinine blood levels were determined before coronary angiography and on the second day after coronary angiography.

The exclusion criteria for the study were as follows: (1) patients with acute coronary syndromes who had undergone primary percutaneous intervention, percutaneous coronary intervention, or coronary artery bypass surgery; (2) patients with functional capacity New York Heart Association classes III and IV; (3) patients who had undergone treatment before and after coronary angiography to prevent CIN (such as saline infusion and bicarbonate treatment).

Coronary Angiography and Collateral Flow Grading

Coronary angiography was performed using the Judkins technique for all patients. Significant stenosis was defined as any major coronary artery with more than 50% narrowing. Grading of collateral flow was performed based on the Rentrop classification [16] as follows: Rentrop 0: no collateral circulation; Rentrop 1: small branches of the occluded vessel were filled by CCC; Rentrop 2: the epicardial segment of the occluded vessel was partially filled with CCC; Rentrop 3: the epicardial segment of the occluded vessel was totally filled with CCC. When more than one occluded blood vessel was present, the vessel with the highest collateral flow was selected for analysis. If more than one collateral flow was observed for the same clogged artery,

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the vessel filled to the highest degree was used for analysis. According to previous studies, collateral circulation at Rentrop 0 and 1 was considered poor CCC, whereas at Rentrop 2 and 3 it was considered good CCC [17].

Diagnosis of CIN

CIN was defined as impairment of renal function and characterized by a 25% or greater increase in serum creatinine from baseline to within 48 h of intravenous contrast media administration [18]. Patients were grouped according to whether they developed CIN or not, i.e., CIN(–) and CIN(+) group.

Statistical Analysis

The statistical software program SPSS for Windows 22 (SPSS Inc., Chicago, IL, USA) was used for the statistical analysis. A normal data distribution was determined using the Kolmogorov-Smirnov test. Categorical variables were presented as numbers and percentages and normally distributed continuous variables were reported as mean ± standard deviation. Continuous variables that were not normally distributed were reported as median (range). Continuous variables without a normal distribution were compared using the Mann-Whitney U test, whereas continuous variables with a normal distribution were compared using the independent-samples t test. The χ^2 test was performed to compare groups of categorical variables. To identify factors that independently affected CIN development after contrast agent exposure, CIN was used as a dichotomous dependent variable, and multivariate logistic regression analysis was performed to identify independent variables. Potential predictors of CIN were first identified using univariate analyses, with a threshold of $p < 0.05$, and were then included as independent variables in regression models. A p value <0.05 was considered statistically significant.

Results

In total, 6,440 coronary angiography patients were investigated, and 214 patients who met the inclusion criteria were included in the study. CIN was diagnosed in 43 patients (20.1%) in the entire study population. A total of 125 out of the 214 patients included in the study had well-developed CCC, whereas 89 patients had poorly developed CCC. The median age was 64 years (43–78) in the CIN(–) group and 69 years (50–76) in the CIN(+) group. Significant differences were observed between the two groups in terms of age ($p < 0.001$). Thirty-three percent of the patients in the CIN(–) group were diabetic, compared to 74% of the patients in the CIN(+) group. The number of diabetic patients was significantly higher in the CIN(+) group ($p < 0.001$). The number of diseased vessels, gender, frequency of hypertension, mean hemoglobin levels, and the percentage of patients with prior myocardial infarction were similar in both groups. Significant differences were not observed between the CIN(–) and the CIN(+) group regarding the use of antihypertensive, antiplatelet, anti-ischemic, and lipid-lowering drugs. Oral antidiabetic drug and insulin use were significantly higher in the CIN(+) group ($p < 0.001$ and $p = <0.001$, respectively). The baseline characteristic features and medications of the patients in both groups are shown in Tables 1 and 2.

Both before coronary angiography and on the second day after coronary angiography, the creatinine levels measured were significantly higher in the CIN(+) group. Good CCC was identified in 112 patients (65.5%) of the CIN(–) group and in 13 patients (30.2%) of the CIN(+) group. Poor CCC was identified in 59 patients (34.5%) of the CIN(–) group and in 30 patients (69.8%) of the CIN(+) group. The frequency of good CCC was significantly higher in the CIN(–) group ($p < 0.001$). The blood creatinine levels and CCC class of the patients in both groups before and after coronary angiography are shown in Table 3. Binary logistic regression analysis using the backward method indicated that age, diabetes, and CCC were risk factors for CIN. The results of logistic regression analyses are presented in Table 4.

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Table 1. Baseline characteristics of the groups

Variable	CIN(–) group (n = 171)	CIN(+) group (n = 43)	p value
Age, years	64 (43–78)	69 (50–76)	<0.001
Females	48 (28%)	14 (33%)	0.563
Smokers	51 (30%)	12 (28%)	0.806
Diabetes	56 (33%)	32 (74%)	<0.001
Hypertension	99 (58%)	31 (72%)	0.089
Hyperlipidemia	63 (37%)	13 (30%)	0.419
Previous myocardial infarction	26 (15%)	8 (19%)	0.587
Body mass index	27.8±1.8	28.4±1.6	0.067
Hemoglobin, g/dL	13.04±1	12.83±0.75	0.122
Number of vessel diseases	2.65±0.87	2.70±0.52	0.678
Ejection fraction, %	50 (40–60)	45 (40–60)	0.207
Contrast volume, mL	55 (40–70)	55 (45–70)	0.754

Values are presented as median (range), n (%), or mean ± standard deviation. CIN, contrast-induced nephropathy.

Table 2. Medications in both groups

Variable	CIN(–) group (n = 171)	CIN(+) group (n = 43)	p value
Acetylsalicylic acid	124 (81%)	56 (88%)	0.772
ACEI-ARB	69 (40%)	19 (44%)	0.649
Beta-blockers	34 (20%)	9 (21%)	0.879
Calcium channel blockers	37 (22%)	7 (16%)	0.438
Statins	64 (37%)	16 (37%)	0.979
Nitrates	28 (29%)	42 (36%)	0.320
Oral antidiabetic drugs	44 (26%)	26 (61%)	<0.001
Insulin	32 (19%)	18 (42%)	0.001

Values are presented n (%). ACEI-ARB, angiotensin-converting enzyme inhibitor-angiotensin receptor blocker; CIN, contrast-induced nephropathy.

Table 3. Serum creatinine levels before and on the second day after coronary angiography and the frequency of poor and good collateral circulation in both groups

Variable	CIN(–) group (n = 171)	CIN(+) group (n = 43)	p value
Cr before CAG, mg/dL	0.82 (0.57–1.45)	0.9 (0.74–1.2)	0.013
Cr on the 2nd day after CAG, mg/dL	0.83 (0.6–1.45)	1.28 (1.15–1.6)	<0.001
Poor CCC	59 (34%)	30 (70%)	<0.001
Good CCC	112 (66%)	13 (30%)	

Values are presented as median (range) or n (%). CAG, coronary angiography; CCC, coronary collateral circulation; Cr, creatinine; CIN, contrast-induced nephropathy.

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Table 4. Results of logistic regression analyses

	p value	OR	95% CI
Age	0.003	1.09	1.03–1.16
Diabetes	0.001	3.96	1.70–9.23
Collateral circulation	0.038	0.42	0.182–0.954

CI, confidence interval; OR, odds ratio.

Discussion

This study was the first to investigate the relationship between CIN and CCC in patients with coronary disease. The main finding of our study was that CIN is less frequently observed in patients with well-developed collateral circulation.

CIN is defined as either a >25% increase in serum creatinine or an absolute increase in serum creatinine of 0.5 mg/dL [19]. To describe CIN, we defined a 25% relative increase in serum creatinine values as "nephric" [18] based on the standards set by other studies. Serum creatinine levels reached a peak 2–5 days after contrast agent exposure and returned to normal within 7–21 days [20]. As in most studies, the serum creatinine levels at 48 h following contrast agent exposure were used to define of CIN [18, 21, 22]. Therefore, we included those patients whose serum creatinine levels were measured on the second day after exposure to the contrast agent into the study. In our study, baseline creatinine levels were higher in the CIN(+) group. This finding can be explained by the higher proportion of diabetic patients in this group. Although there was a difference in terms of basal creatinine in univariate analyses, the variable was not an independent predictor of CIN in logistic regression analysis. This result may be related to the fact that serum creatinine levels >1.5 mg/dL before exposure to the contrast agent are an independent risk factor for the development of CIN. However, none of the patients in our study had baseline blood creatinine levels >1.5 mg/dL. In addition, the small number of cases may be the cause.

The amount of contrast agent used has been reported as a determining factor for the development of CIN [23]. The amount of contrast agent used was similar between the groups in our study. In logistic regression analysis, the contrast agent volume was not a predictor of CIN. This result may be related to the low number of cases and the absence of complicated patients requiring too much contrast.

Various ranges of CIN frequency have been reported, and these differences are related to differences in the diagnostic criteria among the studies as well as the features of the patient populations. Reports have indicated that the frequency of CIN in high-risk patients can reach levels as high as 50% [4]. Baseline creatinine level, diabetes, age, body mass index, uncontrolled hypertension, congestive heart failure, anemia, hypoalbuminemia, contrast volume, and concomitant nephrotoxic drug use are well-known risk factors for CIN. The results of our study showed that CCC was also an independent predictor of CIN development. In our study, the CIN frequency was found to be 20.1% for the entire group. In the CIN(+) group, the frequency of poor CCC was 70%, while it was 34% in the CIN(–) group. In the CIN(+) group, patients with poor CCC were significantly more numerous than the CIN(–) group ($p < 0.001$). We conducted regression analysis using the backward method to determine independent factors affecting CIN development. Logistic regression analysis showed that age, diabetes, and CCC are independent predictors of CIN. The relationship between CIN and CCC observed in both logistic regression analysis and univariate analysis suggests that there is a common denominator between both entities.

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Possible Explanations for the Relationship between CCC and CIN

In their postmortem angiography studies, Baroldi and Scomazzoni [24] showed long ago that the coronary arteries are linked to each other by a wide arterial net that can expand during coronary blockage, and they also observed that this collateral network is developed in newborn hearts. Some researchers have suggested that the transcollateral pressure gradient caused by coronary blockage is an initiating factor for collateral development, whereas other researchers have suggested that ischemia is the main initiating stimulant for collateralization. However, Pohl et al. [25] showed that the only independent factor associated with coronary collateral development in patients with coronary artery disease is the degree of coronary stenosis. No matter whether the initiating cause is ischemia or transcollateral pressure gradient, the endothelium should be healthy and functional so that it can form mature collateral vessels via the expansion of the congenital networks. The importance of the endothelium for the development of collateral vessels in both clinical and experimental studies has been clearly demonstrated.

In an experimental study on rats, tadalafil, a phosphodiesterase-5 inhibitor, was reported to prevent CIN. Tadalafil increases the level of cGMP by blocking the enzyme phosphodiesterase-5, thereby increasing the level of nitric oxide and leading to vasodilation [26]. These findings may indicate the importance of the endothelium in the formation and inhibition of contrast nephropathy. The experimental study by Ziche et al. [13] showed that the promotion of endogenous nitric oxide production increases the proliferation and migration of endothelial cells, whereas the inhibition of nitric oxide production reduces the proliferation and migration of capillary endothelial cells. In addition, numerous studies have revealed that the endothelium is important in the development of coronary collateral vessels [14, 15]. Although the endothelium plays a key role in the development of coronary collateral vessels, it also plays an important role in the development of CIN. The pivotal role of endothelial function in CIN development has been revealed in many studies. Ramponi et al. [27] performed a study using cultured human umbilical vein endothelial cells and showed that contrast agents induced apoptosis in endothelial cells. In another study, Heinrich et al. [28] revealed the direct cytotoxic effect of contrast agents on endothelial cells. Additionally, Fernandez-Rodriguez et al. [29] performed a study on the endothelial cells of the aortic valve from rabbits and showed that contrast agents disrupt endothelial-dependent relaxation via calcium kinetics. The greater frequency of CIN observed in diabetic patients may be caused by pre-existing endothelial dysfunction in these patients. Indeed, it has been shown that higher frequency of CIN was associated with preexisting endothelial dysfunction in patients with diabetes [30]. Although the results of our study suggest that the endothelium is the common denominator in both coronary collateral development and CIN development, further studies are required to further clarify this relationship.

Study Limitations

The most important limitation of the present study is the retrospective nature. The absence of measures of endothelial function is another important limitation.

Conclusion

We found that in patients without CIN, the frequency of good CCC was much higher compared to patients with CIN. Moreover, collateral circulation, age, and diabetes were independent predictors of CIN. A potential explanation for these results is that patients with good CCC have better endothelial function compared to patients with poor CCC.

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Statement of Ethics

The study protocol was approved by the institutional ethics committee.

Disclosure Statement

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