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Iodinated Contrast Media Can Induce Long-Lasting Oxidative Stress in Hemodialysis Patients

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Purpose: Due to their comorbidities, dialysis patients have many chances to undergo radiologic procedures using iodinated contrast media. We aimed to assess time-sequenced blood oxidative stress level after contrast exposure in hemodialysis (HD) patients compared to those in the non-dialysis population. **Materials and Methods:** We included 21 anuric HD patients [HD-coronary angiography (CAG) group] and 23 persons with normal renal function (nonHD-CAG group) scheduled for CAG, and assessed 4 oxidative stress markers [advanced oxidation protein products (AOPP); catalase; 8-hydroxydeoxyguanosine; and malondialdehyde] before and after CAG, and subsequently up to 28 days. **Results:** In the nonHD-CAG group, only AOPP increased immediately after CAG and returned to baseline within one day. However, in the HD-CAG group, all four oxidative stress markers were significantly increased starting one day after CAG, and remained elevated longer than those in the nonHD-CAG group. Especially, AOPP level remained elevated for a month after contrast exposure. **Conclusion:** Our study showed that iodinated contrast media induces severe and prolonged oxidative stress in HD patients.

Key Words: Oxidative stress, contrast media, hemodialysis

INTRODUCTION

The use of iodinated contrast media has been increasing along with the advance in diagnostic and interventional radiology. Wider usage of contrast media has induced more incidences of complications. Contrast-induced nephropathy (CIN) is the most common side effect of contrast which occurs in up to 40% of patients undergoing percutaneous coronary intervention (PCI) based on patients' renal function.[1-5]

Dialysis patients have more cardiovascular disease than individuals with normal renal function, and furthermore, angiography is inevitable in diagnosis and treatment of arteriovenous fistular dysfunction. Thus, they have many chances to be exposed to contrast media. Since there is no doubt that the preservation of residual renal function is very important in dialysis patients, many investigators recommended the preventive strategies in end-stage renal disease (ESRD) patients with remaining renal function.[6] Nevertheless, most of physicians in practical field don't pay particular attention to these patients undergoing the procedure using contrast. Furthermore,

Janousek, et al.[7] recently reported that residual renal function is not significantly influenced by intravascular administration of iso-osmolal iodinated contrast agent (iodixanol) in ESRD, and that its use in these patients is relatively safe and even more recommendable than magnetic resonance imaging with its potential risk of nephrogenic systemic fibrosis. In contrary to the above, however, we have seen that many dialysis patients experience fatigue, malaise, loss of appetite, and general prostration and they have even fear of retesting, after the procedure using iodinated contrast media such as computed tomography (CT) or angiogram. Therefore, we questioned whether contrast media-induced oxidative stress could last and do harm to the organs other than kidney in ESRD patients with no renal excretion of contrast.

The aim of this study was to assess time-sequenced blood oxidative stress level after contrast media exposure in hemodialysis (HD) patients with no renal function, compared to non-dialysis population.

MATERIALS AND METHODS

Patients

We included 21 HD patients who were scheduled for coronary angiography (CAG) from October 2007 to December 2009 (HD-CAG group). They had been on HD at Kwandong University Myongji Hospital for at least a year, and all the HD patients had their urine output <100 mL/day. Only one patient underwent two CAGs, and we regarded her as 2 patients, so that HD-CAG group included total 22 patients. We routinely checked electrocardiogram (ECG) every 6 months in HD patients, and we took echocardiogram if there is any change in ECG compared with previous ones. If there was any abnormality in echocardiogram, we referred the patients to cardiologists for CAG. In this group, one patient had acute myocardial infarction, 2 had unstable angina, 5 had stable angina, and others had abnormal electrocardiogram without symptom. We also recruited nonHD-CAG group composed of 27 individuals with normal renal function who had appointments for CAG in the Cardiology Department. In this group, one patient suffered from acute myocardial infarction, 3 had unstable angina, 7 had stable angina, 6 had abnormal electrocardiogram without symptom, and others were scheduled for CAG to monitor the patency of previously inserted stents.

As controls, we chose 23 healthy volunteers who visited the health promotion center for general health examination and 22 anuric HD patients who did not perform CAG. The Institutional Review Board of Myongji Hospital approved this prospective observational study protocol, and written informed consent was obtained from all participating patients. This study is registered at Clinical Research Information Service (CRIS, www.cris.cdc.go.kr; KCT0000062).

Each HD-CAG patients underwent CAG between 2 dialysis sessions; i.e. if the patient had a HD on Monday, s/he underwent CAG on Tuesday, and the patient who had a HD on Tuesday underwent CAG on Wednesday. After coronary angiography, we provided HD to the patients next early morning. The average time interval from contrast exposure to dialysis initiation was 17.3±9.6 hours.

All HD patients were receiving conventional 4-hour hemodialysis, three times a week, and they remained their HD treatment as prescribed before this study.

Patients who had been injected with iron intravenously were required to stop injection at least 2 weeks before the test, but we let recombinant human erythropoietin and statins maintained. We didn't use any drug with anti-oxidant properties such as vitamin C or N-acetylcysteine, and also did not infuse normal saline or bicarbonate before and after CAG.

Coronary angiography and contrast media

Two cardiologists performed the CAG according to the standard clinical practice by using standard guide catheters, guide wires, and balloon catheters via the femoral approach. Coronary stenting was performed using standard techniques. The contrast dose was left to the discretion of interventional cardiologists. All patients received nonionic, iso-osmolar contrast agents, iodixanol (Visipaque®, Amersham health, Cork, Ireland). Usage amount of contrast medium is recorded.

Laboratory determination and patient outcomes

We measured the biochemical markers including white blood cell, hemoglobin, platelet, blood urea nitrogen, creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), sodium, potassium, total CO_2, calcium, phosphorus, glucose, uric acid, total protein, albumin, total cholesterol, triglyceride, and high density lipoprotein cholesterol in all of the patients prior to CAG. Then, we checked complete blood counts, blood urea nitrogen, and creatinine 2 hours, 1 day, 7 days, and 28 days after CAG. In the healthy control group, blood was drawn when the individuals underwent health examination. In the HD-CAG group, we drew blood samples before and after HD on 1st day after CAG. Then, we extracted samples just when inserting

needles for HD on the 8th and 29th day after CAG. In addition, we collected blood samples from the patients in the HD-control group before and after mid-week HD session (on Wednesday or Thursday), and subsequently, 1 week and 1 month later. The initially obtained values were used in comparison with those of the HD-CAG group as baseline values.

Oxidative stress markers

To quantify the oxidative stress before and after CAG, and subsequently for up to 28 days, we collected venous blood samples and stored plasma in a -80 degrees freezer until analysis. Advanced oxidation protein products (AOPP) levels were assessed by spectrophotometric measurement according to the method of Witko-Sarsat et al.,[8] and the results are reported as chloramine-T equivalents. Other parameters, measured by commercial enzyme-linked immunosorbent assay kits (USCN Life Science Inc. Wuhan, China) according to the manufacturer's instructions as previously reported,[9-11] included catalase, 8-hydroxydeoxyguanosine (8-OHdG), and malondialdehyde (MDA).

Outcome measures

The clinical endpoint of this study was the time course of blood AOPP, catalase, 8-OHdG, and MDA.

Statistical analysis

Continuous data are reported as mean±standard deviation. Categorical data are presented as absolute values and percentages. Differences between the two groups were tested by the Fisher exact or the chi-square test for categorical variables and by the Student t-test or Mann-Whitney test for continuous data. Serial oxidative stress parameters were compared within and between groups using repeated-measures analysis of variance. All statistical analyses were performed using SPSS software version 17.0 (SPSS Inc., Chicago, IL, USA). A 2-tailed p value <0.05 was considered statistically significant.

RESULTS

Of 27 in the nonHD-CAG group, 4 patients were dropped

Table 1. Baseline Demographic and Clinical Characteristics of Study Subjects[†]

	NonHD-CAG (n=23)	Healthy control (n=23)	p value	HD-CAG (n=22)	HD-control (n=22)	p value
Male, n (%)	8 (34.8)	8 (34.8)	1.00	11 (50.0)*	11 (50.0)	1.00
Age, yrs	62.2±9.4	62.5±7.5	0.86	59.1±13.7	60.0±14.5	0.56
Blood pressure, mm Hg						
Systolic	124.5±16.6	121.3±18.7	0.76	138.5±16.3*	136.2±19.6	0.67
Diastolic	76.2±6.7	79.3±8.3	0.82	80.0±13.0	82.1±17.2	0.79
Hypertension, n (%)	17 (73.9)	14 (60.9)	0.30	16 (73.0)	17 (77.3)	0.45
Diabetes, n (%)	9 (39.1)	4 (17.4)	0.05	10 (45.5)	11 (50.0)	0.57
Hyperlipidemia, n (%)	10 (43.5)	5 (21.7)	0.04	11 (50.0)	10 (45.5)	0.57
Liver cirrhosis, n (%)	1 (4.3)	0 (0)	0.06	1 (4.5)	1 (4.5)	1.00
Dialysis vintage, months	-	-	-	52.8±32.4	58.2±26.3	0.21
Medications, n (%)			-			
Aspirin	12 (52.1)	6 (26.1)	0.03	14 (63.6)	16 (72.7)	0.12
Clopidogrel	6 (26.0)	1 (4.3)	0.02	11 (50.0)	9 (40.9)	0.14
Statin	10 (43.5)	5 (21.7)	0.04	11 (50.0)	9 (40.9)	0.14
Erythropoietin	0 (0)	0 (0)	1.00	18 (81.8)*	17 (77.3)	0.26
Smokers, n (%)	2 (8.7)	4 (17.4)	0.06	9 (40.9)*	6 (27.3)	0.07
Acute MI, n (%)	1 (4.3)	-	-	1 (4.5)	-	-
Coronary angiogram finding, n (%)						
Normal	3 (13.0)	-	-	1 (4.5)	-	-
Minimal disease	7 (30.4)	-	-	4 (18.2)	-	-
1-VD	6 (26.0)	-	-	11 (50.0)	-	-
2-VD	5 (21.7)	-	-	4 (18.2)	-	-
Amount of contrast, mL	68.8±16.0	-	-	72.3±31.0	-	-

HD, hemodialysis; CAG, coronary angiography; MI, myocardial infarction; VD, vessel disease; SD, standard deviation.
*p<0.05 vs. nonHD-CAG group.
[†]Values are mean±SD or absolute number with percentages.

out due to failure of obtaining post CAG blood samples. Thus, total 90 patients were included in this study. The baseline characteristics and coronary angiogram findings are compared in Table 1. Among normal creatinine persons, there were more patients with diabetes and hyperlipidemia in the nonHD-CAG group than healthy controls. In addition, there were more patients taking aspirin, clopidogrel or statin in the nonHD-CAG group as well. All the HD patients showed very similar characteristics. In the HD groups, mean dialysis vintage was 55.5 months (range 6-109 months). In the nonHD-CAG group, there were more women than the HD-CAG group (p<0.05). Pre-CAG systolic blood pressure was higher in the HD-CAG group than that of the nonHD-CAG group, but diastolic blood pressure was not different. Concurrent medications were similar in the two CAG-performed groups except erythropoietin as expected. There were more smokers in the HD-CAG group, however, coronary disease profile was not different between the two CAG groups. The number of the patients who underwent just diagnostic CAG rather than PCI was 10 (43.5%) in the nonHD-CAG group and 7 (31.8%) in the HD-CAG group (p>0.05). The amount of contrast used was similar between the two CAG groups.

Like most of dialysis patients, subjects in the HD groups showed lower hemoglobin, total CO_2, and calcium level, and they had higher blood urea nitrogen, creatinine, potassium, and phosphorus levels than the non-HD groups. The laboratory findings were not different between the CAG-performed group and control group in both normal creatinine and HD groups except serum glucose level in normal creatinine groups (Table 2).

During the follow up, there was no patient showing elevated creatinine in the nonHD-CAG group (Table 3).

Oxidative stress markers

Baseline oxidative stress levels were not different between the nonHD-CAG group and healthy control group, except for 8-OHdG (nonHD-CAG vs. healthy control group: 38.7±13.2 μg/L vs. 20.1±12.1 μg/L; p=0.02). In HD groups, there was no difference in baseline oxidative stress markers be-

Table 2. Baseline Laboratory Parameters of the Study Subjects[†]

	NonHD-CAG (n=23)	Healthy control (n=23)	p value	HD-CAG (n=22)	HD-control (n=22)	p value
WBC, $\times10^3/mm^3$	7.5±2.5	7.8±2.2	0.79	9.9±1.3	8.7±1.4	0.67
Hemoglobin, g/dL	12.9±1.9	12.2±3.4	0.65	10.3±1.3*	10.0±1.5	0.58
Platelet, $\times10^3/mm^3$	240.7±93.0	224.4±73.6	0.69	251.0±100.1	242.1±99.6	0.74
BUN, mg/dL	18.1±7.6	16.8±8.4	0.52	49.1±17.2*	52.5±20.3	0.57
Creatinine, mg/dL	1.0±0.2	1.0±0.1	0.82	8.5±2.8*	8.1±5.2	0.77
AST, IU/L	28.7±14.0	24.2±18.2	0.67	38.5±41.5	35.2±21.8	0.82
ALT, IU/L	20.8±11.2	21.5±12.3	0.72	29.5±29.9	26.2±22.4	0.62
Sodium, mEq/L	140.0±4.2	141.2±5.7	0.51	138.3±4.0	135.3±9.2	0.12
Potassium, mEq/L	4.2±0.4	4.0±0.3	0.35	4.8±0.6*	4.9±0.8	0.35
Total CO_2, mEq/L	23.9±1.4	24.1±1.7	0.46	22.2±3.3*	21.9±4.8	0.15
Calcium, mg/dL	9.0±0.6	8.8±0.9	0.22	8.5±0.8*	8.4±0.4	0.13
Phosphorus, mg/dL	3.6±0.6	3.8±0.5	0.45	5.2±2.5*	5.0±0.9	0.23
Glucose, mg/dL	145.2±61.9	105.5±11.2	0.04	183.4±134.7	168.2±105.3	0.45
Uric acid, mg/dL	5.8±1.8	5.2±1.2	0.64	7.7±7.1	8.1±5.2	0.32
Total protein, g/dL	7.2±0.5	6.8±0.9	0.28	7.2±0.7	7.1±0.5	0.84
Albumin, g/dL	4.0±0.5	3.8±0.8	0.35	3.9±0.5	3.7±0.8	0.40
Total cholesterol, mg/dL	171.8±40.2	183.4±38.2	0.33	160.8±41.9	170.8±51.2	0.35
Triglyceride, mg/dL	126.3±99.8	118.2±92.5	0.42	134.7±95.8	140.5±84.6	0.53
HDL cholesterol, mg/dL	41.3±9.4	46.2±8.6	0.22	37.2±15.6	36.8±16.1	0.43
Iron, ug/dL	52.6±20.5	49.8±22.4	0.34	46.2±21.3	44.5±32.1	0.41
Ferritin, ng/mL	443.4±223.2	400.1±198.3	0.28	384.0±208.9	398.1±198.1	0.38
Transferrin saturation, %	33.7±9.8	34.5±10.5	0.62	31.1±10.4	29.9±12.4	0.35

HD, hemodialysis; CAG, coronary angiography; WBC, white blood cells; BUN, blood urea nitrogen; AST, aspartate transaminase; ALT, alanine transaminase; HDL, high density lipoprotein; SD, standard deviation.

*p<0.05 vs. nonHD-CAG group.

[†]Values are mean±SD.

Table 3. Changes in Laboratory Parameters after Angiogram†

	Baseline		1 day		1 wk		1 month	
	NonHD-CAG	HD-CAG	NonHD-CAG	HD-CAG	NonHD-CAG	HD-CAG	NonHD-CAG	HD-CAG
WBC, $\times10^3/mm^3$	7.5±2.5	9.9±1.3	7.1±2.5	8.9±4.7*	7.0±2.3	7.9±3.4	6.6±1.7	7.8±3.7
Hemoglobin, g/dL	12.9±1.9	10.3±1.3	12.2±1.7*	9.8±0.9*	12.0±2.0*	9.7±1.5*	11.8±1.8*	9.8±1.2
Platelet, $\times10^3/mm^3$	240.7±93.0	251.0±100.1	210.0±53.9	236.5±95.3*	221.2±74.0	231.5±104.5	211.8±71.6	234.5±103.9
BUN, mg/dL	18.1±7.6	49.1±17.2	14.5±5.3*	46.5±15.6	14.1±4.0*	55.8±20.5	15.6±4.3	46.9±20.3
Creatinine, mg/dL	1.0±0.2	8.5±2.8	0.9±0.2*	8.1±2.3	0.9±0.2*	8.6±2.8	1.0±0.2	8.4±3.2
AST, IU/L	28.7±14.0	38.5±41.5	28.8±27.3	42.4±41.1	21.6±6.9*	35.0±45.8	21.3±8.8*	26.9±27.9
ALT, IU/L	20.8±11.2	29.5±29.9	15.5±6.2	26.7±20.7	16.9±7.4	32.0±52.8	17.1±6.0	15.6±9.8

WBC, white blood cells; BUN, blood urea nitrogen; AST, aspartate transaminase; ALT, alanine transaminase; HD, hemodialysis; CAG, coronary angiography; SD, standard deviation.
*p<0.05 in comparison to baseline using paired-samples t-test.
†Values are mean±SD.

Table 4. Baseline Oxidative Stress Markers in the Study Subjects†

	NonHD-CAG (n=23)	Healthy control (n=23)	p value	HD-CAG (n=22)	HD-control (n=22)	p value
AOPP (μmol/L)	220.6±75.3	204.9±66.7	0.79	271.7±71.2	241.9±67.1	0.72
Catalase (U/L)	73.7±20.9	60.4±34.2	0.15	81.1±23.2	72.9±11.6	0.26
8-OHdG (μg/L)	38.7±13.2	20.1±12.1	0.02	23.0±5.4	20.8±4.2	0.67
MDA (μmol/L)	3.8±2.6	3.2±1.4	0.52	8.3±1.7*	8.4±2.3	0.52

HD, hemodialysis; CAG, coronary angiography; AOPP, advanced oxidation protein products; 8-OHdG, 8-hydroxydeoxyguanosine; MDA, malondialdehyde; SD, standard deviation.
*p<0.05 vs. nonHD-CAG group.
†Values are mean±SD.

tween CAG and controls (Table 4). Before CAG, AOPP, catalase, and 8-OHdG concentrations did not differ between the two CAG groups (nonHD-CAG vs. HD-CAG group: AOPP, 220.6±75.3 μmol/L vs. 271.7±71.2 μmol/L; catalase, 73.7±20.9 U/L vs. 81.1±23.2 U/L; 8-OHdG, 38.7±13.2 μg/L vs. 23.0±5.4 μg/L; p>0.05), but MDA level was higher in the HD-CAG group (8.3±1.7 μmol/L in HD-CAG group vs. 3.8±2.6 μmol/L in nonHD-CAG group, p<0.05). After contrast injection, however, AOPP tended to increase immediately in the nonHD-CAG group, but not in the HD-CAG group (302.4±39.9 μmol/L in nonHD-CAG group vs. 242.6±57.5 μmol/L in HD-CAG group, p>0.05). One day after CAG, AOPP returned to below the baseline in the nonHD-CAG group and remained until the study end. However, in the HD-CAG group, AOPP concentration increased 1 week after CAG (578.3±135.2 μmol/L) and still high 1 month later (413.2±70.4 μmol/L). In the case of catalase, the nonHD-CAG group showed no change after CAG, however, it increased 1 day after the procedure (115.1±23.9 U/L) and the high level lasted for 1 week (107.2±16.5 U/L) in the HD-CAG group. Similarly, 8-OHdG was elevated 1 day after CAG in the HD-CAG group (51.1±16.6 μg/L), but it returned within 1 week. MDA level was not changed after CAG in the nonHD-CAG group, however, in the HD-CAG group, it elevated 1 day after CAG (10.9±2.3 μmol/L) and further elevation was found after 4 hours of HD session (Fig. 1).

DISCUSSION

The major finding of our present study is that oxidative stress induced by iodixanol is more serious and lasts longer in ESRD patients than in patients with normal renal function.

Dialysis patients have many chances to experience diagnostic and therapeutic procedures because they have a lot of comorbidities. They have significantly increased risks for cancer in several sites such as kidney and bladder, as well as thyroid, lymphomas, and multiple myeloma.[12] They also show a high incidence of peptic ulcers[13] and even more have higher complication rates including hemorrhage.[14] The incidence of cardiovascular diseases is very high in dialysis patients, and it is well known as the most common cause of death in this population.[15] To diagnose and treat these comorbidities mentioned above, radiologic procedures are essential and they usually need contrast media.

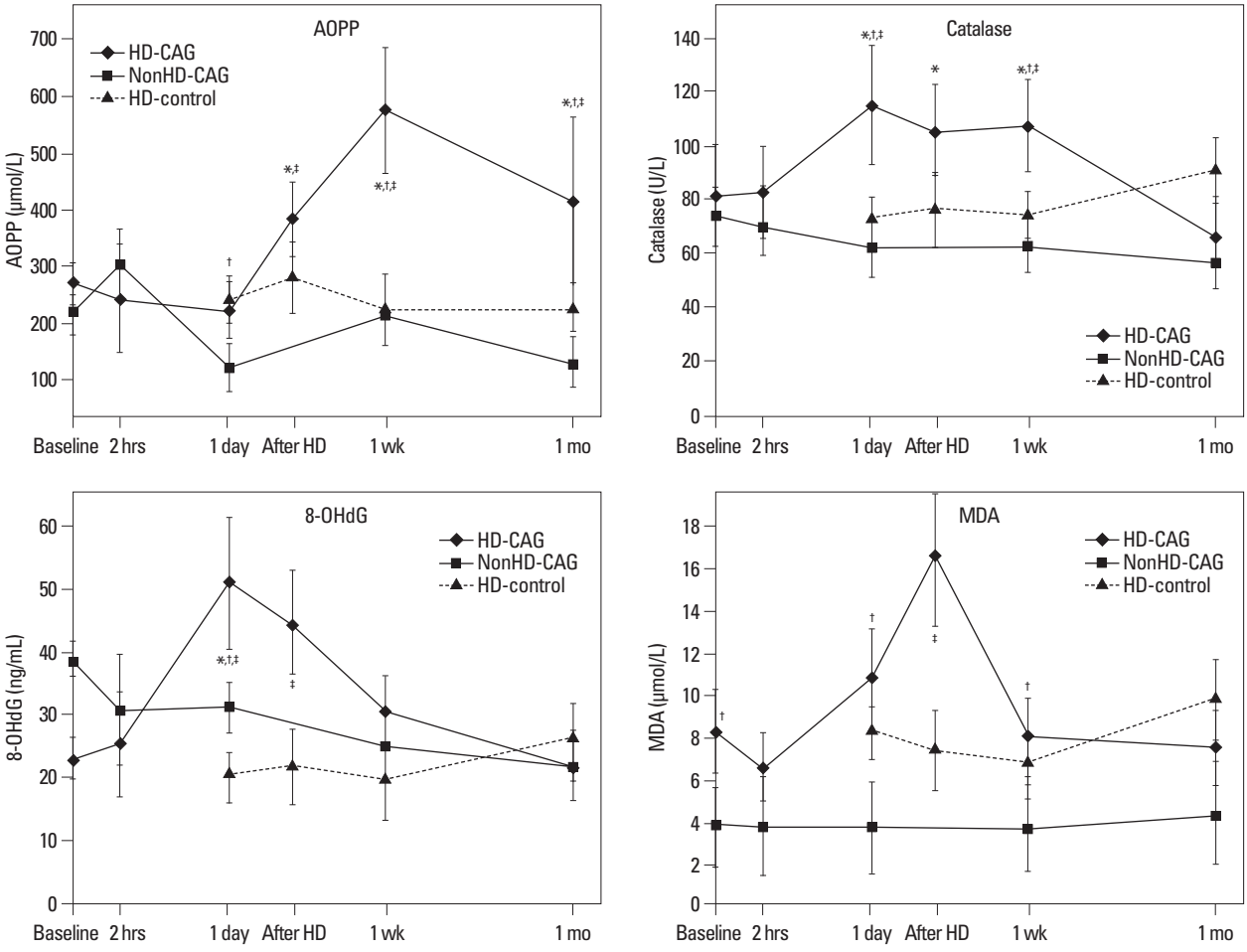

Fig. 1. Changes in the oxidative stress markers after CAG. *p<0.05 vs. baseline. †p<0.05 vs. nonHD-CAG group. ‡p<0.05 vs. HD-control. AOPP, advanced oxidation protein products; 8-OHdG, 8-hydroxydeoxyguanosine; MDA, malondialdehyde; HD, hemodialysis; CAG, coronary angiography.

The toxic effects of iodinated contrast media are considered to be multifactorial. Since the toxicities have been known to be mainly due to osmolarity, viscosity and ionic strength,[16] non-ionic, low-osmolar contrast media were developed. Nevertheless, these technically advanced contrast media still induces CIN via increased urine viscosity or vascular constriction.[17-19] On the other hand, many researchers have elucidated the cellular toxicity of contrast media[20] as well as vascular toxicity.[21] Oxidative stress is considered to play a major role in these types of toxicity.[22] Thus, several antioxidants such as N-acetylcysteine,[23] MESNA (sodium-2-mercaptoethane sulphonate),[24] vitamin C[25] and E,[26] and statins[27] have been evaluated and used for preventing CIN.

In adults, approximately 97% of the injected dose of iodixanol is excreted unchanged in urine within 24 hours, with less than 2% excreted in feces within five days post-injection.[28] In this study, the patients in the HD-CAG group had no or less than 100 mL/day urine output. Thus, they could not excrete the contrast through urine. Iodixanol has been shown to be readily dialyzable.[29] In a study, with a cellulose membrane, approximately 36% of iodixanol was removed from the plasma after 4 hours of dialysis, and approximately 49% of iodixanol was removed in case of using polysulfone membranes.[30] However, there is no report assessing the amount of oxidative stress before and after HD.

Oxidative stress causes a lot of diseases in human body. Neurodegenerative diseases, malignancies, cardiovascular diseases, even aging, fibromyalgia, and chronic fatigue are associated with oxidative stress.[31-33] It is well known that oxidative stress is increased in ESRD patients.[34] In the present study, we could observe slightly elevated oxidative stress levels in HD patients compared with healthy controls, however, only MDA showed statistically significant difference between the two populations. In the HD-CAG group, there was more serious elevation in oxidative stress markers after contrast exposure than nonHD-CAG group, and it was never eliminated by HD performed the next morning. Further elevation of AOPP and MDA level in this group might be

due to HD per se as suggested in a previous report.[35] However, we could find the tendency of elevation of the AOPP, catalase and 8-OHdG level after HD session without statistical significance. Therefore, it is highly possible that HD itself minimally influenced oxidative stress level in this group. To exclude even minor effects of HD on oxidative stress, we took blood samples from HD patients just before HD sessions during the follow up period. Several researchers reported elevated level of oxidative stress markers in patients with unstable angina and myocardial infarction.[36-40] However, we found that the levels of most of oxidative stress markers were not different between CAG-performed group and controls regardless of dialysis provision. It is perhaps due to the facts that only small number of patients in each group undertook CAG for acute coronary syndrome, and that more than half of them were given scheduled CAG without any symptom. Catalase is an intracellular antioxidant enzyme which destroys H_2O_2.[41] The level of catalase has still been the subject of debate in both HD patients[42-44] and in patients with coronary artery disease.[45-47] In the present study, regardless of its absolute value, catalase activity in the serum of nonHD-CAG group showed no change during the study period. In subjects with normal renal function, serum levels of oxidants and antioxidants were found not significantly changed 3 hours after exposure to contrast media, as seen in our study.[48] On the other hand, HD patients showed increased rather than decreased level of catalase after exposure to contrast media. There are two possible explanations. First, oxidative stress due to contrast media induced the expression of this antioxidant enzyme,[41] and second, since catalase is an intracellular enzyme, its increased level after contrast use probably indicated an increased damage of muscle fibers or erythrocytes resulting in its increased leakage into the circulation.[49]

Many studies have revealed that patients with ESRD have higher event rates after coronary revascularization than patients with normal renal function.[50,51] ESRD patients certainly have a lot of comorbidities which can explain this grave outcome; however, we suggest that this might be associated partly with elevated systemic oxidative stress level induced by iodinated contrast media. Indeed, Feng, et al.[52] reported that plasma AOPP concentration was associated with an increased incidence of major adverse cardiac events during the 6-month follow-up period in patients with normal renal function.

Our study has several limitations. First, the sample size is small and this study was performed at a single center. Second, there are more men and more smokers in the HD-CAG group. Male gender and smoking may affect the oxidative stress, but their effect is not certain. We allowed the use of erythropoietin and statins. The proportion of patients on statins was not different. Third, we did not measure catalytic iron. Catalytic iron which is necessary for the catalysis of superoxide anion, hydrogen peroxide, and the generation of the damaging hydroxyl radical[53] plays an important role in causing renal injury as well as acute coronary syndrome.[54,55] Fourth, we couldn't measure subjective symptoms such as fatigue, malaise, and loss of appetite.

To our best knowledge, this is the first report about oxidative stress after the exposure to iodinated contrast media in ESRD patients, and we confirmed the finding by comparing with HD controls who were not exposed to contrast media. Whenever we consider the radiologic procedure using contrast media, we usually don't pay careful attention to patients' condition besides CIN. Thus, ESRD patients are frequently exposed to such procedures. However, some investigators recently have warned about serious radiologic exposure in HD patients,[56,57] and the contrast-induced oxidative stress in dialysis patients should further be considered. Marenzi, et al.[58] reported that N-acetylcysteine reduced the severity of CIN in patients with acute myocardial infarction treated with primary angioplasty. In the above study, they found that N-acetylcysteine administration significantly reduced the need for mechanical ventilation and, however, they failed to elucidate the mechanism. It is quite possible that N-acetylcysteine could prevent oxidative stress not only in kidney but also lung.

Taken together, our present study showed that iodinated contrast media induces severe and prolonged oxidative stress in HD patients. In future, large-scaled studies are required, and furthermore, those studies should also include preventive measures using antioxidants such as N-acetylcysteine.

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