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Relationship between contrast-induced nephropathy and blood methemoglobin levels in acute coronary syndrome patients

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ABSTRACT

Introduction: Contrast-induced nephropathy (CIN) is an iatrogenic complication occurring in patients exposed to contrast agents.
Objectives: We aimed to investigate the relationship between blood methemoglobin (MHb) levels and the development of CIN in patients undergoing coronary angiography (CAG), with or without primary coronary intervention for acute coronary syndrome (ACS).
Patients and Methods: In this retrospective study, 119 patients diagnosed with ACS who underwent coronary angiography were included. MHb levels were measured in patients before and at during the first 1 to 3 hours after the procedure. CIN was defined as an increase in serum creatinine levels by ≥0.3 mg/dL (26.5 µmol/L) from baseline within 48 hours after contrast exposure or an increase of 1.5-1.9 times the baseline value within 7 days.
Results: The relationship between CIN-positive and CIN-negative patients and patients with MHb ≤%1 and MHb >% 1 was similar ($P=0.4$). Multivariate logistic regression analysis showed that an MHb value greater than 1 did not independently predict the development of CIN. Significant differences were observed between these two groups in terms of pre-CAG creatinine levels ($P=0.02$), Mehran risk score (<0.001), hemoglobin levels ($P=0.03$), the presence of hypotension ($P=0.03$), blood pH value ($P=0.03$), left ventricular ejection fraction (LVEF) (<0.001), the presence of diabetes mellitus ($P=0.014$), age ($P=0.001$), and smoking history ($P=0.02$).
Conclusion: Our study demonstrates that traditional risk factors contribute to nephropathy. However, the increased blood MHb levels do not appear to contribute to the development of CIN in ACS patients.

Implication for health policy/practice/research/medical education:
Curent knowledge
• Chronic kidney disease, advanced age, diabetes mellitus, female gender, anemia, hypotension, heart failure and use of contrast material over 100cc are known risk factors for contrast induced nephropathy.
• Preventive treatment methods for these known traditional risk factors have been tried to be developed through many studies.
New knowledge to be investigated
• We tried to investigate whether increased methemoglobin is a risk factor for contrast induced nephropathy.
• Our aim was to contribute to preventive treatment methods for contrast induced nephropathy.
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Introduction

Contrast-induced nephropathy (CIN) is an acute kidney failure that occurs as a result of using contrast agents during diagnostic and therapeutic catheterization procedures. It is responsible for 10-30% of hospital-acquired kidney failure cases and is the third most common cause of kidney failure after impaired kidney perfusion and the use of nephrotoxic drugs (1). In clinical cardiology practice, the primary approach to preventing CIN is a systematic evaluation of the patient's characteristics and risk assessment. Known risk factors for CIN include underlying kidney disease, diabetes mellitus, heart failure,

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acute coronary syndrome (ACS), cardiogenic shock, anemia, contrast volume, and advanced age (2,3). CIN has been associated with increased hospitalization, prolonged length of stay, and high mortality rates (4). Therefore, in addition to the known traditional risk factors, there is curiosity about whether there are other unknown risk factors.

Animal studies have demonstrated that elevated methemoglobin (MHb) levels can lead to kidney failure as demonstrated by biopsy examinations (5,6). Furthermore, in a patient who underwent bronchoscopy with benzocaine spray for local anesthesia, benzocaine-related methemoglobinemia and acute kidney failure were shown to develop (7). Methemoglobinemia is a clinical condition characterized by increased levels of MHb in the blood, resulting in hypoxia and cyanosis due to inadequate oxygen transport to tissues. MHb is formed as a result of the oxidation of iron from the ferrous (Fe^{2+}) to the ferric (Fe^{3+}) form in hemoglobin molecules. Under physiological conditions, it constitutes less than 1% of total hemoglobin in healthy individuals, but if this level exceeds 10%, cyanosis becomes evident (8-10).

Objectives

In this study, we aimed to assess whether MHb levels are a risk factor for the development of CIN in patients undergoing catheterization for ACS. This is the first study to examine the relationship between increased MHb levels and the development of CIN in patients undergoing catheterization for ACS.

Patients and Methods

Study population

The study included patients who were admitted to Mersin city training and research hospital between January 1, 2018 and March 31, 2022, who underwent coronary angiography, with or without percutaneous coronary intervention (PCI), were included in the study.

Inclusion criteria: Inclusion criteria were as follows patients with normal sinus rhythm, glomerular filtration rate (GFR) greater than or equal to 30 cc/min, and no history of dialysis. Additionally, a last contrast exposure duration of at least two weeks patients, which is known to be capable of inducing methemoglobinemia, aged 18 and above who had been exposed to prilocaine as a local anesthetic during coronary angiography, were included (8,10-12).

Exclusion criteria: Exclusion criteria encompassed conditions such as sepsis, diarrhea, arrhythmias, moderate to severe heart valve disease or heart valve prostheses, eGFR less than 30, and patients requiring dialysis.

Methemoglobin measurement

Given that prilocaine has a biological half-life of 55 minutes and previous research has shown that prilocaine-related methemoglobinemia typically develops within the first 1 to 3 hours, the screening process was designed accordingly (13,14). MHb levels were obtained by examining records of measurements taken using the arterial blood gas analyzer, which had the capability to measure MHb levels (15,16). Patients who had pre-procedural arterial blood gas measurements either in the emergency department or the angiography catheterization unit were identified. MHb levels were measured in patients during the first 1 to 3 hours after catheterization. For the purposes of this study, MHb levels greater than 1% were considered elevated.

Data collection

Patient data recorded in the hospital's data system or patient files were retrospectively reviewed. Data included the medical history of the patients, their current medications, the volume of low-osmolar contrast media (iohexol) administered to all patients during coronary angiography, vital signs, biochemical parameters, and complete blood counts. Left ventricular ejection fraction (LVEF) values were obtained through transthoracic echocardiography using a 3.5MHz transducer (Vivid 7 GE Medical System). CIN was defined according to KDIGO (Kidney Disease: Improving Global Outcomes organization) criteria as an increase in serum creatinine levels of ≥0.3 mg/dL (26.5 μmol/L) from baseline within 48 hours after contrast media administration or an increase of ≥1.5-1.9 times the baseline value within 7 days. The eGFR was calculated using the MDRD (Modification of Diet in Renal Disease) formula based on patient records, and patients' body surface areas were used in place of the 1.73 m^2 value (17).

A retrospective search was conducted in the archives of Mersin city training and research hospital, screening a total of 3450 patients who met the specified criteria. Ultimately, 119 patients were included in the study.

Statistical analysis

All analyses were conducted using the demo version of SPSS 26 for Windows (SPSS Inc., Chicago, IL, USA). Numeric variables were presented as mean ± standard deviation, and categorical variables were presented as counts and percentages. To assess whether variables followed a normal distribution, the Kolmogorov-Smirnov and Shapiro-Wilk tests were applied. Student's T-test was conducted to determine if there was a significant difference between the means of two groups. Logistic regression analysis was performed to identify risk factors. The performance of distinguishing cases between the CIN-positive and CIN-negative case groups was evaluated using receiver operating characteristic curve analysis. A *P* value less than 0.05 was considered statistically significant.

Results

In this study, we evaluated a total of 119 patients diagnosed with ACS who underwent coronary angiography. The patients were divided into two groups; those with

MHb≤%1 and MHb>%1. Demographic, basic clinical, and laboratory characteristics are presented in Table 1. Age ($P=0.027$), gender ($P=0.016$), height ($P<0.001$), weight ($P=0.002$), smoking ($P=0.009$), aspirin use (p=0.049), angiotensin-converting enzyme inhibitors/ angiotensin receptor blockers taking ($P=0.007$), calcium channel blockers administration($P=0.001$), clopidogrel ($P=0.015$), and furosemide ($P=0.018$) use, pre-angiography blood pH value ($P=0.008$), and contrast amount used during angiography ($P=0.027$) were statistically significantly different between the two groups (Table 1).

Demographic, basic clinical, and laboratory characteristics of patient groups in terms of CIN development are presented in Table 2. Before angiography; serum creatinine levels ($P=0.02$), Mehran risk score

Table 1. Demographic, clinical and laboratory characteristics of patients with MHb≤%1 and MHb>%1

Variables	MHb ≤%1 (n= 89)	MHb >%1 (n=30)	*P* value
Age (y)	58.8±12.2	64.8±13.9	0.027
Gender, (male), n (%)	68 (76)	16 (53.3)	0.016
Height (cm)	170.7±7.6	164.6±8.3	<0.001
Weight (kg)	81±12,4	72,7±13	0.002
Diabetes mellitus DM, n (%)	35 (39.3)	13 (43.3)	0.7
Hypertension (HT), n (%)	45 (50.6)	20 (66.7)	0.12
Hyperlipidemia (HPL), n/%)	31 (34.8)	16 (53.3)	0.073
Smoking, n (%)	54 (60.7)	10 (33.3)	0.009
STEMI, n/%)	42 (47.2)	10 (33.3)	0.186
Non-STEMI, n/%)	47 (52.8)	20 (66.7)	0.186
HFrEF, n (%)	40 (44.9)	12 (40)	0.641
HFpEF, n (%)	18 (22.2)	10 (33.3)	0.227
No Heart failure, n (%)	31 (34.8)	8 (26.7)	0.42
LVEF%	44.8±9.06	44.4±8.7	0.83
Heart rate/min	80±13.8	83±13.8	0.34
Systolic blood pressure (mm Hg)	126±20.4	128±21	0.7
Diastolic blood pressure (mm Hg)	75±10.5	72.7±10.6	0.32
Cr (mg/dL) prior to CAG	0.81±0.22	0.82±0.22	0.87
Cr (mg/dL) between 48 h-7 day	0.96±0.32	0.96±0.29	0.99
GFR (mL/min/BSA m^2) prior to CAG	104±32.9	92.9±32.7	0.11
GFR (mL/min/BSA m^2) between48h-7day	86.2±27.5	79.3±29.4	0.25
Contrast medium volome (mL)	207.2±82.6	173.3±89.2	0.03
Prillocaine (mg)	206.7±36.3	233.3±75.8	0.07
Mehran score	7.3±4.6	8.3±4.7	0.3
Hemoglobin (g/L)	13.9±1.5	12.95±1.9	0.008
Hematocrit (%)	41.3±3.9	38.9±5.6	0.04
Arterial blood gases			
Ph prior to CAG	7.43±0.47	7.46±0.05	0.008
Ph between 1st and 3rd hours after CAG	7.43±0.66	7.44±0.04	0.2
O2s prior to CAG	99±5.3	96.6±2	0.58
O2s between 1st and 3rd h after CAG	94.9±3.7	95.3±3.4	0.61
Previous medications			
Acetylsalicylic acid, n (%)	35 (39.3)	8 (26.7)	0.049
ACEI/ARB, n (%)	34 (38.2)	20 (66.7)	0.007
Statin, n (%)	24 (27)	12 (40)	0.18
Oral anti-diabetics, n (%)	30 (33.7)	9 (30)	0.708
Insulin, n (%)	6 (6.7)	6 (20)	0.05
Calcium channel blockers, n (%)	9 (10.1)	5 (16.7)	0.001
Beta-blockers, n (%)	23 (25.8)	18 (60)	0.35
Clopidogrel, n (%)	14 (15.7)	11 (36.7)	0.015
Furosemide, n (%)	0	2 (6.7)	0.018
Spironolactone, n (%)	1 (%1.1)	2 (6.7)	0.126

ACEI, Angiotensin-converting enzyme inhibitors; ARB, Angiotensin receptor blockers; BSA, Body surface area; CAG, Coronary angiography; Cr, Creatinine level; GFR, Glomerular filtration rate; HfpEF, Heart failure with preserved ejection fraction; HfrEF, Heart failure with reduced ejection fraction; LVEF, Left ventricular ejection fraction; NONSTEMI, Non ST-segment elevation myocardial infraction; O2s, Oxygen saturation; STEMI, ST-segment elevation hypertension myocardial infarction.

(<0.001), Hg value ($P=0.03$), presence of hypotension ($P=0.03$), blood pH value ($P=0.03$), LVEF value (<0.001), presence of diabetes mellitus ($P=0.014$), age ($P=0.001$), and smoking ($P=0.02$) were different between the two groups. Moreover,O_2 saturation in blood gas taken between the first 1 and 3 hours after angiography ($P=0.008$) and GFR between 48 hours and 7 days ($P<0.001$) were different between the two groups after angiography (Table 2).

The relationship between CIN-positive and CIN-negative patients and those with MHb≤%1 and MHb>%1 in the first 1 to 3 hours after catheterization was similar

Table 2. Demographic, clinical and laboratory characteristics according to CIN positive and CIN negative patients

Variables	CIN (+) 22	CIN (-) 97	*P* value
Age (years)	68.4±11	58.5±12.56	0.001
Sex (Male), n (%)	13 (59)	71 (73.2)	0.2
Height (cm)	166.8±8.97	169.7±7.9	0.14
Weight (kg)	78.5±15.5	79±12.5	0.9
Diabetes mellitus, n (%)	14 (63.6)	34 (35.1)	0.014
Hypertension, n (%)	16 (72.7)	49 (50.5)	0.06
Hyperlipidemia, n/%)	11 (50)	36 (37.1)	0.26
Smoking, n (%)	7 (31.8)	57 (58.8)	0.02
ACS, n (%)	22 (100)	97 (100)	0.26
STEMI, n (%)	12 (54.5)	40 (41.2)	0.26
NONSTEMI, n (%)	10 (45.5)	57 (58.8)	0.26
HFrEF, n (%)	12 (54.5)	40 (41.2)	0.26
HFbEF, n (%)	7 (31.8)	21 (21.6)	0.31
Hypotension, n (%)	3 (13.6)	2 (2.1)	0.03
IABP therapy, n (%)	1 (4.5)	-	0.065
Methemoglobin (MHb) ≥%1	4 (18.2)	26 (26.8)	0.4
LVEF %	38.8±9.9	46±8.2	<0.001
Heart rate/min	83.7±16.7	80.1±13.1	0.27
Systolic blood pressure (mm Hg)	119.7±21.95	128.1±19.9	0.08
Dyastolic blood pressure (mm Hg)	72.8±12.12	74.7±10.2	0.44
Cr (mg/dL) prior to CAG	0.9±0.2	0.8±0.2	0.02
Cr (mg/dL) between 48 h-7 day after CAG	1.38±0.39	0.87±0.19	<0.001
GFR (mL/min/BSA m^2) prior to CAG	89.3±36.7	104±31.8	0.06
GFR (mL/min/BSA m^2) between 48 h-7 day	55.8±23.5	90.9±24.8	<0.001
Contrast medium volume (mL)	222±111.4	193.4±71.4	0.13
Prilocaine (mg)	209±42.6	214.4±52	0.7
Mehran score	11.55±5.06	6.6±4.05	<0.001
Hemoglobin (g/L)	12.96±1.4	13.8±1.62	0.03
Hematocrit (%)	39.1±4	41±4.5	0.07
Arterial blood gases			
MHb level prior to CAG	0.3±0.12	0.32±0.23	0.75
MHb level, the first 1 to 3 hours after CAG	0.62±0.44	0.77±0.64	0.3
Ph prior to CAG	7.46±0.5	7.43±0.48	0.03
Ph between 1^{st}- 3^{rd} hours after CAG	7.43±0.95	7.43±0.51	0.6
O2s prior to CAG	95±3.8	96.4±4.8	0.22
O2s between 1^{st}-3^{rd} hours after CAG	93.2±5.2	95.4±3	0.008
Previous medications			
Acetylsalicylic acid, n (%)	12 (54.5)	41 (42.3)	0.3
ACEI/ARB, n (%)	12 (54.5)	42 (43.3)	0.34
Statin, n (%)	7 (31.8)	29 (29.9)	0.86
Oral anti-diabetics, n (%)	10 (45.5)	29 (29.9)	0.16
Insulin, n (%)	3 (13.6)	9 (9.3)	0.55
CCB, n (%)	3 (13.6)	11 (11.3)	0.77
Beta-blockers, n (%)	6 (27.3)	35 (36.1)	0.43
Clopidogrel, n (%)	7 (31.8)	18 (18.6)	0.19
Furosemide, n (%)	0	2 (2.1)	0.36
Spironolactone, n (%)	1 (4.5)	2 (2.1)	0.53

ACEI, Angiotensin-converting enzyme inhibitors; ARB, Angiotensin receptor blockers; BSA, Body surface area; CAG, Coronary angiography; Cr, Creatinine level; GFR, Glomerular filtration rate; HfpEF, Heart failure with preserved ejection fraction; HfrEF, Heart failure with reduced ejection fraction; LVEF, Left ventricular ejection fraction; NONSTEMI, Non ST-segment elevation myocardial infraction; O2s, Oxygen saturation; STEMI, ST-segment elevation hypertension myocardial infarction.

($P=0.4$). According to multivariate logistic regression analysis, MHb >1% did not independently predict the development of CIN (Table 3).

According to the multivariate logistic regression analyses, age (OR=1.051; 95% CI 0.990-1.115; $P=0.001$), diabetes mellitus (OR=3.81; 95% CI 01.094-13.262; $P=0.014$), Mehran risk score (OR=1.103; 95% CI 0.924-1.316; $P<0.001$), and presence of LVEF (OR=0.918; 95% CI 0.840-1.004; $P=0.001$) were found to be independent predictors of CIN development in patients with ACS undergoing angiography (Table 4).

Receiver Operating Curve analysis was performed to assess the discriminatory power of MHb before catheterization and MHb parameter observed in the first 1 to 3 hours after catheterization on CIN-positive and negative cases. The parameter's classification performance was not statistically significant ($P=0.3499$, $P=0.5427$). The area under the curve was ROC=0.549 and ROC=0.539.

Discussion

This study is the first to investigate whether there is an association between blood MHb levels and the development of CIN in patients with ACS, irrespective of whether primary coronary intervention is performed. Our study demonstrated no statistically significant effect of MHb levels on the development of CIN.

Contrast-induced nephropathy typically develops between 48 hours and seven days after exposure to contrast material (11). In patients with initially normal kidney function, the incidence of CIN is less than 5%. However, in the presence of risk factors, the incidence can range from 20% to 30% (18). In our study, the incidence of CIN in our patients was 18.5%, consistent with the findings of Marenzi et al, who observed CIN in 19% of their patients (19). It is known that contrast agents are nephrotoxic and lead to a decrease in medullary oxygen levels. There is a direct correlation between baseline serum creatinine levels and the development of CIN. In diabetics, renal blood flow is lower compared to non-diabetics. While the risk of CIN is relatively lower in diabetics without pre-existing renal insufficiency, diabetics with impaired kidney function have a significantly higher risk of CIN. It is well-established that the risk of CIN development increases in patients with relevant risk factors such as heart failure and acute myocardial infarction (20,21).

The pathogenesis of CIN involves various mechanisms such as direct toxic effects of contrast agents on renal tubular cells, intrarenal vasoconstriction, contrast agent-induced renal medullary hypoxia, reduction in renal perfusion due to myocardial depression, and hypersensitivity reactions leading to intraluminal obstruction (22).

Similar to all these studies (1-3,20-22), in our study, the development of CIN was found to be associated with baseline creatinine levels, the Mehran risk score, hemoglobin levels, the presence of hypotension, blood pH levels, LVEF, the presence of diabetes mellitus, advanced age, smoking, and oxygen saturation in the blood gas taken within the first 1 to 3 hours after coronary angiography. Our study demonstrated that age, diabetes mellitus, the Mehran risk score, and LVEF are independent predictors of CIN development in patients with ACS undergoing CAG.

There are various causes of acquired methemoglobinemia,

Table 3. Relationship between CIN positive and CIN negative patients and patients with MHb≤1 and MHb>1 measured in blood between the 1st and 3rd hours

Parameters	1.-3.h MHb≤1	1.-3.h MHb>1	*P* value
CIN negative	71 (79.8%)	26 (86.7%)	
CIN positive	18 (20.2%)	4 (13.3%)	0.400
Total	89 (100%)	30 (100%)	

CIN, Contrast-induced nephropathy; MHb, Methemoglobin.

Table 4. Multiple logistic regression to define risk factors contributing to development of CIN

Parameters	OR	95% CI	*P* value
Age	1.051	0.990-1.115	0.001
Diabetes mellitus	3.81	1.094-13.262	0.014
Sex (male)	1.047	0.192-5.718	0.190
Contrast medium volome	1.005	0.995-1.014	0.130
Mehran score	1.103	0.924-1.316	<0.001
GFR prior to CAG	0.997	0.976-1.020	0.059
HFrEF	0.723	0.061-8.560	0.256
HFpEF	1.123	0.158-7.964	0.310
LVEF	0.918	0.840-1.004	0.001

CAG, Coronary angiography; CIN, Contrast-induced nephropathy; GFR, Glomerular filtration rate; HfpEF, Heart failure with preserved ejection fraction; HfrEF, Heart failure with reduced ejection fraction; LVEF, Left ventricular ejection fraction.

including medications (such as dapsone, local anesthetics, nitrates, and certain antibiotics), food and beverages (foods dried with sodium nitrite or sodium nitrate, mushrooms, some vegetables), and exposure to chemicals and environmental substances (smoke, aniline dyes, benzene derivatives) (7-9,12,23).

The pathogenesis of kidney damage due to methemoglobinemia has been investigated in animal models and observed in kidney biopsy specimens. Experimental intravenous MHb administration has resulted in acute renal failure. Biopsies from different regions after MHb administration showed pigment accumulation in distal tubules and collecting ducts, tubular dilation proximal to the sites of pigment accumulation, epithelial cell death, formation of granular cells, and acute tubular necrosis (5-7).

In our study, an increase in MHb levels above 1% was found to be significantly associated with smoking, age, gender, height, weight, aspirin use, ACE/ARB receving, CCB administration, clopidogrel and furosemide use, pre-angiography pH value, and the amount of contrast used during angiography. However, the relationship between patients with CIN-positive and CIN-negative ACS and those with MHb ≤1% and MHb >1% measured between the first and third hours after angiography was similar ($P=0.4$). Multivariate logistic regression analysis did not independently predict the development of CIN in patients with MHb levels above 1%.

Conclusion

The pathogenesis and risk factors for the development of CIN have been well described. Treatments and research are ongoing to protect against the development of CIN in the presence of traditional risk factors, even when the patient's initial kidney function is normal. However, it remains unknown whether there are other unknown risk factors for the development of CIN. In addition to traditional risk factors, an increase in MHb may contribute to the development of CIN in patients with ACS. Further prospective studies are needed to investigate this issue.

Limitations of the study

Although our study is the first to evaluate the relationship between MHb increase and the development of CIN, it has some limitations. Firstly, the MHb levels in the CIN-positive patients in our study were between 1% and 2.9%, and not higher. Secondly, our study is a single-center and retrospective study.

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The English in this document has been checked by at least two professional editors, both native speakers of English.

Authors' contribution

Conceptualization: Oya İmadoğlu.
Data curation: Oya İmadoğlu, Ulaş Türker.
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Supervision: Oya İmadoğlu, Ulaş Türker.
Validation: Oya İmadoğlu.
Visualization: Oya İmadoğlu.
Writing–original draft: Oya İmadoğlu.
Writing–review and editing: Oya İmadoğlu, Ulaş Türker.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

The research conducted in this study adhered to the principles outlined in the Declaration of Helsinki. The study was approved by the local ethics committee, the Mersin University Rectorate Clinical Research Ethics Committee, under decision number 2022-452. Accordingly, written informed consent was taken from all participants before any intervention. Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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