The effect of non-dipper hypertension on contrast-induced nephropathy in coronary artery disease

Deniz Elcik, Ali Dogan, Mehmet Tugrul Inanc, Nihat Kalay**,** Abdurrahman Oguzhan, Ramazan Topsakal

Original Article

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Erciyes University Medicine Faculty, Department of Cardiology, Kayseri, Turkey

Address for correspondence:
Deniz Elcik, MD
Department of Cardiology
Erciyes University Medicine Faculty
Kayseri
Turkey
E-mail: denizelcik@hotmail.com
Phone number: +90 506 251 21 65
Fax number: +90 352 437 76 34

ABSTRACT

Objectives: This study aimed to evaluate non-dipper hypertension for risk of contrast-induced nephropathy in patients with coronary artery disease undergoing percutaneous coronary intervention.

Design: Prospective study

Setting: Department of cardiology, Erciyes University Medical Faculty

Subject: This study prospectively included a total of 161 patients (108 patients with dipper, 53 with non-dipper). Blood pressure (BP) measurements in the clinic were performed using sphygmomanometer. If the mean BP measured during night is less than 10% lower than the mean daytime measurement, these individuals were “non-dipper”.

Intervention: Negative efficacy of non-dipper hypertension on renal.

Main Outcome Measure: Patients were evaluated as contrast-induced nephropathy according to 25 % increase creatinine level.

Results: When both groups were compared for the development of contrast-induced nephropathy, it was detected in 11 (20%) patients in the non-dipper groups and in 8 (7%) (p=0.016) patients in the dipper group. Mehran risk scoring predictor of contrast nephropathy revealed a significant difference between hypertensions (HT) and diabetes mellitus (DM) the groups except for non-dipper hypertension (p: 0.016 and p: 0.028, respectively). The effect of non-dipper hypertension was significant in multivariant analysis among the parameters affecting contrast nephropathy (p: 0.023, OR: 0.99-7.984).

Conclusions: Non-dipper hypertension is a risk factor in the development of contrast-induced nephropathy independently of the risk factors of the Mehran.

KEY WORDS: Coronary artery disease, CIN, Mehran, non-dipper hypertensions

INTRODUCTION

The gold standard in determination of coronary artery disease is still coronary angiography. Agents used for coronary angiography are ionic substances which are not so innocent. Being called as contrasting agents, these substances may cause a range of side effects from allergic events to contrast-induced nephropathy.

Contrast induced nephropathy (CIN) is an important complication of invasive cardiovascular procedures. Patients with coronary artery disease (CAD) have a higher risk of developing CIN after Percutaneous coronary intervention (PCI) [1].

The development of CIN is a major determinant of short- and long-term morbidity and mortality in patients with CAD despite successful PCI [2,3]. Although the pathophysiologic mechanisms of development of CIN are complex and multi-factorial, probable mechanisms include intra-renal vasoconstriction, reduced renal blood flow, oxidative stress, inflammation, endothelial dysfunction, and direct tubular epithelial cell injury by contrast media (CM) [4].

Other patient-related risk factors include serum creatinine level being higher than normal, glomerular filtration rate being < 60 mL/min and this being caused by especially diabetic nephropathy, dehydration, congestive cardiac failure, gout, being over 70 years old and concurrent use of nephrotoxic medications (especially non-steroidal anti-inflammatory medications, angiotensin converting enzyme inhibitors, aminoglycosides, loop diuretics, mannitol, metformin). Patient-related risk factors also include diabetes mellitus, hypertension, low hematocrit level, hypotension, multiple myeloma, percutaneous coronary interventions, and left ventricle ejection fraction being < 40%[5]. The risk of development of contrast-induced nephropathy can be assessed beforehand by Mehran risk score.

Cardiovascular parameters such as blood pressure, heart rate and coronary tonus change throughout the day due to circadian rhythm [6]. The ambulatory blood pressure measurement data for normal individuals indicates that the blood pressure is at the highest level in the morning hours, tends to decrease throughout the day and is at the lowest level at night [7]. According to this classification based on ambulatory blood pressure, the mean blood pressure during night being more than 10% lower than the mean daytime value is called dipper hypertension, and no change or less than 10% change is called non-dipper hypertension.

It is known that there is direct proportion between blood pressure level, and the grade of endothelial dysfunction, vasculardamage and end-organ damage [8]. Individuals with non–dipper blood pressure have been found to have more frequent end-organ damage (ventricular hypertrophy, microalbuminuria, decreased arterial compliance, etc.), and cardiovascular morbidity and mortality [8,9]. In the present study, we investigated whether non-dipper hypertension at admission is an independent risk factor for the development of CIN in patients with CAD treated PCI.

SUBJECTS AND METHODS

Study population

This study prospectively included a total of 161 patients (108 patients with dipper, 53 with non-dipper) after the exclusion criteria were applied. All patients were informed about the study objective and

gave informed written consent. Local ethics committee decision was taken before starting the study (2013/326).Patients with coronary artery disease who had normal coronary angiography plans and arterial blood pressure with or without medication were included in the study. Coronary artery disease diagnosis was made based on international criteria. Patients below the age of 18 and above the age of 85, with the history of acute and/or chronic renal failure, chronic and acute hepatic failure, malignancy, previous CAD, with resistant hypertension, and with cardiogenic shock were excluded from the study. Moreover, standard medical treatment (Beta-blocker, ACE inhibitor, ASA, clopidogrel and statin) was initiated for all patients based on their hemodynamic status.

Laboratory Assessments

At the time of admittance, Tripotassium-Ethylenediaminetetraacetic acid (EDTA) based complete blood count, and from the blood samples taken into Isotherm-Gel Clot Activator based biochemistry tubes, biochemistry parameters (fasting blood glucose, renal function tests, liver functions tests, total lipid profile), sedimentation and complete blood count were studied for all patients. To assess the inflammatory status of the participants, C-reactive protein level was measured using BN2 nephelometer (Dade Behring, Schwalbach, Germany).

Coronary Angiography

Selective coronary angiography was taken in all patients from femoral approach using standard Judkins technique. Coronary angiography analyses were performed by specialist cardiologists. The patients were evaluated to have normal coronary arteries if they had no angiographic plaque formation in all epicardial coronary arteries (including sub-branches), no irregular margins, no ectasia and no slow flow, to have coronary artery disease if they had at least one of the conditions mentioned above. Patients diagnosed with coronary artery disease were considered to have obstructive coronary artery disease if they had ≥50% stenosis in at least one coronary artery. Patients who had < 50% stenosis in at least one coronary artery were considered to have non-obstructive coronary artery disease.

Ambulatory blood pressure measurement

Blood pressure measurements in the clinic were performed using sphygmomanometer according to European Society of Hypertension. Ambulatory blood pressure measurement(ABPM) was performed using MicrolifeWatchBP device in the 24-hour period after the patient was included based on inclusion criteria using a cuff proper for the patient's arm diameter. BP measurements were taken every 30 minutes during daytime (between 07:00 and 22:00) and every 60 minutes during night (22:00-07:00). Night, daytime and 24-hour BP measurements obtained from the measurements made for 24 hours were analyzed. The percentage of night time BP decrease was calculated using "Night BP decrease (%) = (Daytime BP – Night KB) x 100 / Night BP" formula. If the mean BP measured during night is less than 10% lower than the mean daytime measurement, these individuals were considered to be "non-dipper", and if the difference is 10% or more, to be "dipper". This procedure was performed at the patient's first admittance and on day 3, the groups were formed based on the average of both measurements.

Statistical Analysis

The distribution normality of the variables was tested using Kolmogorov-Smirnov test. Baseline characteristics of the patients were assessed between the groups using student's t test or Mann Whitney U test for numerical variables, and Chi-square test for categorical variables. Analysis results were assessed within 95% confidence interval, and p being <0.05 was considered to be a statistically significant difference. Covariates of parameters that found an important in univariate analysis were added to the multivariate analysis model. SPSS 21.0 software (Version 21, SPSS Inc, Chicago, IL, USA) was used for basic statistical analysis.

RESULTS

A total of 161 patients, 53 being in the non-dipper group (mean age 64.6±8.7 years) and 108 in the dipper group (mean age 61.2±11.2 years) were included into the study. 74% (n= 39) of the non-dipper group patients and 82% (n= 88) of the dipper group patients were males (p=0.378). Similar results was observed between the groups for smoking status, hyperlipidemia, history heart rate, systolic blood pressure and diastolic blood pressure at admittance (p=0.684, p=0.379, p=0.427, p=0.295, p=0.164, respectively) (table 1). Echocardiography parameters were similar in two groups. (Table 2).

No significant difference was observed between the patients' biochemical and hematological parameters (hemoglobin, hematocrit, white blood cells, CRP, platelet count, creatinine, glucose and cholesterol values) (Table 1).

When the dipper and non-dipper groups were compared for the prevalence of coronary artery disease, the number of patients with multivascular involvement was 24 (46%) in the non-dipper group and 48 (45%) in the dipper group. However, no statistically significant difference was observed between two groups (p=0.910).

When both groups were compared for the development of contrast-induced nephropathy, it was detected in 11 (20%) patients in the non-dipper groups and in 8 (7%) (p=0.016) patients in the dipper group (Table 3). Mehran risk scoring predictor of contrast nephropathy revealed a significant difference between HT and DM groups except for non-dipper hypertension (p: 0.016 and p: 0.028, respectively). The effect of non-dipper hypertension was significant in multivariant analysis among the parameters affecting contrast nephropathy (p: 0.023, OR: 0.99-7.984) (Table 4).

DISCUSSION

To the best of our knowledge, this is the first study to determine the value of non-dipper hypertension in predicting CIN for patients with CAD treated with urgent PCI. In addition, in this study we found that non-dipper hypertension causes contrast-induced nephropathy independent from Mahren risk score.

CIN is an important complication in the use of iodinated CM, which accounts for a significant number of cases of hospital-acquired acute kidney injury. CIN is the third most common cause of acute kidney injury in patients admitted to hospital, after ischemic and drug induced injury [10]. Studies have shown a strong association between CIN and adverse clinical outcomes, including cardiovascular

complications, provision of dialysis, and death [11, 12]. Previous studies confirmed that the incidence of CIN in patients who have no risk factor for CIN is < 2%, but the incidence in patients who are at a high risk for CIN is increased to 90% [3]. In our study, the incidence of CIN (11.6%) is in agreement with recent data in patients undergoing coronary PCI [13]. CIN is associated with prolonged hospitalization and increased cost. Furthermore, CIN occurs more frequently after unplanned coronary interventions and the development of CIN is a sign of poor short- and long-term mortality after PCI in CAD despite successful coronary revascularization [14-16]. Therefore, the early identification of patients at risk of CIN is crucial to guide prophylactic therapy and diminishing the incidence of CIN in high-risk patients.

Arterial blood pressure physiologically changes throughout the day. Physiologically, blood pressure at night should be more than 10% lower than the daytime blood pressure and this is called dipper activity. If the night blood pressure drops less than 10% from the daytime value, it is called non-dipper activity [17]. “Non-dipper” blood pressure is seen approx. 25% of the hypertensive cases, and when sub-groups such as diabetics are included, the prevalence increases even more [18]. The necessity to make such classification comes from the finding that cardiovascular morbidity and mortality is different between two groups. Individuals with non–dipper blood pressure have been found to have more frequent end-organ damage (ventricular hypertrophy, microalbuminuria, decreased arterial compliance, etc.), and cardiovascular morbidity and mortality [8,9,19].

Hypertensive renal damage is defined as the renal damage which starts or accelerates due to the effect of systemic blood pressure load (systolic, mean diastolic, pulse pressure, and blood pressure variability). It is known that there is direct proportion between blood pressure level, and the grade of endothelial dysfunction, vascular damage and end-organ damage. Following renal hemodynamic adaptation and glomerular hydrostatic increase, glomerular capillary semi permeability gets impaired, and as a result, albuminuria which is the most important indicator of progressive renal disease is seen. Renal hemodynamic changes due to systemic pressure increase such as increased intraglomerular pressure, changes in glomerular vascular permeability and tubular albumin reabsorption insufficiency are implicated for the occurrence of microalbuminuria in hypertensive individuals. Furthermore, in their study, Garcia-Ortiz *et al*. [20] reported that albumin/creatinine ratio is negatively associated with the drop in systolic and diastolic BP at night. In their study, glomerular filtration rate was only associated with diastolic decrease. Also, in their study, Hermida*et al*. [21] detected a significant association between circadian model and renal damage.

Previous studies have shown that microalbuminuria is the indicator of endothelial dysfunction and end-organ damage, and in their study, Bianchi *et al*. found high microalbuminuria prevalence in non-dipper[22]. We think that in addition to the endothelial dysfunction and microalbuminuria caused by non-dipper hypertension through nitric oxide (NO), the renal ischemia induced by renal vasoconstriction due to impaired equilibrium of NO which is known as endothelium-derived relaxing factor (EDRF) and endothelin plays the most important role in the pathogenesis of CIN [23]. In their study comparing non-dipper and dipper patient groups for endothelial dysfunction, Higashi *et al*. have assessed the 24-hour urinary excretion of nitric oxide final product nitrite/nitrate and cyclic guanosine monophosphate as a marker of endothelial dysfunction. In conclusion, 24-hour urinary nitrite/nitrate and cyclic guanosine monophosphate level was found to be significantly lower in the non-dipper patient group [24]. Moreover, obtaining positive results in

studies of pre-procedural medical therapy for the prevention of endothelial dysfunction caused by contrast-induced nephropathy and the fact that these therapies are mostly involve anti-hypertensive agents may be considered as another evidence that endothelial dysfunction is involved in the association between hypertension and contrast-induced nephropathy [25].

CONCLUSION

In conclusion, this study detected that non-dipper hypertension is an independent risk factor for the development of contrast-induced nephropathy, and we think that contrast-induced nephropathy can be decreased by the pre-procedural diagnosis and treatment of non-dipper hypertension.

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REFERENCES

1. Senoo T, Motohiro M, Kamihata H*, et al*. Contrast-induced nephropathy in patients undergoing emergency percutaneous coronary intervention for acute coronary syndrome. Am J Cardiol 2010; 105:624-8.
2. Oksuz F, Yarlioglues M, Cay S,*et al.* Predictive Value of Gamma-Glutamyl Transferase Levels for Contrast-Induced Nephropathy in Patients with ST-Segment Elevation Myocardial Infarction Who Underwent Primary Percutaneous Coronary Intervention. Am J Cardiol 2015; 116:711-6.
3. Rihal CS, Textor SC, Grill DE,*et al*. Incidence and prognostic importance of acute renal failure after percutaneous coronary intervention. Circulation 2002; 105:2259–64.
4. Goldenberg I, Matetzky, S. Nephropathy induced by contrast media: pathogenesis, risk factors and preventive strategies. Canadian Medical Association Journal 2005; 172:1461-71.
5. AyşegülZümrütdalKontrastMaddeNefropatisiİçhastalıklarıDergisi 2012; 19: 23-27.
6. Millar-Craig MW, Bishop CN, Raftery EB. Circadian variation of blood-pressure. Lancet 1978;1:795-7.
7. Seo WS, Oh HS. The circadian rhythms of blood pressure and heart rate in hypertensive subjects: dippers and non-dippers. Yonsei Med J 2002;43:320-8.
8. Pierdomenico SD, Bucci A, Costantini F*, et al.* Circadian blood pressure changes and myocardial ischemia in hypertensive patients with coronary artery disease. J Am Coll Cardiology 1998;31:1627-34.

9. Ohkubo T, Hozawa A, Yamaguchi J *et al.* Prognostic significance of the nocturnal decline in blood pressure in individuals with and without high 24-h blood pressure: The Ohasoma study. J Hypertens 2002;20:2183-9. 50.
10. Waikar SS, Liu KD, Chertow GM. Diagnosis, epidemiology and outcomes of acute kidney injury. Clin J Am Soc Nephrol 2008; 3:844-61.
11. Gruberg L, Mintz GS, Mehran R,*et al.* The prognostic implications of further renal function deterioration within 48 h of interventional coronary procedures in patients with pre-existent chronic renal insufficiency. J Am Coll Cardiol 2000; 36:1542-8.
12. James MT, Samuel SM, Manning MA, *et al.* Contrast-induced acute kidney injury and risk of adverse clinical outcomes after coronary angiography: a systematic review and meta-analysis. Circ Cardiovasc Interv 2013; 6:37-43.
13. Tsai TT, Patel UD, Chang TI, *et al*. Contemporary incidence, predictors, and outcomes of acute kidney injury in patients undergoing percutaneous coronary interventions: insights from the NCDR Cath-PCI registry. JACC Cardiovasc Interv 2014; 7:1-9
14. Fox CS, Muntner P, Chen AY, Alexander KP, Roe MT, Wiviott SD. Short-term outcomes of acute myocardial infarction in patients with acute kidney injury: a report from the national cardiovascular data registry. Circulation 2012; 125:497–504.
15. Kaya A, Kaya Y, TopçuS, *et al.* Neutrophil-to-lymphocyte ratio predicts contrast-induced nephropathy in patients undergoing primary percutaneous coronary intervention. Angiology 2014; 65:51-6.
16. McCullough PA, Stacul F, Becker CR, *et al.* CIN Consensus Working Panel. Contrast-Induced Nephropathy (CIN) Consensus Working Panel: executive summary. Rev Cardiovasc Med 2006; 7:177-97.
17. Fujii T, Uzu T, Nishimura M, *et al.* Circadian rhythm of natriuresis is disturbed in nondipper type of essential hypertensions. Am J Kidney Dis 1999;33:29-35.
18. Atasoyu ME, Ünver S, Cingözbay Y, Evrenkaya TR, Tülbek MY. Gençnormotansifvehipertansifbireylerdeayaktankanbasıncıizlemisonuçları. TürkNefrolojiDiyalizveTransplantasyonDergisi 2001; 10: 115-22
19. Verdecchia P, Schilacci G, Borgioni C. Altered circadian blood pressure profile and prognosis. Blood pressure monitoring 1997;2:347-52. 51.
20. García-Ortiz L, Gómez-Marcos MA, Martín-Moreiras J *et al*. Pulse pressure and nocturnal fall in blood pressure are predictors of vascular, cardiac and renal target organ damage in hypertensive patients (LOD-RISK study). Blood Press Monit 2009; 14 (4): 145-151
21. Hermida RC, Calvo C, Ayala DE *et al.* Administration time-dependent effects of valsartan on ambulatory blood pressure in hypertensive subjects. Hypertension 2003; 42 (3): 283-290.
22. Bianchi S, Bigazzi R, Baldari G, *et al.* Diurnal variations of blood pressure and microalbuminuria in essential hypertension. Am Journal Hypertension 1994;7:23-29.
23. Rudnick MR, Berns JS, Cohen RM, Goldfarb S. Contrast media-associated nephrotoxicity. CurrOpin Nephrol Hypertens 1996; 5: 127-133.

24. Higashi Y, Nakagawa K, Kimura M *et al.* Circadian variation of blood pressure and endothelial function in patients with essential hypertension: a comparison of dippers and non-dippers. J Am Coll Cardiol 2002;40:2039-43.

25. Briquori C, Marenzi G. Contrast-induced nephropathy: Pharmacological prophylaxis. Kidney Int 2006;69:30-8.

Table 1: Basal characteristics and hemodynamic parameters between groups

Variable	Dipper group n=108	Non-dipper group n=53	*P*-volume
Age	61.2 ± 11.2	64.6 ± 8.7	0.049
Gender (M/F)	88/20	39/14	0.408
BMI (kg/m2)	27.3 ± 5.1	28.2 ± 2.5	0.537
Hemoglobin (g/dl)	14.0 ± 1.6	13.7 ± 1.7	0.386
Hematocrit (%)	42.3 ±5.2	41.8 ± 5.9	0.431
White Blood Cell (10^3µL)	9.1 ± 3.5	8.7 ± 3.8	0.267
CRP	17.8 ± 4.3	16.7 ± 4.9	0.286
Platelets(10^3µL)	264.5 ± 70.6	275.3 ± 83.7	0.525
Creatinine (mg/dl)	0.8 ± 0.2	0.8 ± 0.1	0.931
Glucose (mg/dl)	127 ± 13	122 ± 18	0.366
Total cholesterol (mg/dl)	173.2 ± 42.6	183.1 ± 39.7	0.358
LDL (mg/dl)	114.7 ± 31.2	121.0 ± 28.2	0.449
HDL mg/dl)	37.7 ± 8.2	36.0 ± 8.3	0.563
Triglycerides (mg/dl)	155.9 ± 71.4	165.8 ± 77.6	0.441
Diabetes mellitus	9 (8%)	9 (16%)	0.028
Hypertension	7 (8%)	12 (22%)	0.016
Smoking	22 (40%)	17 (34%)	0.684
Hyperlipidemia	3 (5%)	4 (7%)	0.379
Heartbeat (dk)	71 ± 10	73 ± 10	0.427
Systolic blood pressure (mmhg)	128.3 ± 10.6	120.7 ± 11.9	0.295
Diastolic blood pressure (mmhg)	74.2 ± 10.1	75.7 ± 10.1	0.164

BMI: Body mass index; LDL: Low density lipoprotein; HDL: High density lipoprotein

Table 2: Echocardiography findings between groups

Variable	Dipper group n=108	Non-dipper group n=53	*P*-volume
LVEF %	47.3 ± 7.8	45.3 ± 7.4	0.149
Systolic PAB (mmhg)	30.9 ± 9.9	32.1 ± 10.7	0.167
LVDD (cm)	4.7 ± 0.6	4.9 ± 0.7	0.212
LVSD (cm)	3.1 ± 0.5	3.0 ± 0.4	0.101
IVSD	1.0 ±0.2	1.1 ± 0.2	0.631

LVEF: Left ventricular ejection fraction, LVDD: Left ventricular diastolic diameter, LVSD: Left ventricular systolic diameter, IVSD: Interventricular systolic diameter

Table 3: Mehran evaluation of groups with and without contrast nephropathy

Variable	CIN (-) group n=142	CIN (+) group n=19	*P*-volume
Age	60 ± 10.8	55 ± 9.8	0.159
Hypotension	0	0	
IABP	0	0	
Diabetes mellitus	36	10	0.028
Creatinine (mg/dl)	0.81 ± 0.2	0.82 ± 0.2	0.325
Hemoglobin (g/dl)	13.9 ± 1.6	13.6 ± 2	0.644
Contrast (cc)	101.5± 29.6	115.2± 32.9	0.06
Heart failure	0	0	

IABP: Intra-aortic balloon pump; CIN: Contrast induced nephropathy

Table 4: Multivariate analysis of parameters affecting contrast nephropathy.

Covariates		Multivariate Analysis	*P*-volume
	HR	95%CI	p
Non-dipper HT	3.834	0.999-7.984	0.023
DM	3.772	0.991-7.989	0.025
HT	2.538	0.821-6.733	0.025

HT: hypertensions; DM: diabetes mellitus