

Microvascular resistance in response to iodinated contrast media in normal and functionally impaired kidneys

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SUMMARY

Contrast-induced nephropathy (CIN) is considered to result from intrarenal vasoconstriction, and occurs more frequently in impaired than in normal kidneys. It was hypothesized that iodinated contrast media would markedly change renal blood flow and vascular resistance in functionally impaired kidneys. Thirty-six patients were enrolled (32 men; mean age, 75.3 ± 7.6 years) undergoing diagnostic coronary angiography and were divided into two groups based on the presence of chronic kidney disease (CKD), defined as an estimated glomerular filtration rate (eGFR) of < 60 mL/min per 1.73 m² (CKD and non-CKD groups, $n = 18$ in both). Average peak velocity (APV) and renal artery resistance index (RI) were measured by Doppler flow wire before and after administration of the iodinated contrast media. The APV and the RI were positively and inversely correlated with the eGFR at baseline, respectively (APV, $R = 0.545$, $P = 0.001$; RI, $R = -0.627$, $P < 0.001$). Mean RI was significantly higher ($P = 0.015$) and APV was significantly lower ($P = 0.026$) in the CKD than in the non-CKD group. Both APV ($P < 0.001$) and RI ($P = 0.002$) were significantly changed following contrast media administration in the non-CKD group, but not in the CKD group (APV, $P = 0.258$; RI, $P = 0.707$). Although renal arterial resistance was higher in patients with CKD, it was not affected by contrast media administration, suggesting that patients with CKD could have an attenuated response to contrast media.

Key words: arterial pressure, contrast media, nephropathy, chronic renal insufficiency.

INTRODUCTION

Contrast media activates various factors that increase renal vasoconstriction and reduce renal blood flow.¹ Although several studies have evaluated renal blood flow after the administration of contrast media by estimating para-aminohippurate clearance in humans,^{2–4} few studies have directly measured renal artery resistance and blood flow.

Fractional flow reserve (FFR) is a physiologically significant index that reflects epicardial coronary artery stenosis.⁵ A recent clinical trial showed that FFR could predict clinical outcomes following percutaneous coronary intervention.⁶ The myocardial microcirculatory resistance (IMR) index is a measure of vascular resistance in the whole organ that reflects microvasculature function and appears to be an appropriate predictor of microvascular damage after myocardial infarction.⁷ Notably, both FFR and IMR can be assessed using a Doppler flow wire.

The risk of contrast-induced nephropathy (CIN) increases in patients with chronic kidney disease (CKD), which is identified by an estimated glomerular filtration rate (eGFR) of < 60 mL/min per 1.73 m². Special precautions should be taken when administering contrast to these patients.^{8,9}

The aims of this study were to investigate changes in renal artery resistance during cardiac catheterisation using a Doppler flow wire, and to compare renal vascular responses to iodinated contrast media between patients with and without CKD.

RESULTS

Patient characteristics

Table 1 summarises the clinical characteristics of the 36 patients. There were 18 patients in the CKD group (50%) and 18 in the non-CKD group (50%). Mean age and prevalence of hyperuricemia were significantly higher in patients with CKD than in those without CKD, while mean haemoglobin was significantly higher in patients without CKD than in those with CKD. Because patients were separated into groups based on eGFR, renal functional indexes (creatinine, cystatin C, and eGFR) were significantly different between groups, respectively. The total volume of contrast media used and the amount of time taken to

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Received 24 April 2015; revision 27 July 2015; accepted 11 August 2015.

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Table 1 Patient characteristics

Characteristic	eGFR \geq 60 mL/min/1.73 m ²	eGFR < 60 mL/min/1.73 m ²	<i>P</i> value
Patient number	18	18	
Age, years	61.3 \pm 13.2	75.3 \pm 7.6	< 0.001
Sex, male (%)	16 (89)	16 (89)	1.000
Hypertension (%)	14 (78)	12 (67)	0.711
Hyperlipidaemia (%)	15 (83)	13 (72)	0.691
Diabetes mellitus (%)	5 (28)	10 (56)	0.176
Hyperuricemia (%)	1 (6)	9 (50)	0.007
Smoking (%)	4 (22)	2 (11)	0.658
Clinical presentation (%)			
CAD	14 (78)	16 (89)	0.658
Prior MI	7 (39)	7 (39)	1.000
Medication (%)			
Statin	12 (67)	11 (61)	1.000
ACE-I	3 (17)	4 (22)	1.000
ARB	9 (50)	9 (50)	1.000
β -blockers	9 (50)	10 (56)	1.000
Calcium channel blockers	11 (61)	8 (44)	0.505
Diuretics	4 (22)	6 (33)	0.711
Laboratory data			
Hb (g/dL)	14.4 \pm 2.0	12.7 \pm 1.7	0.009
UA (mg/dL)	5.6 \pm 1.0	6.2 \pm 1.3	0.126
BNP (pg/mL)	33.7 \pm 49.9	66.2 \pm 46.8	0.052
HbA1c (%)	6.2 \pm 1.2	6.8 \pm 1.2	0.192
Cre (mg/dL)	0.84 \pm 0.10	1.53 \pm 0.83	0.001
eGFR (mL/min/1.73 m ²)	71.2 \pm 8.9	41.5 \pm 14.6	< 0.001
Cystatin C (mg/L)	0.86 \pm 0.16	1.48 \pm 0.61	< 0.001
LVEF (%)	64.6 \pm 11.8	60.2 \pm 10.9	0.246
Contrast media volume (mL)	89.5 \pm 24.4	75.2 \pm 25.5	0.095
Administration time (min)	41.8 \pm 11.5	41.3 \pm 13.9	0.907
Renal flow reserve			
MBP (mmHg)	96.3 \pm 19.5	92.8 \pm 9.6	0.488
APV (cm/s)	38.9 \pm 8.1	31.5 \pm 10.6	0.026
RI (cm/s/mmHg)	2.61 \pm 0.63	3.46 \pm 1.27	0.015

Values are numbers (%) or mean \pm standard deviation.

ACE-I, angiotensin converting enzyme inhibitors; APV, average peak velocity; ARB, angiotensin receptor blockers; BNP, brain natriuretic peptide; CAD, coronary artery disease; Cre, creatinine; eGFR, estimated glomerular filtration rate; Hb, haemoglobin; HbA1c, haemoglobin A1c; MBP, mean blood pressure; MI, myocardial infarction; LVEF, left ventricular ejection fraction; RI, renal artery resistance index; UA, uric acid.

administer the contrast media were similar between groups ($P = 0.095$ and $P = 0.907$, respectively).

Doppler flow wire findings

Results from the Doppler flow wire analyses at baseline are summarised in Table 2. Baseline renal artery resistance index (RI) and average peak velocity (APV) differed significantly between groups. In simple linear regression analysis, APV was significantly positively correlated ($R = 0.545$) and RI was inversely correlated with the eGFR at baseline ($R = -0.627$; Fig. 1). Table 2 also details changes in RI and APV during the administration of iodinated contrast media. In non-CKD patients, APV decreased significantly and RI increased significantly during the administration of contrast media; however, APV and RI did not

Table 2 Changes in doppler flow wire findings

Variable	Baseline	Post-administration	<i>P</i> value
MBP (mmHg)	94.5 \pm 15.2	92.2 \pm 13.0	0.124
APV (cm/s)	35.2 \pm 10.0	32.2 \pm 9.0	0.001
RI (cm/s per mmHg)	3.04 \pm 1.08	3.26 \pm 1.10	0.014
eGFR < 60 mL/min per 1.73 m ²			
MBP (mmHg)	92.8 \pm 9.6	90.4 \pm 10.9	0.082
APV (cm/s)	31.5 \pm 10.6	30.2 \pm 10.6	0.258
RI (cm/s per mmHg)	3.46 \pm 1.27	3.51 \pm 1.24	0.707
eGFR \geq 60 mL/min per 1.73 m ²			
MBP (mmHg)	96.3 \pm 19.5	94.0 \pm 14.9	0.404
APV (cm/s)	38.9 \pm 8.1	34.1 \pm 6.8	< 0.001
RI (cm/s per mmHg)	2.61 \pm 0.63	3.00 \pm 0.90	0.002

Data are presented as mean \pm standard deviations.

APV, average peak velocity; eGFR, estimated glomerular filtration rate; MBP, mean blood pressure; RI, renal artery resistance index.

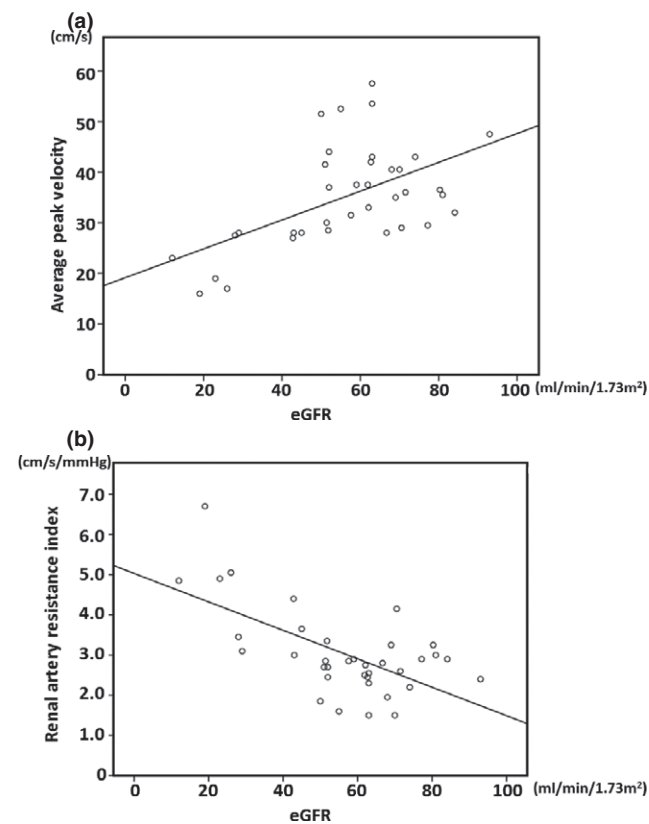


Fig. 1 Simple linear regression analysis. Correlations of estimated glomerular filtration rate (eGFR) with average peak velocity ($R = 0.545$; $P = 0.001$) and the artery resistance index ($R = -0.627$; $P < 0.001$).

change in patients with CKD ($P = 0.258$ and $P = 0.707$, respectively).

Changes in renal markers

Table 3 shows changes in renal biomarkers after contrast media administration. Serum creatinine and cystatin C levels were not

Table 3 Serial changes in renal markers

Renal function	Baseline	24 h	<i>P</i> value
eGFR \geq 60 mL/min per 1.73 m ²			
Creatine (mg/dL)	0.78 \pm 0.12	0.78 \pm 0.97	0.577
Cystatin C (mg/L)	0.86 \pm 0.16	0.83 \pm 0.14	0.146
eGFR < 60 mL/min per 1.73 m ²			
Creatinine (mg/dL)	1.40 \pm 0.80	1.41 \pm 0.76	0.635
Cystatin C (mg/L)	1.48 \pm 0.61	1.45 \pm 0.57	0.443

Data are presented as mean \pm standard deviation.
eGFR, estimated glomerular filtration rate.

different before and 24 h after administration of contrast media in either group.

DISCUSSION

Patients with CKD show a higher incidence of CIN,^{8,9} which is considered to develop mainly due to intrarenal vasoconstriction.¹ Therefore, it was hypothesized that renal artery resistance in patients with CKD may change following iodinated contrast media administration. In the present study, patients with normal renal function showed significantly increased RI and decreased APV following such administration; however neither index changed following contrast administration in patients with CKD. A previous study assessing renal artery resistance using a Doppler flow wire positively correlated APV with renal blood flow in humans,¹⁰ and Doppler flow wire was found to be superior for estimating both renal blood flow and renal artery resistance. Accordingly, RI and APV were measured directly using a Doppler flow wire in this study.

Relationship of eGFR with APV and RI

The kidney has various functions including excretory, endocrine and metabolic roles. The GFR is a component of excretory function, and it is generally reduced following various types of structural damage; most other kidney functional parameters decline in parallel with such decreases in GFR.¹¹ It is impossible to measure GFR in humans directly, and it is instead measured indirectly based on the clearance of exogenous filtration markers by the kidney. However, the relationships between renal haemodynamics and GFR have not yet been directly validated in humans.

Chronic kidney disease is associated with a loss of functioning nephrons, and the remaining nephrons compensate by increasing their intraglomerular pressure to maintain GFR.¹² For the first time, this study has demonstrated a correlation between eGFR and APV. The APV reflects renal blood flow, with the number of functioning nephrons declining along with declines in renal blood flow. Conversely, an inverse correlation was found between eGFR and RI. In the field of cardiovascular medicine, IMR estimated using a Doppler flow wire reflects microvasculature function, thus the inverse correlation shown herein suggests that RI could reflect whole-organ microcirculatory resistance after structural and functional damage to the kidney.

Differing responses of patients with and without CKD to contrast media

Various factors contribute to the pathogenesis of CIN such as vasoconstriction, hypoxia, oxidative stress and direct tubular toxicity,^{1,13,14} and iodinated contrast media activates the release of renal vasoconstrictors (e.g., adenosine or endothelin (ET)).^{15–18} Here, the contrast media apparently increased renal microvascular resistance and decreased renal blood flow in normally functioning kidneys, possibly indicating renal vasoconstriction due to contrast media. Another study using colour-coded Doppler ultrasound indicated a significant transit increase in renal artery resistance within a few minutes of intravenous contrast media infusion,¹⁹ although the cohort studied consisted primarily of patients with normal renal function, similar to the non-CKD group in the present investigation.

Contrary to our expectations, iodinated contrast media neither significantly increased renal artery resistance nor decreased renal blood flow in CKD patients. However, the risk of CIN is not low in patients with CKD, and indeed, special precautions should be taken when administering contrast media to these patients.^{8,9} Indeed, because intrarenal vasoconstriction is considered the main mechanism contributing to CIN,¹ several studies have tested renal vasoconstrictor antagonists, ET receptor antagonists and calcium channel blockers to prevent CIN. Vasodilators were found to be potentially detrimental or ineffective for reducing the risk of CIN,^{20–24} while another study showed that administration of iodinated contrast media to patients with CKD (defined by a serum creatinine concentration \geq 1.8 mg/dL) did not decrease total renal blood flow, estimated using a renal thermodilution catheter.²⁵ Together, these previous findings support our current data.

In addition, this study showed a difference in the renal arterial response to iodinated contrast media between patients with and without CKD. Similarly, in an experimental model, renal blood flow in rats with normal renal function temporarily decreased after exposure to contrast media, whereas in those with impaired renal function, the renal blood flow did not decrease.²⁶ Indeed, several experimental studies have shown attenuated functional derangement against acute structural damages, including hypoxic stress, in CKD,^{27,28} and a recent experimental study using magnetic resonance imaging demonstrated less haemodynamic change following hypoxic stress in mice models of CKD than in normal mice.²⁹ Further research is therefore needed to evaluate the differing renal artery responses to iodinated contrast media in patients with both normal and impaired kidney function.

In conclusion, the administration of iodinated contrast media increased renal microvascular resistance and decreased renal blood flow in patients without CKD. In contrast however, patients with CKD showed no significant change in renal microvascular resistance or renal blood flow following iodinated contrast media administration. These findings suggest that patients with CKD could have a dysregulated renal vascular response to iodinated contrast media, and the primary cause of CIN may not be renal artery vasoconstriction.

The present study has several limitations. The findings are from a single centre and involve a relatively small number of patients. Therefore, the present data should be considered as exploratory and hypothesis-generating. Second, acute kidney injury should be defined by an absolute change in serum

creatinine of 0.3 mg/dL over a 24–48 h time period.³⁰ In this study, therefore, CIN was defined as an absolute increase of serum creatinine of 0.3 mg/dL at 24 h after baseline. Because no patients developed acute kidney injury, no comment could be made on RI changes in the early phase of CIN development. Third, although renal blood flow changes induced by a bolus injection of contrast media are dynamic, with brief transient vasodilatations, followed by protracted vasoconstriction,⁴ the present data were based on samples collected at one time point, within 1 h of the initiation of repeated small-volume injections of radiocontrast media. It is therefore possible that the reaction to iodinated contrast media in patients with CKD might be slower compared with that in non-CKD patients, and that samples might need to be collected over a longer time period to determine additional differences in these patients' responses to contrast media. Fourth, because 90% and 10% of the total renal blood flow is normally distributed to the cortex and medulla, respectively, and several studies have shown that changes in renal plasma flow are not uniform and that contrast media appear to exert regional effects within the kidney,^{31–33} APV might be almost equivalent to cortical blood flow. Fifth, although it was hypothesized that APV reflects renal blood flow, renal blood flow might be influenced by vessel size, thus the relationship of renal blood flow to APV and RI could not be properly assessed since the vessel size was not considered.

METHODS

Patient population

Thirty-six patients were enrolled (32 men; mean age, 75.3 ± 7.6 years; range, 39–91 years) who underwent diagnostic coronary angiography from July 2013 to April 2014 and who consented to participate after a full explanation of the study's purpose, nature, and risks of all procedures. Patients underwent angiography for coronary artery disease ($n = 30$) and atypical chest pain ($n = 6$). There were no complications associated with insertion of the Doppler flow wire into the renal artery. Patients

diagnosed with acute or recent (within 1 month from onset) myocardial infarction (MI) during this period and those receiving haemodialysis were excluded from the study.

Patients were divided into two groups based on the presence of CKD, which was defined by an eGFR < 60 mL/min/1.73 m². Patients who met the eGFR criteria were classified into the CKD group, and special precautions were taken.^{8,9} Patients not meeting the eGFR criteria for CKD were classified into the non-CKD group. The calculations of eGFR were made using the Modification of Diet in Renal Disease study equation modified with the Japanese coefficient: $\text{eGFR (mL/min per 1.73 m}^2\text{)} = 194 \times \text{serum creatinine}^{-1.094} \times \text{age}^{-0.287} \times 0.739$ (for women).³⁴

Study protocol

All patients in our study were scheduled for elective angiography without coronary intervention, and data on patients' sex, history of diabetes mellitus (DM), hypertension, and MI were collected from medical records. Blood samples were obtained from the antecubital vein in the fasting state before the procedure. DM was defined as a fasting plasma glucose concentration ≥ 126 mg/dL, self-reported clinician-diagnosed diabetes, or a haemoglobin A1c level $\geq 6.5\%$.³⁵ Hypertension was defined as systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, or existing administration of antihypertensive drugs.³⁶ Echocardiography was performed to evaluate left ventricular ejection fraction.

Isotonic saline (0.9%) was administered intravenously from 12 h before the procedure to 12 h after contrast exposure at a rate of 1 mL/kg per hour. After the introduction of a 5-French (Fr) sheath into the radial artery, a 5-Fr right coronary catheter was positioned at the ostia of both renal arteries. A 0.014-inch Doppler flow wire (FloWireTM; Volcano, Mountain View, CA, USA) was introduced into the renal artery under fluoroscopy for injection of diluted iodinated contrast media. After baseline flow velocity was measured, renal angiography was performed to exclude renal artery stenosis using a small quantity of iodinated contrast media (vessel diameter, 4.34 ± 0.88 mm; % diameter

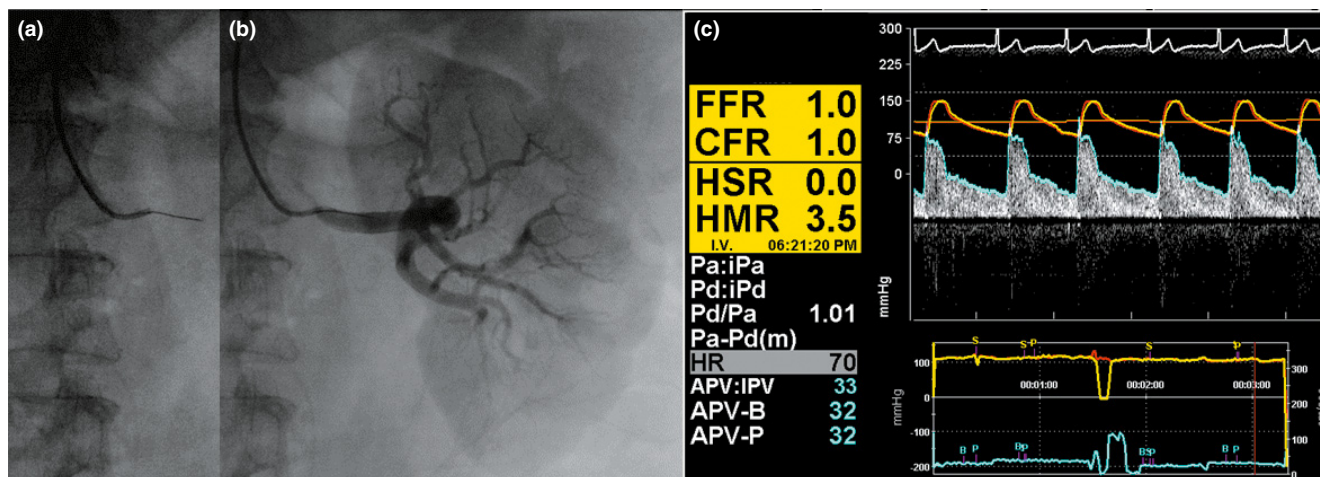


Fig. 2 Example of renal angiography and measurements by Doppler flow wire. (a) A 5-French right coronary catheter is positioned at the ostium of the left renal artery, and the Doppler flow wire is introduced into the left renal artery. (b) Renal angiography. (c) The Doppler flow wire measures average peak velocity and renal artery resistance index.

stenosis, $4.30 \pm 2.39\%$), and no patients were excluded because of the presence of renal artery stenosis. Subsequently, routine coronary angiography was performed using standard techniques. After angiography, both renal arteries were measured again using the same techniques. The RI was calculated as the ratio of mean blood pressure and APV (Fig. 2). A low osmolar contrast media, iopamidol (Iopamiron; 350 mg iodine/mL), was used, with the amount of contrast media used for each patient recorded after the procedure.

Serum cystatin C and creatinine levels were assessed from samples taken just before and 24 h after administration of contrast media. Serum cystatin C level was measured by latex agglutination immunoassay. Serum creatinine level was determined by enzymatic assay.

The medical ethics committee at Nippon Medical School Chiba Hokusoh Hospital approved this study protocol (No. 368), and written informed consent was obtained from all patients before the catheterisation procedures. This study conformed to the Declaration of Helsinki.

Statistical analysis

All statistical analyses were performed using SPSS software (version 11.0.1; SPSS, Chicago, IL, USA). Categorical variables are presented as frequencies, and these were compared using Fisher's exact test. Continuous quantitative data are presented as mean \pm standard deviation and were evaluated with an unpaired Student's *t*-test. The changes in measured Doppler flow wire and renal markers in each group before and after administration of contrast media were tested with a paired Student's *t*-test. The correlation between two parameters was evaluated by linear regression analysis. All differences were evaluated at the 95% level of significance ($P < 0.05$).

ACKNOWLEDGEMENTS

OK received research grants from the Ishibashi Yukiko Foundation, which had no role in the design or conduct of this research. The authors also thank Inter-Biotech (<http://www.inter-biotech.com>) for the English language editing of this paper.

DISCLOSURE

The authors declare no competing interests.

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