Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.3232-19
Intern Med 59: 909-916, 2020
http://internmed.jp

【 ORIGINAL ARTICLE 】

A Clinical Association between an Increasing Renal Resistive Index and the Atherosclerotic Burden in Patients with a Preserved Renal Function

Ippei Watanabe[1], Yodo Shintani[2], Shigenori Terada[3], Takahiro Fujii[1], Shunsuke Kiuchi[1], Rine Nakanishi[1], Tomoyuki Katayanagi[2], Muneyasu Kawasaki[2], Keiichi Tokuhiro[2], Hidefumi Ohsawa[2] and Takanori Ikeda[1]

Abstract:

Objective A positive correlation is observed between the progression of renal impairment and the increasing risk of cardiovascular disease. Our aim was to examine the relationship between the renal resistive index (RRI) assessed by duplex sonography and the extent of atherosclerosis in patients without renal impairment undergoing vascular imaging studies.

Methods The RRI was evaluated pre-procedurally among 106 outpatients with an estimated glomerular filtration rate (eGFR) ≥60 mL/min/1.73 m^2 undergoing clinically-driven coronary computed tomography angiography (CCTA). In those subjects, a carotid artery ultrasound scan was also performed to evaluate carotid artery disease. We investigated the association between the RRI and the atherosclerotic extent, defined by the presence of coronary artery calcium (CAC)>0 and carotid intima-media thickness (cIMT)≥1.0 mm.

Results Multi-site atherosclerosis (CAC>0 and cIMT≥1.0 mm) was found in 31 patients. The RRI was significantly increased with an increasing number of atherosclerotic vessels (absence of atherosclerosis: 0.65±0.04 vs. single-site atherosclerosis: 0.67±0.06 vs. multi-site atherosclerosis: 0.71±0.05, p<0.001). A multivariate logistic regression analysis showed that RRI>0.70 [odds ratio (OR): 4.05, 95% confidence interval (CI), 1.37-12.0, p=0.01], cardio ankle vascular index (CAVI)≥9.0 (OR: 8.18, 95% CI: 2.47-27.1, p<0.01), diabetes (OR: 4.34, 95% CI: 1.37-13.7, p=0.01) and an eGFR>90 mL/min/1.73 m^2 (OR: 5.89, 95% CI: 1.39-25.1, p=0.01) were associated with multi-site atherosclerosis.

Conclusion The RRI, a sub-clinical renal parameter is an atherosclerotic marker in patients without renal impairment.

Key words: renal resistive index, atherosclerosis, vascular disease, sub-clinical renal dysfunction

(Intern Med 59: 909-916, 2020)
(DOI: 10.2169/internalmedicine.3232-19)

Introduction

The progression of kidney disease is a major risk factor for the development of atherosclerosis, as it leads to an increased incidence of cardiovascular events (1).

Of importance, atherosclerotic changes in the renovascular system gradually develop before overt renal impairment occurs, along with other vascular risk factors, such as hypertension, hyperlipidemia, and diabetes (2, 3). Therefore, it is important to detect sub-clinical renal impairment in patients, particularly those with other cardiovascular risk factors (4, 5). The renal resistive index (RRI) is a renal parameter, measured by Doppler ultrasound (6). It characterizes the percentage reduction in the end diastolic blood flow in renal vessels in relation to their maximal systolic blood

[1]Department of Cardiovascular Medicine, Toho University School of Medicine, Japan, [2]Cardiovascular Centre of Misato Central General Hospital, Japan and [3]Department of Cardiology, Shin-Oyama Shimin Hospital, Japan
Received for publication April 22, 2019; Accepted for publication September 26, 2019
Correspondence to Dr. Ippei Watanabe, ltwanabeappleforeleven@gmail.com

flow (7) and has been found to be useful for predicting renal mortality in a variety of kidney diseases (8-10). However, studies have reported that an increasing RRI is correlated with the development of atherosclerotic renovascular disease (11, 12). As renal impairment progresses, intrarenal resistance and compliance increase, owing to anatomical and functional alterations of the micro-circulation in the kidney. The RRI can reflect reductions in the number and areas of the post-glomerular capillaries, which lead to increased scarring of the kidney (7, 13). Of importance, given that the development of atherosclerosis is a systemic vascular problem, the RRI might be related to intrarenal and extrarenal atherosclerosis with the progression of renal impairment (14, 15). Therefore, recent studies have addressed the clinical association between the RRI and atherosclerotic vascular disease in patients with renal impairment (16, 17). In addition, there is a positive correlation between the increase in the RRI with the renal impairment and the increase in the incidence of cardiovascular events (18, 19). However, the clinical significance of the RRI for the atherosclerotic burden before overt renal impairment remains unclear.

In the present study, we assessed whether or not an increased RRI is associated with the atherosclerotic extent in patients without renal impairment.

Materials and Methods

Study population

A total of 106 outpatients without renal impairment [estimated glomerular filtration rate (eGFR)≥60 mL/min/1.73 m^2] undergoing clinically driven coronary computed tomography angiography (CCTA) were enrolled in this cross-sectional study during 2016 and 2017. Before the administration of contrast agent for CCTA, the assessment of the renal function including the serum creatinine levels, eGFR and RRI, was performed. Subsequently, following cardiovascular examinations, carotid ultrasound, echocardiography, ankle brachial index and cardio ankle vascular index (CAVI) evaluations were performed within three months of enrollment. Information on the patients' medical history, prescribed drugs and current smoking status was also collected. The eGFR was calculated using the following equation: eGFR (mL/min/1.73 m^2)=194×serum creatinine (mg/dL)-1.094×age (years)-0.287×0.739 (for women) (20). Patients with severe valvular disease and an impaired renal function (eGFR <60 mL/min/1.73 m^2) were excluded from the study. Hypertension was defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg or if the patients were being treated by antihypertensive drugs. Diabetes was defined according to the guidelines of the American Diabetes Association as a fasting glucose concentration ≥126 mg/dL, HbA1c level ≥6.5% (21) or the use of antihyperglycemic drugs. Dyslipidemia was defined as high density lipoprotein-cholesterol (HDL-C) <40 mg/dL and/or low density lipoprotein-cholesterol (LDL-C) ≥140 mg/dL and/or triglyceride (TG) ≥150 mg/dL or the use of lipid-lowering medications. The Framingham risk score (FrSc) was calculated in each patient (22).

Ethical statements

This study was conducted according to the guidelines of the Declaration of Helsinki and was approved by the relevant ethics committee at Misato Chuo Central General Hospital. Informed consent was obtained from all patients.

The RRI measurement

Renal ultrasonographic examinations were performed using duplex Doppler sonography (Aplio 400; Toshiba, Tokyo, Japan) by two well-trained technologists who specialize in sonography and were blind with respect to the clinical data of the participants. In brief, each patient was placed in a supine position, and their intraparenchymal renal vessels were visualized by color and spectral Doppler sonography (Fig. 1). The greatest longitudinal kidney length was determined by a B-mode measurement. For the RRI measurements, blood flow velocities were measured from the segmental arteries located in the upper, middle and lower third of the kidney by pulsed-wave Doppler sonography. The Doppler angle was <60°. The peak systolic (centimeters per second) and end-diastolic (centimeters per second) velocities of each vessel were measured to calculate the RRI using the following formula: RRI=(peak systolic velocity - end-diastolic velocity)/peak systolic velocity. Three values from three sets of measurements were averaged to obtain the mean RRI for each vessel. The mean RRI value for the right and left kidneys was used for the analysis. The RRI was dichotomized at >0.70 or ≤0.70, which is an accepted cut-off value (23).

The coronary artery disease evaluation by CCTA

Patients underwent CCTA with a 64-slice MDCT scanner (LightSpeed VCT; GE Medical Systems, Waukesha, USA) with 64×0.625-mm section collimation, a 350- or 400-ms rotation time, a 120-kV tube voltage, and a pitch from 0.16 to 0.18, depending on the patient's heart rate. The estimated mean radiation dose was 15-18 mSv. The anatomical landmarks for the contrast-enhanced study were initially determined by a non-contrast scan. Thereafter, to calculate the exact arrival time of the contrast agent in the coronary arteries, test bolus tracking with 10 mL of a non-ionic contrast agent was immediately applied to calculate with a region of interest in the proximal part of the ascending aorta. Finally, a contrast-enhanced scan with retrospective electrocardiogram gating was performed after the administration of the contrast medium (220 mg I/kg body weight/10 s) during a single breath hold. We utilized an image analysis software program (CardIQ; GE Healthcare, Chicago, USA) for the image reconstruction on a dedicated computer workstation (Advantage Workstation Ver. 4.2; GE Healthcare). A standard kernel was used as the reconstruction filter. Depending on the patient's heart rate, either a half-scan or multi-

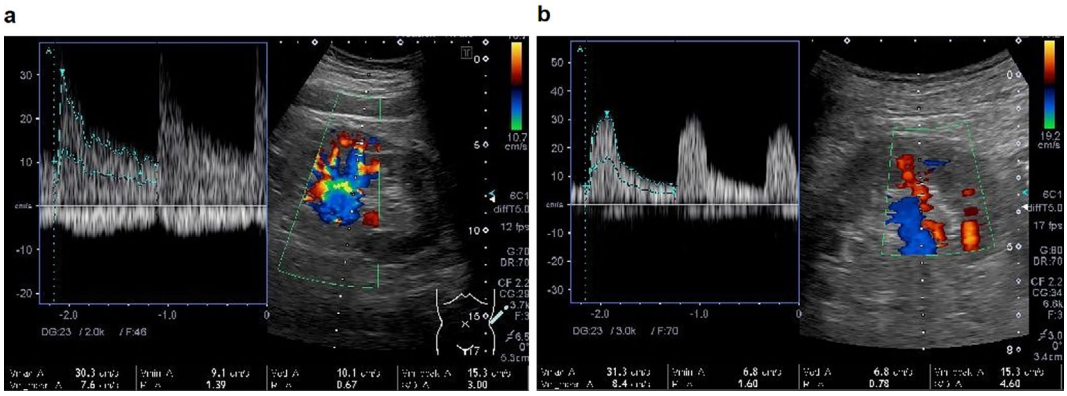

Figure 1. **Color Doppler imaging of the RRI. RRI: renal resistive index**

segment reconstruction algorithm was selected, or the optimal cardiac phase with the fewest motion artifacts was chosen. Beta-blockers and sublingual nitrates were used if necessary. Coronary artery calcium (CAC) was defined as a focus of at least 4 contiguous pixels with a CT density of > 130 Hounsfield units and quantified using the Agatston method (24). All CCTA images were evaluated by a radiologist and a cardiologist. Atherosclerotic lesions were classified visually as obstructive (≥50% luminal narrowing) or non-obstructive (<50% luminal narrowing). Coronary artery disease was defined as any previous percutaneous or surgical coronary revascularization or the presence of any coronary stenosis of at least 50%.

The measurement of the carotid intima-media thickness (cIMT)

Longitudinal and transverse projections of carotid arteries were obtained by high-resolution real-time ultrasound using duplex ultrasonography with a high-resolution 7.5-MHz transducer (Aplio 400; Toshiba). The patients were each placed in a supine position, and their necks were slightly hyperextended so that their bilateral carotid arteries could be optimally visualized. From measurements obtained from multiple images, plaque formation was identified as a wall thickness of ≥1.0 mm (25). The cIMT was measured as the distance from the leading edge of the first echogenic line to the leading edge of the second echogenic line. Three measurements of the carotid artery were made to determine the cIMT. One measurement was made at the thickest point of the carotid artery wall as defined by a visual examination, and the other two were made at points 1-cm proximal and 1-cm distal to the thickest site. The average of six measurements was taken as the mean cIMT value for each patient.

The definition of atherosclerotic vessels and patient groups

The presence of atherosclerotic vessels was defined when patients had a CAC>0 in the coronary artery and/or a cIMT ≥1.0 mm in the carotid artery. Patients were divided into three groups according to the number of atherosclerotic vessels: absence of atherosclerosis, single-site atherosclerosis and multi-site atherosclerosis.

Statistical analyses

Data were analyzed using the Statistical Package for R (R Development Core Team, Vienna, Austria) (26). Data were expressed as the mean±standard deviation or as the median and interquartile range. The Kolmogorov-Smirnov test was applied to test for normal distribution. Continuous variables were compared using Student's *t*-test. Pearson's chi-squared test or Fisher's exact test was used, as appropriate, for categorical data expressed as percentages. A multivariate logistic regression analysis was used to identify the independent contributions of several factors for the presence of multi-site atherosclerosis after adjusting for confounding factors that were considered statistically significant ($p<0.05$) in the univariate analysis. The discriminative abilities of the FrSc, RRI and other cardiovascular risk factors were evaluated by a receiver operating characteristics (ROC) curve analysis for the presence of multi-site atherosclerosis. In addition, the incremental value of the RRI to the FrSc and other risk factors for assessing the atherosclerotic extent was analyzed by the net reclassification improvement (NRI) and integrated discrimination improvement (IDI).

Results

Baseline characteristics

One hundred and six outpatients without renal impairment were enrolled in this study. Single-site atherosclerosis was found in 51 patients and multi-site atherosclerosis in 31. Compared with patients lacking atherosclerosis and with single site-atherosclerosis, patients with multi-site atherosclerosis tended to be older and more diabetic and had higher eGFR values and lower serum creatinine levels (Table 1). There was no marked relationship between the presence of prescribed drugs and the number of atherosclerotic vessels. More patients had a history of percutaneous coronary intervention in the multi-site atherosclerosis group than in the other groups. The CAVI and E/e' values were increased according to the number of atherosclerotic vessels.

Table 1. Baseline Characteristics.

	Absence of atherosclerosis: n=24	Single-site atherosclerosis: n=51	Multi-site atherosclerosis: n=31	p value
Age, years	60.4±10.6	67.4±9.8	67.7±7.2	<0.01
Male, n (%)	15 (62.5)	44 (86.2)	26 (83.8)	0.06
Dyslipidemia, n (%)	15 (62.5)	33 (64.7)	21 (67.7)	0.93
Diabetes, n (%)	2 (8.3)	11 (21.5)	16 (51.6)	<0.001
Hypertension, n (%)	16 (66.6)	41 (80.3)	26 (83.8)	0.26
Hyperuricemia, n (%)	7 (29.1)	10 (19.6)	10 (32.2)	0.40
Current smoking, n (%)	9 (37.5)	27 (52.9)	16 (51.6)	0.43
Family history of CVD, n (%)	5 (20.8)	9 (17.6)	7 (22.5)	0.81
Prior PCI, n (%)	1 (4.1)	18 (35.2)	15 (48.3)	<0.001
Prior stroke, n (%)	1 (4.1)	2 (3.9)	1 (3.2)	1.0
Antidiabetics, n (%)	1 (4.1)	10 (19.6)	14 (45.1)	<0.01
Antihypertensives, n (%)	16 (66.6)	42 (82.3)	23 (74.1)	0.28
RAAS inhibitors, n (%)	9 (37.5)	24 (47.0)	15 (48.3)	0.71
Calcium channel blockers, n (%)	6 (25.0)	13 (25.4)	11 (32.2)	0.61
Beta blockers, n (%)	6 (25.0)	18 (35.2)	10 (32.2)	0.71
Diuretics, n (%)	4 (16.6)	10 (19.6)	5 (16.1)	0.75
Lipid-lowering therapy, n (%)	15 (62.5)	30 (58.8)	18 (58.0)	0.93
BMI, kg/m^2	26.5±4.9	25.0±4.2	24.3±3.4	0.15
Heart rate, bpm	73.0±9.9	80.6±14.5	73.9±13.3	0.02
Systolic blood pressure, mmHg	131.5±13.9	134.6±19.4	137.3±21.6	0.53
Diastolic blood pressure, mmHg	79.4±9.5	80.0±9.8	79.3±13.0	0.95
Creatinine, mg/dL	0.73±0.13	0.77±0.11	0.70±0.12	0.01
eGFR, mL/min/1.73 m^2	77.7±11.3	74.9±10.1	83.0±12.1	<0.01
Total cholesterol, mg/dL	198.6±37.1	183.9±31.6	186.0±47.2	0.28
Triglyceride, mg/dL	130.6±85.5	135.4±58.3	118.4±55.2	0.51
LDL, mg/dL	114.0±29.9	101.3±22.0	107.9±60.2	0.39
HDL, mg/dL	62.1±19.3	60.6±15.5	57.4±18.3	0.57
Uric acid, mg/dL	5.6±2.2	5.6±1.0	5.3±1.3	0.62
CAVI	8.0±1.6	8.9±1.7	9.5±1.4	<0.01
LVEF, %	66.6±6.2	65.8±8.3	67.2±7.0	0.71
E/e'	10.1±2.8	11.3±3.1	13.5±3.8	<0.001
FrSc	12.2±3.5	13.3±2.4	13.6±3.1	0.18
RRI	0.65±0.04	0.67±0.06	0.71±0.05	<0.001

CVD: cardiovascular disease, PCI: percutaneous coronary intervention, RAAS: renin angiotensin aldosterone system, BMI: body mass index, eGFR: estimated glomerular rate, LDL: low-density lipoprotein, HDL: high-density lipoprotein, CAVI: cardio ankle vascular index, LVEF: left ventricular ejection fraction, FrSc: Framingham risk score, RRI: renal resistive index

Table 2. Independent Predictors of RRI.

	Beta coefficient	p value
Age	0.002	<0.001
Dyslipidemia	-0.02	<0.01
Diabetes	0.03	<0.01
E/e'	0.003	0.01
LVMI	0.001	0.16
CAVI	0.0002	0.90
Systolic blood pressure	0.0005	0.11
Diastolic blood pressure	-0.0007	0.12

CAVI: cardio ankle vascular index, RRI: renal resistive index, LVMI: left ventricular mass index

Factors associated with an increased RRI

After adjusting for the E/e', CAVI, systolic blood pressure and diastolic blood pressure, a multivariate linear regression analysis found that the age, diabetes and dyslipidemia were associated with the RRI (Table 2).

An increased RRI is associated with the atherosclerotic extent in patients without renal impairment

The RRI was greater in patients with either cIMT≥1.0 mm or CAC>0 than in those with other values (Fig. 2a, b). Furthermore, the RRI increased according to the number of atherosclerotic vessels (Fig. 2c) and was numerically greater in patients with coronary artery disease assessed by CCTA than those without (Fig. 2d). After adjusting for an age ≥60 years old and E/e'>13 as well as a history of percutaneous coronary intervention (PCI), a multivariate logistic regres-

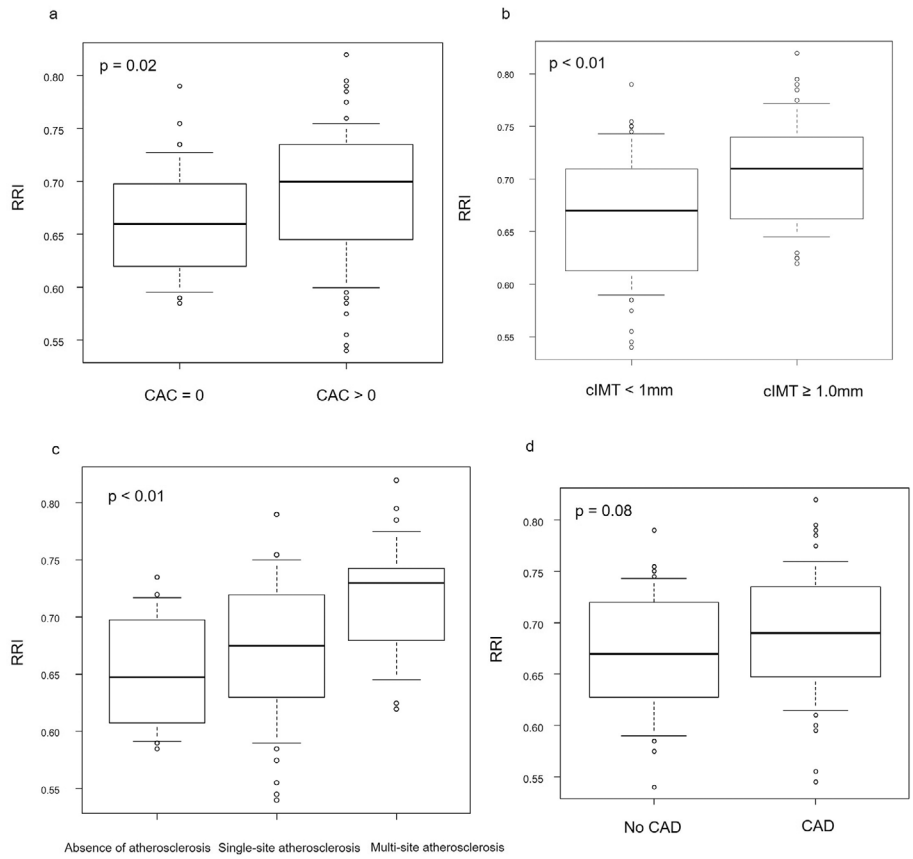

Figure 2. **a: Difference in the RRI between CAC=0 and CAC>0. b: Difference in the RRI between cIMT<0 and cIMT≥1.0 mm. c: Difference in the RRI according to the number of atherosclerotic vessels. RRI: renal resistive index, CAC: coronary artery calcium, cIMT: carotid intima-media thickness**

Table 3. **Multivariate Logistic Regression Analysis Relating RRI to Multi-site Atherosclerosis.**

	Multivariate analysis	
	OR, 95% CI	p value
CAVI≥9.0	8.18, 2.47-27.1	<0.01
RRI>0.70	4.05, 1.37-12.0	0.01
Diabetes	4.34, 1.37-13.7	0.01
eGFR>90 mL/min/1.73 m^2	5.89, 1.39-25.1	0.01
Age≥60	3.70, 0.38-35.3	0.25
E/e'>13	0.41, 0.11-1.54	0.19
Prior PCI	1.46, 0.43-4.88	0.53

OR: odds ratio, CAVI: cardio ankle vascular index, RRI: renal resistive index, eGFR: estimated glomerular rate, PCI: percutaneous coronary intervention, 95% CI: 95% confidence interval

sion analysis showed that CAVI≥9.0, diabetes, an eGFR>90 mL/min/1.73 m^2 and an RRI>0.70 were associated with multi-site atherosclerosis. (Table 3). In Table 4, we assessed the incremental value of the RRI added to common atherosclerotic risks related to multi-site atherosclerosis. The inclusion of the RRI successfully reclassified patients from the model of FrSc plus diabetes in the analysis by NRI and IDI. In the ROC curve analysis, there was a tendency towards statistical significance for an increase in AUC by the RRI added to FrSc+diabetes.

Discussion

In the present study, we investigated the clinical association between an increased RRI and the extent of atherosclerotic burden in patients without renal impairment. A stepwise increase in the RRI was observed according to the number of atherosclerotic vessels. Of note, a significant relationship between an RRI>0.70 and the presence of multi-site atherosclerosis (CAC>0 and cIMT≥1.0 mm) was found in a multivariate logistic regression analysis after adjusting for other cardiovascular risks.

With the development of systemic atherosclerosis, an increase in arterial stiffness predisposes the renal circulation to a greater hemodynamic load, leading to greater renal vascular resistance. Therefore, studies have explored the relationship between an increased RRI and the progression of renal impairment and development of atherosclerosis, leading to organ damage (7, 14). Of note, the evaluation of the RRI before overt renal impairment may give us additional information on cardio-renal syndrome. Our present data were consistent with those of previous reports describing the relationship between an increased RRI and extra-renal arterial stiffness and target organ damage. Both the CAVI and RRI showed stepwise increases according to the number of athe-

Table 4. Incremental Value of RRI Relating to Multi-site Atherosclerosis in Addition to Cardiovascular Risks.

Model	NRI	p value	IDI	p value	AUC	p value
FrSc+diabetes	-	-	-	-	0.63	-
(FrSc+diabetes)+RRI	0.47 [0.07-0.88]	0.02	0.08 [0.02-0.14]	<0.01	0.77	0.05

	New risk category					
	Low risk	Intermediate risk	High risk	Very high risk	Total	% reclassified
Patients with the multi-site atherosclerosis						
Old risk category						
Low risk	1	0	0	0	1	0
Intermediate risk	4	2	3	0	9	78.0
High risk	0	1	2	3	6	67.0
Very high risk	0	0	3	12	15	20.0
Patients without the multi-site atherosclerosis						
Old risk category						
Low risk	12	1	1	0	14	0
Intermediate risk	17	3	6	1	27	89.0
High risk	5	3	12	1	21	43.0
Very high risk	0	0	8	5	13	62.0

AUC: area under the curve, FrSc: Framingham risk score IDI: integrated discrimination improvement, NRI: net reclassification improvement, RRI: renal resistive index

rosclerotic vessels, and we observed a correlation between these two, suggesting that an increased RRI is related to systemic arterial stiffness [r=0.25, 95% confidence interval (CI) 0.07-0.42, p<0.01]. Although we found no association between the RRI and left ventricular ejection fraction, we found that the RRI correlated with the left ventricular mass index (LVMI) and E/e', a combination parameter of the early filling velocity and relaxation velocity to define the diastolic function as well as (LVMI: r=0.28, 95% CI 0.10-0.45, p<0.01, E/e': r=0.32, 95% CI 0.13-0.48, p<0.01). This is similar to the results obtained by Komuro, showing that an increased RRI was associated with left ventricular hypertrophy with an impaired diastolic function in patients with cardiovascular disease (19). In addition, according to the data from Ennezat et al., the RRI was increased in patients with diastolic dysfunction, with a subsequent increase in cardiovascular events (27). Therefore, the RRI may reflect the low cardiac output due to diastolic dysfunction among patients with increased arterial stiffness.

Among patients without overt renal impairment, the RRI might be affected by comorbid diseases, such as hypertension, diabetes and dyslipidemia with indelible renal impairment. Of note, our data were consistent with those of previous reports demonstrating the positive relationship between the presence of diabetes and an increased RRI (28, 29). Accordingly, in patients with diabetes without overt renal impairment, an increased RRI was associated with sub-clinical renal dysfunction defined by the degree of proteinuria (30). In patients with diabetes, an increased RRI was associated with the progression of both microvascular and macrovascular renal impairment and thought to be an important determinant of renal mortality (13, 31). Interestingly, renal hyperfiltration - defined as an eGFR>90 mL/min/1.73 m^2 - was associated with multi-site atherosclerosis in our study. Hyperfiltration caused by diabetic nephropathy is already known to be associated with endothelial dysfunction with a subsequent risk of cardiovascular events (32). In the present study, diabetic patients showed hyperfiltration more frequently than those without diabetes (50.0% vs. 23.3%, p=0.03). However, there was no marked relationship in the RRI between patients with and without hyperfiltration in our study (0.67±0.06 vs. 0.68±0.05, p=0.52). This is consistent with the data of Mancini et al. showing that diabetes is associated with the renal volume, renal area index and RRI, although no correlation has been noted among those parameters (30).

To further analyze the significance of an increased RRI for the extent of atherosclerotic burden, we conducted a re-categorization analysis in addition to the risk estimation models for the presence of multi-site atherosclerosis. We demonstrated that patients were successfully recategorized by adding information on the RRI from the model of FrSc plus diabetes assessed by the NRI and IDI analyses. These results suggested that assessing the RRI gives additive value to the evaluation of the atherosclerotic extent in patients at an increased atherosclerotic risk, particularly those without renal impairment.

Finally, we investigated the association between the RRI and coronary artery disease diagnosed by CCTA. While a statistical tendency was noted, an increased RRI was not

found to be associated with the presence of coronary artery disease. Similar to findings concerning the relationship with the CAVI, the RRI may be closely to arterial stiffness as well as the extent of atherosclerotic burden but not to focal obstructive stenosis, as we were unable to determine any marked relationship between the RRI and the degree of coronary stenosis. Indeed, it seemed difficult to detect the relationship between the RRI and local coronary stenosis caused by increased shear stress, plaque rapture and other unknown factors. A further investigation involving a larger sample size will be required to clarify this issue.

Our findings demonstrated that the RRI is a marker of atherosclerotic extent before overt renal dysfunction. However, a number of different pathophysiological mechanisms are involved in the development of cardiovascular disease in patients with renal dysfunction. Accordingly, a reduced eGFR is associated with the activation of the renin angiotensin aldosterone system, enhanced oxidative stress, inflammatory response and the accumulation of uremic toxins (33, 34). Therefore, assessing the RRI may play an important role in detecting early-stage cardio-renal syndrome by reflecting systemic atherosclerotic vascular damage. In addition, according to data from the REACH registry, diseased vascular beds increases and cardiac death frequently occurs with the progression of renal dysfunction (35). Therefore, the sub-clinical renal function as assessed by the RRI may help prevent future cardiovascular events.

Several limitations associated with the present study warrant mention. First, it was performed at a single center. Second, the assessment of the renal function was partially limited by the lack of information on proteinuria in patients. Third, since this cross-sectional study was open to all-comers except for patients with overt renal dysfunction, we did not exclude patients with known coronary artery disease. Therefore, the pretest probability for systemic atherosclerotic disease might be higher among patients with a history of coronary revascularization. Fourth, the statistical power was limited because of the relatively small sample size and the study design. In addition, we did not have access to full patient histories regarding diabetic characteristics, including the age of onset and duration, which might have contributed to the relationship between the RRI and diabetes. Fifth, the impact of the RRI as a subclinical renal parameter on the atherosclerotic vasculature could not be fully clarified because the RRI was affected by other cardiovascular risk factors, including the age and presence of hypertension and diabetes. A further investigation is required to clarify the relationship between the renal function and subsequent cardiovascular events in this study population.

Conclusion

The RRI is a clinical marker associated with coronary and carotid atherosclerosis in patients without renal impairment.

The authors state that they have no Conflict of Interest (COI).

References

1. Bock JS, Gottlieb SS. Cardiorenal syndrome: new perspectives. Circulation **121**: 2592-2600, 2010.
2. Zhang J, Wang Y, Li L, et al. Diabetic retinopathy may predict the renal outcomes of patients with diabetic nephropathy. Renal Fail **40**: 243-251, 2018.
3. Harper CR, Jacobson TA. Managing dyslipidemia in chronic kidney disease. J Am Coll Cardiol **51**: 2375-2384, 2008.
4. Leoncini G, Viazzi F, Parodi D, et al. Mild renal dysfunction and subclinical cardiovascular damage in primary hypertension. Hypertension **42**: 14-18, 2003.
5. Ishii R, Fujita S, Kizawa S, et al. Association between absolute blood eosinophil count and CKD stages among cardiac patients. Heart and vessels **31**: 198-205, 2016.
6. Iwakura Y, Ito S, Morimoto R, et al. Renal resistive index predicts postoperative blood pressure outcome in primary aldosteronism. Hypertension **67**: 654-660, 2016.
7. Calabia J, Torguet P, Garcia I, et al. The relationship between renal resistive index, arterial stiffness, and atherosclerotic burden: the link between macrocirculation and microcirculation. J Clin Hypertens (Greenwich) **16**: 186-191, 2014.
8. Aboyans V, Tanguy B, Desormais I, et al. Prevalence of renal artery disease and its prognostic significance in patients undergoing coronary bypass grafting. Am J Cardiol **114**: 1029-1034, 2014.
9. Bige N, Levy PP, Callard P, et al. Renal arterial resistive index is associated with severe histological changes and poor renal outcome during chronic kidney disease. BMC Nephrol **13**: 139, 2012.
10. Wybraniec MT, Chudek J, Bozentowicz-Wikarek M, Mizia-Stec K. Prediction of contrast-induced acute kidney injury by early post-procedural analysis of urinary biomarkers and intra-renal Doppler flow indices in patients undergoing coronary angiography. J Interv Cardiol **30**: 465-472, 2017.
11. Bruno RM, Daghini E, Versari D, et al. Predictive role of renal resistive index for clinical outcome after revascularization in hypertensive patients with atherosclerotic renal artery stenosis: a monocentric observational study. Cardiovasc Ultrasound **12**: 9, 2014.
12. Crutchley TA, Pearce JD, Craven TE, Stafford JM, Edwards MS, Hansen KJ. Clinical utility of the resistive index in atherosclerotic renovascular disease. J Vasc Surg **49**: 148-155, 155.e1-155.e3, discussion 155, 2009.
13. Radermacher J, Ellis S, Haller H. Renal resistance index and progression of renal disease. Hypertension **39**: 699-703, 2002.
14. Doi Y, Iwashima Y, Yoshihara F, et al. Association of renal resistive index with target organ damage in essential hypertension. Am J Hypertens **25**: 1292-1298, 2012.
15. Raff U, Schmidt BM, Schwab J, et al. Renal resistive index in addition to low-grade albuminuria complements screening for target organ damage in therapy-resistant hypertension. J Hypertens **28**: 608-614, 2010.
16. Pearce JD, Craven TE, Edwards MS, et al. Associations between renal duplex parameters and adverse cardiovascular events in the elderly: a prospective cohort study. Am J Kidney Dis **55**: 281-290, 2010.
17. Delsart P, Meurice J, Midulla M, Bauters C, Haulon S, Mounier-Vehier C. Prognostic significance of the renal resistive index after renal artery revascularization in the context of flash pulmonary edema. J Endovasc Therapy **22**: 801-805, 2015.
18. Viazzi F, Leoncini G, Derchi LE, Pontremoli R. Ultrasound Doppler renal resistive index: a useful tool for the management of the hypertensive patient. J Hyperten **32**: 149-153, 2014.
19. Komuro K, Yokoyama N, Shibuya M, et al. Associations between increased renal resistive index and cardiovascular events. J Med Ultrason (2001) **43**: 263-270, 2016.
20. Matsuo S, Imai E, Horio M, et al. Revised equations for estimated GFR from serum creatinine in Japan. Am J Kidney Dis **53**: 982-

992, 2009.
21. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care **33** (Suppl): S62-S69, 2010.
22. Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. Circulation **97**: 1837-1847, 1998.
23. Tublin ME, Bude RO, Platt JF. Review. The resistive index in renal Doppler sonography: where do we stand? AJR Am J Roentgenol **180**: 885-892, 2003.
24. Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte M Jr, Detrano R. Quantification of coronary artery calcium using ultrafast computed tomography. J Am Coll Cardiol **15**: 827-832, 1990.
25. Jung JM, Young Kwon D, Han C, Park MH. Metabolic syndrome and early carotid atherosclerosis in the elderly. J Atheroscler Thromb **21**: 435-444, 2014.
26. Kanda Y. Investigation of the freely available easy-to-use software 'EZR' for medical statistics. Bone Marrow Transplant **48**: 452-458, 2013.
27. Ennezat PV, Marechaux S, Six-Carpentier M, et al. Renal resistance index and its prognostic significance in patients with heart failure with preserved ejection fraction. Nephrol Dial Transplant **26**: 3908-3913, 2011.
28. Bruno RM, Daghini E, Landini L, et al. Dynamic evaluation of renal resistive index in normoalbuminuric patients with newly diagnosed hypertension or type 2 diabetes. Diabetologia **54**: 2430-2439, 2011.
29. Bruno RM, Salvati A, Barzacchi M, et al. Predictive value of dynamic renal resistive index (DRIN) for renal outcome in type 2 diabetes and essential hypertension: a prospective study. Cardiovasc Diabetol **14**: 63, 2015.
30. Mancini M, Masulli M, Liuzzi R, et al. Renal duplex sonographic evaluation of type 2 diabetic patients. J Ultrasound Med **32**: 1033-1040, 2013.
31. Radermacher J, Mengel M, Ellis S, et al. The renal arterial resistance index and renal allograft survival. New Engl J Med **349**: 115-124, 2003.
32. Kanbay M, Ertuglu LA, Afsar B, et al. Renal hyperfiltration defined by high estimated glomerular filtration rate: a risk factor for cardiovascular disease and mortality. Diabetes Obes Metab **21**: 2368-2383, 2019.
33. Kumar U, Wettersten N, Garimella PS. Cardiorenal Syndrome: Pathophysiology. Cardiol Clin **37**: 251-265, 2019.
34. Watanabe I, Tatebe J, Fujii T, et al. Prognostic utility of indoxyl sulfate for patients with acute coronary syndrome. J Atheroscler Thromb **26**: 64-71, 2019.
35. Dumaine RL, Montalescot G, Steg PG, Ohman EM, Eagle K, Bhatt DL. Renal function, atherothrombosis extent, and outcomes in high-risk patients. Am Heart J **158**: 141-148.e1, 2009.

The Internal Medicine is an Open Access journal distributed under the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License. To view the details of this license, please visit (https://creativecommons.org/licenses/by-nc-nd/4.0/).

Ⓒ 2020 The Japanese Society of Internal Medicine