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Link of renal microcirculatory dysfunction to increased coronary microcirculatory resistance in hypertensive patients

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Abstract

Background: *This study investigated the correlation between renal microcirculation and coronary microcirculation in hypertensive patients.*

Methods: *Participants consisted of 231 consecutive candidates who were referred to the Second Affiliated Hospital of Wenzhou Medical University from March 2014 to May 2016 for elective coronary angiography due to suspected myocardial ischemia. All participants were evaluated for the index of microvascular resistance (IMR), coronary flow reserve (CFR), and fractional flow reserve (FFR) using a pressure wire. Blood and urine samples were collected for determination of the levels of urinary microalbuminuria (mALB), β2-microglobulin (β2-MG), serum cystatin C (CysC), and uric acid (UA). All participants were categorized into two groups according to the renal microcirculatory function.*

Results: *Participants in the observation group had a higher IMR (31 ± 5 vs. 22 ± 6; $p < 0.01$) and a lower FFR (0.84 ± 0.10 vs. 0.87 ± 0.09 U; $p < 0.05$) during hyperemia than those in the control group. Linear regression tests revealed that mALB, β2-MG, CysC, and UA levels were positively correlated with IMR ($r = 0.610$, 0.553, 0.701, and 0.647, respectively, $p < 0.01$). The hs-CRP levels were positively correlated with IMR ($r = 0.419$, $p < 0.01$). Multiple regression analysis indicated that renal microcirculation was an independent predictor of IMR.*

Conclusions: *Renal microcirculatory dysfunction in hypertensive patients is characterized by higher IMR and lower FFR; in addition, it is closely correlated with an increased coronary microcirculatory resistance.* (Cardiol J 2017; 24, 6: 623–632)

Key words: renal microcirculation, coronary microcirculation, index of microvascular resistance, fractional flow reserve

Introduction

Renal and coronary microcirculation are important components of the circulatory system. Due to the special structure of the kidney, renal microcirculation is most susceptible to microvascular damage and is usually the site where the earliest microvascular injury occurs [1]. Hypertensive nephropathy, a type of hypertension-linked renal damage, is a common complication of hypertension. Long-term arterial hypertension initiates endothelial damage and microvascular injury, subsequently causing a series of pathological changes in the kidney such as glomerular alterations [2, 3]. In the clinic, due to changes in the function of the glomeruli, the levels of several biochemical indexes, including the levels of urinary microalbuminuria (mALB), β2-microglobulin (β2-MG), serum cys-

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tatin C (CysC), and uric acid (UA), are increased. Hence, these indexes reflect the functional status of renal microcirculation and are important indicators of early renal damage [4].

Currently, three major indexes are used in clinical practice to evaluate coronary microcirculatory function. Both coronary flow reserve (CFR) and fractional flow reserve (FFR) are important indicators of coronary microcirculatory function, while the index of microvascular resistance (IMR) is used to evaluate coronary microvascular function [5, 6]. Among these three indexes, both the FFR and IMR can be simultaneously measured with a guide wire carrying temperature and pressure sensors; in addition, they reflect coronary physiology more stably and more accurately when compared with CFR [7]. For instance, IMR has been shown to be independent of the severity of epicardial coronary stenosis [8–10], and its increase indicates microcirculatory dysregulation [11]. Also, IMR has diagnostic and prognostic values for a variety of cardiovascular events [12–17]. Moreover, some cardiovascular risk factors such as diabetes and smoking can affect IMR [18, 19]. Similarly, FFR has become an important assessor for coronary artery function and is superior to CFR, as demonstrated in a number of clinical trials [20, 21]. Hence, simultaneous determination of FFR and IMR has been recommended to evaluate coronary physiology and pathophysiology comprehensively [5].

Recent studies have shown that patients with a slight decrease in renal function exhibit an increased cardiovascular event rate [22–24], but exact underlying mechanisms are not completely known. A link between a decline in creatinine clearance and an impaired CFR has been shown [25]; however, the relationship between the FFR and IMR has not been reported. This study aimed to investigate the relationship between renal microcirculatory dysfunction and an increased coronary vascular resistance in hypertensive patients. The outcomes of the present study are expected to provide evidence for renal microcirculatory dysfunction to be used as an indicator for evaluation and prediction of increased coronary vascular resistance in hypertensive patients.

Methods

Participant selection

A total of 231 consecutive hypertensive patients who visited the Second Affiliated Hospital of Wenzhou Medical College for coronary angiography between March 2014 and May 2016 were selected for this study. Indications for coronary angiography included unexplained chest pain, chest symptoms, and potential myocardial ischemia as revealed by a variety of noninvasive examinations (e.g., treadmill and stress echocardiography). Patients having one or more of the following were excluded from this study: diabetes, asthma, acute and chronic myocardial infarction, collateral circulation revealed by coronary angiography, uncontrolled heart failure, severe bradycardia, stroke, connective tissue disease, autoimmune disease, cancer, acute and chronic infection, and a variety of acute and chronic kidney diseases except for hypertension-linked nephropathy. After application of inclusion and exclusion criteria, 96 patients with a degree of 50–70% stenosis as revealed by coronary angiography were included in this study, and all 96 patients underwent coronary pressure guide wire measurements. Based on renal microcirculatory function status, these patients were divided into two groups: an observation group and a control group. The observation group consisted of 52 patients with abnormal renal microcirculation, which included 30 males and 22 females, with a mean age of 56 ± 12 years old. The control group contained 44 patients with normal renal microcirculation, including 28 males and 16 females, with a mean age of 56 ± 11 years. All participants signed an informed consent form. This study was approved by the Ethics Committee at the Second Affiliated Hospital of Wenzhou Medical College. The general information of the participants in these two groups are shown in Table 1.

Measurement of biochemical parameters

The patients fasted overnight and blood was collected the following early morning. An ADYIA 2400 automatic biochemical analyzer was used to determine serum UA and CysC levels with UA enzyme method and latex-enhanced immunoturbidimetric assay, respectively. The middle portion of the first urine collected from patients in the morning under unstressed conditions was used to determine the β2-MG (IMMULITE2000 chemiluminescence immunoassay analyzer, USA) and mALB (IMMAGE800 immune turbidity analyzer) levels. No preservatives were added to the collected urine. The criteria used to determine renal microcirculatory dysfunction were as follows: (1) mALB ≥ 30 mg/L (range: 0–19 mg/L); (2) serum UA, male ≥ 380 μmol/L (range: 149–416 μmol/L), female ≥ 360 μmol/L (range: 89–357 μmol/L); (3) CysC ≥ 1.4 mg/L (range: 0.51–1.09 mg/L); (4) urinary β2-MG ≥ 0.3 mg/L (range: 0.013–0.293 mg/L).

Table 1. Comparison of demographic and basic biochemical data between the control and observation groups.

Characteristic	Observation group (n = 52)	Control group (n = 44)	P
Age [years]	56 ± 12	56 ± 11	0.897
Gender, male	30 (58%)	28 (64%)	0.553
BMI [kg/m^2]	28.69 ± 5.34	27.42 ± 4.30	0.206
Smoker	23 (44%)	19 (43%)	0.948
Diabetes mellitus	18 (36%)	17 (39%)	0.683
Dyslipidemia	19 (37%)	19 (43%)	0.507
Previous PCI	6 (12%)	5 (11%)	0.979
FBG [mmol/L]	6.01 ± 1.17	5.92 ± 0.95	0.667
Creatinine [μmol/L]	78	72	0.054
TC [mmol/L]	5.28 ± 0.64	5.28 ± 0.79	0.992
TG [mmol/L]	1.70 ± 0.53	1.65 ± 0.60	0.628
LDL-C [mmol/L]	3.11 ± 0.53	3.09 ± 0.62	0.828
HDL-C [mmol/L]	1.38 ± 0.33	1.46 ± 0.49	0.321
SBP [mm Hg]*	139 ± 12	138 ± 13	0.676
DBP [mm Hg]*	78 ± 11	75 ± 10	0.207
mALB [mg/L]	120.7 ± 29.3	50.6 ± 22.9	0
UA [μmol/L]	380 ± 111	318 ± 111	0.008
CysC [mg/L]	1.67 ± 0.75	1.19 ± 0.51	0.001
β2-MG [μg/L]	294 ± 58	184 ± 68	0
Hs-CRP	3.7 ± 1.5	2.5 ± 0.9	0
Medications:			
Metoprolol (50 mg/d)	39 (75%)	32 (73%)	0.800
Amlodipine (5 mg/d)	29 (56%)	21 (48%)	0.432
Aspilin	52 (100%)	44 (100%)	1.000
Clopidogrel	52 (100%)	44 (100%)	1.000
Atorvasatin	52 (100%)	44 (100%)	1.000
Nitrates	30 (58%)	29 (66%)	0.410
Losartan (50 mg/d)	31 (60%)	28 (64%)	0.687
LVEF [%]	55 ± 7	56 ± 8	0.516

Values are expressed as mean ± standard deviation for quantitative variables and n (%) for qualitative variables; *Data from ambulatory blood pressure; BMI — body mass index; CysC — serum cystatin C; DBP — diastolic blood pressure; FBG — fasting blood glucose; HDL-C — high-density lipoprotein cholesterol; hs-CRP — high-sensitivity C-reactive protein; LDL-C — low-density lipoprotein cholesterol; LVEF — left ventricular ejection fraction; mALB — microalbuminuria; PCI — percutaneous coronary intervention; SBP — systolic blood pressure; TC — total-cholesterol; TG — triglycerides; UA — uric acid; β2-MG — β2-microglobulin

Among these indexes, mALB was the primary indicator; while serum UA, serum CysC, and urinary β2-MG were secondary indicators. The patient was diagnosed with renal microcirculatory dysfunction when he/she had the primary indicator and one of the three secondary indicators.

Coronary angiography

Digital subtracted angiography was performed with a cardiovascular imaging system (Innova-2100, GE, USA). 6 F Judkins catheters were used for all patients and passed through the radial artery for left or right coronary angiography, whichever was selected. Preoperatively, all patients were orally administered with the same doses of clopidogrel, aspirin, and atorvastatin calcium. After sheath puncture, 200 μg of nitroglycerin and 5,000 IU of heparin were routinely injected.

Measurement of coronary artery pressure

A pressure guide wire (St. Jude Medical, Inc., USA) was used to measure the coronary artery

pressure for all patients. Coronary angiography showed critical coronary artery stenosis. Briefly, (1) the pressure sensor was opened to air, its pressure was set to zero, and zero calibration was made for the pressure guide wire *in vitro*; (2) The 6 F guiding catheter was delivered to the coronary ostia, and the pressure guide wire passed through the catheter port, followed by calibration of pressure and temperature so that the tip of the guide wire and guiding catheter had an equivalent pressure, which was comparable to the mean aortic pressure (Pa), as a reference pressure. The temperature after correction served as a reference for the change of subsequent temperatures; (3) The guide wire passed through the lesion and reached more than two-thirds of the total length of the vessel; (4) nitroglycerin (200 μg) was administered into the coronary artery; (5) 3 mL of 0.9% sodium chloride (room temperature) was rapidly injected. The pressure guide wire recorded the first temperature curve when sodium chloride passed through the coronary ostia, and the second temperature curve was recorded when sodium chloride flowed to the distal end sensor of the guide wire. The time difference between these two temperature curves was defined as the average conduction time (Tmn). A baseline mean transit time (bTmn) was obtained from three continuous operations; (6) Adenosine (140 μg/kg/min, 3–6 min) was infused through the elbow vein to generate the maximum coronary hyperemia, and then step 5 was repeated to obtain hyperemic mean transit time (hTmn); (7) At the conclusion of the procedure, the screen simultaneously displayed Pa at resting and hyperemia as well as the distal coronary artery pressure (Pd).

Calculation of the index of microvascular resistance

The IMR was calculated as described previously [20]: (1) The simplified formula IMR = PdTmn was used for mild-to-moderate coronary stenosis with a FFR > 0.80; (2) IMR = PaTmn [(Pd – Pw) / (Pa – Pw)] was used for severe coronary stenosis with FFR < 0.80, in which Pw indicates coronary artery wedge pressure, i.e. average pressure of the distal lesion when the coronary artery is completely narrowed or balloon-incarcerated.

Statistical analysis

All statistical analyses were performed with SPSS 20.0 software (USA). Measurement data underwent the normality test for normal distribution examination. Continuous variables were expressed as the mean ± standard deviation (SD), and the independent t test was used for data comparison between two groups. Numerical data were expressed as n (%), and significance was determined with the χ^2 test. Linear correlation analysis was used to evaluate the relationship between indicators of renal microcirculation and IMR. Multiple linear regression models were used to evaluate associations between exposure and outcome variables. Both non-adjusted and multivariate-adjusted models were used. It was defined that exposure variables were mALB, β2-MG, serum UA, and CysC and that the outcome parameter was IMR. Other variables with a p value < 0.1 in univariate analyses were included in stepwise multiple regression models. P < 0.05 was considered statistically significant.

Results

Comparison of demographic and basic biochemical data between the control and observation groups

First, demographic and basic biochemical data of participants between the control and observation groups were compared. There were no significant differences with regard to age, sex, blood pressure, blood lipids, or blood glucose between these two groups (p > 0.05). However, the levels of urinary mALB and β2-MG as well as serum UA, CysC, and high-sensitivity C-reactive protein (hs-CRP) were significantly higher in the observation group than in the control group (p < 0.01) (Table 1). These data suggest that patients in the observation group had renal microcirculatory dysfunction.

Comparison of coronary angiography data between the control and observation groups

Next, clinical data obtained from coronary angiography between the control and observation groups were compared. As shown in Table 2, no significant differences in the cumulative number of diseased coronary arteries, morphological characteristics, distribution of lesions, or Thrombolysis in Myocardial Infarction (TIMI) flow grade were observed between these two groups (p > 0.05).

Comparison of coronary physiological indicators after adenosine injection between the control and observation groups

Next, hyperemia was induced in patients with an adenosine injection and clinical data were compared between control and observation groups. Under hyperemic conditions, the control and observation groups showed comparable Pa values

Table 2. Comparison of procedural characteristics between the control and observation groups.

		Observation group (n = 52)	Control group (n = 44)	P
Culprit vessel number	1	21 (40%)	21 (48%)	0.470
	2	19 (37%)	14 (32%)	0.628
	3	12 (23%)	9 (20%)	0.757
Lesion location of FFR and IMR	LAD	30 (58%)	23 (52%)	0.595
	LCX	14 (27%)	12 (27%)	0.969
	RCA	8 (15%)	9 (20%)	0.517
TIMI flow grade	0	0	0	1
	1	0	0	1
	2	4 (8%)	2 (5%)	0.526
	3	48 (92%)	42 (95%)	0.526
Total number of lesions		71	62	
Lesion characteristics	A+B1	30 (42%)	29 (47%)	0.601
	B2+C	41 (58%)	33 (53%)	0.601
Lesion distribution	LMCA	5 (7%)	4 (6%)	0.892
	LAD	34 (48%)	28 (45%)	0.753
	Circumflex	18 (25%)	15 (24%)	0.877
SYNTAX Score		29	24	0.635

FFR — fractional flow reserve; IMR — index of microvascular resistance; LAD — left anterior descending artery; LMCA — left main coronary artery; LCX — left circumflex artery; RCA — right coronary artery; TIMI — Thrombolysis in Myocardial Infarction

Table 3. Comparison of coronary physiological indicators after adenosine injection between control and observation groups.

Characteristic	Observation group (n = 52)	Control group (n = 44)	P
Arterial pressure [mm Hg]	84 ± 8	85 ± 8	0.370
Fractional flow reserve	0.84 ± 0.10	0.87 ± 0.09	0.045
Coronary flow reserve	1.83 ± 0.38	1.99 ± 0.54	0.086
Index of microvascular resistance	31 ± 5	22 ± 6	0.000

($p > 0.05$). The observation group had significantly lower FFR ($p < 0.05$) and higher IMR ($p < 0.01$) compared to the control group, but no significant difference in CFR was noted between these two groups ($p > 0.05$) (Table 3).

Determination of the correlation of urinary mALB and β2-MG as well as serum UA and CysC with the index of microvascular resistance

Next, linear regression analysis was used to explore the correlation of urinary mALB and β2-MG as well as serum UA and CysC with the IMR within each group. As shown in scatter plots in Figure 1, each of these four indexes, mALB, β2-MG, serum UA, and CysC, had a positive correlation with the IMR in each individual group.

Correlation analysis between hs-CRP levels and index of microvascular resistance

Linear regression analyses showed that hs-CRP levels were positively correlated with IMR ($r = 0.419$, $p < 0.01$, Fig. 2).

Determination of univariate and multivariate factors related to an increased index of microvascular resistance

Multivariate regression analysis was used to identify the factors that were correlated to an increased IMR in hypertensive patients. As shown

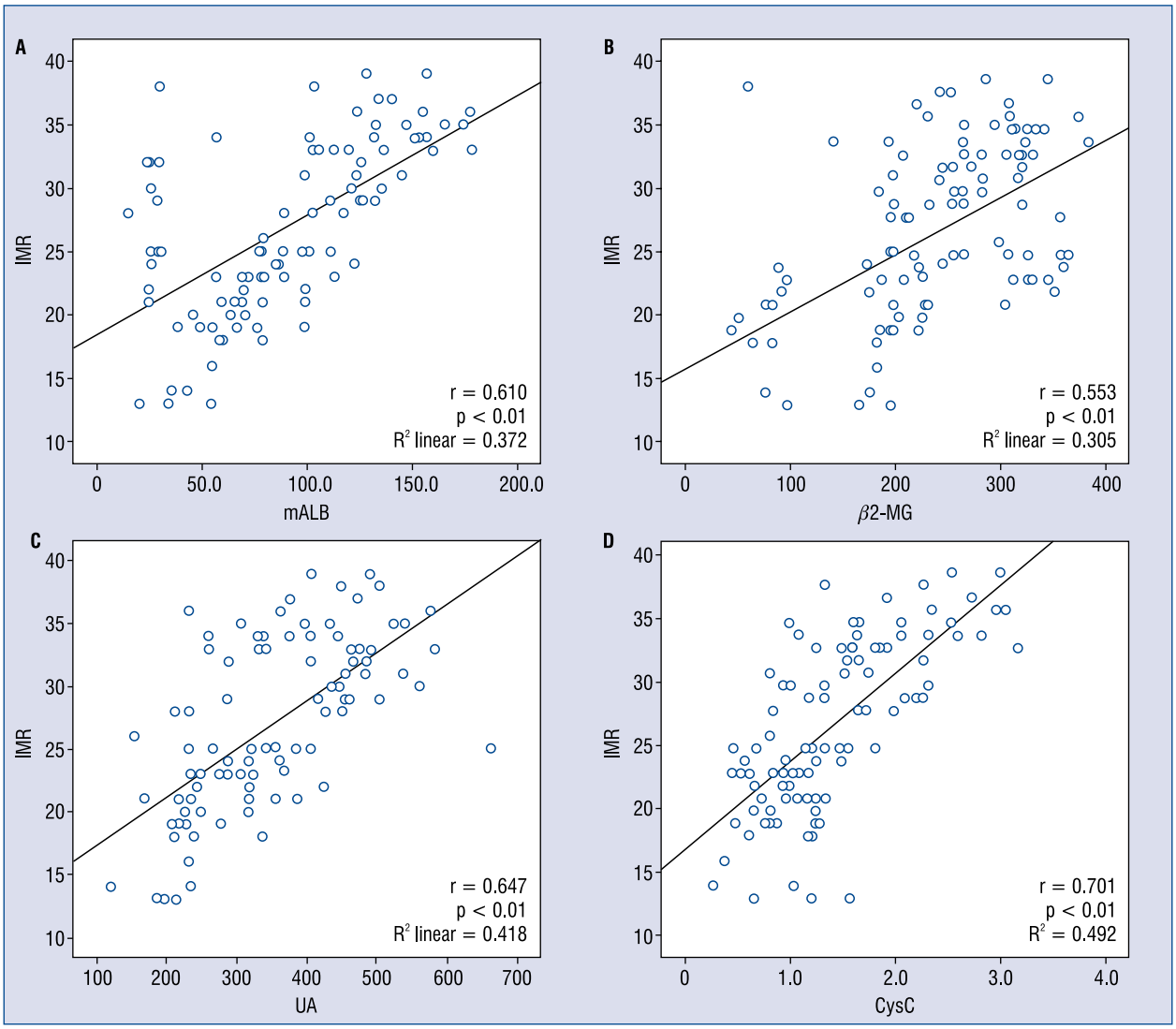

Figure 1. Correlation between renal microcirculatory dysfunction and increased coronary microcirculatory resistance in hypertensive patients; **A.** Correlation between microalbuminuria (mALB) and the index of microvascular resistance (IMR); **B** Correlation between β2 microglobulin (β2-MG) and the IMR; **C.** Correlation between uric acid (UA) and the IMR; **D.** Correlation between serum cystatin C (CysC) and the IMR.

in Table 4, the levels of urinary mALB and β2-MG as well as serum UA and CysC were determined as independent predictors for IMR elevation.

Discussion

The major finding from this study was a strong correlation between renal microcirculatory dysfunction and increased coronary microcirculatory resistance in hypertensive patients. Therefore, hypertensive patients with poorer renal function were more prone to develop higher coronary microcirculatory resistance than those with normal renal function.

The microcirculatory system is composed of arterioles, capillaries, and venules. The renal microcirculation is a balloon-shaped mesh structure that is not in direct contact with the veins and forms the glomerular capillary and peritubular vascular network. In the early stage of hypertensive nephropathy, two major pathological events occur: 1) increased permeability of the glomerular filtration membrane and/or impaired protein recovery of renal tubules resulting in elevated levels of urinary mALB and β2-MG as well as serum CysC and UA, and 2) small arteries have low blood flow and low velocity during both systole and diastole [26, 27]. CysC is released by glomerular filtration and then

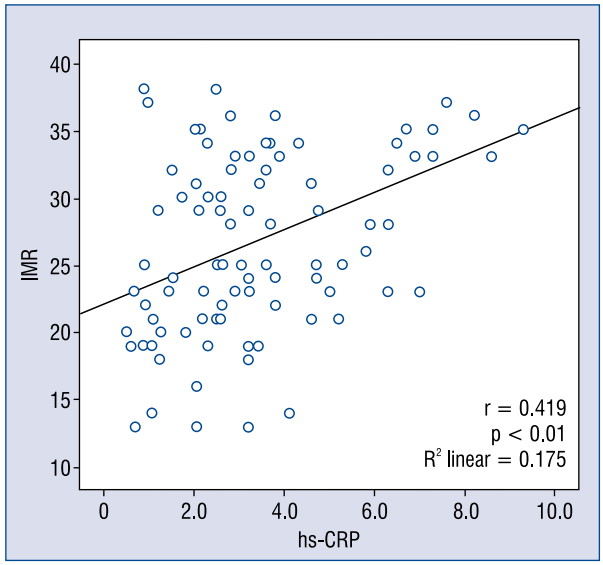

Figure 2. Correlation analysis between high-sensitivity C-reactive protein (hs-CRP) levels and index of microvascular resistance (IMR) in hypertensive patients.

is reabsorbed through the proximal tubules. Hence, the circulating levels of CysC reflect changes in the glomerular filtration rate. In addition, renal tubules are sensitive to ischemia, which results from a hypertension-linked decrease in renal perfusion, and renal tubular injury causes high levels of serum UA [28]. Therefore, levels of urinary mALB and β2-MG as well as serum UA and CysC reflect renal microcirculatory function, among which mALB is the major indicator of early kidney damage and vascular lesions resulting from hypertension [29]. In the present study, these four biochemical indexes to evaluate the renal microcirculatory function in hypertensive patients were used.

Previous studies have shown a strong correlation between chronic kidney disease and cardiovascular events/increased all-cause mortality, and this correlation is not affected by traditional risk factors [30]. For instance, patients with chronic kidney disease associated with an elevated CFR had an increased incidence of long-term cardiovascular

Table 4. Determination of factors related to an increased index of microvascular resistance.

	Univariate OR	Logistic 95% CI	Regression P	Multivariate OR	Logistic 95% CI	Regression P
Age	–0.1	–0.2–0.0	0.062			
BMI	0.2	–0.1–0.5	0.182			
Smoking	7.0	4.6–9.3	< 0.001	1.63	–0.1–3.4	0.078
Diabetes mellitus	6.9	4.4–9.3	< 0.001			
Male gender	4.7	2.1–7.3	0.001			
Dyslipidemia	–1.7	–4.4–1.1	0.238			
Previous PCI	2.6	–1.6–6.9	0.228			
LVEDD	0.1	–0.2–0.3	0.621			
Ejection fraction	0.0	–0.2–0.1	0.702			
ACEI/ARB	–0.6	–3.4–2.2	0.681			
Beta-blocker	–2.0	–5.1–1.0	0.198			
Nitrates	0.2	–2.6–3.0	0.863			
CCB	0.4	–2.3–3.2	0.758			
Creatinine	0.1	0.0–0.2	0.228			
mALB	0.1	0.1–0.1	< 0.001	0.04	0.02–0.06	< 0.001
UA	0	0.0–0.0	< 0.001	0.01	0.006–0.022	< 0.001
CysC	6.9	5.5–8.3	< 0.001	3.30	2.00–4.60	< 0.001
β2-MG	0	0.0–0.1	< 0.001	0.02	0.01–0.03	< 0.001

ACEI — angiotensin-converting enzyme inhibitor; ARB — angiotensin receptor blocker; BMI — body mass index; BMI — body mass index; CCB — calcium channel blockers; CI — confidence interval; CysC — serum cystatin C; LVEDD — left ventricular end-diastolic dimension; mALB — microalbuminuria; OR — odds ratio; PCI — percutaneous coronary intervention; PCI — percutaneous coronary intervention; UA — uric acid; β2-MG — β2-microglobulin

events [31, 32]. End-stage renal disease has also been shown to be tightly linked to the coronary slow-flow phenomenon [31], which often suggests the presence of increased coronary microcirculatory resistance [33]. A more recent study has revealed that a variety of heart and kidney diseases can influence each other through neuroendocrine feedback mechanisms at an early stage [34]. For example, mALB-positive hypertensive patients often have more severe coronary artery stenosis than mALB-negative patients, and this prediction is independent of other risk factors, including diabetes, hyperlipidemia, smoking, obesity, and age [35]. On the other hand, serum CysC has been shown to be a risk predictor of adverse cardiovascular outcomes in patients with cardiovascular diseases [36, 37], and it has been proposed to have a clinical value in stratification of acute coronary syndrome [38, 39]. In the present study, it was found that occurrence rate of coronary lesions in the observation group was slightly higher than that in the control group, but no statistical significance was observed. The potential cause for this insignificance may have been due to the small sample size used in the present study. However, lower FFR but a higher IMR in the observation group than in the control group was found, suggesting the correlation of renal microcirculatory dysfunction and an increased coronary microcirculatory resistance. Further, it was found that each of these early indicators of renal dysfunction was an independent risk factor for increased IMR. Therefore, in the presence of hypertension, it was believed that the progression of kidney and coronary diseases share common mechanisms. In addition, a previous study has shown that renal microcirculatory lesions usually occur earlier in hypertensive patients than coronary lesions [1], implying that a variety of indicators for kidney microcirculation may also provide an early warning to some degree for the development of coronary lesions. However, this premise needs to be further corroborated in a large-scale multi-centered study in future. Consistent with previous findings [40, 41], it was also revealed that early renal dysfunction is an independent predictor of coronary heart disease, but the underlying mechanisms are not completely understood and merit further investigation.

It has been well documented that endothelial dysfunction and inflammation play important roles in the development of chronic hypertensive kidney disease and adverse cardiovascular events [42, 43] and that microalbuminuria often indicates nonspecific injuries to blood vessels [44]. For instance, Tsioufis et al. [45] have reported that mALB-positive hypertensive patients had higher CRP levels than mALB-negative patients. Since CRP is the strongest inflammatory marker of atherosclerosis and is a strong predictor of vascular events [46], the above finding argued that the mALB-positive hypertensive patients were under systemic stress. Consistent with the above observation, in the present study, we found that the hs-CRP level in the observation group was significantly higher than that in the control group, suggesting that inflammation may be an important mechanism underlying renal microcirculatory dysfunction and increased resistance of coronary microcirculation. Mechanistically, CRP has been shown to stimulate monocytes to release proinflammatory cytokines, such as interleukin-6 and tumor necrosis factor-β, and to mediate the generation of intercellular adhesion molecule and vascular cell adhesion molecule, resulting in increased anti-inflammatory responses and endothelial dysfunction [47]. Also, the generation of UA is accompanied by the production of oxygen free radicals and hydrogen peroxide, which contribute to increased inflammation and NO inactivation, thus damaging endothelial cells and causing the coronary slow-flow phenomenon [48, 49]. In addition, high levels of UA may promote low-density lipoprotein cholesterol oxidation and lipid peroxidation, thus amplifying oxidative stress, promoting atherosclerotic plaque formation, increasing vascular resistance, and eventually slowing blood flow [49, 50].

Limitations of the study

Some limitations of this study need to be acknowledged. For example, the present study had a small sample size and was a single center study. Also, patients with normal coronary or mild or severe coronary stenosis were excluded from this study, which potentially brought in sample selection bias. In addition, drug use prior to coronary angiography might also have potentially affected IMR measurement.

Conclusions

In conclusion, it was demonstrated in the present study that impaired renal microcirculation is closely associated with an increased coronary microcirculatory resistance and that renal microcirculation is an independent risk factor for coronary microcirculation in hypertensive patients. Our findings also suggest that it is highly likely that hypertension-linked renal microcirculatory impairment and an increase in coronary microcirculatory resistance share a common pathological basis.

Conflict of interest: None declared

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