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Endothelial vasomotor dysfunction in the brachial artery predicts the short-term development of early stage renal dysfunction in patients with coronary artery disease

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ABSTRACT

Background: This study examined whether endothelial vasomotor dysfunction in the brachial artery predicted early renal dysfunction in patients with coronary artery disease (CAD). Endothelial function in the renal vasculature plays an important role in the regulation of renal hemodynamics. As endothelial dysfunction is a systemic disorder, there may be a relationship between endothelial function in the brachial artery and renal vasculature.

Methods: Flow-mediated endothelium-dependent dilation (FMD) in brachial artery and renal functional parameters were measured in 757 patients with CAD without macroalbuminuria.

Results: In a cross-sectional data, an impaired FMD was associated with higher serum creatinine levels and urinary albumin excretion (UAE), lower creatinine clearance rate and estimated glomerular filtration rate (eGFR) at baseline in multiple linear regression analysis. In a follow-up study including a subgroup of 448 patients with normal renal function (serum creatinine level <1.0 mg/dL, UAE <25 mg/day and eGFR ≥ 60 mL/min/1.73 m^2 at baseline), 96 patients had an endpoint of early stage renal dysfunction (serum creatinine levels ≥ 1.2 mg/dL, UAE ≥ 30 mg/day and/or eGFR <60 mL/min/1.73 m^2) during 12 month follow-up. Multivariate logistic regression analysis showed that impaired FMD was significantly associated with progression to the early stage renal dysfunction after adjustment with age, diabetes mellitus, hypertension and C-reactive protein levels.

Conclusions: Endothelial vasomotor dysfunction in the brachial artery is independently associated with progression from normal renal function to early stage renal dysfunction in patients with CAD. Measurement of FMD may therefore be useful for assessing risk of future renal dysfunction.

1. Introduction

Chronic kidney disease is associated with a high prevalence of cardiovascular events [1,2]. There is evidence that treatment at the earliest possible stage of renal dysfunction is more effective for preventing progression to end-stage renal disease and subsequent cardiovascular disease [3–7]. It is therefore clinically important to detect this group of patients who are at high risk of developing early stage renal disease [7]. Microalbuminuria, a marker of early stage renal dysfunction, is related to renal microvasculopathy, characterized by preglomerular arteriolar involvement and tubulointerstitial changes [1,2,8]. Experimental studies indicate that endothelial dysfunction in the renal vasculature is involved in the development of renal microvasculopathies and microalbuminuria [9–11]. As endothelial dysfunction is a systemic disorder [12], it is possible that there is a relationship between endothelial dysfunction in the systemic arteries and renal vasculature [13–15]. A previous cross-sectional study showed that an impaired endothelial vasomotor response in the forearm was associated with mild to moderate renal dysfunction in hypertensive patients without previous cardiovascular diseases [16]. In contrast, *in vitro* measurement of endothelium-dependent dilation in isolated internal thoracic arteries showed no significant relationship with the presence of mild to moderate renal dysfunction in patients with coronary artery disease (CAD) [17]. Therefore, it remains controversial whether there is an association between endothelial vasomotor dysfunction in systemic arteries and renal dysfunction in patients with cardiovascular disease and advanced atherosclerotic burden. It also remains unknown whether

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endothelial vasomotor dysfunction in systemic arteries precedes renal dysfunction, thereby providing a predictive value of future development of renal dysfunction. In the present study, we examined whether endothelial vasomotor dysfunction in the brachial artery provided prognostic information on the development of early stage renal dysfunction in patients with CAD that is linked with chronic kidney disease.

2. Methods

2.1. Study patients

This study included 757 consecutively enrolled patients with stable CAD without macroalbuminuria (≥300 mg/day) at Yamanashi University Hospital from January 1, 2002 to Dec 31, 2006. All the patients had a routine screen following enrollment in the study that included measurement of flow-dependent dilation (FMD) in the brachial artery using B-mode ultrasound images, serum creatinine levels, 24 h urine albumin excretion (UAE) and calculation of creatinine clearance (CCr) and estimated glomerular filtration rate (eGFR). All patients had angiographic evidence of organic diameter stenosis >70% of at least one major coronary artery (single-vessel disease $n=175$; two-vessel disease $n=302$; and three-vessel disease $n=280$). The exclusion criteria were: 1) a history of dialysis, 2) use of contrast media 3 months prior to enrollment, 3) congestive heart failure (≥New York Heart Association classification III), 4) secondary hypertension, 5) renal artery stenosis, 6) polycystic kidney disease, 7) chronic inflammatory diseases, 8) major injury or surgery 3 months prior to enrollment, and 9) other serious diseases. The baseline characteristics of the patients in the study are summarized in Table 1. All the patients gave written, informed consent for the study at enrollment and received the standardized medications outlined in Table 1. This study was conducted in accordance with the guidelines approved by the ethics committee of Yamanashi University Hospital and conformed with the principles outlined in the 1975 Declaration of Helsinki.

2.2. Measurements of renal function

Creatinine levels in serum and urine were measured by an enzymatic method using an auto-analyzer (Mitsubishi Kagaku Iatron, Tokyo, Japan). Serum creatinine levels were measured on 2 days a week apart, with the average value being used in the analyses. CCr was calculated from 24 h urine creatinine concentration and the serum creatinine concentration on the same day, and the value normalized to a surface area of 1.73 m^2 [6]. GFR was estimated by Modification of Diet in Renal Disease study equation [1]. Urinary albumin levels were measured by immunonephelometry, and fasting plasma high sensitivity C-reactive protein (CRP) levels by rate nephelometry (Dade Behring, Marburg, Germany).

2.3. Measurements of endothelial vasomotor function of the brachial artery assessed by flow-mediated dilation (FMD)

Vasodilator responses in the brachial arteries were measured using B-mode ultrasound images with a 7.5-MHz linear array transducer (HP-5500, Phillips Corp., Tokyo, Japan) according to a method validated in our previous studies [18,19]. Briefly, after baseline measurements of the diameter and flow velocity in the brachial artery, a blood pressure cuff was placed around the forearm and inflated to a pressure of 250 to 300 mm Hg for 5 min and then released. Measurements of the artery diameter during the reactive hyperemia were taken 45 to 90 s after cuff deflation. Sublingual nitroglycerin (300 μg) was then administered and the measurements repeated 3 min later. The responses of the vessel diameters to reactive hyperemia and nitroglycerin were expressed as the percentage increase in diameter from the baseline value. The diameters of the vessel responses were assessed at three points along a 10-mm length of the artery, and the values averaged. Blood flow was calculated by multiplying the velocity–time integral of the Doppler flow signal by heart rate and cross-sectional area of the vessel. The increase in brachial blood flow was calculated as the maximum flow recorded in the first 15 s after cuff deflation and was expressed as a percentage increase in flow from the baseline value.

2.4. Prospective study

Of the 757 patients in the cross-sectional study, a subset of 465 patients with normal renal function, defined as having all of the following criteria: serum creatinine levels <1.0 mg/dL, UAE <25 mg/day and eGFR ≥60 mL/min/1.73 m^2 at the time of the enrollment [1,2,6,20,21], were selected to examine the predictive value of FMD for the progression from normal renal function to the early stage renal dysfunction. All these patients had follow-up visits at our institution every 3 months for a period of 12 months in order to measure serum creatinine and 24 h UAE levels. The endpoint was development of early stage renal dysfunction, defined as occurrence of one or more of the following events: serum creatinine level ≥1.2 mg/dL, UAE level ≥30 mg/day and eGFR <60 mL/min/1.73 m^2 [1,2,6,20,21]. CCr was not included in the criteria of development of early stage renal dysfunction during follow-up because of difficulty in blood sampling for serum creatinine measurement during collecting urine for 24 h at home. As shown in Table 1, all the patients continued their standardized medications during the follow-up period. Patients with any of the following events during the follow-up period were withdrawn from the prospective study; use of contrast media, use of non-steroidal anti-inflammatory drugs for ≥3 days, cardiovascular events, major injury or surgery, chronic inflammatory diseases and other serious diseases. Our preliminary data showed 15% of patients with normal renal function at baseline (serum creatinine level <1.0 mg/dL, UAE <25 mg/day and eGRF ≥60 mL/min/1.73 m^2) developed serum creatinine levels ≥1.2 mg/dL, UAE ≥30 mg/day and/or eGRF <60 mL/min/1.73 m^2 during the 12 month follow-up period. Based on the data, we calculated 450 patients were required to provide our two-sided multiple logistic models with sufficient statistical power of 0.80 ($\beta=0.20$ and $\alpha=0.05$), which justified the number of patients ($n=465$) included in this prospective study.

Table 1
Baseline characteristics of the study patients.

	Normal renal function[a] ($n=448$)	Total patients ($n=757$)
Age (years)	65.6 ± 9.6	67.3 ± 9.3
Gender (male) (%)	77.0	74.1
Previous MI (%)	16.3	15.9
Current smoker (%)	27.9	26.4
Hypertension (%)	46.4	49.2
Diabetes mellitus (%)	26.1	35.4
Hyperlipidemia (%)	49.1	45.9
BMI (kg/m^2)	25.4 ± 2.6	25.4 ± 2.6
Systolic BP (mmHg)	131 ± 12	132 ± 12
HbA1c (%)	5.9 ± 1.4	6.0 ± 1.4
CRP (mg/dL)	0.11 (0.04, 0.30)	0.12 (0.05, 0.30)
LVEF (%)	61 ± 14	62 ± 15
Renal functional parameters		
Serum creatinine (mg/dL)	0.7 (0.6, 0.8)	0.8 (0.6, 1.3)
CCr (mL/min/1.73 m^2)	89 (77, 103)	78 (57, 94)
UAE (mg/day)	6.0 (3.6, 12.1)	9.2 (4.3, 20.5)
eGFR (mL/min/1.73 m^2)	85 (71, 110)	66(39, 93)
Vascular ultrasound parameters		
FMD (%)	5.6 ± 1.8	5.1 ± 1.8
Dilation to NTG (%)	18.7 ± 2.4	18.9 ± 2.9
Resting arterial diameter (mm)	4.2 ± 1.4	4.3 ± 1.4
Resting arterial blood flow (mL/min)	192 ± 48	193 ± 47
Increase in arterial blood flow (%)	240 ± 66	243 ± 67
Medication use		
Statin (%)	30.4	34.2
ACEI/ARB (%)	44.4	46.6
CCB (%)	31.9	39.1
Diuretics (%)	8.7	13.9
Insulin (%)	6.5	7.7

Values are expressed as mean ± SD, median (inter quartile ranges), and percentage of frequencies. Hypertension, defined as >140/90 mmHg or use of antihypertensive medication; diabetes mellitus, defined according to the American Diabetes Association criteria or taking an anti-diabetic medication. Hyperlipidemia, defined according to the National Cholesterol Education Program guidelines or taking lipid lowering medication. MI, myocardial infarction; BP, blood pressure; LVEF, left ventricular ejection fraction; CCr, creatinine clearance; UAE, urinary albumin excretion; eGFR, estimated glomerular filtration rate; FMD, flow-mediated dilation of brachial artery; NTG, nitroglycerin; CCB, calcium channel blocker.
[a] Normal renal function, defined as described in text.

2.5. Statistical analysis

Data are expressed as either the mean value ± SD, median and interquartile range (25 and 75th percentiles) or frequencies (%). The Shapiro–Wilk test showed that the levels of serum creatinine, UAE, CCr, eGFR and CRP levels were not distributed normally, and therefore these data were expressed as the median and interquartile range, and they were log-transformed when these data were statistically analyzed. The baseline clinical parameters were compared using Student's unpaired *t* test or Chi-square analysis where appropriate. In the cross-sectional study, the independent relationship of FMD with serum creatinine levels, UAE, CCr and eGFR at baseline was examined in the multivariate linear regression analysis using the baseline clinical parameters as covariates that had a significant relationship with serum creatinine levels, UAE, CCr and eGFR in the univariate linear regression analysis. In the longitudinal follow-up study, the predictive value of FMD for development of early stage renal dysfunction was examined by multivariate logistic regression analysis using covariates that had a statistically significant difference between patients with and without development of the early stage renal dysfunction. The Hosmer–Lemeshow goodness-of-fit test was used to assess the logistic model fit. Odds ratios (ORs) were estimated with 95% confidence intervals (CIs). The *c*-statistics using receiver operating characteristic (ROC) curve analysis for logistic model was used to examine the incremental effect of FMD on the predictive value of conventional risk factors for the