International Journal of Cardiology 173 (2014) 481–486

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Endothelial function and cardiovascular events in chronic kidney disease

Yoshihiro Hirata [a,1], Seigo Sugiyama [a,b,*,1], Eiichiro Yamamoto [a], Yasushi Matsuzawa [c], Eiichi Akiyama [a,c], Hiroaki Kusaka [a], Koichiro Fujisue [a], Hirofumi Kurokawa [a], Junichi Matsubara [a], Koichi Sugamura [a], Hirofumi Maeda [a], Satomi Iwashita [a], Hideaki Jinnouchi [d,e], Kunihiko Matsui [f], Hisao Ogawa [a]

[a] Faculty of Life Sciences, Department of Cardiovascular Medicine, Graduate School of Medical Science, Kumamoto University Kumamoto, Japan
[b] Cardiovascular Division Diabetes Care Center, Jinnouchi Hospital Kumamoto, Japan
[c] Division of Cardiology, Yokohama City University Medical Center Yokohama, Japan
[d] Diabetes Care Center, Jinnouchi Hospital Kumamoto, Japan
[e] Division of Preventive Cardiology, Department of Cardiovascular Medicine, Kumamoto University Hospital Kumamoto, Japan
[f] Department of General Internal Medicine, Yamaguchi University Hospital Ube, Japan

ARTICLE INFO

Article history:
Received 11 February 2014
Accepted 12 March 2014
Available online 20 March 2014

Keywords:
Endothelial dysfunction
Chronic kidney disease
Coronary artery disease
Cardiovascular events
Cohort study

ABSTRACT

Background: As patients with chronic kidney disease (CKD) are at high risk of developing coronary artery disease (CAD), it is important to stratify their cardiovascular risk. We investigated whether peripheral endothelial dysfunction is associated with the presence of CAD in patients with CKD and is a predictor of cardiovascular events.
Methods: We enrolled 383 CKD patients with at least one coronary risk factor. Peripheral endothelial function was assessed by reactive hyperemia peripheral arterial tonometry index (RHI). The presence of CAD was determined by coronary angiography. Cardiovascular events were assessed during follow-up.
Results: Ln-RHI was significantly lower in risk factor-matched CKD patients ($n = 323$) than risk factor-matched non-CKD patients ($n = 323$) (0.527 ± 0.192 vs. 0.580 ± 0.218, $p = 0.001$). In CKD patients ($n = 383$), Ln-RHI was significantly lower in CAD (0.499 ± 0.183, $n = 262$) than non-CAD (0.582 ± 0.206, $n = 121$) ($p < 0.001$) patients. Multivariate logistic regression analysis identified Ln-RHI as an independent factor associated with the presence of CAD ($p = 0.001$). During a mean follow-up period of 30 months, 90 cardiovascular events were recorded in CKD patients. Multivariate Cox hazard analysis identified low-Ln-RHI as an independent predictor of cardiovascular events (hazard ratio = 2.70, 95% confidence interval = 1.62–4.51, $p < 0.001$). The predictive value of combined Ln-RHI and Framingham risk score (FRS) was evaluated by net reclassification index (NRI) and C-statistics, which showed significant improvement (NRI = 22%, $p < 0.001$) (C-statistics: FRS = 0.49, FRS + Ln-RHI = 0.62, $p = 0.005$).
Conclusions: Endothelial function was significantly impaired in CKD patients and correlated with the presence of CAD. Severe endothelial dysfunction was an independent and incremental predictor of cardiovascular events in CKD.

Trial Registration:
Unique identifier: UMIN000010432.
URL: http://www.umin.ac.jp/ctr/.

1. Introduction

Patients with chronic kidney disease (CKD) are at increased risk of coronary artery disease (CAD), and CAD is a major cause of death for these patients [1]. The increasing number of CKD patients places an importance on stratifying cardiovascular risks in patients with CKD. While patients with CKD are at high risk of cardiovascular events, not all CKD patients are equally predisposed to CAD and cardiovascular complications. Physicians sometimes hesitate to perform coronary angiography to assess CAD in CKD patients because of potential contrast media-induced kidney dysfunction. Various methods for cardiovascular risk stratification have been proposed in patients with CKD, although the Framingham risk model lack predictive power for CKD patients and there are currently no useful predictive parameters for the future occurrence of cardiovascular events [2,3].

Endothelial dysfunction correlates with cardiovascular diseases and plays an important role in all stages of atherosclerosis, leading to obstructive CAD [4] and cardiovascular events. Furthermore, endothelial dysfunction is implicated in increased frequency of cardiac events, even in the absence of CAD, suggesting that endothelial dysfunction could be involved in any cardiovascular manifestations [5,6]. The role of endothelial dysfunction in CKD has been described [7], but to our

* Corresponding author at: Faculty of Life Sciences, Department of Cardiovascular Medicine, Graduate School of Medical Science, Kumamoto University, 1-1-1 Honjo, Chuo-ku, Kumamoto 860-8556, Japan. Tel.: +81 96 373 5175; fax: +81 96 362 3256.
E-mail address: ssugiyam@kumamoto-u.ac.jp (S. Sugiyama).
[1] Yoshihiro Hirata and Seigo Sugiyama contributed equally to the study.

http://dx.doi.org/10.1016/j.ijcard.2014.03.085
0167-5273/

knowledge, there is no information on correlations between endothelial dysfunction and CAD/future cardiovascular events in patients with CKD.

In this study, we hypothesized that peripheral endothelial dysfunction is associated with the presence of CAD in patients with CKD and investigated the prognostic significance of peripheral endothelial function using reactive hyperemia peripheral arterial tonometry (RH-PAT) examination for risk stratification in stable patients with CKD.

2. Methods

2.1. Study subjects and protocol

We performed a prospective cohort study to investigate the clinical significance of peripheral endothelial function in high-risk CKD patients. We recruited 920 consecutive stable patients with at least one coronary risk factor (hypertension, diabetes mellitus [DM], dyslipidemia, current smoking, and family history of CAD) who were referred to Kumamoto University Hospital for coronary angiography (CAG) because of suspected CAD or abnormal electrocardiography and/or echocardiography between August 2006 and January 2013. Patients with at least one coronary risk factor included those with and without CKD for cross-sectional investigation of the effects of peripheral endothelial function on the presence of CKD. The RH-PAT index (RHI) was used to assess peripheral endothelial function and was measured in all study participants before CAG using fingertip RH-PAT by Endo-PAT2000. RHI was further compared between CKD patients and non-CKD patients after matching risk factors: number of patients, age, sex, equal incidence of hypertension, DM, dyslipidemia, and CAD (risk factor-matched CKD patients and risk factor-matched non-CKD patients). Exclusion criteria included patients on hemodialysis, as RH-PAT examination cannot be performed correctly in these patients because of the A-V shunt in the arm. The presence of CAD was determined by CAG. CKD patients were prospectively followed until October 2013 or until the occurrence of cardiovascular events (Fig. 1 and Supplemental Fig. 1).

The study protocol conformed to the principles of the Declaration of Helsinki. Written informed consent was obtained from all patients. This study is registered at the University Hospital Medical Information Network (UMIN) Clinical Trials Registry (UMIN000010432).

2.2. eGFR/urinary protein assessment and definition of CKD

The estimated glomerular filtration ratio (eGFR) was calculated using the Japanese Society of Nephrology formula [8]. Urinary protein was measured semi-quantitatively by a urine dipstick test (Uro-Labstix; Siemens Japan, Tokyo, Japan) (negative and ±: urinary protein <30 mg/dl; 1+: urinary protein 30–99 mg/dl; 2+: urinary protein 100–299 mg/dl; 3+: urinary protein 300–999 mg/dl; and 4+: urinary protein >1000 mg/dl). Proteinuria was defined as urinary protein excretion of >30 mg/dl. CKD was defined as a low eGFR of <60 ml/min/1.73 m^2 or a high eGFR of >60 ml/min/1.73 m^2 with proteinuria [9]. Non-CKD was defined as a high eGFR of ≥60 ml/min/1.73 m^2 without proteinuria. CKD patients were divided into two groups depending on eGFR (mild CKD: eGFR 30 ≤eGFR < 60 ml/min/1.73 m^2 or higher eGFR of >60 ml/min/1.73 m^2 with proteinuria; moderate CKD: eGFR <30 ml/min/1.73 m^2).

2.3. RH-PAT examination

RH-PAT has been described previously [10]. RH-PAT was conducted in the morning after subjects had fasted, before taking medications and before CAG. Non-invasive RH-PAT was measured with a blood pressure cuff placed on an upper arm (study arm), while the contralateral arm served as a control (control arm). The PAT probe was placed on a finger of each hand. After a 5-min equilibration period, the blood pressure cuff was inflated on the study arm to 60 mmHg above the systolic pressure or 200 mmHg for 5 min, and then the cuff was deflated to induce reactive hyperemia. RH-PAT data were digitally analyzed online (Endo-PAT2000 software, version 3.0.4 and 3.4.4, Itamar Medical Ltd, Caesarea, Israel). RHI was calculated as the ratio of the average amplitude of the PAT signal over 1 min starting 1.5 min after cuff deflation (control arm, A; occluded arm, C) divided by the average amplitude of the PAT signal of a 2.5-min period before cuff inflation (baseline) (control arm, B; occluded arm, D). RHI values were automatically calculated by the online computer based on the ratio of (C/D)/(A/B). Because RHI values are not normally distributed, we calculated the natural logarithmic transformed RHI values as the Ln-RHI for use in regression analyses, as reported previously [11,12]. The reproducibility of RH-PAT technology has been confirmed in previous studies [11–14].

2.4. Coronary angiography and CAD classification

CAD was defined as coronary artery stenosis (>75% narrowing of the arterial diameter) in at least one coronary artery using quantitative coronary angiography. Based on the CAG results, CKD + CAD patients were divided into two groups according to the Gensini score and synergy between percutaneous coronary intervention with TAXUS and cardiac surgery (SYNTAX) score. We divided CKD + CAD patients using a cutoff value for the Gensini score of ≥40, as reported previously [15], and used a cutoff value for the SYNTAX score of ≥12, representing the median value of CKD + CAD patients.

2.5. Follow-up and cardiovascular events

After RH-PAT and CAG, CKD patients were prospectively followed at outpatient clinics until October 2013 or until the occurrence of the end point (composite cardiovascular events), defined as cardiovascular death, non-fatal myocardial infarction, unstable angina pectoris, non-fatal ischemic stroke, hospitalization for heart failure decompensation, or coronary revascularization. Based on the RH-PAT results, the mean value of Ln-RHI (Ln-RHI: 0.525) was used to divide CKD patients into the low-Ln-RHI and high-Ln-RHI groups.

2.6. Statistical analysis

Continuous variables with normal distribution are expressed as mean ± standard deviation. Categorical data are presented as frequencies and percentages. The Shapiro–Wilk test was used to evaluate the distribution of continuous data. Skewed variables are expressed as median values (25–75%). Significant clinical parameters associated with CAD in simple logistic regression analysis, and several factors reported previously to correlate significantly with CAD, were entered into multivariate logistic regression analysis. The Hosmer–Lemeshow test for goodness of fit was used for model calibration. We also calculated the cumulative incidence of cardiovascular events using the Kaplan–Meier method and compared such incidence to the log-rank test. To account for confounding variables, a propensity score was calculated for each patient using a logistic regression model in which the dependent variable was low-Ln-RHI (≤0.525). Independent variables

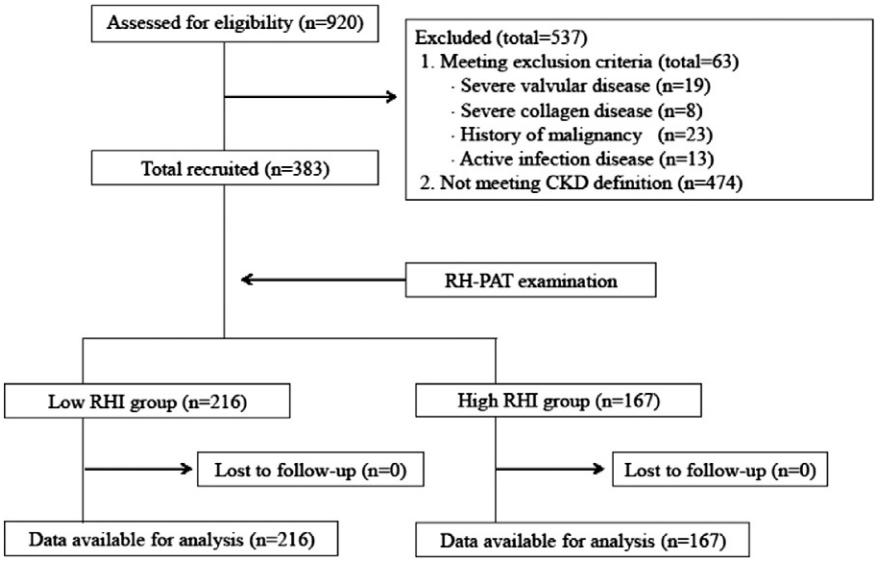

Fig. 1. Flow chart showing the protocol used in the study.