International Journal of Cardiology 254 (2018) 284–290

Contents lists available at ScienceDirect

International Journal of Cardiology

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

Chronic kidney disease is associated with vascular smooth muscle dysfunction but not with endothelial dysfunction

Yumiko Iwamoto [a,1,2], Tatsuya Maruhashi [a,1,2], Masato Kajikawa [d,3], Nozomu Oda [a,3], Shinji Kishimoto [a,3], Shogo Matsui [a,3], Haruki Hashimoto [a,3], Yoshiki Aibara [b,3], Farina Mohamad Yusoff [b,3], Takayuki Hidaka [a,3], Yasuki Kihara [a,4], Kazuaki Chayama [c,4], Kensuke Noma [b,d,3], Ayumu Nakashima [e,3], Chikara Goto [f,3], Yukihito Higashi [b,d,*,1,5]

[a] Department of Cardiovascular Medicine, Graduate School of Biomedical and Health Sciences, Hiroshima University, Hiroshima, Japan
[b] Department of Cardiovascular Regeneration and Medicine, Research Institute for Radiation Biology and Medicine, Hiroshima University, Hiroshima, Japan
[c] Department of Gastroenterology and Metabolism, Biomedical Sciences, Graduate School of Biomedical and Health Sciences, Hiroshima University, Hiroshima, Japan
[d] Division of Regeneration and Medicine, Hiroshima University Hospital, Hiroshima, Japan
[e] Department of Stem Cell Biology and Medicine, Graduate School of Biomedical and Health Sciences, Hiroshima University, Hiroshima, Japan
[f] Hirohsima International University, Hiroshima, Japan

ARTICLE INFO

Article history:
Received 13 September 2017
Received in revised form 25 October 2017
Accepted 31 October 2017

Keywords:
Chronic kidney disease
Flow-mediated vasodilation
Endothelial function
Nitroglycerine-induced vasodilation
Vascular smooth muscle dysfunction

ABSTRACT

Backgrounds: Nitroglycerine-induced vasodilation (NID) is usually assessed as a control test for flow-mediated vasodilation (FMD). However, NID per se is impaired in patients with high cardiovascular risk. The purpose of this study was to investigate the associations of chronic kidney disease (CKD) with NID and FMD.
Methods: We measured NID and FMD in a total of 1567 adult subjects without end-stage renal disease (ESRD), 28% of whom had CKD as judged by measurements of estimated glomerular filtration rate (995 men and 572 women; mean age, 59.0 ± 16.9 years; age range, 18 to 92 years).
Results: NID was significantly smaller in patients with CKD than in those without CKD (10.8 ± 6.0% vs. 12.7 ± 5.7%, $P < 0.001$). The prevalence of vascular smooth muscle dysfunction, defined as NID of less than the division point for the lowest quartile, was significantly higher in patients with CKD than in those without CKD (37.5% vs. 21.5%, $P < 0.001$). Multivariate analysis revealed that CKD was independently associated with vascular smooth muscle dysfunction (OR: 1.36, 95% CI: 1.02 to 1.81, $P = 0.04$). FMD was significantly smaller in patients with CKD than in those without CKD (3.1 ± 2.8% vs. 4.0 ± 3.0%, $P < 0.001$). The prevalence of endothelial dysfunction, defined as FMD of less than the division point for the lowest quartile, was significantly higher in patients with CKD than in those without CKD (31.7% vs. 23.1%, $P = 0.002$). However, CKD was not independently associated with endothelial dysfunction in an age- and sex-adjusted model (OR: 0.95, 95% CI: 0.71 to 1.26, $P = 0.72$).
Conclusions: Non-ESRD CKD is independently associated with vascular smooth muscle dysfunction but not with endothelial dysfunction.

1. Introduction

Endothelial dysfunction is an initial step in the process of atherosclerosis and plays a critical role in the development of this condition, leading to cardiovascular complications [1]. In addition, endothelial function has been shown to be an independent predictor of cardiovascular events [2,3]. Therefore, there is considerable research interest in the assessment of endothelial function for risk stratification in subjects with cardiovascular risk factors. Recently, flow-mediated vasodilation (FMD), a vascular dilatory response of the brachial artery to reactive hyperemia, has been widely used for the assessment of endothelial function in humans [4–7]. Nitroglycerine-induced vasodilation (NID), a vascular dilatory response of the brachial artery to administered nitroglycerine, has been used as a control test for FMD measurement to confirm that the vascular dilatory response to reactive hyperemia is not affected by underlying vascular smooth muscle dysfunction or vascular structural alterations but is truly a consequence of endothelium-dependent vasodilation [8,9]. However, recent studies have shown that NID per se is impaired in patients with multiple cardiovascular risk factors or a history of cardiovascular disease (CVD) [10–12]. Moreover,

* Corresponding author at: Department of Cardiovascular Regeneration and Medicine, Research Institute for Radiation Biology and Medicine, Hiroshima University, 1-2-3 Kasumi, Minami-ku, Hiroshima 734-8551, Japan.
E-mail address: yhigashi@hiroshima-u.ac.jp (Y. Higashi).
[1] Drafting the article and conception of this study.
[2] Yumiko Iwamoto and Tatsuya Maruhashi contributed equally to this work.
[3] Performing the ultrasonography.
[4] Revising the article critically for important intellectual content.
[5] This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

https://doi.org/10.1016/j.ijcard.2017.10.122
0167-5273/

we recently reported that impaired NID is associated with a higher incidence of cardiovascular events [13]. These findings suggest that NID in the brachial artery can be used not only as a diagnostic marker but also as a prognostic marker of atherosclerosis.

Chronic kidney disease (CKD) is an independent predictor of cardiovascular events. It has been reported that patients with end-stage renal disease (ESRD) have a much higher incidence of cardiovascular death than that in the general population and that cardiac disease is the leading cause of death in patients on chronic dialysis [14–16]. Recent studies have also shown that non-ESRD CKD is independently associated with an increased risk of cardiovascular mortality and cardiovascular events [17,18]. It has been shown that endothelial function assessed by FMD in the brachial artery is significantly impaired in patients with CKD, especially in patients with ESRD, compared with that in subjects without CKD, although it is controversial whether CKD is independently associated with FMD [19–23]. As for the relationship between CKD and NID, it has been shown that NID is significantly impaired in patients with ESRD compared with that in subjects without ESRD. However, the relationship between non-ESRD CKD and NID has not been fully investigated. Although measurement of NID in patients with non-ESRD CKD was performed as a control test in several studies, previous studies were limited to small numbers of or highly selected subjects [19–24]. In addition, it has not been determined whether non-ESRD CKD is independently associated with NID. We therefore investigated the relationship between non-ESRD CKD and NID in a large number of well-characterized subjects with or without CKD.

2. Methods

2.1. Subjects

Between April 2007 and April 2017, a total of 2743 subjects were recruited for measurement of vascular function from the subjects who underwent health-screening examinations or who visited the outpatient clinic at Hiroshima University Hospital. Of the 2743 subjects, 1862 subjects underwent measurement of both FMD and NID of the brachial artery. Subjects who had received nitrate treatment ($n = 112$) and chronic hemodialysis ($n = 23$), subjects with estimated glomerular filtration rate (eGFR) <15 ml/min/1.73 m^2 ($n = 10$), and subjects with missing information on eGFR ($n = 150$) were excluded. Finally, 1567 subjects (995 men and 572 women; mean age, 59.0 ± 16.9 years; age range, 18 to 92 years) were enrolled in this study. Hypertension was defined as treatment with oral antihypertensive agents or systolic blood pressure ≥ 140 mm Hg and/or diastolic blood pressure ≥ 90 mm Hg, in a sitting position, on at least 3 different occasions [25]. Diabetes was defined according to the American Diabetes Association recommendation [26]. Dyslipidemia was defined according to the third report of the National Cholesterol Education Program [27]. We defined smokers as those who had ever smoked. Coronary artery disease included angina pectoris, myocardial infarction, and unstable angina. Cerebrovascular disease included ischemic stroke, hemorrhagic stroke, and transient ischemic attack. Peripheral artery disease was defined as current intermittent claudication with ankle-brachial index <0.9 or a history of intervention, including angioplasty and bypass graft. The eGFR was calculated using the Japanese eGFR equation [28]. CKD was defined as eGFR <60 ml/min/1.73 m^2 and GFR stage was graded according to the Kidney Disease Improving Global Outcomes recommendations; eGFR of at least 90 ml/min/1.73 m^2 (G1), 60–89 to ml/min/1.73 m^2 (G2), 45–59 ml/min/1.73 m^2 (G3a), 30–44 ml/min/1.73 m^2 (G3b), and 15–29 ml/min/1.73 m^2 (G4) [29]. The ethical committees of our institutions approved the study protocol. This study was performed in accordance with the Declaration of Helsinki. Written informed consent for participation in the study was obtained from all the subjects.

2.2. Study protocol

We measured vascular responses to reactive hyperemia and sublingually administered nitroglycerine in the brachial artery. The subjects fasted the previous night for at least 12 h. The subjects were kept in the supine position in a quiet, dark, air-conditioned room (constant temperature of 22 °C to 25 °C) throughout the study. A 23-gauge polyethylene catheter was inserted into the left deep antecubital vein to obtain blood samples. FMD was measured 30 min after maintaining the supine position. After completion, we next measured NID with confirmation that the brachial artery diameter had recovered to the baseline value. The observers were blind to the form of examination.

2.3. Measurement of FMD and NID

Vascular response to reactive hyperemia in the brachial artery was used for assessment of endothelium-dependent FMD. A high-resolution linear artery transducer was coupled to computer-assisted analysis software (UNEXEF18G, UNEX Co, Nagoya, Japan) that used an automated edge detection system for measurement of brachial artery diameter. A blood pressure cuff was placed around the forearm. The brachial artery was scanned longitudinally 5 to 10 cm above the elbow. When the clearest B-mode image of the anterior and posterior intimal interfaces between the lumen and vessel wall was obtained, the transducer was held at the same point throughout the scan by a special probe holder (UNEX Co) to ensure consistency of the image. Depth and gain setting were set to optimize the images of the arterial lumen wall interface. When the tracking gate was placed on the intima, the artery diameter was automatically tracked, and the waveform of diameter changes over the cardiac cycle was displayed in real time using the FMD mode of the tracking system. This allowed the ultrasound images to be optimized at the start of the scan and the transducer position to be adjusted immediately for optimal tracking performance throughout the scan. The baseline longitudinal image of the artery was acquired for 10 s, and then the blood pressure cuff was inflated to 50 mm Hg above systolic pressure for 5 min. The longitudinal image of the artery was recorded continuously until 3 min after cuff deflation. Changes in brachial artery diameter were immediately expressed as percentage change relative to the vessel diameter before cuff inflation. FMD was automatically calculated as the percentage change in peak vessel diameter from the baseline value [(Peak diameter − Baseline diameter) / Baseline diameter].

The response to nitroglycerine was used for assessment of endothelium-independent vasodilation. After acquiring baseline rest images for 30 s, a sublingual tablet (75 μg nitroglycerine) was given, and images of the artery were recorded continuously until the dilation reached a plateau after administration of nitroglycerine. We carefully checked in the mouth to confirm that tablet had been dissolved and absorbed a few minutes after administration of nitroglycerine. Subjects in whom the sublingually administered nitroglycerine tablet was not dissolved during the measurement were excluded from this study. NID was automatically calculated as a percent change in peak vessel diameter from the baseline

Table 1
Clinical characteristics of the subjects.

Variables	Total	Non-CKD	CKD	
	($n = 1567$)	($n = 1226$)	($n = 341$)	*P* value
Age, y	59.1 ± 16.8	55.9 ± 17.1	70.3 ± 9.6	<0.001
Male, n (%)	995 (63.4)	797 (65.0)	198 (58.1)	0.02
Body mass index, kg/m^2	23.9 ± 3.9	24.0 ± 4.0	23.7 ± 3.4	0.24
Systolic blood pressure, mm Hg	131.4 ± 18.4	131.2 ± 17.7	132.2 ± 20.6	0.38
Diastolic blood pressure, mm Hg	78.0 ± 12.0	78.5 ± 12.0	76.3 ± 11.9	0.004
Heart rate, bpm	70.0 ± 12.1	69.9 ± 11.8	70.3 ± 12.9	0.51
Total cholesterol, mmol/L	4.97 ± 0.98	4.96 ± 0.95	5.00 ± 1.07	0.52
Triglycerides, mmol/L	1.57 ± 1.09	1.56 ± 1.08	1.62 ± 1.13	0.37
HDL cholesterol, mmol/L	1.53 ± 0.43	1.53 ± 0.43	1.50 ± 0.42	0.16
LDL cholesterol, mmol/L	2.89 ± 0.87	2.89 ± 0.86	2.90 ± 0.91	0.77
Glucose, mmol/L	6.26 ± 2.14	6.17 ± 2.03	6.59 ± 2.49	0.002
HbA1c, %	5.6 ± 0.9	5.6 ± 0.8	5.8 ± 1.1	<0.001
Creatinine, μmol/L	72.9 ± 24.0	65.8 ± 13.0	98.3 ± 34.8	<0.001
eGFR, ml/min/1.73 m^2	73.4 ± 19.3	80.3 ± 15.3	48.8 ± 10.1	<0.001
CKD stage				
G1/G2, n	278/948	278/928	0/0	
G3a/G3b/G4, n	251/63/27	0/0/0	251/63/27	
Smoker, n (%)	847 (54.4)	663 (54.5)	184 (54.1)	0.89
Complications				
Hypertension, n (%)	1203 (76.8)	910 (74.2)	393 (85.9)	<0.001
Dyslipidemia, n (%)	1072 (68.6)	806 (66.0)	266 (78.2)	<0.001
Diabetes mellitus, n (%)	463 (29.6)	328 (26.8)	135 (39.6)	<0.001
Cardiovascular disease, n (%)	326 (21.3)	212 (17.6)	114 (34.8)	<0.001
Coronary artery disease, n (%)	182 (11.7)	98 (8.1)	84 (24.9)	<0.001
Cerebrovascular disease, n (%)	113 (7.3)	66 (5.5)	47 (14.0)	<0.001
Peripheral artery disease, n (%)	131 (8.6)	89 (7.4)	42 (12.7)	0.003
Medication use				
Antihypertensive drug, n (%)	988 (63.3)	729 (59.7)	259 (76.2)	<0.001
Antidiabetic drug, n (%)	283 (18.1)	195 (15.9)	88 (25.8)	<0.001
Statin, n (%)	534 (34.5)	358 (29.5)	176 (52.2)	<0.001
Insulin, n (%)	37 (2.4)	17 (1.4)	20 (5.9)	<0.001
Baseline brachial artery diameter, mm	4.11 ± 0.66	4.10 ± 0.66	4.14 ± 0.66	0.30
Flow-mediated vasodilation, %	3.8 ± 3.0	4.0 ± 3.0	3.1 ± 2.8	<0.001
Endothelial dysfunction, n (%)	391 (25.0)	284 (23.1)	108 (31.7)	0.002
Nitroglycerine-induced vasodilation, %	12.3 ± 5.8	12.7 ± 5.7	10.8 ± 6.0	<0.001
Vascular smooth muscle dysfunction, n (%)	391 (25.0)	263 (21.5)	128 (37.5)	<0.001

CKD indicates chronic kidney disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein; eGFR, estimated glomerular filtration rate.