International Journal of Cardiology 261 (2018) 196–203

Contents lists available at ScienceDirect

International Journal of Cardiology

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

Endothelial dysfunction, abnormal vascular structure and lower urinary tract symptoms in men and women

Shogo Matsui [a], Masato Kajikawa [b], Tatsuya Maruhashi [a], Yumiko Iwamoto [a], Nozomu Oda [a], Shinji Kishimoto [a], Haruki Hashimoto [a], Takayuki Hidaka [a], Yasuki Kihara [a], Kazuaki Chayama [c], Eisuke Hida [d], Chikara Goto [e], Yoshiki Aibara [f], Ayumu Nakashima [f], Farina Mohamad Yusoff [f], Kensuke Noma [b,f], Yoshitaka Kuwahara [g], Akio Matsubara [h], Yukihito Higashi [b,f,*]

[a] *Department of Cardiovascular Medicine, Institute of Biomedical and Health Sciences, Hiroshima University, Hiroshima, Japan*
[b] *Division of Regeneration and Medicine, Medical Center for Translational and Clinical Research, Hiroshima University Hospital, Hiroshima, Japan*
[c] *Department of Gastroenterology and Metabolism, Institute of Biomedical and Health Sciences, Hiroshima University, Hiroshima, Japan*
[d] *Department of Biostatistics and Data Science, Osaka University Graduate School of Medicine, Osaka, Japan*
[e] *Hiroshima International University, Hiroshima, Japan*
[f] *Department of Cardiovascular Regeneration and Medicine, Research Institute for Radiation Biology and Medicine, Hiroshima University, Hiroshima, Japan*
[g] *Nagakubo Hospital, Tokyo, Japan*
[h] *Department of Urology, Institute of Biomedical and Health Sciences, Hiroshima University, Hiroshima, Japan*

A R T I C L E I N F O

Article history:
Received 20 December 2017
Received in revised form 30 January 2018
Accepted 9 February 2018

Keywords:
Lower urinary tract symptoms
Endothelial dysfunction
Flow-mediated vasodilation
Nitroglycerine-induced vasodilation
Pulse wave velocity

A B S T R A C T

Background: Lower urinary tract symptoms (LUTS) is not only common symptoms in elderly men and women but also risk of future cardiovascular events. The purpose of this study was to evaluate the relationships of vascular function and structure with LUTS in men and women.
Methods: We investigated flow-mediated vasodilation (FMD) and nitroglycerine-induced vasodilation (NID) as vascular function, brachial-ankle pulse wave velocity (baPWV) as vascular structure, and LUTS assessed by International Prostate Symptom Score (IPSS) in 287 men and 147 women.
Results: IPSS was significantly correlated with traditional cardiovascular risk factors, Framingham risk score, FMD, NID and baPWV. Moderate to severe LUTS was associated with the prevalence of coronary heart disease in men but not in women. In men, FMD and NID were significantly lower in the moderate to severe LUTS group than in the none to mild LUTS group (2.1 ± 2.0% vs. 4.0 ± 3.0% and 9.3 ± 6.1% vs. 12.8 ± 6.6%, $P < 0.001$, respectively). baPWV was significantly higher in the moderate to severe LUTS group than in the none to mild LUTS group (1722 ± 386 cm/s vs. 1509 ± 309 cm/s, $P < 0.001$). In multivariate analysis, FMD was independently associated with a decrease in the odds ratio of moderate to severe LUTS in men (OR: 0.83, 95% CI, 0.72–0.95; $P = 0.008$) but not in women. NID and baPWV were not independently associated with moderate to severe LUTS either in men or women.
Conclusions: These findings suggest that endothelial dysfunction is associated with LUTS in men. LUTS in men may be useful for a predictor of cardiovascular events.
Clinical trial registration information: URL for Clinical Trial: http://UMIN; Registration Number for Clinical Trial: UMIN000003409.

1. Introduction

Lower urinary tract symptoms (LUTS) is common symptoms in elderly men and women and impairs quality of life (QoL) [1–3]. Recently, several lines of evidence have shown that atherosclerosis plays a critical role in the maintenance and development of LUTS [4–7]. Indeed, coexistence of LUTS and atherosclerotic status such as aging, diabetes mellitus, hypertension, dyslipidemia, smoking and metabolic syndrome is generally found [8–10]. It is clear that LUTS per se is a risk factor for cardiovascular events, especially in men [7,11,12]. In addition, it has been reported that nocturia is independently associated with increased all-cause mortality [13].

Endothelial dysfunction is established as an initial step of atherosclerosis, leading to cardiovascular diseases [14,15]. Measurements of flow-mediated vasodilation (FMD) of the brachial artery as an index of

* Corresponding author at: Department of Cardiovascular Regeneration and Medicine, Research Institute for Radiation Biology and Medicine (RIRBM), Hiroshima University, 1-2-3 Kasumi, Minami-ku, Hiroshima 734-8551, Japan.
E-mail address: yhigashi@hiroshima-u.ac.jp (Y. Higashi).

https://doi.org/10.1016/j.ijcard.2018.02.041
0167-5273/

endothelium-dependent vasodilation and nitroglycerine-induced vasodilation (NID) as an index of endothelium-independent vasodilation are useful for assessing vascular function [16,17]. In addition, both FMD and NID are useful predictors of future cardiovascular events [18–20]. It is well known that pulse wave velocity (PWV) is an index of vascular structure assessed by arterial stiffness [21]. Several investigators have shown that PWV reflects cardiovascular risk factors and cardiovascular diseases and is a predictor for future cardiovascular events [21,22].

Previous studies demonstrated that vascular dysfunction and abnormal vascular structure subsequent to chronic bladder ischemia contribute to the pathogenesis, maintenance and development of LUTS, suggesting a strong relation between atherosclerosis and LUTS [4,5,23–26]. However, there is little information on the relationships of vascular function and structure with LUTS in a clinical setting. Therefore, we evaluated the associations of vascular dysfunction and abnormal vascular structure with LUTS in men and women.

2. Methods

2.1. Subjects

This study was a single center cross-sectional study. A total of 434 subjects (mean age, 63 ± 16 years) were recruited from people who underwent a health checkup at Hiroshima University Hospital between April 2016 and June 2017. Subjects with urologic cancer, neurologic disease and previous pelvic surgery were excluded from the study. Urinalysis was performed in all patients for excluding urinary tract infection. Subjects receiving antidepressants, sleep medication or anti-arrhythmic drugs were also excluded. Subjects with hypertension were defined as those taking oral antihypertensive agents or with systolic blood pressure of >140 mm Hg or diastolic blood pressure of >90 mm Hg measured in a sitting position on at least 3 different occasions. Diabetes mellitus was defined according to the American Diabetes Association recommendation [27]. Dyslipidemia was defined according to the third report of the National Cholesterol Education Program [28]. Smokers were defined as those who had ever smoked. One pack-year was equivalent to 20 cigarettes per day for 1 year. Insomnia was defined in accordance with Athens Insomnia Scale, which is a self-rating scale designed for quantifying sleep difficulty based on the basis of the Tenth Revision of the International Classification of Disease and Related Health Problems [29,30]. Framingham risk score was calculated in accordance with risk factors: age, total cholesterol level, high-density lipoprotein cholesterol level, systolic blood pressure, and smoking status [31]. Peripheral artery disease was defined as current intermittent claudication with ankle-brachial index <0.9 or chronic ischemic rest pain or a history of previous angioplasty and bypass graft. Coronary heart diseases included angina pectoris, myocardial infarction, and unstable angina. Cardiovascular diseases were defined as peripheral artery disease, coronary heart disease, and stroke including ischemic stroke, hemorrhagic stroke, and transient ischemic attack.

2.2. Study protocol

Vascular function was assessed in all subjects using measurements of FMD and NID in brachial artery, and vascular structure was assessed in all subjects using measurement of brachial-ankle PWV (baPWV) as an index of arterial stiffness. The subjects fasted overnight for at least 12 h and the study began at 08:30 h. The subjects remained in a 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. After 30 min of maintaining a supine position, baPWV, FMD and NID were measured. The observers were blind to the form of examination.

2.3. Assessment of LUTS

All subjects completed the International Prostate Symptom Score (IPSS) questionnaire, a clinically validated questionnaire (seven symptom questions and one QoL question) for assessing the presence and severity of LUTS [1,32,33]. LUTS was classified as none (IPSS of 0), mild (IPSS of 1–7), moderate (IPSS of 8–19) and severe (IPSS of ≥20). LUTS was also subclassified as storage symptoms (frequency, urgency, and nocturia) and voiding symptoms (incomplete emptying, weak stream, intermittency, straining). In men, benign prostate hyperplasia (BPH) was defined as a previous history or prostate enlargement assessed by transabdominal ultrasound and computed tomography [1,34].

2.4. Measurements of FMD and NID

We evaluated the vascular response to reactive hyperemia in the brachial artery for assessment of endothelium-dependent FMD. A high resolution linear artery transducer was coupled to computer assisted analysis software (UNEX18G, 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 5–10 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 settings 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. Pulsed Doppler flow was assessed at baseline and during peak hyperemic flow, which was confirmed to occur within 15 s after cuff deflation. Blood flow velocity was calculated from the Doppler data and was displayed as a waveform in real time. The baseline longitudinal image of the artery was acquired for 30 s, and then the blood pressure cuff was inflated to 50 mm Hg above systolic pressure for 5 min. The longitudinal images of the artery were recorded continuously until 5 min after cuff deflation. Pulsed Doppler velocity signals were obtained for 20 s at baseline and for 10 s immediately after cuff deflation. Changes in brachial artery diameter were immediately expressed as the 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. Percentage of FMD [(Peak diameter–Base line diameter)/Baseline diameter] was used for analysis. Blood flow volume was calculated by multiplying the Doppler flow velocity (corrected for the angle) by the heart rate and vessel cross-sectional area ($-r^2$). Reactive hyperemia was calculated as the maximum percentage increase in flow after cuff deflation compared with baseline flow.

The response to nitroglycerine was used for assessment of endothelium-independent vasodilation [35]. After acquiring baseline rest image for 30 s, a sublingual tablet (nitroglycerine 75 μg) was given and imaging of the artery was done continuously for 5 min. NID was automatically calculated as a percentage change in peak vessel diameter from the baseline. Percentage of NID [(Peak diameter–Baseline diameter)/Baseline diameter] was used for analysis.

2.5. Measurement of baPWV

The measurement of baPWV, which is used for assessing aortic stiffness, was determined by two pressure sensors, placed on the right ankle and left brachial arteries to record each pulse wave simultaneously, and the time lag (t) between the notches of the two waves, using a pulse wave velocimeter (Form PWV/ABI, model BP-203RPE, Colin Co.). The distance (D) between the two recording sensors was calculated automatically by inputting the value of individual height. The PWV value was calculated as $PWV = D/t$. PWV was measured for five consecutive pulses, and averages were used for analysis.

2.6. Statistical analysis

Results are presented as means ± SD for continuous variables and percent (%) for categorical variables. A probability value of <0.05 was considered statistically significant. Categorical values were compared by means of the $\chi 2$ test. Continuous variables were compared by using ANOVA for multiple groups. Receiver operating characteristic (ROC) curve analysis was performed to assess the sensitivity and specificity of IPSS for predicting a previous history of cardiovascular disease. Multiple logistic regression analysis was performed to identify independent variables associated with moderate to severe LUTS. Age, gender, presence of insomnia, hypertension, diabetes mellitus and smoking history, and use of diuretics were entered into the multiple logistic regression analysis. As sensitivity analysis, we investigate the association between LUTS and vascular function using a propensity score-matched population. A logistic regression model was used to estimate the propensity of moderate to severe LUTS in men or women based on variables associated with LUTS, including age, body mass index, presence of insomnia, hypertension, diabetes mellitus and smoking history, and Framingham risk score. Subjects with moderate to severe LUTS were matched 1:1 with those with none or mild LUTS in accordance with propensity scores using a caliper width of 0.2 standard deviations of the logit of the propensity score. The data were processed using the software package Stata version 9 (Stata Co, College Station, TX, USA).

3. Results

3.1. Baseline clinical characteristics

Baseline clinical characteristics of all subjects are summarized in Table 1. Of the 434 subjects, 287 (66.1%) were men, 147 (33.9%) were women, 85 (19.6%) had coronary heart disease, and 55 (12.7%) had stroke. Twenty-three subjects (5.3%) were being prescribed medication for LUTS. In men, 20.6% had BPH. On the basis of IPSS, all of the subjects were categorized into two groups as follows: none or mild LUTS (IPSS of 0–7) and moderate to severe LUTS (IPSS of >7). In men, there were significant differences in traditional cardiovascular factors, including age, prevalence of hypertension, diabetes mellitus, dyslipidemia, and smoking history, and cardiovascular diseases between the two groups (Table 1). In women, there were significant differences in age, prevalence of insomnia, hypertension, and stroke, and percentage of subjects receiving diuretics between the two groups (Table 1).