Journal of the American Society of Hypertension 4(6) (2010) 265–271

Research Article

Renal dysfunction impairs circadian variation of endothelial function in patients with essential hypertension

Koji Yamamoto, MD, Yutaka Takeda, MD, PhD, Sumiyo Yamashita, MD, PhD, Tomonori Sugiura, MD, PhD, Yoshimasa Wakamatsu, MD, Michio Fukuda, MD, PhD, Nobuyuki Ohte, MD, PhD, Yasuaki Dohi, MD, PhD*, and Genjiro Kimura, MD, PhD

Department of Cardio-Renal Medicine and Hypertension, Nagoya City University Graduate School of Medical Sciences, Mizuho-ku, Nagoya, Japan

Manuscript received July 27, 2010 and accepted September 20, 2010

Abstract

Some cardiovascular disorders disturb circadian variation of endothelial function. We investigated whether deterioration of renal function alters circadian variation of endothelial function in patients with hypertension. Endothelial function was assessed by the peak forearm blood flow (FBF) response to reactive hyperemia, and 24-hour ambulatory blood pressure monitoring was performed in 25 patients with essential hypertension (61 ± 17 years). Relationships among renal function, 24-hour blood pressure, and endothelial function were analyzed. The ratio of nighttime to daytime mean arterial pressure was inversely correlated with estimated glomerular filtration rate (eGFR) ($r = -0.43, P = .03$). The FBF response to reactive hyperemia examined at 21:00, but not at 6:30 or 11:30, was significantly correlated with eGFR ($r = 0.44, P = .03$). Furthermore, the ratio of FBF response measured at 21:00 to that measured at 6:30 was independently correlated with eGFR ($\beta = 0.47, P = .02$). Renal dysfunction is associated with the derangement of circadian variation of both endothelial function and blood pressure. Nocturnal blood pressure is elevated, and evening endothelial function deteriorates in parallel with a decline in renal function in hypertensive patients. J Am Soc Hypertens 2010;4(6):265–271.

Keywords: Chronic kidney disease; forearm blood flow; reactive hyperemia; plethysmography.

Introduction

Chronic kidney disease is an emerging issue in public health. The risk of cardiovascular disease increases as renal function worsens, even in subjects with only a mild decline in glomerular filtration rate or mild albuminuria.[1,2] The mechanism underlying the cardio-renal connection is not yet fully understood.

Endothelial dysfunction has been reported in individuals with chronic kidney disease,[3–6] although the relationship between the severity of renal dysfunction and endothelial dysfunction is not clear. Because vascular endothelial dysfunction is an initial step in the development of arteriosclerosis and predicts future cardiovascular events,[7–9] this may be a key to understanding the cardiorenal connection. In general, blood pressure (BP) falls during sleep and rises around waking, producing a circadian rhythm. However, in individuals with renal dysfunction, this pattern is altered, and nocturnal BP is elevated as renal function deteriorates.[10,11] This alteration in the circadian rhythm is quite important, because nocturnal BP is one of the most powerful predictors of cardiovascular events among several BP measurements,[12] and nondipping status (BP fall during sleep <10%) is associated with an increased risk of cardiovascular events.[13–15] Indeed, endothelial function is impaired in hypertension[16–19] to a greater extent in

This study was supported by Research Grants for Cardiovascular Diseases (C-2001-5) from the Ministry of Health and Welfare of Japan, as well as Grants from Nagoya City University, Salt Science Research Foundation (No. 04C1), Metabolic Disorders Treatment Research Foundation, Aichi Kidney Foundation, Japan Cardiovascular Research Foundation, and Grant-in-Aid for Scientific Research (B#19390232 & C#17590836) from Ministry of Education, Culture, Sports, Science, and Technology of Japan through Japan Society for the Promotion of Science.

Conflict of interest: none.

*Corresponding author: Yasuaki Dohi, MD, PhD, Department of Cardio-Renal Medicine and Hypertension, Nagoya City University Graduate School of Medical Sciences, Mizuho-cho, Mizuho-ku, Nagoya 467-8601, Japan. Tel: +81-52-853-8221; fax +81-52-852-3796.

E-mail: ydohi@med.nagoya-cu.ac.jp

1933-1711/$ - see front matter
doi:10.1016/j.jash.2010.09.004

nondippers than in dippers (BP fall during sleep $\geq$10%).[20] Thus, renal insufficiency may produce endothelial dysfunction through a disturbance of the BP circadian rhythm.

Recent studies reported morning attenuation of endothelial function in healthy people.[21–24] This circadian variation of endothelial function is altered in patients with ischemic and nonischemic heart disease,[25,26] suggesting that derangement of the circadian variation of endothelial function is another phenotype of endothelial dysfunction. Therefore, the present study was designed to investigate the relationship between renal function and the circadian variation of endothelial function to test the hypothesis that renal dysfunction deranges the circadian variation of endothelial function in patients with hypertension.

Patients and Methods

Study Patients

We studied 25 consecutive inpatients with essential hypertension (6 men and 19 women; mean age 61 $\pm$ 17 years; range, 21–82 years). Hypertension was defined as an untreated office BP $\geq$140 mm Hg in systole and/or $\geq$90 mm Hg in diastole, or the use of antihypertensive drugs with a previous diagnosis of hypertension. Secondary hypertension was excluded by a detailed medical history, and appropriate physical, biochemical, and radiological examinations. Subjects were inpatients in the Nagoya City University Hospital between April 2007 and June 2009 for participation in a program for management of hypertension, which included detailed evaluation of BP abnormalities and lifestyle education. Patients on hemodialysis, or with a history of clinically relevant heart disease, atrial fibrillation, cerebral infarction, or inflammatory disease, were excluded from the study. Estimated glomerular filtration rate (eGFR) was calculated using the formula of the Japanese Society of Nephrology.[27]

The study was designed in accordance with the Declaration of Helsinki and the study protocol was approved by the Ethics Committee of Nagoya City University. Written informed consent for participation was obtained from all patients prior to the start of the study.

Study Protocol

Patients were served a low-salt diet (6 g/day) during the hospital stay and data collection began at least 8 days after admission. Cigarette smokers were instructed to quit smoking before hospitalization. All antihypertensive drugs were withdrawn on the day of admission. If patients developed critically high BP (systolic BP >180 mm Hg and/or diastolic BP >105 mm Hg) after withdrawal of antihypertensive medications, the medications were recommenced for the safety of those patients and were not changed throughout the study period. Fasting blood samples were taken on the morning of the ninth day after admission, and urine samples were collected for 24 hours after blood sampling. Ambulatory blood pressure (ABP) monitoring was started at 10:00 on the ninth day. Forearm blood flow (FBF) response to reactive hyperemia was measured three times within 24 hours: at 06:30 (in the early morning after waking and before breakfast), 11:30 (4 hours after breakfast), and 21:00 (4 hours after dinner).

Ambulatory 24-hour Monitoring of Blood Pressure

ABP was noninvasively monitored every 30 minutes for 24 hours using a validated automatic device (model ES-H531, Terumo, Tokyo, Japan). Before monitoring, the accuracy of the device was checked against a mercury column to ensure that the difference was not greater than $\pm$ 5 mm Hg. Patients were asked to report the time they went to bed and the time they got up. Mean arterial pressure (MAP) was calculated as diastolic blood pressure plus one-third of the pulse pressure. The nighttime BP was calculated as the average of the readings while in bed, and the daytime BP was the average of the remaining readings. Artifacts in ABP measurements were defined according to criteria described previously[10,28] and were omitted from the analysis.

Endothelial Function

Endothelial function was noninvasively assessed using a mercury-filled silastic strain-gauge plethysmograph (EC-6, D.E. Hokanson, Inc., Bellevue, WA) in response to reactive hyperemia as previously described.[29] Briefly, the subjects were asked to rest in a supine position in a quiet, temperature-controlled laboratory (22°C–25°C) for at least 15 minutes. A strain gauge that had been electrically calibrated before the first use was attached to the widest part of the upper left forearm, connected to a plethysmography device, and supported above the right atrium. To exclude the hand circulation from the measurements, a wrist cuff was inflated to a pressure 50 mm Hg above the systolic blood pressure for 1 minute before each measurement and throughout the measurement of FBF. To obtain reactive hyperemia, FBF was occluded by inflating the cuff on the left upper arm at a pressure 50 mm Hg above the systolic blood pressure for 5 minutes. After the release of cuff occlusion, FBF was measured for 3 min. The upper arm congesting cuff was inflated to 40 mm Hg for 7 seconds in each 15-second cycle to occlude venous outflow from the arm using a rapid cuff inflator (E-20, D.E. Hokanson, Inc.). After the measurements of reactive hyperemia, 0.3 mg of nitroglycerin was administered sublingually for the measurement of endothelium-independent vasodilation. FBF was expressed as mL/min/100 mL of forearm tissue volume.