Loss of nighttime blood pressure dipping as a risk factor for coronary artery calcification in nondialysis chronic kidney disease

Hoon Young Choi, MD, PhD, Chan Joo Lee, MD, PhD, Jung Eun Lee, MD, PhD, Hyun Su Yang, MS, Ha Yan Kim, MS, Hyeong Cheon Park, MD, PhD, Hyeon Chang Kim, MD, PhD, Hyuk-Jae Chang, MD, PhD, Sung-Ha Park, MD, PhD, Beom Seok Kim, MD, PhD.

Abstract

Diurnal variations in blood pressure (BP) loss are closely associated with target organ damage and cardiovascular events. The quantity of coronary artery calcification (CAC) correlates with the atherosclerotic plaque burden, and an increased quantity indicates a substantially increased risk of cardiovascular events. This study investigated the nighttime diurnal variation in BP loss associated with CAC in patients with chronic kidney disease (CKD).

Of the 1958 participants, we enrolled 722 participants with CKD without a history of acute coronary syndrome or symptomatic coronary artery disease. CAC was measured with computed tomography. BP was measured using 24-hour ambulatory BP monitoring. Central BP was measured using a SphygmoCor waveform analysis system.

Participants with CAC had significantly higher 24-hour systolic, daytime systolic, and nighttime systolic ambulatory BP and central systolic BP. The percentage of participants with dipping loss was significantly higher among those with CAC. Multivariate logistic regression analysis indicated that dipping loss and dipping ratio were independently associated with CAC after adjusting for traditional and nontraditional cardiovascular risk factors and other BP parameters, including measurements of office-measured BP and central BP. The dipping status improved risk prediction for CAC after considering traditional risk factors and office-measured BP, using the net reclassification improvement and integrated discrimination improvement.

Nighttime loss of diurnal variation in BP is an independent risk factor for CAC in CKD patients.

Abbreviations: ABPM = Ambulatory blood pressure monitoring, ACEis = Angiotensin-converting enzyme inhibitors, ARBs = Angiotensin receptor blockers, BBs = Beta blockers, BP = Blood pressure, CAC = Coronary artery calcification, CAD = Coronary artery disease, CCBs = Calcium channel blockers, CKD = Chronic kidney disease, CPP = Calcium-phosphate product, CVD = Cardiovascular disease, DBP = Diastolic BP, eGFR = Estimated glomerular filtration rate, HbA1C = Hemoglobin A1C, HDL = High-density lipoprotein, IDI = Integrated discrimination improvement, LDL = Low-density lipoprotein, NRI = Net reclassification improvement, PP = Pulse pressure, SBP = Systolic BP, UACR = Urine albumin-to-creatinine ratio.

Keywords: blood pressure, chronic kidney disease, coronary artery calcification, dipping

1. Introduction

Cardiovascular disease (CVD) is a major cause of death in chronic kidney disease (CKD) patients.[1–3] CVD risk has been reported to increase early during the natural history of CKD and has shortened the time to progression to dialysis therapy in large population studies.[4,5]

Coronary artery calcification (CAC) measured using computed tomography is a noninvasive method of assessing the burden of coronary atherosclerosis. Patients with CKD have been shown to have higher CAC scores and higher incidence rates for future development of de novo CAC, even in the absence of baseline CAC. Cross-sectional analyses have also reported a relationship between lower estimated glomerular filtration rate (eGFR) and increased CAC.[6–8] Interestingly, the optimal cut-off score for CAC that is used to predict obstructive coronary artery disease (CAD) is higher for patients with moderate CKD than for patients without significant CKD.[9]

Blood pressure (BP) control has an important role in CVD and the progression of kidney failure in CKD patients.[10,11] Hypertension may be involved in the arterogenic process, which is considered a mechanism of CAC.[12,13] Recently, not only high BP but also diurnal variations in BP have been reported to be associated with CVD events and stroke in CKD patients.[13–15] Nighturnal nondipping, which is an abnormal elevation of nocturnal BP compared with daytime BP, has been considered to reflect the loss of diurnal BP variation. The prevalence of nondipping is relatively high in patients with diabetes or reduced renal function.[13,16,17] In a prospective cohort study, abnormal diurnal variations in BP were associated with CAC in young,
healthy adults, even though they had optimal BP.\(^{[18]}\) In contrast, another cross-sectional study showed that BP dipping was not significantly associated with CAC score, although average BP levels determined by 24-hour ambulatory BP monitoring (ABPM) showed an improved ability to predict the presence of CAC.\(^{[19]}\)

The present study investigated whether nighttime dipping loss was associated with CAC and whether this relationship was maintained after adjustment for traditional or nontraditional atherosclerosis risk factors and other parameters of BP for CKD patients. In addition, this study attempted to elucidate the predictive value of 24-hour BP measurements for CAC in CKD patients.

2. Methods

2.1. Participants

Participants in the Cardiovascular and Metabolic Disease Etiology Research Center High-Risk Cohort [(CMERC-HI): Individualized prevention strategy for high-risk patients in CVD: prospective cohort study NCT02003781; ClinicalTrials.gov] were screened.\(^{[20]}\) Of the 1958 participants who were enrolled into the CMERC-HI cohort between November 2013 and May 2016, participants with CKD, defined as an increased urine albumin-to-creatinine ratio (UACR) (≥17 for men and ≥25 mg/g for women) and eGFR ≥60 mL/min/1.73 m\(^2\) or eGFR < 60 mL/min/1.73 m\(^2\), were enrolled in this study. Participants with atrial fibrillation or those who underwent dialysis or kidney transplantation were excluded (Fig. 1).\(^{[21,22]}\)

A medical history assessment and physical examination were performed to gather additional information, including sex, hypertension, diabetes, use of anti-hypertensive agents [such as angiotensin receptor blockers (ARBs) or angiotensin-converting enzyme inhibitors (ACEis), beta blockers (BBs), and calcium channel blockers (CCBs)], statin use, BP, and body mass index (kg/m\(^2\)). Laboratory findings included hemoglobin, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, calcium-phosphate product (CPP), fasting serum glucose, uric acid, serum albumin, hemoglobin A1C (HbA1C), eGFR, and UACR.\(^{[23,24]}\) eGFR was calculated from serum creatinine values by using the CKD Epidemiology Collaboration (CKD-EPI) creatinine equation adjusted for age, sex, and race.\(^{[25]}\)

This study was approved by the Institutional Review Board of Severance Hospital, Yonsei University College of Medicine, Seoul, Korea (4-2013-0581). The study was performed in accordance with the ethical principles of the 1975 Declaration of Helsinki. All patients provided informed consent.

2.2. Blood pressure and hydration status measurement

Office BP was measured using an oscillometric Omron HEM-7080IC automatic BP device (IntelliSense; Omron, Kyoto, Japan). Three consecutive seated BP readings were recorded at intervals of 3 to 5 minutes. Office BP was calculated as the mean of the 3 BP readings. Pulse pressure (PP) was obtained by the difference between the systolic and diastolic pressure readings.

The 24-hour ABPM was performed using a Takeda TM-2430 instrument (A&D Medical, Tokyo, Japan), with readings taken every 30 minutes. Daytime and nighttime periods were defined according to information provided by the patient. The ambulatory BP readings at 24 hours, daytime, and nighttime were averaged. Nighttime dipping was defined as > 10% decrease in mean systolic BP (SBP) at night, and dipping status was presented as dipping loss and dipping ratio. Loss of dipping was
defined as no nighttime dipping,[26] and the dipping ratio was defined as the ratio of the mean nighttime SBP to the mean daytime SBP.[11] Higher systolic ABPM status was defined as a mean SBP ≥130 mm Hg as measured using 24-hour ABPM.[26]

Central BP was measured using a SphygmoCor waveform analysis system (AtCor Medical, Sydney, NSW, Australia) as previously reported.[17,24]

2.3. Coronary artery calcification score measurement

Participants were scanned using 320-detector row computed tomography (Aquilion ONE; Toshiba Medical Systems Corporation, Tokyo, Japan). A nonenhanced prospective electrocardiogram was performed to measure the CAC score with the following parameters: rotation time, 275 ms; slice collimation, 0.5 mm; slice thickness, 3.0 mm; tube voltage, 100 kV; and automatic tube current modulation (SURE Exposure 3D standard; Toshiba Medical Systems Corporation, Otawara, Japan). Images were analyzed in a core workstation by using dedicated software (TeraRecon V. 4.4.11.82.3430.Beta; TeraRecon, Foster City, CA). The CAC score was measured using the Agatston method.[25,30]

The total CAC score was the sum of all individual calcified lesions identified within the area of the coronary arteries. CAC scores >100 U indicated CAC.[22,31]

2.4. Statistical analysis

All continuous variables are reported as the median (Q1–Q3). All continuous variables are reported as the median (Q1–Q3). Table 1 summarizes the BP parameters of participants classified according to CAC. Office SBP, office DBP, and PP were significantly higher for participants with CAC than for those without CAC. Participants with CAC had significantly higher 24-hour systolic ABPM, daytime systolic ABPM, and nighttime systolic and diastolic ABPM than participants without CAC. Central BP was also significantly higher for participants with CAC than for those without CAC (128.0 [112.0–141.0] mm Hg; P < .0001) (Table 2). The loss of dipping percentage and dipping ratio were significantly higher among participants with CAC (56.0% vs 44.4%, P = .003; 0.92 [0.86–0.97] vs 0.90 [0.84–0.95], P = .001) (Fig. 2).

Table 1. Characteristics of all participants, classified by CAC.

|                         | All participants (n = 722) | Participants without CAC (n = 472) | Participants with CAC (n = 250) | P     |
|-------------------------|---------------------------|------------------------------------|---------------------------------|-------|
| Age, y                  | 65.0 [56.0–71.0]          | 62.0 [52.0–69.0]                   | 69.0 [62.0–73.0]                | < .001|
| Sex [male, n (%)]       | 316 (43.8)                | 187 (39.6)                         | 129 (51.6)                      | .002  |
| Hypertension [yes, n (%)] | 640 (88.6)               | 418 (88.6)                         | 222 (88.8)                      | .023  |
| Diabetes [yes, n (%)]   | 334 (46.3)                | 169 (35.8)                         | 165 (66.0)                      | < .001|
| ACEI or ARB use [yes, n (%)] | 409 (56.6)              | 285 (60.4)                         | 124 (49.0)                      | .005  |
| BB use [yes, n (%)]     | 225 (31.2)                | 134 (28.4)                         | 91 (36.4)                       | .027  |
| CCB use [yes, n (%)]    | 314 (43.5)                | 191 (40.5)                         | 123 (49.2)                      | .024  |
| Statin use [yes, n (%)] | 351 (48.6)                | 216 (45.8)                         | 135 (54.0)                      | .035  |
| BMI, kg/m²               | 25.1 [22.9–27.5]          | 25.0 [22.8–27.6]                   | 25.1 [23.3–27.2]                | .536  |
| Hemoglobin, g/dL         | 13.0 [12.0–14.0]          | 13.0 [12.0–14.0]                   | 13.0 [11.0–14.0]                | .022  |
| LDL-cholesterol, mg/dL   | 45.3 [38.0–54.0]          | 46.0 [39.0–56.0]                   | 44.0 [36.0–51.0]                | < .001|
| HDL-cholesterol, mg/dL   | 90.0 [71.0–112.0]         | 94.0 [74.0–115.0]                  | 83.0 [65.0–103.0]               | < .001|
| CPP                     | 36.0 [27.0–36.0]          | 36.0 [27.0–36.0]                   | 36.0 [30.0–40.0]                | .127  |
| Fasting glucose, mg/dL   | 104.0 [94.5–124.0]        | 101.0 [93.0–115.0]                 | 111.0 [97.0–134.0]              | < .001|
| eGFR, ml/min/1.73 m²     | 56.4 [32.4–67.3]          | 56.8 [32.6–67.3]                   | 55.2 [32.7–67.3]                | .071  |
| UACR, mg/l              | 120.0 [33.0–324.0]        | 129.0 [32.0–352.0]                 | 112.0 [39.0–271.0]              | .597  |

Data are expressed as number (%) or median [Q1–Q3].
ACEI = angiotensin-converting enzyme inhibitors; ARB = angiotensin II receptor blockers; BB = beta blockers; BMI = body mass index; CAC = coronary artery calcification; CCB = calcium channel blockers; CPP = calcium-phosphate product; eGFR = estimated glomerular filtration rate; HbA1C = hemoglobin A1C; HDL = high-density lipoprotein; LDL = low-density lipoprotein; UACR = urine albumin-to-creatinine ratio.

3. Results

3.1. Participant characteristics

Baseline characteristics of the participants are summarized in Table 1. The 722 CKD patients who were included had a median age of 63.0 years. The median eGFR level was 56.4 mL/min/1.73 m² and the median UACR was 120 mg/L. Clinical characteristics and biochemical findings of patients without and with CAC are also summarized in Table 1. Two-hundred fifty patients demonstrated high CAC scores (>100U). Age, male sex, diabetes prevalence, B B or CCB use, and statin use were significantly greater for participants with CAC than for those without CAC, whereas the use of ACEi or ARB was greater for participants without CAC. The prevalence of hypertension was similar between the 2 groups. Participants with CAC had higher fasting glucose and HbA1C levels and lower hemoglobin, LDL cholesterol, and HDL cholesterol levels than those without CAC. CPP, eGFR, and UACR values were not significantly different (Table 1).

Table 2 summarizes the BP parameters of participants classified according to CAC. Office SBP, office DBP, and PP were significantly higher for participants with CAC than for those without CAC. Participants with CAC had significantly higher 24-hour systolic ABPM, daytime systolic ABPM, and nighttime systolic and diastolic ABPM than participants without CAC. Central BP was also significantly higher for participants with CAC than for those without CAC (128.0 [112.0–141.0] vs 116.0 [107.0–129.0] mm Hg; P < .0001) (Table 2). The loss of dipping percentage and dipping ratio were significantly higher among participants with CAC (56.0% vs 44.4%, P = .003; 0.92 [0.86–0.97] vs 0.90 [0.84–0.95], P = .001) (Fig. 2).
3.2. Association of the coronary artery calcification score with cardiovascular risk variables and blood pressure parameters

Univariate logistic regression analysis to examine the association of individual study covariates with CAC identified the following risk factors that were included in multivariate models: cardiovascular conventional risk factors, including sex, age, diabetes, hypertension, and HDL cholesterol; medications, such as use of ACEi or ARB, BB, CCB, and statins; laboratory parameters, such as hemoglobin, CPP, glucose, uric acid, albumin, HbA1C, eGFR, and UACR; BP parameters, including office SBP, higher ABPM, daytime systolic ABPM, and central SBP; dipping loss; and dipping ratio. Male sex, older age, diabetes, lower HDL cholesterol and hemoglobin, and higher glucose and HbA1C were significant risk factors affecting CAC. In addition, higher office SBP, higher PP, higher systolic ABPM, higher daytime systolic ABPM, and higher central SBP affected CAC. Loss of dipping and dipping ratio were also significant risk factors affecting CAC (odds ratio (OR), 1.60; confidence interval (CI), 1.17–2.18; P = .003; OR, 20.00; CI, 3.10–129.00; P = .002) (Table 3).

CAC was used as a dependent variable for multivariate logistic regression analysis, and dipping status was entered as an independent variable. We adjusted for traditional cardiovascular risk factors (including age, sex, diabetes, hypertension, and HDL cholesterol), laboratory parameters (such as hemoglobin, CPP, and HbA1C), medications (including anti-hypertensives and statins), and BP parameters (such as office SBP, PP, higher ABPM, daytime systolic ABPM, and central SBP) to investigate the effects of dipping on CAC. Dipping loss and higher dipping ratio were significantly associated with higher CAC scores after adjustment for traditional risk factors (loss of dipping: OR, 1.70; CI,
Table 4
Sequential multivariate logistic regression analysis according to dipping status.

| Variables                      | Loss of dipping OR (95% CI) | P  | Dipping ratio OR (95% CI) | P  |
|--------------------------------|-----------------------------|----|---------------------------|----|
| Adjusted by traditional risk factors | 1.70 (1.19–2.43)            | .004 | 23.12 (2.65–201.49)       | .004 |
| Adjusted by traditional risk factors + labs | 1.72 (1.17–2.52)            | .006 | 13.66 (1.38–134.99)       | .025 |
| Adjusted by traditional risk factors + meds | 1.64 (1.14–2.37)            | .008 | 19.14 (2.10–174.75)       | .009 |
| Adjusted by traditional risk factors + eGFR + UACR | 1.50 (1.02–2.20)            | .040 | 12.537 (1.25–126.27)      | .032 |
| Adjusted by traditional risk factors + Office SBP | 1.72 (1.19–2.47)            | .004 | 24.97 (2.78–224.24)       | .004 |
| Adjusted by traditional risk factors + PP | 1.69 (1.17–2.43)            | .005 | 22.13 (2.45–199.7)        | .006 |
| Adjusted by traditional risk factors + Higher ABPM | 1.70 (1.18–2.44)            | .004 | 19.43 (2.20–171.59)       | .008 |
| Adjusted by traditional risk factors + Daytime systolic ABPM | 1.91 (1.32–2.77)            | .001 | 40.61 (4.40–374.54)       | .001 |
| Adjusted by traditional risk factors + Central SBP | 1.60 (1.08–2.37)            | .019 | 18.12 (1.65–198.60)       | .018 |

Traditional risk factors: male sex, age, diabetes, hypertension, HDL cholesterol. Labs: hemoglobin, HbA1C, and GFR. Meds: ACEi or ARB, CCB, BB, and statin use. ABPM = ambulatory blood pressure monitoring, ACE = angiotensin-converting enzyme inhibitors, ARB = angiotensin II receptor blockers, BB = beta blockers, CCB = calcium channel blockers, CI = confidence interval, GFR = estimated glomerular filtration rate, HbA1C = hemoglobin A1C, HDL = high-density lipoprotein, OR = odds ratio, PP = pulse pressure, SBP = systolic blood pressure, UACR = urine albumin-to-creatinine ratio.

1.19–2.43; P = .004; dipping ratio: OR, 23.12; CI, 2.65–201.49; P = .004. In addition, the multivariate logistic regression analysis revealed that dipping loss and higher dipping ratio were independently correlated with CAC after sequential adjustment for traditional risk factors together with nontraditional risk factors, laboratory parameters, including hemoglobin, CPP, and HbA1C, medications such as stents and anti-hypertensives, eGFR, and UACR. Loss of dipping and higher dipping ratio were also independently associated with CAC after sequential adjustment for traditional risk factors and any BP parameters such as office SBP, PP, higher ABPM, daytime systolic ABPM, and central SBP (Table 4).

To evaluate the improvement of risk prediction with the addition of dipping loss for CAC, we determined the NRI and IDI indices. Loss of dipping provided improved risk prediction for CAC. NRI was 0.113 (P = .001) and IDI was 0.012 (P = .006) after accounting for traditional risk factors and office SBP. The dipping ratio also improved the risk prediction for CAC: NRI was 0.088 (P = .004) and IDI was 0.012 (P = .006) after accounting for traditional risk factors and office SBP.

4. Discussion
Early diagnosis or prevention of CVD is important for CKD patients because they face markedly increased CVD morbidity and mortality rates that cannot be fully explained by traditional risk factors alone.12 However, imaging modalities to identify target organ damage, the management of BP in CKD patients is usually based on BP measurements in a clinical setting due to its simplicity.1315 The present study elucidated the association between higher CAC and dipping status after adjustment for other BP parameters, including office-measured BP and central BP measured using a SpysmogCor waveform analysis system. Our data suggested that CKD patients who had loss of diurnal variation in BP during 24-hour ABPM should be closely monitored for the presence of CAC, even if they have optimal office-measured BP results. This study also determined that the dipping status improved risk prediction for CAC using NRI and IDI after accounting for traditional risk factors and office-measured BP. Central hemodynamic and arterial stiffness have been reported to be associated with CVD in advanced CKD and end-stage renal disease.153739 In addition, central SBP and PP may predict CVD events and end-organ damage more accurately than brachial BP.34 In our data, central SBP was significantly higher for CKD patients with CAC, and increased central SBP together with other BP parameters was significantly associated with higher CAC in the univariate regression analysis. After adjustment for central SBP and traditional risk factors in the multivariate regression analysis, dipping loss and higher dipping ratio were significantly associated with CAC. However, a significant association was shown between the loss of diurnal variation and CAC for the participants without CKD in this cohort data (data not shown). Therefore, the association between CAC and loss of diurnal variation in BP may be evident only for participants with CKD.

The amount of CAC correlates closely with the amount of atherosclerosis, and this forms the basis for the use of scoring to improve risk prediction beyond clinical variables in the general population.14 The extent of CAC is directly proportional to increased cardiovascular event rates, and CAC scores of 100 (or 75th percentile) indicate high CVD risk. A meta-analysis by Fletcher et al43 showed that with a CAC score between 1 and 100, the relative risk of major adverse cardiovascular events doubles (hazard ratio, 2.1), but the risk is 3–17-fold higher for an Agatston score above this range. However, CAC is more common in patients with CKD, and atherosclerotic plaques have higher calcium content than those in patients without CKD. The mean Agatston scores were shown to be higher than those for controls: 175 U higher for patients with stage 2 CKD and 693 U higher for patients with stage 3 CKD.43 A Chronic Renal
Insufficiency Cohort study investigator demonstrated that the severity of CKD and CAC scores had a graded relationship.[6] A single-center study showed that the highest CAC score quartile was associated with a 2.5-fold increase in all-cause mortality compared with the lowest quartile for patients with proteinuria and diabetes with mild to moderate stages of CKD.[3,4,5]

Although the mechanism underlying the loss of diurnal variation is unclear, it has been shown to be a consequence of autonomic dysfunction, volume overload, and abnormal sodium processing in CKD.[3,17,46–48] Anemia and disturbances of calcium-phosphate metabolism, which are important clinical indicators of the severity of CKD and are closely related to kidney failure, were also correlated with the loss of diurnal variation.[48]

Our data revealed that participants with CAC had lower hemoglobin levels and comparable CPP levels than participants without CAC. However, hemoglobin and CPP did not show any correlation with loss of dipping (data not shown). Loss of dipping and higher dipping ratio were independent risk factors for CAC in CKD patients after adjusting for covariates such as hemoglobin and CPP in this study.

One strength of this study was its analysis of many forms of BP measurement, including office BP, PP, 24-hour ABPM, and central BP, which have recently been applied in clinical settings. Moreover, the diurnal BP variation loss was shown to be associated with CAC at all CKD stages in the present study. We enrolled patients with mild CKD (stage 1 or 2), defined as the presence of increased urine albumin excretion and eGFR ≥60mL/min, and moderate to advanced CKD (stages 3–5), defined as eGFR <60mL/min. Our data indicated that LDL cholesterol, which has been recognized as a CVD risk factor, was significantly lower and that statin use to prevent CVD was higher in patients with CAC. These findings implied that patients with CAC should be monitored with 24-hour ABPM for diurnal BP variation loss, even if they have already received treatment and have been monitored carefully.

This study has several limitations. First, our observations were cross-sectional, and we used a small sample size; therefore, the precise relationship between dipping and CAC remains unclear. Prospective studies should be performed to determine whether dipping loss can predict the progression of CAC in CKD. Second, urinary sodium excretion levels were not obtained; therefore, we could not determine whether the loss of dipping was induced by impaired renal sodium excretion. Finally, diagnostic coronary angiography could not be checked to confirm the relationship between the loss of diurnal variation in BP and the presence of CAC due to nephrotoxicity related to radiocontrast use in CKD patients.

In conclusion, nighttime loss of diurnal variation in BP was significantly correlated with CAC and was an independent risk factor for high CAC scores in CKD patients. Patients who do not demonstrate dipping during 24-hour ABPM should be monitored carefully for the development of CAC. Measurement of 24-hour ABPM may predict CAC in CKD patients.

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