Original Article

CMJ

www.cmj.ac.kr

Impacts of Coronary Artery Calcification on Intradialytic Blood Pressure Patterns in Patients Receiving Maintenance Hemodialysis

Seongyup Yeo[1], Ji In Moon[1], Jungho Shin[1,*], Jin Ho Hwang[1], Iksung Cho[2], and Su Hyun Kim[1]

Divisions of [1]Nephrology and [2]Cardiology, Department of Internal Medicine, Chung-Ang University Hospital, Chung-Ang University College of Medicine, Seoul, Korea

Intradialytic blood pressure abnormalities are associated with adverse outcomes in patients with end-stage renal disease on dialysis. Vascular calcification is a common complicating feature, but whether this complication results in intradialytic blood pressure abnormalities remains uncertain. Therefore, this study investigated the relationship between coronary artery calcium score and intradialytic blood pressure abnormalities in patients with end-stage renal disease on maintenance hemodialysis. Thirty-six patients who received nongated chest computed tomography scans were included. Intradialytic hypotension was defined as a minimum intradialytic systolic blood pressure of <100 mmHg or a pre-dialysis blood pressure − minimum intradialytic systolic blood pressure >30 mmHg. Intradialytic hypertension was defined as >10 mmHg increase in systolic blood pressure (pre- to post-dialysis). Patients were classified as 22 (61.1%) with coronary artery calcium score <400 and 14 (38.9%) with coronary artery calcium score ≥400. Median systolic and diastolic blood pressures were equivalent, but median pulse pressure was higher in patients with coronary artery calcium score ≥400 than in those with scores <400. Coronary artery calcium score was comparable according to both intradialytic hypotension and hypertension, and had no correlation with systolic blood pressure fall and nadir systolic blood pressure. Coronary artery calcium score predicted the occurrence of cardiovascular events and all-cause mortality (hazard ratio 1.001 and 1.001; p=0.058 and 0.010). Coronary vascular calcification could be irrelevant to intradialytic blood pressure abnormalities in patients with end-stage renal disease on dialysis.

Key Words: *Vascular Calcification; Dialysis; Blood Pressure; Hypotension; Hypertension*

Article History:
Received October 21, 2019
Revised November 4, 2019
Accepted November 7, 2019

Corresponding Author:
Jungho Shin
Division of Nephrology, Department of Internal Medicine, Chung-Ang University Hospital, 102 Heukseok-ro, Dongjak-gu, Seoul 06973, Korea
Tel: +82-2-6299-3171
Fax: +82-2-6299-2626
E-mail: junghoshin@cau.ac.kr

INTRODUCTION

Patients with end-stage renal disease (ESRD) who are on maintenance hemodialysis experience a decrease in blood pressure (BP) during their dialysis treatment, because the fluid retained during the interdialytic period is removed by ultrafiltration.[1] Intradialytic BP patterns are also influenced by antihypertensive medications, the sympathetic nervous system, cardiac and vascular diseases, and the hemodialysis treatment.[1,2] Deviations from the typical course, known as intradialytic hypotension and hypertension, can complicate dialysis and result in adverse outcomes such as all-cause mortality and cardiovascular events.[2] Therefore, efforts to understand the pathophysiology of intradialytic BP abnormalities and prevent these complications are warranted. Intradialytic hypotension occurs when the rate of fluid removal exceeds that of plasma refill, conversely, intradialytic hypertension is associated with volume overload.[2] However, volume factors may not be sufficient to explain the pathophysiology of intradialytic BP abnormalities, and an investigation of other causes including cardiovascular abnormalities is needed.[2]

Cardiovascular disease is the major cause of death in patients with ESRD.[3] Various traditional and uremia-related factors have been established as causative for the disproportionate burden of cardiovascular disease in the ESRD

https://doi.org/10.4068/cmj.2020.56.1.27

population.[4] One of the common uremia-related factors is vascular calcification, which is caused by abnormal endocrine and mineral metabolism.[5] Various studies have reported that vascular calcification can be a predictor of increased cardiovascular morbidity and mortality.[5-7] Moreover, recent studies have shown a significant relationship between the vascular calcification that was assessed by plain radiograph and intradialytic hypotension in patients with ESRD on hemodialysis.[8,9] These studies indicated that vascular calcification could result in a predisposition for intradialytic hypotension. Therefore, the assessment of vascular calcification may be useful for predicting the occurrence of intradialytic hypotension as well as the probability of cardiovascular events in patients with ESRD on maintenance hemodialysis.

In this study, we assessed the degree of coronary artery calcification as an indicator for the burden of cardiovascular disease using images obtained from nongated chest computed tomography (CT), and examined the correlation between calcification and intradialytic BP patterns in patients with ESRD on maintenance hemodialysis. We evaluated the impacts of coronary artery calcification on intradialytic BP abnormalities and further investigated their independent impacts on cardiovascular events and all-cause mortality.

MATERIALS AND METHODS

1. Patients

This study recruited adult patients with ESRD who underwent outpatient maintenance hemodialysis three times a week between October 2011 and April 2016. Of the 141 outpatients, we enrolled 40 who had chest CT images. The baseline was defined as the time when body composition was assessed, and we allowed 3 to 12 months to elapse after the CT conductance in order to avoid the acute ill periods needing CT. This study included a total of 36 patients who had clinical and body composition data, and who had follow-up periods of at least one month.

The included patients were reviewed from the baseline until death, loss to follow-up, or the study end point (August 2017). This study was approved by the Institutional Review Board (IRB) of Chung-Ang University Hospital (IRB number: C2016146[1889]). The IRB waived the need for written consent from the patients, because this study had a retrospective design, and the subjects were de-identified.

2. Coronary artery calcification imaging and scoring

The included 36 patients received CT scans for the following reasons: 12 for identification of pneumonia; six for evaluation of new lesions such as infiltration or effusion on chest X-ray; six for differential diagnosis of malignancy due to a lung nodule; six for evaluation of chronic respiratory symptoms such as cough, sputum, or dyspnea; three for monitoring of cancer recurrence after treatment; and three for surveillance of health examination. The CT images revealed the following: 12 normal or nonspecific findings; seven cases of pneumonia; six chronic stable lesions including chronic bronchitis, emphysema, bronchiectasis, and tuberculosis sequelae; five fluid-retention related lesions; three bases of acute bronchitis; two of active tuberculosis; and one of diffuse alveolar hemorrhage. After the CT scans, the patients received either outpatient or inpatient management, and were followed-up on for at least four months or until death, loss to follow-up, or the study end point.

Chest CT images were acquired on 3 mm standard nongated CT scanners (Brilliance 64 and Brilliance iCT 256, Philips Healthcare, Cleveland, OH, USA; or LightSpeed Pro 16 and Optima 660, GE Medical systems, Milwaukee, WI, USA) with or without contrast. The coronary artery calcium score (CACS) was measured using the scoring system (in units) developed by Agatson et al.[10] Thereafter, patients were categorized into two groups: CACS <400 or ≥400.

3. BP measurements

The enrolled patients underwent hemodialysis using either a Fresenius 5008s (Fresenius Medical Care, Homburg, Germany) or Artis (Gambro Dasco SpA, Medolla, Italy) machine. Transition of machines did not occur. The patients were treated with bicarbonate dialysis fluid at a normal temperature (36.0-36.5℃). Dialysis was conducted three times a week for four hours per session with a 200-350 mL/min blood flow. The intradialytic BP was obtained in the supine position using an automated device built into the hemodialysis machine that was calibrated regularly.

Four-week BP measurements were obtained before the body composition examination. Intradialytic hypotension was defined as either the requirement for fluid administration or the following criteria[11]: minimum intradialytic systolic BP <100 mmHg (Nadir100) or pre-dialytic systolic BP − minimum intradialytic systolic BP ≥30 mmHg (Fall30). Conversely, intradialytic hypertension was defined as an increase in systolic BP ≥10 mmHg during hemodialysis.[12] Patients that had a ≥30% exposure period during their hemodialysis sessions and who met the defined intradialytic hypotension or hypertension during their 12 treatment sessions were classified as having these complications.

4. Body composition analysis

Body composition was assessed using a multifrequency BIA device (InBody S10, Biospace, Seoul, South Korea). A total of eight electrodes were placed on the surfaces of the thumbs, fingers of the hands, and balls of the feet and heels in the supine position. The measurement was made within 30 minutes of starting the first dialysis session after the weekend. The BIA-derived parameters included intracellular water, extracellular water (ECW), and total body water (TBW). The ECW/TBW was used for the volume status estimation.[13] All BIA tests were performed using the same technique by nursing staff trained in the manufacturer's protocol.

5. Data collection

Demographic and clinical data were collected from the

TABLE 1. Baseline characteristics according to CACS

Variables	CACS <400 N=22	CACS ≥400 N=14	p
Age, years	68 (58, 76)	72 (67, 75)	0.203
Male sex, n (%)	11 (50.0)	9 (64.3)	0.400
Dialysis vintage, months	24 (11, 64)	82 (43, 112)	0.002
Access type, n (%)			0.717
Fistula	14 (63.6)	7 (50.0)	
Graft	7 (31.8)	6 (42.9)	
Catheter	1 (4.5)	1 (7.1)	
Comorbidities, n (%)			
Diabetes	11 (50.0)	9 (64.3)	0.400
Hypertension	21 (95.5)	11 (78.6)	0.277
Coronary artery disease	8 (36.4)	8 (57.1)	0.221
Heart failure	3 (13.6)	5 (35.7)	0.217
Cerebrovascular disease	3 (13.6)	6 (42.9)	0.111
Peripheral artery disease	0 (0.0)	1 (7.1)	0.389
Liver disease	1 (4.5)	0 (0.0)	1.000
Chronic lung disease	3 (13.6)	2 (14.3)	1.000
Charlson comorbidity index	6 (5, 8)	8 (6, 8)	0.089
Anti-hypertensive agents, n (%)			
ACE inhibitor or ARB	10 (45.5)	11 (78.6)	0.083
β-blocker	6 (27.3)	8 (57.1)	0.073
Calcium channel blocker	7 (31.8)	6 (42.9)	0.501
Number of anti-hypertensives, n (%)			0.217
0-2	19 (86.4)	9 (64.3)	
≥3	3 (13.6)	5 (35.7)	
Diuretics, n (%)	17 (77.3)	4 (28.6)	0.006
Erythropoiesis-stimulating agents, n (%)	16 (72.7)	12 (85.7)	0.441
Laboratory data			
Hemoglobin, g/dL	10.3 (9.4, 11.4)	10.6 (9.8, 11.2)	0.713
Albumin, g/dL	3.9 (3.6, 4.1)	3.6 (3.3, 3.8)	0.035
Calcium, mg/dL	8.8 (8.2, 9.1)	8.7 (8.2, 9.1)	0.737
Phosphate, mg/dL	5.1 (3.7, 6.0)	4.7 (3.9, 5.8)	0.553
Intact parathyroid hormone, pg/mL	203 (85, 403)	159 (76, 413)	0.785
Uric acid, mg/dL	7.8 (6.2, 8.8)	6.9 (5.5, 8.1)	0.109
Sodium, mmol/L	138 (135, 139)	136 (133, 137)	0.116
Total carbon dioxide, mmol/L	22.8 (20.5, 25.1)	23.6 (22.0, 25.7)	0.311
C-reactive protein, mg/dL	1.7 (0.7, 5.7)	5.8 (1.6, 16.3)	0.102
Kt/V_{urea}	1.6 (1.4, 1.8)	1.6 (1.6, 1.8)	0.432
Protein catabolic rate, g/kg/day	1.0 (0.9, 1.2)	0.9 (0.7, 1.1)	0.102
Interdialytic weight gain, kg	2.0 (1.6, 2.9)	1.5 (1.2, 2.4)	0.191
Ultrafiltration rate, L/hr per kg	7.6 (6.2, 8.7)	6.7 (4.9, 7.9)	0.296
ECW/TBW	0.40 (0.39, 0.41)	0.41 (0.39, 0.42)	0.102
Systolic BP, mmHg			
Pre-dialysis	146 (134, 155)	157 (142, 166)	0.061
Post-dialysis	142 (134, 149)	149 (137, 169)	0.071
Diastolic BP, mmHg			
Pre-dialysis	73 (67, 80)	61 (58, 77)	0.083
Post-dialysis	77 (70, 83)	67 (56, 76)	0.049
Pulse pressure, mmHg			
Pre-dialysis	71 (55, 80)	81 (76, 106)	0.010
Post-dialysis	68 (55, 76)	85 (72, 99)	0.002
Intradialytic hypotension*, n (%)			
Nadir100	3 (13.6)	2 (14.3)	1.000
Fall30	11 (50.0)	6 (42.9)	0.676
Intradialytic hypertension†, n (%)	9 (40.9)	7 (50.0)	0.593
CACS	120 (4, 233)	1435 (1148, 2472)	<0.001

Continuous variables are expressed as median (25th, 75th percentile), and categorical variables are expressed as numbers (percentage). ACE: angiotensin-converting enzyme, ARB: angiotensin II receptor blocker, BP: blood pressure, CACS: coronary artery calcium score, ECW/TBW: the ratio of extracellular water to total body water.

*Intradialytic hypotension is defined as a minimum intradialytic systolic BP <100 mmHg (Nadir100) or pre-dialytic systolic BP − minimum intradialytic systolic BP ≥30 mmHg (Fall30).

†Intradialytic hypertension is defined as an increase in systolic BP ≥10 mmHg during hemodialysis.

patients' electronic medical records and included age, sex, height, cause of ESRD, duration of renal replacement therapy, dialysis access type, and medications used such as antihypertensive agents and erythropoiesis-stimulating agents. In addition, dialysate sodium levels, interdialytic weight gain, and ultrafiltration rates were obtained. The comorbidity burden was assessed using the modified Charlson Comorbidity Index.[14] Age was not included in the modified Charlson Comorbidity Index b,ut was used for the multivariate analysis adjustment.

All of the patients' blood samples were drawn under fasting conditions before the first-in-week dialysis sessions, except for postdialysis blood urea nitrogen. The laboratory data included hemoglobin, albumin, blood urea nitrogen, calcium, phosphate, intact parathyroid hormone, uric acid, sodium, total carbon dioxide, and C-reactive protein levels. Dialysis adequacy (Kt/V_{urea}) and normalized protein catabolic rates were estimated using a single-pool urea kinetic model.[15]

6. Statistical analysis

Continuous variables were expressed as a median (25th, 75th percentile) and were compared using the Wilcoxon rank-sum test. Categorical variables were expressed as a number (percentage) and were compared between groups using the chi-square test. Pearson correlation coefficients were calculated to find the associations among CACS and the mean values of intradialytic systolic BP fall (pre-dialytic systolic BP − minimum intradialytic systolic BP) and nadir systolic BP (minimum intradialytic systolic BP). Univariate and multivariate Cox proportional hazard models were used to determine the hazard ratio (HR) for cardiovascular events and all-cause mortality. Cardiovascular events referred to cardiac death, acute coronary syndrome, cerebrovascular accident, acute exacerbation of heart failure, or acute peripheral artery occlusion. Variables with a $p<0.10$ in the univariate analyses were included in the multivariate models. All statistical analyses were performed using SPSS Statistics version 18.0 (IBM Corp., Armonk, NY, USA). A two-sided p value <0.05 was considered significant.

RESULTS

1. Baseline characteristics according to CACS

The 36 patients in this study were followed up for a median of 25 (13, 47) months, and their median CACS was 236 (82, 1316). The patients were classified based on their CACS into a group of 22 (61.1%) with a CACS <400 and a group of 14 (38.9%) with a CACS ≥400. Table 1 shows the differences of baseline characteristics between the two groups. The patients with a CACS ≥400 had higher dialysis duration, lower prescription rates of diuretics, and lower levels of albumin than those with a CACS <400 (p=0.002, 0.006, and 0.035, respectively). However, interdialytic weight gain, ultrafiltration rate, and ECW/TBW showed no difference between the two groups.

2. Intradialytic BP patterns according to the CACS groups

BP measurements over the course of dialysis treatment were compared between the patients with a CACS <400 and ≥400 (Fig. 1). The median systolic and diastolic BP differed at some time points. However, the pulse pressure was higher in the CACS ≥400 group than in the CACS <400 group during treatment (p=0.010, 0.002, 0.011, 0.011, and 0.002). The median systolic BP fall was −23 (−31, −12) mmHg in the CACS <400 group and −19 (−40, −16) mmHg in the CACS ≥400 group (p=0.619), and the median nadir systolic BP was 120 (113, 127) mmHg and 124 (112, 140) mmHg, respectively (p=0.377).

3. Relationship between CACS and intradialytic BP abnormalities

We explored the relationship between CACS and intradialytic BP abnormalities. No difference in the prevalence of intradialytic BP abnormalities was observed between the two CACS groups (Table 1). We further assessed CACS according to the type of intradialytic BP abnormalities (Fig. 2). The median CACS was comparable, irrespective of both intradialytic hypotension (Nadir100 and Fall30) and intradialytic hypertension (p=1.000, 0.661, and 0.626, respectively).

In addition, the relationships among CACS, intradialytic systolic BP fall, and nadir systolic BP were evaluated (Fig. 3). An association between systolic BP fall and nadir systolic BP ($r=-0.4$; p=0.010) was observed; however, CACS showed no association with the others (p=0.277 and 0.415).

4. Impacts of CACS and intradialytic BP abnormalities on cardiovascular events and mortality

We investigated the association of CACS and intradialytic BP abnormalities with the occurrence of cardiovascular events and all-cause mortality, and if they affected each other. Cardiovascular events occurred in seven patients, and deaths occurred in six patients during the study period. Tables 2 and 3 show HRs for cardiovascular events and all-cause mortality. CACS was associated with cardiovascular events, but this association disappeared after adjustments for age and pulse pressure (HR 1.001; p=0.058). Conversely, CACS was a predictor for all-cause mortality and was independent of both age and the comorbidity index (HR 1.001; p=0.010). We did not find any association between intradialytic BP abnormalities and outcomes.

DISCUSSION

We retrospectively investigated the association between CACS and intradialytic BP patterns. Patients with a high CACS had wider intradialytic pulse pressure than those with a low CACS. However, we observed no difference in the prevalence of intradialytic hypotension and hypertension between the two CACS groups. Patients with intradialytic hypotension or hypertension had comparable CACS to those without intradialytic BP abnormalities. In addition, we found no correlation between CACS and intra-

dialytic systolic BP fall and nadir systolic BP. We further explored the impacts of CACS and intradialytic BP abnormalities on outcomes and identified that CACS predicted the occurrence of cardiovascular events and all-cause mortality, but intradialytic hypotension (Nadir100 and Fall30) and hypertension were not associated with outcomes.

CACS is a strong predictor of coronary artery disease, cardiovascular events, and all-cause mortality regardless of chronic kidney disease status.[16] CACS is usually quantified using electrocardiographic-gated CT in order to minimize motion artifacts from the beating heart and provide fine cuts through the coronary arteries. However, CACS can be detected and quantified on nongated chest CT scans, and this method has been shown to correlate well with CACS obtained from electrocardiographic-gated scans.[17,18] Given this evidence, we hypothesized that CACS quantified from nongated chest CT scans could be predictive for cardiovascular events also in patients with ESRD on maintenance hemodialysis. In this study, patients with a high CACS had longer dialysis vintages and slightly higher comorbidity burdens compared to those with a low CACS, which demonstrates that the extent of calcification increases with longer times on hemodialysis, as shown in previous studies.[5,19] In addition, we found that a high CACS from nongated chest CT scans was associated with an increased rate of cardiovascular events and all-cause mortality in this retrospective ESRD population. As far as we know, our study is the first to use nongated chest CT scans to measure CACS to predict outcomes in patients with ESRD as well as the general population.[20,21]

Pulse pressure is influenced by vascular elasticity, which decreases as calcium accumulates within the vessel wall. Previous studies demonstrated strong correlations between calcification and arterial stiffening.[22,23] Arterial stiffness is an important determinant of pulse pressure, and its measurement is valuable for the evaluation of car-

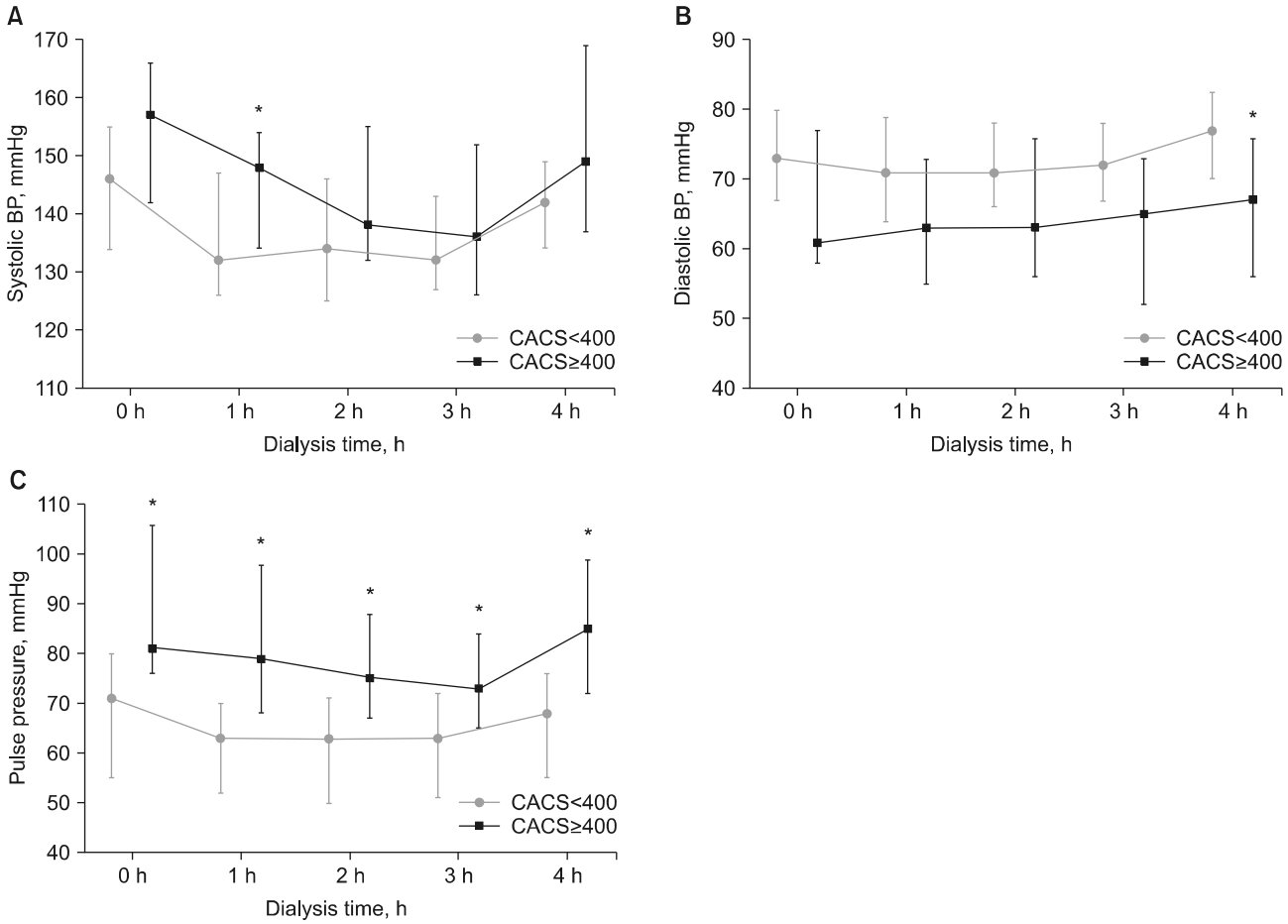

FIG. 1. BP measurements over the course of dialysis treatment according to the CACS group. (A, B) Median systolic and diastolic BPs changed from 146/73 mmHg pre-dialysis to 142/77 mmHg post-dialysis in the CACS <400 group; on the other hand, BPs changed from 157/61 mmHg to 149/67 mmHg in the CACS ≥400 group. Patients with CACS ≥400 had slightly higher systolic BPs and lower diastolic BPs than those with CACS <400 (p for systolic BPs = 0.061, 0.017, 0.227, 0.377, and 0.071; p for diastolic BPs = 0.083, 0.095, 0.066, 0.053, and 0.049). (C) Median pulse pressures over the dialysis treatment were wider in the CACS ≥400 group compared to the CACS <400 group (p=0.010, 0.002, 0.011, 0.011, and 0.002). Pulse pressure at pre-dialysis was 71 (55, 80) mmHg in the CACS <400 group and 81 (76, 106) mmHg in the CACS ≥400 group; Pulse pressure then changed to 68 (55, 76) mmHg and 85 (72, 99) mmHg at post-dialysis in the two groups, respectively. BP: blood pressure, CACS: coronary artery calcium score. *p<0.05.

diovascular risk. This study shows that the presence of coronary artery calcification is related to widened pulse pressure, and we deduced that CACS could be a marker for arterial stiffness. A previous study by Haydar et al.[24] also reported that pulse wave velocity, which is a measure of arterial stiffness, was related to the degree of CT-derived CACS in patients with chronic kidney disease; moreover, they found that the correlation was independent of BP. We extrapolated that CACS is a measure of arterial stiffness and is predictive for atherosclerotic cardiovascular events independent of pulse pressure, although the statistical significance on cardiovascular events is weakened after the adjustment.

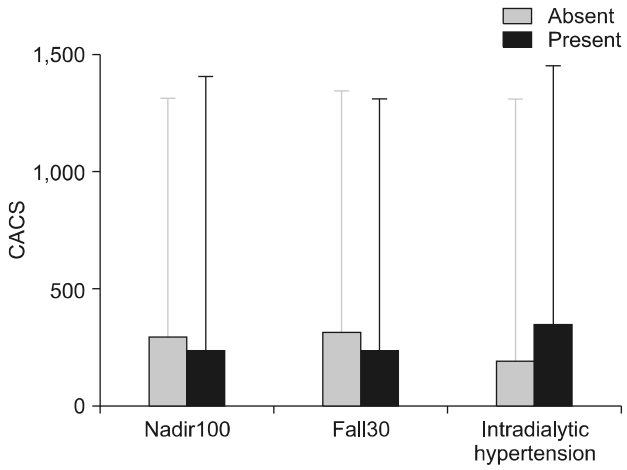

FIG. 2. CACS according to the presence of intradialytic hypotension or hypertension. Median CACS was compared between patients with and without intradialytic BP abnormalities. CACS of patients with intradialytic hypotension (Nadir100 or Fall30) was 237 (62, 1416) or 237 (37, 1314), respectively, and these were similar to those without the complication (Nadir100: CACS 295 [80, 1318]; p=1.000; Fall30: CACS 314 [119, 1348]; p=0.661). In addition, CACS was 350 (37, 1458) in patients with intradialytic hypertension and 194 (82, 1316) in those without intradialytic hypertension (p=0.626). Intradialytic hypotension is defined as a minimum intradialytic systolic BP <100 mmHg (Nadir100) or pre-dialytic systolic BP − minimum intradialytic systolic BP ≥30 mmHg (Fall30). Intradialytic hypertension is defined as an increase in systolic BP ≥10 mmHg. BP: blood pressure, CACS: coronary artery calcium score.

This study discovered that coronary artery calcification is not associated with either intradialytic hypotension or hypertension. Intradialytic hypotension occurs when the rate of fluid removal exceeds that of plasma refill, which results in a decrease of the effective arterial blood volume. Based on this mechanism, a reduction in the ultrafiltration rate during dialysis treatments can prevent this complication.[25] Although the study could not estimate whether the impacts of calcification on intradialytic BP abnormalities depend on volume factors, the patients had comparable ECW/TBW, interdialytic weight gain and ultrafiltration rate between the groups. However, reduction of the ultrafiltration rate may not be enough to prevent intradialytic hypotension. Our previous study showed that patients with a considerable decrease in systolic BP during dialysis had a similar volume status and prescribed ultrafiltration rates to those with normal BP patterns.[26] Thus, an investigation of other causes, such as autonomic dysfunction or cardiovascular abnormalities, is needed to understand the pathophysiology of intradialytic hypotension.[2] On the other hand, intradialytic hypertension is associated with volume overload and other causal factors such as endothelial dysfunction.[2,26,27] Vascular calcification may be a predisposing factor for intradialytic BP ab-

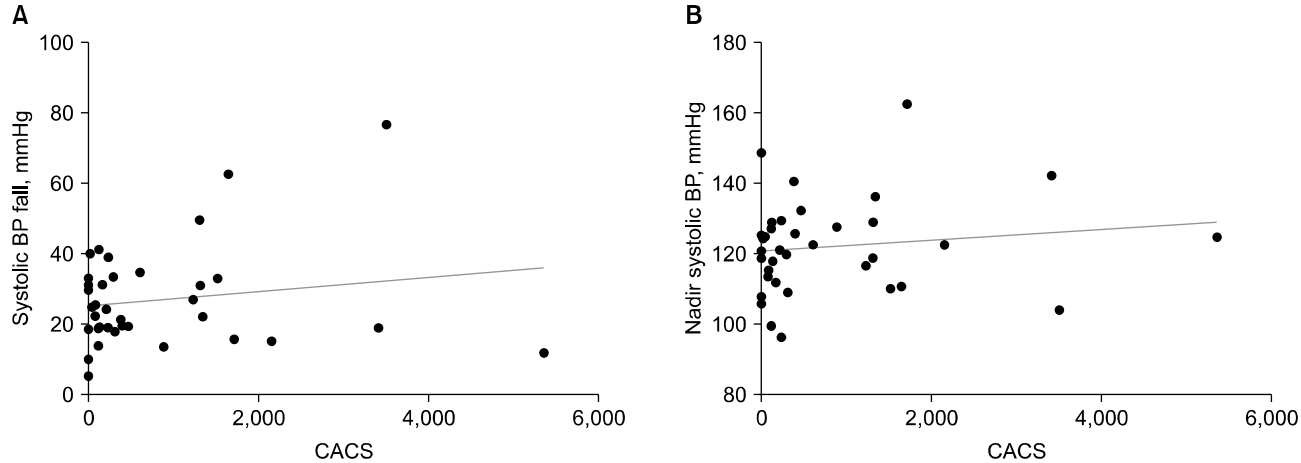

FIG. 3. Correlation of CACS with intradialytic systolic BP fall or nadir systolic BP. (A, B) Correlation was analyzed to find whether CACS influences the degree of systolic BP fall or the lowest systolic BP during the dialysis treatment. Linear regression analyses showed that CACS was not associated with either intradialytic systolic BP fall or nadir systolic BP (r=0.2 and 0.1; p=0.277 and 0.415). Intradialytic systolic BP fall refers to pre-dialytic systolic BP − minimum intradialytic systolic BP. Nadir systolic BP refers to minimum intradialytic systolic BP. BP: blood pressure, CACS: coronary artery calcium score.

TABLE 2. Impact of CACS and intradialytic BP abnormalities on cardiovascular events

Variables	HR (95% CI) Univariate analysis	p	HR (95% CI) Multivariate analysis*	p
Age	1.1 (1.0, 1.3)	0.017	1.2 (1.0, 1.4)	0.054
Male	0.7 (0.2, 3.1)	0.628		
Charlson comorbidity index	1.2 (0.9, 1.5)	0.213		
ECW/TBW, %	1.3 (0.8, 2.2)	0.240		
Ultrafiltration rate, L/hr per kg	1.0 (0.9, 1.1)	0.675		
Pre-dialysis pulse pressure, mmHg	1.1 (1.0, 1.2)	0.002	1.1 (1.0, 1.1)	0.013
Intradialytic hypotension †				
Nadir100	2.4 (0.5, 12.4)	0.296		
Fall30	3.3 (0.6, 17.3)	0.151		
Intradialytic hypertension ‡	0.5 (0.1, 2.6)	0.409		
CACS	1.001 (1.000, 1.002)	0.025	1.001 (1.000, 1.003)	0.058

CACS: coronary artery calcium score, ECW/TBW: the ratio of extracellular water to total body water.
*Variables with a p<0.10 in univariate analyses are included in multivariate models.
† Intradialytic hypotension is defined as a minimum intradialytic systolic BP <100 mmHg (Nadir100) or pre-dialytic systolic BP minimum intradialytic systolic BP ≥30 mmHg (Fall30).
‡ Intradialytic hypertension is defined as an increase in systolic BP ≥10 mmHg.

TABLE 3. Impact of CACS and intradialytic BP abnormalities on all-cause mortality

Variables	HR (95% CI) Univariate analysis	p	HR (95% CI) Multivariate analysis*	p
Age	1.2 (1.0, 1.3)	0.018	1.2 (1.0, 1.5)	0.015
Male	0.9 (0.2, 4.4)	0.880		
Charlson comorbidity index	1.3 (1.0, 1.6)	0.068	1.2 (0.8, 1.9)	0.393
ECW/TBW, %	1.3 (0.8, 2.3)	0.297		
Ultrafiltration rate, L/hr per kg	1.0 (0.8, 1.3)	0.712		
Pre-dialysis pulse pressure, mmHg	1.0 (1.0, 1.1)	0.141		
Intradialytic hypotension †				
Nadir100	1.2 (0.1, 10.3)	0.866		
Fall30	0.6 (0.1, 3.1)	0.522		
Intradialytic hypertension ‡	1.3 (0.3, 6.3)	0.764		
CACS	1.001 (1.000, 1.001)	0.012	1.001 (1.000, 1.002)	0.010

CACS: coronary artery calcium score, ECW/TBW: the ratio of extracellular water to total body water.
*Variables with a p<0.10 in univariate analyses are included in multivariate models.
† Intradialytic hypotension is defined as a minimum intradialytic systolic BP <100 mmHg (Nadir100) or pre-dialytic systolic BP minimum intradialytic systolic BP ≥30 mmHg (Fall30).
‡ Intradialytic hypertension is defined as an increase in systolic BP ≥10 mmHg.

normalities because of its role in cardiovascular events and mortality.[5-7] Previous studies on Korean patients with ESRD receiving hemodialysis found a relationship between vascular calcification and intradialytic hypotension,[8,9] which was in contrast to our study's findings. These previous studies scored aortic arch and abdominal aortic vascular calcification using a plain-chest radiograph and lateral radiograph of the abdomen, respectively. The current study had a smaller sample size than these two previous studies, but we used the more accurate CT-image measure to assess vascular calcification. Although the conflicting results are noteworthy, it may be the result of differences in the arteries used. The previous studies used he aorta, but we used the coronary arteries where calcification of atherosclerotic plaques is more prominent, even in dialysis patients.[28] In other words, CACS from the coronary arteries mainly quantifies intimal calcification, but aortic calcification is dependent on both intimal and medial calcification. Nevertheless, how intimal or medial calcification induces a drop in BP during hemodialysis remains unclear. Until further studies determine the pathophysiologic mechanism, we cannot conclude whether the presence of vascular calcification is a risk factor for intradialytic hypotension or if it is an independent condition that occurs in distressed patients with ESRD on hemodialysis. Likewise, some studies have established that patients with intradialytic hypertension had stiff arteries assessed by pulse wave velocity,[29,30] but the relationship of either arterial stiffness or

vascular calcification with intradialytic hypertension remains unclear. In summary, this study concludes that calcified vessels may be unconnected to intradialytic BP abnormalities, so further research is essential to clarify the vascular factors that cause a considerable BP drop or rise over the course of dialysis treatment. The current study is the first to evaluate the relationship between CACS and intradialytic BP abnormalities in patients with ESRD.

The current study has several limitations. First, we used a small sample size from a single center, which limits the power of the results and may ignore some differences. However, we could deduce that CACS was irrelevant to both intradialytic hypotension and hypertension using three different analyses. In addition, we could deduce that CACS has an independent impact on outcomes, regardless of either intradialytic hypotension or hypertension. Second, we used retrospective data, which may result in an information bias. However, errors of classification or outcome measurement did not occur, because our data was obtained from electronic medical records and did not include the subjects' recall. Third, most patients receive chest CT scans in acute ill states, which could influence the occurrence of outcomes. As a result, we looked into the reasons why the chest CTs were carried out, and the baseline time was elapsed to at least three months after the CT conductance. Fourth, we need to comment on the technique used for scoring CACS; this study did not conduct standardized measurements of CACS, and therefore problems with accuracy may exist. However, we could generate significant findings by our technique, which corresponded to previous trials.[20,21] Furthermore CACS obtained from nongated CT scans for lung cancer screening has been demonstrated as a valuable biomarker in diagnosis and risk prediction for coronary heart disease.[31]

In conclusion, we investigated the impact of coronary artery calcification on intradialytic BP patterns in patients with ESRD on maintenance hemodialysis. CACS measured using nongated chest CT scans was associated with widened pulse pressure, but was not related to either intradialytic hypotension or hypertension. The current study shows that coronary artery calcification might be unrelated to intradialytic BP abnormalities.

CONFLICT OF INTEREST STATEMENT

None declared.

REFERENCES

1. Dinesh K, Kunaparaju S, Cape K, Flythe JE, Feldman HI, Brunelli SM. A model of systolic blood pressure during the course of dialysis and clinical factors associated with various blood pressure behaviors. Am J Kidney Dis 2011;58:794-803.
2. Assimon MM, Flythe JE. Intradialytic blood pressure abnormalities: the highs, the lows and all that lies between. Am J Nephrol 2015;42:337-50.
3. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med 2004;351:1296-305.
4. Stenvinkel P, Carrero JJ, Axelsson J, Lindholm B, Heimbürger O, Massy Z. Emerging biomarkers for evaluating cardiovascular risk in the chronic kidney disease patient: how do new pieces fit into the uremic puzzle? Clin J Am Soc Nephrol 2008;3:505-21.
5. Goodman WG, Goldin J, Kuizon BD, Yoon C, Gales B, Sider D, et al. Coronary-artery calcification in young adults with end-stage renal disease who are undergoing dialysis. N Engl J Med 2000;342:1478-83.
6. Blacher J, Guerin AP, Pannier B, Marchais SJ, London GM. Arterial calcifications, arterial stiffness, and cardiovascular risk in end-stage renal disease. Hypertension 2001;38:938-42.
7. Okuno S, Ishimura E, Kitatani K, Fujino Y, Kohno K, Maeno Y, et al. Presence of abdominal aortic calcification is significantly associated with all-cause and cardiovascular mortality in maintenance hemodialysis patients. Am J Kidney Dis 2007;49:417-25.
8. Kim SY, Hong YA, Yoon HE, Chang YK, Yang CW, Kim SY, et al. Vascular calcification and intradialytic hypotension in hemodialysis patients: clinical relevance and impact on morbidity and mortality. Int J Cardiol 2016;217:156-60.
9. Cho A, Lee YK, Oh J, Yoon JW, Shin DH, Jeon HJ, et al. The relationship between intradialytic hypotension and vascular calcification in hemodialysis patients. PLoS One 2017;12:e0185846.
10. Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte M Jr, Detrano R. Quantification of coronary artery calcium using ultrafast computed tomography. J Am Coll Cardiol 1990;15:827-32.
11. Flythe JE, Xue H, Lynch KE, Curhan GC, Brunelli SM. Association of mortality risk with various definitions of intradialytic hypotension. J Am Soc Nephrol 2015;26:724-34.
12. Inrig JK, Patel UD, Toto RD, Szczech LA. Association of blood pressure increases during hemodialysis with 2-year mortality in incident hemodialysis patients: a secondary analysis of the Dialysis Morbidity and Mortality Wave 2 Study. Am J Kidney Dis 2009;54:881-90.
13. Davies SJ, Davenport A. The role of bioimpedance and biomarkers in helping to aid clinical decision-making of volume assessments in dialysis patients. Kidney Int 2014;86:489-96.
14. Beddhu S, Bruns FJ, Saul M, Seddon P, Zeidel ML. A simple comorbidity scale predicts clinical outcomes and costs in dialysis patients. Am J Med 2000;108:609-13.
15. Depner TA, Daugirdas JT. Equations for normalized protein catabolic rate based on two-point modeling of hemodialysis urea kinetics. J Am Soc Nephrol 1996;7:780-5.
16. Polonsky TS, McClelland RL, Jorgensen NW, Bild DE, Burke GL, Guerci AD, et al. Coronary artery calcium score and risk classification for coronary heart disease prediction. JAMA 2010;303:1610-6.
17. Kirsch J, Buitrago I, Mohammed TL, Gao T, Asher CR, Novaro GM. Detection of coronary calcium during standard chest computed tomography correlates with multi-detector computed tomography coronary artery calcium score. Int J Cardiovasc Imaging 2012;28:1249-56.
18. Hecht HS, Cronin P, Blaha MJ, Budoff MJ, Kazerooni EA, Narula J, et al. 2016 SCCT/STR guidelines for coronary artery calcium scoring of noncontrast noncardiac chest CT scans: a report of the

Society of Cardiovascular Computed Tomography and Society of Thoracic Radiology. J Cardiovasc Comput Tomogr 2017;11:74-84.
19. Civilibal M, Caliskan S, Kurugoglu S, Candan C, Canpolat N, Sever L, et al. Progression of coronary calcification in pediatric chronic kidney disease stage 5. Pediatr Nephrol 2009;24:555-63.
20. Xie X, Zhao Y, de Bock GH, de Jong PA, Mali WP, Oudkerk M, et al. Validation and prognosis of coronary artery calcium scoring in nontriggered thoracic computed tomography: systematic review and meta-analysis. Circ Cardiovasc Imaging 2013;6:514-21.
21. Hughes-Austin JM, Dominguez A 3rd, Allison MA, Wassel CL, Rifkin DE, Morgan CG, et al. Relationship of coronary calcium on standard chest CT scans with mortality. JACC Cardiovasc Imaging 2016;9:152-9.
22. Guérin AP, London GM, Marchais SJ, Metivier F. Arterial stiffening and vascular calcifications in end-stage renal disease. Nephrol Dial Transplant 2000;15:1014-21.
23. Raggi P, Bellasi A, Ferramosca E, Islam T, Muntner P, Block GA. Association of pulse wave velocity with vascular and valvular calcification in hemodialysis patients. Kidney Int 2007;71:802-7.
24. Haydar AA, Covic A, Colhoun H, Rubens M, Goldsmith DJ. Coronary artery calcification and aortic pulse wave velocity in chronic kidney disease patients. Kidney Int 2004;65:1790-4.
25. Kooman J, Basci A, Pizzarelli F, Canaud B, Haage P, Fouque D, et al. EBPG guideline on haemodynamic instability. Nephrol Dial Transplant 2007;22 Suppl 2:ii22-44.
26. Shin J, Yeo S, Hong JY, Hwang JH, Kim SH. Impact of intradialytic blood pressure changes on cardiovascular outcomes is independent of the volume status of maintenance hemodialysis patients. J Am Soc Hypertens 2018;12:779-88.
27. Chou KJ, Lee PT, Chen CL, Chiou CW, Hsu CY, Chung HM, et al. Physiological changes during hemodialysis in patients with intradialysis hypertension. Kidney Int 2006;69:1833-8.
28. Vervloet M, Cozzolino M. Vascular calcification in chronic kidney disease: different bricks in the wall? Kidney Int 2017;91:808-17.
29. Georgianos PI, Mpoutsiouki F, Sabani E, Stamatiadis DN, Liakopoulos V, Balaskas EV, et al. Hemodialysis patients with intradialytic rise in blood pressure display higher baseline aortic stiffness and negligible drop in augmentation index with dialysis. Int Urol Nephrol 2016;48:601-8.
30. Raikou VD, Kyriaki D. The association between intradialytic hypertension and metabolic disorders in end stage renal disease. Int J Hypertens 2018;2018:1681056.
31. Ravenel JG, Nance JW. Coronary artery calcification in lung cancer screening. Transl Lung Cancer Res 2018;7:361-7.