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Vascular calcification and intradialytic hypotension in hemodialysis patients: Clinical relevance and impact on morbidity and mortality

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ABSTRACT

Background: Vascular calcification (VC) and intradialytic hypotension (IDH) indicate morphological and functional disorders of the cardiovascular system in hemodialysis (HD) patients. However, their relationship and combined effects on clinical outcomes remain undetermined.
Methods: HD patients (n = 443) whose plain chest radiographs were examined for aortic arch VC were included. IDH was defined as nadir systolic blood pressure <90 mm Hg or need for bolus fluid. We investigated the relationship between VC and IDH, and their clinical significance for cardiovascular events (CVEs) and death.
Results: VC was found in 57 HD patients (12.9%). IDH was more prevalent in patients with VC compared with those without VC (35.1% vs. 18.7%; $P = 0.004$). VC was independently associated with a 2.12-fold increase in the risk of IDH (95% confidence interval [CI], 1.03–4.36). In multivariate analysis, compared with patients with neither VC nor IDH, the coexistence of VC and IDH was independently associated with death (hazard ratio [HR], 3.83; 95% CI, 1.62–9.08) and CVE (HR, 3.77; 95% CI, 1.53–9.33), whereas VC or IDH alone was not. Patients with both VC and IDH had the highest risk for a composite event (HR, 3.56; 95% CI, 1.79–7.08). Significant synergistic interaction was observed between VC and IDH (P for interaction = 0.009).
Conclusions: VC was independently associated with IDH. Coexistence of VC and IDH was associated with higher risk of death and CVEs than either factor alone. There was a synergistic interaction between VC and IDH for the risk of a composite event.

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1. Introduction

Patients receiving hemodialysis (HD) have an increased risk of cardiovascular disease [1,2]. Multiple factors including diet, abnormal endocrine and mineral metabolism trigger the vascular calcification (VC) and it is a prevalent disorder in HD patients [3–5]. Many studies have shown that VC is associated with atherosclerotic ischemia, impaired brain circulation, and decreased coronary perfusion [5,6]. Therefore, VC is considered as a morphological marker of vascular pathology and is a significant risk factor for cardiovascular morbidity and mortality in HD patients [7].

Intradialytic hypotension (IDH) is the most common adverse complication of HD. Hemodynamic instability induces a life-threatening condition that leads to multiorgan ischemia and also contributes to the long-term risk for cardiovascular events (CVEs) and patient death [8,9]. Therefore, IDH is an important functional disorder of the cardiovascular system that can affect the clinical outcome of HD patients. Interestingly, blood pressure is linked to mineral bone disorder in HD patients. VC and IDH share common risk factors [10–13]: age, the presence of diabetes, and dialysis duration. VC is also related to functional disorders of the cardiovascular system, including left ventricular dysfunction and peripheral artery malfunction, which may increase the risk of IDH [14,15].

However, there are few data relating to the association between VC and IDH and the clinical significance. We undertook this study to test the hypothesis that VC is independently associated with IDH in HD patients and that patients with both VC and IDH would have the highest risk for death and CVEs compared with those with VC or IDH alone. We also explored the combined effect of VC and IDH on morbidity and mortality.

2. Subjects and methods

2.1. Study population

We included maintenance HD patients treated at Daejeon St. Mary's Hospital from January 2004 to November 2014. Patients were eligible if

Abbreviations: CVE, cardiovascular events; IDH, intradialytic hypotension; HD, hemodialysis; VC, vascular calcification.

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they were examined with plain chest radiographs for aortic arch VC and they had received more than 1 month of HD treatment in our center. The subjects with the following criteria were excluded to avoid potential bias related to blood pressure: current treatment for infection, major surgery, clinically overt signs of hemorrhage, acute heart failure with pulmonary edema, acute myocardial infarction, acute cerebral stroke, or an incomplete medical record. A total of 443 patients were enrolled in this study. The study population was classified according to the presence and absence of VC, and each of these groups was subdivided into two groups depending on the presence or absence of IDH.

2.2. HD prescription and procedures

All patients received the in-center HD treatment, and 4 h of treatment per HD session was prescribed. The blood flow rate was prescribed as 250–280 mL/min and dialysate flow rate was 500 mL/min. The dry weight was assessed by clinical examination with the help of plain chest X-ray. The ultrafiltration volume was determined as predialysis weight minus dry weight. Brachial blood pressure was monitored every hour using the cuff method throughout the HD session, with special attention paid to the period during which the patients showed hemodynamic instability or hypotensive symptoms or signs. Bolus fluid (hypertonic saline or glucose solution) was administered when systolic blood pressure (SBP) was <90 mm Hg or when the patient had hypotensive symptoms of cramping, headache, lightheadedness, vomiting, or chest or abdominal discomfort.

2.3. Data collection and definitions

The baseline demographics, risk factors for CVEs, laboratory data, antihypertensive medication, and HD procedure data were collected at the time of IDH assessment. VC of the aortic arch was identified using plain radiographs. Aortic arch calcification was observed by a single-blinded observer, and the total length of calcification was measured by adding the length of the separate linear calcific densities along the aortic arch [16]. A length of calcification >2 cm along the aortic arch was defined as VC. An IDH episode was defined as a nadir SBP <90 mm Hg or the requirement for bolus fluid administration [9]. Patients who had ≥30% exposure to IDH episodes during 1 month of HD treatment were classified into the IDH group. Body mass index (BMI) was calculated as the ratio of weight in kilograms divided by the square of height in meters. Mean pre-HD SBP and diastolic blood pressure (DBP) were calculated for each patient from the values for 1 month of HD treatment.

2.4. Outcome measures

The primary endpoint for the study was the association between VC and IDH. The secondary endpoint was a composite of patient death or a CVE after IDH assessment. A CVE was defined as the occurrence of coronary artery disease (coronary artery bypass surgery, percutaneous intervention, or myocardial infarction), heart failure, ventricular arrhythmia, sudden death, cerebrovascular accident (cerebral infarction, transient ischemic attack, or cerebral hemorrhage), or peripheral arterial disease (peripheral vascular revascularization, amputation, peripheral ulcer, or gangrene).

2.5. Statistical analysis

Data are expressed as the mean ± standard deviation. Differences between two groups were identified using Student's *t* test. Categorical variables were compared using the chi-square test or Fisher's exact test. Binary logistic regression analysis was used to identify the independent association between VC and IDH. The Cox proportional-hazards model was used to identify the independent variables related to the patient death or CVE. Multivariate models included the significantly associated parameters according to their weight in the univariate testing and clinically fundamental parameters. The confounders entered into the analysis were age (10-year increments), HD duration (1-month increments), BMI (1 kg/m^2 increments), diabetes, previous CVE, mean SBP (10 mm Hg increments), hemoglobin concentration (1 g/dL increments), serum levels of albumin (1 g/dL increments) and phosphorus (per 1 mg/dL increments), and type of vascular access. We conducted formal tests for interaction by including a VC–IDH interaction term in addition to the main effects to the fully adjusted models. The cumulative event rates were estimated by the Kaplan–Meier method and compared using the log-rank test. A P value of <0.05 was considered significant. The statistical analyses were performed using SPSS software (version 20.0; SPSS, IBM Corp., Armonk, NY).

3. Results

3.1. Baseline demographic characteristics and laboratory data

Among the 443 HD patients, 57 patients (12.9%) had VC at the aortic arch. Table 1 shows the baseline characteristics of the study population. Among the patients with VC, those with IDH were less likely to have diabetes and used calcium channel blockers less frequently compared with those without IDH. Among the patients without VC, there were a smaller percentage of males in those with IDH compared with those without IDH, and patients with IDH had a longer duration of HD, lower smoking rate, and higher levels of hemoglobin and serum calcium. The use of a catheter, β-blocker, or calcium channel blocker was less frequent, and the ultrafiltration volume was greater in patients with IDH. In both patients with and without VC, the mean pre-HD SBP and DBP were significantly lower in patients with IDH than in those without IDH.

3.2. Relationship between VC and IDH

The prevalence of IDH was compared according to the presence or absence of VC: IDH was observed in 20 patients with VC and in 72 patients without VC. The incidence of IDH was significantly higher in patients with VC than in those without VC (35.1% vs. 18.7%; $P = 0.004$). The number of episodes of a nadir SBP <90 mm Hg during assessment was higher in patients with VC than in those without VC (1.9 ± 2.0 vs. 1.1 ± 1.9; $P = 0.006$). The number of bolus fluid administrations was also greater in patients with VC (0.25 ± 0.29 vs. 0.15 ± 0.22; $P = 0.012$).

Table 2 shows the determinants of IDH in HD patients. In the univariate analysis, the presence of VC was significantly associated with IDH occurrence (odds ratio [OR], 2.36; 95% confidence interval [CI], 1.29–4.30; $P = 0.005$). In the multivariate analysis, VC was an independent determinant of IDH (OR, 2.12; 95% CI, 1.03–4.36; $P = 0.042$), and male gender, diabetes, use of a calcium channel blocker, pre-HD SBP, and ultrafiltration were independently associated with IDH.

3.3. Composite of patient deaths and CVE

During the follow-up, 77 deaths (17.4%) and 91 CVEs (20.5%) occurred in all patients. The highest cumulative event rate for the composite of death or CVE was observed in patients with both VC and IDH (69.8%, $P = 0.003$; Fig. 1). Patients with either VC or IDH only had a 48.8% and 41.1% cumulative event rate, respectively, but these values were not significantly higher compared with those of patients with neither VC nor IDH (40.1%; $P = 0.171$ and $P = 0.687$, respectively). Patients with both VC and IDH also had the highest cumulative event rate for mortality (47.9%; $P = 0.003$) compared with 32.3%, 20.3%, and 20.3% for those with VC only, with IDH only, and with neither, respectively. The Kaplan–Meier event curves showed similar patterns for CVEs as those observed for composite event in the four groups: 51.1%, 36.6%, 31.7%, and 31.7% for patients with both VC and IDH, with VC only, with IDH only, and with neither, respectively ($P = 0.080$).

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