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Original Article

Relationship between pulmonary hypertension, peripheral vascular calcification, and major cardiovascular events in dialysis patients

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Abstract

Background: Pulmonary hypertension (PHT) is a recently recognized complication of chronic kidney disease. In this study, we investigated the association between PHT, peripheral vascular calcifications (VCs), and major cardiovascular events.
Methods: In this retrospective study, we included 172 end-stage renal disease (ESRD) patients undergoing dialysis [hemodialysis (HD)=84, peritoneal dialysis=88]. PHT was defined as an estimated pulmonary artery systolic pressure >37 mmHg using echocardiography. The Simple Vascular Calcification Score (SVCS) was measured using plain radiographic films of the hands and pelvis.
Results: The prevalence of PHT was significantly higher in HD patients (51.2% vs. 22.7%). Dialysis patients with PHT had a significantly higher prevalence of severe VCs (SVCS ≥ 3). In multivariate analysis, the presence of severe VCs [odds ratio (OR), 2.68], mitral valve disease (OR, 7.79), HD (OR, 3.35), and larger left atrial diameter (OR, 11.39) were independent risk factors for PHT. In addition to the presence of anemia, severe VCs, or older age, the presence of PHT was an independent predictor of major cardiovascular events in ESRD patients.
Conclusion: The prevalence of PHT was higher in HD patients and was associated with higher rates of major cardiovascular events. Severe VCs are thought to be an independent risk factor for predicting PHT in ESRD patients. Therefore, in dialysis patients with PHT, careful attention should be paid to the presence of VCs and the occurrence of major cardiovascular events.

Introduction

Emerging evidence suggests that pulmonary hypertension (PHT), a recently recognized complication of end-stage renal disease (ESRD), is closely associated with cardiac, pulmonary, and systemic diseases and also with increased mortality [1]. The prevalence of PHT is known to range from 18.8% to 68.8% in hemodialysis (HD) patients and from 0% to 42% in peritoneal dialysis (PD) patients [2]. The possible causes of PHT in dialysis patients are classified into three categories: (1) increased cardiac output caused by an arteriovenous fistula, anemia, or hypervolemia; (2) increased pulmonary vascular resistance caused by uremic endothelial dysfunction, pulmonary embolism, pulmonary artery calcifications, or other comorbid diseases including chronic obstructive pulmonary disease or connective tissue disease; and (3) elevated pulmonary capillary wedge pressure caused by

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systolic and diastolic heart failure or mitral valve disease [3]. In a previous study on dogs, high parathyroid hormone levels provoked pulmonary artery calcifications, and this resulted in decreased pulmonary vascular compliance [4]. Although this result indicated that extraosseous calcifications might be a risk factor for PHT, results in human studies about the association between PHT and pulmonary artery calcification or parathyroid hormone levels have been conflicting [5–9]. Medial artery calcification is a common complication in patients with chronic kidney disease (CKD) contributing to increased cardiovascular mortality, and multiple factors including abnormal calcium phosphate metabolism, uremia, oxidative stress, and inflammation are known to be important in vascular calcification (VC) development. In this study, we examined the association between PHT, peripheral VCs, and major cardiovascular events in dialysis patients.

Methods

Study population

In this retrospective study, we included 172 ESRD patients undergoing dialysis (HD = 84, PD = 88) who had been enrolled in previous cross-sectional studies performed in March 2009 [10,11]. In the previous studies, 198 stable dialysis patients (HD = 105, PD = 93) who had been followed in the dialysis center of Korea University Anam Hospital with over 6-mo duration of dialysis were enrolled. Among 198 patients, 26 without echocardiographic data were excluded from this study. Baseline characteristics, including sex, age, body weight, height, dialysis duration, causes of ESRD, and history of hypertension, diabetes, ischemic heart disease, and chronic obstructive pulmonary disease were recorded. The mean values of serum albumin, low-density lipoprotein (LDL) cholesterol, alkaline phosphatase, calcium, phosphate, hemoglobin, and C-reactive protein (CRP) that had been measured every month for 18 months were used. The data collection on baseline characteristics, laboratory tests, and echocardiographic findings was based on the enrollment date of the previous studies. The electronic medical records of enrolled patients from March 2009 to December 2013 were reviewed to check for the development of major cardiovascular events including acute myocardial infarction and stroke. For acute myocardial infarction, we included non-ST elevation and ST elevation myocardial infarction. We defined stroke as an abrupt onset of focal neurological deficit with intracranial infarction or hemorrhage on brain imaging studies, during the follow-up period. This study was approved by the Institutional Review Board of Korea University, Anam Hospital.

Echocardiography

Standard two-dimensional, M-mode, Doppler echocardiography was performed for all patients. We used the modified Bernoulli equation to calculate pulmonary artery systolic pressure (PASP) as follows: PASP = 4 × (tricuspid systolic jet)^2 + 10 mmHg (estimated arterial pressure). PHT was defined as an estimated PASP > 37 mmHg. Left ventricular (LV) mass was calculated with the following formula: LV mass (g) = 0.8 × {1.04 [(LVIDd + PWTd + SWTd)^3 − (LVIDd)^3]} + 0.6, where LVIDd is the left ventricle internal diameter, diastole; PWTd is the posterior wall thickness, diastole; and SWTd is the septum wall thickness, diastole. This was indexed for body surface area to yield the LV mass index [12]. LV systolic dysfunction was defined as LV fractional shortening ≤ 25%. Mitral valve disease was defined as mitral valve stenosis or regurgitation with more than moderate degree. Aortic valve disease was also defined as stenosis or regurgitation of aortic valve with more than moderate degree.

Simple Vascular Calcification Score and parathyroid hormone level

The Simple Vascular Calcification Score (SVCS) was measured using plain radiographic films of both hands and pelvis. The pelvic radiographic film was arbitrarily divided into four sections by two imaginary lines (a horizontal line over the upper limit of both femoral heads and a median vertical line over the vertebral column). For each hand, the film was divided by a horizontal line over the upper limit of the metacarpal bones. Only the linear calcifications in the iliac, femoral, radial, and digital arteries were counted. The presence of linear calcifications in each section was counted as a score of 1, and the absence of calcifications was counted as a score of 0; the SVCS was the sum of all sections, ranging from 0 to 8. Adragao et al [13] found that an SVCS ≥ 3 was an independent predictor of cardiovascular mortality and cardiovascular events. According to this result, we defined severe VCs as an SVCS ≥ 3. We also defined an intact parathyroid hormone level < 150 pg/mL as the low parathyroid hormone group and an intact parathyroid hormone level > 300 pg/mL as the high parathyroid hormone group based on the Kidney Disease Outcomes Quality Initiative guidelines [14].

Statistical analysis

Statistical analyses were performed using SPSS, version 20.0 (SPSS, Inc., Chicago, IL, USA). Data are presented as the means ± standard deviation or median (interquartile range), according to distribution. Continuous variables were analyzed using the Student *t* test for normally distributed data or the Mann–Whitney test for non-normally distributed data. The Pearson χ^2 test was used to analyze nominal data. In multivariate analysis, a binary logistic regression model was used. The major cardiovascular events-free survivals were determined based on survival curves using the Kaplan–Meier method and log-rank test. The effect of prognostic factors on major cardiovascular events was examined using the Cox proportional regression model. All parameters used in the cross-sectional study were evaluated using a univariate Cox proportional hazard model. Those covariates with $P < 0.20$ in the univariate model were considered for the multivariate Cox regression analysis. Patients were censored at kidney transplantation ($n = 28$), last follow-up ($n = 45$), and death ($n = 21$). A P value < 0.05 was considered statistically significant.

Results

Baseline characteristics according to dialysis modality

The mean age of the patients was 56.3 ± 13.2 years. Seventy-four patients (43.0%) had a history of diabetes, and 152 patients (88.4%) had hypertension. The most common cause of ESRD was diabetes mellitus, followed by hypertension, glomerulonephritis, and polycystic kidney disease. There was no statistically significant difference in the causes of ESRD or comorbidities according to dialysis modality. Of the 172 dialysis patients, 63 (36.6%) had PHT, and the median dialysis