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Original Paper

Risk Factors for New-Onset Cardiac Valve Calcification in Patients on Maintenance Peritoneal Dialysis

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Key Words
Cardiac valve calcification · Peritoneal dialysis · Risk factor

Abstract
Objective: Patients with end-stage renal disease are susceptible to cardiac valve calcification (CVC) due to mineral metabolism disorders and other factors. The purpose of this study was to investigate the risk factors for new-onset CVC in patients on maintenance peritoneal dialysis (PD). ***Methods:*** This study included patients who underwent PD catheter insertion from January 2006 to June 2013 in our Peritoneal Dialysis Center. Clinical data were collected on CVC status during echocardiography evaluations (twice) at an interval of >6 months. The data collected included intact parathyroid hormone, C-reactive protein (CRP), serum phosphorus (P), serum calcium (Ca), albumin (Alb), prealbumin and the use of five types of antihypertensive drugs, statins, active vitamin D_3 and Ca tablets. ***Results:*** In total, 194 patients – 105 (54.1%) men, average age 60.5 ± 13.0 years – were included. CVC was present in 50 (25.8%) patients during PD catheter placement. After an average PD duration of 20.9 ± 10.4 months, CVC was detected in 97 patients (50.0%). New-onset CVC was found in 62 patients (32.0%). Multivariate logistic regression analysis revealed that only serum P levels (p = 0.01, OR = 2.569), Alb levels (p = 0.04, OR = 0.935), dialysis duration (p = 0.03, OR = 1.039) and CRP levels (p = 0.02, OR = 1.031) were associated with CVC. ***Conclusion:*** Serum P, Alb and CRP levels as well as dialysis duration are independent risk factors for CVC.

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Introduction

Cardiac valve calcification (CVC) is common in patients with chronic kidney disease (CKD), and the incidence of CVC in patients with end-stage renal disease is five to ten times that of non-renal disease patients [1]. Previous research has shown that increased calcium (Ca), phosphorus (P), blood lipids, parathyroid hormone (PTH) and chronic inflammatory mediator release result in an increased incidence of CVC in patients with CKD [2–6]. The Kidney Disease: Improving Global Outcomes (KDIGO) Guidelines for Chronic Kidney Disease-Mineral and Bone Disorder proposed target values of serum P, Ca and PTH in these patients [7]. However, ideal control and regular follow-up monitoring are still difficult, leading to an increase in the risk of ectopic calcification in CKD patients. Additionally, CVC is considered a strong predictor of morbidity and mortality due to atherosclerosis, arterial calcification, left ventricular hypertrophy and cardiovascular disease [2, 3, 8]. Given its increased incidence in end-stage renal disease patients and the associated high risk, it is critical to clarify the mechanism underlying the development and progression of CVC.

Currently, few studies have investigated new-onset CVC during dialysis, and the results are controversial. A cross-sectional study in our center has shown that age, history of diabetes mellitus, Ca-P product level and hypoprealbuminemia are independent risk factors for aortic valve calcification (AVC). Age, Ca-P product level and hypoprealbuminemia are also independent risk factors for mitral valve calcification (MVC); however, the evidence is insufficient, and this conclusion needs to be demonstrated by cohort studies [5]. Previous cohort studies have indicated that age, history of diabetes mellitus as well as total cholesterol (TC), PTH and C-reactive protein (CRP) levels are risk factors for new-onset CVC in peritoneal dialysis (PD) patients. However, the main limitations of existing studies are related to their small sample size and short follow-up period [6]. Moreover, several cohort studies have failed to prove a relationship between CKD-mineral and bone disorder-related factors and CVC. In the absence of a unified consensus, this study was conducted in our center to elucidate the relationship between blood biochemical indices, drug use and dialysis duration and new-onset CVC in patients on maintenance PD.

Methods

Study Subjects

There were 318 patients who underwent PD catheter insertion in our Peritoneal Dialysis Center from January 2006 to June 2013. All patients undergoing echocardiography during the catheterization period were followed up for a specified period; the number undergoing a second echocardiographic examination in our hospital was 253. The exclusion criteria consisted of (1) without a second echocardiographic examination (n = 65); (2) an interval of <6 months between the two echocardiographic examinations (n = 41); (3) renal transplantation between the two echocardiographic examinations (n = 3), transfer to hemodialysis (n = 11), combined PD and hemodialysis (n = 10) and recovery of renal function (n = 1); and (4) congenital heart disease (n = 3), rheumatic heart disease (n = 3), acute inflammation (n = 2) and hyperthyroid heart disease (n = 1). There were 16 patients with an overlap between exclusion criteron 2 and renal transplantation between the two echocardiographic examinations (n = 3), transfer to hemodialysis (n = 2), combined PD and hemodialysis (n = 10) and recovery of renal function (n = 1). Thus, 124 patients were excluded. A total of 194 patients were included in this study.

Study Methods

Measurement Indices. Clinical data including age, gender, body mass index (BMI), catheterization date, outcome condition, outcome time, time of echocardiography (twice), CVC status, history of diabetes, and use of statins, Ca tablets, active vitamin D_3, diuretics, Ca channel blockers, renin-angiotensin system blockers, α- and β-receptor blockers as well as combination preparations were collected from all patients. Moreover, we collected the first set of fasting blood biochemical indices from all patients during hospitalization for cath-

eterization, including serum creatinine, urea nitrogen, albumin (Alb), prealbumin (PA), alkaline phosphatase (AP), PTH, serum Ca, serum P, CRP, triglyceride (TG), TC, high-density lipoprotein and low-density lipoprotein levels.

Echocardiographic Examination. CVC was defined as the presence of one or multiple strong echos (>1 mm) in the aortic valve, mitral valve or mitral annulus. All included patients received echocardiography (Model GE Vivid E9) in the ultrasound room of our hospital. None of the echocardiographic technicians knew the patients' detailed clinical conditions.

Statistical Analysis. Data were expressed as mean ± SD or median (interquartile range) based on the distribution type. The statistical analysis was performed using SPSS 19.0 (IBM SPSS, Somers, N.Y., USA). Two groups of data with a normal distribution were compared with the t test, skewed data were compared with the Mann-Whitey U test, and categorical data were compared with the χ^2 test. Univariate logistic regression analysis was performed to estimate the relative risk of different risk factors that influenced CVC. Factors with a p value <0.10 were entered into the multivariate regression analysis. A p value <0.05 (two-tailed) was considered statistically significant.

Results

Clinical Data

In total, 194 patients were included, while 124 patients were excluded from this study. Comparison of the baseline demographics in the included and excluded patients show no statistical significance (table 1).

Among the included 194 patients, there were 105 men and 89 women with an average age of 60.5 ± 13.0 years. The average BMI was 22.4 ± 3.4. There were 52 patients with a history of diabetes, 167 patients who used Ca tablets, 14 patients who used statins, 98 patients who used active vitamin D_3 preparations, 126 patients who used diuretics, and 183 patients who used single or a combination of two or more antihypertensive drugs. At the time the patients underwent the second echocardiographic examination, their average dialysis vintage was 20.9 ± 10.4 months. There were 55 patients who used 1.25% Ca concentration dialysate and 7 patients who used 1.75% Ca concentration dialysate in the CVC group, while there were 123 patients who used 1.25% Ca concentration dialysate and 9 patients who used 1.75% Ca concentration dialysate in the non-CVC group.

CVC

A total of 50 patients had CVC at baseline, including 44 cases of AVC, 3 cases of MVC and 3 cases of AVC associated with MVC. After at least 6 months of PD, CVC was detected in 97 patients. Among the patients who did not exhibit CVC at baseline, there were 30 cases of AVC, 7 cases of MVC or mitral annular calcification and 10 cases of AVC associated with MVC after >6 months of PD. Among the patients who exhibited AVC at baseline, there were 13 cases of AVC and MVC after PD. Among the patients with MVC or mitral annular calcification, there were 2 cases of AVC and MVC after PD. In total, 32% of the patients had new-onset CVC.

The New-Onset CVC and Non-CVC Groups

Compared to the non-CVC group, the new-onset group had greater BMI (p = 0.02), longer dialysis duration (p = 0.003), a higher proportion of patients using statins (p = 0.001), a higher proportion of patients with diabetes (p = 0.03), higher serum P levels (p = 0.04) and lower serum Alb levels (p = 0.02); the differences were statistically significant. No significant differences were found between the two groups with regard to age, gender, serum Ca, PTH, CRP, PA, AP, TG and TC levels, or the proportion of patients using antihypertensive drugs, Ca tablets and active vitamin D_3 preparations (table 2).

Table 1. Comparison of baseline demographics in included and excluded patients

Variable	Included group (n = 194)	Excluded group (n = 124)	p
Age, years	60.5±12.9	58.3±13.8	0.21
Female gender	89 (45.9%)	64 (51.6%)	0.43
BMI	22.4±3.4	22.1±2.9	0.33
CCB, yes	179 (92.2%)	112 (90.3%)	0.54
a-Receptor blocker, yes	63 (32.5%)	30 (24.2%)	0.13
β-Receptor blocker, yes	69 (35.6%)	38 (30.6%)	0.37
Almarl, yes	45 (23.2%)	32 (25.8%)	0.60
RAAS blocker, yes	128 (66.0%)	76 (61.3%)	0.72
Diuretic, yes	126 (64.9%)	69 (55.6%)	0.10
Active vitamin D_3, yes	98 (50.5%)	65 (52.4%)	0.74
Ca tablets, yes	167 (86.1%)	104 (84.6%)	0.13
Statins, yes	14 (7.1%)	8 (6.4%)	0.79
Diabetes, yes	52 (26.8%)	22 (21.5%)	0.12
Ca concentration of PD fluid			0.16
1.25 mmol/l	178 (91.8%)	115 (92.8%)	–
1.75 mmol/l	16 (8.2%)	9 (7.2%)	–
PTH, pg/dl	218.4 (100.75–380)	171.0 (87.72–408.95)	0.35
CRP, mg/l	5.4 (4.7–7.3)	5.0 (4.1–7.2)	0.18
Creatinine, μmol/l	727.32±324.53	768.68±356.51	0.09
Urea, mmol/l	23.88±10.08	27.45±14.88	0.11
PA, g/l	0.27±0.11	0.28±0.09	0.83
AP, U/l	96.81±90.4	86.91±37.72	0.24
Serum total Ca, mmol/l	2.06±0.27	2.00±0.29	0.52
Serum P, mmol/l	1.76±0.51	1.80±0.68	0.56
TC, mmol/l	4.37±1.29	4.27±1.21	0.55
Low-density lipoprotein, mmol/l	2.69±0.85	2.58±1.09	0.32
High-density lipoprotein, mmol/l	1.07±0.40	1.11±0.35	0.44
TG, mmol/l	1.66±1.09	1.53±1.06	0.31
Serum Alb, g/l	32.12±5.69	31.59±5.91	0.43

Data are expressed as n (%), mean ± SD or median (interquartile range).
CCB = Ca channel blocker; RAAS = renin-angiotensin-aldosterone system.

Risk Factors for the New-Onset CVC Group

First, we used new-onset CVC as the dependent variable for the univariate regression analysis, and the results revealed that history of diabetes, serum P, CRP and Alb levels, BMI, dialysis duration and use of statins were significantly associated with CVC (table 3). Next, multivariate logistic regression analysis showed that dialysis duration and serum P and CRP levels were independently positively correlated with new-onset CVC; however, serum Alb level was independently negatively correlated with CVC (table 4).

Discussion

Due to a metabolic imbalance of Ca and P, CKD patients have the risk of death 20 times that of healthy individuals [4]. Valvular heart disease is common in CKD patients. AVC has a higher incidence than MVC in dialysis patients, and the atrial valve is the most common site of valvular abnormalities [5, 6]. Our study showed that a relatively high proportion of CKD patients had CVC. Patients undergoing maintenance PD had a relatively fast progression rate

Table 2. Comparison of clinical parameters between the CVC and non-CVC patients on maintenance PD

Variable	CVC group (n = 50)	Non-CVC group (n = 144)	p
Age, years	61.6±12.5	60.0±13.2	0.41
Female gender	32 (51.6%)	57 (43.2%)	0.27
BMI	23.2±3.8	22.0±3.1	0.02
Dialysis duration, months	24.3±10.5	19.5±10.0	0.003
CCB, yes	58 (93.5%)	121 (91.7%)	0.67
α-Receptor blocker, yes	26 (41.9%)	37 (28.0%)	0.05
β-Receptor blocker, yes	26 (41.9%)	43 (32.6%)	0.20
Almarl, yes	16 (25.8%)	29 (22.0%)	0.56
RAAS blocker, yes	43 (69.4%)	85 (64.4%)	0.50
Diuretic, yes	35 (56.5%)	91 (68.9%)	0.09
Active vitamin D_3, yes	31 (50.0%)	67 (50.8%)	0.92
Ca tablets, yes	50 (80.6%)	117 (88.6%)	0.13
Statins, yes	10 (16.1%)	4 (3.1%)	0.001
Diabetes, yes	23 (37.1%)	29 (22.0%)	0.03
Ca concentration of PD fluid			0.29
1.25 mmol/l	55 (88.7%)	123 (93.2%)	–
1.75 mmol/l	7 (11.3%)	9 (6.8%)	–
PTH, pg/dl	220.5 (88.8–421.0)	208.3 (117–373.3)	0.73
CRP, mg/l	5.5 (4.0–9.05)	5.2 (4.9–7.17)	0.70
Creatinine, μmol/l	709.7±313.7	735.6±330.3	0.61
Urea, mmol/l	22.3±7.8	24.6±10.9	0.14
PA, g/l	0.29±0.13	0.27±0.10	0.24
AP, U/l	78.9±37.8	105.2±105.6	0.06
Serum total Ca, mmol/l	2.06±0.30	2.06±0.25	0.99
Serum P, mmol/l	1.87±0.65	1.71±0.42	0.04
TC, mmol/l	4.26±1.06	4.42±1.38	0.44
Low-density lipoprotein, mmol/l	2.71±0.82	2.68±0.87	0.85
High-density lipoprotein, mmol/l	1.08±0.38	1.07±0.42	0.72
TG, mmol/l	1.60±0.93	1.69±1.17	0.61
Serum Alb, g/l	30.7±5.1	32.8±5.9	0.02

Data are expressed as n (%), mean ± SD or median (interquartile range).
CCB = Ca channel blocker; RAAS = renin-angiotensin-aldosterone system.

of CVC after at least 6 months of dialysis. A prospective study reported that the proportion of patients with MVC was 26.3%, and that of AVC was 57.8% after 1 year of follow-up [6]. The present study showed that the proportions of new-onset AVC, MVC and AVC associated with MVC were 16.94, 10.3 and 5.1%, respectively, after an average period of dialysis treatment of 23.2 ± 3.8 months. Compared to our results, earlier studies have reported similar or higher proportions of CVC development and progression in PD or hemodialysis patients [9], possibly related to the population, the model of the cardiac ultrasound machine, the sensitivity of the cardiac ultrasound machine (89–94 and 76% sensitivity to AVC and MVC, respectively [10]) and the measurement and assessment by echocardiographic technicians.

The incidence of CVC has been reported to significantly increase with aging in the general population. Similarly, age is an independent risk factor for CVC in hemodialysis or PD patients [5, 6]. The present study showed that age was not associated with the progression of CVC; however, dialysis duration was an independent risk factor for the development of CVC, possibly because the body experiences a prolonged period of internal environment disorder

Table 3. Univariate logistic regression

Variable	β	p	OR	95% CI
Age	0.01	0.41	1.010	0.986–1.034
Statins	1.817	0.003	6.154	1.847–20.503
Diabetes	0.739	0.03	2.095	1.083–4.052
BMI	0.107	0.02	1.133	1.017–1.218
CRP	0.028	0.01	1.029	1.006–1.051
Serum Ca	0.001	0.999	1.001	0.325–3.081
Serum P	0.607	0.05	1.836	1.000–3.369
PA	1.664	0.24	5.280	0.337–82.669
Alb	–0.065	0.02	0.937	0.887–0.990
TC	–0.099	0.44	0.906	0.706–1.162
Dialysis duration	0.046	0.002	1.048	1.017–1.079
TG	–0.074	0.61	0.929	0.698–1.236

Table 4. Multivariate logistic regression

Variable	β	p	OR	95% CI
Statins	–1.153	0.11	3.169	0.777–12.923
Diabetes	0.736	0.06	2.088	0.963–4.529
Dialysis duration	0.038	0.03	1.039	1.004–1.075
Alb	–0.067	0.04	0.935	0.877–0.997
Serum P	0.943	0.01	2.569	1.227–5.377
BMI	0.095	0.07	1.099	0.992–1.217
CRP	0.031	0.02	1.031	1.006–1.057

with an extended duration of dialysis. This uremia is a risk factor that promotes cardiovascular calcification [11].

Increased Ca levels have been reported to be an independent risk factor for CVC in dialysis patients [3, 12]. Clinical studies also have shown that hyperphosphatemia is closely associated with the development and progression of vascular calcification, CVC and even death in CKD patients [3, 13]. Gallieni et al. [4] found that the serum Ca and P levels were unrelated to CVC. We also found that the serum Ca level was unrelated to CVC; nonetheless, the serum P level was an independent risk factor for CVC. Laboratory studies have shown that serum P can induce osteoblast/chondrocyte-like cell changes in the vascular smooth muscle phenotypes. Serum P positively regulates osteoblast transcription factors (e.g., Runx2/Cbfa1, Msx2 and Sox9), expression of the pro-calcification enzyme AP and secretion of matrix vesicles, thereby promoting mineralization by the formation of hydroxyapatite [14, 15]. In addition, elevated P induces vascular smooth muscle apoptosis and release of apoptotic bodies, which in turn form the initial nidus for vascular calcification [15]. The serum P increased vascular smooth muscle calcification is dose-dependent (from 1.6 to 3.0 mmol/l) [14, 16]. Similar reactions may occur in the heart valves. Additionally, Portale et al. [17] proposed that increased serum P levels may cause a reduction in the synthesis of 1,25-dihydroxyvitamin D. Decreased 1,25-dihydroxyvitamin D levels can cause a decrease in myocardial contractility [18] and an increase in the development of coronary artery calcification [19]. Another study proposed that an increased serum P level may directly damage vascular smooth muscle [13]. Two prospective studies, by Gallieni et al. [4] and Avila-Diaz et al. [6], showed that the serum P level was unrelated to CVC in PD patients. This result might be related to the study population,

study period and use of non-Ca-based P-binding agents such as lanthanum carbonate and sevelamer. Non-Ca-based P-binding agents have only been available in China since 2014. Furthermore, lack of medical insurance has limited their usage. Both drugs have been used in other countries for many years, which may affect the results of the studies. Moreover, withdrawal of patients (death, loss and dialysis conversion) was a factor in the above two studies, resulting in inconsistent patient populations from pre- to post-treatment and thus affecting the research findings.

Multiple studies have shown that PD patients have a high incidence of coexistence of inflammation and malnutrition, known as the inflammation-dystrophy syndrome [2, 20, 21]. This syndrome is a strong predictor of cardiovascular disease and death in dialysis patients [20]; however, the underlying mechanism is not fully understood. Zapolski [2] proposed that reduced serum Alb, reduced TC, increased CRP and increased β_2-microglobulin levels are effective indices that reflect the severity of inflammation-dystrophy syndrome. The present study showed that reduced serum Alb and increased CRP levels were two risk factors for the progression of CVC. Research has suggested that a low level of inflammation may be present in the body of patients with subclinical atherosclerosis. We speculate that uremic patients with CVC have a similar reaction. In inflammatory conditions, the levels of various inflammatory cytokines (e.g., interleukin 1, tumor necrosis factor and CRP) are increased, causing loss of appetite, reduction in the intake of dietary protein and reduced synthesis but increased decomposition of muscle protein, leading to malnutrition [22]. Malnutrition and inflammation may contribute to atherosclerosis by increasing oxidative stress [21]. Inflammation may contribute to an increase in oxidation products, while malnutrition can reduce the body's antioxidant defense capacity [23]. Moreover, clinical and laboratory studies have shown that CRP can reduce serum Alb levels, activate the complement system and stimulate peripheral blood mononuclear cells to synthesize a membrane glycoprotein that activates the clotting response to promote cardiovascular damage [24]. Reduced serum Alb levels may reflect more serious atherosclerosis resulting from the uremic state, other nutrient deficiencies (e.g., folic acid and vitamin B_{12} deficiencies cause an increase in homocysteine levels, a risk factor for atherosclerotic heart disease) or the inflammatory state [25] and promote endothelial injury [26].

The present study was a single-center observational study with a small sample size. The results need to be further verified by multicenter studies with a large sample size. Additionally, due to the small number of patients with MVC, the present retrospective study did not separately discuss risk factors for the progression of AVC and MVC. Due to research limitations, only one index (i.e., CRP) was included to reflect the impact of inflammation, and other factors such as interleukin 1 and interleukin 6 were not included. Thus, multi-index prospective studies are needed to verify our results.

In summary, this study found that long-term PD patients have a high incidence of CVC with rapid progression. Long dialysis duration, increased serum P and decreased serum Alb levels as well as an inflammatory state are independent risk factors that lead to new-onset CVC in PD patients.

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Statement of Ethics

This study was approved by the Hospital Ethics Committee.

Disclosure Statement

The authors certify that none of them has any financial or other conflict of interest in connection with this paper.

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