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Association of Inflammation and Malnutrition with Cardiac Valve Calcification in Continuous Ambulatory Peritoneal Dialysis Patients

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Abstract. Cardiac valve calcification (VC) has long been regarded as a consequence of aging and abnormal calcium-phosphate metabolism in uremic patients. In view of the recent recognition of association among inflammation, malnutrition, and atherosclerosis, the possible role of inflammation and malnutrition in VC was investigated. Inflammatory markers (including C-reactive protein [CRP], fibrinogen, and basal metabolic rate) and nutritional status (assessed using serum albumin, subjective global nutrition assessment, and handgrip strength) were examined, in addition to calcium phosphate parameters and other traditional cardiovascular risk factors, including gender, smoking habits, BP, and lipid profile, in relation to VC in 137 patients who were on continuous ambulatory peritoneal dialysis. Compared with patients with no VC, patients with VC not only were older (60 [10] *versus* 54 [12] yr; $P = 0.005$), had higher plasma phosphate (1.89 [0.52] *versus* 1.64 [0.41] mmol/L; $P = 0.003$), and had higher parathyroid hormone (83 [40, 145] *versus* 38 [16, 71] pmol/L; $P = 0.001$) but also had higher CRP (4.5 [0.1, 13.4] *versus* 0.2 [0.1, 4.4] mg/L; $P = 0.004$), had higher fibrinogen (6.6 [1.9] *versus* 5.7 [1.3] g/L; $P = 0.002$), and had lower serum albumin (26 [4] *versus* 29 [3] g/L; $P = 0004$). Twenty-three percent of patients with VC *versus* 17% of patients with no VC were moderately to severely malnourished according to subjective global nutrition assessment ($P = 0.05$). Even after adjustment for patients' age, duration of continuous ambulatory peritoneal dialysis, diabetes, and calcium $\times$ phosphate product, cardiac VC remained strongly associated with CRP (odds ratio, 1.05; $P = 0.026$) and albumin (odds ratio, 0.85; $P = 0.01$). The data suggest that VC not only is a passive degenerative process but also involves active inflammation, similar to that seen in atherosclerosis. The presence of uncontrolled hyperphosphatemia and hyperparathyroidism further accelerates the progression of calcification. The data also indicate that VC and atherosclerosis should be considered as associated syndromes, sharing similar pathogenic mechanisms, namely active inflammation.

Mortality in end-stage renal failure patients has been reported to be at least 15-fold greater than in age-matched controls (1), among which cardiovascular deaths account for more than 40% of the total mortality (2,3). It is widely recognized that dialysis patients are at higher risk of developing accelerated atherosclerosis, coronary artery disease, and congestive cardiac failure. However, less well appreciated is that calcific complications involving different cardiac structures in these patients also contribute to increased cardiac morbidity and mortality (4,5). Previous studies showed increased incidence of mitral annulus calcification in patients with chronic renal failure compared with age-matched controls (6–8). Calcification of the mitral annulus can cause mitral regurgitation (6) or stenosis or both (7,8) and often is associated with aortic valve calcification (VC). Aortic VC, in severe degree, can cause aortic stenosis (9–11) and regurgitation (12). Calcific deposits also increase the risk of cardiac conduction disturbance (13,14) and increase risk of death (15). However, the cause of premature calcification of the mitral and aortic valves in dialysis patients has not been defined clearly.

Autopsy studies have consistently shown an association between coronary artery calcifications and atherosclerosis (16,17). These studies also noted an association between coronary artery calcification and cardiac VC. In addition, presence of coronary artery calcification was shown to be predictive of coronary artery disease in individuals both with and without renal failure (18), indicating that both atherosclerosis and calcification may be sharing similar pathogenetic mechanisms. Recent studies noted associations among inflammation, malnutrition, and atherosclerosis (19). Inflammation has been shown to increase risk of atherosclerosis in individuals both with (20–22) and without renal failure (23,24). One study also reported an association between hypoalbuminemia and vascular disease (25). Whether calcification of cardiac valves shares similar pathogenetic factors as atherosclerosis or should be considered as part of the atherosclerotic process remains unknown. We therefore undertook this study to determine the

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prevalence of cardiac VC in end-stage renal failure patients who were on continuous ambulatory peritoneal dialysis (CAPD) and to identify risk factors associated with the development of cardiac VC. In particular, we examined the possible role of inflammation and malnutrition in VC in dialysis patients.

Materials and Methods

Patient Selection

The study population was composed of 137 patients who had been maintained stably on CAPD for at least 3 mo. All of them were of Chinese origin. All study participants gave written informed consent for the study. The study protocol was approved by the Human Ethics Committee of the Chinese University of Hong Kong.

Echocardiography

Echocardiography was performed using a Vingmed GE System V sonographic machine and a 3.3-MHz probe. All echocardiographic images were analyzed by cardiologists who were blinded to clinical details of patients. VC was defined as bright echoes on one or more cusps of more than 1 mm in either mitral or aortic valves or both. Sensitivity and specificity for echocardiographic detection of calcium in both the mitral and the aortic valves have been reported to be 76% and 89 to 94%, respectively (26).

Data Collection

Demographic data including age at study, gender, duration on dialysis, presence of underlying diabetes, underlying cause of renal failure, and smoking history were collected. Study participants were classified as current smoker (if they were still smoking), ex-smoker (if they had quitted smoking), or non-smoker (if they had never smoked). Both current and ex-smokers were considered to have positive smoking history. Systolic and diastolic BP was measured on every follow-up visit. Serum biochemical parameters were collected on every regular follow-up visit at 6- to 8-wk intervals preceding echocardiography in each patient, and these results were averaged to obtain a mean value for each measurement. They included measurements of hemoglobin, hematocrit, plasma calcium, phosphate, alkaline phosphatase, parathyroid hormone (PTH), and calculations of the calcium $\times$ phosphate product ($Ca \times PO_4$). Other biochemical parameters, including PTH and lipid profile (which include total cholesterol, HDL cholesterol, LDL cholesterol, and triglyceride [TG]) were measured every 3 mo, and the results also were averaged to obtain a mean value. PTH was determined by Immulite immunoassay (Diagnostic Products Corporation, Los Angeles, CA). Total, HDL, and LDL cholesterol and TG were measured after overnight fasting. Systolic and diastolic BP and all other biochemical data also were collected for the 12 mo preceding echocardiography or before parathyroidectomy if this had been done.

Assessment of Inflammation

Degree of inflammation was assessed by levels of C-reactive protein (CRP) and fibrinogen. CRP was measured using an immunoassay kit (Berkman, Fullerton, CA). The detection limit of CRP is 0.1 mg/L. Levels below 0.1 mg/L are expressed as 0.1 mg/L. Fibrinogen was measured by a prothrombin time-derived and turbidimetric clot detection method using the ACL Futura (Instrumentation Laboratory, Lexington, MA). Basal metabolic rate was performed in all patients using indirect calorimetry after having an overnight fast for 12 h and was expressed in kilocalories per kilogram of dry body weight. Dry body weight was defined as the body weight measured after the abdomen was completely drained of peritoneal fluid.

Assessment of Nutritional Status

Nutritional status was assessed on the basis of the following parameters: body weight and height, body mass index (the weight in kilograms divided by the square of the height in meters), serum albumin, handgrip strength (HGS), and subjective global nutrition assessment (SGNA). Serum albumin was measured using the bromcresol purple method. Bimonthly serum albumin was averaged for the 12 mo preceding echocardiography or before parathyroidectomy if this had been done. Nutritional status was assessed by experienced research staff using SGNA (27), and patients were graded to have normal, mild, moderate, or severe malnutrition status accordingly. Research staff who performed SGNA were blinded to all clinical and biochemical details of patients. HGS was assessed using a hand dynamometer. HGS of the nondominant arm was measured three times, and the average of the best two readings was taken to be the final HGS (28).

Statistical Analyses

Statistical analysis was performed using SPSS 10.0 for Windows software (SPSS, Inc., Chicago, IL). Results are presented as mean $\pm$ SD for normally distributed data and as median (interquartile range) for data not normally distributed. Categorical data were compared between groups by χ^2 test. Continuous data were compared between groups using unpaired *t* test for normally distributed variables or using Mann-Whitney *U* test for variables not normally distributed. Multiple logistic regression analysis was performed to assess the relative importance of the different risk factors associated with cardiac VC. Significance was taken at the 5% level.

Results

The mean age of the 137 CAPD patients was 56 yr (range, 22 to 77 yr). There were 65 men and 72 women. The mean duration of CAPD was 45 mo (range, 5 to 151 mo). The cause of renal failure was chronic glomerulonephritis in 42 patients (30.7%), diabetic nephropathy in 33 patients (24.1%), hypertensive nephrosclerosis in 13 patients (9.5%), obstructive uropathy in 10 patients (7.3%), polycystic kidney disease in 8 patients (5.8%), and tubulointerstitial disease in 4 patients (2.9%). Underlying renal diagnosis was not known in 27 patients (19.7%). Among the 137 patients, 93 patients (68%) had normal mitral and aortic valves, whereas 44 (32%) had either mitral or aortic VC or both. Twenty-one patients (15%) were noted to have calcification over the aortic valve, and 34 patients (25%) had calcification of the mitral valve. Eleven (8%) patients had calcification involving both mitral and aortic valves.

Clinical, biochemical, and nutritional parameters were compared between patients with no cardiac VC (No VC group; $n = 93$) and patients who had either mitral or aortic VC or both, grouped together as VC group ($n = 44$). The demographic data of patients with and without VC are shown in Table 1. No difference was noted in the gender distribution between patients with and without VC. Patients with cardiac VC were significantly older (60 ± 10 *versus* 54 ± 12 yr; $P = 0.005$). Indeed, the prevalence of VC was much higher in patients age 51 or older compared with those younger than 50 (Figure 1A).

There also was a trend toward longer duration of dialysis (45 [25, 75] *versus* 36 [21, 57] mo; $P = 0.177$; Figure 1B) and higher incidence of diabetes (36 *versus* 26%; $P = 0.230$) among patients with VC, although it was statistically insignificant. Positive history of smoking was noted in a greater percentage of patients with VC compared with those with no VC (50 *versus* 33%; $P = 0.090$; Table 1).

In terms of calcium-phosphate metabolism, patients with VC showed significantly higher mean plasma calcium (2.64 ± 0.19 *versus* 2.57 ± 0.17 mmol/L; $P = 0.022$), phosphate (1.89 ± 0.52 *versus* 1.64 ± 0.41 mmol/L; $P = 0.003$), and resulting higher $Ca \times PO_4$ product (5.01 ± 1.46 *versus* 4.24 ± 1.11; $P = 0.003$) compared with patients with no VC (Table 2). Indeed, the prevalence of calcification seemed to be especially increased with plasma calcium over 2.8 mmol/L or phosphate over 2.5 mmol/L or $Ca \times PO_4$ product over 4 (Figure 2, A through C). VC patients also had more severe hyperparathyroidism as indicated by higher ALP (149 [113, 274] *versus* 111 [83, 163] mmol/L; $P = 0.001$) and PTH (83 [40, 145] *versus* 38 [16, 71] pmol/L; $P = 0.001$) compared with patients with no VC (Table 2). The prevalence of VC was increased especially in patients with PTH over 100 pmol/L (Figure 2D). History of parathyroidectomy was noted in 14% patients with VC *versus* 3% patients with no VC ($P = 0.031$). No difference was noted in the percentage of patients who received vitamin D therapy (VC *versus* no VC group, 50 *versus* 39%, respectively; $P = 0.096$; Table 2).

One-yr mean systolic and diastolic BP was not significantly different between patients with and without VC. However, patients with VC were using a slightly higher number of antihypertensives for BP control compared with patients with no VC (1.68 ± 1.09 *versus* 1.48 ± 1.07; $P = 0.317$), although it was statistically insignificant. No difference was noted in the mean total, HDL, and LDL cholesterol and TG between patients with and without VC. The percentage of patients who were treated with lipid-lowering drugs also was similar between patients with and without VC. There was a trend toward lower hemoglobin in the VC group (9.1 ± 1.3 *versus* 9.5 ± 1.6 g/dl; $P = 0.123$). However, no difference was noted in the frequency of erythropoietin (EPO) use for patients with and without VC (Table 2). Despite a tendency toward a lower hemoglobin, VC patients who were receiving EPO received a higher cumulated EPO dosage (192 [106, 192] *versus* 185 [96,192] $\times 10^3$ units; $P = 0.174$) compared with those with no VC.

Patients with VC were significantly more malnourished than patients with no VC. This was reflected by the more severe degree of hypoalbuminemia (26 ± 4 *versus* 29 ± 3 g/L; $P = 0.004$) and lower HGS in patients with VC (12 [8, 18] *versus* 16 [8, 23] kg; $P = 0.051$; Table 3). The prevalence of VC was particularly increased in patients with serum albumin below 28 g/L (Figure 3A) or HGS below 20 kg (Figure 3B). Twenty-three percent of patients with VC *versus* 17% of patients with no VC were graded to have moderate to severe malnutrition according to subjective global assessment (Table 3). Patients with VC also had a higher degree of inflammation as denoted by higher CRP (4.5 [0.1, 13.4] *versus* 0.2 [0.1, 4.4] mg/L; $P = 0.004$) and higher fibrinogen (6.6 ± 1.9 *versus* 5.7 ± 1.3 g/L; $P = 0.002$; Table 3). Indeed, the prevalence of calcification was especially increased when CRP was more than 5 mg/L (Figure 3C) or fibrinogen was more than 6 g/L (Figure 3D). There also was a trend toward a higher basal metabolic rate (22.3 ± 3.6 *versus* 21.2 ± 3.6 kcal/kg dry body weight; $P = 0.109$) for patients with VC, although it was statistically insignificant. No significant correlation, however, was noted between CRP and basal metabolic rate. Only very weak association was noted between fibrinogen and basal metabolic rate ($R = 0.17$, $P = 0.007$), which suggests that the presence of inflammation may not necessarily be associated with increase in resting energy expenditure.

Even after adjustment for the effect of age, duration of dialysis and diabetes, $Ca \times PO_4$ product (odds ratio [OR],

Table 1. Demographic data of CAPD patients with or without cardiac VC[a]

Demographic	VC ($n = 44$)	No VC ($n = 93$)	P Value
Male [n (%)]	20 (46)	45 (48)	0.855
Age [mean (SD)]	60 (10)	54 (12)	0.005
Current/ex-smoker [n (%)]	22 (50)	31 (33)	0.090
Duration of CAPD (mo)[b]	45 (25, 75)	36 (21, 57)	0.177
Diabetes mellitus [n (%)]	16 (36)	24 (26)	0.230
Underlying renal diagnosis [n (%)]			
chronic glomerulonephritis	11 (25)	31 (33)	0.400
diabetic nephropathy	14 (32)	19 (20)	
hypertensive nephrosclerosis	6 (14)	7 (8)	
polycystic kidney disease	1 (2)	7 (8)	
obstructive	2 (5)	8 (9)	
others	2 (2)	2 (2)	
unknown	8 (18)	19 (20)	

[a] CAPD, continuous ambulatory peritoneal dialysis; VC, valve calcification.
[b] Expressed in median (interquartile range).

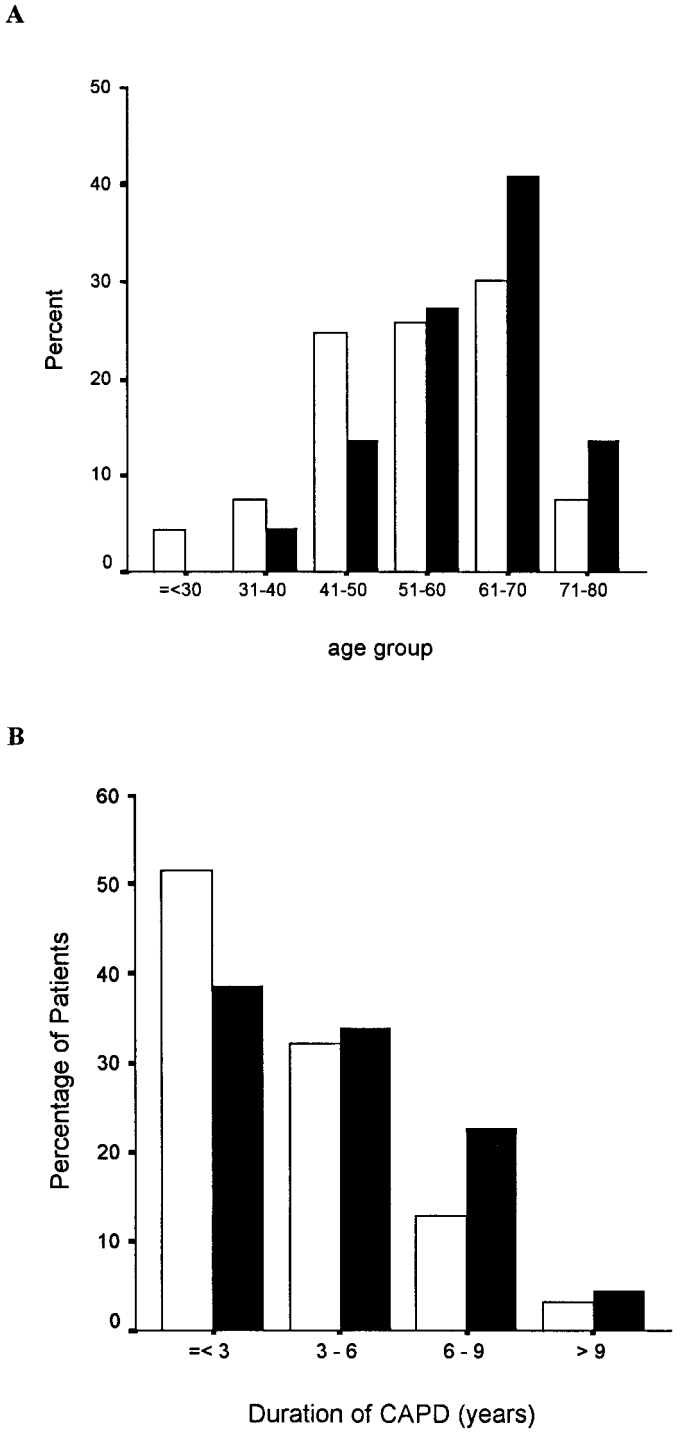

Figure 1. Prevalence of cardiac valve calcification (VC) in relation to age (A) and duration (B) of continuous ambulatory peritoneal dialysis (CAPD). □, no valve calcification (VC); ■, VC.

2.17; 95% confidence interval [CI], 1.44 to 3.27; $P = 0.0002$), serum albumin (OR, 0.85; 95% CI, 0.75 to 0.96; $P = 0.01$), and CRP (OR, 1.05; 95% CI, 1.01 to 1.10; $P = 0.026$) remained strongly associated with cardiac VC in CAPD patients (Table 4).

Indeed, the prevalence of VC was studied in relation to the total number of risk factors present, namely high $Ca \times PO_4$ product ≥ 5, malnutrition (as denoted by serum albumin ≤ 28 g/L), and inflammation (as indicated by CRP ≥ 10 mg/L). A significant stepwise increase in the prevalence of VC was noted with the presence of increasing number of calcification risk factors (number of risk factors, 0 [21%] *versus* 1 [24%] *versus* 2 [52%] *versus* 3 [86%]; $P < 0.001$; Figure 4).

Interaction among CRP, albumin, and $Ca \times PO_4$ in predisposing patients to VC is shown in Figure 5. Calcification was at its lowest prevalence (20.8%) when $Ca \times PO_4 < 5$ and there was no evidence of malnutrition and inflammation (M-ve, I-ve: albumin >28 g/L; CRP <10 mg/L). Prevalence of VC increased in the presence of either malnutrition (M+ve, I-ve: albumin ≤ 28 g/L; CRP <10 mg/L) or inflammation (M-ve, I+ve: albumin ≤ 28 g/L; CRP ≥ 10 mg/L), indicating an independent contribution of inflammation and malnutrition to this increased risk of calcification. The prevalence of VC increased significantly to 57% in the presence of both malnutrition and inflammation without an increased $Ca \times PO_4$ product (M+ve, I+ve: albumin ≤ 28 g/L; CRP ≥ 10 mg/L), indicating possible synergism of these two factors in predisposing to VC (Figure 5A). However, among patients with $Ca \times PO_4$ product ≥ 5 (Figure 5B), prevalence of VC was only 25% without evidence of malnutrition and inflammation (M-ve, I-ve). The prevalence increased in the presence of either inflammation (M-ve, I+ve) or malnutrition (M+ve, I-ve), suggesting an independent contribution of inflammation and malnutrition, other than high $Ca \times PO_4$ product, to this increased risk of VC. The prevalence of calcification was the highest (85.7%) when both malnutrition and inflammation (M+ve, I+ve) coexisted with a $Ca \times PO_4$ product ≥ 5. This indicated that inflammation, malnutrition, and high $Ca \times PO_4$ all contributed significantly and independently to an increased risk of VC. That the presence of both inflammation and malnutrition substantially increased the risk of calcification more than the presence of either factor alone, irrespective of the $Ca \times PO_4$ product level, confirmed synergism of these two factors in predisposing to VC.

Discussion

Renal failure patients on dialysis are at increased risk of developing calcification of different cardiac structures (29), which contribute to the increased cardiovascular mortality observed in this population. In this study, we performed the largest single-center review of cardiac VC among renal failure patients on CAPD. Our results indicate that calcification of heart valves is a frequent finding among CAPD patients. One third of our CAPD patients had calcification of either the mitral or the aortic valve or both, with the prevalence higher for mitral compared with aortic VC. The prevalence of mitral VC in our peritoneal dialysis (PD) patients was similar to that of hemodialysis (HD) patients reported in the literature, ranging from 10 to 40% (9,30–32), yet the prevalence of aortic VC was much lower compared with that observed in HD patients, ranging from 28 to 55% (33,34). One potential explanation is that the presence of arteriovenous fistulas in HD patients may increase cardiac output and as a result increase mechanical stress on the valve cusps, hence increasing the risk of premature VC (33,35). Further comparative studies are needed to

Table 2. Hemodynamic and biochemical parameters of patients with and without cardiac VC

Parameter	VC ($n = 44$)	No VC ($n = 93$)	P Value
Systolic BP (mmHg)	148 (18)	145 (16)	0.226
Diastolic BP (mmHg)	81 (9)	82 (10)	0.467
No. of antihypertensives	1.68 (1.09)	1.48 (1.07)	0.317
Hemoglobin (gm/dl)	9.1 (1.3)	9.5 (1.6)	0.123
Hematocrit (%)	27 (4)	28 (5)	0.595
N (%) on erythropoietin	21 (48)	39 (42)	0.582
Calcium (mmol/L)	2.64 (0.19)	2.57 (0.17)	0.022
Phosphate (mmol/L)	1.89 (0.52)	1.64 (0.41)	0.003
Calcium × phosphate product	5.01 (1.46)	4.24 (1.11)	0.003
Alkaline phosphatase (mmol/L)[b]	149 (113, 274)	111 (83, 163)	0.001
Parathyroid hormone (pmol/L)[b]	83 (40, 145)	38 (16, 71)	0.001
N (%) with parathyroidectomy	6 (14)	3 (3)	0.031
N (%) receiving vitamin D	22 (50)	36 (39)	0.267
Total cholesterol (mmol/L)	5.28 (1.36)	5.59 (1.16)	0.177
HDL cholesterol (mmol/L)	1.11 (0.33)	1.18 (0.44)	0.387
LDL cholesterol (mmol/L)	3.22 (1.00)	3.52 (0.97)	0.100
Triglyceride (mmol/L)[b]	1.75 (1.05, 2.80)	1.79 (1.19, 2.53)	0.623
N (%) on lipid-lowering therapy	6 (14)	15 (16)	0.803

[a] Continuous data expressed as mean (SD) unless specified otherwise.
[b] Expressed as median (interquartile range).

determine whether PD is indeed associated with a lower incidence of aortic VC.

Consistent with previous studies (31,33–35), we noted that patients with VC were significantly older. The prevalence of VC was significantly higher in patients who were older than 50 yr (38%) compared with those who were younger than 50 yr (19%). With logistic regression analysis, age was one of the most important predictor for VC. We also noted a trend toward increased risk of VC with increasing duration on dialysis, although not as significant as that reported previously (33). However, because nearly 40% of the VC was already present within first 3 yr on dialysis (Figure 1B), a prospective study will be needed to determine whether calcification is already present at the time of initiation of dialysis or it develops subsequently during dialysis. This will provide further evidence regarding whether potential risk factors for VC should be modified as early as in the predialysis phase of chronic renal failure to prevent subsequent development of VC.

Our data are compatible with previous reports of VC in dialysis patients (33,35) in that elevated $Ca \times PO_4$ product was strongly associated with the development of VC. The risk of VC increased markedly with $Ca \times PO_4$ product above 4, and this risk increased further with increasing $Ca \times PO_4$ product. A $Ca \times PO_4$ product of 7 or above was invariably associated with the development of VC (Figure 2C). This increase in $Ca \times PO_4$ product was associated with an increase in both plasma calcium and phosphate, although more significantly so for phosphate. The risk of VC in our PD patients was particularly increased when plasma calcium was more than 2.8 mmol/L (Figure 2A) or phosphate was more than 2.5 mmol/L (Figure 2B). This degree of hyperphosphatemia was related partly to secondary hyperparathyroidism, which itself also strongly predisposed to VC. Significant positive correlation was noted between the level of PTH and the degree of hyperphosphatemia ($R = 0.505$, $P < 0.001$). This suggests that more effective treatment of secondary hyperparathyroidism may improve both calcium and phosphate control and hence reduce the development of VC in dialysis patients.

Valvular calcification also was observed in patients without hypercalcemia, hyperphosphatemia, and hyperparathyroidism, indicating that other factors may be responsible for the development of VC. Our study clearly demonstrated a novel association of inflammation and malnutrition with VC in dialysis patients. Previous studies suggested a strong association among malnutrition, inflammation, and atherosclerosis (MIA syndrome) in chronic renal failure patients (19). An association between hypoalbuminemia and vascular disease also has been reported in dialysis patients (25). In our study, we demonstrated an increase in the risk of valvular calcification with increasing inflammation as denoted by increased circulating CRP and fibrinogen. A strong association also was noted between the degree of hypoalbuminemia and valvular calcification. Likewise, other nutrition markers, including HGS and SGNA, showed similar association with VC. However, further prospective studies are needed to determine whether malnutrition triggers the inflammatory process or *vice versa*.

Our finding provides support for the concept that VC not only is a passive, degenerative process but also involves active inflammation similar to that seen with atherosclerosis of central and peripheral arteries. Indeed, recent studies showed that using *Salmonella typhi* vaccine to generate an acute systemic inflammatory response causes temporary but profound dys-

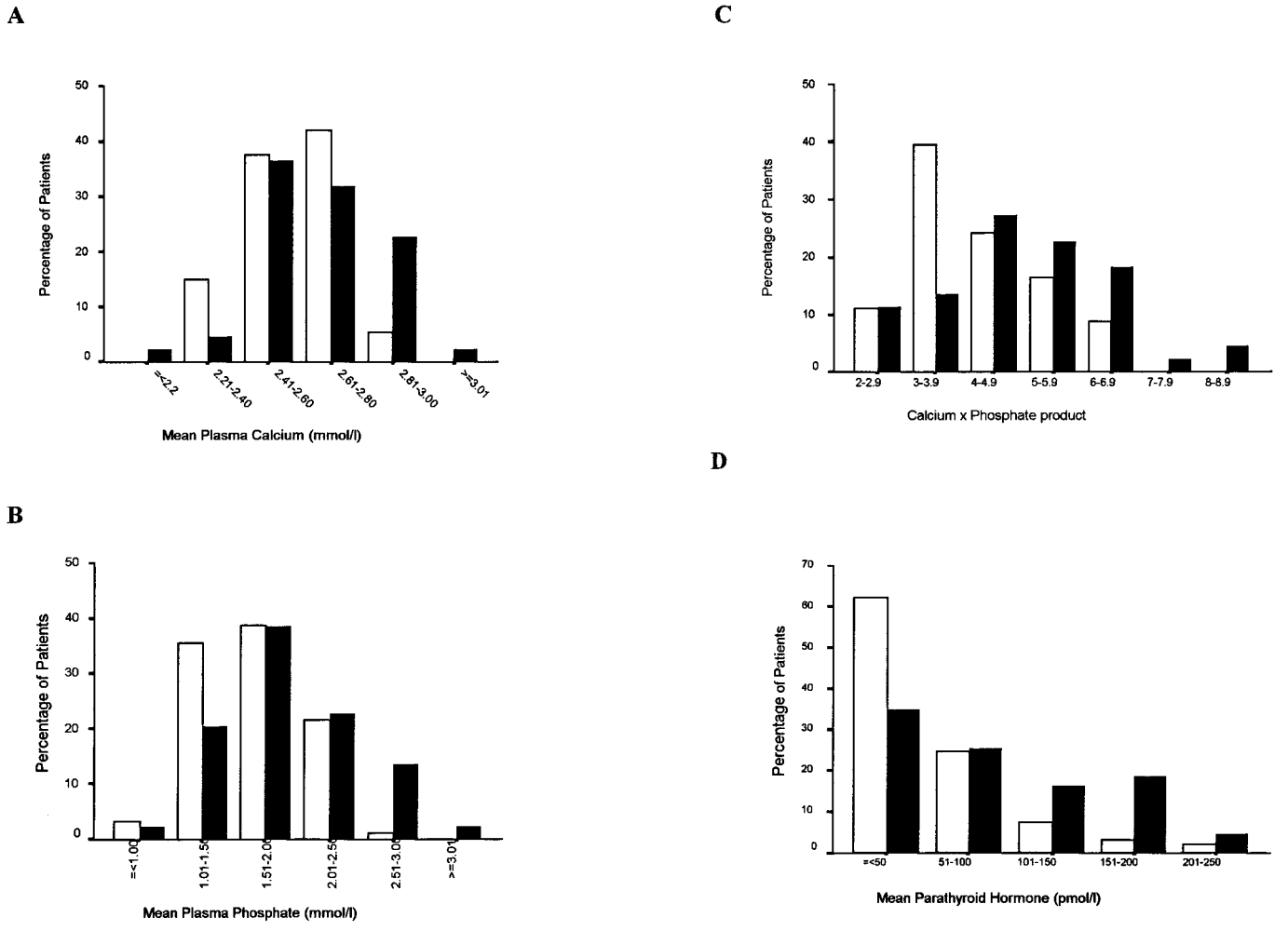

Figure 2. Prevalence of cardiac VC in relation to plasma calcium (A), phosphate (B), calcium × phosphate ($Ca \times PO_4$) product (C), and parathyroid hormone (D). □, no VC; ■, VC.

Table 3. Association of inflammation and malnutrition with cardiac VC in CAPD patients[a]

Parameter	VC (n = 44)	No VC (n = 93)	P Value
Body weight (kg)	57 (8)	57 (11)	0.912
Body height (m)	1.57 (0.08)	1.57 (0.08)	0.799
Body mass index (kg/m^2)	23.3 (3.1)	22.9 (3.5)	0.546
Serum albumin (g/L)	26.6 (3.6)	28.7 (3.3)	0.001
Handgrip strength (kg)	13.4 (7.4)	17.5 (9.9)	0.008
Subjective global assessment [n (%)]			
normal	21 (48)	56 (60)	0.050
mild	13 (30)	21 (23)	
moderate	7 (16)	16 (17)	
severe	3 (7)	0 (0)	
C-reactive protein (mg/L)[b]	4.5 (0.1, 13.4)	0.2 (0.1, 4.4)	0.004
Fibrinogen (g/L)	6.6 (1.9)	5.7 (1.3)	0.002

[a] Continuous data expressed as mean (SD) unless specified otherwise.
[b] Expressed as median (interquartile range).

function of vascular endothelium in humans, confirming the role of inflammation in initiating atherosclerosis (36). We hypothesized that cardiac VC, like atherosclerosis, involves active inflammation with valvular endothelial damage and macrophage activation, which further lay down osteopontin and enhance VC (37). Indeed, the role of inflammation in VC

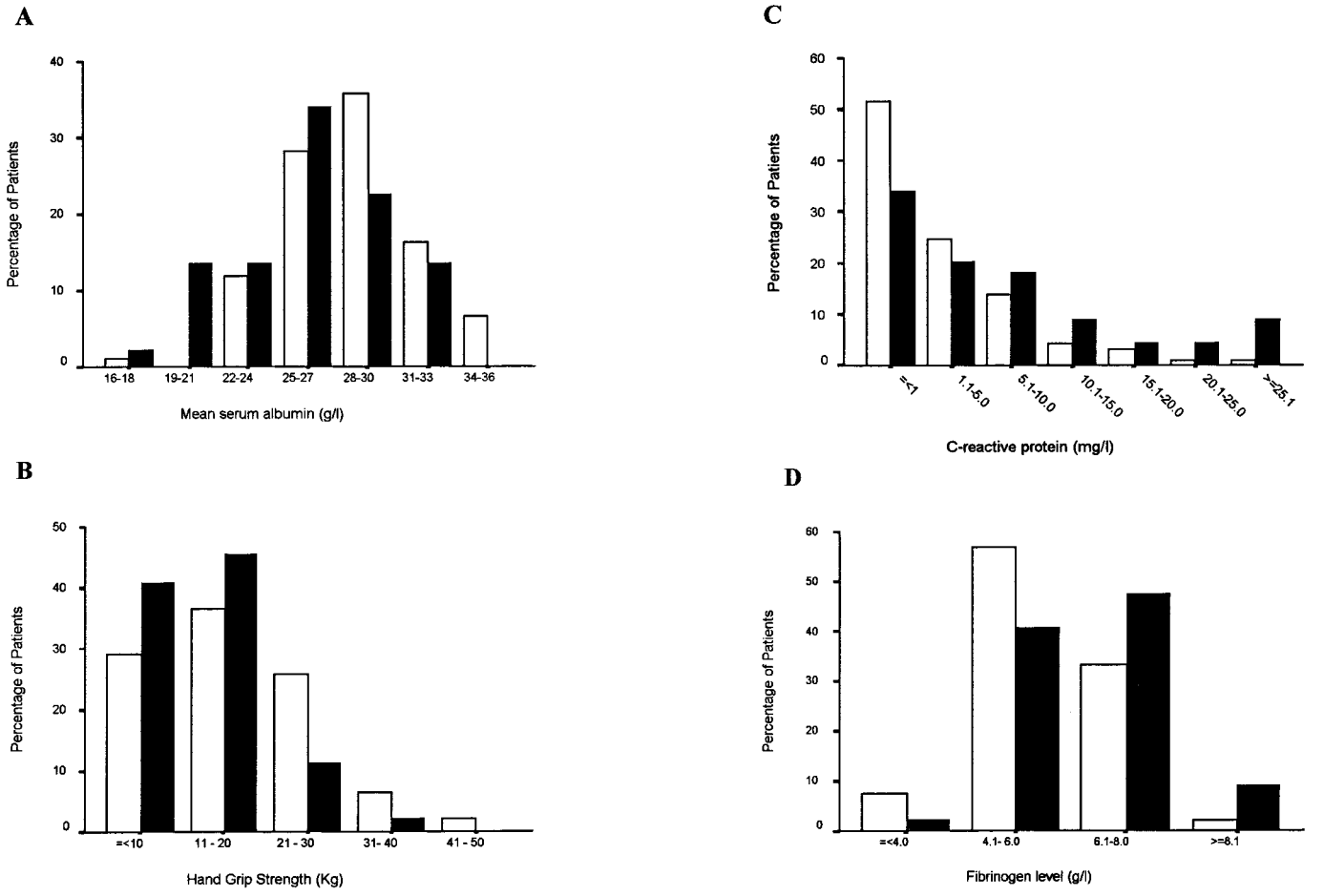

Figure 3. Prevalence of cardiac VC in relation to nutritional status as assessed by serum albumin (A) and handgrip strength (B) and degree of inflammation as assessed by C-reactive protein (CRP; C) and fibrinogen level (D). □, no VC; ■, VC.

Table 4. Logistic regression analysis showing the importance of C-reactive protein and albumin in predicting cardiac VC even after adjusting for age, duration of CAPD, diabetes, and calcium × phosphate product.

Risk Factors	OR	95% CI	*P* Value
Age	1.07	1.02–1.12	0.004
Duration of CAPD	2.91	1.07–7.89	0.752
Diabetes	2.91	1.07–7.89	0.036
Calcium × phosphate product	2.17	1.44–3.27	0.0002
Serum albumin	0.85	0.75–0.96	0.011
C-reactive protein	1.05	1.01–1.10	0.026

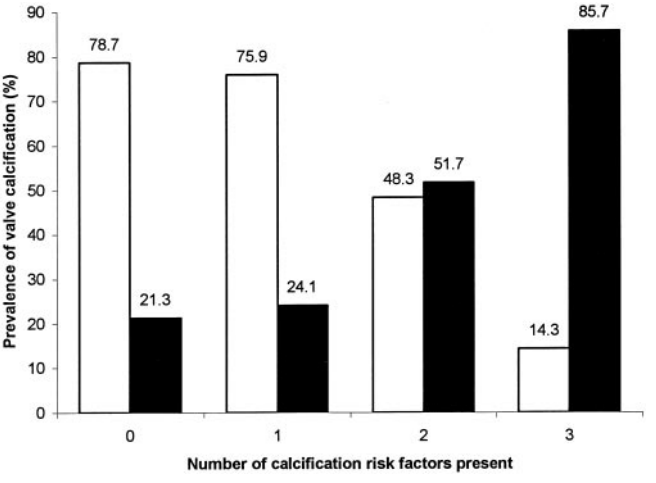

Figure 4. Prevalence of VC in relation to the number of risk factors present. Risk factors for calcifications include a high Ca × PO_4 product ≥5, inflammation (CRP ≥10 mg/L), and malnutrition (serum albumin ≤28 g/L). □, no VC; ■, VC. $P < 0.01$.

is evidenced by the accumulation of macrophages and T lymphocytes other than LDL and lipoprotein(a) in early aortic VC (36,38,39). Within regions of lipoprotein accumulation are areas of microscopic calcification, and macrophages within the lesions produce osteopontin, a protein that further modulates tissue calcification (40). Osteopontin also coexists similarly with intimal macrophages in calcific human mitral annulus, indicating that cardiac VC is indeed an actively mediated phenomenon (41). Recent findings of increased circulating soluble adhesion molecules in patients with nonrheumatic aortic stenosis also adds strength to the hypothesis that inflamma-

tion underlies the VC process (42). Indeed, increased circulating soluble adhesion molecules have been reported to be associated with malnutrition, inflammation, cardiovascular disease, and mortality in predialysis patients (43). However, more recent studies also noted that tumor necrosis factor-α , a proinflammatory cytokine secreted mainly by macrophages, enhanced *in vitro* calcification of vascular cells by increased expression and activity of alkaline phosphatase, an enzyme important in matrix mineralization (44). This finding, together with previous reports of mice showing an association between tumor necrosis factor-α and calcified vascular lesions (45), provides further evidence that inflammation does play an active role in mediating the process of calcification. The presence of increased CRP and fibrinogen, together with hypoalbuminemia and lower HGS in CAPD patients with VC, is consistent with the hypothesis that inflammation and malnutrition mediate the valvular calcification process other than the presence of uncontrolled hyperphosphatemia, hyperparathyroidism, and resulting high $Ca \times PO_4$ product.

Previous autopsy studies showed an association between coronary artery calcification and atherosclerosis (16,17). These studies also confirmed a link between coronary artery calcification and cardiac VC (16,17). Moreover, significant correlation was noted between valvular calcification and aortic atheroma in nonuremic patients, indicating that valvular calcification may indeed be a marker for atherosclerosis of the aorta (46). Our current study

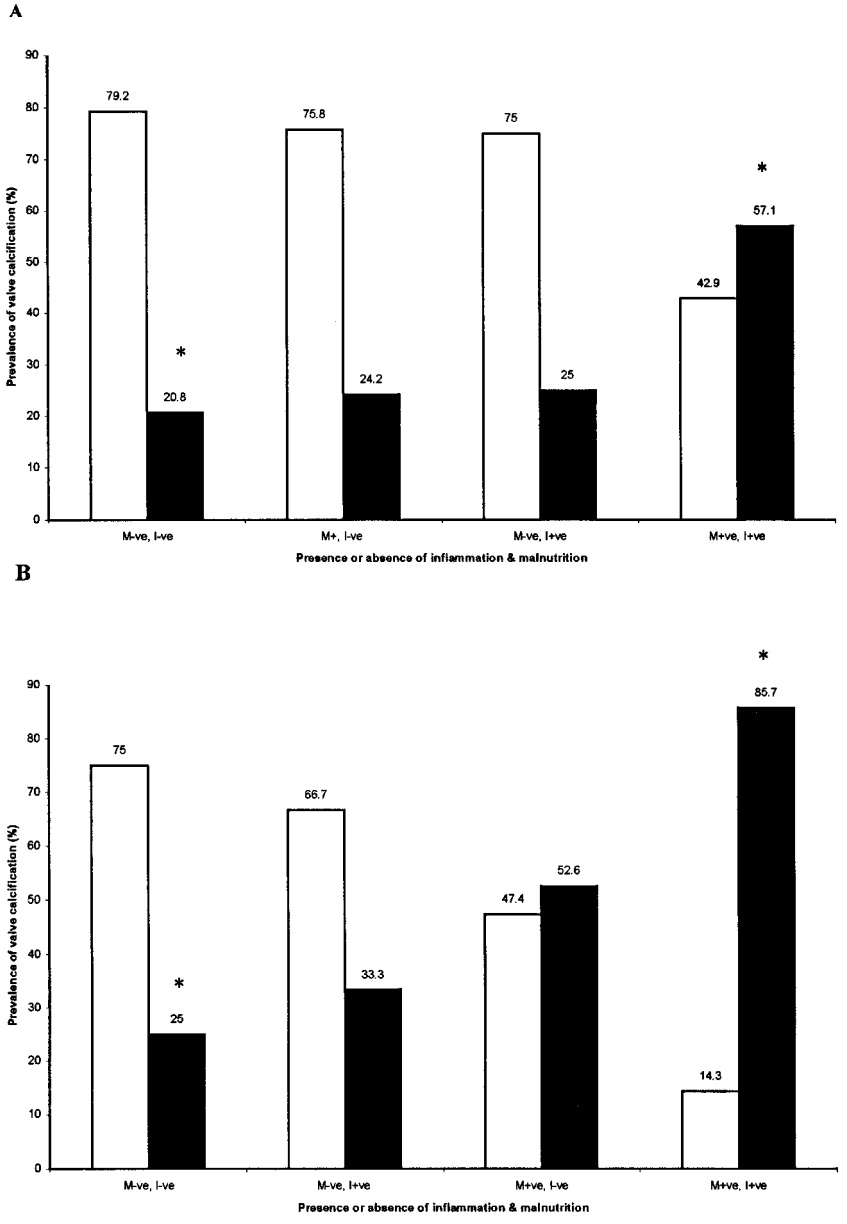

Figure 5. Prevalence of cardiac VC in relation to the presence (I+ve: CRP $\geq$ 10 mg/L) or absence (I-ve: CRP $<$ 10 mg/L) of inflammation and presence (M+ve: albumin $\leq$ 28 g/L) or absence (M-ve: albumin $>$ 28 g/L) of malnutrition with $Ca \times PO_4$ product <5 (A) and $Ca \times PO_4$ product ≥ 5 (B). □, no VC; ■, VC. *, $P < 0.05$ in A; $P < 0.01$ in B.

demonstrated that certain risk factors for atherosclerosis, such as positive smoking history and presence of diabetes, also increased risk of VC. Although no significant difference was noted in the average systolic and diastolic BP between patients with and without VC, there was a trend toward a greater number of antihypertensive use among patients with VC. There also was higher preponderance of VC among patients with renal failure secondary to hypertensive nephrosclerosis. These findings indicate that both cardiac VC and coronary atherosclerosis may indeed be associated syndromes, with the severity of VC reflecting the extent of coronary atherosclerosis.

It is intriguing to note, however, that although both calcification and atherosclerosis shared similar association with inflammation and malnutrition, some other established risk factors for atherosclerosis, such as male gender and hyperlipidemia, were not shown to increase risk of VC. On the contrary, there was a trend toward lower total, HDL, and LDL cholesterol as well as TG in patients with VC, although it was statistically insignificant. There also was no difference in the use of lipid-lowering therapy between patients with and without VC. One possible explanation is that different risk factors act at different time points in the process of VC. As VC involves a very long-standing process and probably represents the end stage of an active disease process (36), the importance of lipid status as well as hemodynamic factors in the early development of VC may have been underestimated when only 1-yr data preceding echocardiography were used to predict the subsequent risk of calcification. Further prospective studies with baseline as well as serial echocardiographic and biochemical measurements will be needed to clarify the role of hyperlipidemia and hypertension in VC in dialysis patients.

In summary, apart from confirming the importance of aging, diabetes, uncontrolled hyperphosphatemia, and hyperparathyroidism in the development of VC, our study demonstrates a strong association of inflammation and malnutrition with cardiac VC, similar to that of atherosclerosis (MIA syndrome). This finding is in keeping with the concept that calcification and atherosclerosis are associated syndromes and that cardiac VC may be a marker for the presence of underlying coronary or generalized atherosclerosis. The presence of calcification of cardiac valves may be the tip of the iceberg, representing underlying generalized atherosclerosis and vascular calcification. Further prospective long-term studies with baseline echocardiographic measurements relating the presence of inflammation and malnutrition to the development of cardiac VC as well as coronary artery disease and mortality will be required to answer this important question.

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