# Close Association of Vascular and Valvular Calcification and Prognosis of Patients on Continuous Ambulatory Peritoneal Dialysis

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*In the present study, we examined the association between vascular and valvular calcification and the prognosis of patients on continuous ambulatory peritoneal dialysis (CAPD). Data were collected from the records of patients introduced onto CAPD therapy during 1999 – 2006 at the Department of Nephrology, Saitama Medical University. At the start of CAPD, cardiac and vascular echography were used to examine 162 patients (average age: 56 ± 5 years; 58 men, 104 women; 43 with and 119 without diabetes) for evaluation of vascular and valvular calcification. Both vascular and valvular calcification were found in 32 patients. Vascular calcification was found in 16, and valvular calcification in 11. Over 5 years, 11 patients suffered from cardiovascular disease (7 with stroke, 4 with myocardial infarction). All of these patients had vascular or valvular calcification at the start of CAPD therapy.*

*We also used Cox hazard analysis to examine values for Ca, P, Ca × P, intact parathyroid hormone (iPTH), and lipids. None of these values were independent contributory factors for incidence of cardiovascular disease in patients on CAPD.*

*These data suggest the importance of vascular and valvular echography to evaluate patients on CAPD, especially at the start of CAPD therapy. Vascular and valvular calcification are important factors for determining the prognosis of patients on CAPD.*

**Key words**
Calcium, phosphate, parathyroid hormone, cardiovascular disease

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## Introduction

Cardiovascular disease accounts for more than 50% of deaths in patients receiving dialysis therapy (1). In patients with end-stage renal disease (ESRD), valvular and vascular calcifications are increasingly being recognized as both causes and markers of morbidity and mortality (2). The incidences of those calcifications are not only substantially higher in the ESRD population than in age- and sex-matched patients with angiographically confirmed coronary artery disease, but they also progress rapidly within a short period (3). In the general population, valvular and vascular calcifications indicate a manifestation of generalized atherosclerosis and are associated with poor outcome (4). However, in patients with ESRD, diffuse media calcification of arterial vessels with no relation to atheromatosis is prevalent even in young patients (5).

Calcification of the mitral and aortic valves has previously been emphasized as a powerful predictor of mortality and cardiovascular death in long-term dialysis patients (6–8). Recently, clinical studies have supported the association between vascular calcification and cardiac changes in patients with ESRD (9). Vascular calcification in the media of medium and small vessels in ESRD patients is very marked and may displace intimae, causing luminal narrowing (2). This process may be applicable to coronary arteries, contributing to cardiovascular complications. Further, recent publications have suggested that hyperphosphatemia, positive Ca balance, and elevated Ca × P product (all of which are closely associated with calcification) contribute to mortality in patients with ESRD (10, 11).

With the foregoing information in mind, we undertook a prospective study to analyze the influence of

cardiac valvular and vascular calcifications on cardiac mortality in patients receiving continuous ambulatory peritoneal dialysis (CAPD).

## Patients and methods

This prospective study was initiated in the Department of Nephrology of Saitama Medical University, Saitama, Japan, in 1999. Altogether, 162 patients receiving CAPD were eligible and were observed over a period of 5 years. Exclusion criteria for the study included underlying malignancy and congenital heart diseases. All patients provided informed consent. The protocol was approved by the Human Research Ethics Committee of Saitama Medical University.

Echocardiography with a 3.3-mHz multiphase array probe was used to obtain two-dimensional echocardiograms in subjects lying in the left decubitus position. Two-dimensional assessment of the aortic valve and mitral valve was performed together with continuous-wave Doppler ultrasound on the basis of the parasternal long-axis and short-axis views. All echocardiography exams were performed according to the recommendations of the American Society of Echocardiography (12). Cardiac valve calcification was defined as bright echoes of more than 1 mm on one or more cusps of the aortic valve or on the mitral annulae. Left ventricular mass index was calculated by the Penn convention formula.

Vascular calcification was studied by radiography series that included the thorax, abdomen, pelvis, and extremities. Vascular calcification was diagnosed when found in any of the examined areas.

Laboratory data collected included hematocrit and serum Ca, P, and creatinine concentrations. The Ca × P product was calculated for each subject.

The CAPD treatment consisted of 3 – 4 daily 1.5 – 2 L exchanges using a dialysis solution containing lactate and 1.5 g/dL or 2.5 g/dL dextrose. All patients were treated using a disconnect system. Patients with a parathyroid hormone level greater than 150 pg/mL by intact molecular assay (iPTH) were treated with 1,25-$(OH)_2$D3 and $CaCO_3$ supplements; patients with iPTH levels lower than 70 pg/mL were treated with $CaCO_3$ to reduce the degree of hyperphosphatemia. Doses were adjusted according to serum levels of Ca and P. Lipid-lowering drugs, primarily statin derivatives, were administered if serum cholesterol levels exceeded 240 mg/dL.

### *Statistical analyses*

Continuous data are summarized as mean ± standard deviation. Comparisons between patients with and without valvular or vascular calcification (or both) were performed at study baseline using unpaired *t*-test for mean data. Factors predictive of cardiovascular mortality were identified with Cox regression analysis evaluated by Wald test. Free rate analyses from nonfatal and fatal cardiovascular events were performed using the Kaplan–Meier method and log-rank test. Significance was accepted at a $p$ value of less than 0.05.

## Results

Table I outlines the baseline characteristics of subjects with and without calcification. We observed no significant differences in age, blood pressure, serum Ca and P, iPTH, total cholesterol, and albumin among the three groups. During the mean follow-up of 63.5 months (range: 60 – 72 months), 10 patients (4 with and 6 without calcification) were transferred to hemodialysis. Altogether, 12 deaths occurred during the follow-up period; half of those deaths were attributed to cardiovascular causes. Six patients with calcification and no patients without calcification died during this period. Using Cox regression analysis, calcification—valvular or vascular or both together—was predictive of nonfatal and fatal cardiovascular events (risk ratio: 27.96; 95% confidence interval: 8.35 to 93.62; $p < 0.0001$; Figure 1), independent of age, male sex, duration of dialysis therapy, and diabetes status.

## Discussion

In the present study, valvular and vascular calcifications were both strong and independent predictors of cardiovascular deaths in patients receiving CAPD. Our findings extend those of Braun *et al.* (13), who showed a profound age-related effect on vascular calcification, and are consistent with the recent cross-sectional survey of Raggi *et al.* (14), who demonstrated association between age, diabetes mellitus, dialysis vintage, higher serum Ca and P, and coronary calcification in maintenance HD. Furthermore, our study confirms the findings of Wang *et al.* (15) that cardiac calcifications predict all-cause and cardiac mortality in long-term peritoneal dialysis patients.

In the present study, myocardial infarction and stroke were major causes of cardiovascular events. No invasive data on CAPD patients in this study were

TABLE I Characteristics of patients with and without calcification

| | *Total* | *Calcification* | | | |
|---|---|---|---|---|---|
| | | *Vascular and valvular* | *Valvular* | *Vascular* | *None* |
| Patients (*n*) | 162 | 32 | 11 | 16 | 103 |
| Age (years) | 56±2 | 57±5 | 55±8 | 57±9 | 55±4 |
| Male sex [*n* (%)] | 58 (36) | 6 (25) | 6 (55) | 6 (38) | 38 (37) |
| Diabetes mellitus [*n* (%)] | 43 (27) | 20 (63) | 5 (45) | 8 (50) | 10 (10) |
| Systolic blood pressure (mmHg) | 154±4 | 156±8 | 154±9 | 152±7 | 154±5 |
| Diastolic blood pressure (mmHg) | 78±2 | 78±5 | 79±4 | 78±8 | 76±5 |
| Serum Ca (mg/dL) | 7.2±0.6 | 7.4±0.8 | 7.3±0.9 | 7.4±1.0 | 7.1±0.8 |
| Serum P (mg/dL) | 6.8±0.5 | 6.9±1.0 | 6.6±1.2 | 7.2±1.0 | 6.4±0.6 |
| Ca×P | 49±6 | 51±7 | 49±8 | 54±10 | 47±7 |
| Parathyroid hormone (pg/dL) | 256±38 | 354±56 | 285±46 | 326±28 | 213±54 |
| Total cholesterol (mg/dL) | 202±13 | 205±36 | 212±19 | 195±24 | 190±15 |
| Low-density lipoprotein (mg/dL) | 102±8 | 103±8 | 110±12 | 100±15 | 99±6 |
| Serum albumin (g/dL) | 3.6±0.4 | 3.5±0.3 | 3.4±0.8 | 3.5±0.7 | 3.7±0.5 |
| Left ventricular mass index (g/m$^2$) | 106±12 | 116±4[a] | 118±5[a] | 121±11[a] | 101±5 |

[a] $p < 0.05$ as compared with patients with no calcification.

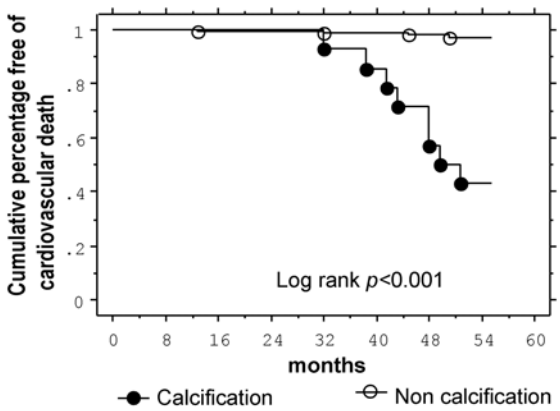


FIGURE 1 Cumulative percentage free of nonfatal and fatal cardiovascular disease events. In patients with calcification as compared with patients without calcification, we observed a significant increase in nonfatal and fatal cardiovascular events over 5 years.

available, but it can be assumed that valvular or vascular calcification and coronary artery disease were closely associated with the decreased survival of patients with calcifications. Also, a high prevalence of left ventricular hypertrophy was detected in patients with calcifications, indicating the presence of coronary artery disease in these patients. Sharma *et al.* (8) strongly emphasized the importance of mitral annular calcification for prediction of cardiovascular mortality in renal transplant candidates. On the other hand, other studies have proposed a frequent association of vascular calcification and cardiac valve calcification (13,14). It is therefore likely that the observed higher cardiac mortality of CAPD patients with calcifications is in part a result of an association with cardiovascular diseases and cardiac structural abnormalities. In the present study as well as in other previous studies (16,17), valvular or vascular calcifications (or both) were not associated with smoking, hypertension, or hyperlipidemia, which are known as the risk factors for cardiovascular diseases, indicating other factors found in patients with chronic kidney disease, such as anemia, inflammation, low albumin, hypocalcemia, hyperphosphatemia, and so on are responsible (18).

In the present study, we did not measure highly sensitive C-reactive protein (hsCRP) for evaluation of inflammation; however, we observed no significant differences in the levels of serum albumin and hemoglobin between the two groups. Several studies have demonstrated that the ongoing increased Ca load and the poor Ca × P control are responsible for accelerating the progression of calcification in patients with chronic kidney disease (19–21). In the present study, CAPD patients with valvular or vascular calcification had higher serum Ca, P, Ca × P, and iPTH that did those without calcifications; however, the *p* values did not reach significance. Previously Wang *et al.* (15) reported that peritoneal dialysis patients

with valvular calcification had significantly higher serum Ca, P, Ca × P, and iPTH than did those without calcifications. In results from the United States Renal Data System, hyperphosphatemia and increased Ca × P were independent risk factors for mortality in hemodialysis patients (11). In that study, the mortality rate reported was higher than our current data show, indicating that the ESRD patients in that study might have been more severely ill. Alternatively, the treatment of Ca and P abnormalities may have been different.

In the present study, 4 CAPD patients with calcifications experienced stroke. In previous data reporting the relationship between calcifications and cardiovascular mortality, the relationship between calcifications and stroke has been less discussed. All 4 patients with stroke were found to have cerebral embolisms. Benjamin *et al.* (22) reported that the presence of mitral annular calcification doubled the risk of stroke independently of traditional risk factors. It is possible that Ca spicules from the mitral annulus could embolize and that the presence of left atrial enlargement found in the present study in CAPD patients with calcification and atrial fibrillation might predispose to embolic events.

A high prevalence of left ventricular hypertrophy in CAPD patients with calcifications was found in the present study. Huting and Schutterle (23) reported that a relationship between blood pressure and mitral annular calcification in which the rise of systolic pressure on the left ventricular wall increases pressure on the valve and accelerates its usual aging process. On the other hand, Fernández–Vega (24) did not find any differences in the incidence of left ventricular hypertrophy between patients with or without calcifications.

## Conclusions

Our study confirms that valvular or vascular calcifications (or both) at the start of dialysis therapy are not infrequent findings. Echocardiography demonstrates that these calcified tissues are associated with left ventricular hypertrophy. In addition to these structural abnormalities, Ca and P dysregulation may contribute to tissue damage. These two mechanisms might contribute to cardiovascular events in CAPD patients. Vascular and valvular calcification are important factors for determining the prognosis of patients on CAPD.

## References


1 Patient Registration Committee, Japanese Society for Dialysis Therapy, Tokyo, Japan. An overview of regular dialysis treatment in Japan as of 31 December 2003. Ther Apher Dial 2005;9:431–58.

2 Umana E, Ahmed W, Alpert MA. Valvular and perivalvular abnormalities in end-stage renal disease. Am J Med Sci 2003;325:237–42.

3 Ruilope LM, van Veldhuisen DJ, Ritz E, Luscher TF. Renal function: the Cinderella of cardiovascular risk profile. J Am Coll Cardiol 2001;38:1782–7.

4 Keelan PC, Bielak LF, Ashai K, *et al.* Long-term prognostic value of coronary calcification detected by electron-beam computed tomography in patients undergoing coronary angiography. Circulation 2001;104:412–17.

5 Adragao T, Pires A, Lucas C, *et al.* A simple vascular calcification score predicts cardiovascular risk in haemodialysis patients. Nephrol Dial Transplant 2004;19:1480–8.

6 Salgueira M, Toro ND, Moreno–Alba R, Jimenez E, Areste N, Palma A. Vascular calcification in the uremic patient: a cardiovascular risk? Kidney Int 2003;63(Suppl 85):S119–21.

7 Al-Absi AI, Wall BM, Aslam N, *et al.* Predictors of mortality in end-stage renal disease patients with mitral annulus calcification. Am J Med Sci 2006;331:124–30.

8 Sharma R, Pellerin D, Gaze DC, *et al.* Mitral annular calcification predicts mortality and coronary artery disease in end stage renal disease. Atherosclerosis 2007;191:348–54.

9 Ganesh SK, Stack AG, Levin NW, Hulbert–Shearon T, Port FK. Association of elevated serum $PO_4$, Ca×$PO_4$ product, and parathyroid hormone with cardiac mortality risk in chronic hemodialysis patients. J Am Soc Nephrol 2001;12:2131–8.

10 Block GA, Port FK. Re-evaluation of risks associated with hyperphosphatemia and hyperparathyroidism in dialysis patients: recommendations for a change in management. Am J Kidney Dis 2000;35:1226–37.

11 Block GA, Hulbert–Shearon TE, Levin NW, Port FK. Association of serum phosphorus and calcium ×phosphate product with mortality risk in chronic hemodialysis patients: a national study. Am J Kidney Dis 1998;31:607–17.

12 Schiller NB, Shah PM, Crawford M, *et al.* Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. American Society of Echocardiography Committee on Standards, Subcommittee on Quantitation of Two-Dimensional Echocardiograms. J Am Soc Echocardiogr 1989;2:358–67.

13 Braun J, Oldendorf M, Moshage W, Heidler R, Zeitler E, Luft FC. Electron beam computed tomography in the evaluation of cardiac calcification in chronic dialysis patients. Am J Kidney Dis 1996;27:394–401.
14 Raggi P, Boulay A, Chasan–Taber S, *et al.* Cardiac calcification in adult hemodialysis patients. A link between end-stage renal disease and cardiovascular disease? J Am Coll Cardiol 2002;39:695–701.
15 Wang AY, Wang M, Woo J, *et al.* Cardiac valve calcification as an important predictor for all-cause mortality and cardiovascular mortality in long-term peritoneal dialysis patients: a prospective study. J Am Soc Nephrol 2003;14:159–68.
16 Boon A, Cheriex E, Lodder J, Kessels F. Cardiac valve calcification: characteristics of patients with calcification of the mitral annulus or aortic valve. Heart 1997;78:472–4.
17 Parfrey PS, Foley RN, Harnett JD, Kent GM, Murray DC, Barré PE. Outcome and risk factors for left ventricular disorders in chronic uraemia. Nephrol Dial Transplant 1996;11:1277–85.
18 Arima H, Nakamoto H, Okada S, *et al.* Risk factors for vascular complications in patients on peritoneal dialysis. Adv Perit Dial 2006;22:192–7.
19 Bardaji A, Martinez–Vea A, Valero A, *et al.* Cardiac involvement in autosomal-dominant polycystic kidney disease: a hypertensive heart disease. Clin Nephrol 2001;56:211–20.
20 Maher ER, Pazianas M, Curtis JR. Calcific aortic stenosis: a complication of chronic uraemia. Nephron 1987;47:119–22.
21 Raine AE. Does antihypertensive therapy modify chronic allograft failure? Kidney Int Suppl 1995;52:S107–11.
22 Benjamin EJ, Plehn JF, D'Agostino RB, *et al.* Mitral annular calcification and the risk of stroke in an elderly cohort. N Engl J Med 1992;327:374–9.
23 Huting J, Schutterle G. Cardiovascular factors influencing survival in end-stage renal disease treated by continuous ambulatory peritoneal dialysis. Am J Cardiol 1992;69:123–7.
24 Fernández–Vega F, Abellán J, Vegazo O, *et al.* Angiotensin II type 1 receptor blockade to control blood pressure in postmenopausal women: influence of hormone replacement therapy. Kidney Int 2002;62(suppl 82):36–41.

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