Vascular calcification (VC) and arterial stiffness (AS) are major contributors to cardiovascular disease, and in chronic kidney disease, VC and AS are correlated. Disorders of calcium and phosphate metabolism contribute to the progression of VC and to increases in AS. The efficacy of cinacalcet (CIN) in reducing AS in patients on continuous ambulatory peritoneal dialysis (CAPD) has not been determined.

The present study enrolled 19 CAPD patients (12 women, 7 men; mean age: 62.2 ± 3.6 years) with serum intact parathyroid hormone (iPTH) greater than 500 ng/dL (mean value: 675 ± 106 ng/dL) in whom daily oral treatment with CIN 25 mg was started. If administration of CIN for 3 months failed to reduce the level of iPTH to less than 300 ng/dL, the dose of CIN was increased to 50 mg daily. Before the start of CIN and at 3 years after the start of CIN, pulse wave velocity (PWV) was determined.

In 11 patients, levels of iPTH were reduced to less than 300 ng/dL; levels in the rest of the patients remained high. We observed no significant differences in PWV before CIN and at 3 years after CIN start (1856 ± 198 cm/s vs. 1726 ± 187 cm/s). Multivariate regression analysis of PWV demonstrated that both systolic blood pressure and changes in serum levels of phosphate contributed to decreases in PWV.

In patients receiving CAPD, VC and AS might be the result of higher systolic blood pressure and increased serum levels of phosphate.

Key words
Cinacalcet, hyperparathyroidism, phosphate, systolic blood pressure, arterial stiffness

Introduction
Cardiovascular disease is the most common cause of death in patients requiring renal replacement therapy, and many factors contribute to cardiovascular disease in patients with diabetes mellitus, hypertension, and dyslipidemia. In addition, vascular abnormalities (vascular calcifications, arteriosclerosis, atherosclerosis) have increasingly been recognized recently for their excellent prognostic value (1). Arterial stiffening is the result of a complex interaction between structural and functional changes in vessel walls and is evaluated using brachial–ankle pulse wave velocity (PWV) (2). The mechanisms contributing to increased arterial stiffness in patients on dialysis therapy are not entirely explained, but may include arterial calcification, chronic volume overload, increased mechanical stress because of hypertension, chronic micro-inflammation, sympathetic overactivity, activation of the renin–angiotensin system, and lipid peroxidation, among others (3). Among these factors associated with a strong impact on arterial stiffness, vascular calcification plays a central role. Hyperphosphatemia and an increased
Ca×P product are important and well-known clinical contributors to vascular calcification in dialysis patients (4). In addition to Ca and P, parathyroid hormone (PTH) has been emphasized for its role in vascular calcification (5).

Calcimimetics, which are positive allosteric modulators of the Ca-sensing receptor, may be of great potential value. In clinical practice, they are currently used alone or in combination with other treatments to control the vascular calcification process. In the present study, we examined the efficacy of cinacalcet (CIN) in reducing arterial stiffness in patients on continuous ambulatory peritoneal dialysis (CAPD).

Methods
Patients with hyperparathyroidism undergoing CAPD were eligible for inclusion in the study. All patients were required to have been diagnosed with hyperparathyroidism, which was defined as a serum level of intact PTH greater than 500 ng/dL. The following exclusion criteria were used:

- Myocardial infarction within the preceding 6 months
- Clinically significant valvular disease
- History of cerebrovascular accident within the preceding 6 months
- Any condition that would have precluded a patient from remaining on the study, such as alcohol or drug abuse, chronic liver disease, malignant disease, or psychiatric disorder

The study enrolled 19 CAPD patients (12 women, 7 men; mean age: 62.2 ± 3.6 years; mean CAPD duration: 6.3 ± 1.6 months) with a mean serum intact PTH value of 675 ± 106 ng/dL, in whom daily oral treatment with CIN 25 mg was started. If CIN for 3 months failed to lower a patient’s level of intact PTH to less than 300 ng/dL, the dose was increased to 50 mg daily. The vitamin D dose and any Ca supplements or phosphate binders were adjusted at the discretion of the treating physicians.

To measure PWV, the brachial–ankle PWV and ankle–brachial index (ABI) were determined. Using the Form PWV/ABI (Omron Health Care, Kyoto, Japan), PWV, blood pressure, electrocardiogram, and heart sounds were simultaneously recorded after a rest of at least 15 minutes. Briefly, the patients were examined in the supine position after at least 5 minutes of rest. Electrocardiography electrodes were placed on both wrists; a microphone for detecting heart sounds was placed at the left edge of the sternum; and blood pressure cuffs were wrapped both on a brachium and an ankle. The cuffs were connected to a plethysmographic sensor (for determination of volume pulse form) and an oscillometric pressure sensor (for determination of blood pressure). Volume waveforms for the brachium and ankle were stored, and the sampling time was 10 s, with automatic gain analysis and quality adjustment.

Statistical analysis
All data are presented as mean ± standard deviation. Multiple comparisons were performed using analysis of variance with a Kruskal–Wallis test and
subsequent Dunn test. A simple regression analysis for correlations between the variables and a multiple regression analysis to identify the variables associated with PWV were performed. A value of \( p < 0.05 \) was required for statistical significance.

**Results**

*Baseline characteristics*
Table I shows baseline data for the patients.

*Effect of CIN on blood pressure*
Oral administration of CIN showed no effect on either systolic and diastolic blood pressure throughout the study (Table II).

*Effect of CIN on serum Ca and P*
No changes in serum levels of Ca and P were observed throughout the study [Figure 1(A,B)].

*Effect of CIN on serum levels of intact PTH*
A significant reduction in intact PTH was observed 1 year after the start of treatment [Figure 1(C), \( p < 0.0001 \)] and was maintained throughout the study (\( p < 0.001 \)).

**Table I** Characteristics of the study patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>62.2±3.6</td>
</tr>
<tr>
<td>Sex (men/women)</td>
<td>7/12</td>
</tr>
<tr>
<td>Diabetes (yes/no)</td>
<td>4/15</td>
</tr>
<tr>
<td>Dialysis duration (years)</td>
<td>6.3±1.6</td>
</tr>
<tr>
<td>Serum calcium (mg/dL)</td>
<td>8.4±1.0</td>
</tr>
<tr>
<td>Serum phosphate (mg/dL)</td>
<td>6.1±1.5</td>
</tr>
<tr>
<td>Weekly CCr (L)</td>
<td>56.5±3.8</td>
</tr>
<tr>
<td>Intact PTH (ng/dL)</td>
<td>675±106</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>139±20</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>79±12</td>
</tr>
</tbody>
</table>

CCr = creatinine clearance; PTH = parathyroid hormone; BP = blood pressure.

**Table II** Serial changes in systolic and diastolic blood pressure (BP) and pulse wave velocity (PWV)

<table>
<thead>
<tr>
<th>Variable</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic BP (mmHg)</td>
<td>139±20</td>
<td>138±18</td>
<td>137±19</td>
<td>136±20</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>79±12</td>
<td>78±15</td>
<td>76±21</td>
<td>76±20</td>
</tr>
<tr>
<td>PWV (cm/s)</td>
<td>1856±198</td>
<td>1832±234</td>
<td>1781±173</td>
<td>1726±187</td>
</tr>
</tbody>
</table>

**Figure 1** Serum levels of (A) calcium, (B) phosphate, and (C) intact parathyroid hormone (PTH) in the study patients.
Effect of CIN on PWV

During treatment with CIN, no changes in PWV were observed (Table II). However, significant correlations were observed between systolic blood pressure and PWV \( [p < 0.002, \text{Figure 2(A)}] \) and between serum levels of phosphate and PWV \( [p < 0.001, \text{Figure 2(B)}] \).

Discussion

In the present study, close associations between systolic blood pressure and PWV and between levels of serum phosphate and PWV were demonstrated in CAPD patients during 3 years of treatment with CIN. However, treatment with CIN did not directly induce any significant changes in PWV despite marked reductions in serum levels of intact PTH.

In CAPD and hemodialysis (HD) patients alike, CIN has been reported to reduce levels of intact PTH and also levels of serum Ca, P, and Ca×P (6).

Several studies on PWV and possible associated factors have been reported. Cheng et al. (12) demonstrated an inverse correlation between serum albumin and increased PWV. Zhe et al. (13) reported that, in CAPD patients, traits of the metabolic syndrome were closely associated with increased PWV after adjustment for confounders. Stompór et al. (14) found that aortic PWV values in patients on CAPD were associated with systolic blood pressure and serum levels of markers related to chronic inflammation such as C-reactive protein, interleukin 6, and plasma fibroblast growth factor β. Findings in the present study (carried out in relatively older people on CAPD) accord with the report from Laurent and Boutouyrie (15) that arterial stiffness measured by PWV correlates with systolic blood pressure in older hypertensive subjects.

If, as shown in animal models, PTH is directly

![Figure 2](image-url) Correlations between (A) systolic blood pressure (SBP) and pulse wave velocity (PWV), and (B) between serum level of phosphate and PWV in the study patients.
related to the regulation of vascular remodeling (16), it is likely that PWV would decrease if PTH were to be lowered. Despite reducing levels of intact PTH in the patients of the present study, no significant changes in PWV were observed. Thus, many factors appear to be involved in the regulation of vasculopathy of patients on dialysis therapy. Whether a reduction in intact PTH will result in decreased vascular calcification remains to be clarified.

Observational studies show that elevated serum P is positively correlated with mortality, and in end-stage renal disease patients with serum P values greater than 6.5 mg/dL, an increased risk of death was observed (17). Moreover, even relatively small elevations in serum P (in the high-normal range) have been correlated with increased risks for cardiovascular and all-cause mortality in patients with chronic kidney disease (18). From those observations, mild hyperphosphatemia has been suggested to possibly be an important driver of vascular abnormalities in patients on CAPD. Indeed, in the present study, despite a lack of significant change in serum levels of phosphate, those serum levels were significantly correlated with PWV. Although no study has examined the association of arterial stiffness and phosphate, we propose that serum P might be one of the important factors regulating arterial stiffness under the control of parathyroid hormone in dialysis patients.

We are aware that our study is limited by its observational nature, coupled with its small number of subjects. Consequently, an exploration of other factors associated with PWV (such as dyslipidemia) could not be performed, nor could analysis of the exact dose of phosphate binder and vitamin D that might affect arterial stiffness be conducted. However, at our center, strict guidelines for the prescription of those agents had to be followed, according to guidelines issued by the Japanese Society for Dialysis Therapy.

Conclusions
Arterial stiffness in patients receiving CAPD might be a result of higher systolic blood pressure and of increased serum levels of phosphate under CIN treatment.

Disclosures
The authors have no potential conflicts of interest relevant to this article to declare.

References


Corresponding author:
Hiromichi Suzuki, MD PhD, Department of Nephrology, Saitama Medical University, 38 Morohonngo, Moroyama-machi, Iruma-gun, Saitama 350-0495 Japan.
E-mail: iromichi@saitama-med.ac.jp