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# Radial augmentation index may be an effective predictor of vascular calcification in patients on peritoneal dialysis

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**ABSTRACT**

Vascular calcification (VC) is an important promoter of cardiovascular disease (CVD) in patients undergoing peritoneal dialysis (PD). Several indices can be used to evaluate VC, including the abdominal aortic calcification index (AACI) and carotid artery intima–media thickness (IMT); however, simpler and lesser expensive predictors, such as the radial augmentation index (RAI), should be investigated. A total of 101 patients undergoing PD were recruited to measure RAI, AACI, and carotid artery IMT and perform echocardiography. Fifty healthy controls (HCs) were recruited to undergo RAI measurement. RAI in patients undergoing PD was significantly higher than the RAI in HCs (86.25%±8.39% vs. 76.05%±9.81%, $p < 0.05$). Patients undergoing PD and who suffer with diabetic mellitus, hypertension, and CVD had more severe VC than those without the abovementioned diseases. In patients with PD, RAI was positively correlated with AACI ($r = 0.671$, $p < 0.05$) and carotid artery IMT ($r = 0.596$, $p < 0.05$). RAI was positively correlated with left ventricular end-diastolic dimensions (LVDd; $r = 0.678$, $p < 0.05$), left ventricular mass index ($r = 0.595$, $p < 0.05$), and negatively correlated with early-diastolic mitral inflow velocity/late-diastolic mitral inflow velocity ($r = -0.342$, $p < 0.05$) and left ventricular ejection fraction ($r = -0.497$, $p < 0.05$). Multiple linear regression analysis showed that RAI was associated with AACI, LVDd, age, and serum phosphate ($p < 0.05$). RAI might be an effective predictor of VC and cardiac structural/functional abnormalities in patients undergoing PD.

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## Introduction

Cardiovascular disease (CVD) is the leading cause of death in patients undergoing peritoneal dialysis (PD) [1–3]. Increasingly, vascular calcification (VC), which eventually leads to severe heart disease, is being accepted as an independent risk factor for CVD in patients undergoing PD [4,5]. Therefore, indices that can be used to evaluate VC are crucial for prevention of CVD.

The abdominal aortic calcification index (AACI) and carotid artery intima–media thickness (IMT) are, in general, recognized as common indices for atherosclerosis evaluation and VC [1,6,7]. However, the AACI and IMT: (i) detect abnormalities only if vascular structures have been clearly damaged; and (ii) are indices of organic lesions. Hence, useful functional indices are needed to assess VC. In addition, computed tomography (CT), radiography, and ultrasound examination are expensive and are not available immediately when they are needed, and patients must make appointments for examinations and wait for long periods of time [8]. In addition, more medical staff are needed for the abovementioned examinations, especially diagnostic doctors and technicians with rich clinical experience. Therefore, simple, rapid, and less expensive indices are needed to evaluate VC to aid CVD prevention in patients undergoing PD.

Radial augmentation index (RAI) is a surrogate indicator of aortic stiffness [9,10]. It can be measured directly or by the measurement of waveforms of central arterial pressure. RAI also provides information about cardiac afterload and vascular properties. It is closely related to changes in vessel function.

Watanabe and colleagues reported that RAI was associated significantly with the calcium score for coronary arteries in 161 patients with known or suspected coronary artery disease [11]. Fischer-Rasokat and coworkers showed that premature vascular disease in

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younger patients with coronary artery disease was reflected only by an increased RAI, and not by systolic blood pressure (SBP) or pulse pressure [12]. In addition, there was a significant increase in RAI in patients with peripheral obstructive vascular disease compared with healthy individuals. RAI appears to be an essential indicator of peripheral obstructive arterial disease [13]. The RAI is a useful and readily obtainable parameter for vascular aging. Kohara and colleagues showed that in 632 people without CVD, when comparing individuals in their twenties with those in their seventies, RAI increased 1.56-fold in males and 1.49-fold in females [14]. Therefore, RAI is a useful index of vascular function. However, few studies have focused on the relationship between RAI and VC and cardiac function in patients undergoing PD.

We wished to investigate the relationship between RAI and AACI, carotid artery IMT, and echocardiography parameters. We wanted to know whether the RAI was a simpler, quicker, and less expensive predictor of VC and cardiac structural/functional abnormalities in patients undergoing PD.

## Materials and methods

### Study design

The present study was a cross-sectional observational study conducted at the Department of Nephrology of the First Affiliated Hospital of Dalian Medical University (Dalian, China). The study was conducted in compliance with the ethical principles of the Helsinki Declaration and approved by the Ethics Review Board for Human Research at the First Affiliated Hospital of Dalian Medical University (Study number: LCKY2012-20). Written informed consent was obtained from all participants.

Enrolled patients had RAI, AACI, and carotid artery IMT measured and underwent echocardiography. Healthy controls (HCs) underwent RAI measurement only.

### Study population

All patients undergoing PD at our center were screened for study inclusion between 1st February 2013 and 31st January 2014. Patients with stable vital functions who had undergone PD for $>3$ months were included in the study.

The exclusion criteria were patients: (1) undergoing hemodialysis (HD); (2) with disease in peripheral blood vessels resulting in difficulties in measuring RAI; (3) severe arrhythmia; (4) acute myocardial infarction or heart failure within six months; low blood pressure (BP) (systolic BP [SBP] $<90$ mmHg and/or diastolic BP [DBP] $<60$ mmHg).

HCs were recruited from the Medical Examination Center at the First Affiliated Hospital of Dalian Medical University.

### Variables

The outcomes of interest were VC indices, including RAI, AACI, and carotid artery IMT. Several important covariates relating to cardiac structure/function were also measured, including left ventricular end-diastolic dimension (LVDd), left ventricular mass index (LVMI), left ventricular ejection fraction (LVEF) and early-diastolic mitral inflow velocity/late-diastolic mitral inflow velocity (*E/A* ratio). General information (age, sex, height, body weight, the body mass index [BMI]), and serum levels of calcium, phosphate, hemoglobin, and creatinine, were recorded.

### Radial augmentation index and blood pressure

SBP and DBP were measured in the right upper arm. The left radial arterial waveform was recorded using the tonometric method with an automatic waveform analyzer (HEM-9000AI; Omron Healthcare, Kyoto, Japan), as described previously [14–16], after 10 min of rest in a sitting position. RAI was calculated automatically using the following equation [14,16]:

$$\text{RAI} = (\text{second peak SBP} - \text{DBP})/(\text{first peak SBP} - \text{DBP}) \times 100\%.$$

RAI was corrected by an average heart rate of 75 bpm. The final value of mean arterial pressure (MAP) and RAI was the mean value of measurements in triplicate at intervals of 1 min.

### Abdominal aortic calcification index

Each patient underwent abdominal CT with 15 CT slices at 1-cm intervals above the bifurcation of the common iliac arteries. AACI was calculated semi-quantitatively in 15 CT slices using a method reported previously [17]. Evaluation of AACI was made by two independent observers and recorded as the mean of measurements in duplicate.

### Carotid artery intima–media thickness

Carotid artery IMT was assessed using a color Doppler ultrasound diagnostic machine (HDI 5000; Philips

Table 1. General data from patients on peritoneal dialysis and healthy controls.

| Parameter | Patients undergoing PD | Healthy controls | $p$ Value |
|---|---|---|---|
| Number (M/F) | 101 (58/43) | 50 (29/21) | 0.92 |
| Age (years) | 58.21 ± 13.4 | 57.17 ± 15.03 | 0.65 |
| Height (cm) | 164.63 ± 6.64 | 164.56 ± 6.30 | 0.95 |
| Body weight (kg) | 64.09 ± 6.92 | 63.88 ± 6.80 | 0.86 |
| BMI (kg/m$^2$) | 23.74 ± 3.00 | 22.66 ± 2.78 | 0.87 |
| MAP (mmHg) | 113.39 ± 10.65 | 98.05 ± 9.82 | <0.01 |
| Creatinine (μmol/L) | 978.29 ± 163.18 | 56.34 ± 17.21 | <0.01 |
| Calcium (mmol/L) | 2.08 ± 0.24 | 2.36 ± 0.17 | <0.01 |
| Phosphate (mmol/L) | 1.94 ± 0.65 | 0.99 ± 0.24 | <0.01 |
| Hemoglobin (g/L) | 90.70 ± 13.47 | 132.3 ± 16.12 | <0.01 |

PD: peritoneal dialysis; M: male; F: female; BMI: body mass index; MAP: mean arterial pressure.

Medical Systems, Best, The Netherlands). It was measured on the far wall of the common carotid artery 1 cm proximal to the origin of the bulb on both sides [18]. IMT was defined as the distance between the leading edge of the lumen interface and the media–adventitia interface of the far wall [18]. The mean value of the two measurements was used for the analysis. If an atherosclerotic plaque was present in the artery, IMT was measured in the plaque-free wall [19]. The measurement was made by two independent examiners after the individual had rested for 10 min.

### Echocardiography

Echocardiography was undertaken using a color Doppler ultrasound diagnostic machine (HDI 5000; Philips Medical Systems) after the individual had rested for 10 min. LVDd, LVEF, and the *E/A* ratio were calculated. The LVMI was calculated using the Devereux formula. Echocardiography was carried out by two independent examiners according to recommendations set out by the American Society of Echocardiography [20]. The recorded parameters were the mean values of measurements in duplicate.

### Statistical analysis

Results are presented as mean ± standard deviation. Data were analyzed using SPSS v17.0 (IBM, Armonk, NY, USA). Continuous variables were tested using the Student's $t$ test. The association between quantitative variables was analyzed using Pearson's correlation analysis. Multiple linear regression analysis was carried out using stepwise methods with RAI as a dependent variable and AACI, IMT, LVDd, LVMI, LVEF, and *E/A* ratio as independent variables. $p < 0.05$ was considered statistically significant.

## Results

### Demographic and clinical parameters of the study population and comparison with radial augmentation index

A total of 101 patients undergoing PD with stable vital functions and 50 HCs matched with patients undergoing PD were enrolled. The demographic and clinical characteristics of patients and HCs are shown in Table 1. There was no significant difference between the two groups in terms of age, sex, height, body weight, or BMI. However, patients undergoing PD had a higher MAP (113.39 ± 10.65 mmHg vs. 98.05 ± 9.82 mmHg, $p < 0.01$), serum creatinine (978.29 ± 163.18 μmmol/L vs. 56.35 ± 17.21μmmol/L, $p < 0.01$) and phosphate (1.94 ± 0.65 mmol/L vs. 0.99 ± 0.24 mmol/L, $p < 0.01$), and lower levels of calcium in serum (2.08 ± 0.24 mmol/L vs. 2.36 ± 0.17 mmol/L, $p < 0.01$) and hemoglobin (90.70 ± 13.47 g/L vs.132.3 ± 16.12 g/L, $p < 0.01$), compared with HCs. RAI in patients undergoing PD was significantly higher compared with RAI in HCs (86.25 ± 8.39% vs. 76.05 ± 9.81%, $p < 0.05$; Figure 1).

### Severe vascular calcification in patients with diabetic mellitus, hypertension, and cardiovascular disease

AACI, carotid artery IMT, and RAI were compared between patients with diabetic mellitus, hypertension, and CVD and patients without the abovementioned diseases (Table 2). The results showed that patients undergoing PD with diabetic mellitus, hypertension, and CVD had higher AACI scores, an increased carotid artery IMT, and a higher RAI than those without such diseases, suggesting that these diseases contribute to VC.

### Correlation between radial augmentation index, abdominal aortic calcification index and carotid artery intima–media thickness

AACI and carotid artery IMT are common indices used to evaluate VC, so their correlation was assessed first. AACI was positively correlated with carotid artery IMT ($r = 0.723$, $p < 0.05$; Table 3, Figure 2(A)). RAI was positively correlated with AACI ($r = 0.671$, $p < 0.05$; Figure 2(B)) and carotid artery IMT ($r = 0.596$, $p < 0.05$; Figure 2(C)). These data suggest that RAI might be a useful predictor of VC.

To further analyze the correlation between RAI and independent variables (AACI and carotid artery IMT), stepwise multiple linear regression analysis was performed (Table 4). Although carotid artery IMT was

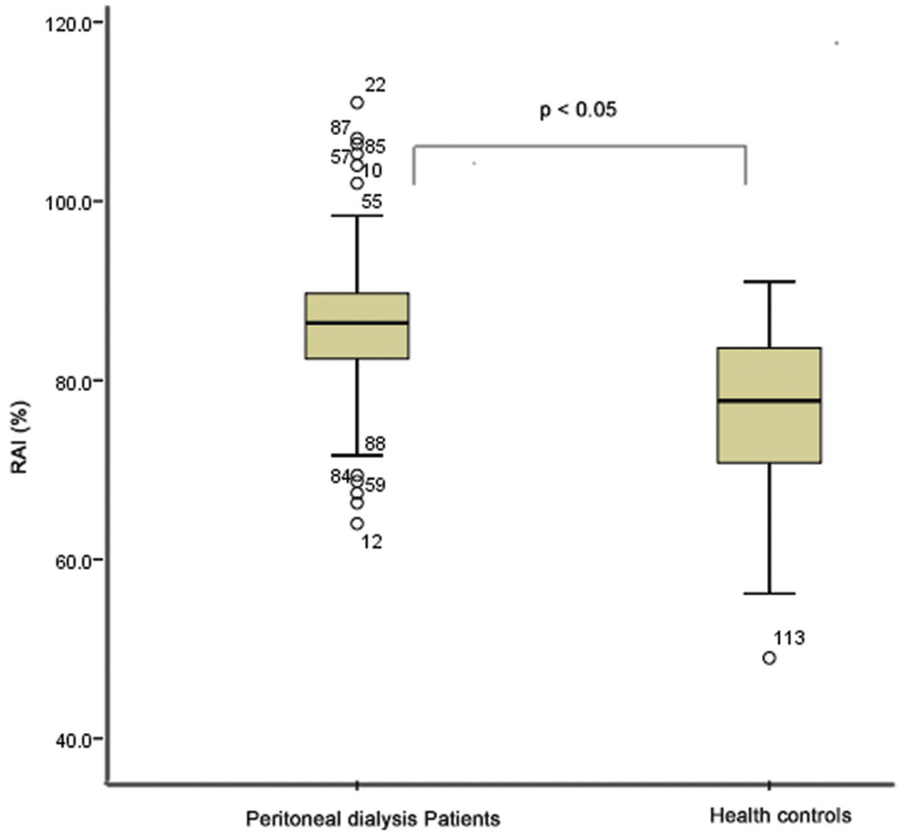


Figure 1. Histogram of radial augmentation index (RAI) in patients undergoing peritoneal dialysis (PD) and in healthy controls. RAI (86.25 ± 8.39%) in patients undergoing PD was significantly higher compared with healthy controls (76.05 ± 9.81%; $p < 0.05$).

Table 2. Indices of vascular calcification in patients with or without DM, HTN, and CVD.

| Patients (*n*%) | AACI | IMT (mm) | RAI (%) |
|---|---|---|---|
| Patients with DM (37, 36.63%) | 69.03 ± 17.27* | 11.57 ± 2.12* | 92.17 ± 10.43* |
| Patients without DM (64, 63.37%) | 58.26 ± 13.41 | 9.47 ± 1.83 | 83.58 ± 7.25 |
| Patients with HTN (79, 78.22%) | 66.84 ± 16.12* | 10.92 ± 1.98* | 89.62 ± 8.31* |
| Patients without HTN (22, 21.78%) | 59.35 ± 14.39 | 9.64 ± 1.85 | 82.94 ± 6.17 |
| Patients with CVD (67, 66.34%) | 67.71 ± 15.97* | 11.08 ± 1.92* | 88.72 ± 9.85* |
| Patients without CVD (34, 33.66%) | 60.34 ± 13.13 | 9.43 ± 1.87 | 83.36 ± 7.29 |

AACI: abdominal aortic calcification index; IMT: intima–media thickness; RAI: radial augmentation index; DM: diabetes mellitus; HTN: hypertension; CVD: cardiovascular disease.
*$p < 0.05$ compared with patients without DM, patients without HTN, and patients without CVD.

Table 3. Pearson's correlation analysis between RAI and indices of vascular assessment (AACI and carotid artery IMT) in patients undergoing peritoneal dialysis.

| Variable 1 | Variable 2 | *r* | *p* Value |
|---|---|---|---|
| RAI | | | |
| | AACI | 0.671 | <0.05 |
| | IMT | 0.596 | <0.05 |
| AACI | | | |
| | IMT | 0.723 | <0.05 |

RAI: radial augmentation index; AACI: abdominal aortic calcification index; IMT: intima–media thickness.

important, RAI was associated only with AACI ($p < 0.05$), thereby suggesting the accuracy of CT imaging for VC evaluation.

## Correlation between radial augmentation index and cardiac parameters

Correlation between RAI and cardiac parameters was also analyzed in patients undergoing PD (Table 5, Figure 3). RAI was positively correlated with LVDd ($r = 0.678$, $p < 0.05$; Figure 3(A)) and LVMI ($r = 0.595$, $p < 0.05$; Figure 3(B)), but negatively correlated with the *E/A* ratio ($r = -0.342$, $p < 0.05$; Figure 3(C)) and LVEF ($r = -0.497$, $p < 0.05$; Figure 3(D)). Similarly, stepwise multiple linear regression analysis was conducted to further analyze the correlation between RAI and cardiac parameters and showed that RAI was associated only with LVDd ($p < 0.05$; Table 4).

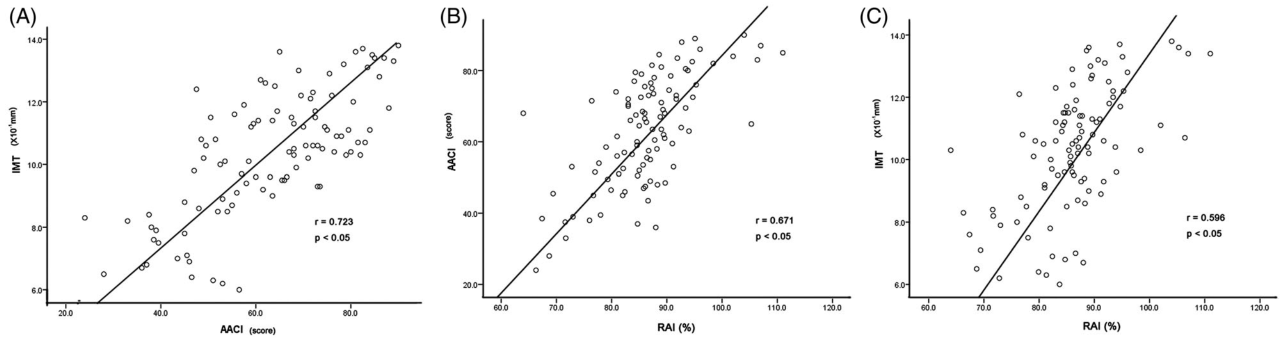


Figure 2. Correlation between abdominal aortic calcification index (AACI) and carotid artery intima–media thickness (IMT), and the correlation between radial augmentation index (RAI) and indices of vascular assessment (AACI and carotid artery IMT) in patients undergoing PD. AACI was positively correlated with carotid artery IMT, and RAI was positively correlated with AACI and carotid artery IMT.

Table 4. Stepwise multiple linear regression analysis between dependent variable (RAI)[a] and independent variables (AACI and LVDd).

| | Unstandardized coefficients | | Standardized coefficients | | |
|---|---|---|---|---|---|
| Model | *B* | Standard error | Beta | *t* | *p* Value |
| (Constant) | 40.314 | 7.219 | | 5.584 | 0.000 |
| AACI | 0.196 | 0.065 | 0.357 | 3.035 | 0.003 |
| LVDd | 0.481 | 0.143 | 0.394 | 3.350 | 0.001 |
| Age | 0.279 | 0.093 | 0.362 | 3.182 | 0.002 |
| Phosphate | 0.347 | 0.103 | 0.381 | 3.294 | 0.001 |

[a]Dependent variable: RAI.
RAI: radial augmentation index; AACI: abdominal aortic calcification index; LVDd: left ventricular end-diastolic dimensions.

Table 5. Pearson's correlation analysis between RAI and cardiac indices (LVDd, LVMI, LVEF, and *E/A* ratio) in patients undergoing peritoneal dialysis.

| Variable 1 | Variable 2 | *r* | *p* Value |
|---|---|---|---|
| RAI | | | |
| | LVDd | 0.678 | $<0.05$ |
| | LMI | 0.595 | $<0.05$ |
| | *E/A* | $-0.342$ | $<0.05$ |
| | LVEF | $-0.597$ | $<0.05$ |

RAI: radial augmentation index; LVDd: left ventricular end-diastolic dimension; LVMI: left ventricular mass index; LVEF: left ventricular ejection fraction; *E/A* ratio: early diastolic mitral inflow velocity/late-diastolic mitral inflow velocity.

### *Correlation between radial augmentation index and clinical parameters*

It is well-known that some clinical parameters are important during the process of VC, such as age, serum calcium, serum phosphate, and intact parathyroid hormone. Therefore, stepwise multiple linear regression analysis was used to assess the correlation between RAI and clinical parameters (age, sex, BMI, serum calcium, serum phosphate, and intact parathyroid hormone). The results show that RAI is associated with age and serum phosphate ($p < 0.05$; Table 4), evidencing the importance of aging and a high phosphate concentration.

## Discussion

Increasing evidence from clinical trials has shown that VC can become a major problem for patients on long-term PD. After a 5-year follow-up, Shikou and colleagues found that all patients undergoing PD who died from CVD had VC at PD initiation [21]. In some studies, >80% of patients on long-term PD had their treatment complicated by VC [22].

AACI and carotid artery IMT are thought to be effective indices of VC [1,6,7]. However, they are not routine clinical measurements, and positive results often suggest severe vascular impairment. In addition, the main changes in VC are increasing vascular stiffness and reduced vascular compliance, which results in increasing pulse pressure. Inevitably, left ventricular hypertrophy, cardiac ischemic changes, and heart failure develop gradually.

RAI used to be employed as a reliable indicator of peripheral vascular health. RAI is a reliable measure of arterial stiffness in people suffering from diabetes mellitus and in young patients with asymptomatic vascular disease, suggesting an important association with vascular function [13]. In the present study, RAI was positively correlated with AACI and carotid artery IMT, which showed that vessel flexibility was coincident with

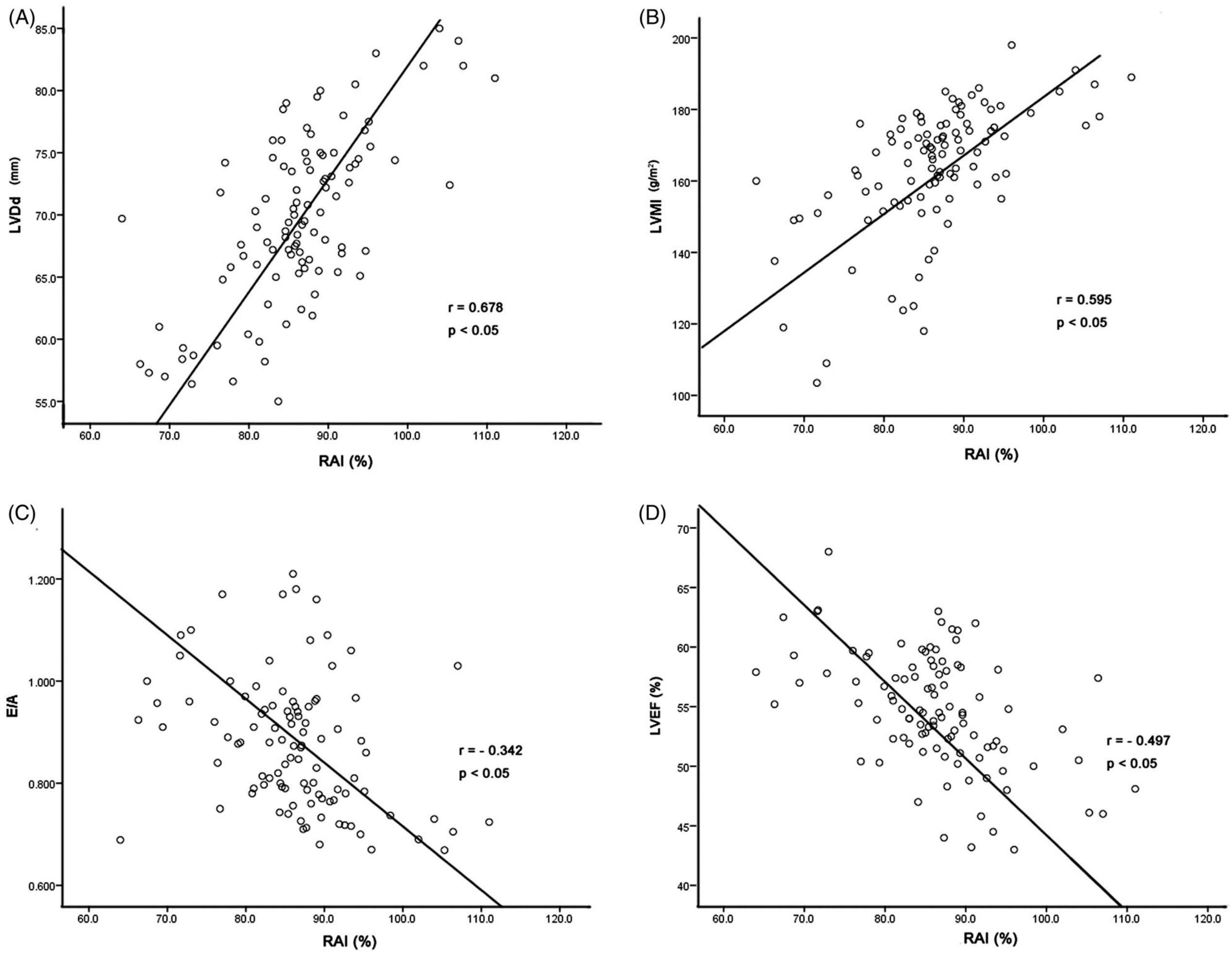


**Figure 3.** Correlation between RAI and echocardiography cardiac parameters. RAI was positively correlated with left ventricular end-diastolic dimensions (LVDd) and left ventricular mass index (LVMI), and negatively correlated with early-diastolic mitral inflow velocity/late-diastolic mitral inflow velocity (*E/A* ratio) and left ventricular ejection fraction (LVEF).

structural damage. Hence, patients undergoing PD should be followed up regularly, and vessel flexibility should be monitored. RAI may be an effective predictor of VC and atherosclerosis in patients undergoing PD. Since RAI can be measured easily and patients need not wait for a long time, it should be performed regularly in the follow up of patients with PD to evaluate VC, which will help to improve prognosis for patients.

In the present study, AACI was strongly correlated with carotid artery IMT, a finding that has also been documented in older females [23]. However, after multiple linear regression analysis, RAI was associated only with AACI. Although carotid artery IMT has been demonstrated as a useful index of VC, it was not associated with RAI after multiple linear regression analysis in the present study. There may be two reasons for this result. First, many patients underwent catheterization of the internal jugular vein without an ultrasound guide because of emergency hemodialysis (HD), which may have influenced the examination result because impairment of carotid arteries is common during catheterization. The second possible reason was the different levels of experience of the two examiners who measured carotid artery IMT.

Nishiura and coworkers showed that RAI was significantly higher in patients undergoing HD than in HCs ($p < 0.001$). Multiple regression analysis showed that RAI was significantly associated with AACI [15], but carotid artery IMT was not measured in their study. Therefore, the findings of Nishiura and colleagues, and the findings of our study suggest that RAI was closely associated with VC, not only in patients undergoing HD, but also in patients undergoing PD. RAI could be applied to screen for VC in patients undergoing PD. However, arteriovenous fistula of the arms is used frequently for vascular access in hemodialysis dialysis. RAI might not be measured in the same arm when RAI is compared, and some patients undergoing HD may have no measurement results because of arteriovenous fistulas in both arms. It may be better to measure RAI to evaluate VC in patients undergoing PD (without arteriovenous fistula in the arms).

Left ventricular hypertrophy is a predictor of mortality in patients with end-stage renal disease [24,25]. In the present study, RAI was positively correlated with LVDd and LVMI. Hence, an index of vessel flexibility (RAI) was also positively correlated with changes in cardiac structure. Regarding cardiac function, RAI was negatively correlated with the *E/A* ratio (an index of diastolic function) and LVEF (an index of systolic function). Therefore, RAI may be a useful index of changes in cardiac structure, but also a sensitive index of cardiac function. Furthermore, after multiple linear regression analysis, RAI was associated only with LVDd, suggesting the importance of changes in cardiac structure. In patients undergoing HD, RAI was closely associated with a history of cardiovascular accidents in a study by Nishiura and coworkers [15]. Therefore, RAI may also be a predictor of CVD in patients undergoing PD.

In the present study, the analysis results show that RAI was associated with AACI and LVDd; however, since some clinical parameters also play an important role in the process of VC, the analysis results show that RAI is associated with age and serum phosphate, which demonstrated that aging and serum phosphate were crucial for VC [26,27]. Therefore, serum phosphate should be controlled despite inevitable aging. Meanwhile, serum calcium and intact parathyroid hormone should also be corrected because they influence serum phosphate.

There were also some limitations of the present study. First, it was a cross-sectional observational study, and we did not follow up patients to monitor cardiovascular accidents, so we could not draw the conclusion that RAI may be a predictor of CVD in patients undergoing PD. Second, AACI and carotid artery IMT were not measured in HCs, so there was no comparison of VC between patients undergoing PD and HCs. Third, it was a single-center study, and the sample size was small. Further research is needed to recruit more participants, including patients undergoing PD and HCs. The fourth is that the study only recruited patients with PD, and there was no comparison between patients with PD and patients with HD.

## Conclusion

RAI was positively correlated with indices of VC and cardiac structure and was negatively associated with indices of cardiac function. RAI is an effective predictor of VC in patients undergoing PD. RAI measurement is convenient, noninvasive, and inexpensive, and could be used to monitor VC.

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## Disclosure statement

The authors declare that they have no conflicts of interest regarding the publication of this manuscript.

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