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Original article

# The impact of peripheral artery disease on left ventricular diastolic function

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ABSTRACT

*Background:* Peripheral artery disease (PAD) is often accompanied by heart failure with preserved ejection fraction (HFpEF). Left ventricular (LV) diastolic dysfunction is related to HFpEF. The aim of this study was to compare LV diastolic function between patients with or without PAD.

*Methods:* One thousand one hundred twenty-one patients (male 56%, mean age 68 ± 13 years) with available preserved LV systolic function assessed by echocardiography (ejection fraction ≥50%) were enrolled from a single-center database between January 2013 and May 2015. PAD was defined as ankle brachial index <0.9 or previous history of lower extremity bypass and/or endovascular therapy. Diagnosis of LV diastolic dysfunction was based on the American Society of Echocardiography and European Association of Cardiovascular Imaging guidelines. The prevalence of LV diastolic dysfunction was compared between patients with PAD and those without PAD.

Multivariate analysis was performed by logistic regression analyses to assess predictors of LV diastolic dysfunction.

*Results:* Two hundred patients (18%) had PAD. Patients with PAD had higher $E/e'$ (15.3 ± 7.4 vs 11.8 ± 5.5, $p < 0.01$), tricuspid regurgitation velocity (2.37 ± 0.33 vs 2.19 ± 0.28 m/s, $p < 0.01$), left atrial volume index (40.6 ± 20.2 vs 32.1 ± 13.6 mL/m$^2$, $p < 0.01$), and lower $e'$ (5.68 ± 1.70 vs 6.38 ± 2.07 cm/s, $p < 0.01$) than patients without PAD. The prevalence of LV diastolic dysfunction was higher (31% vs 12%, $p < 0.01$) in patients with PAD compared to patients without PAD. Multivariate analysis showed that PAD was an independent predictor of LV diastolic dysfunction (adjusted odds ratio: 1.77, 95% confidence interval: 1.13–2.65, $p = 0.01$).

*Conclusion:* The prevalence of LV diastolic dysfunction was higher in patients with PAD than patients without PAD.



## Introduction

Peripheral artery disease (PAD) is a disease with poor prognosis. The presence of PAD shows a high risk of cardiovascular morbidity and mortality, which includes a high prevalence of polyvascular diseases, including coronary artery disease (CAD) and cerebrovascular diseases (CVD) [1–4]. PAD is also associated with an almost two-fold increase in the prevalence of heart failure (HF) [5]. PAD is commonly observed in HF patients with a prevalence from 6.8% to 17.1% [6,7]. HF with preserved ejection fraction (HFpEF) comprises about half of all HF cases [8,9]. A previous study reported that approximately 10% of patients with HFpEF have concomitant PAD [10,11]. HFpEF is mainly based on left ventricular (LV) diastolic dysfunction. Although one previous study suggested a high prevalence of LV diastolic dysfunction in patients with PAD [12], the association between LV diastolic function and PAD remains unclear. In this study, we compared LV diastolic function using echocardiography between patients with PAD and without PAD.

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## Materials and methods

### Study design and subjects

We performed a retrospective analysis using a single center database from Hyogo College of Medicine: university hospital. One thousand one hundred twenty-one patients whose ankle-brachial index (ABI) was measured within 3 months before or after echocardiography were enrolled between January 2013 and May 2015. Patients with EF <50%, lack of date for echocardiography, or moderate-to-severe valvular disease were excluded. LV diastolic function in patients with or without PAD was assessed using echocardiography. The prevalence of LV diastolic dysfunction was compared between patients with PAD and those without PAD.

The study protocol conformed to the Declaration of Helsinki and was approved by our institutional ethics committee.

### Echocardiography

Echocardiography was performed by experienced sonographers using an iE-33, CX-50 (Philips Healthcare, Andover, MA, USA), Artida, Aplio 300 (Toshiba Medical System Co., Tochigi, Japan), or Pro-Sound F75 (Hitachi-Aloka Medical, Tokyo, Japan). We conducted standard, comprehensive, M-mode (motion-mode), two-dimensional echocardiography and Doppler studies according to the American Society of Echocardiography (ASE) guidelines [13]. LV dimension at end-diastole (LVDd), LV dimension at end-systole (LVDs), interventricular septum thickness (IVST), posterior LV wall thickness (PWT), and left atrial dimension were measured using M-mode in the parasternal long-axis view. LVEF was calculated by Simpson's rule. The left atrial volume index (LAVI) in the apical four- and two-chamber views was measured using a modified Simpson's method. Mitral annulus velocity (e′) and the E/e′ ratio was measured at the septal annulus on tissue Doppler imaging. LV mass (g) was calculated using the following equation: LV mass = $0.8 \times \{1.04[(\mathrm{LVDd} + \mathrm{IVST} + \mathrm{PWT})^3 - (\mathrm{LVEDD})^3]\} + 0.6$ [14]. The value was corrected for the body surface area (LV mass index). Diagnosis of LV diastolic dysfunction was based on ASE/European Association of Cardiovascular Imaging (EACVI) guidelines [15]. The four variables of diastolic dysfunction and their abnormal cut-off values were: (1) annular $e'$ velocity: septal $e' < 7$ cm/s, lateral $e' < 10$ cm/s; (2) average $E/e'$ ratio >14 (septal; $E/e' > 15$ lateral; $E/e' > 13$); (3) LAVI >34 mL/m$^2$; and (4) peak tricuspid regurgitation (TR) velocity >2.8 m/s. LV diastolic dysfunction was defined as having more than half of these conditions.

### Definitions

PAD was defined as ABI < 0.9 or previous history of lower extremity bypass and/or endovascular therapy (EVT). Hypertension was diagnosed as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, or having been treated for hypertension. Dyslipidemia was defined as serum low-density lipoprotein cholesterol ≥140 mg/dL, high-density lipoprotein cholesterol <40 mg/dL, triglycerides ≥150 mg/dL, or having been treated for dyslipidemia. The diagnosis of diabetes mellitus was based on World Health Organization criteria or on having been treated with insulin and/or an oral hypoglycemic agent. Hyperuricemia was defined as a serum uric acid level ≥7.0 mg/dL, or having been treated for dyslipidemia. Chronic kidney disease (CKD) was defined as estimated glomerular filtration rate <60 mL/min/1.73 m$^2$. History of HF was defined as admission for treating HF. CAD was defined as a history of at least one of the following: stable angina, unstable angina, percutaneous coronary intervention, coronary artery bypass surgery, or myocardial infarction. CVD was defined as a history of symptomatic cerebral infarction or either transient cerebral ischemic attack.

### Statistical analysis

Continuous variables are reported as mean and standard deviation when normally distributed or as median (interquartile range) when not normally distributed. Differences in the continuous variables of the two groups were compared using unpaired Student's $t$-test for normal distributions. The frequencies of the two groups were compared with $\chi^2$ tests. Odds ratios and 95% confidence intervals were calculated by logistic regression analysis. Variables with $p < 0.10$ by univariate analysis were inserted into the multivariate model to evaluate the predictors of LV diastolic dysfunction. Variables with a significant influence in the multivariate model were defined as independent risk factors. Statistical significance was accepted at $p < 0.05$. JMP software (v. 13.1; SAS Institute, Cary, NC, USA) was used to perform the analyses.

## Results

### Baseline characteristics

The baseline characteristics and medications are shown in Tables 1 and 2. The mean age was 68 ± 13 years and 56% of patients were male. Two hundred patients (18%) were found to have PAD. Sixty-six patients (33%) had no symptoms, 109 patients (54.5%) had intermittent, and 25 patients (12.5%) had critical ischemia in patients with PAD. There were some differences in baseline characteristics and medications between patients with PAD and those without PAD.

### Echocardiographic parameters

The echocardiographic parameters are shown in Table 3. No significant difference in ejection fraction was observed between the two groups. IVST (0.93 ± 0.16 vs 0.87 ± 0.19 cm, $p < 0.01$), PWT (0.89 ± 0.13 vs 0.85 ± 0.14 cm, $p < 0.01$) and LV mass index (LVMI) (94.6 ± 25.0 vs 87.3 ± 24.5 g/m$^2$, $p < 0.01$) were higher in patients with PAD than those without PAD. Regarding parameters of LV diastolic function, patients with PAD had higher $E/e'$ (15.3 ± 7.4 vs 11.8 ± 5.5, $p < 0.01$), TR velocity (2.37 ± 0.33 vs 2.19 ± 0.28 m/s, $p < 0.01$), LAVI (40.6 ± 20.2 vs 32.1 ± 13.6 mL/m$^2$, $p < 0.01$), and lower $e'$ (5.68 ± 1.70 vs 6.38 ± 2.07 cm/s, $p < 0.01$) than patients without PAD.

Each echocardiographic parameter of LV diastolic dysfunction was more frequently observed in patients with PAD than those without PAD: i.e. septal $e' < 7$ cm/s (82% vs 69%, $p < 0.01$), $E/e' > 15$ (septal) (41% vs 18%, $p < 0.01$), TR velocity >2.8 m/s (9% vs 2%, $p < 0.01$), and LAVI >34 mL/m$^2$ (54% vs 30%, $p < 0.01$). The prevalence of LV diastolic dysfunction was significantly higher in patients with PAD than those without PAD (31% vs 12%, $p < 0.01$) (Fig. 1). Comparing patients with PAD by severity of PAD, the prevalence of LV diastolic dysfunction was 36%, 27%, and 32% in patients with asymptomatic PAD, intermittent claudication, and critical ischemia, respectively ($p = 0.48$). (Fig. 2).

### The predictors for LV diastolic dysfunction

Table 4 shows univariate and multivariate analyses for the predictors of LV diastolic dysfunction. The multivariate logistic regression analysis showed that PAD was an independent predictor of LV diastolic dysfunction (adjusted odds ratio: 1.77, 95% confidence interval: 1.13–2.65, $p = 0.01$).

**Table 1**
Patient baseline characteristics.

| | Overall ($n$ = 1121) | PAD ($n$ = 200) | Non-PAD ($n$ = 921) | $p$-Value |
|---|---|---|---|---|
| Age (yrs) | 68 ± 13 | 76 ± 9 | 67 ± 14 | <0.01 |
| Male | 624 (56) | 131 (66) | 493 (54) | <0.01 |
| BMI | 22.8 ± 3.6 | 22.2 ± 3.4 | 22.9 ± 3.6 | <0.01 |
| Systolic blood pressure (mmHg) | 129.6 ± 20.6 | 131.6 ± 22.0 | 129.2 ± 20.3 | 0.15 |
| Diastolic blood pressure (mmHg) | 70.6 ± 12.9 | 69.8 ± 11.1 | 70.9 ± 11.8 | 0.06 |
| Hypertension | 790 (70) | 176 (88) | 614 (67) | <0.01 |
| Dyslipidemia | 421 (38) | 81 (41) | 340 (37) | 0.34 |
| Diabetes mellitus | 354 (32) | 84 (42) | 270 (29) | <0.01 |
| Hyperuricemia | 156 (14) | 38 (19) | 118 (13) | 0.02 |
| History of HF | 35 (3) | 14 (7) | 21 (2) | <0.01 |
| Smoking | 375 (33) | 98 (49) | 277 (30) | <0.01 |
| CKD | 325 (29) | 93 (47) | 232 (25) | <0.01 |
| Hemodialysis | 77 (7) | 27 (14) | 50 (5) | <0.01 |
| CAD | 173 (15) | 74 (37) | 99 (11) | <0.01 |
| OMI | 30 (3) | 14 (7) | 16 (2) | <0.01 |
| CVD | 90 (8) | 20 (10) | 70 (8) | 0.26 |
| Atrial fibrillation | 119 (11) | 46 (23) | 73 (8) | <0.01 |

Date given as mean ± SD or number (percentage).
PAD, peripheral artery disease; BMI, body mass index; HF, heart failure; CKD, chronic kidney disease; CAD, coronary artery disease; OMI, old myocardial infarction; CVD, cerebrovascular disease.

**Table 2**
Patient baseline medications.

| | Overall ($n$ = 1121) | PAD ($n$ = 200) | Non-PAD ($n$ = 921) | $p$-Value |
|---|---|---|---|---|
| Aspirin | 246 (22) | 95 (48) | 151 (16) | <0.01 |
| Statin | 337 (30) | 71 (36) | 266 (29) | 0.06 |
| Beta blocker | 230 (21) | 76 (38) | 154 (17) | <0.01 |
| Calcium-channel blocker | 500 (45) | 107 (54) | 393 (43) | <0.01 |
| ACE-inhibitor or ARB | 475 (42) | 107 (54) | 368 (40) | <0.01 |
| Diuretic | 190 (17) | 47 (24) | 143 (16) | <0.01 |

Date given as number (percentage).
PAD, peripheral artery disease; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker.

**Table 3**
Baseline echocardiography parameters.

| | Overall ($n$ = 1121) | PAD ($n$ = 200) | Non-PAD ($n$ = 921) | $p$-Value |
|---|---|---|---|---|
| LVDd, cm | 4.68 ± 0.48 | 4.62 ± 0.51 | 4.69 ± 0.48 | 0.11 |
| LVDs, cm | 2.87 ± 0.41 | 2.85 ± 0.43 | 2.89 ± 0.41 | 0.53 |
| EF, % | 68.4 ± 6.6 | 67.5 ± 7.2 | 68.6 ± 6.4 | 0.07 |
| IVST, cm | 0.88 ± 0.19 | 0.93 ± 0.16 | 0.87 ± 0.19 | <0.01 |
| PWT, cm | 0.86 ± 0.14 | 0.89 ± 0.13 | 0.85 ± 0.14 | <0.01 |
| LAD, cm | 3.78 ± 0.68 | 4.04 ± 0.75 | 3.72 ± 0.65 | <0.01 |
| $E$, cm/s | 71.5 ± 24.6 | 81.3 ± 30.2 | 69.4 ± 22.8 | <0.01 |
| $E/e'$ | 12.4 ± 6.0 | 15.3 ± 7.4 | 11.8 ± 5.5 | <0.01 |
| $e'$, cm/s | 6.25 ± 2.02 | 5.68 ± 1.70 | 6.38 ± 2.07 | <0.01 |
| TR, m/s | 2.22 ± 0.30 | 2.37 ± 0.33 | 2.19 ± 0.28 | <0.01 |
| LAVI, ml/m$^2$ | 33.6 ± 15.3 | 40.6 ± 20.2 | 32.1 ± 13.6 | <0.01 |
| LVMI, g/m$^2$ | 88.6 ± 24.8 | 94.6 ± 25.0 | 87.3 ± 24.5 | <0.01 |

Data given as mean ± SD.
LVDd, left ventricular dimension at end-diastole; LVDs, left ventricular dimension at end-systole; EF, ejection fraction; IVST, interventricular septum thickness; PWT, posterior left ventricular wall thickness; LAD, left atrial dimension; TR, tricuspid regurgitation; LAVI, left atrial volume index; LVMI, left ventricular mass index.

## Discussion

We evaluated LV diastolic function using echocardiography. Patients with PAD had higher $E/e'$, TR velocity, and LAVI, and lower $e'$ than those without PAD. The prevalence of LV diastolic dysfunction was higher in patients with PAD. Multivariate analyses showed that PAD was an independent predictor of LV diastolic dysfunction.

Only one previous study suggested the association of diastolic dysfunction in patients with PAD [12]. In that study, however, diastolic dysfunction was not evaluated by ASE criteria, but diagnosed using only $E/e'$. In addition, the number of patients in the study was small ($n$ = 120) and the relationship between PAD and LV diastolic function remains unclear. In the current study, we evaluated LV diastolic function using echocardiography in 1121 patients and applied the ASE/EACVI guidelines for the diagnosis of LV diastolic dysfunction. We showed a higher prevalence of LV diastolic dysfunction in patients with PAD, regardless of severity of PAD. Thus, our study suggests that patients with PAD have increased risk of LV diastolic dysfunction and should be evaluated using echocardiography to observe LV diastolic function in addition to LV systolic function.

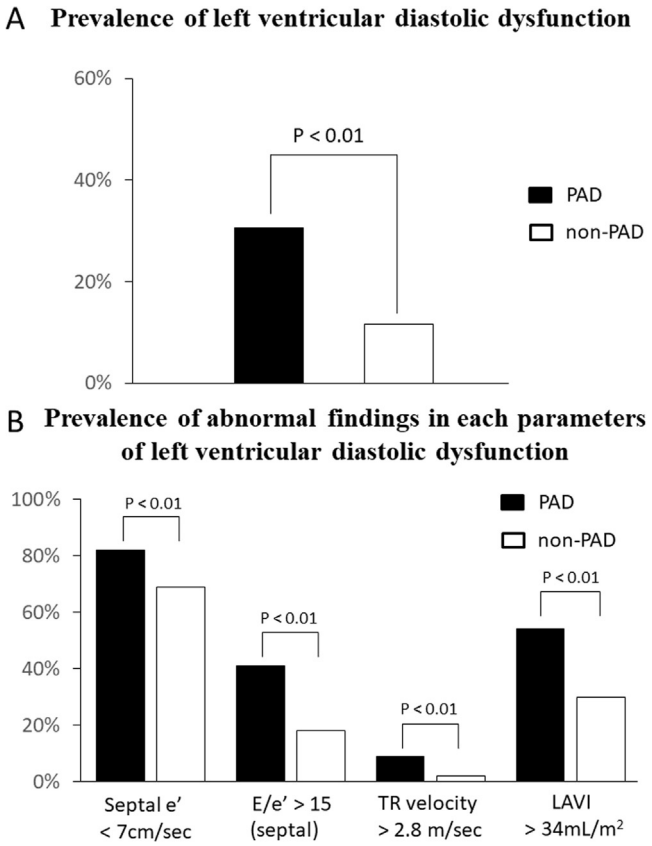


**Fig. 1.** (A) Prevalence of left ventricular diastolic dysfunction and (B) abnormal findings in each parameters of left ventricular diastolic function in patients with peripheral artery disease (PAD) and without PAD. TR, tricuspid regurgitation; LAVI, left atrial volume index.

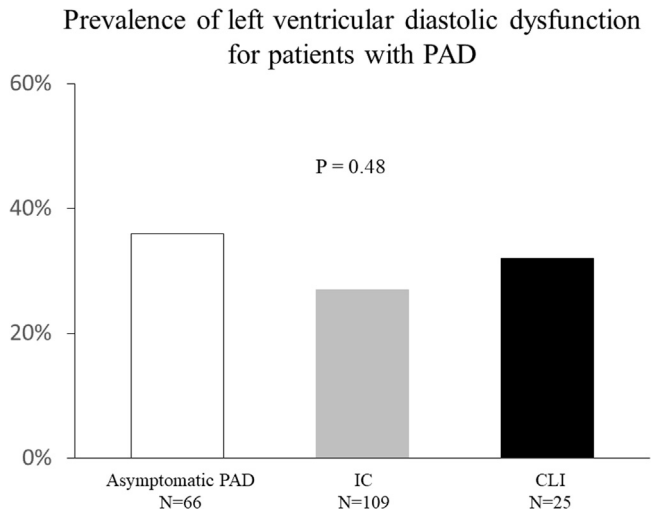


**Fig. 2.** Prevalence of left ventricular diastolic dysfunction for patients with PAD. PAD, peripheral artery disease; IC, intermittent claudication; CLI, critical limb ischemia.

Recent studies have reported that LV diastolic dysfunction is caused by inflammation and oxidative stress, which are known to be induced by several factors, including diabetes, hypertension, and age [16,17]. Clinical studies also reported that diabetes, hypertension, and age showed independent associations with LV diastolic dysfunction [18,19]. In the current study, age, hypertension, and some medications for hypertension were independently associated with LV diastolic dysfunction. Patients with PAD had more cardiovascular risk factors [20] and shared with them of LV diastolic dysfunction. However, PAD was an independent predictor of LV diastolic dysfunction even after adjustment for these risk factors.

Systemic atherosclerosis is advanced in patients with PAD, which results in increased arterial stiffness. Previous studies have reported that pulse wave velocity was increased in patients with PAD [21]. Notably, increased arterial stiffness has also been reported to be associated with LV myocardial stiffness and LV diastolic dysfunction [22–24]. Arterial stiffening increases LV

**Table 4**
Univariate and multivariate analysis for predictors of left ventricular diastolic dysfunction.

| Predictors | Univariate model | | Multivariate model | |
|---|---|---|---|---|
| | Odds ratio [95% CI] | *p*-Value | Odds ratio [95% CI] | *p*-Value |
| PAD | 3.34 [2.32–4.80] | <0.01 | 1.77 [1.13–2.65] | 0.01 |
| Age | 1.06 [1.04–1.08] | <0.01 | 1.04 [1.02–1.06] | <0.01 |
| Female | 1.38 [1.00–1.92] | 0.05 | 2.42 [1.57–3.70] | <0.01 |
| BMI | 0.97 [0.93–1.02] | 0.22 | | |
| Hypertension | 3.82 [2.32–6.27] | < 0.01 | 1.57 [1.03–2.61] | <0.01 |
| Dyslipidemia | 0.88 [0.63–1.24] | 0.48 | | |
| Diabetes mellitus | 1.45 [1.03–2.04] | 0.03 | 1.27 [0.85–1.89] | 0.24 |
| Hyperuricemia | 1.43 [0.92–2.21] | 0.11 | | |
| History of HF | 19.2 [8.82–41.8] | <0.01 | 5.86 [2.34–14.7] | <0.01 |
| Smoking | 1.35 [0.96–1.89] | 0.08 | 1.43 [0.93–2.20] | 0.10 |
| CKD | 3.63 [2.59–5.09] | <0.01 | 1.57 [0.99–2.47] | 0.06 |
| Hemodialysis | 3.69 [2.24–6.07] | <0.01 | 2.76 [1.45–5.25] | <0.01 |
| CAD | 2.00 [1.35–2.99] | <0.01 | 1.13 [0.66–1.92] | 0.66 |
| OMI | 0.87 [0.30–2.52] | 0.80 | | |
| CVD | 0.95 [0.52–1.76] | 0.88 | | |
| Atrial fibrillation | 4.35 [2.87–6.59] | <0.01 | 1.68 [1.01–2.80] | 0.05 |
| Aspirin | 1.47 [1.01–2.13] | <0.01 | 0.65 [0.40–1.14] | 0.12 |
| Statin | 0.98 [0.69–1.41] | 0.93 | | |
| Beta blocker | 5.19 [3.66–7.36] | <0.01 | 2.78 [1.82–4.27] | <0.01 |
| Calcium-channel blocker | 1.71 [1.23–2.38] | <0.01 | 1.21 [0.80–1.85] | 0.36 |
| ACE-inhibitor or ARB | 2.02 [1.45–2.81] | <0.01 | 1.15 [0.75–1.77] | 0.52 |
| Diuretic | 3.39 [2.35–4.90] | <0.01 | 1.68 [1.06–2.65] | 0.03 |

PAD, peripheral artery disease; BMI, body mass index; HF, heart failure; CKD, chronic kidney disease; CAD, coronary artery disease; OMI, old myocardial infarction; CVD, cerebrovascular disease; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker.

afterload and central pulse pressure, which causes myocyte hypertrophy and subendocardial ischemia that may impair myocardial relaxation and promote myocardial fibrosis. These changes reduce LV compliance and induce LV diastolic dysfunction [22,25,26]. In our study, patients with PAD had higher IVST, PWT, and LVMI. Increased arterial stiffness likely caused LV wall thickening and LV diastolic dysfunction in patients with PAD.

EVT for PAD was previously reported to confer cardiorenal protection [27,28]. Eguchi et al. reported that EVT treatment reduced blood pressure levels, carotid augmentation index, and central pressure in patients with PAD. The reductions in augmentation index and central pressure were associated with changes in IVST, PWT, and LVMI [27]. In addition, Nozato et al. reported that EVT of PAD reduces blood pressure and may improve long-term prognosis [28]. Thus, EVT might improve LV diastolic dysfunction in patients with PAD and further study is needed in this field.

This study had several limitations. First, the study was a retrospective investigation in a single center and our patient population was a subgroup selected from the overall patients who had received routine echocardiography. In most cases, echocardiography was performed as a screening test for cardiovascular disease in patients with hypertension, diabetes, or PAD. The information, such as baseline diseases and reasons why patients received echocardiography was unfortunately unclear. Second, PAD was diagnosed based on ABI and medical history. However, ABI has a substantial limitation for diagnosis of PAD, particularly in patients undergoing hemodialysis. Third, the $e'$ and $E/e'$ ratio were only measured at the septal annulus. Finally, ABI and echocardiography were not measured on the same day.

## Conclusion

The prevalence of LV diastolic dysfunction was higher in patients with PAD than those without PAD. These findings suggest that patients with PAD should be evaluated not only for LV systolic but also diastolic function in echocardiography.

## Conflict of interest

None declared.

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