ORIGINAL RESEARCH ARTICLE

The impact of left ventricular diastolic dysfunction for the prognosis in patients with lower extremity arterial disease

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Abstract

Aims   Lower extremity arterial disease (LEAD) and left ventricular diastolic dysfunction (LVDD) share many risk factors, but the characteristics of LVDD and its association with prognosis in patients with LEAD have not been fully examined.
Methods and results   We investigated the impact of LVDD on the clinical outcomes in LEAD patients. LVDD was classified according to the newest suggested classification by the American Society of Echocardiography. Survival analysis for mortality (primary endpoint) and major adverse cardiac events (MACE; secondary endpoint) was calculated with all clinical variables and adjusted by multivariate Cox regression. We consecutively enrolled 221 controls and 464 LEAD patients from outpatient clinics and hospitals. The prevalence of LVDD was proportional to the severity of LEAD defined by the Rutherford class. The difference of LVDD severity is significant when compared with the control and LEAD patients or LEAD patients who underwent endovascular therapy (EVT), and it is also proportional to the LEAD severity. The grade of LVDD was a significant factor in predicting MACE and mortality in LEAD patients after multivariate Cox regression analysis [hazard ratio (HR) = 2.11, 95% CI = 1.47–2.83, $P = 0.026$; HR = 1.47, 95% CI = 1.02–2.02, $P = 0.041$]. This impact remained significant in LEAD patients who underwent EVT.
Conclusions   The degree of LVDD may predict MACE and mortality in LEAD patients. Whether early identification of LVDD in LEAD patients is helpful warrants further large-scale prospective randomized studies.

Keywords   Cardiac diastolic dysfunction; Heart failure with preserved ejection fraction; Lower extremity arterial disease; Prognosis

Introduction

Lower extremity arterial disease (LEAD) is often associated with various comorbidities, including congestive heart failure, myocardial infarction (MI), and cerebrovascular disease.[1-3] Numerous cohort studies have reported that the clinical outcome of LEAD patients is grave, and the rate of major adverse cardiovascular events (MACE) and mortality is higher than in the general population. Moreover, LEAD is an independent risk factor for mortality in patients with cardiovascular disease.[4] Therefore, it is important to treat LEAD patients with great attention to improve the overall prognosis.

Endovascular therapy (EVT) is a well-established procedure to improve the clinical outcome of the leg and is advocated by current guidelines.[5,6] The procedure leads to tremendous improvements in claudication, rest pain, and wound healing according to many cohort studies.[7-9] However, patients who undergo this procedure are not necessarily free from other adverse cardiovascular events, such as MI or mortality. It is important to find modifiable clinical factors that may reduce MACE and mortality in these patients. Thirty to fifty per cent of patients hospitalized for heart failure present with diastolic dysfunction.[10] In previous studies, left ventricular diastolic dysfunction (LVDD) may contribute to grave cardiovascular outcomes.[11,12] The newest guidelines from

the American Society of Echocardiography released in 2016 have added the pressure gradient of the tricuspid valve as an important variable for grading the severity of LVDD, which gives healthcare professionals more information in treating LVDD patients.13 Previous studies showed that peripheral artery disease increases the risk for adverse outcomes in heart failure with preserved ejection fraction (HFpEF) and is associated with HF rehospitalization and cardiovascular event.14-16 On the contrary, relevant investigation regarding LVDD or HFpEF in LEAD is still lacking.

Although atherosclerosis is prevalent in patients with LVDD, the data on LEAD patients are scarce. In the present study, we evaluated the prevalence of LVDD in patients with LEAD compared with controls from the general population. In addition, we examined the relationship between LVDD and the clinical outcomes of LEAD patients, as well as LEAD patients who underwent EVT.

Materials and methods

Study design

The study was a prospective, observational study performed in a tertiary medical centre. No previous trial results were available regarding LEAD patients with LVDD, so an adequate power calculation was not possible. The study was conducted with approval from the local ethics committee and in accordance with the declaration of Helsinki. All patients gave written informed consent prior to the procedures.

Patient selection

Patients with LEAD were included if they had symptoms of claudication, unhealed wounds, ulcers, or gangrene. Ankle blood pressure measurements, ultrasonographic duplex, and pelvic and lower limb computed tomography angiogram (CTA) examinations of the arteries were performed. Patients were included if they have evidences of stenosis of a lower limb artery with at least one of the following criteria: (i) symptoms of claudication, unhealing wounds, or gangrene combined with an ankle–brachial index ≤ 0.90 or (ii) symptoms of claudication combined with ultrasonographic or computed tomography evidence of arterial occlusive disease in the ipsilateral extremity. Control subjects were recruited from the general population for the same complaints of claudication, unhealed wounds, ulcers, or gangrene in the same period in which we enrolled the LEAD patients. The control subjects have also undergone all the non-invasive evaluation as well. We use the Rutherford classification (RC) to evaluate the clinical severity of LEAD, which is defined by objective findings (Stage 0: asymptomatic; Stage 1: mild claudication;

Stage 2: moderate claudication; Stage 3: severe claudication; Stage 4: rest pain; Stage 5: ischaemic ulceration not exceeding ulcers of the digits of the foot; Stage 6: severe ischaemic ulcers or frank gangrene). The exclusion criteria in this study (for both LEAD group and control group) included the following: (i) younger than 20 years, (ii) patients did not accept echocardiography for LVDD grading, and (iii) patients not followed in our hospital.

Echocardiographic diastolic dysfunction grade

All patients received echocardiography using a CX50 xMATRIX echocardiography system (Philips Healthcare, Best, The Netherlands) along with analysis by Philips QLAB 10 software. Subjects were divided into three groups in accordance with their DD grade, which was recently proposed by the American Society of Echocardiography and the European Association of Cardiovascular Imaging in 2016.13 The 2016 DD grade was evaluated with several parameters, including mitral inflow velocity and mitral peak velocity of the late filling ratio (E/A), peak E velocity, peak velocity of the TR jet, medial and lateral e', E/e' ratio, and left atrial volume index (LAVI). In brief, subjects would be clarified as having LVDD if they have the following structural and/or functional alterations of the heart: (i) LAVI > 34 mL/m^2 or a left ventricular mass index (LVMI) ≥115 g/m^2 for men and ≥95 g/m^2 for women and (ii) an average E/e'' >14, a septal e' velocity <7 cm/s, or a lateral e' velocity <10 cm/s. Other echocardiographically derived measurements are abnormal longitudinal strain or tricuspid regurgitation velocity (TRV; e.g. TRV > 2.8 m/s).13 Three types of abnormal filling patterns are also recognized conventionally in LVDD patients in sinus rhythm: (i) When the mitral inflow pattern shows an E/A ratio ≦0.8 as well as a peak E velocity of ≦50 cm/s, the corresponding grade of diastolic dysfunction is Grade I. (ii) When the mitral inflow pattern shows an E/A ratio≧2, LA mean pressure is elevated and is considered as Grade III diastolic dysfunction. (iii) When mitral inflow shows an E/A ≦0.8 and the peak E velocity >50 cm/s, or if the E/A ratio is >0.8 but <2, then other criteria including: peak TRV > 2.8 m/s, average E/e' >14 or LAVI >34 mL/m^2 should be evaluated. If the above three parameters are available and only one or zero of the three exceed the cut-off value, the patient is with Grade I diastolic dysfunction. If two of three or all three parameters exceed the cut-off values, then there is Grade II diastolic dysfunction. Otherwise, the diastolic dysfunction grade could not be evaluated and should not be reported.13

Endpoints

The primary outcome of this study was defined as all-cause mortality, while the secondary endpoints were MACE,

including hospitalization due to heart failure, MI, recurrent coronary artery disease, and stroke.

Follow-up

All the patients either visited our outpatient clinic at least every 3 months or were interviewed by telephone annually. Information regarding the primary and secondary study outcomes was documented in chart records or via telephone interviews. For each patient, the time to death or cardiovascular events was calculated from the initial date of enrolment to the date on which the primary or secondary outcome occurred.

Statistics

Data are expressed as either the mean ± standard deviation or as frequencies or percentages. The χ^2 test, two-sample t-test, and Mann–Whitney U test were used to compare baseline characteristics between the three groups of different diastolic dysfunction grades with the Grade 1 group acting as a reference. We first performed a univariate Cox regression analysis to examine factors associated with all-cause mortality and MACE. Predictors in the multiple Cox model were selected from the set of variables that reached statistical significance in the univariate analysis via a forward selection procedure with the significance limit to enter the model set to 0.05. The survival time was defined as the duration between enrolment and the occurrence of an event (defined as either a primary or secondary endpoint). Survival curves were estimated using the Kaplan–Meier method, and the log-rank test was used to compare survival differences.

Multivariate Cox proportional hazard regression analyses were used to derive the adjusted hazard ratios (HRs) for the risk of outcomes in different groups with the Grade I group as a reference. We adjusted for age, sex, risk factors, comorbidities, medication usage, LVMI, and LAVI. Statistical analyses were performed using IBM SPSS Statistics version 21.0 (IBM, Armonk, New York, USA). Two-sided P values <0.05 were considered to indicate statistical significance.

Results

Baseline characteristics

Overall, 464 LEAD patients and 221 age and sex-matched controls were enrolled in the study. All patients were followed up until the end of the study. The median follow-up period for the LEAD group was 254 days, and the maximum and minimum follow-up periods were 412

and 28 days, respectively. Table 1 indicates the baseline characteristics, medications, LEAD grades, and whether the patients received EVT. The control group had similar age, sex, and body mass index to the LEAD group. The LEAD patients had significantly higher rates of diabetes, hypertension, dialysis, and coronary artery disease (CAD) compared with the controls (Table 1). Because most patients in the LEAD group had diabetes, the use of oral hypoglycaemic agents and insulin was significantly higher for the LEAD group. The two most common medications used were angiotensin-converting enzyme inhibitors (74.3%) and statins (70.8%) for LEAD patients. Most LEAD patients received revascularization treatment (85.8%).

Echocardiographic parameters and left ventricular diastolic dysfunction grading

All subjects received echocardiographic examinations. Both groups had preserved LV function (LV ejection fraction >50%). The LVMI was also similar between groups. LEAD patients had significantly higher LAVI, higher mitral inflow E and

Table 1 Baseline demography

	Patients (464)	Controls (221)	P
Patient status			
Age	73 ± 16	71 ± 14	0.11
Male gender	305 (65.7%)	139 (63.1%)	0.49
BMI	23.7 ± 5.7	24.3 ± 6.2	0.21
Risk factors			
Current smoking	203 (43.8%)	86 (39.2%)	0.24
DM	404 (87.2%)	142 (64.2%)	<0.001
HbA1C	7.2 ± 1.6	6.7 ± 1.9	<0.001
HTN	385 (83.1%)	198 (87.2%)	0.31
Dyslipidaemia	367 (79.1%)	179 (81.2%)	0.61
Dialysis	234 (50.4%)	82 (37.1%)	0.0014
Kidney transplantation	45 (9.7%)	7 (3.1%)	0.0019
Atrial fibrillation	84 (18.1%)	34 (15.6%)	0.45
CAD	331 (71.4%)	91 (41.2%)	<0.001
Heart failure	88 (19.0%)	34 (15.6%)	0.28
Stroke	61 (13.3%)	24 (11.2%)	0.45
Albumin, g/dL	3.3 ± 0.7	3.4 ± 0.9	0.11
CRP, mg/dL	4.7 ± 2.1	1.4 ± 1.2	<0.001
Medications			
OHA only	318 (68.7%)	108 (49.1%)	<0.001
With insulin	109 (23.5%)	135 (5.9%)	<0.001
ACEI/ARB	344 (74.3%)	156 (70.5%)	0.35
Beta-blocker	170 (36.7%)	73 (33.1%)	0.39
Statin	329 (70.8%)	161 (72.9%)	0.71
LEAD grade			
I (RC 1–3)	199 (42.8%)	0	N/A
II (RC 4)	48 (10.5%)	0	N/A
III (RC 5–6)	217 (46.7%)	0	N/A
Revascularization strategy			
EVT	398 (85.8%)	0	N/A

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; CAD, coronary artery disease; CRP, C-reactive protein; DM, diabetes mellitus; ; EVT, endovascular therapy; HbA1C, haemoglobin A1C; HTN, hypertension; LEAD, lower extremity artery disease; OHA, oral hypoglycaemic agents.

A waves, and higher mitral inflow E/E' ratios, which indicates that LEAD patients might have a higher percentage of cardiac diastolic dysfunction compared with the control group (*Table* 2).

We also determined whether the patients had LVDD according to the newest recommendations from the American Society of Echocardiography and the European Association of Cardiovascular Imaging.13 Patients with LEAD who underwent EVT had the highest percentages of LVDD, followed by LEAD patients without EVT and the control group (53.5% vs. 48.3% vs. 22.6%; both *P* < 0.0001; *Figure 1A*). There is also a significant association according to the RC grade of LEAD for the development of LVDD. Patients with the most severe LEAD had the highest rate of LVDD (66.8% vs. 43.7% vs. 29.1%; both *P* < 0.0001; *Figure 1B*).

We then classified the LVDD patients from the LEAD and the control group into three groups according to the severity grading from the same recommendations. Patients with LEAD and EVT had higher parentheses of Grades 2 (46.0%) and 3 (30.9%) subjects, while LVDD patients without EVT were mostly Grade 1 (74.0%; *Figure 2A*). Accordingly, LVDD patients with the most severe LEAD (LEAD Grade 3) mostly had Grades 2 (47.0%) and 3 (39.2%) LVDD (*Figure 2B*). The results show that patients with LEAD who receive EVT had highest risk for the development of LVDD, and the severity of LVDD paralleled the severity of LEAD.

Factor associated with mortality or major adverse cardiac events in patients with/without endovascular therapy

Table 3A and *B* summarizes the predictors of mortality and major cardiovascular events in LEAD patients and in LEAD patients who underwent EVT according to univariate and multivariate analyses. Age, LEAD grade, LVDD grade, and LAVI were significant factors associated with mortality after the univariate analysis in LEAD patients and in LEAD patients with EVT (*Table* 3A and *B*). After controlling for all the significant factors determined via the univariate analysis for mortality, LAVI was significantly associated with clinical outcomes. The multivariate Cox analysis revealed that older patients had poorer survival (HR 1.21, 95% CI: 1.02–1.68; *P* = 0.042). Patients with higher LEAD grade and higher LVDD grade still had a poorer prognosis after adjusting for all of the risk factors (HR 1.92, 95% CI: 1.45–2.51, *P* = 0.019; and HR 1.47, 95% CI: 1.02–2.02, *P* = 0.041, respectively).

For LEAD patients receiving EVT, the multivariate analysis revealed that age, LEAD grade, and LVDD grade were still the most important predictors for survival. We also did a univariate analysis for factors associated with MACE in LEAD patients and those who received EVT. Age, diabetes, LEAD grade, LVDD grade, and LAVI were significant factors for MACE in LEAD patients. After adjusting for the significant factors in the univariate analysis, older patients again had poorer MACE-free survival (HR 1.36, 95% CI: 1.02–1.68; *P* = 0.042). Diabetes, greater LAVI, higher LEAD grade (HR 2.47, 95% CI: 1.32–3.68, *P* = 0.011), and higher LVDD grade (HR 2.11, 95% CI: 1.47–2.83, *P* = 0.026) were other independent factors for MACE in LEAD patients. For LEAD patients receiving EVT, multivariate analysis revealed that age (HR 1.44, 95% CI: 1.16–1.79, *P* = 0.038), LEAD grade (HR 2.63, 95% CI: 1.41–3.82, *P* = 0.014), and LVDD grade (HR 1.96, 95% CI: 1.33–2.54, *P* = 0.021) were the most important predictors for MACE (*Table* 3A and *B*).

Left ventricular diastolic function grade and prognosis in lower extremity arterial disease patients with/without endovascular therapy

A total of 17 subjects died during the 1 year follow-up study. The 1 year survival and MACE-free survival rates were 92.4% and 87.1% for the LEAD cohort, respectively. For LEAD patients receiving EVT, the 1 year survival and MACE-free survivals were 90.6% and 80.9%, respectively.

To delineate the influence of LVDD on prognosis in LEAD patients with and without EVT, the Kaplan–Meier plots for mortality and MACE according to LVDD grade were obtained. The results are shown in *Figure 3A and B* (LEAD patients) and *Figure 4A and B* (LEAD patients with EVT). Both mortality and MACE rates increased in patients with higher LVDD grade. A significant relationship was noted for LVDD grade and mortality (*P* for trend = 0.034) and MACE (*P* = 0.038) in LEAD patients and the LEAD-EVT group (*P* for trend = 0.042 for mortality and *P* for trend = 0.026 for MACE, respectively).

Table 2 Echocardiographic parameters in LEAD and control patients

	LEAD patients (464)	Controls (221)	P
LVEF (%)	57.7 ± 8.6	58.1 ± 9.5	0.58
LVEDD (mm)	46.6 ± 11.2	45.7 ± 10.9	0.32
LVESD (mm)	31.2 ± 6.8	30.7 ± 7.5	0.38
IVS (mm)	8.2 ± 2.1	7.9 ± 2.3	0.09
LVPW (mm)	11.2 ± 2.6	10.8 ± 2.7	0.08
LVMI (g/m²)	126.7 ± 38.7	128.9 ± 35.2	0.47
LAVI	37.4 ± 8.3	35.6 ± 7.4	0.006
E	67.2 ± 16.8	54.1 ± 18.2	<0.001
A	85.2 ± 8.3	74.5 ± 9.1	<0.001
E/E' ratio	11.2 ± 4.8	9.5 ± 3.8	<0.001
E/A ratio	0.9 ± 0.3	0.7 ± 0.4	<0.001

A, peak late diastolic transmitral velocities; E, mitral peak early to diastolic transmitral velocities; E', mean of peak early diastolic annular velocity measured at the septal/lateral mitral annulus; IVS, intraventricular septum; LAVI, left atrial volume index; LEAD, lower extremity artery disease; LVEDD, left ventricular end diastolic dimension; LVEF, left ventricular ejection fraction; LVESD, left ventricular end systolic dimension; LVMI, left ventricular mass index; LVPW, left ventricular posterior wall thickness.

FIGURE 1 Prevalence of LV diastolic dysfunction in (A) control patients, peripheral artery disease (PAD) patients, and PAD patients who underwent endovascular therapy (EVT), (B) PAD group classified by Rutherford classification *P < 0.0001. Abbreviations: LEAD, lower extremity arterial disease; LV, left ventricular.
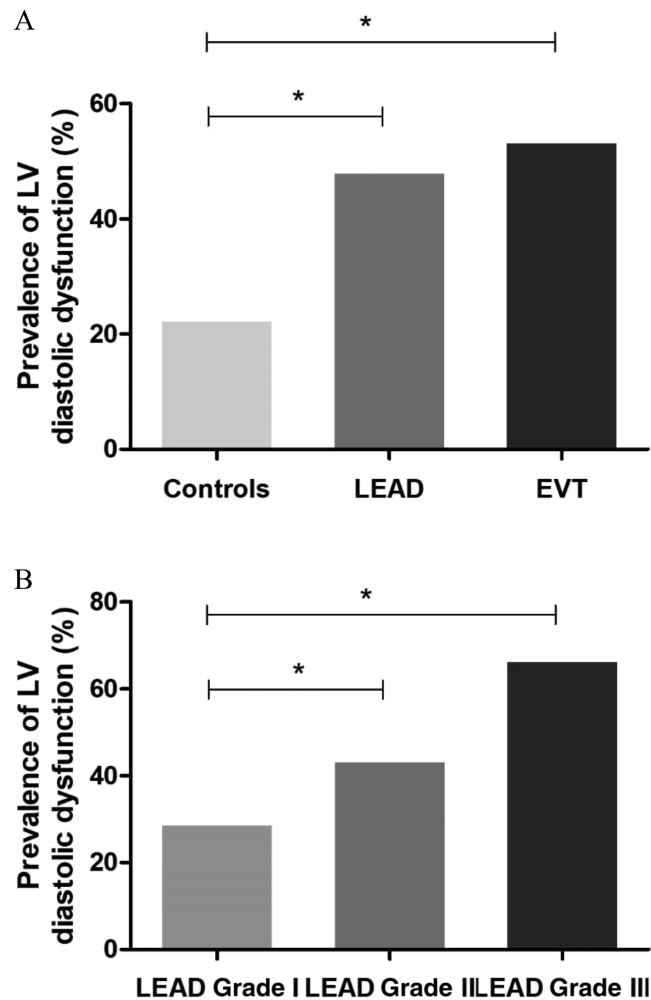

Discussion

To the best of our knowledge, this is the first study to assess the prevalence of different grades of LVDD in LEAD patients and their associations with cardiovascular outcomes, including mortality and major cardiovascular events. The severity of LVDD was independently associated with increased risk of mortality and MACE in LEAD patients according to newest LVDD classification recommendations. Information about the prevalence and severity of LVDD in LEAD patients is scarce, which mainly focused on prognostic significance of LEAD severity in patients with HFpEF.[15-17] Because LVDD leads to grave outcomes and cardiovascular mortality, we must pay much more attention to its impact on LEAD patients. In previous studies, patients with CAD had higher prevalence of LVDD than the normal population. The prevalence of LVDD is even higher in our patient group, where LEAD patients systemically present the most advanced atherosclerosis comparing to CAD.[18,19]

Furthermore, we found that the prevalence of LVDD increases along with clinical severity of RC in LEAD patients. The grade of LVDD is also proportional to the severity of LEAD. There are several possible explanations for this correlation. First, inflammation is an important factor in patients with atherosclerosis, which may also lead to LVDD. Wu *et al*. found that inflammation substantially contributed to LVDD in clinical and animal studies.[20,21] LEAD patients with RC III represent the most severe condition, with symptoms such as ulceration and gangrene and even chronic wound infection, and definitely have higher inflammation compared with mild LEAD. In current study, we showed again that these severe LEAD patients are also with higher grades of LVDD.

FIGURE 2 Distribution of LV diastolic dysfunction in (A) controls, peripheral artery disease (PAD) patients, and PAD patients who underwent endovascular therapy (EVT), (B) PAD patients classified by PAD grade. Abbreviations: LEAD, lower extremity arterial disease; LVDD, left ventricular diastolic dysfunction; LV, left ventricular.
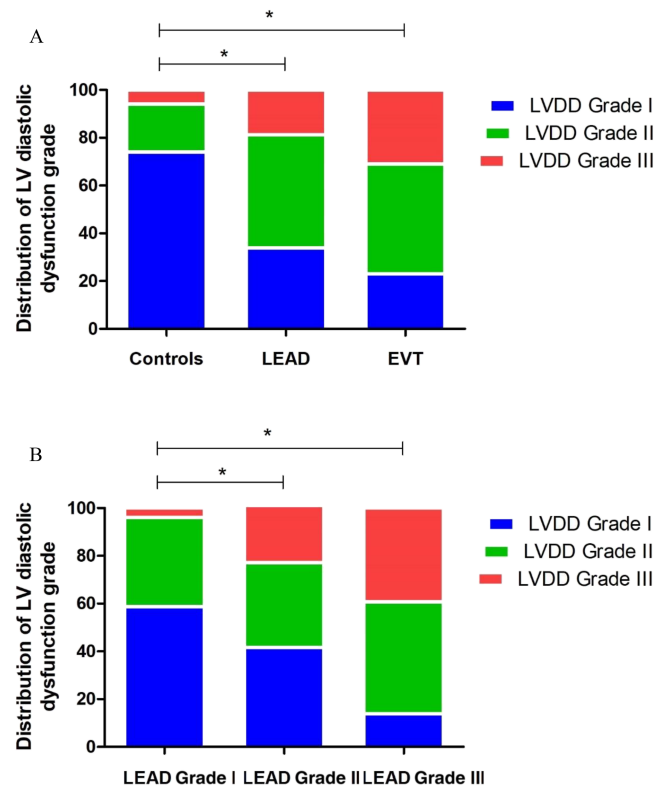
Second, increased aortic stiffness is unique when evaluating LEAD patients. On the other hand, increased arterial stiffness is also associated with LVDD. Eren *et al.* reported a close association between aortic stiffness and LVDD.22 While aortic stiffness increases with LEAD severity, it is no wonder that the status of LVDD is highly associated with LEAD severity. This is possibly from the parallel changing phenomenon in cardiac and aortic walls. The stiffness of cardiac wall may increase when facing stiffer and more resistant aortic wall and thus could lead to more severe LVDD. Based on these two possible explanations, it is a reasonable result that the grade of LVDD closely correlates with LEAD in severity.

We also investigated the impact of LVDD on the clinical outcome in LEAD patients. No previous studies have addressed this issue. In contrast, the impact of LVDD on cardiovascular outcome is widely discussed, but mostly in CAD and congestive heart failure patients. Both Wu *et al.* and Lee *et al.* reported that LVDD leads to increased rates of cardiac events and mortality in patients with CAD, and the odds ratio of mortality is around two times higher.23 Because LEAD patients present the most serious type of atherosclerosis, their cardiovascular comorbidity is even higher.24,25

In previous studies, multiple factors influenced the cardiovascular outcomes in LEAD patients, including age and LEAD grade, which are just like the findings in our LEAD patients.25,26 LVDD remained a significant prognostic factor even after adjusting for as many confounding factors as possible. When the grade of LVDD increased, the clinical outcomes became worse in both mortality and MACE. LVDD may influence the prognosis of LEAD patients for several potential reasons. First, the presence of significant CAD is known to be associated with LEAD, and CVD is a leading cause of morbidity and mortality in LEAD patients. The prevalence of CAD in LEAD patients is high, and they may also share the same prognostic factors in cardiovascular outcomes, such as LVDD. In addition, LVDD has also been proposed to be an independent marker of mortality in different groups of patients and usually precedes LV systolic dysfunction. It may in turn lead to worse outcomes, such as hospitalization for heart failure.

In a previous evaluation of diastolic dysfunction using the 2009 DD grading system, the severity of diastolic dysfunction was only assessed by the pattern of mitral inflow and the tissue Doppler image. The new proposed diastolic dysfunction grading system emphasizes measurement of the mitral inflow velocities in order to estimate left atrial pressure (LAP) and the peak velocity of the TR jet to evaluate the right ventricle afterload and pulmonary capillary wedge pressure (PCWP).

Table 3 Predictors of mortality and major cardiovascular events in (A) LEAD patients and (B) LEAD patients who underwent EVT.

	Univariate		Multivariate	
(A)	Hazard ratios	P	Hazard ratios	P
Mortality				
Age per decade	1.29 (1.09–1.59)	0.031	1.21 (1.02–1.68)	0.042
Male	1.38 (0.84–1.95)	0.45		
Hypertension	1.27 (0.75–2.14)	0.56		
Diabetes	1.46 (0.64–2.37)	0.61		
Hyperlipidaemia	1.18 (0.85–1.56)	0.53		
CAD	1.54 (0.65–2.49)	0.67		
LEAD grade	1.79 (1.62–2.74)	0.007	1.92 (1.45–2.51)	0.019
LVDD grade	1.49 (1.21–1.95)	0.018	1.47 (1.02–2.02)	0.041
LVMI	1.21 (0.92–1.56)	0.62		
LAVI	1.36 (1.08–1.74)	0.039	1.25 (0.94–1.81)	0.054
Major cardiovascular events				
Age per decade	1.42 (1.11–1.72)	0.035	1.36 (1.06–1.75)	0.040
Male	1.91 (0.59–4.14)	0.39		
Hypertension	2.87 (0.81–4.64)	0.41		
Diabetes	2.13 (1.56–2.82)	0.018	2.02 (1.32–2.68)	0.035
Hyperlipidaemia	1.16 (0.76–1.78)	0.57		
CAD	1.87 (0.74–2.91)	0.44		
LEAD grade	2.71 (1.52–4.16)	0.002	2.47 (1.32–3.68)	0.011
LVDD grade	2.27 (1.69–3.03)	0.005	2.11 (1.47–2.83)	0.026
LVMI	0.999 (0.996–1.002)	0.68		
LAVI	1.31 (1.16–1.51)	0.014	1.28 (1.09–1.62)	0.044

	Univariate		Multivariate	
(B)	Multivariate	P	Hazard ratios	P
Mortality				
Age per decade	1.42 (1.12–1.69)	0.027	1.36 (1.09–1.54)	0.042
Male	1.47 (0.81–2.17)	0.51		
Hypertension	1.36 (0.68–2.27)	0.59		
Diabetes	1.52 (0.62–2.41)	0.65		
Hyperlipidaemia	1.12 (0.89–1.51)	0.41		
CAD	1.61 (0.69–2.22)	0.45		
LEAD grade	1.87 (1.56–2.45)	0.003	1.97 (1.41–2.68)	0.021
LVDD grade	1.58 (1.28–2.01)	0.012	1.42 (1.05–2.28)	0.032
LVMI	1.38 (0.82–1.77)	0.71		
LAVI	1.48 (1.03–1.89)	0.042	1.32 (0.91–1.84)	0.061
Major cardiovascular events				
Age per decade	1.57 (1.26–1.81)	0.028	1.44 (1.16–1.79)	0.038
Male	1.74 (0.46–4.29)	0.48		
Hypertension	2.72 (0.78–4.71)	0.32		
Diabetes	2.27 (1.69–2.71)	0.014	1.94 (1.45–2.41)	0.031
Hyperlipidaemia	1.19 (0.72–1.85)	0.64		
CAD	1.66 (0.64–3.21)	0.58		
LEAD grade	2.81 (1.64–4.01)	0.001	2.63 (1.41–3.82)	0.014
LVDD grade	2.11 (1.72–2.66)	0.004	1.96 (1.33–2.54)	0.021
LVMI	0.97 (0.90–1.03)	0.73		
LAVI	1.36 (1.19–1.48)	0.011	1.22 (1.09–1.41)	0.046

CAD, coronary artery disease; LAVI, left atrial volume index; LEAD, lower extremity artery disease; LVDD, left ventricular diastolic dysfunction; LVMI, left ventricular mass index.

Taken together, the evaluation of LVDD advocated by the latest guidelines may offer a new alternative to predict the clinical outcomes in LEAD patients.

Limitations

To our knowledge, this study is the first to demonstrate the impact of diastolic dysfunction on the cardiovascular outcomes in patients with LEAD. However, several important limitations should be noted. One limitation is that our patient population was a selected subgroup of the overall LEAD population in a single centre. Second, echocardiographic parameters could not be obtained in some cases. Third, the patients had different follow-up time with minimum 28 days that could be due to the high comorbidities and event rates in LEAD patients. These findings may modify the results. Finally, the number of patients in this study was small, and further studies are needed to characterize heart failure in LEAD patients overall.

FIGURE 3 The Kaplan–Meier curves of lower extremity arterial disease patients by grade of left ventricular diastolic dysfunction (LVDD) for (A) major cardiovascular events and (B) all-cause mortality.
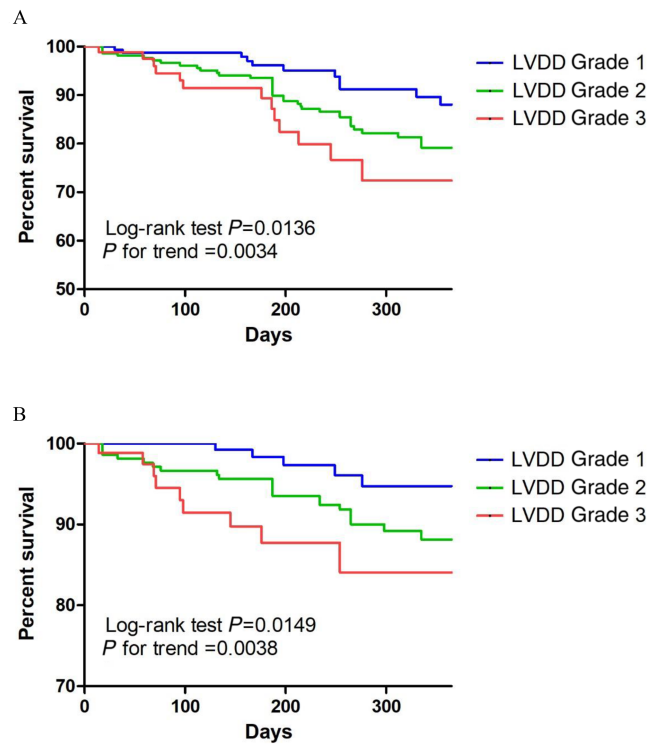
FIGURE 4 The Kaplan–Meier curves of lower extremity arterial disease patients who underwent endovascular therapy by grade of left ventricular diastolic dysfunction (LVDD) for (A) major cardiovascular events and (B) all-cause mortality.
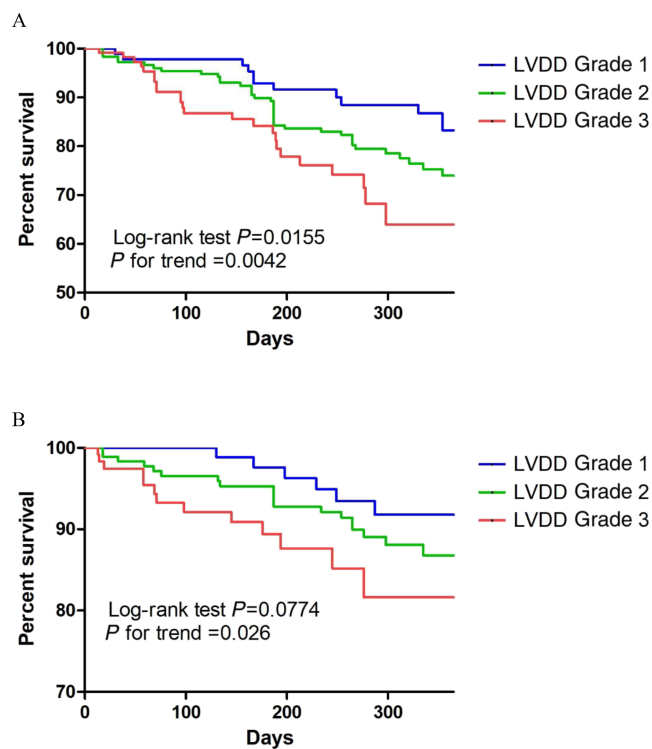
Conclusions

Our results showed that the grade of diastolic dysfunction is highly associated with the severity of LEAD. Furthermore, it also significantly related to clinical outcome of patients with LEAD in terms of MACE and mortality. The new LVDD grading system for 2016 may provide an alternative risk evaluation in LEAD patients and may thus aid in the identification of high-risk individuals before treatment.

Conflict of interest

None declared.

Funding

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