Prognostic Implications of Left Ventricular Global Longitudinal Strain in Predialysis and Dialysis Patients

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Chronic kidney disease (CKD) is a worldwide growing epidemic associated with an increased risk of cardiovascular morbidity and mortality. Left ventricular (LV) global longitudinal strain (GLS) is a measure of LV systolic function associated with prognosis in the general population. However, little is known about the association between LV GLS and survival in patients with CKD. The aim of the present study was to investigate the prognostic implications of LV GLS in predialysis and dialysis patients specifically. LV GLS was measured in a retrospective cohort of predialysis and dialysis patients (CKD stage 3b to 5) who underwent clinically indicated echocardiography between 2004 and 2015. Patients were divided into 4 groups according to quartiles of LV GLS: first quartile (LV GLS ≤10.6%, worst function), second quartile (LV GLS 10.7% to 15.1%), third quartile (LV GLS 15.2% to 17.8%), and fourth quartile (LV GLS ≥17.9%, best function). The primary end point was all-cause mortality. Of 304 patients (62 ± 14 years, 66% male), 65% were in predialysis and 35% in dialysis. During a median follow-up of 29 months (interquartile range 16 to 58 months), 34% of patients underwent renal transplantation and 36% died. Patients with LV GLS ≤10.6% showed significantly worse prognosis compared with the other groups (log-rank test, p <0.001). LV GLS ≤10.6% was significantly associated with increased risk of all-cause mortality (hazard ratio 2.18, 95% CI 1.17 to 4.06, p = 0.014) after correcting for age, gender, albumin levels, atrial fibrillation, and renal transplantation. In conclusion, in predialysis and dialysis patients, severely impaired LV GLS is independently associated with an increased risk of mortality. **(Am J Cardiol 2017;120:500−504)**

Chronic kidney disease (CKD) is a worldwide growing epidemic associated with an increased risk of cardiovascular morbidity and mortality.[1−4] Heart failure is particularly frequent in patients with CKD.[2] Pressure and volume overload and nonhemodynamic factors associated with CKD induce left ventricular (LV) hypertrophy, reduce capillary density, and increase myocardial fibrosis that lead to LV diastolic and systolic dysfunction.[5] These processes have been proposed as important determinants of increased mortality in this population.[5] LV global longitudinal strain (GLS) assessed with 2-dimensional speckle-tracking echocardiography is a marker of LV systolic function and has been shown to correlate with the extent of myocardial fibrosis.[6,7] The incremental prognostic value of LV GLS over conventional echocardiographic parameters of LV systolic function such as LV ejection fraction has been demonstrated in patients with various cardiovascular diseases (ischemic heart disease, valvular heart disease, and heart failure).[8] However, little is known about the association between LV GLS and prognosis in patients with CKD. Accordingly, the aim of the present study was to investigate the prognostic implications of LV GLS in predialysis and dialysis patients specifically.

Methods

From a departmental database of predialysis and dialysis patients, those who were clinically referred for transthoracic echocardiography at the Leiden University Medical Center between 2004 and 2015 were identified and included in this retrospective study. Patients were diagnosed with CKD stage 3b to 5 according to the classification of the Kidney Disease: Improving Global Outcomes 2012 Clinical Practice Guideline for the Evaluation and Management of CKD.[9] Patients younger than 18 years, with limited echocardiographic examination or with inadequate image quality for off-line analysis, were excluded. Clinical data were collected through review of the electronic medical records (HiX; ChipSoft, Amsterdam, the Netherlands) and the departmental cardiology information system (EPD-vision; Leiden University Medical Center, Leiden, the Netherlands) and retrospectively analyzed. Patients were followed up for the occurrence of all-cause mortality through case record review and the national death registry. The occurrence of renal transplantation during follow-up was registered through case record review. The institutional review board approved this retrospective analysis of clinically acquired data.

Baseline clinical variables included demographic parameters, cardiovascular risk factors, medication use, and

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laboratory results. Estimated glomerular filtration rate was calculated by the CKD Epidemiology Collaboration (CKD-EPI) equation.[9] Residual renal function was calculated by the creatinine clearance using the concentration of creatinine in a 24-hour urine specimen and the predialysis plasma creatinine concentration.[10]

Patients were imaged in the left lateral decubitus position using commercially available systems (Vivid 7 or E9; General Electric Vingmed, Milwaukee, Wisconsin) equipped with 3.5-MHz or M5S transducers. The echocardiographic data were digitally stored in cine loop format for off-line analysis (EchoPac 112.0.1; GE Medical Systems, Horten, Norway). Linear dimensions of the left ventricle were measured on M-mode recordings from the parasternal long-axis view.[11] From the apical 4- and 2-chamber views, the LV end-diastolic and end-systolic volumes were measured according to the biplane Simpson's method, and LV ejection fraction was derived.[11] Left atrial volume was measured in the apical 4-chamber view using the disk summation technique and was indexed for body surface area. Right ventricular function was assessed by measuring the tricuspid annular plane systolic excursion on the focused apical 4-chamber view of the right ventricle applying anatomical M-mode.[11] Mitral regurgitation severity was graded semi-quantitatively by measuring the width of the vena contracta from color Doppler data.[12] Pulsed wave Doppler recordings of the mitral inflow were used to measure peak E (early diastolic) and A (late diastolic) wave velocities. LV relaxation was assessed with color-coded tissue Doppler imaging measuring the lateral E′ wave velocity of the mitral annulus in the apical 4-chamber view, and the E/E′ ratio was derived as a measure of LV filling pressures.[13] LV GLS was measured using 2-dimensional speckle-tracking echocardiography on standard routine grayscale images of apical 4-, 2-chamber and long-axis views.[14] Conventionally, LV GLS is presented as negative values because it indicates the shortening of the myocardium relative to the original length.[14] However, the magnitude (absolute value) of LV GLS is presented in this analysis.

Categorical variables were presented as numbers and percentages. Continuous variables with a normal distribution were presented as the mean ± SD and those without a normal distribution were presented as the median and interquartile range. Univariate Cox proportional hazard analysis was performed to identify the demographic, clinical, and echocardiographic variables associated with all-cause mortality. Multivariate survival analysis using Cox proportional hazard model was used to determine the independent association between LV GLS and all-cause mortality. LV GLS and LV ejection fraction were not included in the same model to avoid multicollinearity. The occurrence of renal transplantation during follow-up was introduced as a time-dependent covariate. Patients were divided into 4 groups according to quartiles of LV GLS. Cumulative event-free survival rates from the time of echocardiography were calculated using the Kaplan-Meier method and compared across the quartiles of LV GLS. All statistical tests were 2 sided and a p-value of <0.05 was considered statistically significant. Statistical analyses were performed using the SPSS software, version 20.0 (IBM Corp, Armonk, New York).

Table 1
Characteristics of predialysis and dialysis patients

Variable	N=304
Clinical characteristics:	
Age (years)	62 ± 14
Men	200 (66%)
Chronic kidney disease	
Pre-dialysis	197 (65%)
Dialysis	107 (35%)
Dialysis type (haemodialysis)*	82 (77%)
Dialysis vintage (days)*	157 (53-357)
Renal transplantation future	104 (34%)
Heart rate (beats per minute)	73 ± 15
Systolic blood pressure (mmHg)	136 ± 22
Diastolic blood pressure (mmHg)	77 ± 12
Body mass index (kg/m^2)	25 ± 5
NYHA class III-IV	29 (10%)
Smoker	184 (63%)
Diabetes mellitus	90 (30%)
Hypertension	252 (83%)
Hypercholesterolemia	120 (39%)
Previous myocardial infarction	71 (23%)
Previous CABG/PCI	76 (25%)
Peripheral artery disease	52 (17%)
Atrial fibrillation	63 (21%)
Medications:	
Diuretics	198 (67%)
ACE inhibitor/ARB	184 (62%)
Beta-blocker	182 (61%)
Calcium antagonist	119 (40%)
Statin	181 (61%)
Antiplatelet	99 (33%)
Oral anticoagulation	83 (28%)
Nitrates	34 (11%)
Laboratory results:	
Residual renal function (ml/min)*	5.3 (2.2-8.9)
eGFR CKD-EPI (mL/min/1.73m^2)†	18 ± 7
Creatinine (umol/L)†	312 ± 116
Urea (mmol/L)	22 ± 7
Corrected calcium (mmol/L)	2.2 ± 0.1
Phosphate (mmol/L)	1.4 ± 0.4
Parathyroid hormone (pmol/L)	16 (8-25)
Albumin (g/L)	41 ± 6
Glucose (mmol/L)	6 ± 3
LDL-cholesterol (mmol/L)	2.4 ± 1.1
Hemoglobin (mmol/L)	7.2 ± 1.0

Continuous data are presented as mean ± SD or median (interquartile range). Categorical data are presented as numbers and percentages.

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; CABG = coronary artery bypass graft; CKD-EPI = chronic kidney disease epidemiology collaboration; eGFR = estimated glomerular filtration rate; LDL = low-density lipoprotein; NYHA = New York Heart Association; PCI = percutaneous coronary intervention.

* Measured only in dialysis patients.

† Measured only in predialysis patients.

Results

A total of 304 patients (66% men, mean age 62 ± 14 years) were included. Tables 1 and 2 summarize the clinical and echocardiographic characteristics of the overall patient population. During a median follow-up duration of 29 months (interquartile range 16 to 58 months), 104 (34%) patients underwent renal transplantation and 108 (36%) patients died.