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The prognostic value of left ventricular global peak systolic longitudinal strain in chronic peritoneal dialysis patients

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A B S T R A C T

Background: Although left ventricular (LV) global systolic longitudinal strain (GLS) reliably and accurately assesses LV systolic function and is also a powerful prognostic predictor, the importance and prognostic value of GLS in end-stage renal disease patients receiving maintenance peritoneal dialysis (PD) remain unclear. This study sought to determine the prognostic value of GLS in chronic PD patients.
Methods: This prospective study collected clinical and echocardiographic data from 106 stable PD patients (50.0 ± 13.9 years, 45% male) in a dialysis unit of a university hospital. These patients were enrolled from April 2010 to June 2010 and followed until August 2013 (follow-up duration 30.3 ± 14.3 months). The primary outcomes were the presence of major adverse events (MAEs), defined as all-cause mortality, and major adverse cardiovascular cerebral events (MACCEs), i.e. cardiovascular death, cardiac hospitalization, and stroke.
Results: Twenty-nine patients (27%) reported a primary outcome. Patients with MAEs had worse LV systolic function (MAEs vs. no MAEs, -14.8 ± 2.8 vs. $-17.1 \pm 2.5\%$, $p = 0.003$). Using multivariate Cox regression analyses, being male, having a history of heart failure, diabetes mellitus, an increased pulse pressure ($\geq$60 mm Hg), and GLS $\geq -15\%$ were independent predictors of MAEs. The independent risk factors of MACCEs were a history of diabetes mellitus, an increased pulse pressure, and GLS $\geq -15\%$. After comparison of the overall log likelihood χ^2 of the predictive power, GLS was found to add prognostic information to a model based on traditional risk factors.
Conclusion: GLS $\geq -15\%$ provided additional prognostic information that allowed for the early identification of high-risk PD patients.

1. Introduction

Despite significant advances in dialysis, mortality and morbidity in end-stage renal disease (ESRD) patients receiving maintenance hemodialysis or peritoneal dialysis (PD) remain high and are important unresolved issues [1,2]. The identification of high-risk patients would allow physicians to optimize therapeutic interventions, which may lower morbidity and mortality. Cardiovascular diseases, such as left ventricular (LV) hypertrophy, coronary artery disease (CAD), and heart failure (HF), frequently occur in dialysis patients [3–5]. Importantly, cardiac structural and functional abnormalities are associated with high mortality in ESRD patients [6–8]. Although cardiac geometry and function in ESRD patients have been extensively studied using conventional echocardiography, this method provides a semi-quantitative evaluation and cannot detect subclinical cardiac dysfunction [9].

Compared with conventional echocardiographic measurements, speckle-tracking echocardiography (STE) with myocardial deformation analysis (2D strain) is a more accurate, objective, reproducible, and sensitive modality for assessing cardiac function, even among HF patients with preserved LV ejection fraction (LVEF) and chronic kidney disease patients [10–14]. Previous studies indicated that LV global peak systolic longitudinal strain (GLS) is a load-independent measurement of LV systolic function [14–17]. In the general population, GLS is a powerful prognostic predictor [18,19]. Nevertheless, the prognostic role of GLS has not been validated in PD patients. Thus, we conducted a prospective observational study to assess the prognostic role of GLS in chronic PD patients.

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2. Methods

ESRD patients on continuous PD therapy over 3 months were eligible for this study. These patients were prospectively screened in a single PD unit of the National Cheng Kung University Hospital in Tainan, Taiwan. Patients who were between 18 and 80 years of age, did not have an obvious volume overload, and were willing to join this study were enrolled from April 2010 to June 2010. The exclusion criteria included HF, diagnosed according to the European Society of Cardiology HF criteria [20], presenting with pulmonary edema in the past 6 months, history of acute coronary syndrome in the past 6 months, chronic atrial fibrillation, moderate to severe valvular heart disease (including mitral/aortic regurgitation or stenosis), and inadequate echocardiographic imaging quality. The study adhered to the Declaration of Helsinki and was approved by the Human Research and Ethics Committee of National Cheng Kung University Hospital (IRB number: ER-98-219). All enrolled patients provided informed consent.

Clinical information on co-morbidities, medical history, and current cardiovascular medications was obtained by careful review of each patient's medical record and a self-reported questionnaire. Patient compliance with prescribed medication regimens was reliably ascertained. All participants were primarily dialyzed using conventional lactate-buffered glucose-based PD solutions. Residual renal function (RRF) and daily urine volume were measured from a 24-hour urine sample. RRF was calculated as the mean of the 24-hour creatinine clearance and urea clearance normalized to the standard body surface area of 1.73 m^2 [21]. Patients with a urine volume less than 100 ml/day were assumed to have no RRF. PD adequacy was evaluated by the total weekly Kt/V (product of dialyzer urea clearance and treatment time divided by the urea compartment volume), equal to 7 ∗ (24-hour urea clearance / total body water), with total body water estimated using the Watson formula [22].

After the patient was recumbent for 15 min during the echocardiographic examination, brachial arterial blood pressure was measured by a trained nurse using a validated sphygmomanometer as previously described [23]. Pulse pressure was calculated as the difference between the systolic and diastolic blood pressures. A pulse pressure $\geq$ 60 mm Hg is associated with an increased risk of mortality in PD patients; therefore, the cut-off point for an increased pulse pressure was defined as 60 mm Hg [24].

2.1. Biochemical analysis

Blood samples were collected upon study enrollment. Serum levels of creatinine, hemoglobin, cholesterol, triglycerides, low-density lipoprotein cholesterol, calcium, phosphate, and albumin were measured using routine methods.

2.2. Echocardiography measurements and analysis

All the patients were examined in the left lateral decubitus position using an ultrasound system with a 3.5-MHz probe (Vivid-i, GE Healthcare, Horten, Norway) by one experienced cardiologist and one well-trained echocardiographer who were blinded to all clinical details of the patients. According to the recommendations of the American Society of Echocardiography [25], quantification of the LV mass index (LVMi), LVEF, and left atrial volume index (LAVi) was performed. LV hypertrophy was defined as LVMi > 115 g/m^2 for men and > 95 g/m^2 for women. Pulse tissue Doppler imaging of the mitral annulus movement was performed in the apical 4-chamber view when a sample volume was first placed at the septal side and then at the lateral side of the mitral annulus. To obtain the peak systolic (s′) and early diastolic (e′) velocities, we measured 3 end-expiratory beats and averaged these values for further analysis. We used the average e′ velocity acquired from the septal and lateral sides of the mitral annulus to calculate the ratio of the mitral inflow E velocity to the e′ velocity (average $E/e' = E / [(e'_{septal} + e'_{lateral}) / 2]$). Two-dimensional gray-scale images in three standard apical views (i.e., apical 4-chamber, apical 2-chamber, and apical long-axis) for three cardiac cycles were acquired and stored digitally with a frame rate of 50–90 frames/s for subsequent off-line analysis.

Using automated function imaging (AFI) software (EchoPAC work station, BT11, GE Healthcare, Israel), off-line image analysis was performed by two cardiologists who were blinded to the patient clinical information. Strain and strain rate were measured using the following protocol [11,14,17]. The peak systolic longitudinal strain was obtained from the 3 standard apical views by AFI software, and the average value of peak systolic longitudinal strain from 3 apical views was regarded as GLS (Supplemental figure). Longitudinal systolic strain rate was automatically obtained from the three standard apical views, and six LV segments in the para-sternal short-axis view at the mid-papillary level were then examined to obtain the circumferential strain and systolic strain rate.

2.3. Follow-up and outcome measurements

The patients regularly visited our PD clinic from the day of enrollment until death, cessation of PD, or end of the study. There was only one patient with whom we could not follow up because of immigration to another country. The medical records of enrolled patients during the follow-up period (April 2010 to August 2013) were carefully reviewed. The primary outcomes were major adverse events (MAEs), including all-cause mortality, cardiovascular death, cardiac hospitalization due to cardiovascular events (e.g., decompensated HF with pulmonary congestion, CAD, fatal or non-fatal myocardial infarction (MI), or electrocardiographically documented arrhythmia requiring hospitalization; Supplemental Table 1), scheduled coronary revascularization (i.e., percutaneous transluminal coronary angioplasty and/or coronary artery bypass surgery), thromboembolic or hemorrhagic stroke, or newly diagnosed peripheral artery disease. The secondary outcomes were major adverse cardiovascular cerebral events (MACCEs) [26], i.e., MAEs other than non-cardiovascular death.

2.4. Statistical analysis

Continuous data are presented as the mean ± standard deviation or as the median (interquartile range), depending on the distribution. Dichotomous data are presented as numbers and percentages. Comparisons were conducted using Student's *t*-test or the Mann–Whitney U test for continuous variables, which showed a normal or non-parametric distribution, respectively. A chi-square test or Fisher's exact test was used for categorical variables where appropriate. The relationships between continuous variables were evaluated using Pearson correlation analysis.

We did the receiver operating characteristic (ROC) curve analysis and calculated the areas under the ROC curves (AUC) to evaluate the prognostic performance of different LV echocardiographic parameters for MAEs and MACCEs.

Patients were stratified into two groups according to their GLS value. The Kaplan–Meier method was used with a log-rank test to compare event-free rates between strata. In this analysis, patients who received renal transplantation or were permanently transferred to hemodialysis were censored at the time of alternative renal replacement therapy (RRT). A patient was not censored when he or she reached one of the endpoints within 3 months of transferring to another RRT because such an event should be considered as a reflection of health status during the PD period.

A univariate Cox regression analysis was performed to evaluate factors associated with MAEs or MACCEs. Factors with $p < 0.1$ based on a univariate analysis were used in the multivariate Cox regression analysis to investigate risk factors for MAEs and MACCEs. The final multivariate Cox regression models were validated by a bootstrap resampling procedure with 3000 samples [27,28].