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***Retrospective Study***

**Global longitudinal strain is superior to ejection fraction for detecting myocardial dysfunction in end-stage renal disease with hyperparathyroidism**

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## **Abstract**

### **BACKGROUND**

The estimation of left ventricular ejection fraction (LVEF) by 2D echocardiography (2D-ECHO) is the most used tool to assess LV systolic function (LVSF). Global longitudinal strain (GLS) has recently been suggested as a superior method for several evaluations. This study explored the association and prevalence of LV systolic dysfunction (LVSD) by using these methods in patients with end-stage renal disease (ESRD) and severe hyperparathyroidism (SHPTH); both associated with cardiovascular events (CEs).

### **AIM**

To evaluate the myocardial function in patients with ESRD and SHPTH by using the GLS and LVEF measured through conventional 2D-ECHO.

### **METHODS**

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In 62 patients with ESRD and SHPTH, asymptomatic, and without a history of CEs, LVSF was evaluated by 2D-ECHO, obtaining the EF, by the Simpson biplane method, and GLS by speckle tracking.

## RESULTS

The total patients with ESRD had a preserved LVEF (> 50%) but abnormal GLS (< 13.55%). Additionally, multivariate analysis showed an independent association of GLS and serum parathyroid hormone (PTH), LV mass index, and hemoglobin. Also, PTH was independently associated with lateral e' wave and tricuspid regurgitation velocity.

## CONCLUSION

In patients with SHPTH linked to ESRD, the use of GLS by 2D-ECHO is a more sensitive tool than LVEF for detecting LVSD.

**Key Words:** Left ventricular hypertrophy; Systolic dysfunction; Global longitudinal strain; End-stage renal disease; Parathormone

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**Core Tip:** This study compared global longitudinal strain (GLS) with the often-used left ventricular ejection fraction to estimate ventricular dysfunction in patients with end-stage renal disease. GLS had an advantage to detect dysfunction, but also, it was found that the parathyroid hormone levels were attractive as a complementary tool to predict patient status.

## INTRODUCTION

Cardiovascular disease (CVD) is the most common cause of morbidity and mortality in patients with end-stage renal disease (ESRD). Heart failure (HF) is a cardiovascular event (CE) that may occur simultaneously in these patients<sup>[1-3]</sup>. Chronic elevated pressure, volume overload and nonhemodynamic factors including inappropriate activation of the renin-angiotensin-aldosterone system (RAAS) and alterations in calcium-phosphorus mineral metabolism by an excess of parathyroid hormone<sup>[4,5]</sup> are involved in left ventricular hypertrophy (LVH)<sup>[6,7]</sup>, then, in the myocardial dysfunction in ESRD<sup>[3,8]</sup>.

LV ejection fraction (LVEF) calculated by 2D echocardiography (2D-ECHO) is the most widely used echocardiographic parameter that provides objective information on LV systolic function (LVSF), and it has been used as a prognostic and treatment indicator for CVD<sup>[9-11]</sup>. However, in some studies involving patients with ESRD, LVEF fails as a sensitive parameter for detecting subclinical data of LV systolic dysfunction (LVSD). In this sense, research groups have explored new variables and methods to increase the early and efficient diagnosis and prognosis of patients with LVSD<sup>[12]</sup>. Thus, for example, determination of left atrial volume<sup>[13]</sup>, natriuretic peptides (NPs)<sup>[14]</sup> and catecholamines metabolites in serum (related to sympathetic overactivity)<sup>[15]</sup> have been proposed as advantageous tools.

Special attraction is on alternative 2D-ECHO methods, specifically, predialysis and peritoneal dialysis patients with preserved LVEF (> 50%) showed reduced GLS (15%), which was associated with an increased risk of HF hospitalization and increased mortality<sup>[3]</sup>. Thus, GLS may be a better tool to assess subclinical changes in LVSD in particular cases, for example, where the LVEF is preserved as in those patients subject to volume or pressure overload, or both<sup>[3,16]</sup>. Additionally, studies have mentioned that the variables used to define a preserved LVEF and a reduced GLS are associated with differences between the characteristics of the population studied (race, stage of ESRD, risk factors, and comorbidities). However, despite this variability, GLS is an important

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echocardiographic tool that might be used in patients with ESRD to identify those with a high-risk prognosis for developing HF or other CEs.

In the present study, a comparison was made from echocardiographic changes in patients with ESRD and hyperparathyroidism, the degree of LV remodeling, LVSF using 2D-ECHO, EF (by Simpson's method), and GLS (by Speckle tracking). Additionally, plasma parathyroid hormone (PTH) concentration was considered to increase ability to detect LVSD in patients with ESRD and hyperparathyroidism (a common hormone elevated in ESRD, but poorly explored or linked to CEs in these patients).

## **MATERIALS AND METHODS**

This study was done in patients with asymptomatic ESRD with renal replacement therapy (RRT; dialysis and hemodialysis) and with no history of CEs. The degree of LVDD (I, II or III) was assigned by applying the Nagueh SF, 2020 recommendations<sup>[17]</sup>, and the measurement of plasma PTH in relation to the LVSF and LV diastolic function (LVDF) was explored.

This retrospective and observational study included a total of 77 individuals divided into three groups: healthy individuals with no known disease (Control;  $n = 15$ ), age > 18 years, both genders; patients with ESRD on hemodialysis (ESRD-HD;  $n = 31$ ) and patients with ESRD on peritoneal dialysis (ESRD-PD;  $n = 31$ ). The ESRD groups came from the Nephrology service of Centro Médico SXXI, IMSS. This study was carried out from February 2019 to October 2020.

All patients with ESRD maintained their RRT and were supplemented with calcium and calcitriol following clinical practice guidelines<sup>[18]</sup>. Those individuals with hemodynamic alterations increasing risk on their physical integrity were excluded. A complete medical history was taken. Demographic, clinical and comorbid characteristics were collected. A blood sample was collected in the morning before the RRT, and 4 h later, echocardiography was performed.

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### ***Echocardiography***

Transthoracic echocardiography images were obtained using a commercially available ultrasound system (Ecocardiograph iE33; Philips). Standard 2D Doppler, color, pulsed and continuous wave echocardiographic acquisitions were made. LV dimensions were obtained from images in a long axis parasternal view, and LV mass and body surface area-corrected indexed LV mass were calculated. In addition, the relative wall thickness was obtained as a ratio of  $(2 \times \text{RWTd}) / \text{LVIDd}$ , where RWTd is the back-wall thickness, and LVIDd is the internal diameter of the LV at the end of diastole. The LV end-diastolic and systolic volumes were then measured from the apical views (two and four chambers) using the Simpson biplane method<sup>[19]</sup>. Mitral annulus early diastolic velocity ( $E'$ ) was identified by tissue Doppler imaging in a four-chamber view. Mitral inflow velocities, such as transmitral peak early passive filling velocity ( $E$ ), late diastolic filling velocity caused by atrial contraction ( $A$ ), and deceleration time, were determined using Pw-Doppler over the mitral valve in four-chamber views. The degree of diastolic dysfunction of each patient was assessed<sup>[17]</sup>.

GLS was evaluated by obtaining LV grayscale scatter images from all three apical views. From the 2D images, the endocardial border was manually drawn during the end of the systole, and the thickness of the myocardial region of interest was adjusted to include the entire thickness of the myocardial wall. In each echocardiographic view, the myocardium was automatically divided into six segments. Therefore, the overall maximum systolic longitudinal pressure was calculated by averaging the maximum systolic values of all 18 segments, derived from the three apical views (six segments in each apical view) adjusted to the heart rate.

### ***Biostatistics***

Continuous variables are expressed as the mean  $\pm$  SD. Continuous variables were compared between groups using ANOVA and then a  $\chi^2$  test. A multivariate logistic regression analysis was used, which included the clinical and echocardiographic parameters associated with the univariate analysis as independent variables.  $P < 0.05$

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was considered statistically significant. The statistical analysis was performed with SPSS version 20.

## **RESULTS**

The characteristics were as follows from the total population: 48 participants were female (62%) and 29 (38%) male. According to the division, in the control group, the age was  $34 \pm 13$  years, body mass index (BMI)  $23.4 \text{ kg/m}^2$ , 67% female and 33% male, without relevant comorbidities. The ESRD-HD group age was  $36 \pm 2$  years, BMI  $23.3 \text{ kg/m}^2$ , 84% female and 16% male, 90% presented with hypertension and 6.45% with type 2 diabetes mellitus (T2DM). In the ESRD-PD group, age was  $34 \pm 10$  years, BMI  $22.4 \text{ kg/m}^2$ , 39% female and 61% male, all presented with hypertension, and 16% with T2DM (Table 1).

Patients with ESRD had severe refractory hyperparathyroidism ( $\text{PTH} > 650 \text{ pg/mL}$ ), but calcium ( $\text{Ca}^{2+}$ ), phosphorus (P), and calcium/phosphorus ( $\text{Ca}^{2+}/\text{P}$ ) ratio levels were within normal ranges. There was no significant difference from the control group, suggesting an average plasma calcitriol level. All of our population with ESRD showed LVH. LV mass and LV mass index (LVMI) were substantially increased; LVH concentric type was predominant (ESRD-HD = 80.65% and ESRD-PD = 93.35%) (Table 2).

The 2D-ECHO variables of the population studied are shown (illustrative case in Figure 1), demonstrating that by Simpson's method, LVEF was preserved, while the GLS was substantially reduced compared to the control group ( $21\% \pm 0.58\%$  *vs*  $13.93\%$  and  $13.18\%$ ;  $P < 0.0001$ ; control *vs* ESRD-HD and ESRD-PD). The average GLS was  $-13.55\%$  in all populations with ESRD. This shows that LVEF does not establish systolic dysfunction in patients diagnosed with ESRD, even though they have systolic dysfunction by GLS evaluation (Table 3).

In the bivariate analysis, an association of GLS with hemoglobin, hypertension, PTH, LVH and LVMI was shown. In comparison, the multivariate analysis showed an independent association of GLS and hemoglobin, PTH and LVMI (Table 4).



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This study analyzed the LVDF by obtaining the pattern of transmitral flow rates and their relationship with the tissue velocities at the mitral ring level. The above is related to the fact that the increase in LV filling pressures is the primary physiological consequence of LVDD. These variables were significantly altered in the ESRD population compared to the controls (Table 3).

The tricuspid regurgitation velocity (TRV) and E/e' ratio associated with the decrease in the E/A ratio and the e' septal lateral waves reflect the pattern of altered relaxation and myocardial distensibility during the diastolic phase. Previously reported recommendations were applied<sup>[17]</sup>, and it was found that among individuals with ESRD-HD, 67.74% (*n* = 21) had grade I, 22.58% (*n* = 7) grade II, and 9.67% (*n* = 3) grade III LVDD. Among individuals with ESRD-PD, 84.37% (*n* = 27) had grade I and 15.63% (*n* = 4) had grade II LVDD. The univariate and multivariate analyses (Table 5) showed the associations between the variables studied and PTH. An independent association of serum PTH and lateral e' wave and TRV was shown.

## **DISCUSSION**

Despite the extended use of EF to evaluate myocardial dysfunction, recent proposals promise to improve detection of cardiovascular dysfunction. As an example, 2D-ECHO for measuring left atrial volume is useful to predict diastolic dysfunction in ESRD patients<sup>[13]</sup>. Measuring plasma biomarkers has been suggested to extend diagnostic advantages. Thus, plasma NP levels are reported to be linked to cardiac remodeling<sup>[18]</sup>, survival<sup>[19]</sup> and volume expansion-related LV disorders<sup>[20]</sup> in patients with ESRD<sup>[14]</sup>.

Currently, 2D-ECHO methods remain core in diagnosis and evaluation of patients with CEs. The identification of LV strain changes is crucial for early cardiac damage detection in ESRD<sup>[21-24]</sup>. This study showed that increased LVMI, low hemoglobin levels but high PTH are independent factors associated with GLS alterations. The overall average GLS was 13.55%, with LVEF > 50% in the patient population, which according to the literature, is related to poor prognosis<sup>[25-29]</sup>. In this case, it was suggested that in the population with ESRD, the determination of GLS by 2D-ECHO is highly

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recommended for the assessment of LVSF; being a more powerful tool than LVEF, which can identify systolic myocardial damage<sup>[3,18,19]</sup> during follow-up of patients<sup>[29]</sup>.

In patients with ESRD, bone mineral disorder is correlated with adverse outcomes from cardiovascular causes<sup>[25,30,31]</sup>. Recently, the mineral disorders in the early stages of ESRD have been associated with myocardial remodeling, which is a crucial point for LVH development<sup>[31-33]</sup>. In our study population, the presence of LVH was 100%, with a predominance of the concentric type. In this regard, some studies have directly implicated hyperphosphatemia and hypercalcemia in developing LVH<sup>[7,30]</sup> by regulating several factors<sup>[31,34-36]</sup>. However, it must be considered that the kidney is an essential target organ for PTH, and the interaction with its receptor activates multiple signaling pathways<sup>[37-39]</sup>, triggering numerous changes in the kidney and some other systems<sup>[40]</sup>. As strong evidence of the PTH role in cardioremodeling, studies have shown that patients undergoing parathyroidectomy (PTX) have a substantial reduction in LV mass<sup>[41]</sup>; in contrast, patients with severe hyperparathyroidism and PTX showed a significant decrease in the risk of death from all causes<sup>[42]</sup>. Patients in the current study were supplemented with calcium or analogs; plasma values of Ca, P and Ca/P ratio were within normal ranges, while PTH levels were higher than reference values (PTH > 650 pg/mL). Multivariate analysis showed an independent association of GLS and PTH, suggesting a putative role of PTH in LVSF by diverse mechanisms, including those related to remodeling of subendocardial fibers<sup>[43]</sup>.

Additional research is required to elucidate the mechanisms involved in the PTH modulation of the structure and function of the cardiomyocytes, as the pleiotropic effects are attributed to the interaction of PTH with its receptor <sup>[33,40]</sup>.

PTH serum levels showed an independent association with some diastolic function parameters (Table 5): Particularly e' lateral wave and TRV. The alterations in diastolic function primarily involve the mechanisms of myocardial relaxation and compliance. The signaling pathways involving remodeling and cardiac fibrosis in patients with ESRD are complex and multifactorial, involving alterations in the extracellular matrix proteins, type I collagen, elastin, fibroblasts, and myofibroblasts<sup>[9,44-46]</sup>, which reduce

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myocardial compliance. These effector pathways involve PTH and 25-hydroxy vitamin D3 and several other factors<sup>[34-39,46-51]</sup>. Elevated levels of catecholamine by sympathetic overactivity are reported to be linked to LV disorders and volume excess in ESRD patients<sup>[15]</sup>.

Finally, our results are in line with recent reports supporting that conventional speckle-tracking echocardiography<sup>[52-54]</sup> might help identify LVSD in patients with ESRD and preserved LVEF. Early detection of myocardial morphological and functional changes in the routine evaluation of patients with ESRD can tackle the early stages of disease-independent modifiable risk factors that are associated with adverse CEs.

## **CONCLUSION**

An accurate diagnosis is increasingly important in this type of patient with ESRD with systolic and diastolic myocardial function evaluation, offering integrated, lower cost, and noninvasive information. The use of new diagnostic tools is essential to provide the population with new targeted therapies for defined subsets of patients who may be at risk of developing potential complications. The use of GLS by 2D-ECHO is a more sensitive tool than LVEF to detect of LVSD. For individuals with ESRD and severe hyperparathyroidism refractory to hormone replacement but with normal Ca/P levels, it is essential to recommend the use of GLS as a diagnostic and prognostic tool for systolic myocardial dysfunction; albeit if patients have preserved LVEF.

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