Left Ventricular Function

Association of Subtle Left Ventricular Systolic Dysfunction with Elevated Cardiac Troponin T in Asymptomatic Hemodialysis Patients with Preserved Left Ventricular Ejection Fraction

Yen-Wen Liu,[1,2] Chi-Ting Su,[3] Chih-Chen Chou,[1] Saprina P.H. Wang,[4] Chun-Shin Yang,[5] Yao-Yi Huang,[2] Liang-Miin Tsai,[1] Jyh-Hong Chen[1] and Wei-Chuan Tsai[1]

Background: Increased cardiac troponin T (cTnT) concentrations are associated with a poor prognosis in end-stage renal disease (ESRD) patients. However, the impact of increased cTnT levels on left ventricular (LV) function is not well understood. Therefore, our study focused on LV function in asymptomatic hemodialysis patients with preserved left ventricular ejection fraction (LVEF) and elevated cTnT levels.

Methods: Asymptomatic ESRD patients undergoing maintenance hemodialysis, with LVEF ≥ 50%, underwent echocardiographic examination and further testing to determine serum cTnT, high-sensitivity C-reactive protein (hsCRP) and albumin levels. Subjects were then stratified into one of two groups based on the cTnT level, with a cutoff value of 0.04 ng/mL.

Results: There were no significant differences in gender, age, LVEF, systolic myocardial velocity, and the prevalence of comorbidities (except diabetes mellitus) between these two groups. Patients in the high cTnT group (≥ 0.04 ng/mL) presented with higher hsCRP levels than patients in the low cTnT group (1.50 ± 0.35 mg/dL vs. 0.59 ± 0.62 mg/dL, p = 0.02). Additionally, reduced global LV peak systolic longitudinal strain (GLS) developed in the high cTnT group compared with the low group (-17.1 ± 3.7% vs. -19.4 ± 3.5%, p = 0.004). The deteriorated GLS was an independent factor correlated with higher cTnT levels in asymptomatic hemodialysis patients with preserved LVEF (p = 0.013, 95% CI = 0.71-0.96).

Conclusion: Patients in the high cTnT group presented with higher levels of hsCRP and more reduced GLS than those in the low cTnT group, and reduced GLS was the independent factor of elevated cTnT level. Consequently, we concluded that those asymptomatic hemodialysis patients with elevated cTnT concentrations had LV systolic dysfunction.

Key Words: Cardiac troponin T • End-stage renal disease • LV systolic function • Speckle tracking echocardiography • Strain

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[1]Division of Cardiology, Department of Internal Medicine, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan; [2]Division of Cardiology, Department of Internal Medicine, National Cheng Kung University Hospital Dou-Liou Branch; [3]Division of Nephrology, Department of Internal Medicine, National Taiwan University Hospital Yun-Lin Branch, Yun-Lin; [4]Graduate Institute of Biomedical Engineering, National Cheng Kung University, Tainan; [5]Division of Nephrology, Department of Internal Medicine, Catholic Fu-An Hospital, Yun-Lin, Taiwan.
Address correspondence and reprint requests to: Dr. Wei-Chuan Tsai, Department of Internal Medicine, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, No. 138, Shengli Road, Tainan 704, Taiwan. Tel: 886-6-235-3535 ext. 2388; Fax: 886-6-275-3834; E-mail: wctsai@ksmail.seed.net.tw

INTRODUCTION

Cardiovascular disease (CVD) accounts for the majority of mortality and morbidity in patients with end-stage renal disease (ESRD). Abnormal left ventricular (LV) geometry and function are common in ESRD patients, including LV hypertrophy, LV dilatation, as well as impaired LV systolic and/or diastolic functions. These cardiac abnormalities are assumed to be correlated with a poor cardiovascular prognosis among ESRD patients.[1] Cardiac troponin T (cTnT) is an intact molecule and fre-

quently increased in a proportion of ESRD patients undergoing dialysis.[2,3] Furthermore, it was reported that cTnT might be useful for screening alternations of LV function in hemodialysis patients with LV hypertrophy.[4]

Cardiac function in ESRD patients has been studied extensively by conventional echocardiographic parameters, including cardiac output, fractional shortening, and ejection fraction (EF). These measurements, however, only permit semi-quantitative evaluation, and are insensitive in the early detection of subtly deteriorating cardiac function.[5] Convincing evidence has recently shown that 2-dimensional speckle tracking echocardiography with myocardial deformation analysis (i.e., STE or 2D strain imaging) is a novel, sensitive, objective, and more reproducible modality for assessing the subtle deterioration of cardiac function.[6,7] Among chronic kidney disease patients with preserved LVEF (LVEF ≥ 50%), 2D strain imaging analysis is an efficient tool to detect subtle deterioration of LV systolic function.[8] To date, the impact of elevated cTnT on LV function is not well-illustrated in asymptomatic hemodialysis patients with preserved LVEF. We conducted the present study to explore the association between cTnT levels and LV systolic function by 2D strain imaging in ESRD patients with preserved LVEF.

MATERIALS AND METHODS

Study design

Adult ESRD patients receiving maintenance hemodialysis program, thrice weekly over 3 months, were prospectively enrolled from two community hospitals in Yun-Lin County, Taiwan: National Cheng Kung University Hospital Dou-Liou Branch, and Catholic Fu-An Hospital. Subjects were excluded arising from the following criteria: (1) diagnosis of at least moderate valvular heart disease (including mitral/aortic regurgitation or stenosis); (2) LVEF was < 50%; (3) experience of acute exacerbation of heart failure presenting with pulmonary edema; (4) diagnosis of acute coronary syndrome or atrial fibrillation; (5) over 80 years of age; or (6) inadequate echocardiographic image quality. The study protocol was approved by the Human Research and Ethics Committee of the National Cheng Kung University Hospital. All the enrolled patients gave informed consent.

Clinical information concerning comorbidities, medical history, and current cardiovascular medication was obtained by careful review of each patient's medical record, and a self-reported questionnaire. Patients' compliance with prescribed medication regimens was reliably ascertained. Dialysis adequacy, determined via Kt/V and creatinine clearance, was evaluated based on the recommendations of the Kidney/Disease Outcome Quality Initiative.

Serum biochemistry

Sera were stored at -80 °C until analyses, and thawed to measure the levels of cTnT (4th generation Troponin T STAT immunoassay, ElecSys 2010 System, Roche Diagnostics, Indianapolis, IN, USA), high-sensitivity C-reactive protein (hsCRP, BN II Analyzer, Dade Behring, Glasgow, Delaware, USA), interleukin (IL)-18 (Sandwich ELISA, R&D, Inc., Minneapolis, MN, USA) and carboxy-terminal peptide of procollagen type I (PICP, Orion Diagnostica, Finland). Serum calcium, phosphate, and albumin were measured using routine methods.

Echocardiographic measurements

All patients were examined in the left lateral decubitus position, using a commercially available ultrasound system with a 3.5 MHz probe (Vivid-i, GE Healthcare, Horten, Norway). Tissue Doppler imaging (TDI) and 2D STE were performed as previously described.[6,8] Quantification of LV mass index, volume, and EF was performed according to the recommendations of the American Society of Echocardiography.[9] Left atrial (LA) volume was measured from the standard apical 2- and 4-chamber views at end-systole, and calculated using the biplane area-length method.[9,10] LA volume index (LAVi) was the value of LA volume divided by body surface area.[10] Pulsed TDI of the mitral annulus movement was acquired from the apical 4-chamber view when a sample volume was placed sequentially at the septal and lateral annulus. Peak systolic (S') and early diastolic (e') filling velocities were also measured.[11] Early transmitral velocity to TDI annular early diastolic velocity (E/e') ratio was calculated from the average of the septal and lateral e'. We acquired 2D gray-scale images in the 3 standard apical views (i.e. apical 4-chamber, apical 2-chamber, and api-

cal long-axis) for 3 cardiac cycles and stored digitally with a frame rate of 50-90 frames/second for subsequent off-line analysis.[6,12]

Diameter of the inferior vena cava (IVC)

To evaluate the fluid status of hemodialysis patients, the IVC diameter was measured twice, each at the end of expiration in a subxiphoid location (as described previously).[8] The average value of the measured end-expiratory IVC diameter was defined as IVCe.

Echocardiographic analysis

Two cardiologists (blinded to the patients' clinical information) performed off-line analysis using a commercial software package (EchoPAC work station, BT08, GE Healthcare, Israel). Myocardial deformation was measured as described previously.[6] The peak systolic longitudinal strain was obtained from the three standard apical views by automated function imaging software,[6,8,13,14] and the average value of peak systolic longitudinal strain from the three apical views was characterized as the global LV peak systolic longitudinal strain (GLS). Systolic longitudinal strain rate (LSRs) was simultaneously acquired from these three apical views and averaged for further analysis. Six LV segments on the parasternal short-axis view at the mid-papillary level were also examined to obtain circumferential strain and circumferential strain rate in systole.[8]

Statistical analysis

Continuous data are presented as mean ± standard deviation, and dichotomous data are presented as a number and percentage. Comparisons were carried out using a one-way ANOVA for continuous variables, whereas the chi-square test or Fisher's exact test was used for categorical variables. The relationship among continuous variables was analyzed using linear regression analysis. Stepwise multivariate logistic regression analysis was employed for assessing independent correlated factors. Intra- and inter-rater reliability[8] was assessed for the measurement of strain in two sets of 10 randomly selected subjects using the Bland-Altman limits of agreement.[15] A two-sided p value < 0.05 was considered statistically significant and SPSS software (version 15.0, SPSS Inc, Chicago, IL, USA) was used for statistical analysis.

RESULTS

Clinical characteristics

In total, 109 ESRD patients undergoing maintenance hemodialysis were eligible for inclusion in this study. Patients were subsequently excluded for the following reasons: age ≥ 80 years, atrial fibrillation, severe mitral/aortic regurgitation, LVEF < 50%, or inadequate images for analysis; twenty-four patients (22%) were ultimately excluded. Mean and medium concentrations of cTnT for the enrolled patients were 0.037 ng/mL and 0.04 ng/mL, respectively. Based on the recommendation in previously published studies,[2,3] included patients were categorized into one of two groups according to the cTnT cut-off point of 0.04 ng/mL. Patients in the high cTnT group (n = 38, cTnT ≥ 0.04 ng/mL) were 69.0 ± 10.9 years of age. Patients in the low cTnT group (n = 47, cTnT < 0.04 ng/mL) were 66.0 ± 11.4 years of age. All patients presented with anuria and received adequate hemodialysis (average Kt/V was 1.70 ± 0.26; hemoglobin was 10.2 ± 1.2 mg/dL, and cardiothoracic ratio on chest X-ray was 52 ± 5%). Demographic data, concomitant diseases, and medication(s) have been summarized in Table 1. Patients in the high cTnT group had higher serum hsCRP levels than the low cTnT group (1.50 ± 0.35 mg/dL, vs. 0.59 ± 0.62 mg/dL, respectively, p = 0.02, Table 2).

Evaluation of cardiac function

Conventional and TDI echocardiographic parameters have been summarized in Table 3. All patients showed normal LV end-diastolic volume index (LVEDVi), but had LV hypertrophy. To evaluate LV systolic function, LVEF and S' were measured. No significant difference in these parameters was noted between the two groups of patients. Furthermore, both groups had reverse E/A, high LAVi, and high E/e' values, indicating the presence of increased LV filling pressure, compatible with diastolic dysfunction.

Two cardiologists performed off-line 2D strain imaging analysis (Table 3; note: the more negative value of GLS, the better LV systolic function is). LVEF and S' were not reduced in the high cTnT group; however GLS and LSRs were significantly less negative than in the low cTnT group (Table 3, Figure 1), which indicated that LV systolic function was declined in the high cTnT group. Furthermore, the elevation of cTnT concen-

Table 1. Clinical characteristic of ERSD patients with maintenance hemodialysis

	cTnT ≥ 0.04 ng/ml (n = 38)	cTnT < 0.04 ng/ml (n = 47)	p value
Age (years)	69.0 ± 10.9	66.0 ± 11.4	0.23
Male, n (%)	15 (39.5%)	15 (31.9%)	0.47
BMI (kg/m^2)	22.1 ± 2.7	21.3 ± 3.0	0.19
Heart rate (beats/minute)	83.0 ± 13.5	75.3 ± 11.5	0.08
SBP (mmHg)	145.2 ± 16.6	148.1 ± 14.4	0.41
DBP (mmHg)	76.3 ± 8.7	77.7 ± 9.5	0.52
Hemodialysis duration (years)	6.0 ± 5.0	6.5 ± 4.6	0.68
Clinical characteristics, number (%)			
CAD	15 (39.5%)	14 (29.8%)	0.37
Heart failure under control	5 (13.2%)	4 (8.5%)	0.73
Diabetes mellitus	24 (63.2%)	18 (38.2%)	0.03
Hypertension	33 (86.8%)	40 (85.1%)	1.00
Cardiovascular drugs, number (%)			
CCB	23 (60.5%)	25 (46.8%)	0.57
β-Blocker	17 (44.7%)	22 (46.8%)	0.78
ACE inhibitors/A-II antagonists	18 (47.4%)	29 (61.7%)	0.15
Statin	5 (13.2%)	9 (19.1%)	0.43

ACE, angiotensin-converting enzymes; A-II, angiotensin II; BMI, body mass index; CAD, coronary artery disease; CCB, calcium channel blocker; cTnT, cardiac troponin T; DBP, diastolic blood pressure; ESRD, end-stage renal disease; SBP, systolic blood pressure. Data are expressed as mean ± SD or number (%).

Table 2. Values of serum biomarkers in ERSD patients with maintenance hemodialysis

	cTnT ≥ 0.04 ng/ml (n = 38)	cTnT < 0.04 ng/ml (n = 47)	p value
Calcium (mg/dL)	9.1 ± 0.7	9.3 ± 0.8	0.29
Phosphate (mg/dL)	4.3 ± 1.2	4.5 ± 1.4	0.38
Albumin (g/dL)	3.23 ± 0.37	3.39 ± 0.42	0.07
Cholesterol (mg/dL)	162.9 ± 40.6	162.0 ± 35.5	0.92
Triglyceride (mg/dL)	155.6 ± 56.2	123.4 ± 74.1	0.22
hsCRP (mg/dL)	1.50 ± 0.35	0.59 ± 0.62	0.02
IL-18 (pg/ml)	899.2 ± 413.0	725.6 ± 435.8	0.10
PICP (ng/ml)	876.4 ± 421.1	851.7 ± 363.9	0.79

cTnT, cardiac troponin T; ESRD, end-stage renal disease; HD, hemodialysis; hsCRP, high-sensitivity C-reactive protein; IL, interleukin; PICP, procollagen type I C-terminal peptide. Data are expressed as mean ± SD

trations paralleled the deterioration of LV systolic function (R = 0.451, p < 0.001). Stepwise logistic regression analysis was performed on the significant parameters (i.e. diabetes, hsCRP, GLS, and LSRs) identified by univariate analysis, and GLS (p = 0.013, 95% CI, 0.71-0.96) was the only independent factor of increased cTnT in hemodialysis patients (Table 4).

Evaluation of volume status

In this study, LVEDVi and IVCe were measured to assess the patients' volume status.[8,16] No difference in LVEDVi and IVCe between the two groups was noted (Table 3), and the IVCs were not engorged in either group. These data indicated that the patients included in these two groups were not overhydrated.

Inter- and intra-rater variability

There was no systemic bias detected by Bland-Altman analysis between intra- and inter-rater agreement by using 2D strain imaging analysis. The mean intra- and inter-rater differences [mean ± standard deviation (95% limits of agreement)] were the following: -0.08 ±

Table 3. Echocardiographic results

	cTnT ≥ 0.04 ng/ml (n = 38)	cTnT < 0.04 ng/ml (n = 47)	p value
LV EDVi (ml/m^2)	66.3 ± 15.1	72.1 ± 21.4	0.22
LV mass index (gm/m^2)	155.7 ± 65.1	141.4 ± 37.2	0.26
LV EF (%)	63.8 ± 5.9	65.4 ± 5.5	0.22
Systolic myocardial velocity, S' (cm/sec)	8.4 ± 1.9	8.6 ± 1.8	0.58
LV GLS (%)	-17.1 ± 3.7	-19.4 ± 3.5	0.004
LSRs	-0.92 ± 0.21	-1.01 ± 0.22	0.04
CS (%)	-20.7 ± 5.5	-21.4 ± 6.1	0.61
CSRs	-1.94 ± 0.62	-1.93 ± 0.55	0.93
E (m/sec)	0.79 ± 0.31	0.80 ± 0.31	0.83
A (m/sec)	1.04 ± 0.37	1.03 ± 0.29	0.90
E/A	0.77 ± 0.32	0.83 ± 0.43	0.50
e' (cm/sec)	4.8 ± 1.3	4.9 ± 1.4	0.85
E/e'	16.0 ± 5.4	17.1 ± 8.5	0.48
LAVi (ml/m^2)	35.2 ± 8.7	35.0 ± 7.8	0.93
IVCe diameter (cm)	1.32 ± 0.31	1.23 ± 0.24	0.21

CS, circumferential strain; CSRs, systolic circumferential strain rate; EDVi, end-diastolic volume index; EF, ejection fraction; E/e', early transmitral velocity to tissue Doppler mitral annular early diastolic velocity ratio; GLS, global left ventricular peak systolic longitudinal strain; IVCe, end-expiratory inferior vena cava diameter; LAVi, left atrial volume index; LSRs, systolic longitudinal strain rate; LV, left ventricular. Data are expressed as mean ± SD.

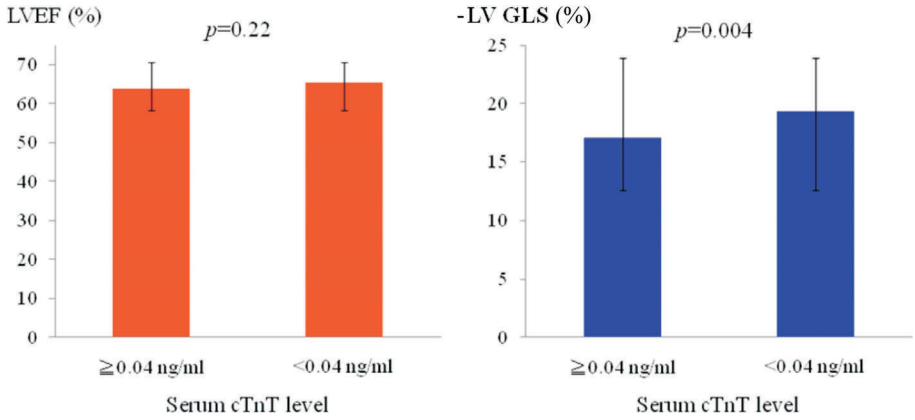

Figure 1. *Comparisons of left ventricular ejection fraction (LVEF), and global LV peak systolic longitudinal strain (GLS) in end-stage renal disease patients with either high (≥ 0.04 ng/mL) or low cTnT (< 0.04 ng/mL) serum concentrations.*

Table 4. Independent factors in hemodialysis patients with increased cTnT level by stepwise multivariate logistic regression analysis

	OR (95% CI)	p value
Clinical characteristics		
Diabetes mellitus	1.04 (0.61-4.94)	0.31
hsCRP (mg/dL)	4.5 (0.36-1.06)	0.08
Echocardiographic parameters		
GLS (%)	8.1 (0.71-0.95)	0.01
LSRs	0.03 (0.08-22.6)	0.85

CI, confidence interval; cTnT, cardiac troponin T; hsCRP, high-sensitivity C-reactive protein; GLS, global left ventricular peak systolic longitudinal strain; LSRs, systolic longitudinal strain rate; OR, odds ratio.

1.14 (-2.32 to 2.16) and 1.40 ± 1.54 (-1.62 to 4.42), respectively, for GLS.

DISCUSSION

This is the first study to show deterioration of LV systolic function, represented as decreased GLS and LSRs in clinically stable hemodialysis patients with preserved LVEF and elevated serum cTnT concentrations. After adjustments for gender, comorbidities, age, and LSRs, GLS was the only independent factor of increased

cTnT levels in clinically stable hemodialysis patients.

Accurately assessing LV systolic function is important in order to prescribe the optimal therapy and evaluate a patient's prognosis. However, LVEF is not a reliable parameter to assess LV systolic function. Using 2D strain imaging analysis, we demonstrated that subtle LV systolic dysfunction develops among patients with advanced-stage CKD, and also in heart failure patients with preserved LVEF.[6,8] In the present study, using 2D strain image analysis, patients with high cTnT levels had more severe cardiac systolic dysfunction than the low cTnT level group. This implied that clinically stable hemodialysis patients with elevated cTnT level and preserved LVEF presented with worse systolic function than those hemodialysis patients without raised cTnT concentrations.

The mechanisms of increased serum cTnT concentrations in asymptomatic hemodialysis patients remain unclear. Possible mechanisms include: alternations in microcirculation,[17] silent ischemic injury,[18] LV hypertrophy,[19] increased LV filling pressure,[3,20] and other myocardial pathologies.[17] In the present study, both groups had diastolic dysfunction, increased LV filling pressure, a similar severity of cardiac fibrosis (as demonstrated by the PICP level), and no significant difference in the prevalence of coronary artery disease (CAD) and congestive heart failure. Furthermore, no correlation between LV mass index and increased cTnT level existed, which may have been due to substantially apparent LV hypertrophy in hemodialysis patients that had been reviewed elsewhere.[2,21] Interestingly, patients in the high cTnT group tend to have high hsCRP levels, which could indicate chronic inflammation in these patients. Besides, the prevalence of diabetes mellitus was higher in the group of patients in the high cTnT group, but diabetes mellitus was not independently associated with elevated cTnT. Apple et al.[22] reported similar findings.

The most noteworthy finding in this study was that LV systolic dysfunction, represented as a decrease in GLS, could develop in hemodialysis patients with increased cTnT levels even without an obvious decline of LVEF. Although myocardial stunning is common in hemodialysis patients and could contribute to the development of heart failure,[23] the mechanisms of LV systolic dysfunction in hemodialysis patients with increased cTnT concentrations are obscure. Previous studies implied that hemodialysis patients with increased cTnT levels presented with significantly greater severity of dilated LV, more impaired LV systolic function, higher LV filling pressure, and higher LV mass index.[3,19,20] Although we did not observe a similar correlation in this study, we did find that ESRD patients with diabetes mellitus had significantly elevated cTnT levels. In postmortem examinations of ESRD patients and in renal failure experimental models, increased cTnT was associated with microvascular disease, decreased capillary density, microinfarct, and myocardial damage.[22-24] Several studies have indicated that diabetes was associated with raised cTnT as well as microvascular disease in ESRD patients.[3,25-27]

Some studies[2,28,29] suggest an association between cTnT concentrations and CAD, but others fail to demonstrate any correlation whatsoever.[3,17,30] Elevation of cTnT in ESRD patients are inconclusive, which implies that the presence of CAD is not presumed to be the sole causal factor. In other words, CAD may not be the sole contributing factor causing deterioration of LV systolic function in ESRD patients with increased cTnT. In ESRD patients, even without CAD, cTnT is indicated as an independent factor with hemodialysis-induced myocardial injury, which is associated with reduced myocardial contractile function.[24] Indeed, diabetic hemodialysis patients, with normal epicardial coronary anatomy, have significantly reduced coronary flow reserve.[31] Therefore, we suggested that the mechanisms of reduced LV systolic function in hemodialysis patients with elevated cTnT concentrations are multi-factorial, and can be caused by a combination of increased LV filling pressures, LV hypertrophy, microvascular disease, decreased capillary density, reduced coronary flow reserve, and hemodialysis-induced myocardial injury.

Sharma et al.[3] demonstrated that high cTnT levels can be a powerful marker of cardiovascular events, and can indicate a poor prognosis in ESRD patients; there was also a strong correlation between poor prognosis and diabetes mellitus, cardiac structural and functional abnormalities.[3] However, elevated cTnT has not been proven to be an indicator of poor prognosis in ESRD patients without heart failure, and in patients with relatively preserved cardiac structure and function. Because LV systolic dysfunction was associated with in-

creased cTnT level in asymptomatic hemodialysis patients with preserved LVEF, strict control of fluid, optimal medical therapy, and coronary revascularization (if indicated) might be necessary in these patients. However, we recognized that further prospective cohort studies are necessary to prove whether asymptomatic hemodialysis patients with preserved LVEF and increased cTnT concentrations have a poor prognosis, and may benefit from intervention to improve prognosis and decrease cardiovascular events.

There are limitations to the current study. The number of enrolled patients was relatively modest. The study design was cross-sectional, and follow-up information of prognosis was not available. In addition, the methods used to evaluate LV diastolic function were relatively limited, but there was no significant difference in diastolic function between the two groups of patients. Furthermore, evaluation of LV diastolic function by 2D strain analysis is not the most reliable method, and may not generate optimal results. Nonetheless, both groups demonstrated LV diastolic dysfunction and increased LV filling pressure.

CONCLUSION

Compared with hemodialysis patients in the low cTnT group (< 0.04 ng/mL), patients in the high cTnT group (cTnT ≥ 0.04 ng/mL) presented with higher hsCRP levels and reduced GLS. Furthermore, reduced GLS is the only independent factor associated with elevated cTnT level. Our study suggests that subtle LV systolic dysfunction existed in clinically stable hemodialysis patients with raised cTnT levels, even though LVEF was preserved.

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