

Original Paper

Serum High-Sensitivity Cardiac Troponin T Is a Significant Biomarker of Left-Ventricular Diastolic Dysfunction in Subjects with Non-Diabetic Chronic Kidney Disease

Masashi Kitagawa^a Hitoshi Sugiyama^{a, b} Hiroshi Morinaga^a
Tatsuyuki Inoue^a Keiichi Takiue^a Yoko Kikumoto^a
Haruhito Adam Uchida^a Shinji Kitamura^a Yohei Maeshima^a
Norihisa Toh^c Kazufumi Nakamura^c Hiroshi Ito^c
Hirofumi Makino^a

^aDepartment of Medicine and Clinical Science, ^bCenter for Chronic Kidney Disease and Peritoneal Dialysis, and ^cDepartment of Cardiovascular Medicine, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan

Key Words

Albuminuria · Annular velocity · Chronic kidney disease · High-sensitivity cardiac troponin T · Left-ventricular diastolic dysfunction · Peak early diastolic mitral annular velocity · Tissue Doppler imaging · Troponin T

Abstract

Background: Chronic kidney disease (CKD) is associated with left-ventricular (LV) diastolic dysfunction (LVDD) which progresses to diastolic heart failure. However, biomarkers predicting LVDD in patients with CKD are largely unknown. **Methods:** In 93 patients with non-diabetic CKD, the relationships among echocardiography, high-sensitivity cardiac troponin T (hs-cTnT), B-type natriuretic peptide (BNP), and renal function were evaluated. LV mass index, peak early diastolic mitral filling velocity (E), peak early diastolic mitral annular velocity (E'), and E/E' were recorded. **Results:** The E' values were significantly decreased and E/E', BNP, and hs-cTnT increased with increasing CKD stage. The CKD patients with LVDD with E' <5 cm/s had a significantly higher hs-cTnT level as well as a significantly higher BNP level compared to those with E' ≥5 cm/s. The area under the receiver-operating characteristic curve for hs-cTnT and BNP to de-

tect $E' < 5$ cm/s was 0.880 ($p = 0.0101$) and 0.741 ($p = 0.0570$), respectively. In multivariate analysis, hs-cTnT and albuminuria were significantly associated with E' , and estimated glomerular filtration rate with the hs-cTnT level, after adjusting for age, cause of CKD, and other parameters. **Conclusions:** These data suggest that hs-cTnT may be a useful biomarker of LVDD in non-diabetic CKD patients.

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Introduction

The prevalence of heart failure with preserved ejection fraction (EF) has increased over time, while the rate of death from this disorder has remained unchanged [1]. Individuals with heart failure with a normal EF are typically older and more likely to be female, and also have a higher likelihood of hypertension, obesity, renal failure, anemia, and atrial fibrillation [1]. In addition, chronic kidney disease (CKD) is associated with an increased mortality in patients with heart failure, and CKD-associated mortality is higher in patients with diastolic than systolic heart failure [2]. The European Working Group on heart failure with a normal EF proposed a new diagnostic algorithm in 2007 [3]. The early diastolic velocity of the longitudinal motion of the mitral annulus (E') reflects the rate of myocardial relaxation. The velocity of the mitral annulus can be recorded by tissue Doppler imaging (TDI), and this has become an essential part of evaluating diastolic function by echocardiography. In patients with a variety of cardiac diseases, the TDI parameters, especially E' , were the most powerful predictors of cardiac death in the subsequent 2 years [4]. Even in the absence of clinical heart failure, left ventricular (LV) diastolic dysfunction (LVDD) is associated with increased rates of future hospitalizations, development of heart failure, and all-cause mortality [5]. Worsening stages of LVDD on echocardiography are associated with an incremental risk in adverse outcomes, including the development of clinical heart failure [6]. Accurately diagnosing LVDD could possibly lead to improved treatments and may have substantial health care implications, from both clinical and resource utilization perspectives.

Cardiac troponin T (cTnT) is the preferred biomarker for the diagnosis of acute myocardial infarction. Elevated troponin levels can be detected in clinical settings in which myocardial injuries occur, as well as in several chronic disease states, including patients with coronary artery disease (CAD), heart failure, and CKD [7–9]. A highly sensitive (hs) assay for cTnT has recently been developed, which determines concentrations that are lower by a factor of 10 than those measurable with conventional assays. In patients with chronic heart failure [10] and chronic CAD [11], circulating cTnT is detectable in almost all individuals with the highly sensitive assay, and higher levels correlate strongly with increased cardiovascular mortality. In patients with renal failure, conventionally assessed cTnT levels may be elevated simply owing to delayed cTnT clearance, but numerous studies have shown the strong prognostic significance of elevated troponin levels in patients with CKD [9, 12, 13].

There have been several reports demonstrating that natriuretic peptides are a valuable tool that can be used to identify patients with severe diastolic dysfunction, however, they do not accurately predict mild or moderate diastolic dysfunction [14–16]. An elevation of B-type natriuretic peptide (BNP) may be a hallmark of diastolic heart failure, independent of LV hypertrophy (LVH) [17]. In patients with heart failure with a normal EF, concentric hypertrophy or remodeling can be observed. In addition, several studies have demonstrated an independent association between troponin levels and the presence of LVH in hemodialysis [18, 19], peritoneal dialysis [20], and non-dialysis-dependent CKD patients [12]. To date, no data are available regarding the usefulness of serum hs-cTnT as a diagnostic marker of LVDD

in patients with non-dialysis CKD. We hypothesized that the serum hs-cTnT may be associated with LVDD, and investigated the relationship between hs-cTnT values and LVDD in CKD patients without clinically apparent heart failure.

Patients and Methods

Patients

Patients admitted to the Renal Unit of the Okayama University Hospital were included in this study. All patients were diagnosed as having CKD according to their estimated glomerular filtration rate (eGFR) and the presence of kidney injury as defined by National Kidney Foundation K/DOQI Guidelines [21, 22]. Patients with cardiogenic shock, congestive heart failure, valvular heart disease, acute coronary syndrome, and other malignancies were excluded. Patients with diabetic nephropathy or nephrotic syndrome were also excluded. Hypertension was defined as systolic blood pressure (SBP) ≥ 140 mm Hg or diastolic blood pressure (DBP) ≥ 90 mm Hg, or the use of antihypertensive drugs. GFR was calculated according to the simplified version of the MDRD (Modification of Diet in Renal Disease) formula [eGFR = $194 \times (\text{sCr})^{-1.094} \times (\text{age})^{-0.287}$ (if female $\times 0.739$)] [23]. All procedures in the present study were carried out in accordance with the institutional and national ethical guidelines for human studies. The Ethical Committee of the Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences approved the study. Informed consent was obtained from each subject. This study was registered with the Clinical Trial Registry of the University Hospital Medical Information Network (registration No. UMIN000003614).

Laboratory Measurements

After fasting overnight, arterial blood pressure was measured by a physician in the morning after a 10-min rest period. The mean arterial pressure (MAP) was calculated as $\text{DBP} + (\text{SBP} - \text{DBP})/3$. Serum and urine samples were obtained from patients in the morning after 12 h of fasting, and all parameters were measured immediately after blood sampling. In addition, aliquots were stored at -80°C until assayed for serum hs-cTnT. Cystatin C concentrations were measured with the sol particle homogeneous immunoassay method (Nescauto GC Cystatin C[®]; Alfresa Pharma, Osaka, Japan) [24]. Plasma BNP was measured by a rapid test system using a fluorescence enzyme immunoassay [E test Tosoh II (BNP); Tosoh Medics, Tokyo, Japan]. Serum hs-cTnT was determined by the Elecsys[®]/cobas eTM cTnT 4th-generation assay (Roche Diagnostics) on the Elecsys 2010/cobas e411 and Modular[®] Analytics E170/cobas e601 immunoanalyzers (Roche Diagnostics) according to the instructions of the manufacturer [11, 25]. The lower limit of detection of the hs-cTnT assay was 3.00 pg/ml.

Echocardiography

Echocardiography was performed using a cardiac ultrasound unit with a 2- to 3.5-MHz transducer. TDI was performed in all patients with images taken based on the guidelines of the American Society of Echocardiography [26]. LV end-diastolic/-systolic dimensions and end-diastolic/-systolic wall thickness of the interventricular septum and LV wall were determined using standard echocardiographic 2-D and M-mode measurements. Both EF and LV mass (LVM) were calculated from the M-mode echocardiogram. LVH was defined as the LVM index (LVMI) >125 g/m² in males and >110 g/m² in females. LVM was calculated according to the formula of Devereux et al. [27], using a correction factor of 0.8. Mitral inflow velocity was traced, and the following variables were derived: peak early (E) and late (A) transmitral flow velocities, and the ratio of early/late peak velocities (E/A).

Tissue Doppler Imaging

A 6-mm sample volume at the septal corner of the mitral annulus was used for the apical four-chamber view. Annular velocities were displayed in spectral pulsed-wave TDI. The early peak diastolic annular velocity (E') was determined from the TDI recordings and the mitral E/E' ratio was calculated. LV filling pressure was considered to be elevated when $E/E' > 15$ and normal when $E/E' < 8$ [28]. Diastolic dysfunction was previously defined when $E' < 8$ cm/s [29–31]. In this study, patients with LVDD with $E' < 5$ cm/s were defined as having severe LVDD [32] because such patients had a worse prognosis than those with $E' \geq 5$ cm/s [4, 33].

Statistical Analysis

Non-normally distributed variables were expressed as medians (interquartile ranges) and normally distributed variables as means \pm SD, as appropriate. $p < 0.05$ was considered to be statistically significant. Variables showing a positively skewed distribution were natural logarithm transformed. Receiver-operating characteristic (ROC) curves were constructed to determine the optimal sensitivity and specificity, and the area under the curve (AUC) was calculated. Between-group comparisons were assessed for nominal variables with the χ^2 test. Differences among the groups were analyzed by one-way ANOVA followed by a post hoc Tukey-Kramer test for multiple comparisons. Spearman's rank correlation was used to determine the correlations between two variables. A multivariate regression analysis was used to assess the predictors for E' and hs-cTnT. Statistical analysis was performed using the JMP software package release 8 (SAS Institute, Cary, N.C., USA).

Results

Patient Characteristics

After the first evaluation, 93 CKD patients with a mean age of 54 ± 14 years were included in the study. The causes of CKD are listed in table 1. A total of 62 patients were on antihypertensive therapy (52 patients were being treated with angiotensin receptor blockers, 10 with angiotensin-converting enzyme inhibitors, 37 with calcium channel antagonists, and 11 with other antihypertensive agents). Statins were administered to 19 patients and antiplatelet therapy to 20 patients. Based on their eGFR levels, patients were classified into stages 1–5 (table 1). Serum levels of biomarkers, including cystatin C, BNP, and hs-cTnT, were significantly elevated with increasing CKD stage. There were significant differences in the mean age, hemoglobin concentration, and LDL cholesterol among patients of different CKD stages. There were no significant differences in the MAP, daily albuminuria, serum albumin, HDL cholesterol, triglycerides, and HbA_{1c} among the CKD groups. Echocardiographic and TDI assessments revealed significant differences in the LVMI, E/A, E' , and E/E' (table 1). There were no significant differences in EF or left atrial diameter among the groups (table 1). All patients demonstrated a normal LV systolic function.

An Increase in Serum hs-cTnT and a Decrease in LV Filling Pressure Are Associated with CKD Stage

Patients in stages 1–5 CKD without diabetes had gradually decreased E' values ($p < 0.0001$; table 1). In addition, gradual increases in serum hs-cTnT levels were observed with increasing CKD stage ($p < 0.0001$; table 1), with an average value of hs-cTnT in patients with eGFR ≥ 90 of 3.56; eGFR 60–89 of 4.52; eGFR 30–59 of 6.86; eGFR 15–29 of 11.10, and eGFR 0–14 ml/min/1.73 m² of 20.41 pg/ml. The highest hs-cTnT concentration was found in patients in stage 5 CKD.

Table 1. Baseline characteristics of the study patients

	CKD stage						p value
	1 (n = 11)	2 (n = 30)	3 (n = 23)	4 (n = 15)	5 (n = 14)	total (n = 93)	
Age, years	33 ± 7	49 ± 14	61 ± 9	64 ± 9	57 ± 12	54 ± 14	<0.0001
Gender, males/females	3/8	17/13	12/11	10/5	8/6	50/43	
Cause of CKD, n							
Glomerulonephritis	10	21	16	1	3	51	
Nephrosclerosis	0	7	5	11	5	28	
Other	1	2	2	3	6	14	
Current medication, n							
ARBs/ACEIs	1	10	18	12	11	52	
CCBs	0	8	12	8	9	37	
MAP, mm Hg	86 ± 10	91 ± 11	93 ± 11	93 ± 13	96 ± 10	92 ± 11	0.1952
eGFR, ml/min/1.73 m ²	102 ± 9	72 ± 9	45 ± 9	23 ± 4	11 ± 3	52 ± 3	<0.0001
Albuminuria, mg/day	123 (17–597)	297 (147–704)	123 (48–864)	418 (92–1,209)	620 (153–1,496)	289 (99–821)	0.1959
Cystatin C, mg/dl	0.8 ± 0.1	1.0 ± 0.2	1.4 ± 0.3	2.5 ± 0.4	3.7 ± 0.7	1.8 ± 1.1	<0.0001
Serum albumin, g/dl	4.2 ± 0.3	3.9 ± 0.6	3.9 ± 0.4	3.8 ± 0.4	3.9 ± 0.5	3.9 ± 0.5	0.2827
Hemoglobin, g/dl	13.7 ± 1.5	14.1 ± 1.8	12.3 ± 1.6	11.0 ± 1.5	11.0 ± 1.9	12.6 ± 2.1	<0.0001
LDL cholesterol, mg/dl	104 ± 38	129 ± 30	113 ± 26	104 ± 30	104 ± 27	114 ± 30	0.0226
HDL cholesterol, mg/dl	60 ± 19	56 ± 16	52 ± 16	50 ± 18	47 ± 13	53 ± 17	0.2324
Triglycerides, mg/dl	77 (75–139)	129 (89–181)	109 (84–174)	132 (86–190)	122 (72–185)	119 (79–171)	0.6931
HbA _{1c} , %	5.2 ± 0.5	5.3 ± 0.4	5.4 ± 0.3	5.3 ± 0.3	5.4 ± 0.5	5.3 ± 0.4	0.3227
BNP, pg/ml	9 (7–16)	19 (5–33)	15 (8–32)	34 (21–68)	29 (9–53)	19 (9–42)	0.0473
hs-cTnT, pg/ml	3	3 (3–4)	5 (3–9)	9 (7–16)	16 (8.5–27)	4 (3–9)	<0.0001
EF, %	68 ± 6	70 ± 6	68 ± 6	70 ± 9	68 ± 6	69 ± 7	0.8585
LVMI, g/m ²	71 ± 20	90 ± 21	92 ± 20	115 ± 36	111 ± 43	96 ± 30	0.0019
LAD, mm	34 ± 7	34 ± 5	34 ± 5	38 ± 6	35 ± 6	35 ± 6	0.1761
E/A	1.6 (1.1–2.3)	1.0 (0.9–1.5)	0.9 (0.8–1.1)	0.8 (0.7–1.0)	0.9 (0.7–1.0)	0.9 (0.8–1.2)	<0.0001
E', cm/s	11.0 ± 3.1	8.9 ± 2.1	7.1 ± 2.4	6.2 ± 1.8	7.0 ± 2.4	7.8 ± 2.6	<0.0001
E/E'	7.6 ± 2.1	7.8 ± 21.9	9.6 ± 2.7	10.2 ± 2.7	8.8 ± 2.6	8.9 ± 2.6	0.0160

Non-normally distributed variables are expressed as medians (interquartile ranges) and normally distributed variables as means ± SD. ACEI = Angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; CCB = calcium channel blocker; LAD = left atrial diameter.

Serum hs-cTnT Correlates with Cardiorenal Markers

In univariate analysis, serum ln hs-cTnT levels correlated negatively with E' (r = -0.5104, p < 0.0001; table 2), but were positively associated with daily albuminuria (r = 0.2574, p = 0.0341), serum cystatin C (r = 0.7751, p < 0.0001), MAP (r = 0.3460, p = 0.0018), and LVMI (r = 0.5195, p < 0.0001; table 2).

Serum hs-cTnT and Plasma BNP Significantly Increase in CKD Patients with E' < 5 cm/s

The non-diabetic CKD patients with severe LVDD detected by E' < 5 cm/s had significantly higher serum hs-cTnT levels compared to those with E' ≥ 5 cm/s (fig. 1a). The average value of hs-cTnT was 7.4 ± 8.3 pg/ml in CKD patients with E' ≥ 5 cm/s, whereas it was 17.0 ± 7.3 pg/ml in those with E' < 5 cm/s. There were significant differences in plasma BNP, another biomarker of heart failure, between CKD patients with E' ≥ 5 cm/s and those with E' < 5 cm/s (fig. 1b).

The ability of using hs-cTnT to detect E' < 5 cm/s in patients with normal systolic function was assessed by ROC analysis (fig. 2). The AUC for the ROC curve when hs-cTnT was used to detect E' < 5 cm/s was 0.880 (p = 0.0101), which denoted moderate accuracy. A hs-

Fig. 1. The distribution of hs-cTnT (**a**) and BNP (**b**) in CKD patients with or without severe LVDD. **a** n = 66 in the $E' \geq 5$ cm/s group and n = 10 in the $E' < 5$ cm/s group. **b** n = 68 in the $E' \geq 5$ cm/s group and n = 10 in the $E' < 5$ cm/s group. Severe LVDD was defined as $E' < 5$ cm/s by TDI.

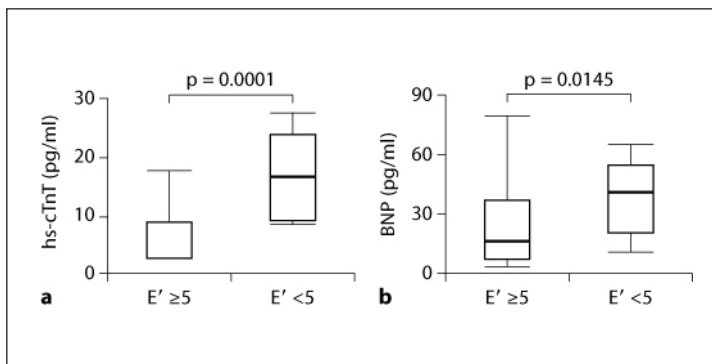


Table 2. Univariate relationships of clinical and echocardiographic indices to ln hs-cTnT

	r value	p value
Age	0.4765	<0.0001
MAP	0.3460	0.0018
eGFR	-0.6867	<0.0001
Albuminuria	0.2574	0.0341
Cystatin C	0.7751	<0.0001
Serum albumin	-0.1253	0.2496
Hemoglobin	-0.4221	0.0001
LDL cholesterol	-0.1754	0.1246
HDL cholesterol	-0.4361	<0.0001
Triglycerides	0.1254	0.2739
HbA _{1c}	0.2593	0.0228
BNP	0.2178	0.0661
EF	-0.0301	0.7964
LVMI	0.5195	<0.0001
LAD	0.3322	0.0034
E/A	-0.4311	0.0001
E'	-0.5104	<0.0001
E/E'	0.3363	0.0032

LAD = Left atrial diameter.

cTnT value of 9 pg/ml had a sensitivity of 100%, and a specificity of 76% (fig. 2a). The AUC for the ROC curve when BNP was used to detect $E' < 5$ cm/s was 0.741 ($p = 0.0570$), which also denoted a moderate degree of accuracy. A BNP value of 20.3 pg/ml had a sensitivity of 90%, and a specificity of 57% (fig. 2b). The AUC for hs-cTnT was therefore greater than that for BNP.

Multiple Regression Analysis for E' and hs-cTnT

Table 3 presents separate multiple regression models for E' and hs-cTnT. After adjustment for age and the cause of CKD, the variable expected to influence E' was hs-cTnT in the biomarker-based model, and albuminuria in the CKD-based model (table 3a). Moreover, the factor expected to influence hs-cTnT was eGFR in the CKD-based model (table 3b).

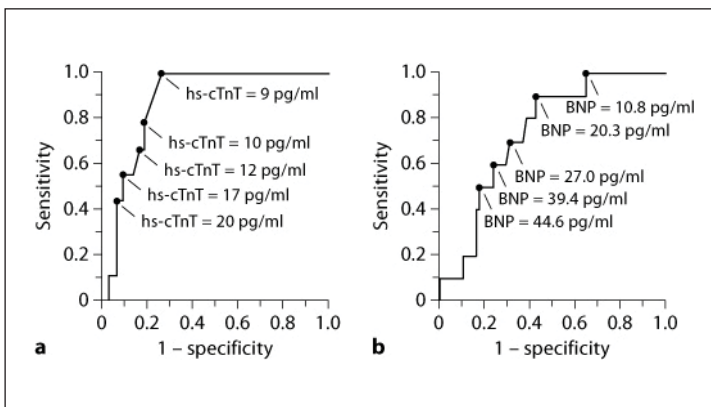


Fig. 2. ROC curve comparing sensitivity and specificity of hs-cTnT (a) and BNP (b) for detecting LVDD with $E' < 5$ cm/s by echocardiography. The AUC for the ROC curve where hs-cTnT was used to detect $E' < 5$ cm/s was 0.880 ($p = 0.0101$). A hs-cTnT value of 9 pg/ml had a sensitivity of 100%, and a specificity of 76%. The AUC for the ROC curve where BNP was used to detect $E' < 5$ cm/s was 0.741 ($p = 0.0570$). A BNP value of 20.3 pg/ml had a sensitivity of 90%, and a specificity of 57%.

Table 3. Multivariate regression analysis of predictors of E' (a) and hs-cTnT (b)

	β	p
a E' (adjusted for age and cause of CKD)		
Echocardiography-based model		
MAP	-0.040599	0.0452
EF	0.022496	0.4741
LVMI	-0.010729	0.1900
Biomarker-based model		
hs-cTnT	-0.058090	0.0332
BNP	0.001469	0.8214
CKD-based model		
eGFR	0.007911	0.3771
Albuminuria	-0.000723	0.0154
b hs-cTnT (adjusted for age and cause of CKD)		
Echocardiography-based model		
MAP	0.142268	0.1511
EF	0.147041	0.3180
E'	-0.888941	0.0845
CKD-based model		
eGFR	-0.160545	<0.0001
Albuminuria	-0.000015	0.9907

Discussion

In our study, we investigated the relationship between serum hs-cTnT and LVDD in patients with CKD and demonstrated that CKD patients with $E' < 5$ cm/s had significantly higher serum hs-cTnT levels compared to those with $E' \geq 5$ cm/s. The AUC for the ROC curve using hs-cTnT to detect $E' < 5$ cm/s was 0.880, which denoted moderate accuracy. Our data suggest that, in addition to plasma BNP, the recently established serum hs-cTnT value may therefore be associated with LVDD in CKD patients. In multivariate analysis, hs-cTnT and albuminuria were significant predictors of E' in the biomarker-based model and the

CKD-based model, respectively, and eGFR was significantly associated with hs-cTnT after adjusting for age and the etiology of kidney disease in non-diabetic CKD patients.

The cTnT concentration measured with a hs-cTnT assay is a prognostic factor for the incidence of cardiovascular death and heart failure in patients with stable chronic heart failure [10], with stable CAD [11], in the general population with a younger age [34], and in senior adults [8]. Our study demonstrated that CKD patients with LVDD indicated by an E' value <5 cm/s had significantly higher hs-cTnT levels compared to those with $E' \geq 5$ cm/s. The median value of serum hs-cTnT was 17.0 pg/ml in CKD patients with LVDD with $E' < 5$ cm/s, and this value corresponded to quartile 4, which has been reported to have the highest cumulative incidence of cardiovascular death [11]. In our study, the difference in the ln hs-cTnT between patients with $E' < 5$ and $E' \geq 5$ cm/s was 1.08 units. The adjusted hazard ratio per unit increase in the natural logarithm of hs-cTnT of the cumulative incidence of cardiovascular death and heart failure was 2.09 and 2.20, respectively [11]. Thus, the hs-cTnT level in patients with LVDD indicated by $E' < 5$ cm/s in this study was substantially higher, which may be sufficient to cause cardiovascular events in CKD patients. Our findings provide valuable insight into the relationship between hs-cTnT and LVDD with $E' < 5$ cm/s. We reported the performance of hs-cTnT for the detection of LVDD with $E' < 5$ cm/s in patients to have a moderate degree of accuracy (AUC = 0.880). However, the AUC for hs-cTnT was greater than that for BNP.

Persistently elevated cardiac troponin is frequently observed among patients with end-stage renal disease [9, 35]. The prevalence of increased troponin values among patients with chronic renal failure in the absence of clinically suspected ischemia, such as in our study, may be the result of small areas of clinically silent myocardial necrosis. However, other causes, such as increased LVM and impaired renal troponin excretion, have also been proposed [36]. cTnT has a molecular weight of 37 kDa and that of cTnI (cardiac troponin I) is 22.5 kDa. cTnI is released from the cell in complexes of TnT-I-C (77 kDa) and TnI-C (40 kDa), while cTnT is released as free TnT or TnT-I-C complexes [35]. Recent studies have shown that both cTnT and cTnI are degraded in myocardial cells, and then released as small molecules that are still detected by the assays [37, 38]. Diris et al. [37] demonstrated that cTnT is split into fragments that range in size from 8 to 25 kDa, even in samples with measured cTnT concentrations that are <10 pg/ml. These fragments are small enough to be cleared by the kidneys, and therefore could be elevated in patients with renal failure owing to delayed clearance. In contrast, Fahie-Wilson et al. [39] and Bates et al. [40] reported that the form of cTnT observed in the serum of patients with kidney failure is predominantly the free intact form, and there is no evidence of cTnT fragments existing in the circulation. Their data are consistent with the view that circulating cTnT in renal failure patients reflects cardiac injury.

CKD is an increasing public health problem [41]. Cardiovascular disease is frequently associated with CKD, which is important, since individuals with CKD are more likely to die of cardiovascular disease than to develop kidney failure. Indeed, the term cardiorenal syndrome has been increasingly used, and a new classification was proposed because a large proportion of patients admitted to the hospital have various degrees of heart and kidney dysfunction [42]. In our cohort, 48 patients (57%) had $E' < 8$ cm/s and 10 patients (12%) had $E' < 5$ cm/s. E' was significantly decreased with increasing CKD stage, and eGFR showed a significant association with $E' < 5$ cm/s. LVDD is very common among CKD patients and may be associated with the subsequent development of heart failure and mortality [43]. In patients with heart failure, the presence of CKD is associated with a worse diastolic function, intracardiac conduction and prognosis [2, 33]. An impairment in the diastolic function in patients with CKD may occur very early, even in the absence of LVH [44]. In hypertensive patients in stage 2–5 CKD, who are free of cardiovascular disease, E' evaluated by TDI was lower with lessening renal function, with very low values in stage 5 CKD, although all patients were free from heart

failure [44]. E' has been demonstrated to be inversely related to the degree of fibrosis in ischemic, as well as normal, myocardial segments [45]. Although the pathogenesis of LVH in CKD patients is considered to be multifactorial, hypertension, alterations in fluid and electrolyte balance, and anemia are identified as the major determinants of LV growth in CKD patients. However, beyond hemodynamic factors, other factors, e.g. inappropriate activation of the renin-angiotensin-aldosterone system, oxidative stress, inflammation and hyperactivation of collagen and muscle cell growth factors, may also play a role in LV growth in CKD.

In this study, albuminuria was the most significant predictor of E' in non-diabetic CKD patients. An association of albuminuria with systolic and diastolic LV dysfunction in diabetic cardiomyopathy in type 2 diabetic patients was previously reported [46]. The mechanism underlying the relationship between LVDD and albuminuria is unclear. In the present study, SBP and pulse pressure were both significantly higher in patients with $E' < 5$ cm/s than in those with $E' \geq 5$ cm/s ($p < 0.001$). Since systemic hypertension could cause glomerular hypertension and hyperfiltration, which leads to albuminuria, it may represent a candidate mechanism responsible for the relationship between LVDD and albuminuria. LVDD may cause volume overload of circulating plasma, thus leading to an increase in renal blood flow. Diastolic dysfunction might be associated with albuminuria via endothelial dysfunction. An impairment in tubular reabsorption of albumin may be one of the causes of albuminuria [47]. Several molecules, including heart-type fatty acid binding proteins, can be synthesized by both cardiomyocytes and distal tubular epithelial cells in the kidneys, so that simultaneous dysfunction of the heart and kidney might occur in CKD patients.

Study Limitations

Several limitations of this study should be noted. First, our sample size is relatively small, and a larger cohort of CKD patients will need to be examined to confirm our findings. Second, given that these results are cross-sectional, we may not draw definitive inferences on their direction or causality. Third, because of the multifactorial causes of diastolic dysfunction, it is possible that we did not fully control for all confounding variables, such as factors for mineral metabolism and vascular parameters.

Conclusion

Among patients with non-diabetic CKD without LV systolic dysfunction who are at increased risk for cardiovascular events, the serum hs-cTnT may be a significant biomarker for LVDD. Further investigation, including an outcome study elucidating the significance of hs-cTnT as a prognostic factor, should be performed in a prospective study in the near future.

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Disclosure Statement

All of the authors declare that they have no competing interests.

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