Chronic kidney disease and subclinical abnormalities of left heart mechanics in the community

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Aims
Cardiovascular disease is the leading cause of death in chronic kidney disease (CKD) patients, although the pathophysiological mechanisms are not fully studied. This study aimed to determine whether CKD could adversely affect subclinical left heart function in a sample of the general population without cardiac disease.

Methods and results
We examined 1158 participants who voluntarily underwent extensive cardiovascular examination including laboratory test and two-dimensional speckle-tracking echocardiography to assess left ventricular global longitudinal strain (LVGLS) and left atrial (LA) reservoir, conduit, and pump strain. According to the estimated glomerular filtration rate (eGFR), participants were classified into four groups; Stage 1 (n = 112; eGFR >90 mL/min/1.73 m²), Stage 2 (n = 818; 60–89 mL/min/1.73 m²), Stage 3a (n = 191; 45–59 mL/min/1.73 m²), and Stage 3b–5 (n = 37; eGFR <45 mL/min/1.73 m²). Progressive declines of LVGLS, LA reservoir, and conduit strain were observed according to the severity of CKD (P < 0.001), while LA pump strain did not differ between the groups. In multivariable analyses, eGFR was associated with LVGLS (standardized β = -0.068, P = 0.019) as well as LA reservoir (standardized β = 0.117, P < 0.001) and conduit strain (standardized β = 0.130, P < 0.001), independent of traditional cardiovascular risk factors, pertinent biomarkers, and LV geometry and diastolic function. The independent association between eGFR and LA strain persisted even after adjustment for LVGLS.

Conclusion
Worsening renal function was independently associated with impaired LV/LA strain in an unselected community-based cohort. The assessment of LV and LA strain may allow better risk stratification in CKD patients.

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Introduction

Chronic kidney disease (CKD) is an increasing global health concern and carries a significant and independent risk for the incident heart failure (HF) and atrial fibrillation (AF). Given the poor prognosis in CKD patients, early identification of individuals at higher risk for HF and AF who may benefit from the preventive therapeutic intervention is of crucial importance. Left ventricular (LV) and left atrial (LA) strain measures derived from speckle-tracking echocardiography can detect subclinical left heart dysfunction. The purpose of the present study was to evaluate the association of renal function with LV and LA phasic strain in a large sample of the general population without overt cardiac disease.

Methods

The present study was derived from the Subclinical Cardiac Dysfunction in General Population (SCADGP) study, a community-based study designed to investigate the prevalence and determinants of subclinical cardiac dysfunction. A total of 1158 participants with normal LV ejection fraction and free from the overt cardiac disease were included in the analyses. Venous blood samples were examined in the fasting condition on the same day as echocardiographic examination. Serum glucose, lipid profiles, C-reactive protein (CRP), and B-type natriuretic peptide (BNP) levels were analysed in all participants. The estimated glomerular filtration rate (eGFR) was calculated using the abbreviated MDRD formula, and participants were classified into four groups; Stage 1 (eGFR ≥90 mL/min/1.73 m²), Stage 2 (60–89 mL/min/1.73 m²), Stage 3a (45–59 mL/min/1.73 m²), and Stage 3b–5 (eGFR <45 mL/min/1.73 m²).

All participants underwent two-dimensional transthoracic echocardiography using a commercially available system in accordance with a standardized protocol. Left ventricular global longitudinal strain (GLS) was calculated by averaging negative peak of longitudinal strain obtained from three apical views including four-chamber, two-chamber, and long-axis views. Left atrial strain was also calculated averaging the positive peak of longitudinal strain from four-chamber and two-chamber apical views. Left atrial strain curve was divided into three phases: LA reservoir strain as peak (maximal) longitudinal LA strain; LA booster pump strain as the second peak longitudinal LA strain between P wave onset and QRS onset; LA conduit strain as the difference of these peaks. Abnormal LVGLS and LA phasic strain was defined as a GLS >-18.6%, and LA reservoir strain <31.4%, LA conduit strain <12.4%, and LA pump strain <13.1%; these values are the 90th percentile of the LVGLS and the 10th percentile of the LA strain distribution in participants from the SCADGP cohort without any conditions associated with left heart remodelling.

Analysis of variance with Tukey–Kramer post hoc analysis or a Kruskal–Wallis test with the post-test Dunn correction was used to compare continuous variables across the CKD severity; the χ² test was used for categorical variables as appropriate. Univariable and multivariable linear regression analyses were conducted to evaluate the association of eGFR with LVGLS and LA phasic strain adjusting for potential covariates with sequential fashion in 4 models; Model 1: adjustment for age and sex; Model 2: adjustment for age, sex, BMI, systolic blood pressure, antihypertensive medication use, diabetes mellitus, hypercholesterolaemia, and smoking status; Model 3: adjustment as in model 2 plus pertinent echocardiographic parameters including LV mass index and E/e’; Model 4: adjustment as in model 3 plus CRP and BNP levels. As for the LA strain measures, additional adjustment for LVGLS was performed (Model 5). A value of P < 0.05 was considered significant.


**Results**

Table 1 summarizes the clinical characteristics, laboratory, and echocardiographic parameters stratified by the renal function.

**Table 1** Clinical characteristics and echocardiographic parameters stratified by the renal function

| eGFR ≥ 90 mL/min/1.73 m² | 60 to 89 mL/min/1.73 m² | 45 to 59 mL/min/1.73 m² | eGFR < 45 mL/min/1.73 m² | P-value |
|---------------------------|--------------------------|-------------------------|--------------------------|---------|
| (n = 112)                 | (n = 818)                | (n = 191)               | (n = 37)                 |         |
| Age (years)               | 55 ± 13                  | 61 ± 11                 | 69 ± 9                   | 74 ± 9 | <0.001 |
| Male gender, n (%)        | 60 (53.6)                | 450 (55.0)              | 116 (60.7)               | 22 (59.5) | 0.474 |
| Body mass index, kg/m²    | 23.5 ± 4.1               | 23.4 ± 3.4              | 23.5 ± 3.0               | 24.0 ± 3.8 | 0.609 |
| Hypertension, n (%)       | 29 (25.9)                | 249 (30.4)              | 89 (46.6)                | 30 (81.1) | <0.001 |
| Diabetes mellitus, n (%)  | 21 (18.8)                | 70 (8.6)                | 14 (7.3)                 | 11 (29.7) | <0.001 |
| Hypercholesterolaemia, n (%) | 36 (32.1)             | 287 (35.1)              | 78 (40.8)                | 24 (64.9) | 0.001 |
| Smoking status            |                          |                         |                          | 0.114   |
| Current, n (%)            | 15 (13.4)                | 89 (10.9)               | 9 (4.7)                  | 2 (5.4)  |
| Past, n (%)               | 27 (24.1)                | 223 (27.3)              | 53 (27.7)                | 8 (21.6)  |
| Never, n (%)              | 70 (62.5)                | 506 (61.9)              | 129 (67.5)               | 27 (73.0)  |
| Systolic blood pressure (mmHg) | 117 ± 15               | 119 ± 15                | 122 ± 15                 | 132 ± 21 | <0.001 |
| Diastolic blood pressure (mmHg) | 74 ± 12                 | 76 ± 10                 | 75 ± 11                  | 74 ± 14  | 0.152 |
| Heart rate (beats/min)    | 72 ± 11                  | 72 ± 11                 | 72 ± 10                  | 75 ± 13  | 0.197 |
| Antihypertensive medication, n (%) | 18 (16.1)           | 178 (21.8)              | 73 (38.2)                | 29 (78.4) | <0.001 |
| Laboratories parameters   |                          |                         |                          |         |
| Glucose (mg/dL)           | 102 ± 28                 | 99 ± 18                 | 100 ± 18                 | 107 ± 23 | 0.042 |
| Total cholesterol (mg/dL)  | 202 ± 32                 | 207 ± 34                | 208 ± 35                 | 195 ± 36 | 0.081 |
| LDL cholesterol (mg/dL)   | 121 ± 30                 | 125 ± 30                | 126 ± 31                 | 115 ± 34 | 0.123 |
| HDL cholesterol (mg/dL)   | 65 ± 18                  | 66 ± 18                 | 66 ± 19                  | 60 ± 16  | 0.202 |
| Triglyceride (mg/dL)      | 112 ± 94                 | 111 ± 88                | 112 ± 78                 | 130 ± 82 | 0.560 |
| Creatinine (mg/dL)        | 0.58 ± 0.11              | 0.75 ± 0.13             | 0.95 ± 0.14***           | 1.82 ± 1.73 *** | <0.001 |
| eGFR (mL/min/1.73 m²)     | 100.3 ± 11.5             | 73.6 ± 7.9              | 54.8 ± 3.9               | 35.5 ± 11.2 *** | <0.001 |
| C-reactive protein (mg/dL)| 0.06 (0.03–0.11)         | 0.04 (0.02–0.09)        | 0.05 (0.03–0.10)         | 0.08 (0.03–0.17) | 0.004 |
| BNP (pg/mL)               | 14.7 (8.5–23.0)          | 15.6 (8.7–26.1)         | 20.5 (11.6–38.7)***      | 28.6 (12.2–52.7)*** | <0.001 |
| Two-dimensional echocardiography |                       |                         |                          |         |
| LV end-diastolic diameter (cm) | 4.6 ± 0.4           | 4.5 ± 0.4               | 4.4 ± 0.5                | 4.5 ± 0.6 | 0.021 |
| LV end-systolic diameter (cm) | 2.8 ± 0.3          | 2.7 ± 0.4               | 2.7 ± 0.4*               | 2.8 ± 0.4 | 0.018 |
| LV mass index (g/m²)      | 72.5 ± 15.7             | 70.2 ± 15.8             | 70.9 ± 17.6              | 79.2 ± 16.5*** | 0.006 |
| LV ejection fraction (%)  | 63.7 ± 3.5              | 63.3 ± 5.6              | 63.6 ± 5.8               | 61.9 ± 5.6 | 0.365 |
| LA volume index (mL/m²)   | 24.7 ± 6.5              | 24.5 ± 7.0              | 24.9 ± 8.0               | 28.9 ± 11.1*** | 0.005 |
| E wave (cm/s)             | 73 ± 15                 | 70 ± 15                 | 68 ± 15                 | 69 ± 17  | 0.017 |
| e’ (cm/s)                 | 9.2 ± 2.9               | 8.3 ± 2.2               | 7.3 ± 1.9*              | 6.5 ± 1.6* | <0.001 |
| E/e’ ratio                | 8.5 ± 2.5               | 8.9 ± 2.7               | 9.7 ± 2.7*              | 11.2 ± 3.4*** | <0.001 |
| Speckle-tracking echocardiography |                   |                         |                          |         |
| LVGLS (%)                 | -21.8 ± 2.7             | -21.4 ± 2.7             | -20.9 ± 2.7*            | -19.9 ± 2.6*** | <0.001 |
| LA reservoir strain (%)   | 41.9 ± 6.0              | 39.3 ± 6.7              | 36.7 ± 6.2***           | 34.6 ± 5.5*** | <0.001 |
| LA conduit strain (%)     | 22.0 ± 7.1              | 19.5 ± 6.4*             | 16.7 ± 6.1***           | 13.7 ± 4.4*** | <0.001 |
| LA pump strain (%)        | 19.9 ± 4.8              | 19.7 ± 5.0              | 20.1 ± 5.2              | 20.9 ± 5.4 | 0.514 |

Values are mean ± standard deviation, n (percentage), or median (25th–75th percentile).

*P < 0.05 compared with eGFR ≥ 90 mL/min/1.73 m².

**P < 0.05 compared with eGFR 60 to 89 mL/min/1.73 m².

***P < 0.05 compared with eGFR 45 to 59 mL/min/1.73 m².

BNP, B-type natriuretic peptide; E, early diastolic transmitral flow velocity; e’, early diastolic mitral annular velocity; eGFR, estimated glomerular filtration rate; GLS, global longitudinal strain; HDL, high-density lipoprotein; LA, left atrium; LDL, low-density lipoprotein; LV, left ventricle.

Correlated with age and the prevalence of cardiovascular risk factors. Left ventricular global longitudinal strain significantly decreased in CKD Stage 3a, while LVEF was similar across the CKD stages. In terms of LA parameters, a significant decrease of LA reservoir and conduit strain was documented in Stage 2 and an increase of LA volume index in Stage 3b, whereas LA pump strain did not differ.
between the groups. As shown in Figure 1, the prevalence of abnormal LVGLS (>18.6%) as well as abnormal LA reservoir (<31.4%) and conduit (<12.4%) strain progressively increased with CKD severity, whereas there was no difference for LA pump strain (P = 0.246). In multivariable analyses, eGFR was associated with LVGLS (standardized β = -0.068, P = 0.019) as well as LA reservoir (standardized β = 0.017, P < 0.001) and conduit strain (standardized β = 0.130, P < 0.001), independent of traditional cardiovascular risk factors, pertinent biomarkers, and LV geometry and diastolic function (Table 2). Of note, even after controlling for LVGLS, eGFR demonstrated a consistent and independent association with LA reservoir and conduit strain (Model 5).

**Discussion**

The present study demonstrated that decreased renal function was significantly associated with LVGLS, LA reservoir, and conduit strain in a large sample of the general population without overt cardiac disease. The observed association was independent of traditional cardiovascular risk factors as well as pertinent laboratory and echocardiographic parameters. The underlying mechanisms linking renal dysfunction and impaired left heart strain are not entirely clear; however, we hypothesize several potential explanations. First, a chronic inflammatory state is observed in CKD, which may be related to LV and LA dysfunction. Indeed, previous studies demonstrated impaired left heart dysfunction in patients suffering from a marked inflammatory state. Second, CKD patients exhibit higher fibroblast growth factor-23 concentration; this growth factor regulates systemic phosphate homeostasis and vitamin D metabolism, serves as a fibrosis-promoting factor, possibly leading to LV and LA dysfunction. Finally, CKD causes activation of the renin-angiotensin and the sympathetic nervous system, which might be involved in the observed associations. Our findings provide valuable information to help clarify the mechanism of increased risk of HF and AF in CKD patients. Furthermore, the assessment of LV and LA strain may allow better risk stratification in CKD patients. Indeed, a previous study showed the necessity of early therapeutic preventive intervention for left heart dysfunction without structural remodelling. Several limitations should be noted. First, we cannot confirm a cause–effect relationship between renal impairment and subclinical LV and LA dysfunction due to the cross-sectional nature of the present study. Second, CKD subjects included in this study had relatively preserved renal function, which may not allow to extend our observations to patients with more advanced CKD or end-stage renal disease. However, our findings suggest that even mild CKD carries an independent risk for subclinical LV and LA dysfunction. Third, while we performed multivariable analyses adjusted for blood pressure and lipid profile and found that eGFR was an independent predictor for impaired LVGLS and LA strain, we could not evaluate the effects of severity and duration of hypertension and hyperlipidaemia. Finally, the impact of congestion on our observation could not be assessed, because the information was not uniformly available in the present study.

In conclusion, reduced renal function was associated with subclinical LV and LA dysfunction in the general population. Our findings may provide important information on the underlying pathophysiological mechanism for higher HF/AF occurrence in CKD patients.

**Table 2** Association of eGFR with LVGLS and LA phasic strain in multivariable linear regression analysis

| LVGLS | LA reservoir | LA conduit | LA pump |
|-------|--------------|------------|---------|
| **Standardized β (95% CI)** | **P-value** | **Standardized β (95% CI)** | **P-value** | **Standardized β (95% CI)** | **P-value** |
| Model 1 | -0.075 (-0.023 to -0.003) | 0.009 | 0.162 (0.047 to 0.095) | <0.001 | 0.177 (0.053 to 0.099) | <0.001 | -0.015 (-0.025 to 0.014) | 0.989 |
| Model 2 | -0.061 (-0.021 to -0.001) | 0.036 | 0.136 (0.035 to 0.084) | <0.001 | 0.145 (0.040 to 0.085) | <0.001 | -0.008 (-0.022 to 0.017) | 0.790 |
| Model 3 | -0.061 (-0.021 to -0.001) | 0.035 | 0.134 (0.033 to 0.082) | <0.001 | 0.135 (0.036 to 0.080) | <0.001 | 0.0001 (-0.020 to 0.020) | 0.964 |
| Model 4 | -0.068 (-0.022 to -0.002) | 0.019 | 0.117 (0.028 to 0.074) | <0.001 | 0.130 (0.034 to 0.078) | <0.001 | -0.015 (-0.025 to 0.015) | 0.626 |
| Model 5 | — | — | 0.105 (0.023 to 0.069) | <0.001 | 0.118 (0.029 to 0.072) | <0.001 | -0.015 (-0.025 to 0.015) | 0.622 |

Model 1: adjusted for age and sex.
Model 2: adjusted for age, sex, BMI, systolic blood pressure, antihypertensive medication use, diabetes mellitus, hypercholesterolaemia, and smoking status.
Model 3: adjusted for variables as in model 2 and LV mass index and E/e'.
Model 4: adjusted for variables as in model 3 and CRP and BNP levels.
Model 5: adjusted for variables as in model 4 and LVGLS.

BMI, body mass index; BNP, B-type natriuretic peptide; CI, confidence interval; CRP, C-reactive protein; E, early diastolic transmitral flow velocity; e', early diastolic mitral annular velocity; eGFR, estimated glomerular filtration rate; GLS, global longitudinal strain; LA, left atrium; LV, left ventricle.
Lead author biography

Kentaro Iwama MD graduated from the University of Tsukuba. He completed residency at the National Center for Global Health and Medicine in 2017. He is a Ph.D. student in cardiovascular medicine at the University of Tokyo. He has a particular interest in echocardiography for the preventive of CV diseases.

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Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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