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ORIGINAL RESEARCH

Atrioventricular and Ventricular Functional Interdependence in Individuals Without Overt Cardiac Disease

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BACKGROUND: Left atrial (LA) and right ventricular (RV) performance play an integral role in the pathophysiology and prognosis of heart failure. We hypothesized that subclinical left ventricular dysfunction adversely affects LA/RV geometry and function even in a preclinical setting. This study aimed to investigate the atrioventricular and ventricular functional interdependence in a community-based cohort without overt cardiovascular disease.

METHODS AND RESULTS: Left ventricular global longitudinal strain (LVGLS), RV free-wall longitudinal strain and LA phasic strain were assessed by speckle-tracking echocardiography in 1080 participants (600 men; 62±12 years) between 2014 and 2018. One hundred and forty-three participants (13.2%) had an abnormal LVGLS (>–18.6%). LA reservoir strain, conduit strain, and RV free-wall longitudinal strain were significantly decreased in abnormal LVGLS group compared with normal LVGLS group (all $P<0.001$). LA and RV dysfunction (LA reservoir strain<31.4% and RVLS>–19.2%) were present in 18.9% and 19.6% of participants with abnormal LVGLS. Decreased LVGLS was associated with worse LA reservoir strain, conduit strain and RV free-wall longitudinal strain (standardized β=–0.20, –0.19 and 0.11 respectively, all $P<0.01$) independent of cardiovascular risk factors. LA and/or RV dysfunction concomitant with abnormal LVGLS carried significantly increased risk of elevated B-type natriuretic peptide levels (>28.6 pg/mL for men and >44.4 pg/mL for women) compared with normal LVGLS (odds ratio, 2.01; $P=0.030$).

CONCLUSIONS: LA/RV dysfunction was present in 20% individuals with abnormal LVGLS and multi-chamber impairment was associated with elevated B-type natriuretic peptide level, which may provide valuable insights for a better understanding of atrioventricular and ventricular interdependence and possibly heart failure preventive strategies.

Key Words: B-type natriuretic peptide ■ longitudinal strain ■ speckle tracking echocardiography ■ ventricular interdependence

Heart failure (HF) is a huge public health concern impacting morbidity, mortality, and healthcare resources. In the United States, HF affects 6.2 million adults and is projected to increase 46% from 2012 to 2030 as the population ages.[1] These forecasts reinforce urgent need for early identification of individuals at higher risk of HF and timely preventive interventions. HF has been widely investigated by assessing abnormalities of the left ventricle (LV).[2,3] LV ejection fraction (LVEF) is a simple and most frequently used index to evaluate LV systolic function; however, more than half of patients with HF exhibit preserved LVEF. Furthermore, LVEF is also limited by significant inter- and intra-observer variability as well as pathophysiological conditions in which the ratio of stroke volume to LV cavity size is preserved. Recently, adverse left atrial (LA) and right ventricular (RV) remodeling accompanied by LV dysfunction has been recognized as an important parameter in HF, and patients with HF with concomitant LA/RV dysfunction experience worse

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CLINICAL PERSPECTIVE

What Is New?

- Left atrial/right ventricular dysfunction assessed by speckle-tracking echocardiography was present in 20% individuals with subclinical left ventricular dysfunction.
- Reduced left ventricular global longitudinal strain was independently associated with left atrial and right ventricular functional remodeling.
- Concomitant left atrial or right ventricular dysfunction accompanied by subclinical left ventricular dysfunction carried significant risk of elevated B-type natriuretic peptide concentration.

What Are the Clinical Implications?

- Comprehensive assessment of cardiac chamber mechanics by deformation imaging at a subclinical stage may add valuable information for the risk stratification of heart failure.

Nonstandard Abbreviations and Acronyms

GLS	global longitudinal strain

cardiovascular outcomes.[4–8] These observations highlight the need for accurate and comprehensive assessment of cardiac chamber mechanics.

Speckle-tracking echocardiography enables the objective and quantitative assessment of subtle myocardial alterations that are undetectable with conventional echocardiography.[9,10] LV global longitudinal strain (GLS) was related to HF severity and found to be an independent predictor for incident HF.[11,12] More recently, deformation imaging has been used to assess LA and RV performance,[10,13] and decreased LA and RV strain was present in ≈ 50% of patients with HF, also predicting unfavorable outcomes.[12,14,15] Although atrioventricular and ventricular interdependence play a crucial role in HF, their alteration in a preclinical setting is not well described, and may help inform the possible preventive strategies for HF occurrence. Furthermore, B-type natriuretic peptide (BNP) level is a powerful predictor of HF,[16,17] but the impact of atrioventricular or ventricular interaction on BNP level is unclear in individuals free of cardiovascular disease. Accordingly, the aims of the present study are to evaluate: (1) the prevalence of LA and RV dysfunction accompanied by subclinical LV dysfunction; (2) whether impaired LVGLS is an independent predictor of LA and RV functional remodeling; (3) the potential correlates of impaired atrioventricular, ventricular interdependence and elevated BNP levels in a community-based cohort without cardiovascular disease.

METHODS

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

Study Population

The study population was derived from the SCADGP (Subclinical Cardiac Dysfunction in General Population) study, which aimed to assess the prevalence and determinants of subclinical cardiac dysfunction in a community-based cohort who voluntarily underwent an extensive cardiovascular health check-up between 2014 and 2018 at the University of Tokyo Hospital.[18] Our hospital provides an extensive health check for the promotion of health and prevention of cardiovascular disease. All participants provided informed consent and the study was approved by the Institutional Review Boards of the University of Tokyo. Among a total of 1243 consecutive SCADGP participants, 1241 underwent laboratory testing, pulmonary function testing, and transthoracic echocardiographic examination. Of the 1241 participants, 161 who met the following criteria were excluded for the following: (1) atrial fibrillation or atrial flutter (n=15), (2) history of coronary artery disease (n=29), (3) LVEF <50% or more than mild valvular heart disease (n=20), and (4) inadequate echocardiographic image quality (n=97). Accordingly, 1080 participants without known cardiovascular disease were included in the analysis (Figure 1).

Risk Factor Assessment

The assessment of cardiovascular risk factors was performed at the time of the health check-up. Hypertension was defined as systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg, or anti-hypertensive medication use. Diabetes was defined by a fasting blood glucose ≥126 mg/dL or the current use of insulin or oral hypoglycemic agents. Hypercholesterolemia was defined as total serum cholesterol >240 mg/dL or the use of lipid-lowering drugs. Chronic obstructive pulmonary disease (COPD) was defined as ratio of forced expiratory volume in the first second to forced vital capacity: FEV1/FVC of <0.7.

Laboratory Testing

Fasting serum glucose, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, C-reactive protein, and BNP concentration were measured in all participants. C-reactive protein

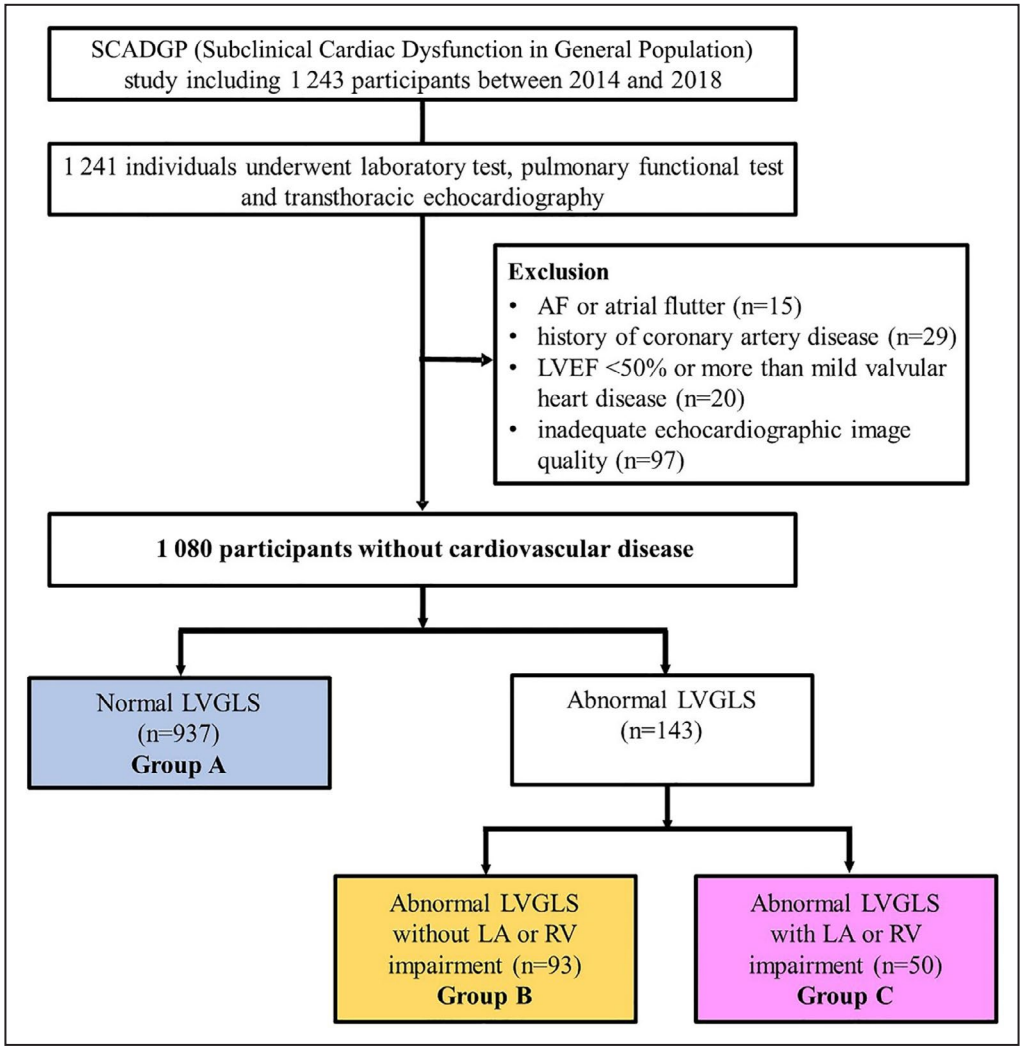

Figure 1. Flowchart illustrating the study population.
AF indicates atrial fibrillation; LA, left atrium; LVEF, left ventricular ejection fraction; LVGLS, left ventricular global longitudinal strain; and RV, right ventricular.

level was determined using the latex agglutination turbidimetric immunoassay method (Eiken Chemical Co., Ltd., Tokyo, Japan), and circulating BNP level was assessed using an immunoenzymometric assay (Tosoh Bioscience, Tokyo, Japan). Elevated BNP level was defined as BNP >28.6 pg/mL for men and >44.4 pg/mL for women, which was derived from a previous large epidemiological study including >12 000 participants.[17]

Echocardiographic Examination

Standard 2-dimensional echocardiography

Echocardiography was performed using a commercially available system (Aplio 300, Toshiba Medical Systems, Tokyo, Japan) by experienced cardiac sonographers masked to clinical information. Conventional echocardiographic measurements were made in accordance with the current recommendations.[19] LV hypertrophy was defined as LV mass indexed to body surface area (LV mass index) >115 g/m^2 for men and >95 g/m^2 for women.[19] LA volume was calculated using the biplane Simpson rule, and then indexed for body surface area. LA enlargement was defined as LA volume index >34 mL/m^2.[19]

RV end-diastolic and end-systolic area were obtained from the apical 4-chamber view, and RV fractional area change (RVFAC) was calculated using the following formula: (RV end-diastolic area–RV end-systolic area)/RV end-diastolic area×100. RV dilatation was defined as RV end-diastolic area index >12.6 cm^2/m^2 in men and >11.5 cm^2/m^2 in women, and impaired RV function as RVFAC <35%.[19]

LV diastolic function was also assessed according to the current guidelines.[20] In brief, pulse-wave Doppler examination of mitral inflow was performed to measure early (E) and late peak velocity (A) from an

apical 4-chamber view. Mitral annular velocities were determined by tissue Doppler imaging, and peak early diastolic velocity (e') of the septal and lateral sides were measured and averaged. Diastolic dysfunction was defined as the presence of ≥3 of the following parameters[20]: (1) average E/e' >14, (2) septal e' velocity <7 cm/s or lateral e' velocity <10 cm/s, (3) maximum velocity of tricuspid regurgitation >2.8 m/s, and (4) LA volume index >34 mL/m^2.

Speckle-tracking echocardiography

Speckle-tracking analysis was performed offline using vendor-independent commercially available software (2D Cardiac Performance Analysis; TomTec Imaging Systems, Germany), as previously described.[18] Briefly, semi-automated border detection was performed using the software, and the endocardial borders of each cardiac chamber were tracked throughout the entire cardiac cycle. Manual correction was performed in case of inaccurate endocardial detection.[13] LV global longitudinal strain (LVGLS) was calculated by averaging the negative peak of longitudinal strain from all 3 apical views. LA strain analysis was calculated by averaging 6 LA segments from the apical 4-chamber and 2-chamber views. Three LA phasic functions including reservoir, conduit, and pump function were determined from the strain curve: LA reservoir strain=peak (maximal) longitudinal LA strain; LA pump strain=LA strain in late diastole; LA conduit strain=LA reservoir strain–LA pump strain (Figure 2A).[13] RV free wall longitudinal strain (RVLS) was evaluated by measuring longitudinal peak systolic strain of the RV free wall from the 4-chamber view (Figure 2B).[13] Smaller absolute strain values of all strain measures correspond to worse cardiac function. Because of the lack of the established normal range for strain measures so far, normal strain values were determined based on the thresholds from our healthy participants. Abnormal LVGLS, LA phasic strain and RVLS were defined as LVGLS >–18.6%, LA reservoir strain <31.4%, LA conduit strain <12.4%, LA pump strain <13.1%, and RVLS >–19.2%, respectively; these values are the 90th percentile of the LVGLS and RVLS, and the 10th percentile of the LA strain distribution in healthy participants from the SCADGP cohort without conditions associated with cardiac remodeling including hypertension, diabetes, coronary artery disease, significant valvular disease, arrhythmias, and body mass index (BMI) >25 kg/m^2. These cutoff values were consistent with previous studies exploring normal strain values.[9,10,21]

Statistical Analysis

Categorical variables are presented as numbers and percentages, and continuous variables as means±SDs or median (interquartile range). Comparison of clinical characteristics and echocardiographic parameters were performed using Chi-square test, Student *t*-test or Wilcoxon rank-sum test as appropriate. Sample size was calculated with 90% power and significance level of 0.05 (target n=231 for LA strain assuming an SD of 7% and to detect a 3% difference, and n=265 for RV strain assuming an SD of 5% and to detect a 2% difference). Multivariable linear regression analyses were constructed to evaluate the association of LVGLS with LA/RV morphological and functional remodeling in 4 sequential models as follows: Model 1 included age and sex; Model 2 included age, sex, hypertension, diabetes, hypercholesterolemia, heart rate, COPD, current smoking and BMI; Model 3 included Model 2 covariates plus LV hypertrophy and diastolic dysfunction; Model 4 included Model 3 covariates plus biomarkers including C-reactive protein and BNP levels. Logistic regression analysis was used to examine the impact of concomitant LA or RV dysfunction accompanied by abnormal LVGLS on elevated BNP levels (>28.6 pg/mL for men and >44.4 pg/mL for women) and corresponding odds ratios (ORs) and 95% CIs were reported. The statistical analysis of the present study was performed retrospectively. Inter-observer variability for LVGLS, LA reservoir, conduit, and pump strain, and RVLS was analyzed in 30 randomly selected subjects assessed by 2 independent and masked observers. Intra-observer variability was also analyzed in 30 participants by the same observer at 2 different time points. The results were analyzed using a Pearson correlation analysis and the Bland-Altman method. A *P* value of <0.05 was considered statistically significant. All statistical analysis was performed with JMP 14 statistical software (SAS Institute, Cary, NC, USA).

RESULTS

Clinical Characteristics and Echocardiographic Measures of the Study Population

Clinical characteristics of the study participants are summarized in Table 1. One hundred and forty-three participants (13.2%) had an abnormal LVGLS (>–18.6%). Participants with abnormal LVGLS were older, more frequently men, and had higher prevalence of hypertension and increased BMI (all *P*<0.05). Table 2 shows conventional and speckle-tracking echocardiographic parameters stratified the presence or absence of abnormal LVGLS. Abnormal LVGLS group had greater LV mass index and higher E/e' ratio (both *P*<0.01). As for LA indices, LA reservoir (36.4±6.3% versus 39.4±6.7%) and conduit strain (16.3±5.8% versus 19.6±6.6%) were significantly decreased in participants with abnormal LVGLS compared with those with normal LVGLS (both *P*<0.001; Table 2), whereas there was no significant

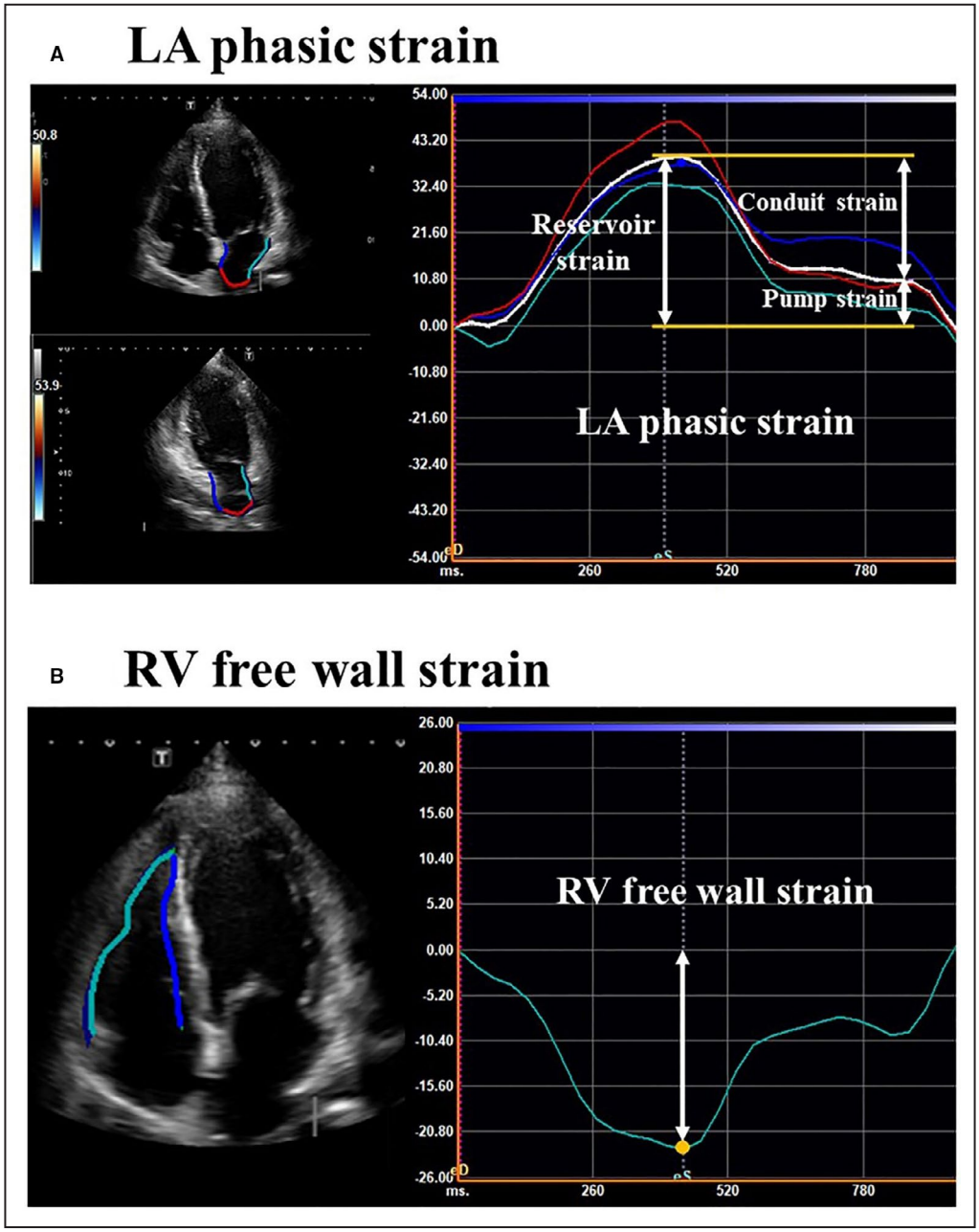

Figure 2. Measurement of left atrium and right ventricle strain using speckle-tracking echocardiography.
Left atrium strain analysis was calculated from the apical 4-chamber and 2-chamber views (A). Right ventricle strain was evaluated by longitudinal peak systolic strain of the right ventricle free wall from the apical 4-chamber view (B). The white curve indicates the average of left atrium strain. LA indicates left atrium; and RV, right ventricle.

difference in LA volume index and pump strain between the 2 groups. In terms of RV parameters, RVLS was significantly reduced in abnormal LVGLS group than in normal LVGLS group (–23.4±5.0% versus –25.4±5.3%, $P<0.001$), while no significant difference was observed in RV size and borderline significance was observed in RVFAC. The prevalence of impaired LA (LA reservoir strain <31.4%) and RV function (RVLS>–19.2%) assessed by speckle-tracking echocardiography was significantly higher in participants with abnormal LVGLS compared witho those with normal LVGLS (18.9% versus 10.0%, $P=0.004$ for LA dysfunction and 19.6% versus 11.7%, $P=0.015$ for RV dysfunction, respectively; Figure 3). In contrast, there was no significant difference in the prevalence of LA dilatation (LA volume index>34 mL/m^2) and decreased

Table 1. Clinical Characteristics of the Study Population

	Entire study participants (N=1080)			Abnormal LVGLS participants (n=143)		
	Normal LVGLS (n=937)	Abnormal LVGLS (n=143)	*P* value	Without LA and/or RV impairment (n=93)	With LA and/or RV impairment (n=50)	*P* value
Age, y	62±12	65±11	0.007	64±11	67±11	0.067
Male sex, n (%)	498 (53.2)	102 (71.3)	<0.001	68 (73.1)	34 (68.0)	0.563
Hypertension, n (%)	302 (32.2)	67 (46.9)	<0.001	47 (50.5)	20 (40.0)	0.292
Diabetes, n (%)	88 (9.4)	21 (14.7)	0.072	15 (16.1)	6 (12.0)	0.624
Hypercholesterolemia, n (%)	347 (37.0)	49 (34.3)	0.577	35 (37.6)	14 (28.0)	0.273
Systolic blood pressure, mm Hg	119±15	125±16	<0.001	125±16	127±15	0.514
Diastolic blood pressure, mm Hg	75±10	77±12	0.003	77±13	79±11	0.386
Heart rate, beats/min	71±10	75±11	<0.001	74±11	77±12	0.141
Current smoking, n (%)	87 (9.3)	14 (9.8)	0.877	12 (12.9)	2 (4.0)	0.138
COPD, n (%)	82 (8.8)	20 (14.0)	0.064	15 (16.1)	5 (10.0)	0.449
Body mass index, kg/m^2	23.2±3.3	24.5±3.5	<0.001	24.4±3.4	24.6±3.6	0.699
Laboratory parameters						
Glucose, mg/dL	99±19	104±21	0.005	105±24	101±16	0.346
Total cholesterol, mg/dL	206±34	204±31	0.346	204±29	202±35	0.696
LDL cholesterol. mg/dL	125±31	124±29	0.776	124±28	124±31	0.918
HDL cholesterol, mg/dL	67±19	59±16	<0.001	59±15	60±18	0.788
Median C-reactive protein, mg/dL	0.04 (IQR, 0.02–0.09)	0.06 (IQR, 0.03–0.11)	0.002	0.05 (IQR, 0.03–0.11)	0.07 (IQR, 0.04–0.12)	0.209
Median B-type natriuretic peptide, pg/mL	16.7 (IQR, 9.4–28.4)	15.1 (IQR, 7.9–31.6)	0.447	15.7 (IQR, 7.4–28.7)	14.6 (IQR, 8.9–38.4)	0.549
Elevated B-type natriuretic peptide level, n (%)	165 (17.6)	33 (23.1)	0.131	18 (19.4)	15 (30.0)	0.211

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

COPD indicates chronic obstructive pulmonary disease; HDL, high-density lipoprotein; IQR, interquartile range; LA, left atrium; LDL, low-density lipoprotein; LVGLS, left ventricular global longitudinal strain; and RV, right ventricular.

RVFAC (<35%) between the 2 groups (*P*=0.73 and 0.68, respectively, also Figure 3).

Association of LVGLS With LA and RV Remodeling

Table 3 presents the association of LVGLS with LA volume index and LA phasic function. Decreased (worse) LVGLS was correlated with decreased LA reservoir and conduit strain, but not with LA volume index and pump strain in unadjusted model. In the multivariable linear regression analysis, LVGLS was associated with LA reservoir and conduit strain in age- and sex-adjusted model (Table 3, Model 1). This association persisted after adjustment for cardiovascular risk factors (Model 2). Further adjustment for LV hypertrophy and LV diastolic dysfunction did not affect the independent association of LVGLS with LA reservoir and conduit strain (Model 3). Finally, even after controlling for pertinent biomarkers including C-reactive protein and BNP levels, LVGLS was significantly and independently associated with LA reservoir and conduit strain (standardized β=−0.20 and −0.19, respectively, both *P*<0.001; Table 3 Model 4). When LA indices were examined as categorical variables, LVGLS was an independent determinant of abnormal LA reservoir (<31.4%) and conduit (<12.4%) strain in a fully adjusted model (adjusted OR, 1.17 and 1.23 per 1% decrease of LVGLS, respectively; both *P*<0.001).

Similarly, in the fully adjusted model including LV morphology and diastolic function, and pertinent biomarkers, LVGLS was independently associated with RVLS (standardized β=0.11, *P*=0.001; Table 4 Model 4), but not with RV size and RVFAC. Multivariable logistic regression analyses also identified that LVGLS carried significantly increased risk for abnormal RVLS (>−19.2%) in the fully adjusted model (adjusted OR, 1.09 per 1% decrease of LVGLS; *P*=0.036).

Impact of Concomitant LA/RV Dysfunction on Serum BNP Level

Among the participants with abnormal LVGLS, 50 individuals (35%) had abnormal LA strain (LA reservoir strain <31.4%) and/or RVLS (>−19.2%), and 93 (65%)

Table 2. Echocardiographic Parameters

	Entire study participants (N=1080)			Abnormal LVGLS participants (n=143)		
	Normal LVGLS (n=937)	Abnormal LVGLS (n=143)	*P* value	Without LA and/or RV impairment (n=93)	With LA and/or RV impairment (n=50)	*P* value
Two-dimensional echocardiography						
LV end-diastolic diameter, mm	45±4	46±4	0.074	46±4	46±5	0.877
LV end-systolic diameter, mm	27±4	29±4	<0.001	28±4	29±4	0.124
LV ejection fraction, %	64.3±5.4	58.4±4.4	<0.001	58.5±4.0	58.1±5.0	0.660
LV mass index, g/m^2	70±15	78±21	<0.001	75±18	83±25	0.020
E wave, cm/s	71±15	64±15	<0.001	64±14	63±17	0.762
A wave, cm/s	68±20	73±21	0.001	72±20	75±23	0.403
E/A ratio	1.14±0.43	0.93±0.31	<0.001	0.95±0.34	0.88±0.23	0.184
e', cm/sec	8.4±2.3	6.9±1.8	<0.001	7.3±1.9	6.2±1.4	<0.001
E/e' ratio	9.0±2.8	9.7±2.9	0.004	9.2±2.6	10.6±3.3	0.009
LA volume index, mL/m^2	25.0±7.5	24.9±7.0	0.876	24.5±6.1	25.6±8.3	0.348
RV end-diastolic area index, cm^2/m^2	8.7±2.1	8.4±2.2	0.090	8.6±2.3	8.0±2.2	0.165
RV end-systolic area index, cm^2/m^2	4.8±1.4	4.8±1.5	0.645	4.8±1.5	4.7±1.5	0.643
RVFAC, %	44.8±7.5	43.5±6.9	0.050	44.3±6.1	41.9±8.1	0.042
TR velocity, m/s	2.3±0.3	2.2±0.2	0.015	2.2±0.2	2.2±0.3	0.263
Estimated PASP, mm Hg	26.4±5.4	25.6±5.5	0.136	25.1±5.3	26.5±5.8	0.180
Speckle-tracking echocardiography						
LVGLS, %	−21.9±2.4	−17.3±1.1	N/A	−17.5±1.0	−17.1±1.2	0.084
LA reservoir strain, %	39.4±6.7	36.4±6.3	<0.001	38.8±4.9	32.0±6.3	<0.001
LA conduit strain, %	19.6±6.6	16.3±5.8	<0.001	17.8±6.0	13.6±4.0	<0.001
LA pump strain, %	19.9±5.1	20.1±5.1	0.597	21.0±5.1	18.4±4.7	0.003
RV free wall strain, %	−25.4±5.3	−23.4±5.0	<0.001	−24.6±3.5	−21.0±6.3	<0.001

Values are mean±SD.

A indicates late diastolic transmitral flow velocity; E, early diastolic transmitral flow velocity; e', early diastolic mitral annular velocity; FAC, fractional area change; GLS, global longitudinal strain; LA, left atrium; LV, left ventricular; PASP, pulmonary artery systolic pressure; RV, right ventricular; RVFAC, RV fractional area change; and TR, tricuspid regurgitation.

had normal LA and RV strain. Participants were then categorized into 3 groups: (1) normal LVGLS group (n=937; Group A); (2) abnormal LVGLS, neither LA nor RV involvement (n=93; Group B); (3) abnormal LVGLS and concomitant LA or RV impairment (n=50; Group C, Figure 1). There was no significant difference in age, sex, BMI, and traditional cardiovascular risk factors as well as LVGLS between groups B and C (Table 1 and 2). However, the prevalence of elevated BNP level was highest in Group C, intermediate in Group B and lowest in Group A (30.0% versus 19.4% versus 17.6%). In the logistic regression analysis, abnormal LVGLS and concomitant LA or RV impairment (Group C) carried a significantly increased risk of elevated BNP compared with normal LVGLS (OR, 2.01; 95% CI, 1.07 to 3.76; *P*=0.030), whereas decreased GLS without LA or RV involvement (Group B) was not associated with elevated BNP levels.

Reproducibility

Excellent correlations were observed in the inter- and intra-observer variabilities for LVGLS, LA reservoir, conduit and pump strain, and RVLS (r=0.96 and r=0.93 for LVGLS, r=0.97 and r=0.97 for reservoir strain, r=0.97 and r=0.97 for conduit strain, r=0.97 and r=0.97 for pump strain, and r=0.94 and r=0.92 for RVLS). In the Bland-Altman analysis, the inter- and intra-observer variabilities were −0.2±1.8% and 0.7±2.3% for LVGLS, 0.5±3.4% and −0.7±3.8% for reservoir strain, −0.1±3.7% and −0.6±4.1% for conduit strain, 0.7±1.9% and −0.1±2.1% for pump strain, and −0.6±4.0% and 0.7±3.8% for RVLS (mean±1.96 SD, respectively).

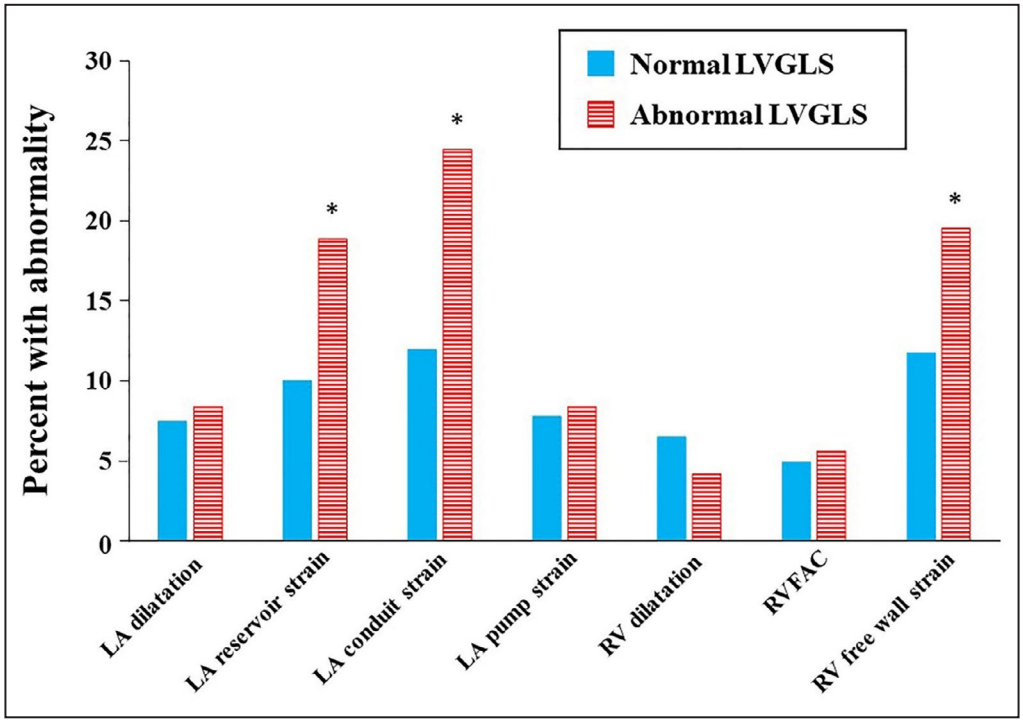

Figure 3. Prevalence of abnormal left atrium and right ventricle echocardiographic indices according to left ventricular global longitudinal strain.
*P<0.05 compared with normal left ventricular global longitudinal strain. LA indicates left atrium; LVGLS, left ventricular global longitudinal strain; RV, right ventricular; and RVFAC, right ventricular fractional area change.

DISCUSSION

In a sample of the general population without overt cardiac disease, we found that (1) LA or RV dysfunction was present in ≈ 30% (20% for each condition) of participants with subclinical LV dysfunction, (2) reduced LVGLS was associated with LA and RV dysfunction assessed by speckle-tracking echocardiography, independent of traditional cardiovascular risk factors, LV geometry and diastolic dysfunction, and (3) concomitant LA/RV dysfunction accompanied by subclinical LV dysfunction carried significant risk of elevated BNP levels.

Atrioventricular and Ventricular Interaction

HF has been conceived mainly as a condition characterized by LV impairment.[2,3] However, recent studies suggested an important role of LA and RV remodeling in the pathophysiology and prognosis in patients with HF. LA enlargement is a robust marker of unfavorable cardiovascular outcomes in various conditions including HF[4,8]; however, LA enlargement is a late and partially irreversible condition with advanced interstitial fibrosis. LA phasic strain accurately reflects the extent of LA structural remodeling, and reduced LA strain precedes LA dilatation.[22] LA dysfunction assessed by LA strain is present in one half of patients with HF; moreover, patients with concurrent LA dysfunction had worse prognosis compared with those without LA dysfunction.[12,14] Similarly, RVLS is a sensitive measure of RV dysfunction and exhibited better correlation with RVEF measured by magnetic resonance imaging than traditional echocardiographic measures.[23] RV dysfunction assessed by RVLS is highly prevalent in patients with HF (>50%), and the coexistence of RV dysfunction with LV dysfunction was related to adverse outcomes.[12,15] Previous population-based studies also investigated the cardiac dysfunction with strain measures, although most of them focused on a single cardiac chamber.[11] In the present study, we performed a comprehensive assessment of LV, RV, and LA mechanics and demonstrated that LA dysfunction was observed in ≈20% of individuals with abnormal LVGLS who had preserved LVEF and no apparent cardiovascular disease including atrial fibrillation. Furthermore, one fifth of participants with impaired GLS also exhibited reduced RVLS and their association was independent of clinical variables and LV morphology and diastolic parameters. On the other hand, 5% to 10% of patients with normal LVGLS showing abnormalities in the LA and RV indices. One possible explanation is

Table 3. Association of LVGLS With LA Volume Index and LA Phasic Function in Univariable and Multivariable Linear Regression Analyses

	LA volume index (mL/m^2)		LA reservoir strain (%)		LA conduit strain (%)		LA pump strain (%)	
	Standardized β (95% CI)	*P* value	Standardized β (95% CI)	*P* value	Standardized β (95% CI)	*P* value	Standardized β (95% CI)	*P* value
Univariable	0.04 (−0.06 to 0.26)	0.209	−0.25 (−0.74 to −0.46)	<0.001	−0.29 (−0.83 to −0.56)	<0.001	0.05 (−0.01 to 0.21)	0.088
Model 1	0.01 (−0.14 to 0.20)	0.742	−0.22 (−0.68 to −0.41)	<0.001	−0.24 (−0.71 to −0.46)	<0.001	0.02 (−0.08 to 0.15)	0.547
Model 2	0.01 (−0.13 to 0.20)	0.694	−0.22 (−0.68 to −0.40)	<0.001	−0.20 (−0.62 to −0.36)	<0.001	−0.03 (−0.17 to 0.06)	0.369
Model 3	−0.01 (−0.19 to 0.12)	0.655	−0.21 (−0.66 to −0.38)	<0.001	−0.20 (−0.60 to −0.35)	<0.001	−0.02 (−0.16 to 0.07)	0.460
Model 4	−0.03 (−0.22 to 0.08)	0.355	−0.20 (−0.63 to −0.36)	<0.001	−0.19 (−0.59 to −0.34)	<0.001	−0.02 (−0.15 to 0.09)	0.615

Model 1: age- and sex-adjusted.
Model 2: adjusted for age, sex, hypertension, diabetes, hypercholesterolemia, heart rate, chronic obstructive pulmonary disease, current smoking and body mass index.
Model 3: adjusted for variables as in Model 2 and left ventricular hypertrophy and diastolic dysfunction.
Model 4: adjusted for variables as in Model 3 and C-reactive protein and B-type natriuretic peptide levels.
LVGLS indicates left ventricular global longitudinal strain; and LA, left atrium.

that LA or RV impairment may precede LV dysfunction under certain specific conditions, although technical factors might also be involved. Furthermore, the higher prevalence of abnormal LA and RV strain compared with LA/RV dilatation and reduced RVFAC might be partially explained by the fact that speckle-tracking echocardiography enables the objective and quantitative assessment of subtle myocardial alterations that are undetectable with conventional echocardiography.

Possible Mechanism Linking Abnormal LVGLS and LA/RV Dysfunction

Several possible mechanisms might account for the independent association between impaired GLS and LA/RV dysfunction. First, hemodynamic disturbances may occur in subjects with abnormal LVGLS even before the development of overt cardiovascular disease or LVEF reduction. Biering-Sørensen T et al. demonstrated that decreased GLS at rest predicted exercise-induced rise in pulmonary wedge pressure in patients with normal LVEF.[24] Second, impaired coronary microcirculation can adversely affect both ventricular and atrial function. Indeed, decreased coronary flow reserve was associated with impaired LVGLS as well as LA and RV functional alteration in individuals with normal LVEF.[25,26] Finally, an anatomical interaction might potentially explain those relationships. LV function modulates LA reservoir function through the systolic downward motion of the LV base.[27] As for ventricular interdependence, LV and RV share the myofibers that encircle both ventricles.[28]

Impact of Atrioventricular and Ventricular Interdependence on BNP

Concentration of BNP is a reliable surrogate of incident HF and also correlated with the disease severity in an established HF condition.[14,16] Patients with HF with concomitant LA or RV dysfunction had significantly greater BNP level compared with those without LA/RV abnormalities, and they had worse cardiovascular outcomes.[14] Our study extends these observations to the subclinical LV dysfunction domain, namely the observation that coexistence of abnormal LVGLS and concomitant LA or RV impairment carried significantly increased risk of elevated BNP. These subjects may have more advanced LV myocardial injury which may explain their greater BNP concentration. From another point of view, individuals with elevated BNP in the community-based cohort may have multi-chamber cardiac impairment. Indeed, previous clinical and experimental studies demonstrated that BNP is secreted from LV as well as RV and LA especially in an early HF setting.[29,30]

Table 4. Association of LVGLS With RV Size and Function in Univariable and Multivariable Linear Regression Analyses

	RV end-diastolic area index (cm^2/m^2)		RV fractional area change (%)		RV free wall strain (%)	
	Standardized β (95% CI)	*P* value	Standardized β (95% CI)	*P* value	Standardized β (95% CI)	*P* value
Univariable	−0.07 (−0.10 to −0.005)	0.031	−0.07 (−0.35 to −0.02)	0.025	0.17 (0.21–0.43)	<0.001
Model 1	−0.08 (−0.11 to −0.01)	0.013	−0.05 (−0.30 to 0.04)	0.137	0.13 (0.13–0.37)	<0.001
Model 2	−0.02 (−0.07 to 0.03)	0.510	−0.05 (−0.31 to 0.04)	0.135	0.11 (0.09–0.34)	<0.001
Model 3	−0.02 (−0.07 to 0.03)	0.476	−0.04 (−0.30 to 0.06)	0.181	0.11 (0.08–0.33)	0.001
Model 4	−0.02 (−0.07 to 0.03)	0.452	−0.05 (−0.31 to 0.05)	0.145	0.11 (0.08–0.33)	0.001

Model 1: age- and sex-adjusted.
Model 2: adjusted for age, sex, hypertension, diabetes, hypercholesterolemia, heart rate, chronic obstructive pulmonary disease, current smoking, and body mass index.
Model 3: adjusted for variables as in Model 2 and left ventricle hypertrophy and diastolic dysfunction.
Model 4: adjusted for variables as in Model 3 and C-reactive protein and B-type natriuretic peptide levels.
LVGLS indicates left ventricular global longitudinal strain; and RV, right ventricular.

Clinical Implication

While current HF studies have reported that >50% patients displayed concomitant LA/RV dysfunction, 30% of individuals exhibited decreased LA or RV function (20% in each) in participants with subclinical LV dysfunction even before the development of HF. This finding may provide insight into the course and pathophysiology of HF development. Of note, the 20% to 30% differences in the prevalence of LA/RV dysfunction between preclinical and overt HF settings may come from the complex interplay of multiple acquired comorbidities such as atrial fibrillation, coronary artery disease and metabolic disorders. Because these factors are partially modifiable, early intervention on them might enable to prevent or delay the occurrence of HF. Comprehensive assessment of cardiac chamber mechanics by deformation imaging at a subclinical stage may add valuable information for the risk stratification for HF. Furthermore, our findings also suggest that individuals with elevated BNP level have multi-chamber impairment even in the preclinical setting. This may partially explain their higher incidence of HF and closer follow-up may be needed. On the other hand, there was a significant overlap for LA and RV strain measures between the groups, a circumstance that should be considered for clinical application.

Strengths and Limitations

Strengths of this study included the large number of individuals free of cardiovascular disease and the comprehensive evaluation of LV, RV, and LA mechanics using state-of-the art non-invasive imaging techniques. Several limitations should be considered. Our cross-sectional study design limits our ability to draw causal inferences. In addition, follow-up and clinical end points were not evaluated in this study. Furthermore, we used internally obtained cutoff values for the cardiac variables examined because of the lack of established normal values; therefore, cannot be directly extended to other populations with different demographic composition and risk profiles. However, our cutoff values of strain measures are comparable with those reported in the previous studies.[9,10,21] Finally, we did not perform right atrial strain measurement.

CONCLUSIONS

The present study demonstrated that LA or RV dysfunction was present in ≈30% (20% in each) of participants with abnormal LVGLS. Impaired LVGLS was independently associated with both LA and RV functional remodeling and concomitant LA or RV dysfunction was associated with elevated BNP levels. Our findings may provide valuable insights for a better understanding of abnormalities in atrioventricular and ventricular interdependence, identification of individuals at higher risk for HF, and possible strategies to prevent HF development.

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