

Blood pressure categorization and subclinical left ventricular dysfunction in antihypertensive medication-naive subjects

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Abstract

Aims The impact of blood pressure (BP) levels on subclinical left ventricular (LV) dysfunction and possible sex-specific difference remains unclarified. This study investigated the relationship between BP categories given in the new 2017 American College of Cardiology (ACC)/American Heart Association (AHA) guideline and subclinical LV dysfunction in subjects free of cardiac disease.

Methods and results We examined antihypertensive medication-naive 858 individuals who underwent extensive cardiovascular health check-up. LV global longitudinal (LVGLS) and circumferential strain (LVGCS) were assessed by two-dimensional speckle-tracking echocardiography. Participants were categorized into four groups: normal BP, elevated BP, isolated diastolic hypertension (IDH), and systolic hypertension (SH). Among the 858 participants, 422 individuals had normal BP, 113 had elevated BP, 160 had IDH, and 163 had SH. Prevalence of abnormal LVGLS ($>-18.6\%$) was greatest in SH (19.0%), followed by IDH (17.5%), elevated BP (14.2%), and normal BP (7.1%, $P < 0.001$); no significant differences were observed for LVGCS ($P = 0.671$). In the multivariable analyses, IDH and SH were associated with impaired LVGLS [adjusted odds ratio (OR) 2.69 and 2.66, $P < 0.001$], and borderline significance was observed for elevated BP (adjusted OR 1.90, $P = 0.060$); there was no significant association between any of the BP groups and LVGCS. In sex-stratified analysis, IDH and SH carried the significant risk of abnormal LVGLS in both sexes, while elevated BP was associated with LVGLS only in women.

Conclusions Isolated diastolic hypertension and SH redefined by ACC/AHA guideline carried significant risk for LVGLS, but not LVGCS. Elevated BP was associated with LVGLS only in women. Our findings provide information on cardiac correlates of the newly established BP categories.

Keywords Blood pressure; Left ventricular strain; Primary prevention; Sex difference; Speckle-tracking echocardiography

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Introduction

The incidence of heart failure (HF) continues to increase despite significant advances of its evaluation and treatment. In the USA, it is estimated that over 8 million adults will suffer from HF by the year 2030, with projected total costs of HF will increase by 130% in the next 20 years to \$70bn.¹ As such, the strategies to reduce HF occurrence have focused on identify-

ing asymptomatic individuals at high risk of HF (i.e. Stage A/B HF). Hypertension is by far the most common antecedent condition in patients with HF. In the Framingham Heart Study, 91% of HF patients had prior hypertension, and hypertension accounted for 59% of incident HF in women and 39% in men.² Although left ventricular (LV) hypertrophy and diastolic dysfunction are discernible manifestations of hypertension-related cardiac remodelling and established

markers for HF occurrence, these conditions have been attributed to extracellular matrix remodelling with collagen deposition and fibrosis, suggesting the presence of partially irreversible conditions and therefore limited effect of therapeutic intervention.^{3–5} Echocardiography-derived LV strain, particularly LV global longitudinal strain (LVGLS), is emerging as a more sensitive and accurate measurement of LV function over conventional parameters; impaired LVGLS was observed in hypertensive patients.^{6,7} The 2017 American College of Cardiology (ACC) and the American Heart Association (AHA) hypertension guideline lowered the threshold categories of hypertension, and blood pressure (BP) level was divided into the normal [systolic BP (SBP) <120 mmHg and diastolic BP (DBP) <80 mmHg], elevated (SBP 120–129 mmHg and DBP < 80 mmHg), and hypertension (SBP ≥ 130 mmHg or DBP ≥ 80 mmHg), a change that resulted in several consequences.⁸ One of these is the redefinition of systolic hypertension, now defined as SBP ≥ 130 mmHg. In addition, isolated diastolic hypertension (IDH) was also redefined as a DBP ≥ 80 mmHg with an SBP < 130 mmHg. However, it is unknown whether these new categories carry a significant risk of unfavourable LV functional remodelling. Understanding the association between BP levels and subclinical LV dysfunction might enhance our understanding of hypertension-related HF and inspire potential preventive strategies. Furthermore, previous studies demonstrated that the pattern and risk of LV remodelling and subsequent HF occurrence caused by high BP differ by sex.^{2,9,10} Therefore, the present study aimed to investigate the association between the new BP

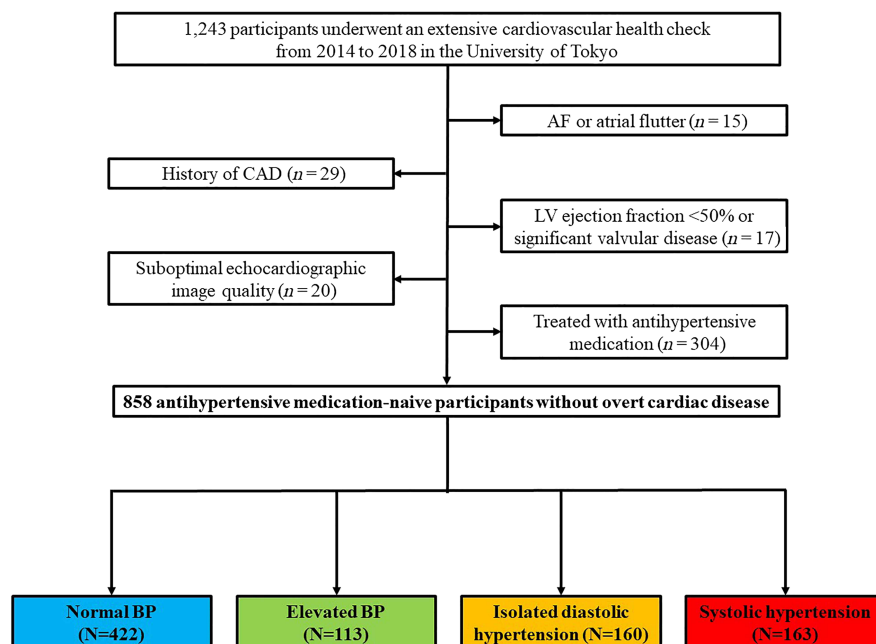
categories and subclinical LV functional remodelling in a community-based cohort without overt cardiac disease and examine possible sex-specific differences.

Methods

Study population

The study population was derived from the Subclinical Cardiac Dysfunction in General Population (SCADGP) study. This study was designed to assess the prevalence and determinants of subclinical cardiac dysfunction in a community-based cohort, which underwent an extensive cardiovascular health check at the University of Tokyo Hospital.¹¹ All participants provided informed consent, and the Institutional Review Board of the University of Tokyo approved the study. Among the 1243 participants enrolled in the SCADGP study, participants who met the following criteria were excluded: history of atrial fibrillation or atrial flutter ($n = 15$), history of coronary artery disease ($n = 29$), decreased LV ejection fraction (<50%) or significant valvular disease ($n = 17$), and suboptimal image quality or incomplete assessment of the echocardiographic parameters ($n = 20$). Furthermore, participants treated with antihypertensive medication ($n = 304$) were also excluded. Thus, the final study group consisted of 858 antihypertensive medication-naïve participants without overt cardiac disease (Figure 1).

Figure 1 Flow chart illustrating the study population. AF, atrial fibrillation; BP, blood pressure; CAD, coronary artery disease; LV, left ventricular.



Blood pressure classification and other risk factor assessment

Blood pressure was measured in sitting position after 5 min of rest using a sphygmomanometer (UDEX-i, Canon Lifecare Solutions Inc., Tokyo, Japan) on the same day as the echocardiographic examination. First, SBP and DBP were classified into the following three categories: normal BP: SBP < 120 mmHg and DBP < 80 mmHg, elevated BP: SBP 120–129 mmHg and DBP < 80 mmHg, and hypertension: SBP ≥ 130 mmHg or DBP ≥ 80 mmHg, according to the new AHA/ACC guideline.⁸ Hypertension was then subsequently divided into two groups; IDH: DBP ≥ 80 mmHg with an SBP < 130 mmHg and systolic hypertension (SH): SBP ≥ 130 mmHg (Figure 1). Diabetes mellitus was defined by the current use of insulin or hypoglycaemic agents, or a fasting glucose of ≥126 mg/dL.¹ Hypercholesterolaemia was defined as total serum cholesterol >240 mg/dL, or the use of lipid-lowering medications.¹ Body mass index (BMI) was calculated using height and weight (kg/m²). Venous blood samples were drawn in the fasting condition. Fasting blood glucose, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, estimated glomerular filtration rate (eGFR), and B-type natriuretic peptide (BNP) were analysed in all participants.

Echocardiographic examination

Two-dimensional echocardiography

Echocardiographic examination was performed using a commercially available system (Aplio 300, Toshiba Medical Systems, Tokyo, Japan) in accordance with a standardized protocol by trained sonographers blinded to the participant's clinical information. The linear dimensions of the cardiac chambers were measured in the standard manner.¹² LV mass was calculated with a validated formula¹³: LV mass (g) = 0.8 (1.04 [(SWT + LVEDD + PWT)³ - LVEDD³]) + 0.6, where SWT is the LV end-diastolic septal wall thickness, LVEDD is the LV end-diastolic diameter, and PWT is the LV end-diastolic posterior wall thickness. Left atrial (LA) volume was measured from the apical two-chamber and four-chamber views using the biplane Simpson's rule.¹² LV mass and LA volume were then indexed for body surface area. LV diastolic parameters were assessed according to the current guideline.¹⁴ Briefly, transmitral diastolic flow was obtained from an apical four-chamber view. Pulsed-wave Doppler examination of mitral inflow was performed to measure early (E) and late peak velocity. Peak early diastolic mitral annular velocity (*e'*) was also measured from tissue Doppler imaging in the lateral and the septal mitral annulus, and the average value was used. The ratio of E to mean *e'* was then calculated (E/*e'*).

Speckle-tracking echocardiography

Speckle-tracking analysis was performed offline using vendor-independent commercially available software (2D Cardiac Performance Analysis, TOMTEC Imaging Systems, Unterschleißheim, Germany). Semi-automated border detection was performed, and LV borders were tracked throughout the entire cardiac cycle. Manual correction was performed in case of inaccurate endocardial detection. LVGLS was calculated averaging the negative peak of longitudinal strain from all three apical views including the four-chamber, two-chamber, and long-axis views, according to the current guideline.¹⁵ LV global circumferential strain (GCS) was calculated from the midventricular parasternal short-axis view. According to the definition of LV strain, negative strain denotes shortening for LVGLS and LVGCS, which results in smaller absolute values representing worse function. Impaired LVGLS and LVGCS were defined as GLS > -18.6% and GCS > -23.2%, which were the 90th percentile of the strain value distribution in the SCADGP participants without any conditions associated with LV remodelling.¹⁶ Excellent inter-observer and intra-observer variabilities for LVGLS and LVGCS measurements were observed in 15 randomly selected participants (*r* = 0.94 and *r* = 0.95 respectively for LVGLS, and *r* = 0.96 and *r* = 0.98 for LVGCS). In Bland–Altman analysis, agreement in LVGLS between the inter-observer and intra-observer measurements was -0.3 ± 2.1% and 0.8 ± 1.9% for LVGLS, and -1.2 ± 2.1% and -0.2 ± 1.4% for LVGCS (mean ± 1.96 standard deviation, respectively).

Statistical analysis

Continuous variables are presented as mean ± standard deviation or median (inter-quartile range) and compared across the four BP categories (normal BP, elevated BP, IDH, and SH) by analysis of variance with Tukey–Kramer *post hoc* analysis or a Kruskal–Wallis test with the post-test Dunn correction, as appropriate. Categorical variables were described as numbers and proportions and compared using the χ^2 test. Univariable and multivariable logistic regression analyses were conducted to evaluate the association between BP categories and abnormal LV strain (GLS > -18.6% and GCS > -23.2%), and corresponding odds ratios (ORs) along with their 95% confidence interval (CI) were calculated. Adjustment for covariates was performed in three sequential models as follows: Model 1: adjustment for age and sex; Model 2: adjustment for age, sex, diabetes mellitus, hyperlipidaemia, current smoking, and BMI; and Model 3: adjustment as in Model 2 plus pertinent laboratory parameters including eGFR and BNP. Analyses were performed in the entire group as well as sex subgroups. A value of *P* < 0.05 was considered significant. Statistical analyses were performed using JMP 14 software (SAS Institute, Cary, NC, USA).

Results

Baseline characteristics

Clinical characteristics and echocardiographic data stratified by the four BP categories are shown in *Table 1*. The mean age was 61 ± 11 years, and 459 (53%) were men. Among the 858 participants, 422 (49.2%) individuals were classified as having normal BP, 113 (13.2%) as elevated BP, 160 (18.6%) as IDH, and 163 (19.0%) as SH (*Figure 1*). Elevated BP and SH groups were older; two hypertensive groups (IDH and SH) had larger BMI compared with normal BP group. There was no significant difference in the prevalence of diabetes mellitus, hyperlipidaemia, and current smoking status across the four groups, while lower HDL cholesterol level was observed in IDH and SH groups.

Blood pressure categories and subclinical left ventricular dysfunction

Elevated BP, IDH, and SH groups exhibited significantly larger LV mass index and lower E/A ratio and e' velocity compared with normal BP group (all $P < 0.05$). E/ e' ratio was higher in participants with elevated BP and SH (both $P < 0.05$), but not in those with IDH. In terms of LV strain, significantly reduced LVGLS was observed in individuals with elevated BP and the two hypertension groups (all $P < 0.05$), whereas there was no significant difference in LVGCS across the four BP categories (also *Table 1*). The prevalence of impaired LVGLS ($> -18.6\%$) was greatest in SH group (19.0%), followed by IDH (17.5%), elevated BP (14.2%), and normal BP groups (7.1%, overall $P < 0.001$; *Figure 2A*); no significant differences were observed for LVGCS (*Figure 2B*). *Table 2* demonstrates

Table 1 Characteristics of the study population

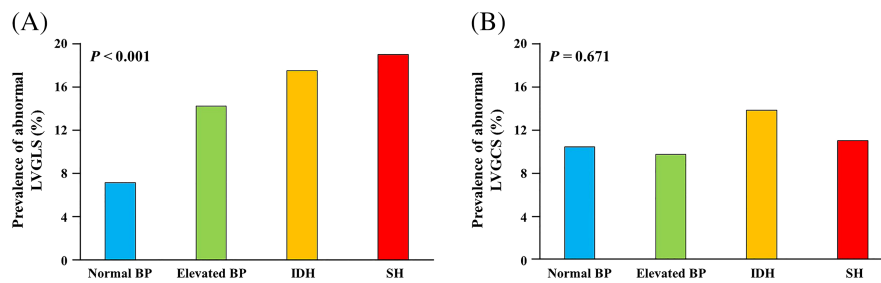
	Normal BP (n = 422)	Elevated BP (n = 113)	IDH (n = 160)	SH (n = 163)	P value
Age (years)	59 ± 12	$65 \pm 10^*$	59 ± 10	$64 \pm 11^*$	<0.001
Men, n (%)	200 (47.4)	63 (55.8)	101 (63.1)	95 (58.3)	0.003
Diabetes mellitus, n (%)	25 (5.9)	8 (7.1)	11 (6.9)	18 (11.0)	0.200
Hyperlipidaemia, n (%)	142 (33.6)	32 (28.3)	56 (35.0)	48 (29.4)	0.512
Current smoking, n (%)	53 (12.6)	11 (9.7)	16 (10.0)	10 (6.1)	0.149
Body height (cm)	163 ± 9	162 ± 9	164 ± 9	162 ± 10	0.046
Body weight (kg)	59 ± 11	60 ± 11	$64 \pm 12^*$	$64 \pm 13^*$	<0.001
Body surface area (m ²)	1.62 ± 0.18	1.64 ± 0.18	$1.70 \pm 0.19^*$	$1.68 \pm 0.20^*$	<0.001
Body mass index (kg/m ²)	22.2 ± 3.0	22.9 ± 2.7	$23.6 \pm 3.2^*$	$24.4 \pm 3.4^*$	<0.001
Systolic blood pressure (mmHg)	106 ± 9	$124 \pm 3^*$	$121 \pm 6^*$	$138 \pm 7^*$	<0.001
Diastolic blood pressure (mmHg)	68 ± 7	$73 \pm 4^*$	$84 \pm 5^*$	$84 \pm 11^*$	<0.001
Laboratory parameters					
Fasting glucose (mg/dL)	95 ± 17	$99 \pm 14^*$	97 ± 14	$101 \pm 19^*$	<0.001
Total cholesterol (mg/dL)	209 ± 35	206 ± 28	210 ± 35	210 ± 34	0.613
LDL cholesterol (mg/dL)	126 ± 30	123 ± 25	129 ± 33	130 ± 29	0.102
HDL cholesterol (mg/dL)	69 ± 19	69 ± 19	$63 \pm 19^*$	$63 \pm 18^*$	<0.001
eGFR (mL/min/1.73 m ²)	74 ± 14	72 ± 13	74 ± 13	73 ± 16	0.459
B-type natriuretic peptide (pg/mL)	15 (9–24)	18 (11–28)*	15 (9–24)	19 (10–30)	0.013
Echocardiographic parameters					
LV end-diastolic diameter (mm)	44.7 ± 4.0	44.6 ± 4.3	45.2 ± 4.5	45.1 ± 4.4	0.272
LV end-systolic diameter (mm)	27.5 ± 3.3	27.5 ± 3.9	27.8 ± 3.7	27.1 ± 3.9	0.188
LV septal wall thickness (mm)	7.8 ± 1.3	$8.2 \pm 1.4^*$	$8.3 \pm 1.4^*$	$8.6 \pm 1.6^*$	<0.001
LV posterior wall thickness (mm)	7.5 ± 1.2	$8.0 \pm 1.2^*$	$8.2 \pm 1.2^*$	$8.3 \pm 1.3^*$	<0.001
Relative wall thickness	0.34 ± 0.06	$0.36 \pm 0.07^*$	$0.36 \pm 0.06^*$	$0.37 \pm 0.06^*$	<0.001
LV ejection fraction (%)	64.1 ± 5.6	63.2 ± 6.1	$62.2 \pm 5.4^*$	62.8 ± 5.5	<0.001
LV mass index (g/m ²)	65.4 ± 12.8	$70.5 \pm 14.6^*$	$71.2 \pm 16.8^*$	$74.0 \pm 16.8^*$	<0.001
E wave (cm/s)	72.5 ± 16.0	68.9 ± 13.5	$68.6 \pm 14.5^*$	$66.2 \pm 14.8^*$	<0.001
A wave (cm/s)	59.5 ± 16.9	$69.8 \pm 17.6^*$	$65.4 \pm 17.6^*$	$74.1 \pm 18.3^*$	<0.001
Deceleration time (ms)	206 ± 38	213 ± 47	211 ± 40	216 ± 43	0.116
E/A ratio	1.32 ± 0.50	$1.05 \pm 0.36^*$	$1.11 \pm 0.34^*$	$0.93 \pm 0.25^*$	<0.001
e' (cm/s)	9.3 ± 2.5	$7.8 \pm 2.1^*$	$8.3 \pm 1.9^*$	$7.3 \pm 1.8^*$	<0.001
E/ e' ratio	8.2 ± 2.5	$9.2 \pm 2.6^*$	8.6 ± 2.4	$9.5 \pm 2.7^*$	<0.001
LA volume index (mL/m ²)	23.0 ± 5.8	25.2 ± 7.7	23.9 ± 6.6	$25.9 \pm 8.1^*$	<0.001
LVGLS (%)	-22.2 ± 2.9	$-21.1 \pm 2.7^*$	$-20.9 \pm 2.6^*$	$-20.8 \pm 2.5^*$	<0.001
LVGCS (%)	-28.3 ± 4.3	-28.3 ± 4.7	-27.6 ± 4.4	-28.6 ± 4.7	0.328

A, late diastolic transmitral flow velocity; BP, blood pressure; E, early diastolic transmitral flow velocity; e' , early diastolic mitral annular velocity; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; IDH, isolated diastolic hypertension; LA, left atrial; LDL, low-density lipoprotein; LV, left ventricular; LVGCS, left ventricular global circumferential strain; LVGLS, left ventricular global longitudinal strain; SH, systolic hypertension.

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

* $P < 0.05$ compared with normal BP group.

Figure 2 Prevalence of abnormal (A) left ventricular global longitudinal strain (LVGLS) and (B) left ventricular global circumferential strain (LVGCS) according to the blood pressure (BP) categories. IDH, isolated diastolic hypertension; SH, systolic hypertension.



the association between BP categories and impaired LV strain. Elevated BP, IDH, and SH were all associated with impaired LVGLS in univariable model (OR 2.16, 2.77, and 3.07, all $P < 0.05$). Multivariable adjustment for age, sex, diabetes mellitus, hyperlipidaemia, smoking status, and BMI attenuated the association between elevated BP and LVGLS (adjusted OR 1.83, $P = 0.075$; Table 2, Model 2), whereas IDH and SH were significantly associated with abnormal LVGLS (adjusted OR 2.60 and 2.57, $P < 0.001$). Even after controlling for eGFR and BNP (Table 2, Model 3), IDH and SH remained significantly associated with LVGLS (adjusted OR 2.69 and 2.66, respectively; both $P < 0.001$), and a non-significant trend was observed between elevated BP and impaired LVGLS (adjusted OR 1.90, $P = 0.060$). In contrast, there was no independent association between all three hypertensive categories and LVGCS (also Table 2).

Sex-specific difference on the association between blood pressure categories and left ventricular global longitudinal strain

In the univariable analysis, IDH and SH carried a significant risk of abnormal LVGLS in both sexes, although a more pronounced association was observed in women (OR 2.85 and 3.66, both $P < 0.05$) than in men (OR 2.36 and 2.55, both $P < 0.05$). Interestingly, elevated BP was associated with LVGLS in women (OR 3.45, $P = 0.017$), but not in men (OR 1.50, $P = 0.346$). In the multivariable logistic regression analysis adjusted for age and traditional risk factors, IDH and SH were significantly associated with abnormal LVGLS in both men and women (Table 3, Model 2), whereas elevated BP was associated with LVGLS only in women. Further adjustment for eGFR and BNP levels did not affect the independent association of elevated BP and hypertension with abnormal LVGLS in women. In additional analyses, we applied sex-specific cut-points for LVGLS ($> -18.4\%$ for men and $> -19.0\%$ for women).¹⁶ IDH and SH carried an independent risk for abnormal LVGLS in the fully adjusted model including traditional risk factors and serum biomarkers in both sex subgroups (adjusted OR 2.59 and 2.38 for men and 2.99 and 2.76 for

women, all $P < 0.05$), whereas elevated BP was related to LVGLS only in women. These results were concordant with our observations from the general analysis.

Discussion

The major findings of the present study were as follows: (i) in a sample of the general population naive to antihypertensive medications and free from overt cardiac disease, high BP was associated with LVGLS, but not LVGCS; (ii) IDH and SH carried an independent risk for abnormal LVGLS; and (iii) elevated BP exhibited significant risk for impaired LVGLS in women but not in men.

Hypertension, left ventricular remodelling, and heart failure

Epidemiological studies identified high BP as a crucial and modifiable risk factor for HF, and approximately 50% of incident HF is attributed to this condition.² LV hypertrophy and diastolic dysfunction are common manifestation of cardiac remodelling in hypertensive patients and are established surrogate markers for HF, although these changes are late and partially irreversible conditions because of interstitial fibrosis and myocardial apoptosis.^{3–5} Speckle-tracking echocardiography has emerged as a sensitive tool for the early detection of LV functional remodelling, with excellent feasibility and reproducibility. Recent studies demonstrated an impaired LVGLS in hypertensive patients,^{6,7} which is identified as an independent and strong predictor for incident HF.¹⁷

Elevated blood pressure and left ventricular strain

The 2017 ACC/AHA guideline revised the definition of hypertension to $\geq 130/80$ mmHg and elevated BP as SBP 120–129 mmHg and DBP < 80 mmHg.⁸ Recent population-based studies examined the prognostic impact of the new BP cate-

Table 2 Association of BP level with impaired LVGLS and LVGCS

	Abnormal LVGLS (> -18.6%)				Abnormal LVGCS (> -23.2%)							
	Elevated BP		IDH		SH		Elevated BP		IDH		SH	
	Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value
Univariable	2.16 (1.13-4.11)	0.020	2.77 (1.60-4.81)	<0.001	3.07 (1.79-5.26)	<0.001	0.92 (0.46-1.86)	0.830	1.37 (0.79-2.37)	0.260	1.07 (0.60-1.91)	0.828
Model 1	1.88 (0.97-3.64)	0.061	2.60 (1.49-4.54)	<0.001	2.71 (1.56-4.69)	<0.001	0.90 (0.44-1.83)	0.773	1.25 (0.72-2.18)	0.425	1.02 (0.56-1.84)	0.951
Model 2	1.83 (0.94-3.55)	0.075	2.60 (1.48-4.57)	<0.001	2.57 (1.45-4.55)	<0.001	0.89 (0.44-1.82)	0.753	1.22 (0.70-2.14)	0.486	0.95 (0.52-1.77)	0.884
Model 3	1.90 (0.97-3.71)	0.060	2.69 (1.52-4.74)	<0.001	2.66 (1.50-4.73)	<0.001	0.91 (0.45-1.87)	0.807	1.24 (0.71-2.18)	0.450	0.98 (0.53-1.81)	0.940

BMI, body mass index; BNP, B-type natriuretic peptide; BP, blood pressure; CI, confidence interval; eGFR, estimated glomerular filtration rate; IDH, isolated diastolic hypertension; LVGCS, left ventricular global circumferential strain; LVGLS, left ventricular global longitudinal strain; SH, systolic hypertension.
 Reference: normal BP. Model 1: adjusted for age and sex. Model 2: adjusted for Model 1 plus diabetes mellitus, hyperlipidaemia, smoking status, and BMI. Model 3: adjusted for Model 2 plus eGFR and BNP.

Table 3 Association between BP level and impaired LVGLS (> -18.6%) in sex subgroup

	Men (n = 459)						Women (n = 399)					
	Elevated BP		IDH		SH		Elevated BP		IDH		SH	
	Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value
Univariable	1.50 (0.65-3.49)	0.346	2.36 (1.21-4.60)	0.012	2.55 (1.31-4.99)	0.006	3.45 (1.24-9.57)	0.017	2.85 (1.04-7.85)	0.042	3.66 (1.45-9.20)	0.006
Model 1	1.39 (0.59-3.28)	0.448	2.42 (1.24-4.72)	0.010	2.46 (1.25-4.83)	0.009	3.05 (1.08-8.59)	0.035	2.81 (1.02-7.75)	0.047	3.07 (1.19-7.94)	0.021
Model 2	1.33 (0.56-3.14)	0.521	2.45 (1.24-4.83)	0.010	2.36 (1.17-4.76)	0.016	3.23 (1.12-9.31)	0.030	2.82 (1.01-7.91)	0.049	2.94 (1.05-8.19)	0.040
Model 3	1.37 (0.57-3.28)	0.477	2.52 (1.27-4.99)	0.008	2.42 (1.20-4.90)	0.014	3.31 (1.14-9.57)	0.027	3.02 (1.07-8.54)	0.037	3.07 (1.09-8.64)	0.033

BMI, body mass index; BNP, B-type natriuretic peptide; BP, blood pressure; CI, confidence interval; eGFR, estimated glomerular filtration rate; IDH, isolated diastolic hypertension; LVGLS, left ventricular global longitudinal strain; SH, systolic hypertension.
 Reference: normal BP. Model 1: adjusted for age. Model 2: adjusted for Model 1 plus diabetes mellitus, hyperlipidaemia, smoking status, and BMI. Model 3: adjusted for Model 2 plus eGFR and BNP.

gories, particularly for individuals with elevated BP. Yano *et al.* examined the association between elevated BP and incident cardiovascular disease including coronary heart disease, hospitalization for HF, stroke, transient ischaemic attack, or intervention for peripheral artery disease in the prospective cohort Coronary Artery Risk Development in Young Adults (CARDIA) study.¹⁸ Elevated BP was significantly and independently associated with cardiovascular disease, although its impact on HF occurrence did not reach statistical significance, partially due to the limited number of HF events. Rattani *et al.* identified elevated BP as independent risk for new-onset atrial fibrillation in the Atherosclerosis Risk in Communities (ARIC) study.¹⁹ Kang *et al.* demonstrated that elevated BP carries significant and independent risk of coronary artery calcification in 96 166 low-risk adults.²⁰ In the present study, borderline significance was observed in the association between elevated BP and abnormal LVGLS. Further investigations with long-term follow-up are warranted to examine the association between elevated BP and HF occurrence.

Isolated diastolic hypertension and left ventricular strain

Particular attention has been dedicated to IDH and its prognostic impact. With the 2017 ACC/AHA guideline, the number of patients with IDH increased substantially (from 1.3% to 6.5%) in comparison with the Joint National Committee 7 Blood Pressure Guideline (JNC-7) guideline.⁸ In the present study, we found that IDH carries a significant risk for impaired LVGLS. However, conflicting results were reported regarding its clinical significance as a cause of cardiovascular disease. Sheriff *et al.* reported that IDH was independently associated with HF occurrence in 5776 community-dwelling older adults from Cardiovascular Health Study (CHS) during 13 years of follow-up.²¹ McEvoy *et al.* studied longitudinal analyses of the ARIC study and failed to demonstrate the association between IDH and HF occurrence during a median follow-up of 25 years.²² These discrepancies may be partially caused by the different populations and co-morbidities. On the other hand, we did not find an independent association between BP level and LVGLS. This is partially explained by the fact that, because longitudinal myofibres are predominantly located in the subendocardial region, GLS is more susceptible to pressure overload and more sensitive to myocardial damage than GCS.²³

Blood pressure level and left ventricular morphology and diastolic function

We also demonstrated significant differences in LV mass index and LV diastolic parameters across the BP groups; differences in age and body size might account for it. Previous ep-

idemiological studies clearly demonstrated the differences of age and body size in hypertensive categories. IDH constitutes the most frequent hypertensive phenotype in younger subjects: 47% of untreated hypertensive patients <50 years of age represent IDH in the USA.²⁴ On the other hand, increased BMI is associated with both BP categories (i.e. IDH and SH).²⁵ We found that IDH patients were younger compared with SH patients, while both hypertensive groups had larger BMI compared with normal BP group. These findings are in line with these previous studies.

Sex difference on hypertensive left ventricular remodelling

High BP plays a prominent role in the development of HF in both men and women, although sex-specific differences were observed regarding the relationship of BP with LV remodelling pattern and subsequent HF development.^{26,27} Women are more likely to present concentric LV hypertrophy, whereas men more commonly develop eccentric LV hypertrophy.^{9,10} Furthermore, hypertension contributes more to development of HF in women than in men according to community-based data. Indeed, the adjusted risk for HF was approximately two-fold higher in hypertensive men, but three-fold higher in hypertensive women compared with their normotensive counterparts.² However, no study has explored the sex-specific differences in hypertensive LV functional abnormalities assessed by speckle-tracking echocardiography. We demonstrate that the relationship between BP level and LV functional remodelling is more pronounced in women. Our finding is in line with previous studies showing greater susceptibility to hypertension-related HF in women.

Mechanisms of sex differences in hypertensive left ventricular remodelling

The underlying mechanisms for the more pronounced association between BP level and LVGLS in women are not entirely clear; however, increased arterial stiffness may contribute to the relationship. High BP causes arterial stiffening, and women appear to be more susceptible than men to the detrimental effects of increased pulsatile load.¹⁶ Furthermore, increased arterial stiffness was associated with coronary microvascular dysfunction assessed by myocardial flow reserve in women, whereas no independent association was observed in men.²⁸ Another possible mechanism could be sympathetic nerve activation, which is a risk factor for BP elevation as well as LV dysfunction.^{29,30} Women show more pronounced sympathetic nervous system activity than men, a factor that may have affected our observations.³¹ Finally, previous studies showed that hypertensive women had more

impaired LV relaxation compared with hypertensive men, a circumstance that might be involved in our observation.³²

Clinical implication

Given the substantial contribution of hypertension to HF development, an early identification of high-risk individuals with abnormal BP level is of crucial importance. Our findings on the association between BP categories and subclinical LV dysfunction provide valuable information regarding hypertensive subclinical cardiac injury and possible preventive strategies for HF development. Further studies are warranted to elucidate whether pharmacological and nonpharmacological therapeutic interventions, such as exercise and dietary counseling, may have beneficial effects on subclinical LV dysfunction and possibly prevent HF development. Furthermore, the underlying pathophysiological mechanisms of sex-specific differences in hypertensive LV functional remodeling should be investigated.

Strengths and limitations

A strength of this study is its comprehensive assessment of LV functional remodeling with novel speckle-tracking deformation imaging in relation to the recently introduced ACC/AHA hypertension guideline in antihypertensive medication-naive individuals free of overt cardiac disease. Nevertheless, several limitations should be acknowledged. First, the study was cross-sectional in design and could not address HF incidence, although impaired LVGLS has been identified as a strong surrogate marker for incident HF in several community-based cohort studies.¹⁷ Second, the study examined a relatively healthy population without overt cardiac disease, which may limit the applicability of the findings to populations with different risk profiles. Finally, although we showed sex-specific differences in the association between BP level and LV remodeling, the underlying pathophysiological mechanisms require further investigation.

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Conclusions

This study demonstrated a significant association of IDH and SH with reduced LVGLS in a sample of the general population without overt cardiac disease. Elevated BP was related to LVGLS only in women. Our findings may enhance our understanding of HF caused by high BP and possible preventive strategies, and may partially explain the susceptibility to hypertension-related HF in women.

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Conflict of interest

None declared.

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Author contributions

K.N. and Y.Y. contributed to the conception and design of the work. K.N., M.D., Y.Y., J.I., N.S., M.H., H.K., T.N., Y.M., H.M., M. R.D.T., S.H., and I.K. contributed to the acquisition, analysis, or interpretation of data for the work. K.N. drafted the manuscript. M.D., Y.Y., J.I., N.S., M.H., H.K., T.N., Y.M., H.M., M.R. D.T., S.H., and I.K. critically revised the manuscript. All authors gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

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