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Original Article

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Normal Reference Values for Left Atrial Strain and Its Determinants from a Large Korean Multicenter Registry

Byung Joo Sun, MD, PhD[1], Jae-Hyeong Park, MD, PhD[1], Minyeong Lee, BSc[2], Jin-Oh Choi, MD, PhD[3], Ju-Hee Lee, MD, PhD[4], Mi-Seung Shin, MD, PhD[5], Mi-Jeong Kim, MD, PhD[6], Hae Ok Jung, MD, PhD[7], Jeong Rang Park, MD, PhD[8], Il Suk Sohn, MD, PhD[9], Hyungseop Kim, MD, PhD[10], Hyung-Kwan Kim, MD, PhD[11], Goo-Yeong Cho, MD, PhD[12], Jin-Sun Park, MD, PhD[13], Chi Young Shim, MD, PhD[14], Sung Hee Shin, MD, PhD[15], Kye Hun Kim, MD, PhD[16], Woo-Shik Kim, MD, PhD[17], and Seung Woo Park, MD, PhD[3]

[1]Division of Cardiology, Department of Internal Medicine, Chungnam National University Hospital, Chungnam National University School of Medicine, Daejeon, Korea
[2]Cardiovascular Center, Chungnam National University Hospital, Daejeon, Korea
[3]Division of Cardiology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea
[4]Division of Cardiology, Department of Internal Medicine, Chungbuk National University School of Medicine, Cheongju, Korea
[5]Division of Cardiology, Department of Internal Medicine, Gil Hospital, Gachon University of Medicine and Science, Incheon, Korea
[6]Division of Cardiology, Department of Internal Medicine, Incheon St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Incheon, Korea
[7]Department of Internal Medicine, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea
[8]Division of Cardiology, Department of Internal Medicine, Gyeongsang National University Hospital, Gyeongsang National University School of Medicine, Jinju, Korea
[9]Department of Cardiology, Kyung Hee University School of Medicine, Kyung Hee University Hospital at Gangdong, Seoul, Korea
[10]Division of Cardiology, Keimyung University Dongsan Medical Center, Daegu, Korea
[11]Division of Cardiology, Department of Internal Medicine, Cardiovascular Center, Seoul National University College of Medicine, Seoul, Korea
[12]Division of Cardiology, Department of Internal Medicine, Seoul National University and Cardiovascular Center, Seoul National University Bundang Hospital, Seongnam, Korea
[13]Department of Cardiology, Ajou University School of Medicine, Suwon, Korea
[14]Division of Cardiology, Severance Cardiovascular Hospital, Yonsei University College of Medicine, Seoul, Korea
[15]Division of Cardiology, Department of Internal Medicine, Inha University College of Medicine, Incheon, Korea
[16]Department of Cardiology, Chonnam National University Hospital, Gwangju, Korea
[17]Cardiovascular Center, Department of Internal Medicine, Kyung Hee University Medical Center, Seoul, Korea

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Address for Correspondence:
Jae-Hyeong Park, MD, PhD
Division of Cardiology, Department of Internal Medicine, School of Medicine, Chungnam National University, Chungnam National University Hospital, 282 Munhwa-ro, Jung-gu, Daejeon 35015, Korea.
E-mail: jaehyeongpark@gmail.com

ORCID iDs
Byung Joo Sun
https://orcid.org/0000-0001-6019-4343
Jae-Hyeong Park
https://orcid.org/0000-0001-7035-286X
Minyeong Lee
https://orcid.org/0000-0002-2228-0440
Jin-Oh Choi
https://orcid.org/0000-0002-2441-2267
Ju-Hee Lee
https://orcid.org/0000-0002-0858-0973
Mi-Seung Shin
https://orcid.org/0000-0002-0273-0109
Mi-Jeong Kim
https://orcid.org/0000-0002-7887-3309
Hae Ok Jung
https://orcid.org/0000-0002-5102-9212
Jeong Rang Park
https://orcid.org/0000-0002-8330-2738

ABSTRACT

BACKGROUND: Left atrial (LA) strain is a novel parameter of LA function. However, its reference value has not been established, and the determining factors for LA strain remain elusive. We aimed to present LA strain with reservoir, conduit, and contractile components and associated parameters in a large-sized group of healthy individuals.
METHODS: The present study was from a prospective multicenter registry in South Korea. Subjects who had no history of cardiovascular disease with adequate images were eligible for inclusion. LA reservoir, conduit, and contractile strains (LAS_{RES}, LAS_{CD} and LAS_{CT}, respectively) were measured. Left ventricular global longitudinal strain (LV GLS) and early

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Il Suk Sohn
https://orcid.org/0000-0001-8004-5185
Hyungseop Kim
https://orcid.org/0000-0001-7056-4221
Hyung-Kwan Kim
https://orcid.org/0000-0001-7950-2131
Goo-Yeong Cho
https://orcid.org/0000-0002-7067-5535
Jin-Sun Park
https://orcid.org/0000-0002-7775-4092
Chi Young Shim
https://orcid.org/0000-0002-6136-0136
Sung Hee Shin
https://orcid.org/0000-0002-8306-9622
Kye Hun Kim
https://orcid.org/0000-0002-6885-1501
Woo-Shik Kim
https://orcid.org/0000-0002-3345-1137
Seung Woo Park
https://orcid.org/0000-0002-2941-515X

Conflict of Interest
The authors have no financial conflicts of interest.

and late diastolic strain rates (DSR_e and DSR_a, respectively) were also evaluated.
RESULTS: Among a total of 324 subjects (mean age: 49 ± 16 years, 167 females), the mean LAS_{RES}, LAS_{CD}, and LAS_{CT} values were 35.9% ± 10.6%, 21.9% ± 9.3%, and 13.9% ± 3.6%, respectively. Mean LV GLS was -20.4% ± 2.2%, and mean DSR_e and DSR_a were 1.6 ± 0.4 s^{-1} and 0.8 ± 0.3 s^{-1}, respectively. With aging, LAS_{RES} and LAS_{CD} showed significant decreases. Factors showing independent associations with LAS_{RES} were age (B = -0.425, p < 0.001), DSR_e (B = 4.706, p = 0.001), and LV GLS (B = -1.081, p < 0.001). Age (B = -0.319, p < 0.001), DSR_e (B = 4.140, p = 0.002), DSR_a (B = -3.409, p = 0.018), and LV GLS (B = -0.783, p < 0.001) showed associations with LAS_{CD}. With LAS_{CT}, only DSR_a showed a correlation (R = 0.277, p < 0.001).
CONCLUSIONS: We presented LA strain in a large-sized group of healthy subjects. Age is a significant determinant of LA function. Associations of LA strain with diastolic strain rates and LV GLS reflect cardiac mechanics.

Keywords: LA function; LA strain; Speckle-tracking echocardiography

INTRODUCTION

The clinical significance of left atrial (LA) remodeling has been shown in a variety of cardiovascular diseases. However, the dynamic feature of LA has been recently highlighted.[1)2)] These studies showed that LA is not simply a conduit chamber but that it has sophisticated actions during a cardiac cycle that performs in close interplay with the left ventricular (LV) mechanics.[1)] Currently, LA volume index (LAVI) is a main parameter of LA remodeling.[1)] However, as LAVI is based on a static volumetric measurement, it has inherent limitations with respect to reflecting the dynamic aspects of LA.[2)] With this background, a novel speckle tracking echocardiography derived index, 'LA strain,' was recently introduced. LA strain may be more suitable to represent LA function.[2)] LA strain has been tested in several clinical studies and shown to be a more useful diagnostic tool than conventional parameters.[3-5)] However, the clinical evidence for using LA strain as a diagnostic tool is insufficient. In addition, applying LA strain in clinical practice is difficult because its reference value has not yet been established for a variety of subject groups. In the present study, we aimed to identify a reference value for LA strain with reservoir, conduit, and contractile components in a large group of healthy Koreans. We also aimed to elucidate determining factors for LA strain.

METHODS

Study outline

Our research group from the Korean Society of Echocardiography recently conducted a prospective nation-wide registry (Normal echOcardiogRaphic Measurements in KoreAn popuLation, NORMAL) including 23 tertiary-referral hospitals in South Korea and constructed a large-sized echocardiographic database of healthy individuals.[6)] The primary objective of the study was to present normal reference values of echocardiography in a Korean population. The eligibility criteria were as follows: 1) an adult aged 20–79 years, and 2) no history of cardiovascular diseases such as hypertension, diabetes mellitus, coronary/peripheral arterial disease, and atrial fibrillation. The NORMAL study required only two-dimensional and Doppler echocardiographic images. The overall database included 1,003 subjects. In a sub-study focusing on strain analysis, 501 subjects (50%) whose exams were performed using a single-vendor machine (GE Medical Systems, Horten, Norway) were

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selected.[7] In the present study, LA strain analysis was finally available for 324 subjects (32%) for whom LA images included the whole LA roof in both apical four-chamber and two-chamber views. The subject clinical characteristics, conventional echocardiographic data, LV systolic strain, and diastolic strain rate were analyzed, with the main focus on LA strain. This study conformed to the ethical guidelines of the Declaration of Helsinki, and the study protocol was approved by the Ethics Committees of all participating centers. Written informed consent was waived because of the non-invasiveness of this study protocol.

Echocardiographic analysis

All routine echocardiographic studies were performed according to current recommendations.[8][9] Images for strain analysis were obtained with 60–90 frames/sec from two consecutive cardiac beats.[10] All image data were digitally stored for analysis in the core laboratory of Chungnam National University Hospital. Two dedicated researchers (SBJ and PJH) who were blinded to clinical information analyzed all strain images using EchoPAC® and BT 201 device (GE Medical Systems, Horten, Norway). LV global longitudinal strain (GLS) and early and late diastolic strain rates (DSR_e and DSR_a) were evaluated according to previously described methods.[10][11]

To measure LA strain, we manually traced the LA endocardium and thus the software automatically tracked the region of interest on the LA wall. A LA strain curve cycle was generated with a configuration by R-R gating that began with the onset of systole.[12] We then defined the following three components of LA function: LA reservoir, conduit, and contractile strains (LAS_{RES}, LAS_{CD}, and LAS_{CT}, respectively). The first peak point was defined as LAS_{RES} (**Figure 1**). Another peak point after the P wave on electrocardiography was defined as LAS_{CT}. We also defined variables LAS_{CD} (LAS_{RES} - LAS_{CT}) and LAS_{CD}/LAS_{CT} ratio. We performed this process in both apical 4-chamber and 2-chamber images and calculated average LA strain values.

Statistical analysis

We presented categorical variables as numbers (%) and continuous variables as mean ± standard deviation (SD). We used independent Student's t-tests to compare numeric data between sex groups. To evaluate differences in LA strain values among age groups defined by decade, we used one-way analysis of variance (ANOVA) with Bonferroni correction with non-parametric means as needed. To determine variables associated with LA stain parameters, Pearson's bivariate correlation test and multiple linear regression analysis were performed. We evaluated intra- and inter-observer measurement variabilities based on intraclass correlation coefficients (ICCs). All reported p-values were two-tailed and a p-value of < 0.05 was accepted as statistically significant. SPSS software version 22 (IBM Corp, Armonk, NY, USA) was used for all statistical analyses.

RESULTS

Subject characteristics

This study included a total of 324 subjects; the mean age was 49 ± 16 years, and there were 167 females (52%) (**Table 1**). The mean systolic and diastolic blood pressures were 120 ± 13 mmHg and 72 ± 10 mmHg, respectively. The mean pulse rate was 68 ± 10 beats/min. For the echocardiographic parameters, the mean LV ejection fraction (LVEF) was 62 ± 4%, the mean LV mass index (LVMI) was 75 ± 14 g/m^2, and the mean LAVI was 27 ± 6 mL/m^2. For Doppler

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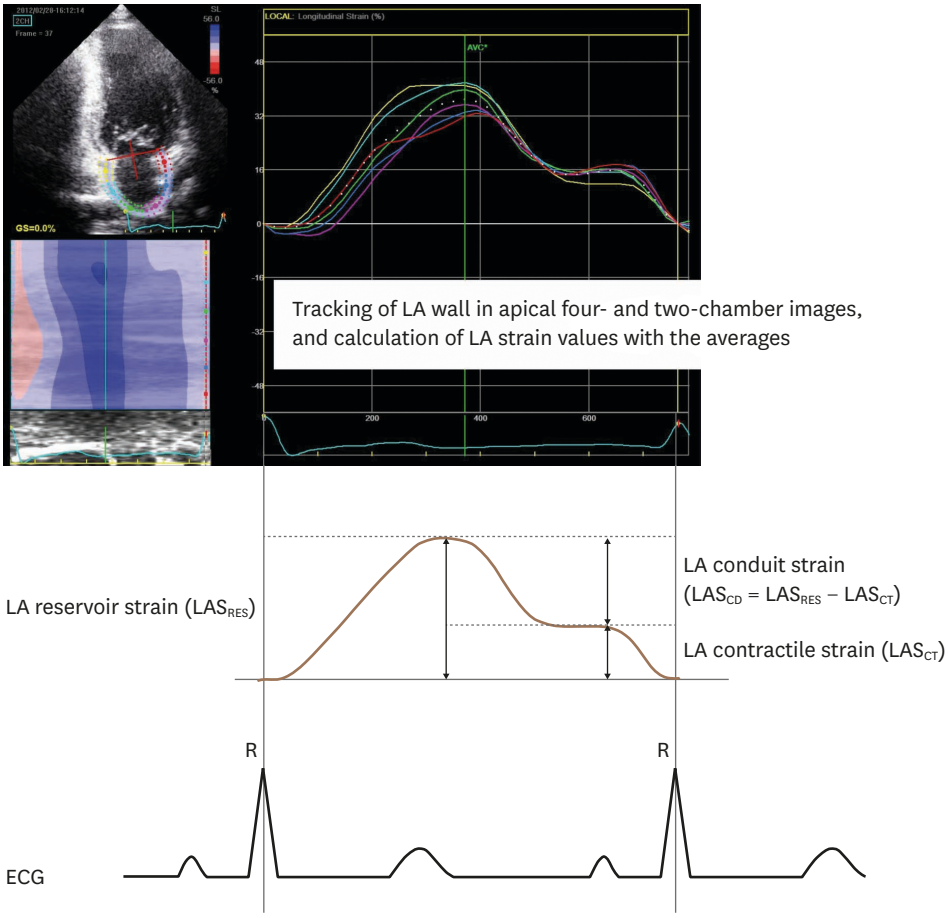

Figure 1. Demonstration of LA strain measurement. ECG: electrocardiography, LA: left atrium.

parameters, septal and lateral mitral annular E′ velocity were 9.3 ± 2.9 cm/s and 12.6 ± 3.7 cm/s, respectively. Septal and lateral E/E′ ratios were 7.9 ± 2.3 and 5.9 ± 1.8, respectively. There was no significant difference in age between the male and female groups. The male group showed a higher body surface area, blood pressure, and LV volumes compared to the female group. However, LVEF and LAVI were not significantly different between male and female groups. The female group presented higher mitral E velocity and E/A ratio without showing significant differences in mitral annular E′ velocity and E/E′ ratios compared to the male group.

LA and LV strain values

In the total subjects, the mean LAS_{RES}, LAS_{CD}, and LAS_{CT} values were 35.9% ± 10.6%, 21.9% ± 9.3% and 13.9% ± 3.6%, respectively, and the mean LAS_{CD}/LAS_{CT} ratio was 1.7 ± 0.8 (**Table 2**). The mean LV GLS was -20.4% ± 2.2%. The mean DSR_e and DSR_a were 1.6 ± 0.4 s^{-1} and 0.8 ± 0.3 s^{-1}, respectively. The female group showed significantly higher LAS_{RES} (37.3% ± 11.0% vs. 34.3% ± 10.0%, p = 0.009) and LAS_{CD} (23.5% ± 9.8% vs. 20.3% ± 8.5%, p = 0.002) than the male group, whereas there was no significant difference in LAS_{CT} between sex groups. The female group showed significantly higher LAS_{CD}/LASCT ratio (1.8% ± 0.8% vs. 1.5% ± 0.7%, p = 0.001). The female group also showed higher LV GLS (-21.2% ± 2.1% vs. -19.5% ± 2.1%, p < 0.001) and DSRe (1.7 ± 0.4 s-1 vs. 1.4 ± 0.3 s^{-1}, p < 0.001), whereas DSR_a did not differ between female and male groups. LAS_{RES}, LAS_{CD}, and LAS_{CD}/LAS_{CT} ratio showed significant decreases with increasing age

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Table 1. Clinical and echocardiographic parameters

	Total (N = 324)	Male (n = 157)	Female (n = 167)	p-value
Age (years)	49 ± 16	50 ± 16	48 ± 15	0.301
Body surface area (m^2)	1.7 ± 0.2	1.8 ± 0.1	1.6 ± 0.1	< 0.001
Body mass index (kg/m^2)	22.9 ± 2.9	23.3 ± 2.4	22.5 ± 3.2	0.001
Systolic blood pressure (mmHg)	120 ± 13	123 ± 12	117 ± 13	< 0.001
Diastolic blood pressure (mmHg)	72 ± 10	74 ± 10	71 ± 10	0.011
Heart rate (beats/min)	68 ± 10	67 ± 10	69 ± 10	0.133
LV end diastolic volume (mL)	103 ± 22	113 ± 21	93 ± 17	< 0.001
LV end systolic volume (mL)	39 ± 10	43 ± 10	35 ± 9	< 0.001
LV ejection fraction (%)	62 ± 4	62 ± 4	63 ± 4	0.162
LV mass index (g/m^2)	75 ± 14	78 ± 14	71 ± 14	< 0.001
LA volume index (mL/m^2)	27 ± 6	27 ± 6	28 ± 7	0.647
E velocity (cm/s)	69 ± 16	66 ± 15	72 ± 17	0.001
A velocity (cm/s)	60 ± 17	60 ± 17	60 ± 16	0.977
E/A ratio	1.2 ± 0.5	1.2 ± 0.4	1.3 ± 0.6	0.030
E′ velocity septal (cm/s)	9.3 ± 2.9	9.1 ± 2.8	9.5 ± 3.0	0.244
E′ velocity lateral (cm/s)	12.6 ± 3.7	12.3 ± 3.7	12.8 ± 3.7	0.254
E/E′ ratio septal	7.9 ± 2.3	7.7 ± 2.2	8.1 ± 2.4	0.090
E/E′ ratio lateral	5.9 ± 1.8	5.7 ± 1.8	6.0 ± 1.8	0.203
Deceleration time (ms)	209 ± 38	211 ± 39	207 ± 38	0.303
Isovolumic relaxation time (ms)	84 ± 15	84 ± 14	84 ± 16	0.677

LA: left atrium, LV: left ventricle.

Table 2. Strain parameter values

	Total (N = 324)	Male (n = 157)	Female (n = 167)	p-value
LA reservoir strain (%)	35.9 ± 10.6	34.3 ± 10.0	37.3 ± 11.0	0.009
Four-chamber (%)	35.4 ± 11.3	33.7 ± 10.3	37.0 ± 11.9	0.008
Two-chamber (%)	36.3 ± 10.9	34.9 ± 10.8	37.7 ± 10.8	0.020
LA conduit strain (%)	21.9 ± 9.3	20.3 ± 8.5	23.5 ± 9.8	0.002
Four-chamber (%)	22.3 ± 9.9	20.5 ± 8.9	24.0 ± 10.4	0.001
Two-chamber (%)	21.5 ± 9.5	20.0 ± 9.0	22.9 ± 9.8	0.005
LA contractile strain (%)	13.9 ± 3.6	14.0 ± 3.7	13.8 ± 3.6	0.645
Four-chamber (%)	13.0 ± 4.1	13.2 ± 4.0	12.9 ± 4.1	0.585
Two-chamber (%)	14.8 ± 4.5	14.9 ± 4.6	14.8 ± 4.4	0.801
LA conduit/contractile strain ratio	1.7 ± 0.8	1.5 ± 0.7	1.8 ± 0.8	0.001
Global LV longitudinal strain (%)	-20.4 ± 2.2	-19.5 ± 2.1	-21.2 ± 2.1	< 0.001
Early diastolic strain rate (s^{-1})	1.6 ± 0.4	1.4 ± 0.3	1.7 ± 0.4	< 0.001
Late diastolic strain rate (s^{-1})	0.8 ± 0.3	0.8 ± 0.3	0.8 ± 0.3	0.966

LA: left atrium, LV: left ventricle.

(**Figures 2A, 2B, and 2D**, respectively; all $p < 0.001$). However, there was no age-related trend for LAS_{CT} (**Figure 2C**). These trends according to age were observed in both male and female groups (**Figure 3**).

Factors associated with LA strain

In Pearson's bivariate analysis, LAS_{RES} showed significant correlations with age ($R = -0.705$, $p < 0.001$), LVMI ($R = -0.310$, $p < 0.001$), E′ velocity ($R = 0.603$, $p < 0.001$), E/E′ ratio ($R = -0.304$, $p < 0.001$), DSR_e ($R = 0.585$, $p < 0.001$), DSR_a ($R = -0.337$, $p < 0.001$), and LV GLS ($R = -0.359$, $p < 0.001$) (**Table 3**). In multiple linear regression analysis, factors showing significant associations with LAS_{RES} were age ($B = -0.425$, $p < 0.001$), DSR_e ($B = 4.706$, $p = 0.001$), and LV GLS ($B = -1.081$, $p < 001$). With LAS_{CD}, age ($B = -0.319$, $p < 0.001$), DSR_e ($B = 4.140$, $p = 0.002$), DSR_a ($B = -3.409$, $p = 0.018$), and LV GLS ($B = -0.783$, $p < 0.001$) showed independent associations while septal E′ velocity showed a trend without statistical significance (**Table 4**). With LAS_{CT}, only DSR_a showed a weak correlation ($R = 0.277$, $p < 0.001$). However, there was no other feasible variable for test of independent association (**Supplementary Table 1**). With LAS_{CD}/LAS_{CT} ratio, age ($B = -0.011$, $p < 0.001$), diastolic blood pressure ($B = -0.010$, $p =$

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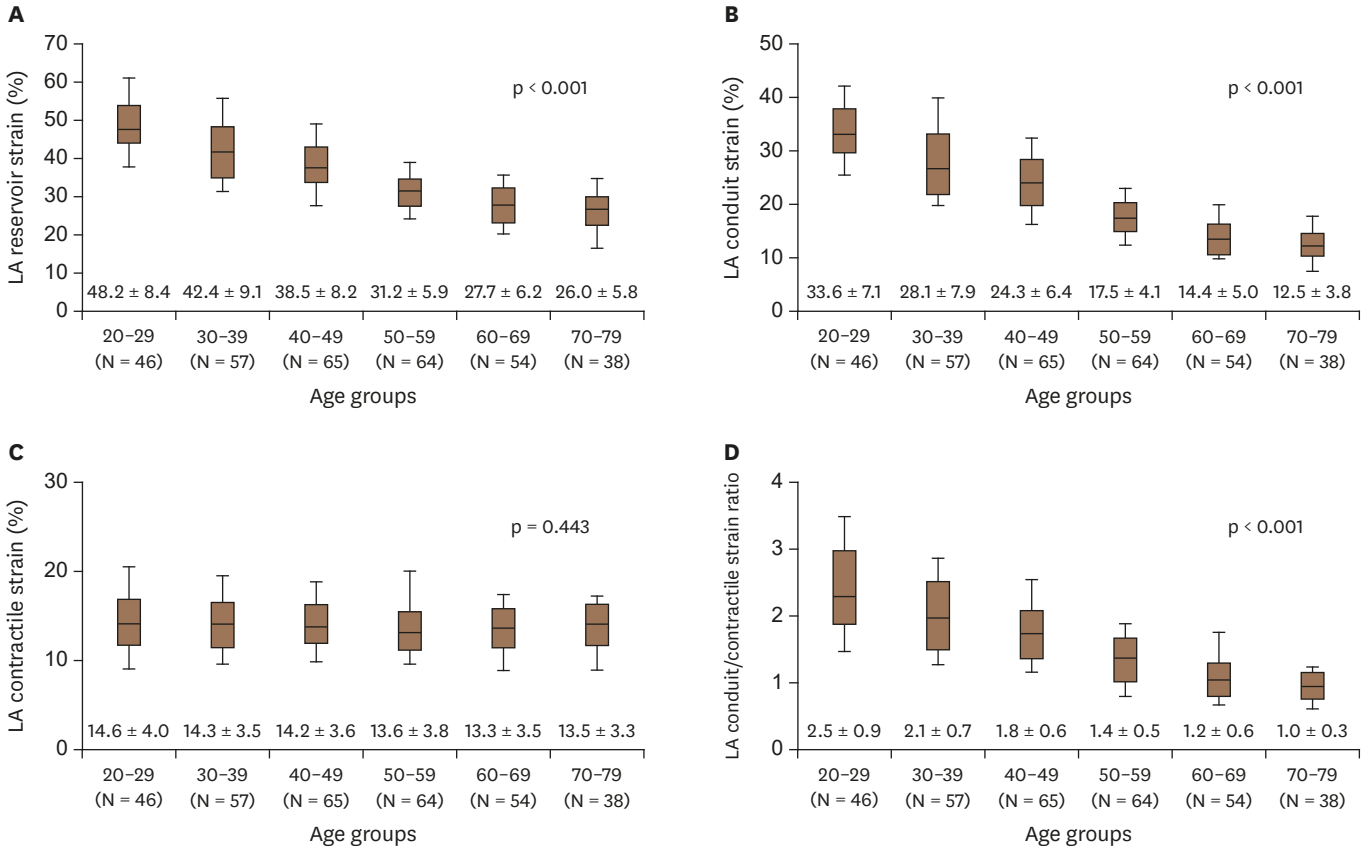

Figure 2. LA strain values according to age groups. LA: left atrium.

0.002), DSR_e (B = 0.602, p < 0.001), and DSR_a (B = -1.158, p < 0.001) showed independent associations (**Table 5**).

Measurement variability

Intra- and inter-observer ICCs for LAS_{RES} were 0.974 (95% confidence interval [CI], 0.946–0.988) and 0.948 (95% CI, 0.889–0.976), respectively (**Table 6**). Intra- and inter-observer ICCs for LAS_{CD} were 0.978 (95% CI, 0.953–0.990) and 0.930 (95% CI, 0.852–0.967),

Table 3. Parameters associated with LA reservoir strain

Variables	Bivariate		Multivariate linear regression		
	R	p-value	B	SE	p-value
Age (years)	-0.705	< 0.001	-0.425	0.028	< 0.001
Male	-0.144	0.009			
Systolic blood pressure (mmHg)	-0.187	0.001			
Diastolic blood pressure (mmHg)	-0.118	0.040			
Heart rate (beats/min)	0.169	0.002			
LV mass index (g/m^2)	-0.310	< 0.001	-0.028	0.028	0.325
LA volume index (mL/m^2)	-0.162	0.004			
E′ velocity septal (cm/s)	0.603	< 0.001	0.128	0.215	0.553
E/E′ ratio septal	-0.304	< 0.001	0.167	0.246	0.497
Early diastolic strain rate (s^{-1})	0.585	< 0.001	4.706	1.465	0.001
Late diastolic strain rate (s^{-1})	-0.337	< 0.001	2.711	1.704	0.113
LV ejection fraction (%)	0.036	0.525			
LV GLS (%)	-0.359	< 0.001	-1.081	0.236	< 0.001

GLS: global longitudinal strain, LA: left atrium, LV: left ventricle.

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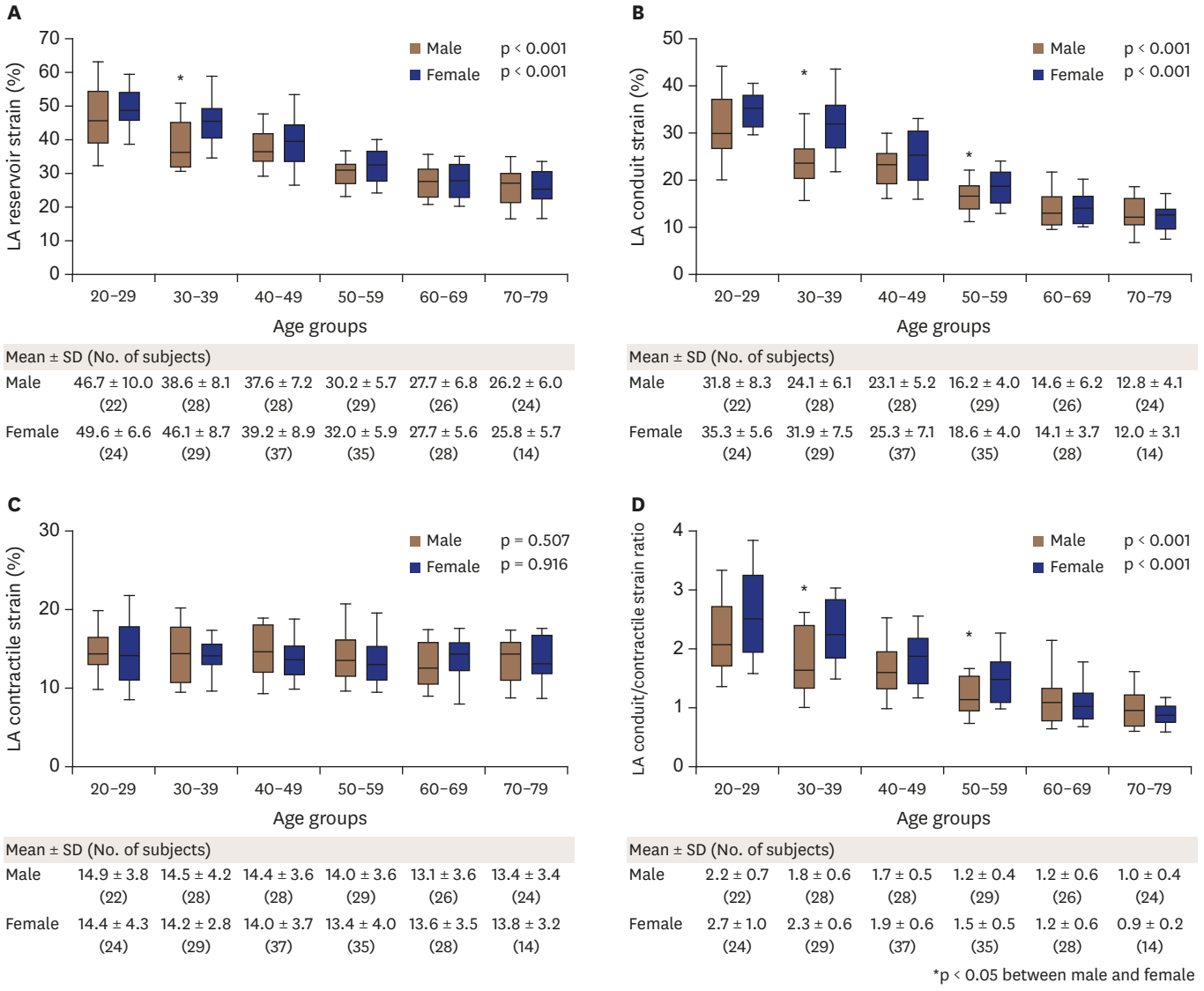

A	Mean ± SD (No. of subjects)					
Male	46.7 ± 10.0 (22)	38.6 ± 8.1 (28)	37.6 ± 7.2 (28)	30.2 ± 5.7 (29)	27.7 ± 6.8 (26)	26.2 ± 6.0 (24)
Female	49.6 ± 6.6 (24)	46.1 ± 8.7 (29)	39.2 ± 8.9 (37)	32.0 ± 5.9 (35)	27.7 ± 5.6 (28)	25.8 ± 5.7 (14)

B	Mean ± SD (No. of subjects)					
Male	31.8 ± 8.3 (22)	24.1 ± 6.1 (28)	23.1 ± 5.2 (28)	16.2 ± 4.0 (29)	14.6 ± 6.2 (26)	12.8 ± 4.1 (24)
Female	35.3 ± 5.6 (24)	31.9 ± 7.5 (29)	25.3 ± 7.1 (37)	18.6 ± 4.0 (35)	14.1 ± 3.7 (28)	12.0 ± 3.1 (14)

C	Mean ± SD (No. of subjects)					
Male	14.9 ± 3.8 (22)	14.5 ± 4.2 (28)	14.4 ± 3.6 (28)	14.0 ± 3.6 (29)	13.1 ± 3.6 (26)	13.4 ± 3.4 (24)
Female	14.4 ± 4.3 (24)	14.2 ± 2.8 (29)	14.0 ± 3.7 (37)	13.4 ± 4.0 (35)	13.6 ± 3.5 (28)	13.8 ± 3.2 (14)

D	Mean ± SD (No. of subjects)					
Male	2.2 ± 0.7 (22)	1.8 ± 0.6 (28)	1.7 ± 0.5 (28)	1.2 ± 0.4 (29)	1.2 ± 0.6 (26)	1.0 ± 0.4 (24)
Female	2.7 ± 1.0 (24)	2.3 ± 0.6 (29)	1.9 ± 0.6 (37)	1.5 ± 0.5 (35)	1.2 ± 0.6 (28)	0.9 ± 0.2 (14)

*p < 0.05 between male and female

Figure 3. LA strain values according to age and sex groups. LA: left atrium.

Table 4. Parameters associated with LA conduit strain

Variables	Bivariate		Multivariate linear regression		
	R	p-value	B	SE	p-value
Age (years)	-0.760	< 0.001	-0.319	0.031	< 0.001
Male	-0.174	0.002			
Systolic blood pressure (mmHg)	-0.251	< 0.001	-0.025	0.024	0.285
Diastolic blood pressure (mmHg)	-0.212	< 0.001			
Heart rate (beats/min)	0.163	0.003			
LV mass index (g/m^2)	-0.346	< 0.001	-0.002	0.022	0.939
LA volume index (mL/m^2)	-0.155	0.005			
E′ velocity septal (cm/s)	0.683	< 0.001	0.320	0.171	0.063
E/E′ ratio septal	-0.338	< 0.001	0.299	0.193	0.121
Early diastolic strain rate (s^{-1})	0.610	< 0.001	4.140	1.331	0.002
Late diastolic strain rate (s^{-1})	-0.492	< 0.001	-3.409	1.432	0.018
LV ejection fraction (%)	0.002	0.976			
LV GLS (%)	-0.335	< 0.001	-0.783	0.192	< 0.001

GLS: global longitudinal strain, LA: left atrium, LV: left ventricle.

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Table 5. Parameters associated with LA conduit/contractile strain ratio

Variables	Bivariate		Multivariate linear regression		
	R	p-value	B	SE	p-value
Age (years)	-0.619	< 0.001	-0.011	0.003	< 0.001
Male	-0.180	0.001			
Systolic blood pressure (mmHg)	-0.277	< 0.001	-0.001	0.003	0.735
Diastolic blood pressure (mmHg)	-0.296	< 0.001	-0.010	0.003	0.002
Heart rate (beats/min)	0.088	0.114			
LV mass index (g/m^2)	-0.313	< 0.001	0.001	0.002	0.712
LA volume index (mL/m^2)	-0.099	0.077			
E′ velocity septal (cm/s)	0.608	< 0.001	0.026	0.018	0.149
E/E′ ratio septal	-0.304	< 0.001	0.014	0.020	0.471
Early diastolic strain rate (s^{-1})	0.459	< 0.001	0.602	0.090	< 0.001
Late diastolic strain rate (s^{-1})	-0.612	< 0.001	-1.158	0.145	< 0.001
LV ejection fraction (%)	-0.043	0.442			
LV GLS (%)	-0.195	< 0.001			

GLS: global longitudinal strain, LA: left atrium, LV: left ventricle.

Table 6. Measurement variabilities for strain values

	Intraclass correlation coefficient (95% CI)	
	Intra-observer	Inter-observer
LA reservoir strain	0.974 (0.946–0.988)	0.948 (0.889–0.976)
LA conduit strain	0.978 (0.953–0.990)	0.930 (0.852–0.967)
LA contractile strain	0.976 (0.949–0.989)	0.942 (0.876–0.973)
LV GLS (%)	0.972 (0.924–0.989)	0.924 (0.812–0.969)
Early diastolic strain rate	0.965 (0.927–0.983)	0.924 (0.843–0.964)
Late diastolic strain rate	0.957 (0.910–0.979)	0.920 (0.834–0.961)

GLS: global longitudinal strain, LA: left atrium, LV: left ventricle.

respectively. For LAS_{CT}, intra- and inter-observer ICCs were 0.976 (95% CI, 0.949–0.989) and 0.942 (95% CI, 0.876–0.973), respectively.

DISCUSSION

LA remodeling means cumulative structural and functional alterations due to hemodynamic stress.[1] Given the absence of other structural abnormalities, the major cause of LA remodeling is elevated LV filling pressure. Therefore, the presence of LA remodeling reflects long-term progression of various cardiovascular diseases.[1] Currently, LAVI is the main parameter of LA remodeling and has advantages of simple measurement and clinical evidence from a variety of cardiovascular disease.[1] However, LAVI essentially represents a static volume. Thus, LAVI has limitations to reflect the unique LA mechanics during the cardiac cycle including reservoir, conduit, and contractile functions.[1][2] The diagnostic sensitivity of LAVI has been shown to be limited to detection of subtle changes in LA function.[4][13]

LA strain, a new parameter of LA remodeling

With this background, a recently introduced parameter, 'LA strain,' has potential advantages to surpass conventional diagnostic tools. Its usefulness has been presented in a few clinical cardiovascular disease entities.[3-5] However, LA strain is still not applied in clinical practice to date. The major limitation of LA strain as a clinical metric is the lack of an established normal reference value.[12] In response to this practical need, here we present reference values for LA strain derived from a large-sized group of healthy subjects and age and sex-specified subgroups.

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The mean LAS_{RES} in our study was 36.3% ± 8.4%. A few previous studies have reported LAS_{RES} values (also described as peak LA strain) in healthy groups.[12][14-16] Pathan et al.[12] performed a meta-analysis of 2,542 healthy subjects and found that the mean LAS_{RES} was 39.4% (95% CI: 38.0%–40.8%). D'Ascenzi et al.[16] also performed a meta-analysis of 2,087 subjects and reported a mean LAS_{RES} of 38% ± 3% (95% CI: 32%–43%). Kim et al.[14] reported a mean LAS_{RES} of 35.7% ± 5.8% in a study of 54 healthy Korean subjects. Although these studies presented LAS_{RES} values similar to our results, one recent international multicenter study by Morris et al.[15] reported a mean LAS_{RES} of 45.5% ± 11.4% from 329 healthy subjects, which is substantially different from our results. For such a variation in values, different clinical features of study subjects might be the major cause. For example, the mean subject age in our study was 49 ± 16 years in contrast to 36.1 ± 12.7 years in the study of Morris et al.[15] In addition, the definitions of 'healthy subject' were not specific. Thus, clinical profiles might differ according to studies. There could be a technical bias because different methods for measuring LA strain have been used.[2] Pathan et al.[12] reported significant heterogeneity in LAS_{RES} values between studies, especially according to the size of study groups (n > 100 vs. n < 100). This suggests that technical fluency might matter. In this regard, our present study examined a large-sized subject group (n = 324). Pathan et al.[12] performed a meta-analysis and reported that mean LAS_{CD} and LAS_{CT} were 23.0% (range of 15.7%–33.4%) and 17.4% (range of 14.0%–25.0%), respectively. However, the numbers of original studies examining LAS_{CD} and LAS_{CT} are limited (14 and 18 studies, respectively). In addition, all of these studies included small numbers of subjects (n = 30–64). In addition, measurement values showed a wide variability. Therefore, more data are required to obtain reliable reference values for LAS_{CD} and LAS_{CT}. The present study is one of the largest original researches to investigate LAS_{CD} and LAS_{CT}.

Determinant factors for LA strain

In the present study, common factors that were associated with LA strain parameters were age, diastolic strain rates, and LV GLS. In particular, the effect of age was evident. Thus, LAS_{RES} and LAS_{CD} presented significant attenuations with aging. Although LAS_{CT} itself showed no significant difference between age groups, considering the significant decrease of LAS_{RES} with age, the contribution of LAS_{CT} seemed to be augmented by age, which was evident by the parameter LAS_{CD}/LAS_{CT}. Liao et al.[17] previously reported that LA contractile strain rate was significantly increased when associated with aging and higher blood pressure. This result was interpreted as a compensatory mechanism due to decreased LA mechanical function. Our study results are consistent with their findings, suggesting that dominant LAS_{CD} in early diastole is the core of intact LA function. A gradual reverse of that pattern with age would be interpreted as a physiologic decline in LA function. A decrease in LA strain means an increase in LA stiffness, indicating an increase in LA fibrous content from a pathological view point.[18] Cumulative myocardial fibrosis with aging has been revealed in various cardiovascular diseases.[19] The impact of age on LA function has also been shown in previous studies.[15][20][21] However, we did not observe any sex-difference in any LA strain parameter. This pattern (a significant association of LA strain with age but not with sex) has also been shown in a previous study.[21] Conversely, sex differences regarding LV systolic and diastolic functions have been previously described, with some studies reporting that females present higher LV systolic strain[22] and mitral annular E′ velocity.[23] The different impact of sex on LV and LA functions may have interesting implications and should be reevaluated in future studies.

Our data show an association between LA function and LV diastolic function. This finding has also been described in several previous studies.[24-26] Singh et al.[27] showed that LA strain

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could be a discriminator regarding the class of diastolic dysfunction. However, a new finding in our data is the relationship between novel strain parameters. That is, LAS_{RES}, $LAS_{CD,}$ and LAS_{CD}/LAS_{CT} each presented a significant association with diastolic strain rates in multivariate analysis, but not with mitral E′ velocity or E/E′ ratio. Our subject group was distinctive from that of previous studies dealing with diastolic dysfunction[20)27)] in that our study subjects had no history of cardiovascular disease. Thus, this study group might have a low probability of clinical diastolic dysfunction. Considering the different subject characteristics, we suggest that the significant association between LA strain parameters and diastolic strain rates in our data might come from the better sensitivity of strain parameters over Doppler indices, although this should be evaluated in future studies.

Another interesting finding was the significant association between LA strain and LV GLS. As mentioned above, LV diastolic dysfunction is the main driver of LA remodeling.[24-26)] Certainly, LV GLS is a representative parameter of systolic function. However, in a previous clinical study regarding heart failure with preserved EF, decreased LV GLS was also associated with diastolic dysfunction.[28)] From a physiologic point of view, LV systole and diastole are not independent functions, but are phasic motions converting to each other.[1)] In addition, intact LV systolic function can induce apical displacement of mitral annulus and full expansion of LA.[1)2)] Thus, the association between LA strain and LV GLS seems reasonable. However, LVEF did not show a significant association, and thus our finding again emphasized the usefulness of strain parameters for evaluating cardiac mechanics.

Technical aspects of LA strain

The advantages of LA strain measurement are its non-invasiveness, feasibility in routine examinations, and simple post-processing,[2)] which are beneficial for clinical application and data accumulation. Compared with Doppler parameters, LA strain has freedom from angle-dependency, which is the biggest advantage. In addition, LA strain is relatively less affected by loading conditions.[29)] However, there are also limitations in LA strain analysis. Currently, several techniques such as speckle-tracking, velocity vector imaging, and edge tracking are available, and technical standardization has not been achieved.[2)] As the LA is located at the far field of imaging, the limited acoustic window could be problematic.[1)] Tracking for thin-wall LA produces a low signal-to-noise ratio, which is another technical challenge.[1)] Nonetheless, as previous studies have reported the high feasibility of LA strain,[14)15)] the technical merits of LA strain seem to outweigh its drawbacks.

Limitations

Since the NORMAL registry was originally not intended for LA strain analysis, our present study included only 32% of overall subjects with suitable images, which could be a source of selection bias. In addition, the clinical information for study subjects was limited to basic characteristics. Thus, there was a limitation with respect to evaluating the clinical meaning of LA strain. Although age showed significant associations with LA strain parameters in this cross-sectional analysis, the true chronological change in LA strain should be evaluated prospectively with a serial echocardiographic follow-up. Furthermore, as we used images obtained by a single-vendor machine (GE Medical Systems, Horten, Norway), the present study results would not be directly applicable to those using different systems.

Conclusions

We presented a reference value for LA strain with reservoir, conduit, and contractile components in a large-sized group of healthy subjects. Age was a physiologic determinant of

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LA function. However, the impact of sex was not evident. Significant associations between LA strain and diastolic strain rates and LV GLS reflect cardiac mechanics. They might emphasize the usefulness of strain parameters over conventional metrics such as mitral E′ and LVEF.

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SUPPLEMENTARY MATERIAL

Supplementary Table 1
Parameters associated with LA contractile strain

Click here to view

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