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Left and Right Atrial Strain in Healthy Caucasian Children by Two-Dimensional Speckle-Tracking Echocardiography

To the Editor:

Strain (ε) analysis has been applied for the analysis of ventricular function[1] and more recently for atrial function.[2-9] Left atrial (LA) ε has been proposed as a valuable marker in heart failure,[2] while the utility of right atrial (RA) ε has been reported in patients with pulmonary hypertension.[5] Studies of LA and RA ε in children with congenital or acquired heart disease are limited.[9,10] As with any other echocardiographic measure, the introduction of atrial ε analysis into routine clinical practice would require the availability of normal values.[11] A recent review and meta-analysis of LA ε nomograms is available for adults,[4] but it did not include data for children. Two pediatric studies of normal atrial ε values have been published thus far.[7,8] Kutty *et al*[8] evaluated two-dimensional (2D) speckle-tracking echocardiographic (STE) ε of the right and left atria in 153 children and young adults (age range, 3 days to 20 years). Ghelani *et al*[7] reported normal LA ε measured by three-dimensional echocardiography in 196 normal subjects (age range, 4 days to 20.9 years). The aim of the present investigation was to establish pediatric nomograms for global longitudinal LA and RA ε by 2D STE imaging from a wide cohort of healthy children.

Healthy Caucasian children evaluated from April 2015 to December 2017 in our outpatient pediatric cardiology department were prospectively recruited. The population included 400 healthy children previously reported in recent publications on other measurements.[11] The inclusion and exclusion criteria have been reported elsewhere.[11] All subjects with clinical, electrocardiographic, or echocardiographic evidence of congenital or acquired heart disease were excluded. Other exclusion criteria were known or suspected neuromuscular disease, genetic syndromes, chromosomal abnormalities, body mass index ≥ 95th percentile for children ≥2 years of age or weight-for-length *Z* score ≥ 2, pulmonary hypertension, systemic hypertension (for children >4 years of age), connective tissue disease, or family history of genetic cardiac disease. All patients underwent complete 2D examinations, and images were digitally stored for subsequent offline analysis. Approval for this study was obtained from the local ethics committee (Study "Bet" No. 390). Parents or legal guardians were informed and agreed to participate by providing written consent.

Echocardiograms were obtained using iE33 systems (Philips Medical Systems, Bothell, WA) with 8- and 5-MHz transducers with simultaneous electrocardiographic monitoring. Images were obtained in the apical four-chamber view. Using offline STE analysis, LA and RA longitudinal reservoir ε (εR) and contractile ε (εC) were measured in the four-chamber view (Figure 1). The left ventricular ε package was used for analysis on a computer workstation (QLAB 9; Philips Medical Systems, Andover, MA) according to recent guidelines[1]; the interatrial septum was included, while the atrial appendages were excluded. After manual placement of basic markers (lateral and septal mitral/tricuspid annulus and septal roof) in end-diastole, the software automatically generated atrial contours and performed STE analysis in seven segments through the cardiac cycle. Manual adjustment of tracking was performed when needed. For each parameter, the mean of three consecutive measurements was obtained. The QRS complex (R-R gating) was used as the initiation of the ε calculation. End-systolic ε values were calculated, with end-systole automatically calculated at aortic valve closure.[1] Two experienced pediatric cardiologists (M.C., E.F.) acquired images and performed measurements. Rates of intraobserver and interobserver variability were calculated from 20 subjects who were randomly selected.

Four age groups were evaluated: group 1, 31 days to ≤24 months; group 2, 2 to ≤5 years; group 3, 5 to ≤11 years; and group 4, 11 to ≤18 years).[11] Considering the four groups, the required sample size was ≥320 and ideally >560 subjects.[11] To examine the relationship between parameters of body size, heart rate (HR), age, and each of the echocardiographic variables, multiple models using linear, logarithmic, exponential, and square-root equations were tested.[11] Among the models that satisfied the assumption of homoscedasticity, the model with the highest R^2 value was considered to provide the best fit. To test the normality of residuals, the Shapiro-Wilk and Kolmogorov-Smirnov tests were used. Age, weight, height, HR and body surface area (BSA) were used as independent variables in regression analyses to predict the mean value

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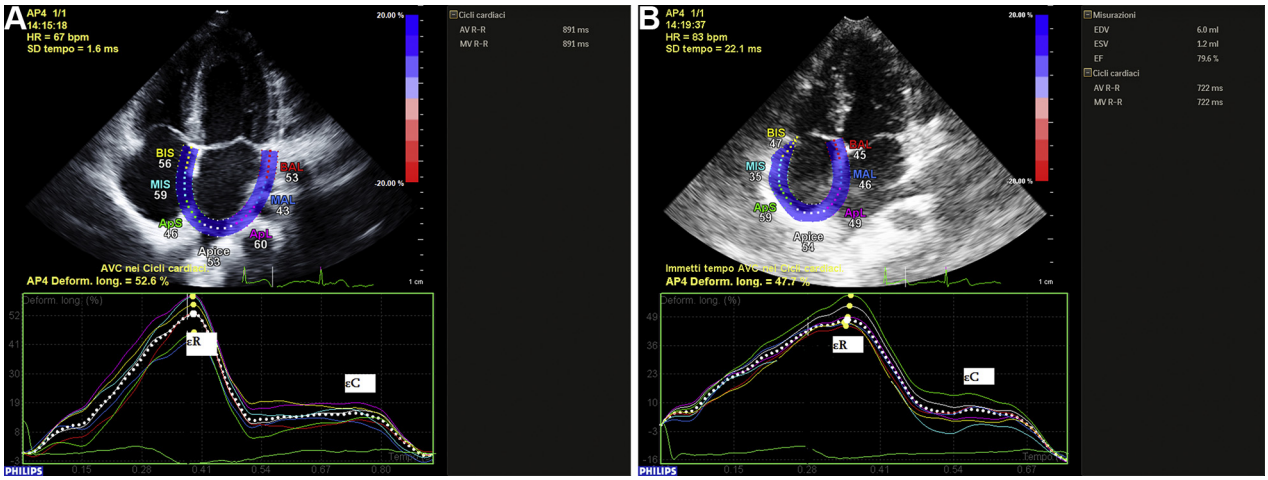

Figure 1 LA **(A)** and RA **(B)** ε analysis in the four-chamber view. *Apice*, Apex; *ApL*, apex lateral; *ApS*, apex septal; *BAL*, basal anterior lateral; *MAL*, medial anterior lateral; *BIS*, basal inferior septal; *MIS*, medial inferior septal.

Table 1 Population characteristics

Demographic	Male	Female	Total
Weight (kg)	30.3 ± 18.1	27.8 ± 16.8	29.1 ± 17.5
	25 (17–40)	23 (15.7–39)	24 (16.5–40)
Height (cm)	123.1 ± 30.7	119.9 ± 31.5	121.6 ± 31.1
	125 (104–145)	120 (100–143)	123 (102–145)
BSA (Haycock) (m^2)	1.00 ± 0.42	0.95 ± 0.40	0.98 ± 0.41
	0.93 (0.70–1.27)	0.87 (0.66–1.26)	0.91 (0.68–1.26)
HR (beats/min)	92.5 ± 24.7	96.9 ± 23.7	94.4 ± 24.3
	87 (77–102)	92 (81–107)	89 (79–104)
Frame rate (frames/sec)	64 ± 17	63 ± 14	62 ± 14
	62 (53–73)	63 (55–72)	61 (54–72)

Data are expressed as mean ± SD and median (interquartile range).

Table 2 Mean and SD of measurements by age group

Measurement	31 d to 24 mo (group 1) (*n* = 117)	2–5 y (group 2) (*n* = 141)	5–11 y (group 3) (*n* = 378)	11–18 y (group 4) (*n* = 200)	*P*	Post Hoc*
LA εR (%)	52.8 ± 10.1	55.7 ± 10.7	58.1 ± 10	57.6 ± 10.5	<.001	1 vs 3.4
LA εC (%)	14.2 ± 6.6	12.7 ± 6.1	14.0 ± 6.7	15.1 ± 7.0	.027	2 vs 4
RA εR (%)	47.1 ± 9.6	49.6 ± 10.2	51.6 ± 10.7	52.0 ± 10.6	<.001	1 vs 3.4
RA εC (%)	11.5 ± 6.0	11.9 ± 5.9	11.8 ± 6.3	12.8 ± 5.8	.278	—

*Bonferroni correction.

Table 3 Mean and SD of measurements by age group, male subjects

Measurement	31 d to 24 mo (group 1) (*n* = 62)	2–5 y (group 2) (*n* = 74)	5–11 y (group 3) (*n* = 206)	11–18 y (group 4) (*n* = 107)	*P*	Post Hoc*
LA εR (%)	54.1 ± 9.0	56.4 ± 11.5	58.0 ± 9.9	56.6 ± 11.1	.084	—
LA εC (%)	14.8 ± 6.5	12.5 ± 6.1	13.4 ± 5.9	14.6 ± 5.8	.086	—
RA εR (%)	47.3 ± 9.6	49.1 ± 10.2	51.1 ± 10.6	51.0 ± 10.1	.071	—
RA εC (%)	11.3 ± 6.3	12.0 ± 5.8	11.5 ± 6.1	12.6 ± 5.6	.509	—

*Bonferroni correction.

Table 4 Mean and SD of measurements by age group, female subjects

Measurements	31 d to 24 mo (group 1) (*n* = 55)	2–5 y (group 2) (*n* = 67)	5–11 y (group 3) (*n* = 172)	11–18 y (group 4) (*n* = 93)	*P*	Post Hoc*
LA εR (%)	51.3 ± 11.1	55.0 ± 9.7	58.2 ± 10.1	58.7 ± 9.8	<.001	1 vs 3.4
LA εC (%)	13.6 ± 6.7	12.9 ± 6.1	14.6 ± 7.5	15.6 ± 8.1	.156	—
RA εR (%)	46.8 ± 9.8	50.2 ± 10.1	52.1 ± 10.8	53.3 ± 11.2	.008	1 vs 3.4
RA εC(%)	11.8 ± 5.7	11.8 ± 6.0	12.1 ± 6.5	13.0 ± 6.2	.584	—

*Bonferroni correction.

of each measurement. The effect of sex was also evaluated as a covariate.[11] Comparisons between age groups were made using one-way analysis of variance, and the Bonferroni correction was used for a post hoc analysis.[11] In each age group, the fifth, 10th, 90th, and 95th percentiles were calculated. Among 850 subject enrolled, the final study population comprised 836 subjects (age range, 31 days to 17 years; mean age, 88.5 months; median age, 84.7 months; interquartile range, 50.1–127.6 months; 46% female). Demographic data are provided in Table 1 and Supplemental Table 1 (available at www.onlinejase.com). Feasibility was similar for LA and RA measurements (96.5% for LA εR, 95.6% for RA εR, 93.9% for LA εC, and 92.6% for RA εC). Feasibility was significantly lower at lower ages ($P < .001$) for all measurements.

The measurements were first modeled with HR, age, weight, height, and BSA. The shape of the distribution for different ε parameters and age groups was very different; however, most subgroups had a normal distribution (Supplemental Tables 2–8, available at www.onlinejase.com). Regressions showed generally low coefficients of determination (R^2) for all LA and RA ε indices (R^2 = 0.002–0.021; Supplemental Tables 2–5, Supplemental Figure 1, available at www.onlinejase.com), hampering the ability to calculate *Z* scores with sufficient reliability. Therefore, data are presented as means ± SD stratified for age groups and by gender (Tables 2–4). Percentile tables are also presented (Supplemental Table 9, available at www.onlinejase.com).

LA and RA longitudinal εR increased with increasing age. LA and RA ε values were significantly lower in group 1 (31–24 months) than in groups 3 and 4 (>5 years; $P < .001$, Tables 2–4). No significant age-related variation was noted for LA and RA εC. The interobserver and intraobserver coefficients of variation showed acceptable reproducibility. The intraobserver difference was 3.2% for LA εR (intraclass correlation coefficient [ICC], 0.896; 95% CI, 0.786–0.956) and 2.8% for RA εR (ICC, 0.959; 95% CI, 0.904–0.983); the interobserver difference was 5.3% for LA εR (ICC, 0.77; 95% CI, 0.528–0.899) and 4.5% for RA εR (ICC, 0.912; 95% CI, 0.799–0.962; Supplemental Table 9, available at www.onlinejase.com).

Our data are in line with previous publications also showing weak relations of atrial ε parameters with BSA and age. In the work of Ghelani *et al*,[7] the relation was $R = 0.14$ for global longitudinal ε and $R = 0.31$ for global three-dimensional ε; R^2 values were not presented. Kutty *et al*[8] found a slightly better relationship: R^2 values for LA εR were 0.18 for age and 0.16 for BSA, respectively. Furthermore, the scatterplots both for RA and LA εR showed no influence of age except for the limited population of lower age groups (0–1 years and 1–5 years).

To date there are only two small studies[7,8] (<200 subjects in each) that investigated functional maturation of atrial ε in children. One used GE technology for imaging and analyses,[8] while the other used Philips technology for image acquisition and vendor-independent software (TomTec, Unterschleissheim, Germany) for analysis.[7] In the present study, we used Philips technology for both image acquisition and analysis. The protocol we used has minor difference from the GE methodology in that we evaluated seven instead of six segments. This may explain the higher reservoir ε values. For example, the mean LA εR in the 11- to 18-year-old age group was 57.6% versus 39% in adults.[4,12,13] Of relevance, in one of the few adult QLAB-based studies,[14] mean LA εR normal values were quite close to ours (e.g., 59.8%).

Interestingly, no other confounders had a significant effect on ε parameters. Kutty *et al*[8] found a significant effect of HR on ε values in their series including neonates, a population in which cardiac function may be strongly influenced by loading conditions and high HR. The exclusion of neonates from our population may have attenuated the relative influence of HR on ε indices.

The present study was limited to the Caucasian ethnic group. However, this eliminated bias due to differing racial compositions and will allow future comparisons with populations of different ethnicities.[11] The feasibility of LA and RA ε measurements in this series is in accordance with previous reports.[7,8] The feasibility was very low in neonates, so we excluded the neonatal subgroup. The low feasibility at high HR is likely a limitation of the software used, and we suggest caution in evaluating atrial ε analyses in neonates. The software used was vendor specific, which was another limitation. Furthermore, atrial ε rates and conduit ε were not measured. The P wave–gating method, considered by some authors to be more appropriate than the R wave–gating method for assessing atrial function contraction, was not evaluated.[6,14] However, the R-wave method of gating has been used in most studies.[4] Last, atrial ε was measured only in the four-chamber view, while few other studies have used additional two- and three-chamber views.[4,8]

In summary, this report of echocardiographic LA and RA ε nomograms by 2D STE imaging from a large population of healthy children using vendor-specific (Philips) software demonstrate little variation of ε parameters with age. Our data can serve as a baseline for 2D STE evaluation of pediatric atrial function in children with congenital heart diseases. The influence of confounders and differences between vendor-specific and vendor-independent software need to be examined in future studies.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found at https://doi.org/10.1016/j.echo.2018.10.002.

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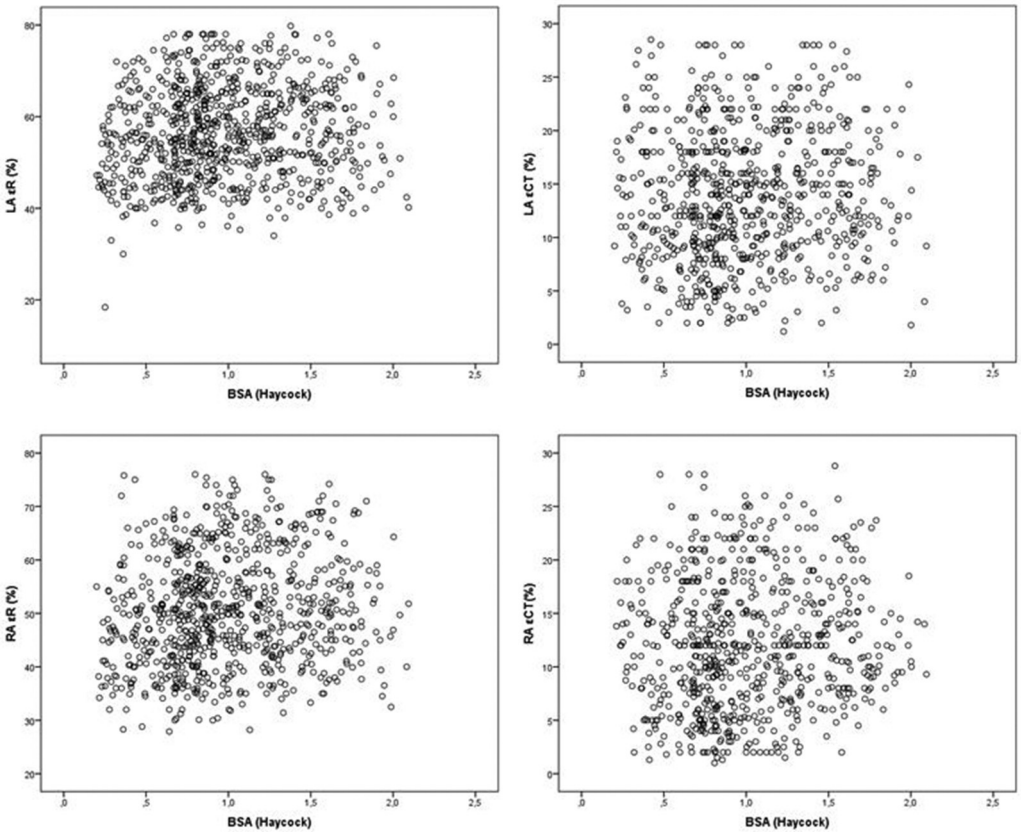

Supplemental Figure 1 Scatterplots showing correlations of atrial ε measures with BSA.

Supplemental Table 1 Number of measurements by age group and gender

Age groups	Male	Female	Total
31 d to 24 mo	62 (13.8)	55 (14.2)	117 (14.0)
2–5 y	74 (16.5)	67 (17.3)	141 (16.9)
5–11 y	206 (45.9)	172 (44.4)	378 (45.2)
11–18 y	107 (23.8)	93 (24.0)	200 (23.9)
Total	449 (100)	387 (100)	836 (100)

Data are expressed as number (percentage).

Supplemental Table 2 Linear regression models using BSA (Haycock) as the independent variable and echocardiographic measurements as dependent variables

Measurement	Intercept	*B*	SEE (√MSE)	R^2	SW	KS	BP	W
LA εR	4.030	0.056	0.185	0.019	<.001	<.001	<.001	<.001
LA εC	2.525	0.073	0.541	0.002	<.001	<.001	<.001	<.001
RA εR	3.913	0.069	0.207	0.021	<.001	<.001	<.001	<.001
RA εC	2.333	0.123	0.621	0.006	<.001	<.001	<.001	<.001

Table shows the coefficients of regression, the SEE, the determination coefficient, normality tests (SW and Lilliefors [KS]), and heteroscedasticity tests (W test and BP test). $\ln(y) = a + b \times \ln(x)$; Z value = {ln[Measurement] − [Intercept + B × ln(BSA)]}/√MSE.
BP, Breusch-Pagan test; *KS*, Kolmogorov-Smirnov test; *SEE*, standard error of the estimate; *SW*, Shapiro-Wilk test; *W*, White test.

Supplemental Table 3 Skew and kurtosis of measurements by age group

	31 d to 24 mo			2–5 y			5–11 y			11–18 y		
Measurement	Skew	Kurtosis	*P*	Skew	Kurtosis	*P*	Skew	Kurtosis	*P*	Skew	Kurtosis	*P*
LA εR	0.17	−0.63	.164	0.25	−0.77	.200	0.06	−0.76	.047	0.16	−0.65	.085
LA εCT	0.31	−0.73	.192	0.29	−0.43	.200	0.22	−0.61	.026	0.15	−0.66	.082
RA εR	0.56	0.09	.200	0.13	−0.78	.200	0.26	−0.52	.032	0.27	−0.80	.016
RA εCT	0.43	−0.40	.200	0.23	−0.83	.200	0.35	−0.71	.002	0.54	−0.28	.002

Supplemental Table 4 Skew and kurtosis of measurements by age group, male subjects

	31 d to 24 mo			2–5 y			5–11 y			11–18 y		
Measurement	Skew	Kurtosis	*P*	Skew	Kurtosis	*P*	Skew	Kurtosis	*P*	Skew	Kurtosis	*P*
LA εR	0.24	−0.96	.200	0.14	−0.82	.200	0.07	−0.65	.200	0.22	−0.55	.200
LA εCT	0.26	−0.84	.200	0.39	−0.37	.200	0.24	−0.60	.084	0.16	−0.66	.200
RA εR	0.37	−0.63	.168	0.23	−0.46	.200	0.32	−0.48	.024	0.19	−0.98	.145
RA εCT	0.37	−0.90	.200	0.47	−0.27	.200	0.36	−0.69	.047	0.56	0.10	.073

Supplemental Table 5 Skew and Kurtosis of measurements by age group, female subjects

	31 d to 24 mo			2–5 y			5–11 y			11–18 y		
Measurement	Skew	Kurtosis	*P*	Skew	Kurtosis	*P*	Skew	Kurtosis	*P*	Skew	Kurtosis	*P*
LA εR	0.20	−0.42	.200	0.38	−0.66	.200	0.06	−0.86	.200	0.14	−0.76	.200
LA εCT	0.39	−0.51	.200	0.12	−0.67	.200	0.17	−0.63	.041	0.13	−0.69	.095
RA εR	0.79	1.10	.003	0.02	−1.06	.200	0.18	−0.54	.200	0.28	−0.78	.177
RA εCT	0.57	0.70	.200	0.03	−1.33	.020	0.33	−0.75	.078	0.51	−0.60	.065

Supplemental Table 6 Percentiles of measurements by age group

	31 d to 24 mo				2–5 y				5–11 y				11–18 y			
Measurement	5th	10th	90th	95th	5th	10th	90th	95th	5th	10th	90th	95th	5th	10th	90th	95th
LA εR (%)	40.0	41.3	66.7	70.3	40.7	42.6	69.5	73.5	42.2	44.8	72.0	75.0	41.5	44.0	72.0	76.0
LA εC (%)	3.8	6.0	24.0	26.2	4.0	4.9	20.0	23.0	4.0	5.9	22.2	24.9	6.0	6.6	23.5	25.8
RA εR (%)	34.5	36.2	60.3	65.6	35.0	36.1	63.6	67.2	35.0	38.0	66.4	70.0	36.5	38.9	67.2	69.2
RA εC (%)	2.8	4.2	19.5	22.0	3.2	4.4	20.0	22.0	2.1	4.0	21.0	23.0	4.5	6.0	22.0	24.0

Supplemental Table 7 Percentiles of measurements by age group, male subjects

	31 d to 24 mo				2–5 y				5–11 y				11–18 y			
Measurement	5th	10th	90th	95th	5th	10th	90th	95th	5th	10th	90th	95th	5th	10th	90th	95th
LA εR (%)	40.2	43.0	66.9	69.3	41.2	43.0	69.5	74.5	42.0	45.0	72.0	75.0	40.2	43.0	69.8	74.0
LA εCT (%)	5.1	6.2	25.0	26.2	4.0	4.8	21.0	23.5	4.3	5.6	22.0	24.0	6.0	6.6	22.2	24.0
RA εR (%)	34.9	36.2	62.7	65.6	35.8	36.2	64.5	67.8	35.0	38.0	65.9	69.9	36.5	37.7	65.8	67.7
RA εC (%)	3.5	4.2	20.2	22.0	3.5	4.5	21.4	24.0	2.3	3.8	20.0	23.0	3.5	6.0	20.2	23.7

Supplemental Table 8 Percentiles of measurements by age group, female subjects

	31 d to 24 mo				2–5 y				5–11 y				11–18 y			
Measurement	5th	10th	90th	95th	5th	10th	90th	95th	5th	10th	90th	95th	5th	10th	90th	95th
LA εR (%)	33.0	40.0	63.8	72.0	40.7	42.6	68.8	73.3	42.2	44.8	72.1	75.0	44.0	45.6	72.3	76.0
LA εC (%)	3.5	5.6	22.1	26.0	3.8	4.9	19.9	23.0	3.6	6.0	23.0	25.5	6.0	6.5	25.0	27.4
RA εR (%)	32.0	36.7	59.2	60.4	35.0	36.1	63.6	65.9	35.0	37.7	67.0	70.1	37.0	39.9	69.0	72.0
RA εCT (%)	2.8	5.0	18.2	20.0	2.6	4.2	20.0	21.0	2.0	4.0	22.0	22.5	4.8	6.0	22.0	24.0

Supplemental Table 9 Inter- and intraobserver analysis

Measurements	ICC Interobserver	*P* value Interobserver	ICC Intraobserver	*P* value Intraobserver	CV (%) Interobserver	CV (%) Intraobserver
LA εR	0.773 (0.528–0.899)	<.001	0.896 (0.768–0.956)	<.001	5.3	3.2
LA εC	0.907 (0.789–0.960)	<.001	0.942 (0.865–0.975)	<.001	10.6	7.6
RA εR	0.912 (0.799–0.962)	<.001	0.959 (0.904–0.983)	<.001	4.5	2.8
RA εC	0.942 (0.867–0.976)	<.001	0.982 (0.957–0.993)	<.001	12.7	7.4

CV, Coefficient of variation; *ICC*, intraclass correlation coefficient.