Supplemental Material

Data S1. A method for subdividing the atria into six regions

First, the boundary between the anterior wall and the roof was defined as the line connecting the 10 o'clock direction of the right superior PV antrum and the 2 o'clock direction of the left superior PV antrum, viewed from the endocardial side. The boundary between the anterior wall and the septum was defined as the line connecting the 10 o'clock direction of the right superior PV antrum and the 10 o'clock direction of the mitral annulus. The boundary between the anterior and lateral walls was defined as a line from the left superior PV at 2 o'clock, through the base of the left atrial appendage, to the mitral annulus at 2 o'clock. The boundary between the septum and the inferior wall was defined as a line from 7 o'clock of the right inferior PV to 7 o'clock of the mitral annulus. The boundary between the roof and the posterior wall was defined as a line from 2 o'clock of the right superior PV to 10 o'clock of the left superior PV, viewed from the endocardial side. The boundary between the posterior wall and the inferior wall was defined as the line connecting the 5 o'clock direction of the right inferior PV and the 7 o'clock direction of the left inferior PV. The boundary between the inferior wall and the lateral wall was defined as the line connecting the 6 o'clock direction of the left lower PV and the 4 o'clock direction of the mitral annulus. An example of subdivision of the LA was shown in Figure 1B.

Data S2. Assessment of intra-observer and inter-observer variability of the segregation

For the assessment of intra-observer variability of the segregation, one observer measured twice the areas of each of the six regions in 25 subjects: five randomly selected subjects from each quartile of the AF group and the control group. The results showed that the mean ICC for the intra-observer variability was 0.826 (0.877 for the anterior wall, 0.820 for the septum, 0.791 for the roof, 0.860 for the inferior wall, 0.745 for the posterior wall, and 0.864 for the lateral wall). In addition, for the assessment of inter-observer variability of the segregation, two independent observers measured the areas of the six regions once each in the 25 subjects. The results showed that the mean ICC for the inter-observer variability was 0.667 (0.596 for the anterior wall, 0.872 for the septum, 0.575 for the roof, 0.617 for the inferior wall, 0.771 for the posterior wall, and 0.572 for the lateral wall)

Table S1. Demographic and clinical factors associated with global LA voltage in the AF group (n = 140)

Variables	Univariate			Multivariate 1		Multivariate 2	
	Coefficients	β	P value	β	P value	β	P value
Age	–0.097	–0.439	< 0.001*	–0.374	< 0.001*	–0.404	< 0.001*
Female	–1.756	–0.371	< 0.001*	–0.433	< 0.001*	–0.467	< 0.001*
Non-PAF, n (%)	–1.394	–0.316	< 0.001*	–0.332	< 0.001*	–0.322	< 0.001*
History of cerebral infarction	–0.015	–0.001	0.981	0.061	0.331	–0.001	0.983
History of congestive heart failure, n (%)	–1.335	–0.221	0.008*	–0.067	0.346	–0.059	0.399
Hypertension, n (%)	–0.519	–0.120	0.157	0.039	0.537	0.059	0.335
Diabetes, n (%)	0.231	0.039	0.642	–0.008	0.894	–0.030	0.620
eGFR, ml/min/1.73m^2	0.030	0.268	0.001*	0.073	0.285	0.059	0.364
LVEF, %	0.036	0.209	0.013*	0.114	0.122	0.095	0.189
LA diameter	–0.119	–0.336	< 0.001*	–0.134	0.068	–	–
LA volume, ml	–0.013	–0.260	< 0.001*	–	–	–0.204	0.006*
Adjusted R^2				0.493		0.525	

*Significant value (P <0.05)

eGFR = estimated glomerular filtration rate; LA = left atrium; LVEF = left ventricular ejection fraction; PAF = paroxysmal atrial fibrillation

β = β-coefficients

Table S2. Relationships between global and regional LA voltage

y axis / x axis		Global LA Voltage (V_{GLA})	Regional LA Voltage (V_{RLA})					
			Anterior	Septum	Roof	Inferior	Posterior	Lateral
Global LA Voltage (V_{GLA})			r = 0.91 y = –0.5+0.8x	r = 0.89 y = –0.2+0.8x	r = 0.82 y = –0.1+0.9x	r = 0.92 y = 0.2+1.1x	r = 0.90 y = –0.4+1.3x	r = 0.81 y = 1.7+1.1x
Regional LA Voltage (V_{RLA})	Anterior	r = 0.91 y = 1.5+1.0x		r = 0.81 y = 1.0+0.8x	r = 0.75 y = 1.2+0.9x	r = 0.79 y = 2.2+1.1x	r = 0.75 y = 1.9+1.2x	r = 0.75 y = 3.2+1.0x
	Septal	r = 0.89 y = 1.3+1.0x	r = 0.81 y = 0.6+0.8x		r = 0.74 y = 1.0+0.9x	r = 0.77 y = 2.0+1.1x	r = 0.78 y = 1.4+1.2x	r = 0.64 y = 3.6+0.9x
	Roof	r = 0.82 y = 1.9+0.7x	r = 0.75 y = 1.1+0.6x	r = 0.74 y = 1.3+0.6x		r = 0.71 y = 2.7+0.8x	r = 0. 77 y = 1.8+1.0x	r = 0.62 y = 4.0+0.7x
	Inferior	r = 0.92 y = 0.7+0.7x	r = 0.79 y = 0.3+0.6x	r = 0.77 y = 0.6+0.6x	r = 0.71 y = 0.8+0.6x		r = 0.79 y = 0.8+0.9x	r = 0.75 y = 2.4+0.8x
	Posterior	r = 0.90 y=1.3+0.6x	r = 0.75 y = 0.9+0.5x	r = 0.78 y = 1.0+0.5x	r = 0.77 y = 0.9+0.6x	r = 0.79 y = 2.0+0.7x		r = 0.68 y = 3.5+0.6x
	Lateral	r = 0.81 y = 0.8+0.6x	r = 0.75 y = 0.2+0.5x	r = 0.64 y = 0.9+0.4x	r = 0.62 y = 1.0+0.5x	r = 0.75 y = 1.2+0.7x	r = 0.68 y = 1.1+0.7x	

All of the p values are < 0.001, LA = left atrium

Data of the shaded row is presented in Figure S3.

Table S3. Relationship between presence of LVA and global LA voltage before and after covariate adjustment in the AF group

	$LVA_{0.1}$ (n = 11)			$LVA_{0.5}$ (n = 18)			$LVA_{1.0}$ (n = 49)			$LVA_{1.5}$ (n = 85)		
	OR	95% CI	p	OR	95% CI	p	OR	95% CI	p	OR	95% CI	p
Covariate adjustment (–)												
Global LA voltage	0.116	0.04–0.308	<0.001*	0.116	0.308–8.553	<0.001*	0.371	0.263–0.523	<0.001*	0.340	0.235–0.493	<0.001*
Covariate adjustment (+)												
Global LA voltage	—	—	—	0.125	0.036–0.425	<0.001*	0.420	0.276–0.640	<0.001*	0.325	0.200–0.526	<0.001*
Age	—	—	—	1.139	0.974–1.331	0.067	1.070	0.994–1.153	0.062	0.980	0.919–1.046	0.551
Female	—	—	—	3.559	0.329–38.473	0.298	0.741	0.198–2.769	0.655	0.766	0.209–2.808	0.687
Non-PAF	—	—	—	1.279	0.052–31.271	0.879	2.465	0.705–8.622	0.152	1.088	0.309–3.826	0.894
LA volume	—	—	—	1.028	1.001–1.055	0.018*	1.003	0.990–1.016	0.583	1.021	1.006–1.036	0.003*

*Significant value (P <0.05)

CI = confidence interval; LA = left atrium; LVA = low-voltage area; OR = odds ratio; PAF = paroxysmal atrial fibrillation

$LVA_{0.1}$ logistic model was unstable due to limited number of patients with $LVA_{0.1}$.

Table S4. Patient characteristics of those who underwent voltage mapping during coronary sinus pacing

Variables	n = 35
Age, years	72 ± 6
Females, n (%)	13 (37)
Non-PAF, n (%)	22 (63)
BMI, kg/m^2	24.5 ± 4.1
History of cerebral infraction	1 (3)
History of congestive heart failure, n (%)	4 (11)
Hypertension, n (%)	19 (54)
Diabetes, n (%)	7 (20)
CHA_2DS_2-VASc score (IQR)	2 (2–4)
eGFR, $ml/min/1.73m^2$	53 ± 18
LVEF, %	67 ± 10
LA diameter, mm	41 ± 6
LA volume, ml	152 ± 43
LA volume/BSA, ml/m^2	93 ± 27
Mean LA voltage, mV	5.5 ± 2.1

AT = atrial tachycardia; BMI = body mass index; BSA = body surface area; eGFR = estimated glomerular filtration rate; IQR = interquartile range; LA = left atrium; LVEF = left ventricular ejection fraction; PAF = paroxysmal atrial fibrillation

Table S5. Comparison between patients receiving amiodarone and those not receiving in Q1

Variables	Amiodarone (+), n = 8	Amiodarone (–), n = 27	*p* value
Age, years	74 ± 7	69 ± 10	0.251
Female, n (%)	3 (38)	15 (56)	0.443
Non-PAF, n (%)	8 (100)	21 (78)	0.299
History of congestive heart failure, n (%)	3 (38)	6 (22)	0.396
Hypertension, n (%)	2 (25)	18 (67)	0.051
Diabetes, n (%)	0 (0)	6 (22)	0.299
eGFR, ml/min/1.73m^2	39 ± 22	55 ± 20	0.085
LVEF, %	63 ± 10	61 ± 12	0.511
LA volume, ml	192 ± 64	168 ± 40	0.347
Mean LA voltage, mV	3.1 ± 0.8	3.0 ± 0.8	0.669
Regional LA voltage, mV			
Anterior	2.2 ± 0.9	1.8 ± 0.8	0.236
Septum	2.4 ± 0.6	2.3 ± 0.8	0.699
Roof	2.7 ± 0.8	2.3 ± 0.9	0.303
Inferior	3.6 ± 1.0	3.6 ± 1.2	0.947
Posterior	3.5 ± 1.3	3.5 ± 1.4	0.985
Lateral	5.5 ± 2.4	4.7 ± 1.6	0.373
Presence of $LVA_{0.1}$, n (%)	2 (25)	9 (33)	1.000
Presence of $LVA_{0.5}$, n (%)	4 (50)	13 (48)	1.000
Presence of $LVA_{1.0}$, n (%)	6 (75)	22 (81)	0.647
Presence of $LVA_{1.5}$, n (%)	8 (100)	27 (100)	–

eGFR = estimated glomerular filtration rate; LA = left atrium; LVA = low-voltage area; LVEF = left ventricular ejection fraction; PAF = paroxysmal atrial fibrillation

Table S6. Patient characteristics in the Non-biopsy and Biopsy groups

Variables	Non-biopsy n = 112	Biopsy n = 28	*P* value
Age, years	68 ± 10	70 ± 10	0.593
Female, n (%)	37 (33)	5 (18)	0.103
Non-PAF, n (%)	66 (59)	17 (61)	0.863
BMI, kg/m^2	24.4 ± 3.7	25.7 ± 3.5	0.076
History of cerebral infraction	11 (10)	1 (4)	0.459
History of congestive heart failure, n (%)	18 (16)	3 (11)	0.569
Hypertension, n (%)	52 (46)	19 (68)	0.040*
Diabetes, n (%)	18 (16)	5 (18)	0.821
CHA_2DS_2-VASc score (IQR)	2 (1–3)	2 (1–3)	0.866
eGFR, $ml/min/1.73m^2$	59 ± 19	57 ± 18	0.657
LVEF, %	65 ± 13	65 ± 12	1.000
LA diameter, mm	41 ± 6	42 ± 7	0.478
LA volume, ml	155 ± 46	163 ± 49	0.415
LA volume/BSA, ml/m^2	93 ± 26	93 ± 25	0.994
Mean LA voltage, mV	5.5 ± 2.1	6.3 ± 2.3	0.069

AT = atrial tachycardia; BMI = body mass index; BSA = body surface area; eGFR = estimated glomerular filtration rate; IQR = interquartile range; LA = left atrium; LVEF = left ventricular ejection fraction; PAF = paroxysmal atrial fibrillation

Figure S1. The global left atrial voltage (V_{GLA}) evaluated by the 1 cm^2-area method showed a strong positive correlation with those evaluated by the all-annotated-point method.

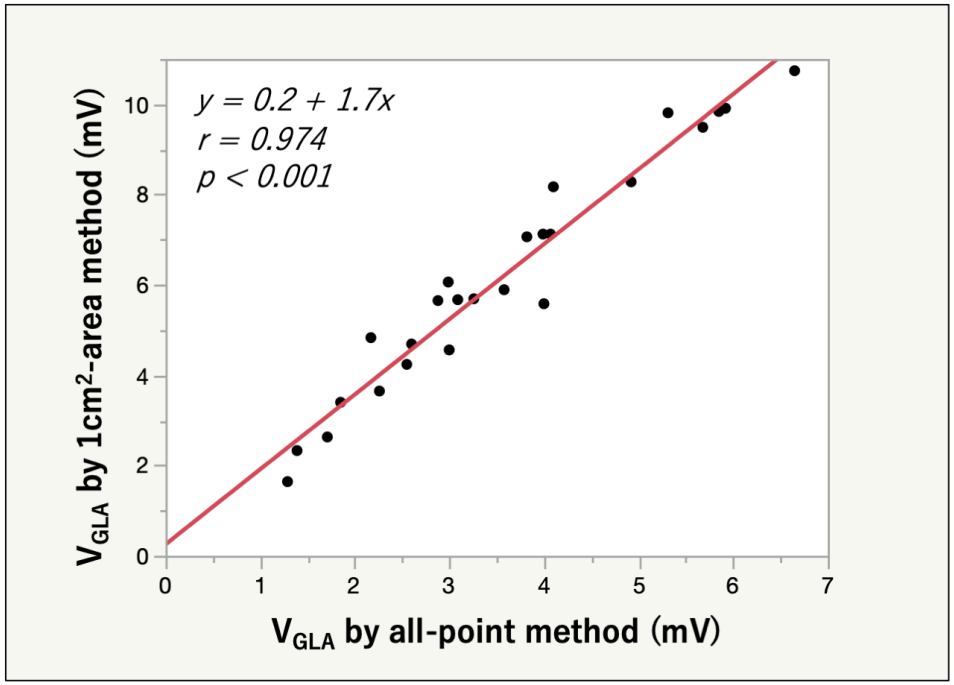


Figure S2. The reginal left atrial voltage (V_{RLA}) evaluated by the 1 cm^2-area method showed strong positive correlations with those evaluated by the all-annotated-point method in all regions.

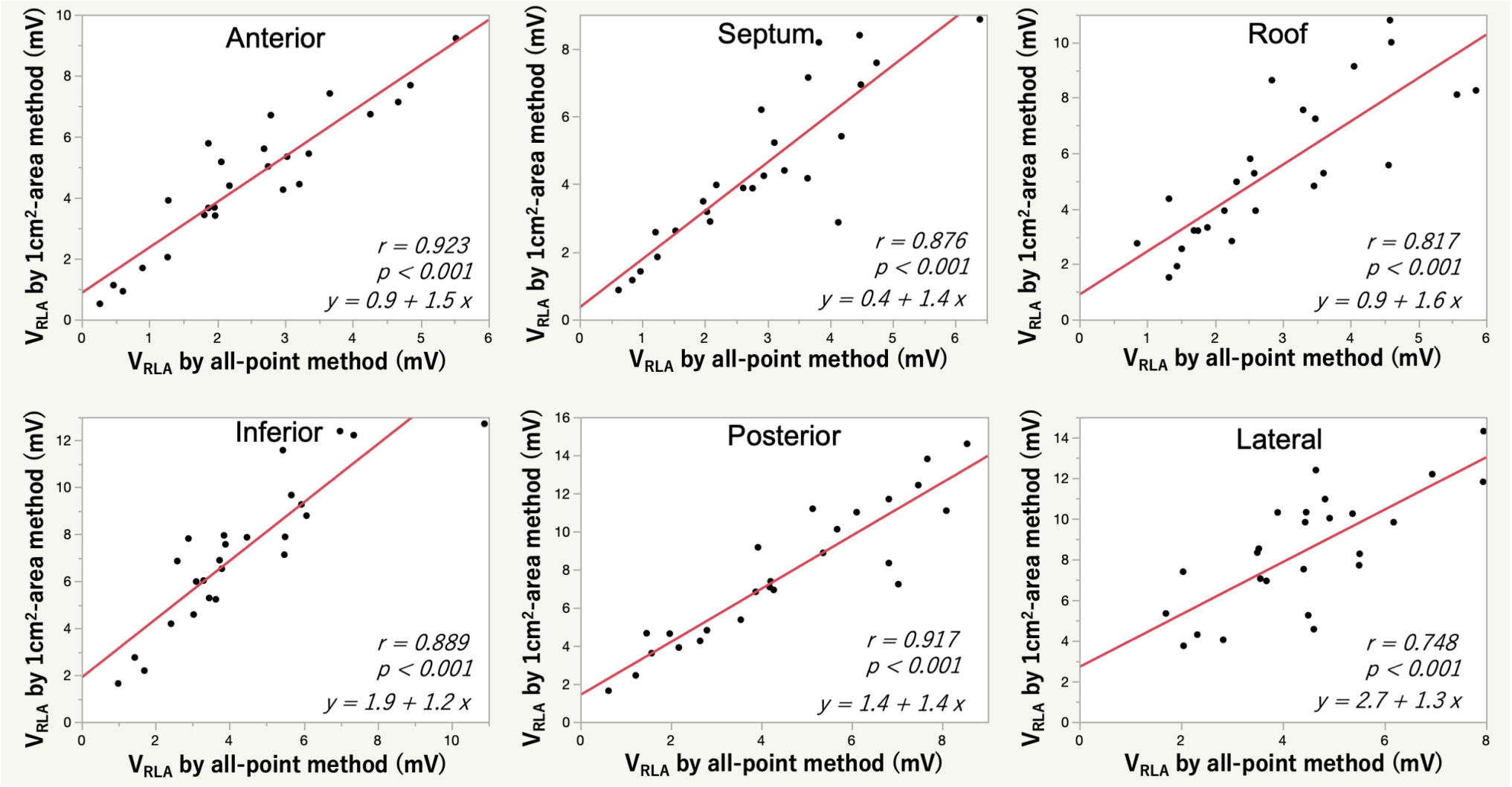


Figure S3. Comparison of V_{GLA} and V_{RLA} between Q4 and the control group. There were no significant differences in V_{GLA} and V_{RLA} at any region between Q4 and the control group. LA, left atrium; V_{GLA}, global LA voltage; V_{RLA}, regional LA voltage

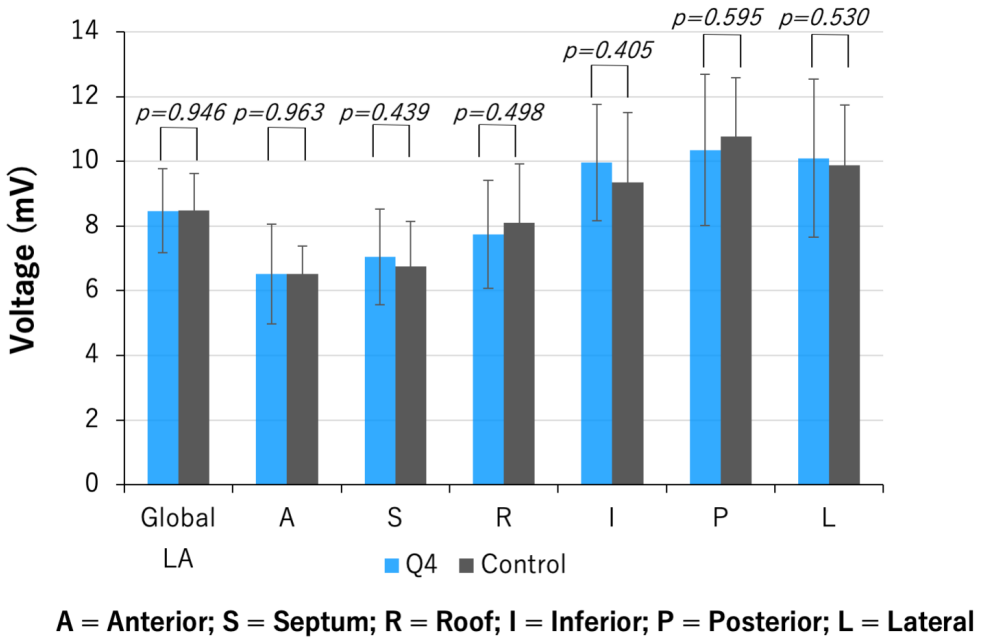


Figure S4. Comparison of relative regional LA voltage (V_{RLA}) in the AF group. The radar chart consists of the mean of relative V_{RLA} of each anatomical region in Q1 to Q3, which was calculated by the formula in the figure. The relative V_{RLA} at any region decreased as the quartile moved down. The ANOVA showed no significant differences between the anatomical regions at any quartile when the lateral wall was excluded. The value of mean V_{RLA} of each anatomical region in Q4 is also shown in the figure. ANOVA, analysis of variance; LA, left atrium; V_{RLA}, regional LA voltage

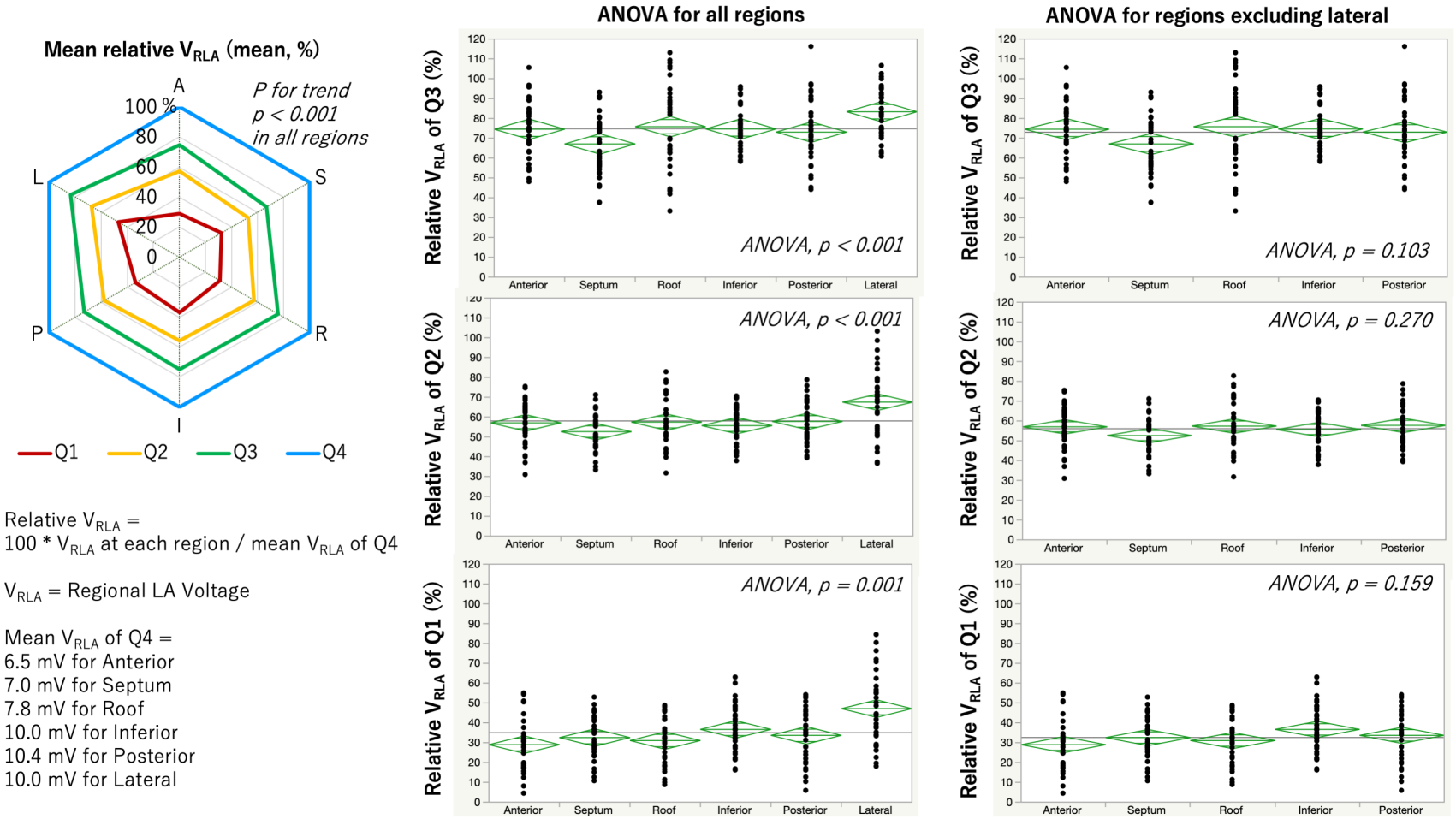


Figure S5. Comparison of regional LA voltage (V_{RLA}) of the anterior wall with the global LA voltage (V_{GLA}) and with the V_{RLA} of other regions. The V_{RLA} of the anterior linearly correlated not only with V_{GLA} but also with the V_{RLA} of other regions. Each dot shows data of each patient. LA, left atrium

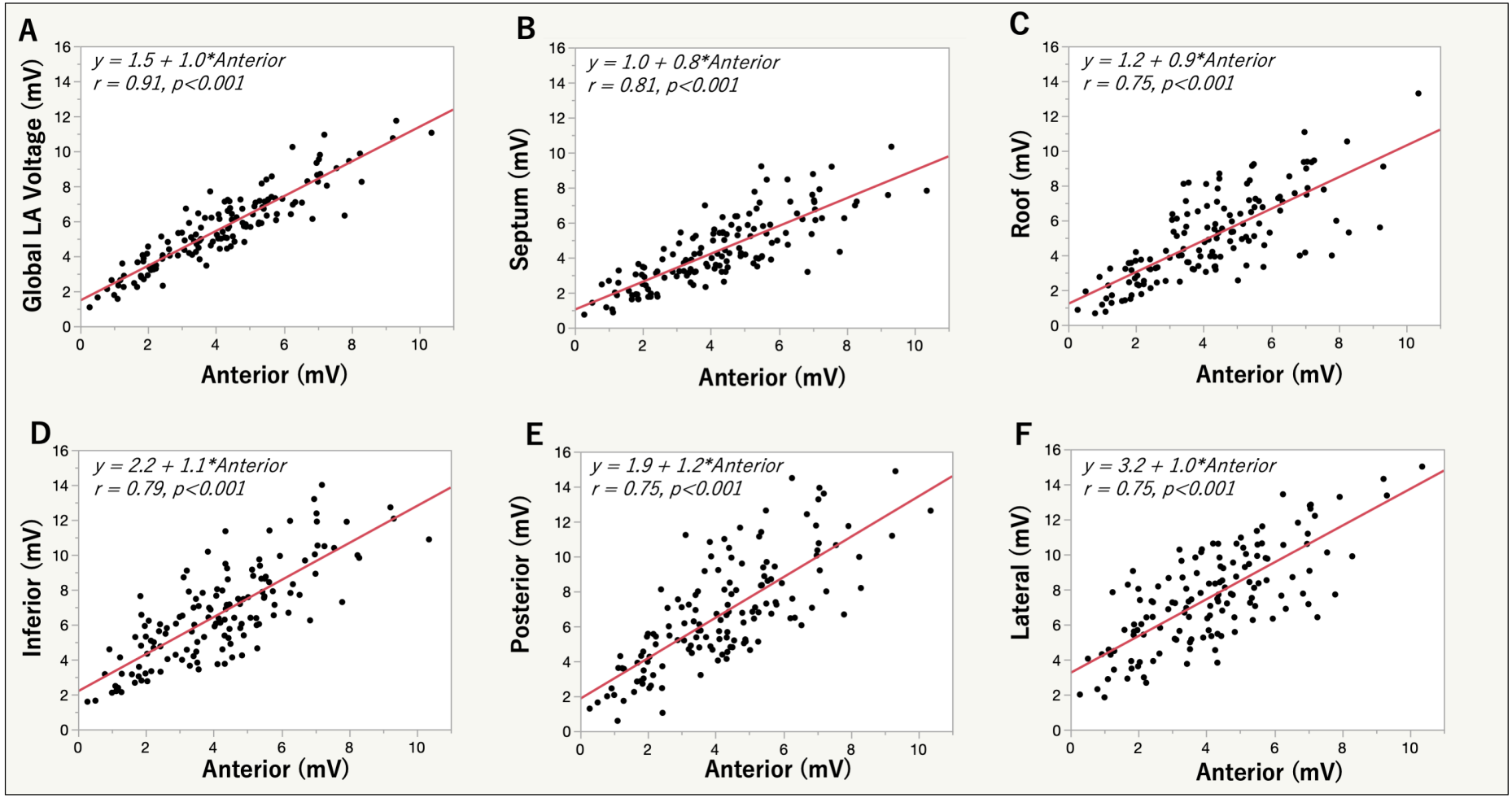


Figure S6. Comparison between the global LA voltage (V_{GLA}), evaluated by a mean of the highest voltage at a sampling density of 1 cm^2, and the median of that. Each dot shows data of each patient. There was a strong linear relationship between them. LA, left atrium

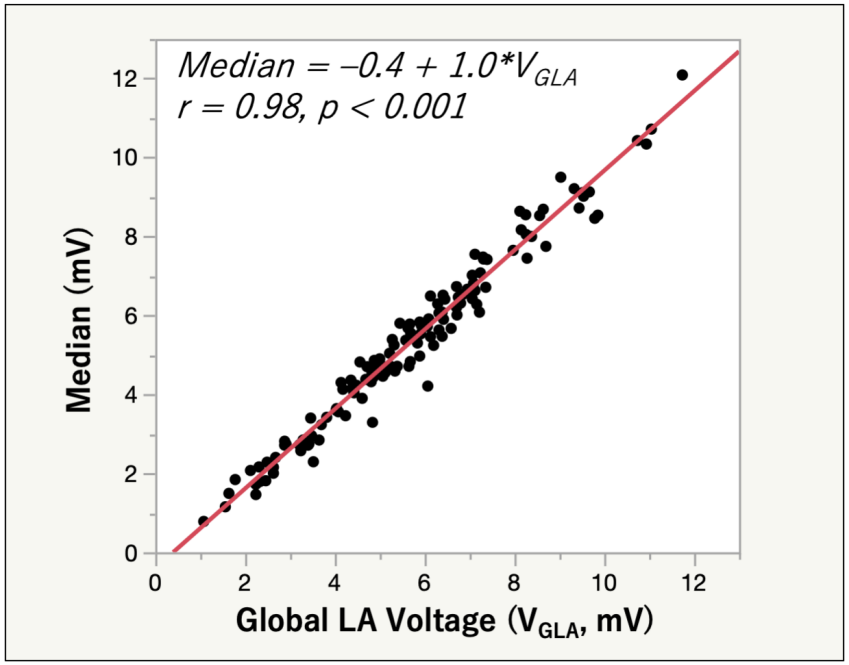


Figure S7. Relationship between the voltage cutoffs of 0.5, 0.75, 1.0, 1.25, and 1.5mV and the LVA extent in the LA at each cutoff in 22 patients with $LVA_{0.5}$ identified. **A**, LVA extent linearly increased as the voltage cutoff increased. **B** and **C**, examples of voltage map at different cutoffs in two patients. LA, left atrium; LAA, left atrial appendage; LSPV, left superior pulmonary vein; LVA, low-voltage area; MV, mitral valve; RSPV, right superior pulmonary vein.

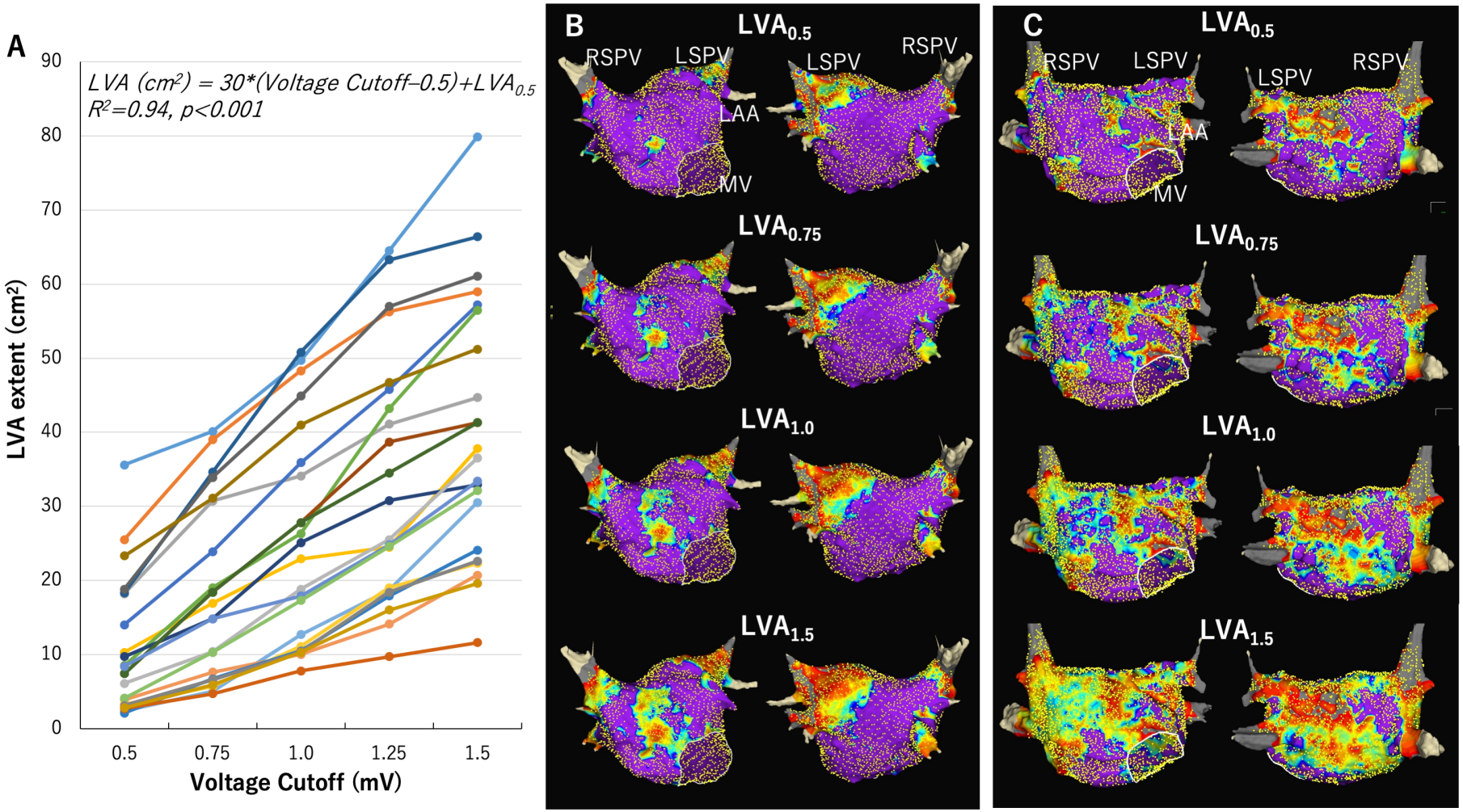


Figure S8. Comparison of an LA voltage map between HRA and CS pacing. A, an example of a same patient during HRA pacing (left) and CS pacing (right) viewed from anterior-posterior and posterior-anterior directions. There was a small difference in the distribution of LVA especially in the posterior wall. **B** to **E**, the relationship of global LA voltage and regional voltages between RAA pacing and CS pacing. There were strong linear relationships. CS, Coronary sinus; HRA, high right atrium; LA, left atrium; LAA, left atrial appendage; LSPV, left superior pulmonary vein; LVA, low-voltage area; MV, mitral valve; RSPV, right superior pulmonary vein.

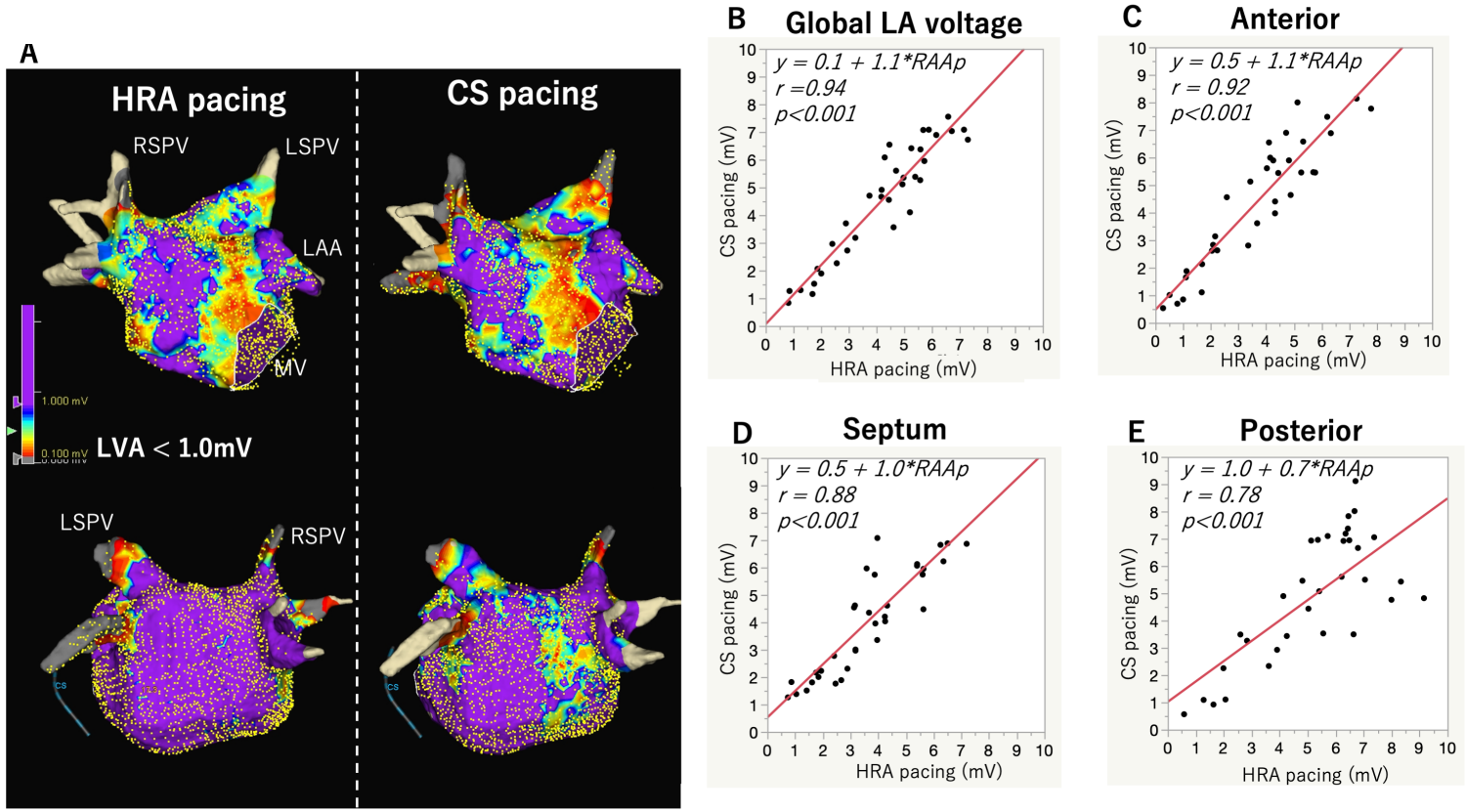
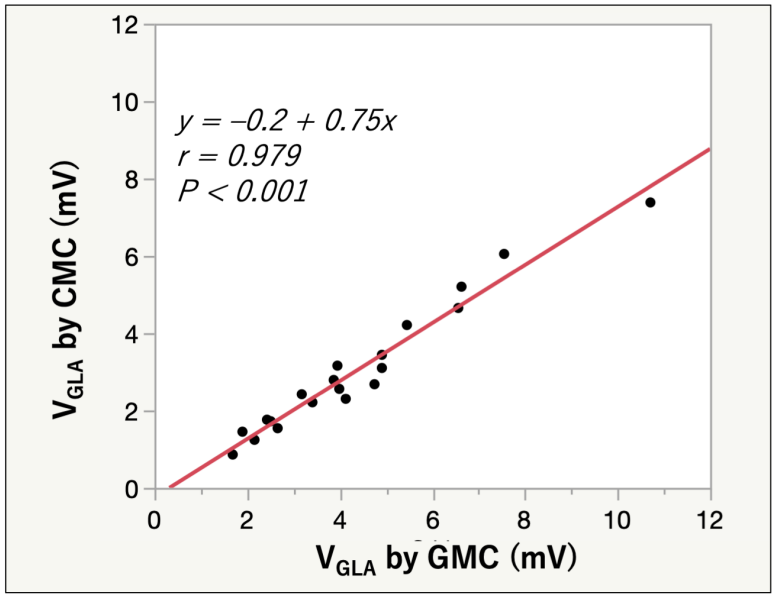


Figure S9. A, Comparison of V_{GLA} between GMC and CMC. There was a strong linear relationship between the two mapping catheters, and V_{GLA} by CMC was 0.75 x V_{GLA} by GMC. B shows the 20-pole CMC with a 1-mm electrode length and 2-mm interelectrode spacing. CMC, circular mapping catheter; GMC, grid mapping catheter; V_{GLA}, global LA voltage



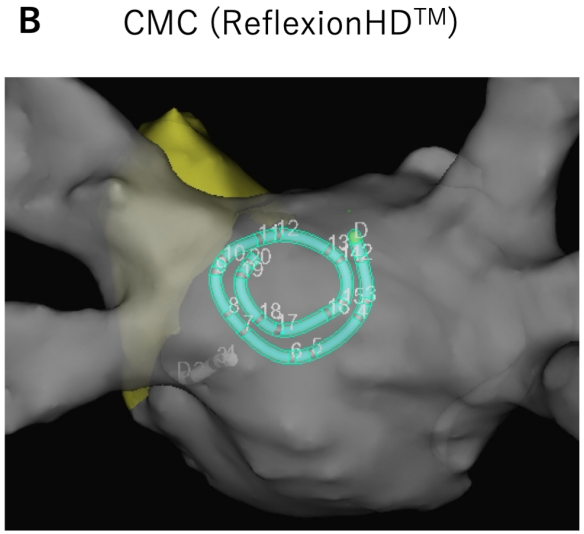


Figure S10. A, Representative cases of voltage map of the LA (upper row), activation map during left atrial (LA) macro-reentrant tachycardia (LAMRT, middle row), and ablation lesions at the critical isthmus (white arrows in lower row). The color gradient indicates serial changes in the electrogram amplitude from purple at ≥ 0.5 mV (voltage cutoff) to gray at <0.1 mV. Critical isthmuses were identified in the LVA. **B**, The inducibility of LAMRTs increased as the quartile moved down to the lower quartile. **C,** The inducibility increased as LVA appeared at lower voltage cutoffs. LAA, left atrial appendage; LSPV, left superior pulmonary vein; MV, mitral valve; RSPV, right superior pulmonary vein.

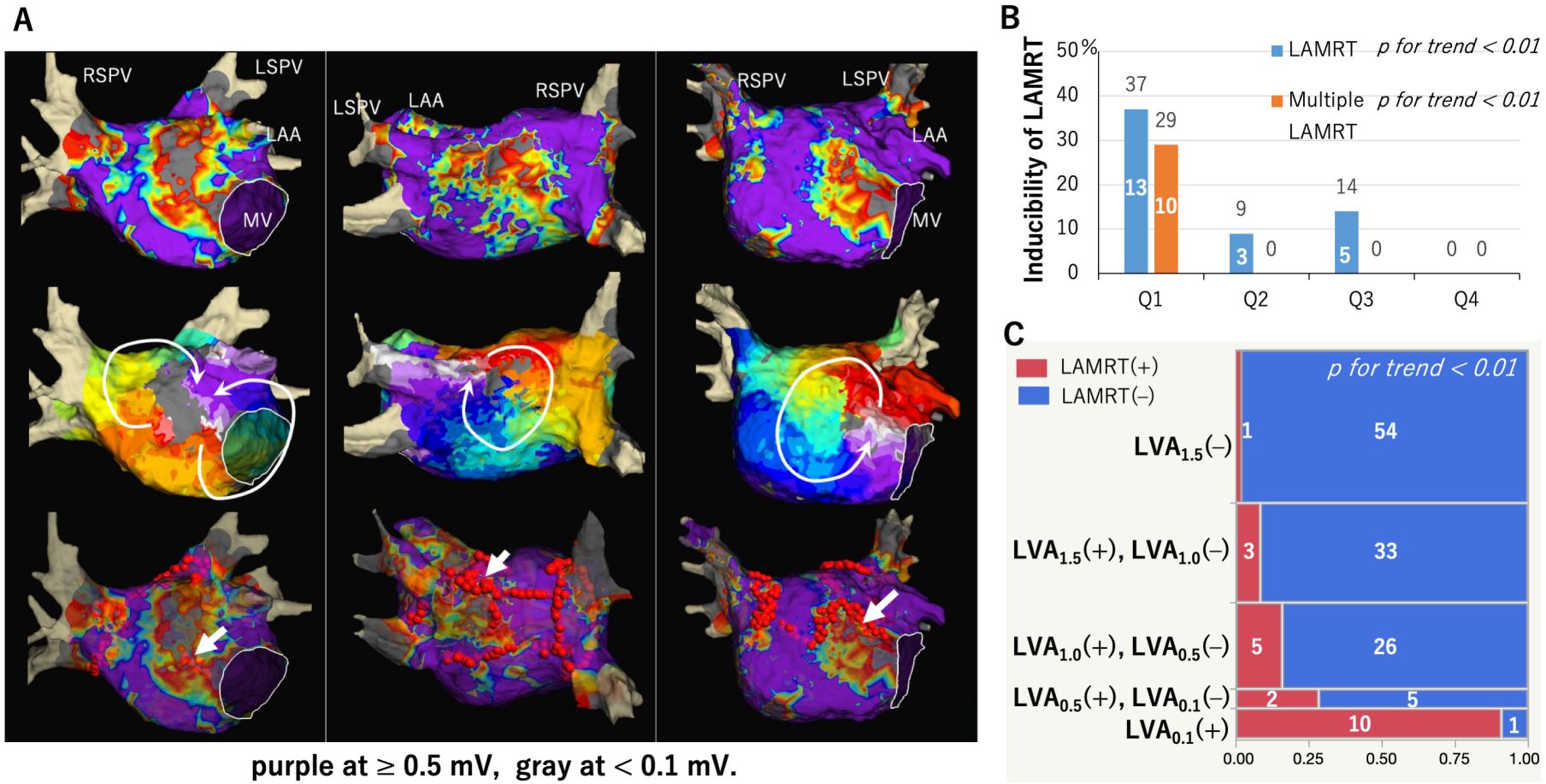


Figure S11. An example of voltage and activation map of the right atrial (RA) septum during high RA pacing. The locations of biopsy site at the limbus of fossa ovalis (FO) and FO were annotated on the geometry. Note that the voltage amplitude at the biopsy site is highest in the RA septum, showing > 11 mV in this case. No slow conduction zone was identified at the biopsy site. FO, fossa ovalis; IVC, inferior vena cava; TV, tricuspid valve; SVC, superior vena cava

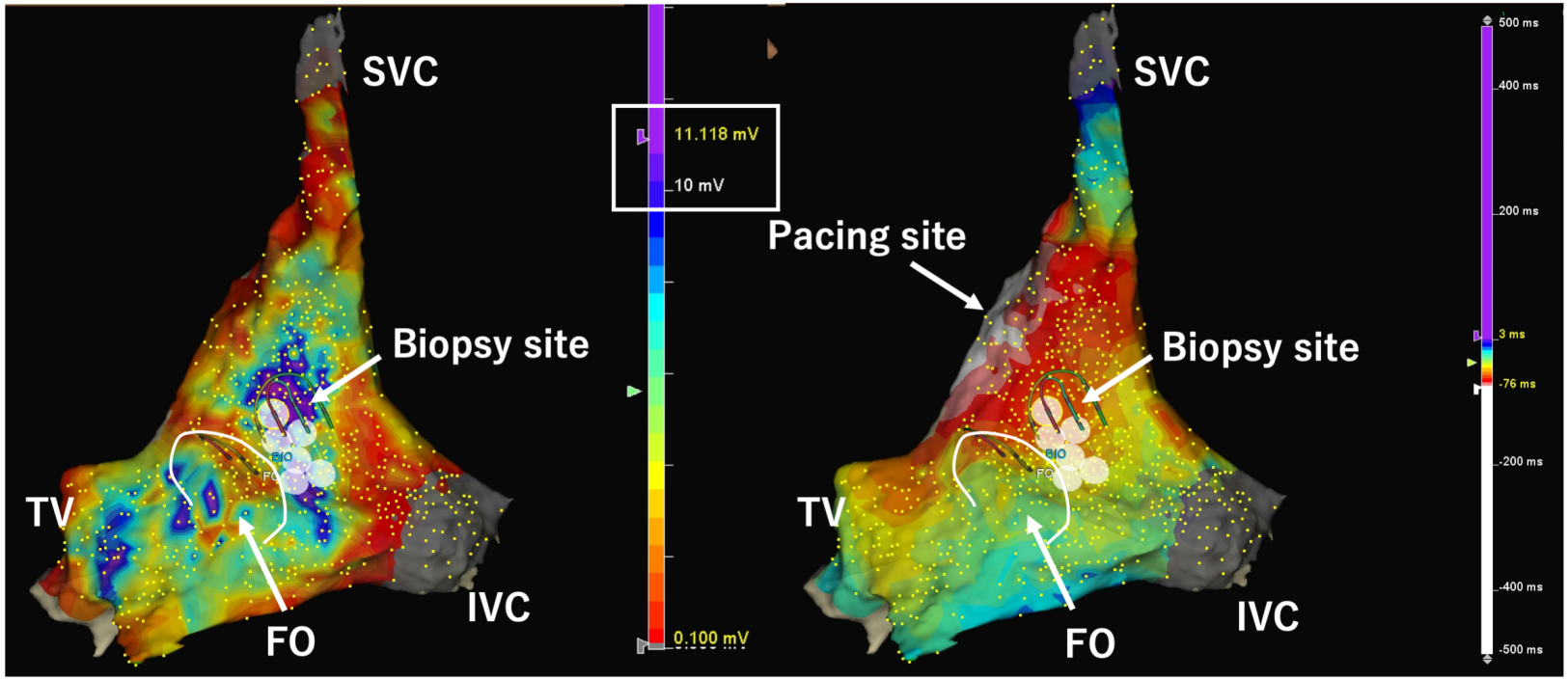


Figure S12. Relationship between V_{GLA} and V_{FO} and between V_{biopsy} and V_{FO}. There was a positive linear relationship between V_{GLA} and V_{FO}, and between V_{biopsy} and V_{FO}. V_{biopsy}, voltage at biopsy site; V_{FO}, voltage at fossa ovalis; V_{GLA}, global LA voltage