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Pacing cycle length–dependent electrophysiologic changes in left atrium: Poor validity of using low-voltage area and slow conduction area under specific pacing cycle length as absolute substrates of atrial fibrillation

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ABSTRACT

BACKGROUND Pacing cycle length (PCL)–dependent changes in left atrial (LA) electrophysiologic properties have not been fully elucidated.

OBJECTIVE We aimed to elucidate these changes using a high-resolution mapping system.

METHODS Forty-eight patients underwent atrial fibrillation ablation with RHYTHMIA HDx. Paired LA maps under a baseline PCL (600 ms) and rapid PCL (300 ms) were acquired after pulmonary vein isolation under right atrial appendage pacing. The PCL-dependent change in the low-voltage area (LVA; area with <0.5 mV bipolar voltage), LA activation time (interval from first LA activation to wavefront collision at lateral wall), regional mean voltage, regional mean wave propagation velocity, and slow conduction area (area with <0.3 m/s wave propagation velocity) were quantitatively analyzed.

RESULTS Under the rapid PCL, the total LVA was significantly increased (7.6 ± 9.5 cm^2 vs 6.7 ± 7.6 cm^2; $P = .031$), especially in patients with a 10 cm^2 LVA on the baseline PCL map (21.5 ± 9.1 cm^2 vs 18.1 ± 6.5 cm^2; $P = .013$). The LA activation time was also prolonged (87.9 ± 16.2 ms vs 84.0 ± 14.0 ms; $P < .0001$). Although the rapid PCL did not decrease the regional mean voltage, it significantly decreased the regional mean wave propagation velocity and increased the slow conduction area in all measured regions.

CONCLUSION LVA and slow conduction area can be emphasized by rapid PCL LA mapping. There may be poor validity in using these areas as absolute atrial fibrillation substrates without considering the PCL-dependent changes.

KEYWORDS Atrial fibrillation; High-resolution mapping; Left atrium; Low-voltage area; Pacing cycle length dependency; Wave propagation velocity

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Introduction

Pulmonary vein isolation (PVI) has been established as an essential strategy for catheter ablation of atrial fibrillation (AF). In addition to targeting AF triggers as performed during PVI, a strategy involving AF substrate ablation has been explored for complex cases. Recent 3-dimensional (3D) electroanatomic mapping systems have enabled the acquisition of high-resolution left atrial (LA) maps, which are crucial in assessing the AF substrate. One of the most frequently used indicators is the low-voltage area (LVA) of the left atrium, usually defined as the area with a <0.5 mV bipolar voltage.[1] Other indicators, including fractionated electrograms and the slow conduction area,[2–4] can also reportedly predict AF recurrence or the slow conduction zone of postablation atrial tachycardia (AT).

Three-dimensional mapping for evaluation of the AF substrate, including the LVA, is routinely performed under sinus rhythm or constant atrial pacing.[5,6] The pacing cycle length (PCL) is determined at the operator's discretion, and most published investigations have been performed with a PCL of

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≥600 ms.[1,7] Studies using the previous-generation 3D mapping system demonstrated a PCL-dependent decrease in the local voltage and conduction velocity in the left atrium.[8,9] Compared with the previous system, however, current high-resolution 3D mapping systems offer better discrimination between healthy and damaged tissues.[10] Therefore, reevaluation of the PCL dependency of LA voltage and conduction properties using the current system might provide a novel understanding. In this study, we performed high-resolution LA mapping under baseline PCL (600 ms) and rapid PCL (300 ms) pacing from the right atrial appendage (RAA) during AF ablation. We evaluated the PCL-dependent changes in the LA voltage and conduction properties in patients with AF using high-resolution LA maps.

Methods

Study population

This prospective observational study included 48 consecutive patients whose high-resolution (≥5000 points) baseline and rapid PCL maps of the left atrium were successfully acquired during AF or AT ablation with the RHYTHMIA HDx mapping system (Boston Scientific, Marlborough, MA) from June 2022 to May 2024. All procedures were performed by a single operator (T.S.). Patients who underwent repeated ablation procedures could be included in the study if their mapping data were acquired before additional ablation other than LA roof or bottom lines. However, patients who underwent LA anterior line, lateral mitral isthmus line, or LA substrate ablation were excluded. Patients with a history of cardiac surgery involving left atriotomy were also excluded. This study complied with the Declaration of Helsinki, and the hospital's institutional review board approved the study protocol. Consent was obtained by an opt-out method. Thirty-seven patients from our previously published investigation[11] were also included in the study.

High-resolution LA mapping

All patients underwent high-resolution LA mapping using an INTELLAMAP ORION catheter (Boston Scientific) and RHYTHMIA mapping system after PVI before the additional ablation to the LA body, except for the LA roof or bottom linear ablation. For patients undergoing redo procedures, the LA mapping was performed at the start of the session or after closing the PVI gaps. The detailed ablation method is described in Supplemental Material 1.

Abbreviations

AF: atrial fibrillation

AT: atrial tachycardia

LA: left atrial

LVA: low-voltage area

PCL: pacing cycle length

PVI: pulmonary vein isolation

RAA: right atrial appendage

We acquired a pair of high-resolution LA maps for each patient under baseline PCL (600 ms nominally) and rapid PCL (300 ms or half the baseline PCL) constant RAA pacing. The baseline PCL was decreased when Wenckebach atrioventricular conduction disturbed the effective mapping due to far-field ventricular electrograms. The mapping was performed under beat acceptance criteria, including the PCL, stability of the local activation time of secondary reference, morphology of local electrocardiograms, catheter movement speed, and respiration gating. The mapping points within a 3-mm distance from the LA shell were set to be projected and used for the analysis. We confirmed that the pacing catheter position was not changed throughout the mapping. To reduce insufficient catheter contact, we performed the mapping ensuring that the LA shell fitted the preprocedurally acquired computed tomography image of the left atrium. In addition, the shapes of the LA shells in the same patients were made to be as identical as possible. The consistency of the mapping quality was checked by evaluating the correlations of the mapping parameters measured under each PCL. The target mapping time of each map was set at <15 minutes.

Analysis of high-resolution LA maps

The LA maps were segmented into 6 regions—anterior wall, septum, inferior wall, lateral wall, LA appendage, and posterior wall—in the same manner as in our previous study.[11] To avoid perforation, we did not tightly contact the mapping catheter to the LA appendage; therefore, the LA appendage was excluded from the analysis. In addition, the LA posterior wall was excluded from the analysis because in some patients, the left and right PVI lines were in proximity on the posterior wall. In this study, the LVA was defined as the <0.5-mV area on the bipolar voltage map. Extremely tiny LVAs were excluded from the analysis. We also measured the LA activation time, defined as the interval from the first LA activation to the collision of the anterior and posterior wavefronts at the lateral wall (Supplemental Material 2).[12,13] We also evaluated the distribution of the fractionated electrogram area, highlighted by the LUMIPOINT Complex Activation, using a 5.0 peak slider threshold.

Quantitative analysis of the 3D electroanatomic maps was performed with EPLab Research Works[14] for calculation of the regional mean voltage (bipolar peak-to-peak voltage), wave propagation velocity, and slow conduction area. The conduction velocity, referred to as the wave propagation velocity in the software, was calculated on the basis of the study by Kojodjojo and associates.[15] Slow conduction area, defined as the area with <0.3 m/s wave propagation velocity,[16,17] was also calculated. The calculation methods are summarized in Supplemental Material 3. Before performing these analyses, we manually excluded obvious misannotated points. Representative pairs of baseline and rapid PCL maps are shown in Figures 1 and 2.

Statistical analysis

Continuous variables are expressed as mean ± standard deviation or median (interquartile range). A P value of <.05 was considered statistically significant. The relationship between 2 continuous variables was evaluated on the basis of the correlation coefficient. Comparisons of changes in the parameters within each patient were performed by a paired t-test.

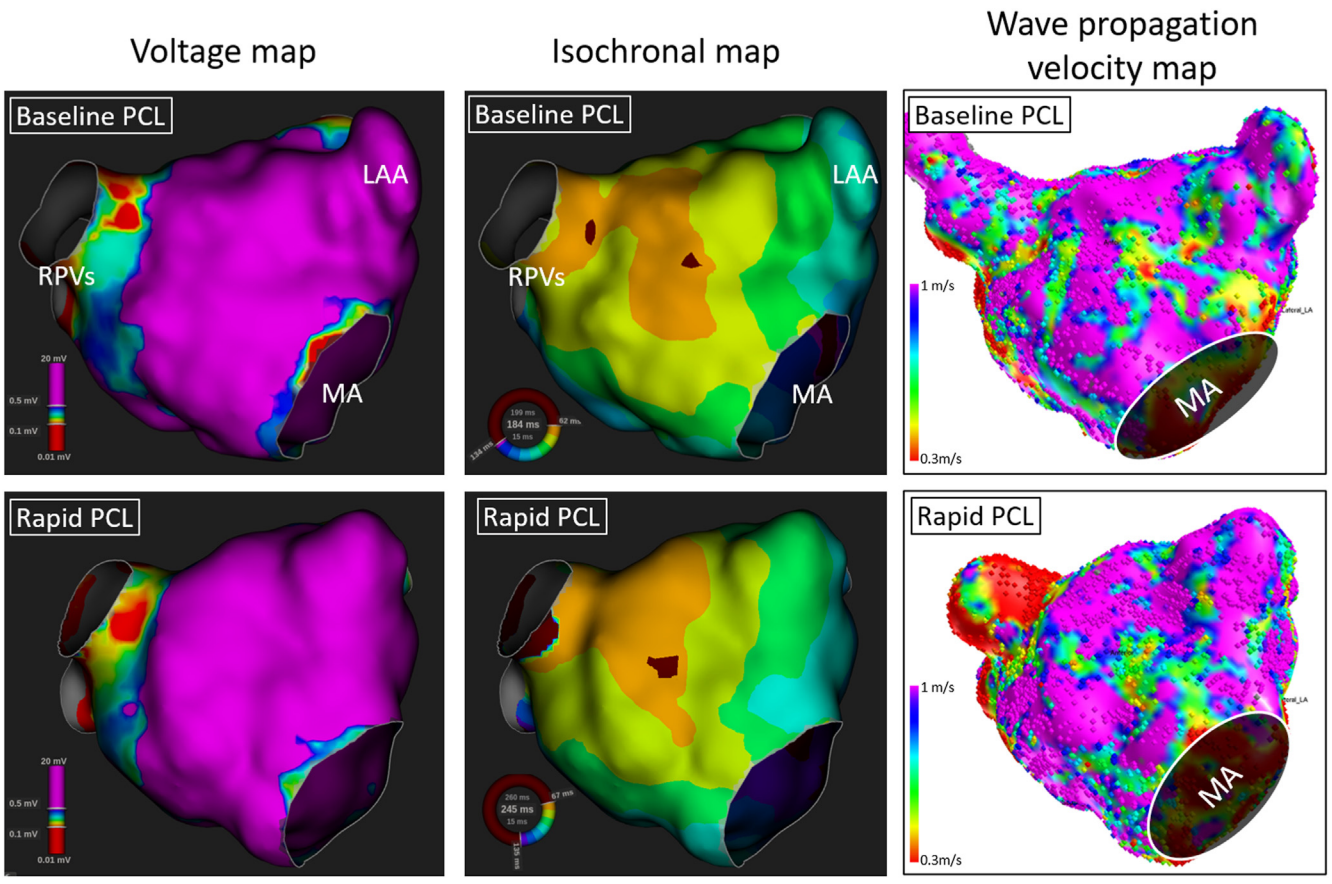

Figure 1
Pacing cycle length (PCL)–dependent changes of left atrial maps in a patient without low-voltage area on the baseline PCL map. Voltage maps (*left column*), isochronal maps (*middle column*), and wave propagation velocity maps (*right column*) of a patient without low-voltage area on the baseline PCL map (600 ms). Each isochronal color represents 10 ms. The slow conduction area (ie, wave propagation velocity of <0.3 m/s) on the wave propagation velocity maps is indicated as a *red* area. Compared with the baseline PCL maps, no remarkable changes were observed on the rapid PCL (300 ms) maps. LAA = left atrial appendage; MA = mitral annulus; RPVs = right pulmonary veins.

All statistical analyses were performed with JMP software, version 14.2.0 (SAS Institute, Cary, NC).

Results

Patients' characteristics

The patients' baseline characteristics are shown in Table 1. Most of the study patients had a preserved left ventricular ejection fraction and moderately enlarged left atrium. Approximately half of the patients had nonparoxysmal AF. Class I antiarrhythmic drugs were discontinued in all patients, but 2 patients continued 100 mg or 75 mg of amiodarone and 1 patient continued 100 mg of bepridil during the periprocedural period.

Baseline and rapid PCL high-resolution LA mapping

The results of high-resolution mapping of the left atrium are shown in Table 2. Compared with baseline PCL mapping, rapid PCL mapping showed a higher number of total mapping points (rapid PCL vs baseline PCL: 12,324 ± 3176 vs 8568 ± 1871 points, the same hereafter; $P < .0001$) and a higher mapping speed (1090 ± 296 points/min vs 604 ± 162 points/min; $P < .0001$). The consistency of the mapping quality throughout the study was validated by the linear correlations of the mapping parameters measured under each PCL (Supplemental Material 4). The LVA was significantly larger on the rapid than on the baseline PCL map (7.6 ± 9.5 vs 6.7 ± 7.6 cm^2; $P = .031$), especially in patients who presented with a broad total LVA (≥10 cm^2) on the baseline PCL maps (21.5 ± 9.1 vs 18.1 ± 6.5 cm^2; $P = .013$; Figure 3A; Table 2). The LVA was dominantly observed in the anteroseptal area on both PCL maps (Supplemental Material 5). The LA activation time was significantly longer on the rapid than on the baseline PCL maps (87.9 ± 16.2 ms vs 84.0 ± 14.0 ms; $P < .0001$; Figure 3B; Table 2). The fractionated electrogram area did not increase on the rapid PCL maps (Supplemental Material 6).

PCL-dependent changes in regional mean voltage, regional mean wave propagation velocity, and slow conduction area

In total, 4207 ± 1425 (3352 ± 849 points of the baseline PCL maps and 5062 ± 1375 points of the rapid PCL maps) were used for this analysis. The numbers of points in each LA

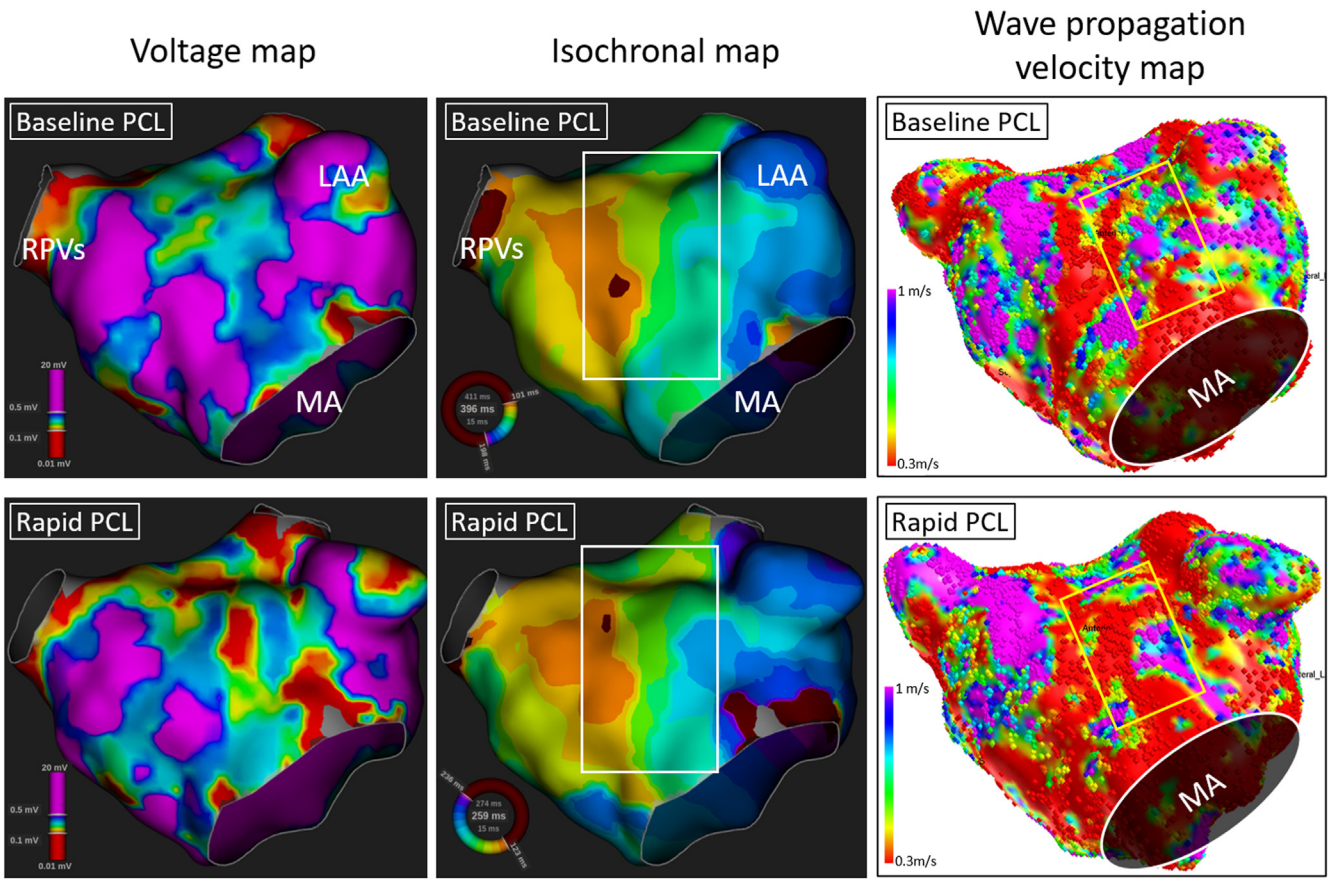

Figure 2
Pacing cycle length (PCL)–dependent changes of left atrial maps in a patient with a broad low-voltage area on the baseline PCL map. Voltage maps (*left column*), isochronal maps (*middle column*), and wave propagation velocity maps (*right column*) of a patient with a broad low-voltage area on the baseline PCL map (600 ms). On the rapid PCL (300 ms) map, the expansion of the low-voltage area and the augmentation of isochronal crowding (*white squares* on the isochronal maps) were observed. The anterior slow conduction area also became broader (*yellow squares* on the wave propagation velocity maps). The figure configuration and abbreviations are as in Figure 1.

region are shown in Supplemental Material 7. The analysis of PCL-dependent changes in the regional mean voltage, regional mean wave propagation velocity, and slow conduction area are shown in Table 3 and Figure 4. The rapid PCL showed a slower regional mean wave propagation velocity and broader slow conduction area in all LA regions measured. On the other hand, the regional mean voltage of each region did not significantly decrease on the rapid PCL maps. These trends were common in both patient groups with $\geq$10 cm^2 or <10 cm^2 total LVA on the baseline PCL maps (Supplemental Material 8). The regional mean voltage of the LA anterior wall showed a PCL-dependent decrease in patients with $\geq$10 cm^2 total LVA on the baseline PCL maps (0.74 $\pm$ 0.29 mV vs 0.81 $\pm$ 0.37 mV; P = .075), although not statistically significant.

Discussion

In this study, we elucidated the following findings by comparing the baseline PCL and rapid PCL maps.

- The efficacy of high-resolution LA mapping was enhanced under a rapid PCL.
- Regarding the LA voltage, rapid PCL maps showed a broader LVA, especially in patients with a broad LVA on baseline PCL maps. However, the decrease of regional mean voltage was statistically insignificant.
- Regarding the LA conduction properties, rapid PCL maps showed a longer LA activation time, slower regional mean wave propagation velocity, and broader slow conduction area than baseline PCL maps.

These results indicate that the PCL can affect both LA voltage and wave propagation velocity, and the LVA and slow conduction area are not absolute substrates but are susceptible to the PCL. Therefore, using these areas observed under specific PCL as absolute AF substrates may be inappropriate.

Relationship between atrial activation frequency and electrophysiologic findings in patients with AF

Patients with AF reportedly have longer atrial refractory periods, slower conduction velocity, and a greater proportion of fractionated electrograms than patients without AF.[18] These electrophysiologic changes resemble those that develop with age.[19] The atrial activation frequency also

Table 1 Baseline characteristics of patients and ablation procedure data (N = 48)

Patient characteristics	
Age, years	67 ± 12
Female sex	15 (31)
Height, cm	164 ± 9
Body weight, kg	67 ± 12
Body mass index, kg/m^2	25 ± 4
Hypertension	25 (52)
Diabetes	8 (17)
Chronic kidney disease (GFR <60 mL/min/kg)	22 (46)
History of stroke or TIA	4 (8)
CHA_2DS_2-VASc score	2.5 ± 1.4
Echocardiographic findings	
LVEF, %	64 ± 12
Left atrial diameter, mm	43 ± 7
AF type	
Paroxysmal AF	23 (48)
Nonparoxysmal AF	25 (52)
No. of AF ablation procedures	
Initial procedure	38 (79)
Repeated procedure (≥2 procedures)	10 (21)
Pulmonary vein isolation	
Radiofrequency ablation[a]	44 (92)
Cryoballoon ablation	4 (8)

Values are presented as n (%) or mean ± standard deviation.
AF = atrial fibrillation; GFR = glomerular filtration rate; LVEF = left ventricular ejection fraction; TIA = transient ischemic attack.
[a]Including 10 patients who underwent radiofrequency pulmonary vein isolation during the previous sessions.

influences these electrophysiologic properties. In general, shorter atrial refractory periods and slow conduction velocities are observed under rapid PCL pacing.[18,20] Lalani and coworkers[21] demonstrated that the atrial conduction velocity was slowed down by rapid PCL pacing and that steep conduction velocity restitution (abrupt slowdown during high-rate pacing) could be associated with electrical remodeling. Although they also found neither a decrease in voltage nor a prolongation of the local electrogram by rapid PCL pacing, Williams and coworkers[22] demonstrated the opposite result:

Table 2 PCL-dependent changes in the mapping speed, left atrial low-voltage area (<0.5 mV) prevalence, and LA activation time

	Baseline PCL	Rapid PCL	*P* value
PCL, ms	600[a]	300[b]	
Mapping points	8568 ± 1871	12,324 ± 3176	<.0001
Mapping time, min	14.8 ± 3.8	11.6 ± 2.5	<.0001
Mapping speed, points/min	604 ± 162	1090 ± 296	<.0001
Total LVA, cm^2			
Overall (N = 48)	6.7 ± 7.6	7.6 ± 9.5	.031
Of those with ≥10 cm^2 total LVA on baseline PCL map (n = 12)	18.1 ± 6.5	21.5 ± 9.1	.013
Of those with <10 cm^2 total LVA on baseline PCL map (n = 36)	2.9 ± 2.4	2.9 ± 2.6	.81
LA activation time, ms	84.0 ± 14.0	87.9 ± 16.2	<.0001

Values are presented as mean ± standard deviation. The P values are based on the results of the paired t-test.
LA = left atrial; LVA = low-voltage area; PCL = pacing cycle length.
[a]750 ms and 666 ms (2 cases each) and 660 ms, 650 ms, and 500 ms (1 case each).
[b]375 ms (1 case), 350 ms (3 cases), and 333 ms (2 cases).

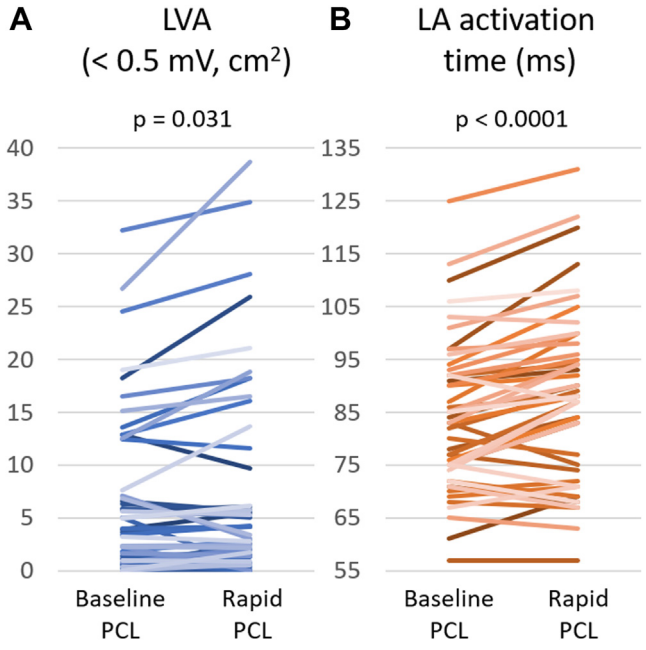

Figure 3
Pacing cycle length (PCL)–dependent changes in left atrial low-voltage area (LVA; <0.5 mV) prevalence and left atrial (LA) activation time. Parallel plots of the PCL-dependent changes in the (**A**) total LVA and (**B**) LA activation time. The *P* values are based on the paired *t*-test.

Table 3 PCL-dependent changes in left atrial regional mean voltage, regional mean wave propagation velocity, and slow conduction area (<0.3 m/s wave propagation velocity)

	Baseline PCL[a]	Rapid PCL[b]	*P* value
Regional mean voltage, mV			
Anterior	1.51 ± 0.70	1.47 ± 0.69	.18
Septum	1.41 ± 0.59	1.49 ± 0.59	.048
Lateral	2.40 ± 0.97	2.24 ± 0.93	.060
Inferior	2.14 ± 0.96	2.11 ± 0.97	.59
Regional mean wave propagation velocity, m/s			
Anterior	0.93 ± 0.15	0.87 ± 0.16	<.0001
Septum	0.89 ± 0.16	0.84 ± 0.16	.0061
Lateral	0.98 ± 0.10	0.85 ± 0.17	<.0001
Inferior	1.04 ± 0.12	1.00 ± 0.12	.0062
Slow conduction area, cm^2			
Anterior	2.40 ± 2.46	3.58 ± 2.89	<.0001
Septum	2.17 ± 1.58	2.72 ± 1.66	.0006
Lateral	0.55 ± 0.45	1.41 ± 1.10	<.0001
Inferior	0.55 ± 0.42	1.01 ±0.70	<.0001

Values are presented as mean ± standard deviation. The *P* values are based on the results of the paired *t*-test.
PCL = pacing cycle length.
[a]750 ms and 666 ms (2 cases each) and 660 ms, 650 ms, and 500 ms (1 case each).
[b]375 ms (1 case), 350 ms (3 cases), and 333 ms (2 cases).

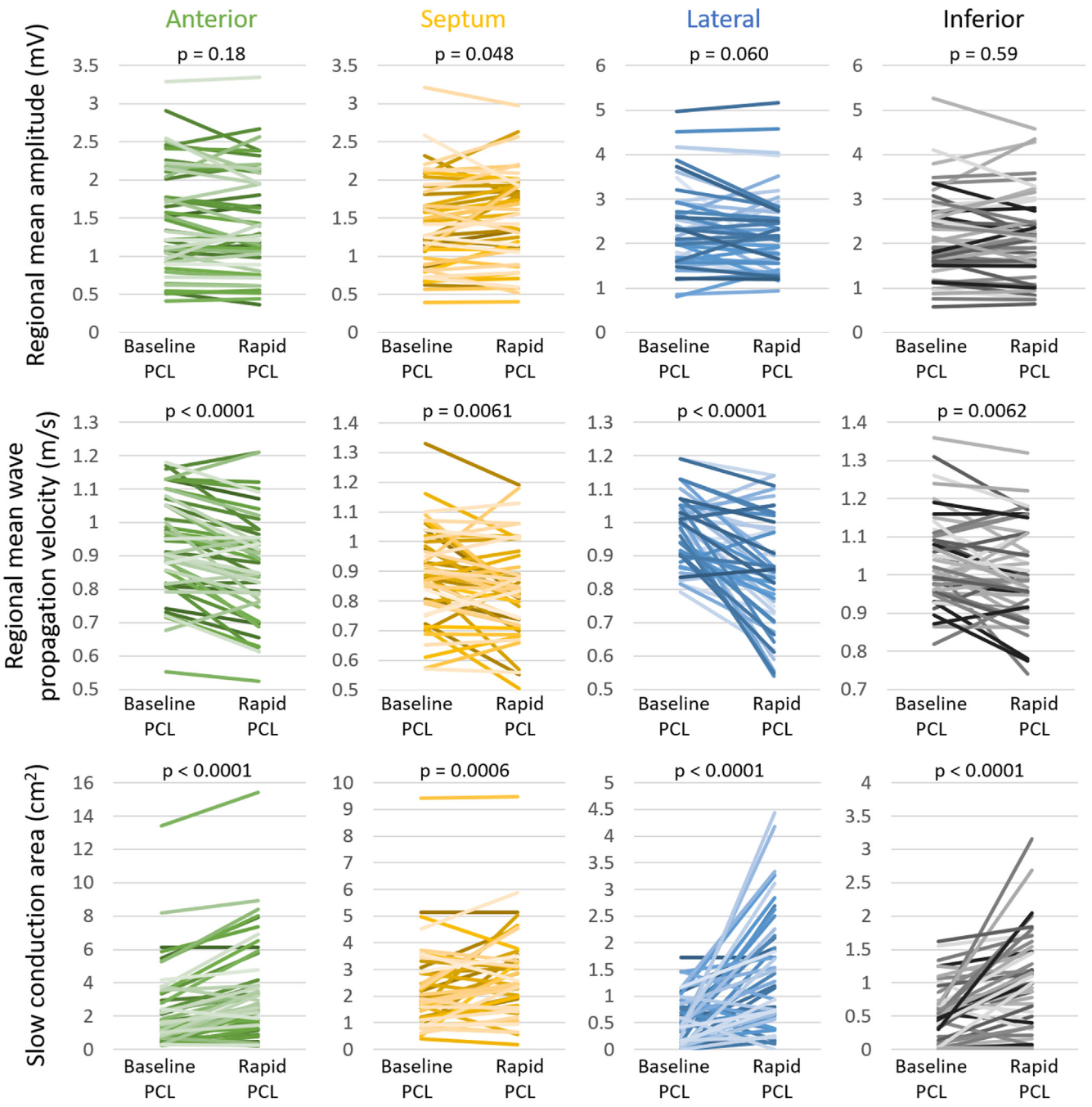

Figure 4
Parallel plots of the pacing cycle length (PCL)–dependent changes in left atrial regional mean voltage, regional mean wave propagation velocity, and slow conduction area (<0.3 m/s wave propagation velocity). The *P* values are based on the paired *t*-test.

that the bipolar atrial voltage could decrease during short-coupling extrastimuli in patients with paroxysmal AF. They also showed that the degree of conduction delay caused by short-coupling extrastimuli was associated with AF inducibility.

PCL-dependent changes in high-resolution LA maps

The advancements of 3D electroanatomic mapping systems have facilitated spatial investigations of atrial electrophysiologic characteristics in recent years. Previous studies have shown that the LVA is related to decreases in the conduction velocity and electrogram fractionation.[13,23] Our recent investigation also validated the results of these studies.[11] These electrophysiologic features are included in the current AF substrate evaluation strategies.[24] These areas have also been found to be associated with postablation AT circuits.[4,17]

PCL-dependent changes in these factors have also been investigated. Wong and colleagues[9] demonstrated a PCL-dependent decrease in the LA voltage and conduction

velocity. Honarbakhsh and coworkers[8,25] reported that the degree of decrease in the pacing PCL-dependent conduction velocity was associated with the local voltage: the non-LVA (>0.5 mV) exhibited a rapid conduction velocity with steep conduction velocity restitution during very rapid PCL (250 ms), and the moderate LVA (0.2–0.5 mV) exhibited a gradual decrease in conduction velocity according to the PCL. The authors also demonstrated that the sites with PCL-dependent conduction slowing were well matched with the localized reentrant AT sites or AF drivers.

In this study, we validated the PCL-dependent changes in electrophysiologic properties by high-resolution LA mapping. In addition, we demonstrated that PCL-dependent increases in the total LVA were prominent in patients with greater values during baseline PCL mapping (Table 2). These data indicated that PCL-dependent LVA increase and conduction slowing are general phenomena, and the LVA increase is likely to occur especially in the electrically remodeled left atrium. However, the regional mean voltage of any LA regions did not significantly decrease on the rapid PCL maps (Table 3). A plausible explanation for the discrepancy is that PCL-dependent voltage reduction is more likely to occur in diseased LA areas than in relatively healthy areas. As a corroborating finding, the regional mean voltage of the LA anterior wall, where the LVA is frequently observed (Supplemental Material 5), presented a PCL-dependent decrease in patients with $\geq$10 cm^2 LVA, although this did not reach statistical significance (Supplemental Material 8). Another explanation for this discrepancy is the higher mapping resolution than in previous studies. With the previous-generation mapping, a larger area might have been interpolated by electrograms with lower amplitude, even if the true LVA was small.[26] The high-resolution mapping in this study might have affected this point.

Clinical implications

These results indicate that PCL-dependent LVA increase and conduction slowing are general phenomena and raise the question of substrate-guided ablation. For example, assuming that the LVA is a dynamic rather than an absolute substrate according to the preceding theory, LVA ablation using an absolute cutoff value (usually 0.5 mV[5-7]) under a specific PCL might cause excessive or insufficient ablation. The same can be said for slow conduction area– or fractionated electrogram–targeted ablation. Although not statistically significant in our study (Supplemental Material 6), Wong and colleagues[9] reported that the electrocardiogram fractionation was also PCL dependent. Similar phenomena have been reported in the study comparing the maps during sinus or paced rhythm and AF rhythm.[27]

Considering the results of this study and previous studies, a lower pacing rate might be suitable for a diseased left atrium to limit the substrate area and to prevent excessive ablation, and a higher pacing rate might be suitable for a healthy left atrium to unmask the potential substrate. Rapid PCL mapping should be considered before substrate-targeted ablation because it is not a time-consuming procedure.

Limitations

This study had several limitations. First, it included a small number of patients from a single center. Second, this study was performed after PVI. However, because the main objective was to compare the features of baseline and rapid PCL maps in the same patients, we believe that the use of post-PVI mapping did not substantially affect the results of the study. Third, by applying the spatial filtering procedure before the wave propagation velocity analysis (Supplemental Material 3), each local activation time was replaced with the average value of the points within a 3-mm radius. Whereas this procedure decreased the impact of the points with outlier local activation time, it canceled out the conduction delay in small areas and thus potentially led to an overestimation of the regional mean wave propagation velocity. Fourth, because the wavefronts from the LA anterior wall and inferior wall collide at the LA lateral wall under RAA pacing, a broader area in the lateral wall can be simultaneously activated than activation by a single wavefront. Therefore, the wave propagation velocity of the lateral wall might have been overestimated in this study. Fifth, only RAA pacing was performed in this study. Therefore, electrophysiologic analyses regarding the anisotropic properties were incomplete. LVA and wave propagation velocity may have been more strongly affected by the pacing site (eg, LA pacing) than PCL.

Conclusion

This study demonstrated PCL-dependent changes in both LA voltage and conduction properties and also indicated the poor validity of using LVA and slow conduction area observed under specific PCL as absolute AF substrates. These PCL-dependent electrophysiologic changes in the left atrium should be considered in performing substrate-targeted ablation.

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Appendix

Supplementary data

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.hrthm.2024.09.034.

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