Evaluation of linear lesion formation and thermodynamics by dragging ablation with the third-generation laser balloon

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BACKGROUND The lesion formation properties of a motorized rotational delivery (RAPID) mode, third-generation laser balloon (LB3) ablation compared to point-by-point laser ablation in patients with atrial fibrillation remain unclear.

OBJECTIVE The purpose of this study was to assess lesion characteristics and thermodynamics in LB3 ablation with a RAPID mode *in vitro* model.

METHODS Chicken muscles were cauterized using LB3 in RAPID mode with 13 W and 15 W and 50% overlapped point-by-point fashion with 7 W/30 seconds, 8.5 W/20 seconds, 10 W/20 seconds, and 12 W/20 seconds. Lesion depth, width, and continuity were compared. Lesion continuity was classified by the visible gap degree categorized from 1 (perfect) to 3 (poor). Thermodynamics and maximum tissue temperatures were assessed under infrared thermographic monitoring. Fifteen and 5 lesions were evaluated per ablation protocol for measurement of lesion size and continuity and for thermographic assessment, respectively.

RESULTS Lesion depth and width were smaller in RAPID mode laser ablation than point-by-point laser ablation ($P < .001$). However, RAPID mode laser ablation revealed sufficient mean lesion depth of 5 mm or more. Lesion continuity was 1 (perfect) in all samples in RAPID mode laser ablation and point-by-point laser ablation ($P = 1$). Infrared thermographic observation demonstrated fast and gapless linear lesion formation with thermal stacking in RAPID mode laser ablation. Maximum tissue temperature was lower in RAPID mode laser ablation than point-by-point laser ablation ($P < .001$).

CONCLUSION RAPID mode LB3 ablation could provide fast, gapless, and acceptable lesion formation with thermal stacking and moderate tissue temperature rise.

KEYWORDS Atrial fibrillation; Linear lesion formation; Point-by-point ablation; RAPID mode ablation; Third-generation laser balloon

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Introduction

In patients with drug-refractory symptomatic atrial fibrillation (AF), catheter ablation is the therapy of choice.[1–3] Pulmonary vein (PV) isolation (PVI) is a major procedural endpoint of catheter ablation.[4,5] In addition to conventional radiofrequency current energy, the diode laser was introduced as an alternative energy for PVI.[6,7] The laser balloon catheter has recently evolved to the latest version, the third-generation laser balloon (LB3) (HeartLight X3; CardioFocus, Marlborough, MA) from the first-generation laser balloon (LB1) (HeartLight; CardioFocus) and second-generation laser balloon (LB2) (HeartLight Excalibur Balloon; CardioFocus).[6–11] LB1 and LB2 are generally point-by-point ablation systems, leading to relatively long procedural times.[6–9] LB3 is newly equipped with a motorized rotational delivery system (RAPID mode) with high power (13 W or 15 W), resulting in a prominent reduction in procedural time compared with LB1 and LB2.[10,11] However, there have been no quantitative reports on the size and continuity of linear lesion and thermodynamics exerted on the tissues by LB3.

Previously, we compared linear lesion size between point-by-point ablation and manually dragging ablation with 5.5 to 12 W using an LB1 *in vitro* model.[12] In that experiment, we concluded that dragging laser ablation with high power (ie, 12 W) provided deep and continuous lesion formation comparable to that of point-by-point laser ablation. Additionally, lesion size depended on dragging speed and power. However, lesion size and continuity and thermal reaction of tissue in RAPID mode LB3 ablation was not clarified.

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KEY FINDINGS

- Understanding the lesion formation property by laser ablation using a motorized rotational delivery system (RAPID mode) with high power (13 W or 15 W) is essential for safe and reliable pulmonary vein isolation with the third-generation laser balloon (LB3) ablation for patients with atrial fibrillation.
- RAPID mode LB3 ablation created gapless linear lesions with acceptable lesion size.
- Lesion depth and width were relatively smaller in RAPID mode LB3 ablation than overlapped point-by-point laser ablation with 7–12 W.
- RAPID mode LB3 ablation revealed thermal stacking effect in thermographic observation, leading to fast and efficient lesion formation.
- Maximum tissue temperatures were relatively lower during RAPID mode laser ablation than overlapped point-by-point laser ablation with 8.5–12 W.

Therefore, we evaluated the size and continuity of the linear lesion and thermodynamics between RAPID mode laser ablation and point-by-point laser ablation using the LB3 *in vitro* model.

Methods

Experimental outline and preparations of the samples

We performed the following 2 experiments: (1) measurements of linear lesion size and continuity; and (2) evaluation of real-time thermographic dynamics of tissue temperature and maximum tissue temperature. The preparation of experimental samples is the same as previously reported.[12] All the measurements of lesions were performed by examiners blinded to each RAPID mode and point-by-point ablation protocol. Commercially obtained chicken breast skeletal muscles were used as experimental samples. The samples pierced with an 18-mm-diameter hollow circular aluminum cylinder to produce a site for LB3 insertion and flat samples were used for the measurement of linear lesion size and thermographic monitoring, respectively. Assuming a circular PV orifice, only the part of flat samples adjacent to LB3 was cauterized and evaluated in thermographic evaluation. As previously described,[12] the lesions became unclear because of discoloration of chicken muscles when those muscles were directly warmed in a saline-filled circulating bathtub. We also hypothesized that the circulating bath was not essential to this experiment, because laser is titrated to cardiac tissue in the clinical setting under optimal PV occlusion where blood is eliminated. Hence, the muscles were wrapped in plastic bags and warmed indirectly to 37°C–38°C in the bathtub maintained at around 38°C.

The muscles were transferred out of the bathtub, and laser titration was immediately performed using LB3 according to each ablation protocol. LB3 was filled with circulating deuterium (D2O) similar to the clinical setting. The materials were cauterized in and outside a laser-shielding box for the measurements of linear lesion size and thermographic evaluation of tissue temperature dynamics, respectively (Figures 1A and 1B). The temperature of the muscles extracted from the bathtub was confirmed using an esophageal temperature probe (Esophaster; Japan Lifeline, Tokyo, Japan) to be maintained at 37°C–38°C for an average of 251 ± 63 seconds even outside the bathtub. Accordingly, laser titration was performed within 180 seconds. The samples for measurements of linear lesion size and continuity were cut into blocks so that the lesion size did not change. This study was approved by the local ethical committee.

Ablation protocols

RAPID mode laser ablation and point-by-point laser ablation were performed based on the normal settings of the laser console. The energy settings of RAPID mode laser ablation and point-by-point laser ablation were as follows: (1) RAPID mode laser ablation, 13 W and 15 W; and (2) point-by-point laser ablation, 7 W/30 seconds, 8.5 W/20 seconds, 10 W/20 seconds, and 12 W/20 seconds (Figure 2A).

Measurements of linear lesion size and continuity

Linear lesion size was measured using a digital caliper with a resolution of 0.1 mm as described previously.[12] First, surface lesion width (w) was measured on the lesion surface (Figure 2B). Next, the samples were cut in the short-axis direction at the middle of the linear lesion, and maximum lesion width (w max) was recorded on the maximum cross-section of the lesion. Third, the samples were incised in the longitudinal direction, and the lesion depth (d) was measured. Lesion depth and surface lesion width were measured at 3 points where the lesion was divided into 4 equal parts. The mean of the measurement at the 3 points was recorded as the lesion depth and surface lesion width. The uniformity of the lesion depth and surface lesion width of each individual lesion was assessed by measurements of differences in the minimum and maximum values of the 3-point measurements in RAPID mode laser ablation and point-by-point laser ablation. Lesion depth and maximum lesion width were calculated independently by 2 blinded examiners and twice by 1 examiner to account for inter/intraobserver variability using 30 randomly chosen lesions.

Regarding lesion continuity, we evaluated the degree of visible gaps as described previously,[12] which was used as a semiquantitative scale categorized as follows: (1) perfect, no visible gap in the lesion; (2) moderate, partial slit-like visible gap in the lesion; and (3) poor, complete slit-like visible gap in the lesion. The visible gap degrees were recorded on the lesion surface and long-axis sectional surface and were defined as the surface and deep visible gaps, respectively. If different visible gap degrees were seen on the same

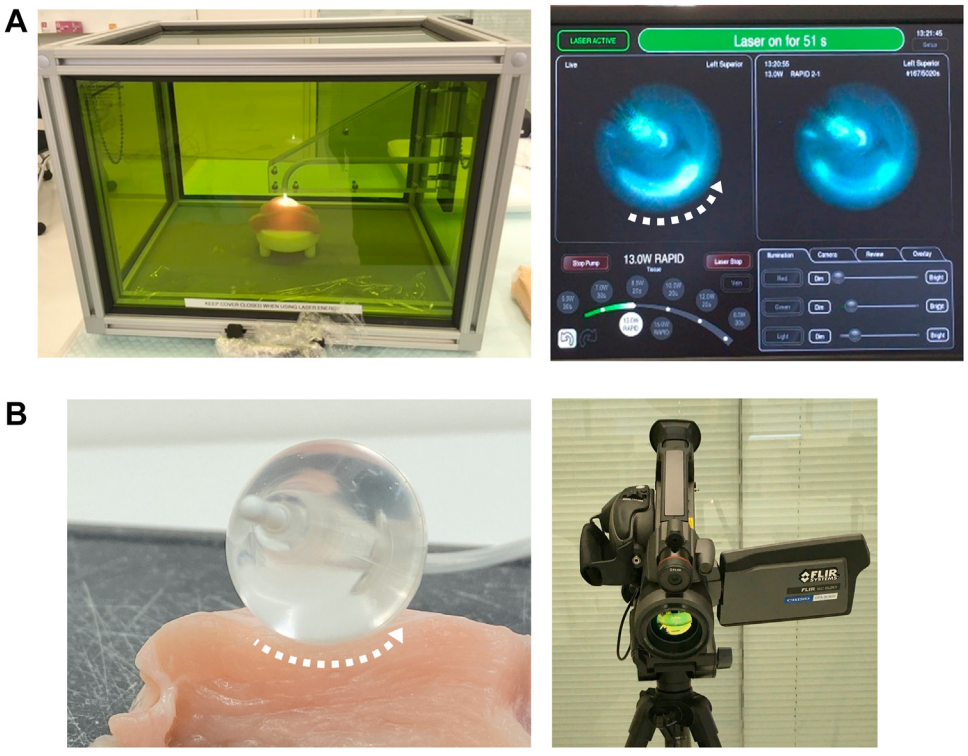

Figure 1 Experimental settings. **A:** Experimental settings for measurements of lesion size. **Left:** Laser was titrated to chicken muscles in a laser-shielding box. **B:** Endoscopic view on the laser console. **B:** Experimental setting for real-time thermographic evaluation of tissue temperature changes. **Left:** A laser balloon was placed on chicken muscles warmed at 37°C–38°C so that the proximal white marker of a laser balloon was aligned with the edge of the muscles. **Right:** Thermographic camera was placed facing the muscles.

lesion surface, the worst visible gap degree was recorded. Fifteen lesions were evaluated per ablation protocol for the measurements of linear lesion size and continuity.

Thermographic evaluation of tissue temperature dynamics

In the thermographic evaluation, LB3 was placed on the flat muscles at a constant vertical distance of 0.5 m from an infrared thermographic camera (FLIR SC620; CHINO Co., Ltd., Tokyo, Japan) with a measurement angle between the sample and infrared thermographic camera of 0°C (Figure 1B). The product specifications of the infrared thermographic camera were as follows: resolution of 640 × 480 pixels per inch, instantaneous field of view of 0.65 mrad, field of view of 24° × 18°, minimum detection distance of 30 cm, minimum detection dimension of 0.2 mm, and measurement temperature range of –40°C to 500°C. These conditions allow for tissue temperature measurement size of 0.35 mm per pixel. The samples were autofocused on the infrared thermographic camera image. If the focus of the image was insufficient to monitor, focus was manually adjusted on the infrared thermographic camera. The temperature scale was adjusted so that temperatures $<30°$ C and $>60°$C became dark blue and white, respectively. Thermographic tissue temperature dynamics and maximum tissue temperature during RAPID mode laser ablation and point-by-point laser ablation were recorded. Five lesions were assessed per ablation protocol for the thermographic measurements.

Pathological evaluation of lesions

Muscles were fixed in 10% formalin immediately after ablation. Those muscles were cut perpendicular to the lesion surface in the longitudinal direction. The samples were embedded in paraffin and incised into 5-μm sections by a motorized microtome. The sections were created by Medi-Ridge Co., Ltd. (Tokyo, Japan). In the previous experiment,[12] we confirmed that lesions were obscured when the sections were stained with hematoxylin-eosin. However, lesions were clearly visualized in this previous experiment as blue or purple portions with Masson trichrome stain. Hence, the sections were stained with Masson trichrome. In each stained section, lesion uniformity and lesion gap were assessed under a light microscope.

Statistical analysis

Continuous variables with a normal distribution and nonparametric variables are given as mean ± standard deviation and median and interquartile range, respectively. Comparison among all the groups was performed using 1-way analysis of variance or the Kruskal-Wallis test. Multiple comparisons were performed by the Tukey test or Dunn test when a statistically significant difference was observed between groups. Inter/intraobserver variability in lesion depth and surface

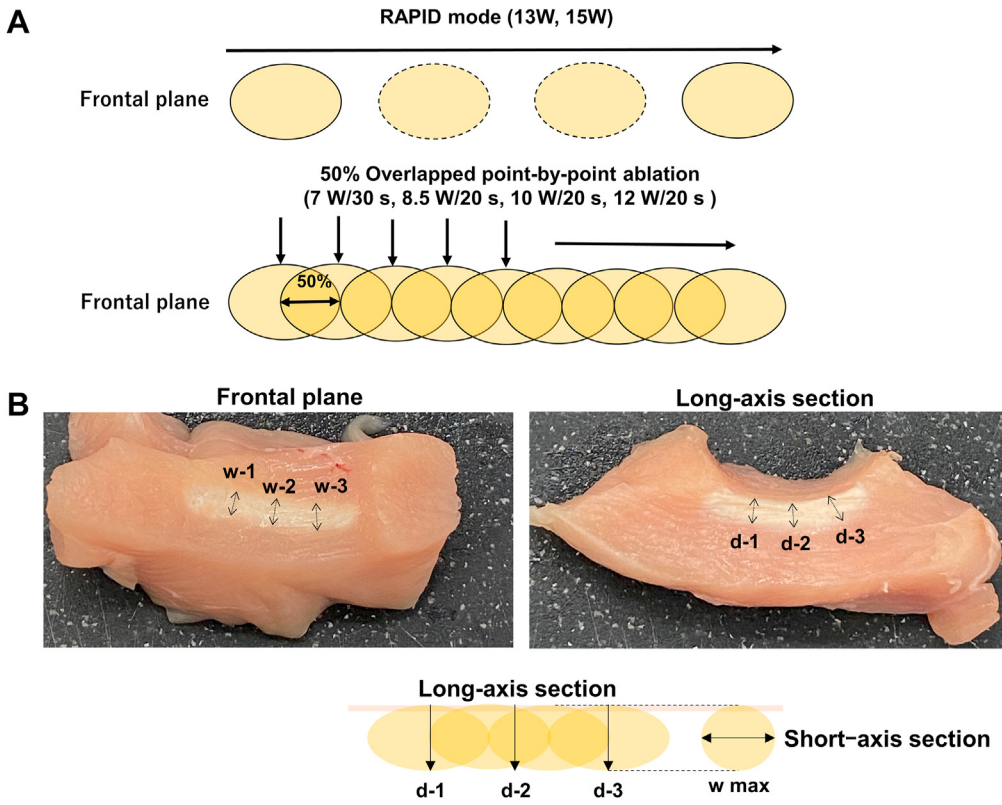

Figure 2 Ablation protocols and measurements of linear lesion size. **A:** Ablation protocols of RAPID mode laser ablation **(top)** and point-by-point laser ablation **(bottom)**. **B:** Linear lesion size was evaluated by surface lesion width (w), lesion depth (d), and maximum lesion width (w max).

lesion width were evaluated using a linear regression model. $P < .05$ was considered significant. All data were calculated using R Version 3.3.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Linear lesion size in RAPID mode laser ablation and point-by-point laser ablation

RAPID mode laser ablation with 13 W and 15 W exhibited sufficient lesion depth of a mean of 5 mm or more. However, lesion depth was relatively smaller in RAPID mode laser ablation even with 13 W or 15 W than point-by-point laser ablation ($P < .01$) (Table 1). In multiple comparisons, lesion depth in RAPID mode laser ablation with 15 W was smaller than those in 50% overlapped point-by-point laser ablation with 12 W/20 seconds and 10 W/20 seconds (both, $P < .01$). Similarly, RAPID mode laser ablation with 13 W demonstrated smaller lesion depth than 50% overlapped point-by-point laser ablation with all energy settings (all, $P < .01$).

Surface lesion width was also smaller in RAPID mode laser ablation than point-by-point laser ablation ($P < .001$). In multiple comparisons, statistical differences were found between 15 W RAPID mode laser ablation and 12 W point-by-point laser ablation and between 13 W RAPID mode laser ablation and point-by-point laser ablation with

Table 1 Linear lesion size and visible gaps for each ablation protocol

	15 W RAPID	13 W RAPID	12 W/20 s, point	10 W/20 s, point	8.5 W/20 s, point	7 W/30 s, point	*P* value
Lesion size							
Depth (mm)	5.4 ± 0.2	5.0 ± 0.4	7.0 ± 0.5	6.5 ± 0.3	6.0 ± 0.2	6.1 ± 0.4	< .001*
Surface lesion width (mm)	4.7 ± 0.2	4.6 ± 0.4	5.6 ± 0.5	5.1 ± 0.4	4.8 ± 0.3	4.9 ± 0.4	< .001*
Maximum lesion width (mm)	6.6 ± 0.5	6.4 ± 0.3	9.1 ± 0.6	8.1 ± 0.4	6.8 ± 0.5	7.3 ± 0.5	< .001*
Visible gap							
Surface	1 (1–1)	1 (1–1)	1 (1–1)	1 (1–1)	1 (1–1)	1 (1–1)	1
Deep	1 (1–1)	1 (1–1)	1 (1–1)	1 (1–1)	1 (1–1)	1 (1–1)	1

Values are given as mean ± standard deviation or median (interquartile range).

The visible gap degree was defined as follows: (1) perfect, no visible gap in the lesion; (2) moderate, partial slit-like visible gap in the lesion;, and (3) poor, complete slit-like visible gap in the lesion. Point = 50% overlapped point-by-point laser ablation; RAPID = RAPID mode laser ablation.

*Comparison between all ablation protocols at each energy setting.

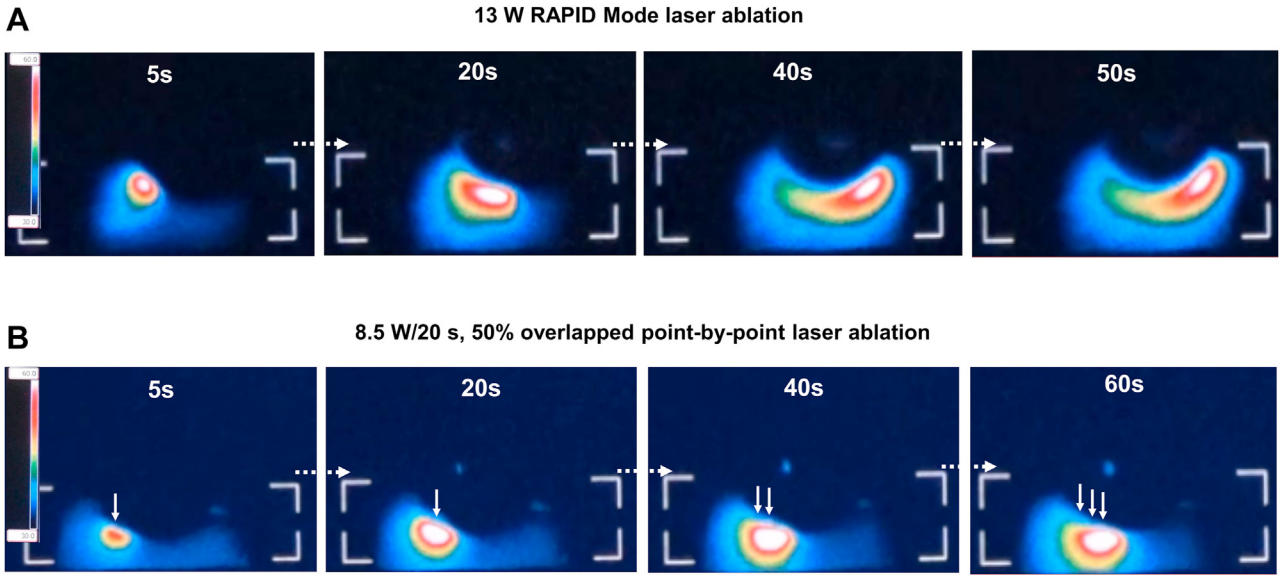

Figure 3 Thermodynamics during RAPID mode laser ablation and point-by-point laser ablation using third-generation laser balloon. Examples of thermal dynamics during RAPID mode laser ablation with 13 W **(A)** and 50% overlapped point-by-point laser ablation with 8.5 W/20 seconds **(B)**. *White area* represents the area heated to >60°C. *White solid arrows* in **B** indicate each point-by-point ablation (see Supplemental Video 1).

12 W/20 seconds and 10 W/20 seconds, respectively (all, $P < .05$). RAPID mode laser ablation also revealed smaller maximum lesion width than point-by-point laser ablation ($P < .001$). In multiple comparisons, both of RAPID mode laser ablations with 15 W and 13 W demonstrated smaller maximum lesion width than point-by-point laser ablation with 12 W/20 seconds, 10 W/20 seconds, and 7 W/30 seconds (all, $P < .01$). No steam pops were observed during any of the protocols of RAPID mode laser ablation and point-by-point laser ablation.

Mean differences in the minimum and maximum values of the 3-point measurements of the lesion depth and surface lesion width for individual lesions were as follows: lesion depth 0.6 ± 0.4 mm and 0.7 ± 0.4 mm, and surface lesion width 0.7 ± 0.3 mm and 0.6 ± 0.3 mm for RAPID mode laser ablation and point-by-point laser ablation, respectively. Linear regression analysis for lesion depth and maximum lesion width revealed excellent correlation for inter/intraobserver variability (interobserver lesion depth: r = .86, $P < .001$; interobserver maximum lesion width: r = .85,

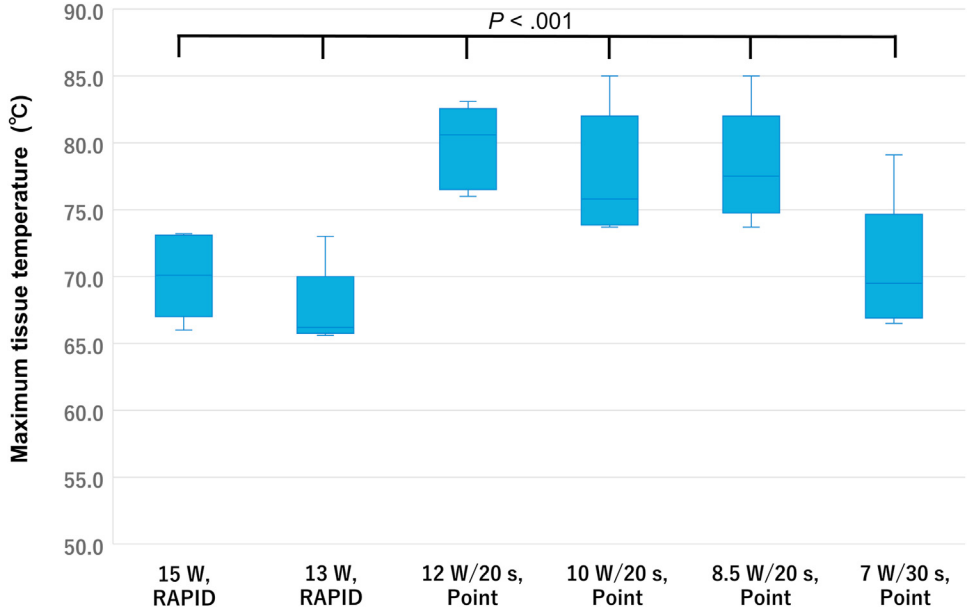

Figure 4 Maximum tissue temperature during RAPID mode laser ablation and point-by-point laser ablation. RAPID mode laser ablation revealed lower maximum tissue temperature than point-by-point laser ablation with 8.5 W or greater. Point = 50% overlapped point-by-point laser ablation; RAPID = RAPID mode laser ablation.

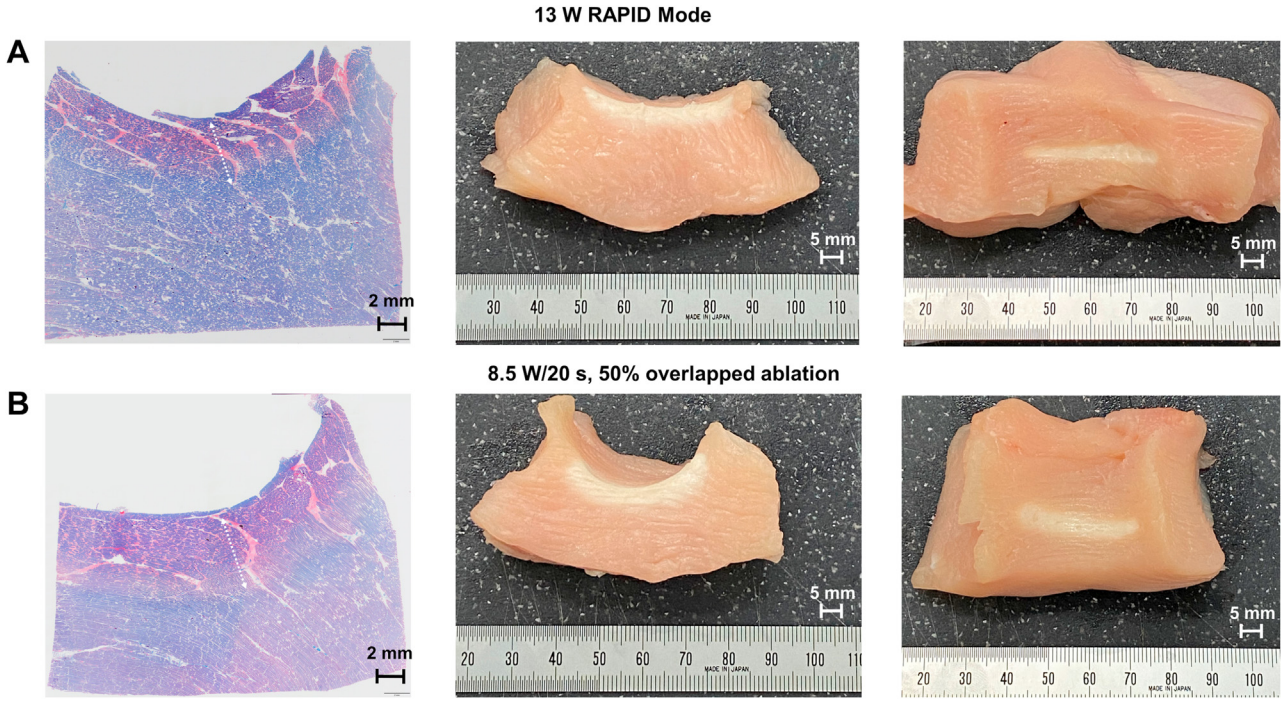

Figure 5 Examples of pathological and gross evaluation of linear lesions. **A:** Example of RAPID mode laser ablation with 13 W. **B:** Example of 50% overlapped point-by-point laser ablation with 8.5 W/20 seconds. **A, B: Left, middle,** and **right** represent a pathological image stained with Masson trichrome, long-axis section of a lesion, and frontal-plane of a lesion, respectively. *White dotted arrows* in pathological images indicate ablated lesions.

$P < .001$; intraobserver lesion depth: r = .90, $P < .001$; intraobserver maximum lesion width: r = .88, $P < .001$).

Lesion continuity in RAPID mode laser ablation and point-by-point laser ablation

Both the surface and visible gap degree were 1 (ie, no visible gap) for all the lesions both in RAPID mode laser ablation and point-by-point laser ablation (both, $P = 1$).

Tissue temperature dynamics during RAPID mode laser ablation and point-by-point laser ablation

Real-time thermographic monitoring revealed that RAPID mode laser ablation had the continuous tissue heating effect (ie, thermal stacking) compared to point-by-point laser ablation. In addition, RAPID mode laser ablation exhibited faster lesion formation than point-by-point laser ablation. Examples of tissue temperature dynamics during RAPID mode laser ablation and point-by-point laser ablation are shown in Figure 3 and Supplemental Video 1. The most heated sites, demonstrated in Figure 3 as white spots, were found slightly deeper than the tissue surface rather than on the tissue surface in both RAPID mode laser ablation and point-by-point laser ablation. Additionally, the areas of the most heated sites were slightly smaller during RAPID mode laser ablation than point-by-point laser ablation. Maximum tissue temperature tended to be lower during RAPID mode laser ablation than point-by-point laser ablation using 8.5–12 W (15 W RAPID mode vs 13 W RAPID mode vs 12 W/20 seconds vs 10 W/20 seconds vs 8.5 W/20 seconds vs 7 W/30 seconds; 70.1°C ± 3.1°C vs 67.5°C ± 3.1°C vs 79.7°C ± 3.1°C vs 77.5°C ± 4.7°C vs 78.2°C ± 4.3°C vs 70.5°C ± 5.0°C; $P < .001$) (Figure 4).

Pathological findings of linear lesions in RAPID mode laser ablation and point-by-point laser ablation

Both in pathological images stained with Masson trichrome and in gross evaluation, it was confirmed that RAPID mode laser ablation created gapless and uniform linear lesions similar to point-by-point laser ablation. Examples of the pathological sections and macroscopic photographs of the lesions created by RAPID mode laser ablation with 13 W and 50% overlapped ablation with 8.5 W/20 seconds are shown in Figures 5A and 5B.

Discussion

Major findings

The characteristics of linear lesions and thermodynamics in RAPID mode laser ablation using LB3 have not been well clarified. This study described the following findings: (1) RAPID mode laser ablation created gapless linear lesions with acceptable lesion size; (2) lesion depth and width were relatively smaller in RAPID mode laser ablation than 50% overlapped point-by-point laser ablation; (3) thermographic observation revealed thermal stacking effect of RAPID mode laser ablation, leading to the fast and efficient lesion formation; (4) maximum tissue temperatures were relatively lower during RAPID mode laser ablation than 50% overlapped point-by-point laser ablation; and (5) pathological

evaluation demonstrated gapless and uniform linear lesion formation in RAPID mode ablation similar to 50% overlapped point-by-point ablation. These findings supported the understanding of linear lesion formation in LB3 PVI in clinical practice.

Problems in point-by-point laser ablation

PVI using LB1 promised durable PVI and a high survival rate from atrial tachyarrhythmia recurrence in patients with AF.[6,7,13] However, relatively longer procedural time was required because of point-by-point ablation system than 1-shot ablation catheter of cryoballoon.[14]

Additionally, Yamamoto et al[15] reported in a single-center study that moderate-to-severe PV stenosis (≥50% reduction in PV cross-sectional area) occurred in 27% of all PVs in point-by-point LB1 PVI, although there was no symptomatic PV stenosis. They reported that the total amount of laser energy was associated with moderate-to-severe PV stenosis in LB PVI along with PV orifice area and ablation in a distal site of PV.

Phrenic nerve injury is another problem. Phrenic nerve palsy is reported to be persistent in substantial cases, although most cases recover over time.[16,17] Additionally, phrenic nerve injury can occur along with a sudden decline in compound motor action potential.[16] Therefore, it is difficult to manage laser energy titration duration for preventing persistent phrenic nerve injury guided by compound motor action potential compared to cryoballoon PVI.[18]

Characteristics of lesion formation and clinical advantages of RAPID mode laser ablation

The green light of the laser energy guide, which can be visualized in the real-time endoscopic image, does not represent the same lesion area for different laser energy settings. That is, laser arc covering 30° does not always change among 8 energy settings from 5.5 W/30 seconds to 15 W RAPID mode. Therefore, a 30%–50% overlap ratio is recommended in point-by-point laser ablation.[6,8,9] However, because lesion size could depend on both power and total laser energy,[19] 30% overlapped point-by-point laser ablation may create conduction gaps on linear lesions depending on laser power or energy. Recently, we reported that 50% overlapped laser ablation enabled a higher rate of first-pass PVI (ie, successful PVI after the initial circular laser ablation) than 25% overlapped laser ablations.[20] That study emphasized the importance of continuity of linear lesion.

However, this experiment showed that RAPID mode laser ablation facilitated fast and gapless linear lesion formation with sufficient lesion size by high-power, short-duration ablation with thermal stacking of tissue, leading to efficient linear lesion formation. Importantly, maximum tissue temperature was lower during RAPID mode laser ablation on real-time thermographic monitoring than during point-by-point laser ablation with power of 8.5 W or more. Recently, Nakahara et al[21] reported that the cutoff value of balloon surface temperature for acute PVI was >58.7°C in a clinical study using the new hot balloon equipped with a novel intratube sensor representing balloon surface temperature equal to tissue temperature. According to this report, RAPID mode ablation can be thought to provide sufficient tissue heating for successful PVI. In this experiment, lesion depth was sufficient but slightly smaller in RAPID mode laser ablation than point-by-point laser ablation. This is also considered to occur because lesion size depends on laser power and time as reported in the previous experiment.[19]

Schmidt et al[11] reported that, in clinical practice, LB3 facilitated faster PVI and a higher survival rate from atrial tachyarrhythmia recurrence at 12 months after the index procedure in patients with paroxysmal AF compared with LB1. They reported that total laser energy required for PVI with RAPID mode ablation using LB3 was about half that of LB1. Considering their clinical study and the results of the present experiment, lesion depth created by RAPID mode laser ablation is acceptable for durable PVI. However, 50% overlapped point-by-point laser ablation with high power (≥8.5 W) may be slightly excessive for PVI. In their pivotal study, no phrenic nerve injury was reported.[11] The reduction of total laser energy for PVI by RAPID mode laser ablation also can be expected to reduce the risk of PV stenosis or collateral damage to the upper gastrointestinal tract. With respect to those points, RAPID mode laser ablation without excessive deep lesion formation and too much tissue temperature rise can be the ideal ablation setting for faster and safer PVI compared to LB1 PVI.

Study limitations

This experiment included some limitations as previously described.[12,19,22] First, the sample used in this experiment was not human cardiac tissue. The laser absorption rate and lesion size could have been influenced by tissue structure, water content, thermal conductivity, heat capacity, and density in addition to laser direction toward the tissue because of the elliptical shape of the PV orifice.[23] A live porcine model verifying endocardial tissue of an actually beating heart might be better for this experiment, as in the previous report.[24] Additionally, because the sample was not a living body muscle, the relationship between tissue edema and the true infarcted area could not be confirmed. Second, transmularity of lesions was not assessed in this experiment. In thicker tissue, the lesion formation pattern could be different. Third, the influence of blood flow near the cauterized tissue was not assumed in this experiment. However, we performed this experiment based on the hypothesis that blood is excluded from the cauterized tissue under optimal PV occlusion and evaluated lesions between different ablation protocols under the same conditions. Fourth, the changes of the linear lesions in the chronic phase including histologic analysis were not evaluated. Furthermore, there are no data on the rates of acute and chronic PVI in patients with AF.

Conclusion

RAPID mode LB3 ablation could provide fast, gapless, and sufficient linear lesion formation in an *in vitro* model along with the characteristics of thermal stacking and moderate maximum tissue temperature rise. The clinical significance of the reduced lesion size and reduced peak temperatures in RAPID mode LB3 ablation should be confirmed in further studies.

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Authorship: All authors attest they meet the current ICMJE criteria for authorship.

Ethics Statement: Commercially obtained chicken breast skeletal muscles were used as experimental samples The study was approved by the Institutional Review Board of Sakakibara Heart Institute.

Appendix

Supplementary data

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.hroo.2022.04.001.

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