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TRANSLATIONAL RESEARCH

Optimal interlesion distance for 90 and 50 watt radiofrequency applications with low ablation index values: experimental findings in a chronic ovine model

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Aims

The optimal interlesion distance (ILD) for 90 and 50 W radiofrequency applications with low ablation index (AI) values in the atria has not been established. Excessive ILDs can predispose to interlesion gaps, whereas restrictive ILDs can predispose to procedural complications. The present study sought, therefore, to experimentally determine the optimal ILD for 90 W–4 s and 50 W applications with low AI values to optimize catheter ablation outcomes in humans.

Methods and results

Posterior intercaval lines were created in eight adult sheep using CARTO and the QDOT-MICRO catheter in a temperature-controlled mode. In four animals, the lines were created with 50 W applications, a target AI value ≥350, and ILDs of 6, 5, 4, and 3 mm, respectively. In the other four animals, the lines were created with 90 W–4 s applications and ILDs of 6, 5, 4, and 3 mm, respectively. Activation maps were created immediately after ablation and at 21 days to assess linear block prior to gross and histological analyses. All eight lines appeared transmural and continuous on histology. However, for 50 W-only applications with an ILD of 3 mm resulted in durable linear electrical block, whereas for 90 W applications, only the lines with ILDs of 4 and 3 mm were blocked. No complications were detected during ablation procedures, but all power and ILD combinations except 50 W–6 mm resulted in asymptomatic shallow lung lesions.

Conclusion

In the intercaval region in sheep, for 50 W applications with an AI value of ∼370, the optimal ILD is 3 mm, whereas for 90 W–4 s applications, the optimal ILD is 3–4 mm.

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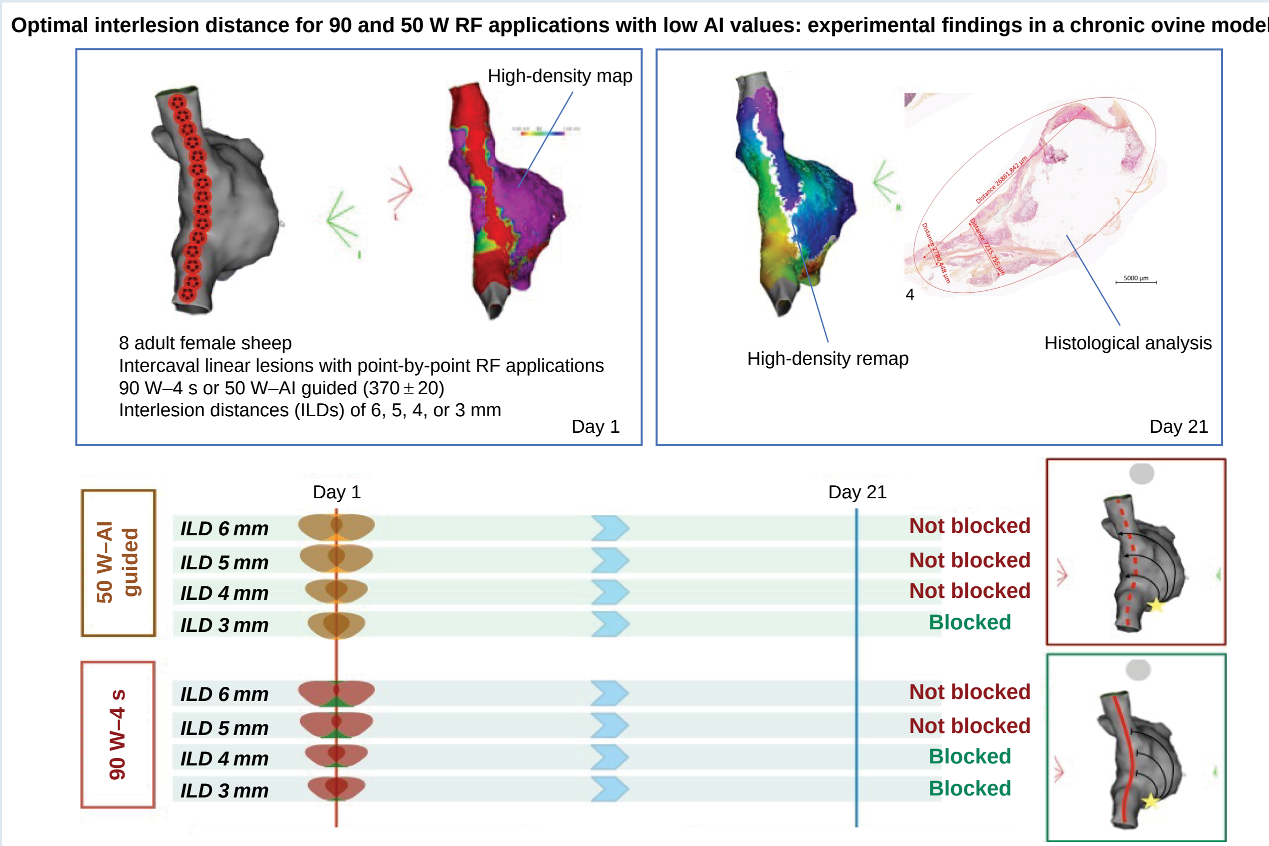
Graphical Abstract



Keywords Interlesion distance • Radiofrequency • High-power • Ovine model • Atrial fibrillation • Pulmonary vein isolation • Thin-walled structures

What's new?

- The interlesion distance (ILD) commonly targeted when performing pulmonary vein isolation with point-by-point radiofrequency (RF) application is <6 mm. However, there is little experimental data to support it.
- Lesions produced with 50 W applications targeting low ablation index (AI) values (i.e. ~350) as well as those produced with 90 W–4 s applications are smaller than those produced targeting higher AI values (i.e. ~500).
- The present study was conducted in a chronic ovine model and sought to determine the optimal ILD for both 50 W with low target AI values and 90 W–4 s RF applications.
- Electrophysiologic as well as histologic evaluations suggest that for 50 W applications with a target AI value of ~370, the optimal ILD is 3 mm, whereas for 90 W–4 s applications, the optimal ILD is 3–4 mm.

Introduction

Pulmonary vein isolation (PVI) with 50 W ablation index (AI)-guided radiofrequency (RF) applications is a safe and effective ablation strategy.[1–4] However, atrial fibrillation (AF) recurrences directly related to PV reconnections are still a concern. In this context, although the interlesion distance (ILD) commonly targeted when performing PV encirclements with 50 W applications is <6 mm,[4] limited experimental evidence exists to support this target. This is particularly relevant for lesions with low AI values (i.e. ~350), which are commonly delivered on thin-walled regions such as the posterior left atrial wall. These low AI applications have been demonstrated to create smaller lesion dimensions compared with higher AI applications (i.e. ~500).[3,5]

Excessive distance between individual lesions can predispose to recovery of conduction across an encirclement (or line) once acute and subacute oedema and inflammation have resolved. Conversely, an ILD that is too small results in excessive ablation with the risk of cardiac perforation or damage to surrounding organs.[6–8] Two clinical studies have shown that 90 W RF applications are less effective at achieving acute PVI compared with 50 W AI-guided strategies.[3,9] It should be noted, however, that in these studies, the ILD targeted during 90 W applications was the same as that used during 50 W applications (i.e. <6 mm) despite data demonstrating that the size of lesions (depth and diameter) produced by 90 W is smaller at high AI values (i.e. ~500).[3,8] Indeed, a recent study suggested that the most appropriate ILD value for 90 W applications is ~4 mm rather than 6 mm.[10]

The objective of the present experimental study was to determine the optimal ILD for both 90 W–4 s and 50 W RF applications in the atria when targeting low AI values. This information can potentially help to safely create durable encirclements (or lines) and, thereby, improve PVI and overall catheter ablation outcomes in humans.

Methods

Study animals

Eight sheep were obtained from an approved vendor (Pessac, France). All animals were female, aged 12 months, and weighed on average 46.4 kg at the time of the study. Experiments were conducted from 6 September to 28 September 2022, at L'Institut de RYthmologie et modélisation Cardiaque (LIRYC), Hôpital Cardiologique Haut Lévêque, Université de Bordeaux, Pessac, France. The local Animal Research Ethics Committee approved animal handling procedures, which were carried out in compliance with the Guiding Principles in the Use and Care of Animals published by the National Institutes of Health (NIH Publication No. 85–23, Revised 1996).

Session 1 (Day 1)

After acclimation, study animals were sedated with ketamine, acepromazine, and buprenorphine. All ablation procedures were carried out under general anaesthesia (induced with propofol and maintained with oxygen-air-isoflurane) and electroanatomic navigation system guidance (CARTO 3, Biosense Webster, Irvine, CA, USA). Activated clotting times (ACTs) were maintained >350 s throughout the procedures. The geometry of the right atrium (RA) was constructed using a PentaRay catheter (Biosense Webster), which was advanced to the RA via the right femoral vein. Individual RF applications were delivered using a QDOT-MICRO ablation catheter (Biosense Webster). Point-by-point RF applications were performed in sinus rhythm (SR) aiming to create a posterior intercaval line. The ablation catheter was oriented to be perpendicular to the endocardial surface during ablation with target contact force (CF) values of ~15 g.[11,12] In all animals, RF applications were delivered with the nGEN RF V1C generator (Biosense Webster) in a catheter–tissue interface temperature-controlled mode. Throughout all cases, the stability icon confirmed the stability of the catheter prior to RF applications. The ablation settings were as follows: (i) catheter stability range for motion ≤3 mm during ≥3 s, (ii) minimum CF ≥10 g during ≥3 s, and (iii) 3 mm (radius) tag size.

In the first four animals, the intercaval lines were created with 50 W AI-guided RF applications. The irrigation rate was of 4–15 mL/min and the targeted temperature below 50°C. The target AI value was 350 since (i) the average thickness of the posterior wall of the LA in humans is ~2–3 mm[13] and (ii) the average depth of the lesions produced by 50 W RF applications for this AI value is ~3–3.5 mm.[1,3,5,8] The distance between the lesions was 6, 5, 4, and 3 mm in Animals 1, 2, 3, and 4, respectively.

In the remaining four animals, the intercaval lines were created with 90 W–4 s RF applications. The irrigation rate was of 2–8 mL/min and the targeted temperature below 65°C. The distance between the lesions was 6, 5, 4, and 3 mm in Animals 5, 6, 7, and 8, respectively.

High-density activation mapping with the PentaRay catheter was then carried out during atrial pacing (either from the RA appendage or the RA lateral wall) to determine whether the lines were blocked. No additional ablation was carried out in any animal even if the lines were not deemed to be blocked. The animals were then awakened and returned to their routine care after recovery.

Session 2 (Day 21)

All animals were taken back to the animal EP laboratory on Day 21. Under general anaesthesia, the intercaval lines performed during the index procedure were reassessed using high-density activation mapping. No additional ablation was carried out in any animal. All study animals were subsequently euthanized by intravenous injection of potassium chloride and were transferred for necropsy, tissue harvest, and macroscopic ablation lesion assessment.

A necropsy was carried out to grossly inspect the thoracic organs for thermal injuries related to RF applications, including inspection of the pericardial sac, trachea, lungs, and oesophagus. The heart was then excised and dissected for visual inspection of cardiac structures and examined for evidence of any adverse event such as perforation, char, and thrombus.

After fixation in 10% natural buffered formalin, the hearts were trimmed to isolate all ablation sites, which were then processed and embedded in paraffin. All paraffin blocks were microtomed (LEICA RM2255 automated rotary microtome) twice serially at 6, 8, or 10 µm before being stained with haematoxylin and eosin (LEICA ST5010 Autostainer XL) for histopathologic analysis. Tissue sections were scanned at ×20 magnification using an Axio scan slide scanner Z1 (Zeiss microscopy). Lesions were then manually delineated and measured using the measurement tool of the ZEN lite software (Zeiss microscopy).

Statistical analysis

Continuous variables are presented as mean ± standard deviation. Data were analysed with SPSS software version 26.0 (SPSS Inc., Chicago, IL).

Results

Details of the index procedures are described in *Table 1*. The intercaval lines could not be completely performed in any animal due to phrenic nerve stimulation being consistently observed while delivering RF energy at the vicinities of the superior or inferior venae cavae. Therefore, all lines were abbreviated.

50 W ablation index–guided lesions

Of the four intercaval line segments performed with 50 W AI-guided RF applications, only the one with an ILD of 3 mm was durably electrically blocked as demonstrated by activation mapping on both Days 1 and 21. Histologic analysis did not identify distinguishing features between blocked and unblocked lines. All four lines exhibited transmural and continuous lesions with a mixture of collagen, granulation tissue, and adipocytes interposed between the cardiomyocytes.

90 W 4 s lesions

Of the 90 W–4 s linear lesions sets, only the two with ILDs of 4 and 3 mm resulted in durable electrical block on Days 1 and 21 (*Tables 2 and 3* and *Figures 1–3*). Similar to 50 W AI-guided lesions, all line segments carried out with 90 W–4 s RF applications exhibited transmurality and continuity with a mixture of collagen, granulation tissue, adipocytes, and cardiomyocytes on histological analysis. However, as observed with the line segments produced with 50 W applications, the functional or non-functional character of the cardiomyocytes was not possible to determine at histology but only by the activation maps.

Adverse events

No complications were detected during the first or second procedures. However, collateral thermal injuries were consistently observed on the lung surface with 90 W–4 s RF applications irrespective of the targeted ILD. Similar lung lesions were observed with 50 W AI-guided RF applications for all ILDs except for 6 mm (*Figure 4*).

Discussion

Main findings

In an *in vivo* model of atrial RF ablation using commercially available technologies and procedural parameters commonly used in clinical practice, our results suggest that (i) when delivering 50 W applications with a low AI value (i.e. ~370), the optimal ILD is <4 mm, and (ii) for 90 W–4 s applications, the optimal ILD is 3–4 mm.

Clinical relevance

Adapting lesions characteristics to cardiac wall thickness is of pivotal importance to achieve high procedural efficacy, maximizing safety without compromising efficiency.[14–18]

The biophysics and expected geometry of RF lesions produced with 50 and 90 W applications have been described in detail.[3,5,8,19–21] Parameters that can modify the geometry of such lesions (e.g. CF, irrigation, power, and catheter stability) have been similarly

Table 1 Principal characteristics of the index ablation procedures (Day 0)

	50 W 6 mm ILD	50 W 5 mm ILD	50 W 4 mm ILD	50 W 3 mm ILD	90 W 6 mm ILD	90 W 5 mm ILD	90 W 4 mm ILD	90 W 3 mm ILD
Animal age (months)	12	12	12	12	12	12	12	12
Animal weight (Kg)	46.4	48.8	47.2	49.3	42.9	44.4	45.1	44
RA volume (mL)	66	82	82	104	85	88	84	70
CF (g)	13.3 ± 1.4	13 ± 1.6	13.7 ± 2.2	13.3 ± 1.5	13.5 ± 1.5	14 ± 0.7	12.6 ± 1.9	13.8 ± 1.8
Total RF applications (*n*)	16	17	19	17	20	21	29	33
Actual interlesion distance (mm)	5.7 ± 0.4	4.8 ± 0.3	4.2 ± 0.3	3.1 ± 0.4	5.5 ± 0.3	4.5 ± 0.3	4.2 ± 0.4	3.3 ± 0.4
Ablation time per point (s)	9.7 ± 0.6	9.1 ± 0.4	8.8 ± 0.2	10.5 ± 1	3.7 ± 0.1	3.8 ± 0.1	3.9 ± 0.1	3.8 ± 0.1
Total ablation time (min)	2.5	2.6	2.8	3	1.2	1.3	1.9	2.1
Mean AI value per point	371 ± 15.1	372 ± 29.7	377 ± 20	374 ± 20.2	N/A	N/A	N/A	N/A
Mean energy delivered per point (J)	486 ± 35.7	458.5 ± 23.3	443.3 ± 11.9	527 ± 51.8	333.9 ± 13.3	341.1 ± 14.7	350.8 ± 8.4	346.2 ± 10.2
Total energy delivered (KJ)	7.2	7,7	8.4	8.9	6.6	7.1	9.8	11
Electrophysiological status of the line	Not blocked	Not blocked	Not blocked	Blocked	Not blocked	Not blocked	Blocked	Blocked
Steam pop	No	No	No	No	No	No	No	No
Char	No	No	No	No	No	No	No	No

AI, ablation index; CF, contact force; ILD, interlesion distance; RA, right atrium.

Table 2 Characteristics of the linear lesions produced with 50 W AI-guided RF applications in the right atria of sheep (Day 21)

50 W linear lesions	6 mm ILD	5 mm ILD	4 mm ILD	3 mm ILD
Maximal tissue thickness (mm)	3.1	4.5	2.13	5
Transmurality of the entire line at histological analysis	Yes	Yes	Yes	Yes
Linear lesion length (mm)	3.7	11.2	14.2	14.6
Inflammatory status	Inactive	Active	Active	Active
Types of tissue present within the linear lesion	Adipose, cardiomyocytes, collagen	Adipose, granulation, collagen, cardiomyocytes	Adipose, granulation, collagen, cardiomyocytes	Adipose, granulation, collagen, cardiomyocytes
Anatomical gaps found at histological analysis	No	No	No	No
Functional gaps unmasked by activation map	Yes	Yes	Yes	No
Collateral damage	No	Yes (lungs)	Yes (lungs)	Yes (lungs)

ILD, interlesion distance.

described.[3,4,8,21,22] However, to date, the optimal distance between adjacent lesions for the purpose of creating an encirclement (or line) as is commonly performed in clinical practice had not been rigorously evaluated experimentally. This value was initially estimated from 30 to 35 W lesions whose geometric characteristics are different than those seen with 50 and 90 W applications.[3,8,22]

The ILD is critical to procedural success and safety. Excessive distance between adjacent lesions may predispose to gaps and therefore recovery of conduction across linear lesions sets once acute or subacute oedema and inflammation have dissipated. Conversely, targeting an ILD that is too small can result in unnecessary ablation lesions, tissue heating, and therefore a greater risk of cardiac perforation or damage to the surrounding organs.[6–8]

As depicted in *Figure 5*, the findings of our work explain why 90 W RF applications with an ILD of 3–4 mm[10,14,23] led to higher first-pass isolation rates and better post-procedural outcomes without compromising safety vs. a 90 W strategy targeting an ILD of 5–6 mm.[3,17,18]

Table 3 Characteristics of the linear lesions produced with 90 W applications in the right atria of sheep (Day 21)

90 W linear lesions	6 mm ILD	5 mm ILD	4 mm ILD	3 mm ILD
Maximal tissue thickness (mm)	3.2	4.5	7.2	2.4
Transmurality of the entire line at histological analysis	Yes	Yes	Yes	Yes
Linear lesion length (mm)	33.5	24.1	26.8	36.8
Inflammatory status	Active	Active	Active	Active
Types of tissue present in the linear lesion	Adipose, granulation, collagen, cardiomyocytes	Adipose, granulation, collagen, cardiomyocytes	Adipose, granulation, collagen, cardiomyocytes	Adipose, granulation, collagen, cardiomyocytes
Anatomical gaps found at histological analysis	No	No	No	No
Functional gaps unmasked by activation map	Yes	Yes	No	No
Collateral damage	Yes (lungs)	Yes (lungs)	Yes (lungs)	Yes (lungs)

ILD, interlesion distance.

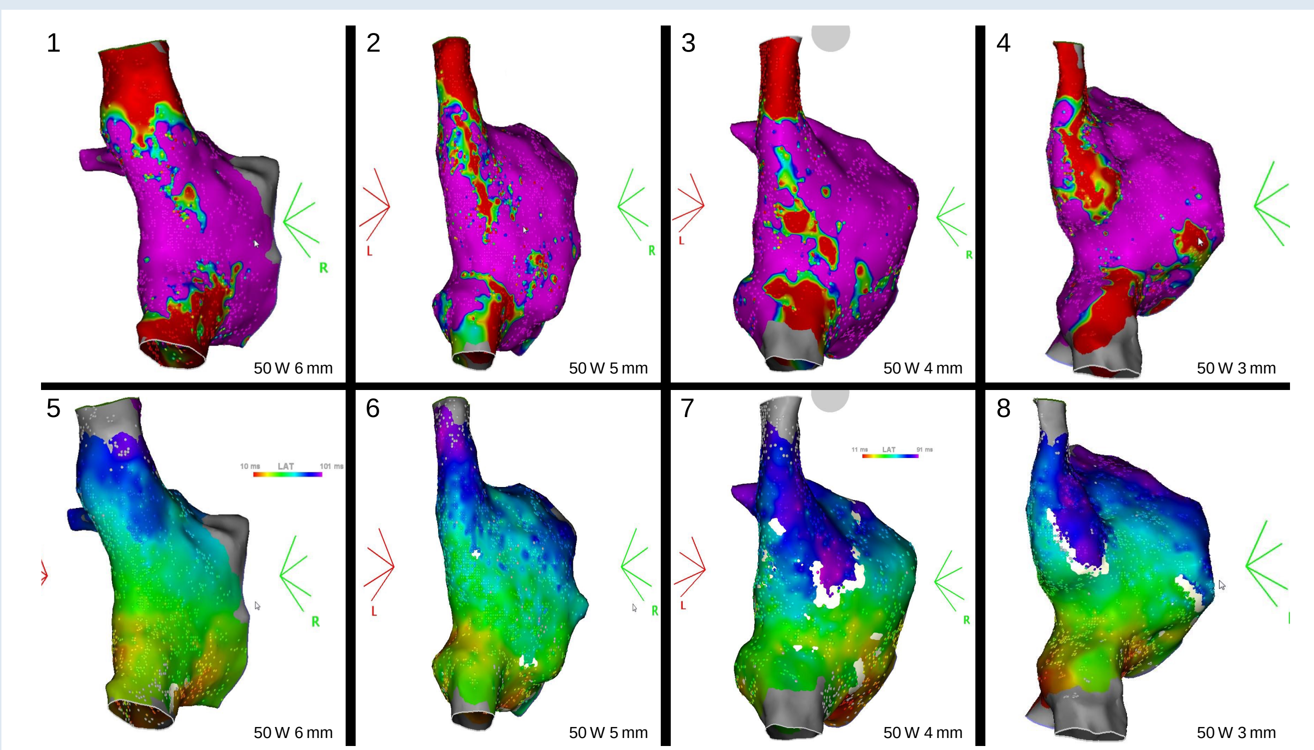


Figure 1 *Panels 1–4*: Voltage maps made 21 days after ablation showing intercaval line segments produced with 50 W AI-guided RF applications and interlesion distances of 6, 5, 4, and 3 mm, respectively. *Panels 5–8*: Activation maps made 21 days after ablation during pacing from the inferolateral wall of the RA. In animals with an interlesion distance of 6 and 5 mm, no block along the line segments is visible (panels 5 and 6). In the animal with an interlesion distance of 4 mm, the line segment is not blocked (panel 7). Finally, in the animal with an interlesion distance of 3 mm, the line segment is blocked (panel 8).

Available data and study findings

Experimental data indicate that the maximal diameter of RF lesions produced with 50 W applications for ≍13–15 s (i.e. AI values of 450–500) varies between 9 and 10 mm.[1,3,5,8] This implies that targeting AI values of ~350 (application durations of ~7–10 s), as is commonly done on the posterior wall of the left atrium, is expected to yield smaller lesions, suggested to be between 6 and 8 mm.[1] Distances of 6 and even 5 mm between the centres of two adjacent lesions of such diameters could

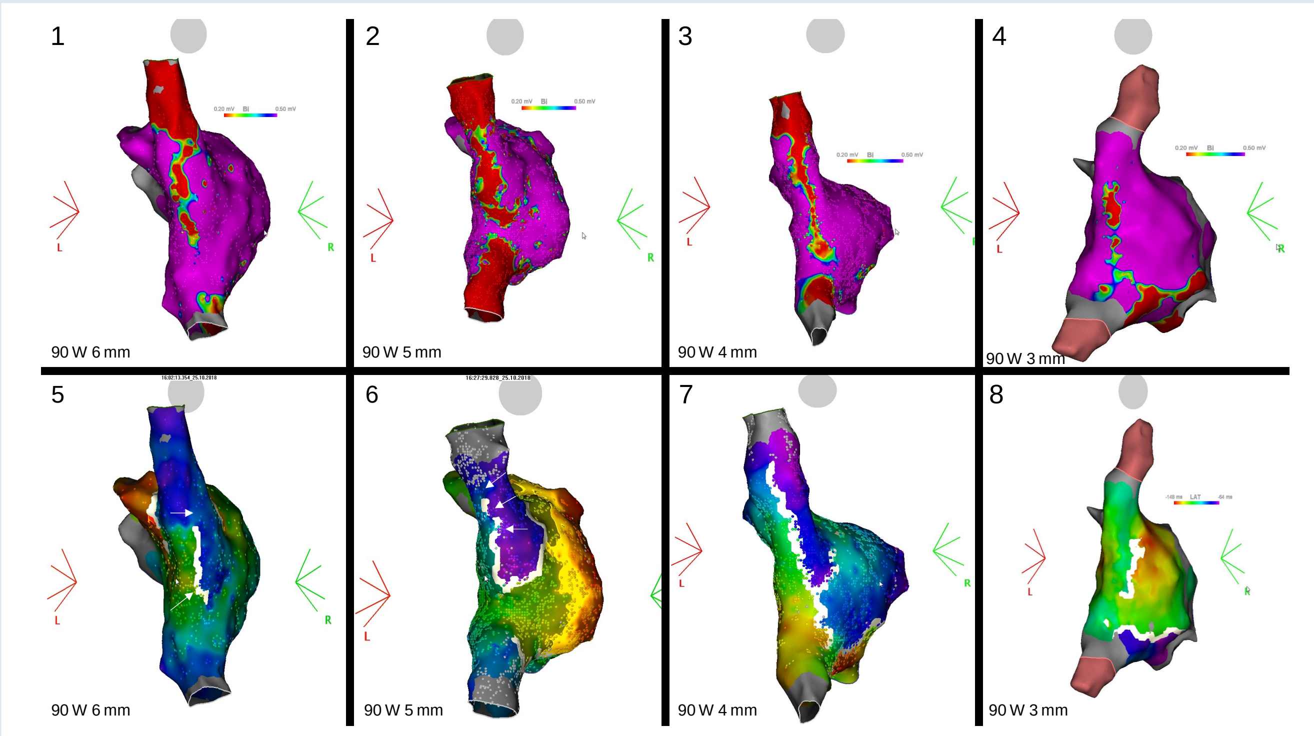


Figure 2 *Panels 1–4*: Voltage maps made 21 days after ablation showing intercaval line segments produced with 90 W–4 s RF applications and interlesion distances of 6, 5, 4, and 3 mm, respectively. *Panels 5–8*: Activation maps made 21 days after ablation during pacing either from the RA appendage or the lateral wall of the RA. The line segments drawn with interlesion distances of 6 and 5 mm are not blocked (arrows: panels 5 and 6), while those with interlesion distances of 4 and 3 mm are blocked (panels 7 and 8).

favour gaps within linear lesions sets. Likewise, it has been shown that the diameter of the lesions produced with 90 W–4 s applications varies between 6 and 8 mm,[3,8] implying that ILDs of 6 and 5 mm might be too large (*Figure 5*).

The above is supported by the results of a randomized study of patients undergoing point-by-point PVI with RF applications in which an ILD of 3–4 mm resulted in a significantly higher first-pass PVI rate when compared with 5–6 mm. The difference was so large that the study was terminated early for superiority.[6] Importantly, the inferiority of an ILD of 5–6 mm was seen despite using power settings of 25–35 W (with AI values ranging from 350 to 500).[6] The lesions produced with 30 W are larger in diameter than those produced with 50 and 90 W,[8] suggesting that an ILD of 5–6 mm would yield even worse first-pass PVI rates when using the higher power settings. Finally, we have recently showed that 90 W–4 s RF applications within the posterior aspect of the PVs were as effective and safe as a more standard 50 W-only AI-guided strategy when using an ILD of ∼4 mm.[13]

The results of our experimental study align well with the above data. The activation maps demonstrated that ILDs of 6 and 5 mm resulted in gaps within our linear lesion sets with both 50 W applications with AI values of ∼370 and 90 W–4 s applications. In contrast, linear lesion sets created with an ILD below 4 mm yielded durable electrical block out to 21 days with both power settings. This makes sense given that the lesions produced with 50 W applications targeting low AI values (i.e. ∼350) and those produced with 90 W–4 s applications have similar dimensions (*Figure 5*).

It should be emphasized that an ILD of 3–4 mm compared with 6 mm inexorably leads to an increase in the number of RF applications delivered and consequently to an extension of the RF application time. However, this constraint related to lesion geometry is counterbalanced by an increase in the durability and effectiveness of encirclements/lines made without compromising the safety as shown in our experimental study as well as in clinical studies.[10,14,23]

Safety concerns

In our study, most lines made with 50 W and all lines made with 90 W caused collateral damage. However, the collateral lesions were consistently shallow (*Figure 4*) and were not associated with damage to organ integrity or impact on animal health status or survival regardless of the ILD used. This is in keeping with data from other experimental studies in which both 50 and 90 W applications have consistently caused collateral damage that was not clinically evident.[1,3,19] In humans, large clinical studies have shown that 50 W applications have a very low risk of clinically manifesting procedural complications.[1–4] Likewise, 90 W–4 s applications have thus far not been associated with a higher risk of complications in humans despite their considerable thermal latency.[3,6,8,9,23–25] Nevertheless, given the consistent finding of (mild) collateral damage in large animal studies, caution is advised when creating RF lesions in higher risk regions of the atria, such the posterior wall.

Limitations

Our study has several limitations: (i) triphenyl tetrazolium chloride staining of fresh tissue sections was not performed but could have allowed us to distinguish between necrotic and stunned cardiomyocytes at RF lesion sites. (ii) Interlesion distances <3 mm were not evaluated in our pre-clinical study. However, the use of such small ILDs is rare as a routine strategy in clinical practice as it results in a high degree of lesion superimposition. Although unpublished, in a pre-clinical canine study, delivering two 90 W–4 s applications with 4 s interval between them

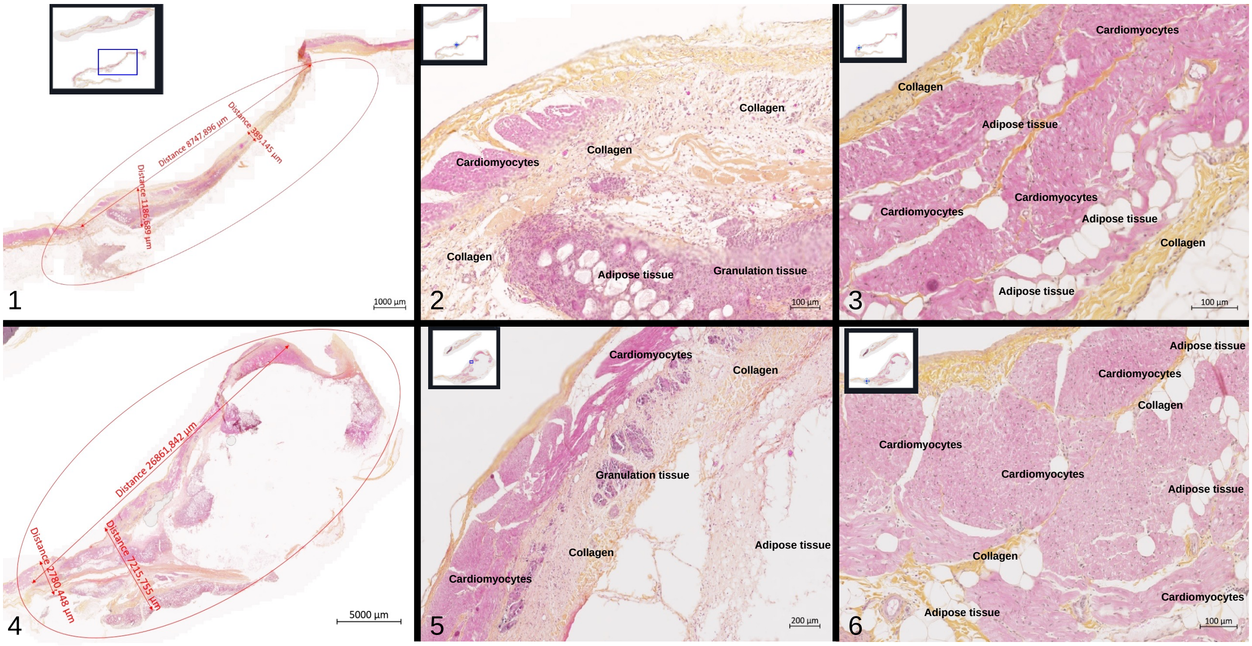


Figure 3 *Panels 1–2*: Intercaval linear lesion created with 50 W AI-guided RF applications. The interlesion distance targeted was 5 mm. The linear lesion was deemed transmural and continuous on histological analysis (*Panel 1*). The lesion was made of adipose and granulation tissues, collagen, and cardiomyocytes (*Panel 2*). The visualized cardiomyocytes were likely still functional and, therefore, may have supported electrical conduction through the line, thus explaining the absence of any line of block at the activation map as shown in *Figure 1*. *Panel 3*: Healthy cardiomyocytes and other tissues outside the lesion area. *Panels 4–6*: Intercaval linear lesion created with 90 W–4 s RF applications. The interlesion distance targeted was 4 mm. The linear lesion was deemed transmural and continuous on histological analysis *(Panel 4)*. The lesion was made of adipose and granulation tissues, collagen, and either non-functional or necrotic cardiomyocytes (*Panel 5*). Indeed, this linear lesion was deemed as blocked on the activation map shown in *Figure 2*. *Panel 6*: Healthy cardiomyocytes and other tissues outside the lesion area.

Figure 4 Superficial and mild collateral injury visible on the left lung 21 days after RF applications using 50 W with an interlesion distance of 5 mm.

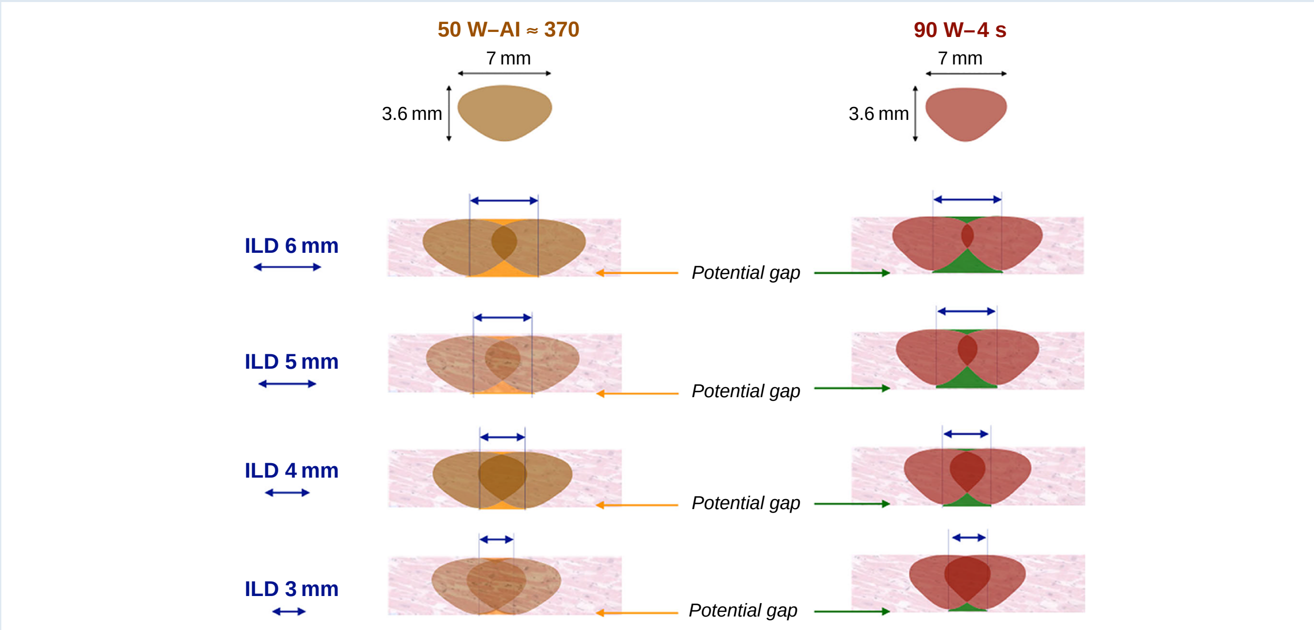


Figure 5 Theoretical diagrams of lesions produced with RF applications of 50 W and AI values of ∼370 and with 90 W–4 s based on published experimental studies.[1,3,6] In both types of lesions, which have similar dimensions, the risk of potential gaps between lesions is low for an ILD ≤4 mm, while it becomes significant above 4 mm.

caused a meaningful temperature rise (from 67.5 to 76.3°C) and produced 40% deeper lesions in both beating hearts and thigh muscles. This implies that a reduced interlesion distance carries a substantial risk of extramurality. (iii) The durability of linear block was assessed at 21 days. It is possible that delaying the remapping procedure could have identified more gaps in conduction, although this is felt to be unlikely. (iv) The optimal ILD for 50 W application with high AI values (i.e. ∼500), which is commonly used at thick-walled areas of the atria such as the anterior aspects of the PVs, the roof, and the mitral isthmus, was not assessed in our study. The lesions produced with 50 W applications and AI values ≍500 have diameters and depths of ∼10 and 5.5 mm, respectively,[1,5,8] for which ILDs of 5–6 mm may be adequate.[4] (v) Relatively few animals were used to determine the optimal ILD in the atria for both 50 and 90 W applications. In addition, each of the eight ablation strategies studied (50 and 90 W with an ILD of 3, 4, 5, and 6 mm) was tested only in a single sheep. Therefore, although the data from our study appear consistent and in agreement with the geometry of the lesions produced by 50 and 90 W applications, our findings must be confirmed by studies with a larger number of animals. (vi) The intercaval region in sheep may not mimic exactly the thickness of the posterior LA wall in humans. To confirm our findings a similar study could be carried out in swine or another animal model.

Conclusions

The optimal ILDs for 50 W applications with a target AI value of 370 and for 90 W–4 s applications are <4 mm and 3–4 mm, respectively, when ablating thin-walled atrial structures, such as the posterior intercaval region.

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Conflict of interest: C.H. and J.C. are employees of Biosense Webster, Inc. The other authors report no conflict.

Data availability

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

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