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A RAndomized Trial to compare the acute reconnection after pulmonary vein ISolation with Laser-BalloON versus radiofrequency Ablation: RATISBONA trial

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Abstract

Introduction: Dormant conduction and acute reconnection in the pulmonary veins (PV) during a PV isolation can be detected by performing an adenosine provocation test (APT). Visually guided laser balloon ablation (VGLB) creates deep transmural lesions, thus causing less acute reconnection. This study compared the acute PV reconnection rate after isolation with VGLB or with RF using an APT.

Methods and results: Patients with paroxysmal AF were randomized to PVI with the VGLB or RF ablation. Each PV underwent an APT at least 20 minutes after successful isolation with injection of 18 mg adenosine. Primary endpoint was the difference between the two ablation methods regarding acute PV reconnection rate detected with APT. A total of 50 patients were randomized into the study (25 VGLB). The basic characteristics and mean procedure time were not different between the two groups. Note that 96% of the 97 targeted PVs in the VGLB group and 98% of the 96 targeted PVs in the RF group could be isolated ($P = 0.41$). APT was performed at similar times (after 28 minutes in VGLB-arm vs. after 31.5 minutes in RF-arm; $P = 0.12$). Significantly less PVs were reconnected during APT in the VGLB group than in the RF group (10 PV [10.8%] vs. 29 PV [30.9%]; $P = 0.001$).

Conclusion: The acute PV reconnection rate is significantly less after PVI with VGBL than with RF. The clinical significance of this apparently better procedural efficiency of the VGBL ablation should be assessed with new randomized studies looking at AF recurrence.

KEYWORDS

adenosine, atrial fibrillation, CardiFocus, catheter ablation, laser balloon ablation, reconnection

1 | INTRODUCTION

Since the pioneering study of Haissaguerre et al., pulmonary vein isolation (PVI) is the cornerstone in atrial fibrillation (AF) ablation procedures.[1] Unfortunately, in 30–50% of the cases AF recurs despite of complete electrical disconnection of the PVs index procedure. The major cause of recurrence is reconnection of the initially isolated PVs. Indeed, 80% of the patients with recurrence of AF demonstrate at least one reconnected PV.[2,3] A way to recognize the PVs which might reconnect in the future is to administer adenosine during the index procedure and look for the so-called "dormant conduction."[4] Indeed, after PVI with radiofrequency (RF) energy, 17–30% of isolated PVs in 35–59% of patients were reconnected after adenosine provocation test (APT).[5,6] Moreover, some studies including a meta-analysis indicate a higher rate of AF recurrence in patients with PV reconnection after adenosine administration.[5,6] The reconnection of PVs probably depends on the degree of transmural damage during the index procedure, which corresponds to acute efficiency of the ablation lesion and can be appreciated with adenosine administration.

Point-by-point ablation with RF energy is technically challenging and achieving a transmural and contiguous ring of necrosis might be difficult. To overcome these problems, balloon catheters using other energy sources such as cryo- or laser-energy had been developed.[7,8]

The visually guided laser balloon ablation (VGLB) (HeartLight, CardioFocus Inc, Marlborough, MA, USA) is a unique system by which a compliant balloon occludes the PV ostium and the laser energy can be applied with the help of an endoscope under direct visualization around the PV, thus creating histologically proven deep and concrete ablation lesions. We recently published a pilot study in patients treated with PVI with VGLB, where a very low reconnection (6.7% of the PVs) rate with APT was detected.[9]

Here, we are presenting the results of the RATISBONA trial, which compares in a randomized fashion the acute efficiency of PVI with VGBL versus RF with APT in patients with paroxysmal AF.

2 | METHODS

Patients with drug-refractory paroxysmal AF and those who provided written informed consent were enrolled in the study. The study complied with the Declaration of Helsinki and the protocol was approved by the ethical commission of the University of Regensburg. Informed consent had been obtained from all patients enrolled.

Inclusion criterion was paroxysmal and symptomatic AF according to the current AF classification criteria.[10] Exclusion criteria were asthma or known allergy to adenosine; left atrial (LA) thrombus; LA > 55 mm; left ventricular EF < 35%; previous LA ablation for AF; NYHA class IV symptoms; myocardial infarction within the previous 60 days; unstable angina; any history of cardiac valve surgery; uncontrolled bleeding; active infection; severe pulmonary disease; and a previous cardiac valve surgery.

2.1 | Study protocol

Patients were randomized in a 1:1 fashion to PVI with either VGLB or RF ablation. Either a computed tomography (CT) scan or cardiac magnetic resonance imaging (CMR) was required before the procedure to obtain the LA anatomy.

2.2 | Ablation procedure

In all patients, a LA thrombus was excluded either with a transesophageal echocardiography or with cardiac computer tomography. The ablation procedure was performed under continued oral anticoagulation with phencoumaron (target INR 2.0–3.0) or with dabigatran 110 mg 1-0-1 according to institutional standards. Ablation procedure was performed in sedation using continuous infusion of propofol 1% and midazolam, respectively, with fentanyl boluses. General anesthesia was used only in patients with sleep apnea syndrome and in those who wished general anesthesia (in 5 patients). An esophageal temperature probe (Circa S-Cath, Circa Scientific, Englewood, CO, USA) was inserted transorally to continuously monitor esophageal temperature during ablation. If it exceeded 39.5°C, energy delivery was terminated in both groups. Patients who were not in sinus rhythm at the start of the procedure were electrically cardioverted to perform the ablation in sinus rhythm. Cardiac signals were recorded with a standard EP recording system (Labsytem Pro-EP, Boston Scientific, Marlborough, MA, USA).

2.3 | RF-ablation

Venous sheaths were placed in both groins (two 7F sheaths in the V. femoralis left, two 8.5F SL0 sheaths in V. femoralis right; St. Jude Medical, St. Paul, MN, USA). After placing a 6F octapolar catheter into the coronary sinus and a 6F quadripolar catheter along the His bundle region, a double transseptal puncture was performed using a modified Brockenbrough technique. Unfractionated heparin boluses were administered to maintain activated clotting time between 300 and 350 seconds.

A circumferential mapping catheter and a 3.5-mm mapping/ablation catheter (LassoNav and Navistar Thermocool SF; Biosense Webster Inc., Diamond Bar, CA, USA) were placed in the left atrium. An electroanatomic map of the left atrium was obtained with the Lasso catheter (CartoFAM Module) and was merged with the CT image of the left atrium (CartoMerge Module). After obtaining the baseline PV potentials with the Lasso catheter, RF ablation was applied around the PV ostia and at the carina between ipsilateral PVs. RF energy was titrated from 30 W at the posterior wall to 40 W for 30 seconds at the anterior wall at a maximal temperature of 43°C and a flush rate of 15 mL/min. Ablation was continued until the disappearance of the PV potentials.

2.4 | VGLB-ablation

The only difference in the venous access was the exchange of one 8.5F SL0 sheath for a 15F steerable sheath. A circular mapping catheter (Lasso Non-Nav, Biosense Webster Inc.) was introduced into each target PV to record baseline PV electrograms and to guide the VGLB catheter into the target vein. The balloon was inflated aiming a complete occlusion of the PV ostium. The grade of the achieved occlusion was defined as grade I for complete occlusion of the ostium (360°) or if a less than complete occlusion was achieved, as grade II (270°–359°), III (180°–269°), or IV (<180°), accordingly. To avoid gaps between ablation lesions, we created laser lesions with a 30–50% lesion overlap using the adjustable 30° aiming arc of laser beam, as suggested by the previous preclinical and clinical studies (Figure 1). Another important issue was the titration of the laser power. If we could obtain a very good tissue contact, maximal power (12 W for 20 seconds) had been chosen. Applying high laser power in areas without complete occlusion and overlying blood causes an overheating of the balloon ending in balloon disruption. In such regions, lower energy levels must be chosen from 5.5 W (overlying blood) to maximal 7 W (overlying but moving blood) for a longer time (30 seconds). If the contact area between two ipsilateral PVs, i.e., the carina region, was not wide, laser power of 8.5–10 W for 20 seconds had been applied (Figure 1).

After the first PVI encircling, the balloon was deflated and the PV potentials were assessed with the circular mapping catheter. If not isolated, we looked for the gap by leaving the circular catheter in the PV, if possible, or we ablated the suspected area of gap.

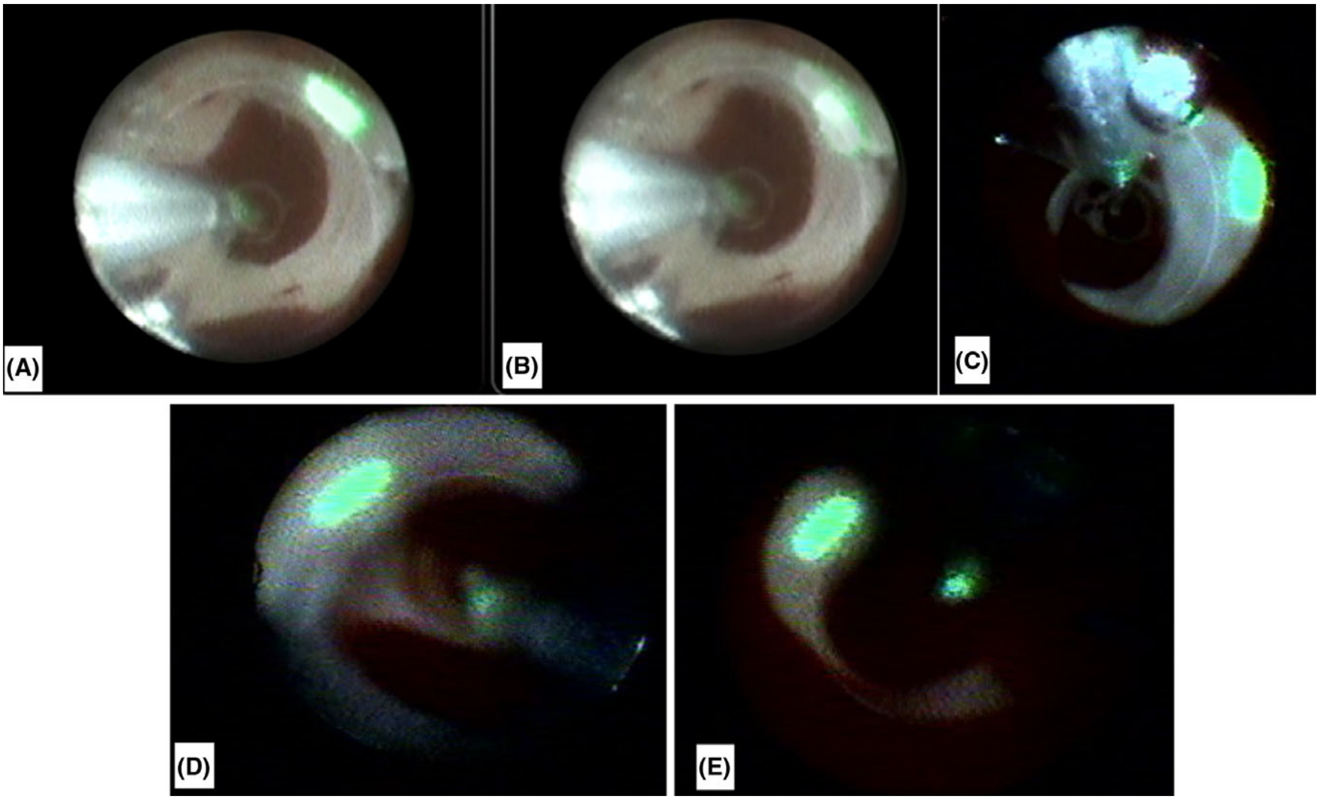

FIGURE 1 A, A complete occlusion of the PV ostium was achieved with laser balloon. the whole circumference of the PV ostium can be seen and the maximal power of laser energy (12 W for 20 seconds) can be applied because there is no interference with blood. The first laser ablation (the green point) was applied at 1 o'clock (imagining the circumference of the PV ostium like the display of an analog watch). B, The second laser ablation was applied at 2 o'clock with 50% overlapping with the first ablation lesion (the last and the actual applications can be seen in the screen of the laser console to facilitate the overlapping). C, There is overlying blood at 8–9 o'clock; thus, the occlusion is less than optimal. This represents an occlusion grade of II, because more than 270° of the circumference of the ostium can still be seen. The ablation power should be reduced in regions with overlying blood as mentioned in the text. In D, there is no enough tissue contact from 2 o'clock to 6 o'clock, thus occlusion grade III. E, Representing the worst condition with less than half of the ostium with good contact, a balloon occlusion grade of IV [Color figure can be viewed at wileyonlinelibrary.com]

During ablation of the right-sided PVs, phrenic nerve pacing was performed to prevent phrenic nerve injury.

2.5 | Adenosine provocation test

Each isolated PV underwent an APT for at least 20 minutes after isolation. This waiting period was chosen to exclude early spontaneous recovery and was limited to 40 minutes after isolation to standardize the APT timing. After excluding spontaneous recovery of the PV conduction, an adenosine bolus of 18 mg followed by a saline flush was administered through a femoral vein. Intracardiac recordings were continuously monitored. Atrial demand pacing just under the current sinus rhythm was started simultaneously with the adenosine bolus to avoid a sinus arrest that would otherwise lead to an underdetection of PV reconnection. Adenosine effect was recognized when at least a P wave was blocked or sinus bradycardia or arrest occurred necessitating atrial pacing. PV reconnection was diagnosed when the circular mapping catheter detected PV potentials in a previously isolated PV. A PV reconnection was classified as temporary if the PV signals disappear again after the effect of adenosine diminished or as permanent if the PV stayed reconnected even after the effect of adenosine had ceased. In the case of temporary reconnection, it was left to the discretion of the physician to perform additional ablations and to test the PV again with APT.

2.6 | Statistical analysis

In the studies, the PV reconnection rate after administration of adenosine was reported within a range of 17–30% following RFA and 7% following VGLB.[5,6,9] A total sample size of 180 PV gives an 80% power at a two-sided significance level of 0.05 assuming a reconnection rate of 20% and 7% in the equally sized RF and VGLB group, respectively. Accounting for about 5% nonisolatable PV, we aimed to recruit a total of 50 patients with about 200 PV.

Values are distributed as means ± SD for normally distributed continuous variables, median, and interquartile range (IQR) for skewed distributions (assessed by means of Kolmogorov–Smirnow one sample test) and counts and percentages for categorical variables. Statistical analysis was conducted using Student's *t*-test (unpaired) for continuous variables with normal distribution and Mann–Whitney U test for variables with nonnormal distribution. The chi-square test or Fisher's exact test was used to compare the categorical variables in different groups. Statistical significance was defined as $P < 0.05$. Statistical analysis was performed using SPSS 21 (SPSS Inc., Chicago, IL, USA).

TABLE 1 Patient demographics

	VGLB (n = 25)	RF (n = 25)	P-value
Age, years	59.7 ± 10,4	65.3 ± 11.5	0.08
Male	13 (52)	12 (48)	0.77
Duration of AF, years	12 (9–42)	16 (8–67)	0.70
Hypertension	21 (84)	19 (76)	0.49
Diabetes mellitus	6 (24)	5 (20)	0.73
Coronary artery disease	6 (24)	7 (28)	0.75
Myocardial infarction	4 (16)	4 (16)	1.0
Coronary artery bypass grafting	0 (0)	2 (8)	0.50
Congestive heart failure	4 (16)	3 (12)	1.0
Stroke or transient ischemic attack	3 (12)	4 (16)	1.0
Body mass index, m/kg^2	28 (25–36)	28 (25–30)	0.90
Left atrial diameter, mm	41.3 ± 5.1	44.8 ± 7.6	0.15
Ejection fraction, %	60.9 ± 3.8	60.6 ± 5.1	0.83
Atrial flutter ablation	3 (12)	3 (12)	1.0
Antiarrhythmic medications (Class I or III)	10 (40)	8 (32)	0.47
EHRA 1/2/3/4	1 (4)/5(20)/13(52)/6(24)	0/12(48)/7(28)/6(24)	0.13

Values are mean ± SD, n (%), or median (IQR). EHRA = European Heart Rhythm Association.

TABLE 2 Procedural data

	VGLB (n = 25)	RF (n = 25)	P-value
Procedure time, min[a]	232 ± 38	237 ± 60	0.70
Ablation time, min[b]	157 ± 34	177 ± 49	0.11
Fluoroscopy time, min	30 (22–36.5)	11 (7.5–14.5)	<0.001
Fluoroscopy dose, cGym^2	1,849 (1,504–3,074)	1,114 (645–1,755)	0.002

Values are mean ± SD, or median (IQR).
[a]Defined as time from venous access to sheath removal.
[b]Defined as time from the end of the second transseptal puncture to sheath removal.

3 | RESULTS

A total of 50 patients were randomized at a 1:1 fashion into the VGLB or RF ablation. All patients had paroxysmal AF. None of the patients had received any cardioversions.

3.1 | Patients and procedural characteristics

There were no significant differences in basic clinical characteristics between the groups (Table 1).

Although total and LA procedure times were equal in both arms, fluoroscopy times were significantly shorter in the RF arm (Table 2).

Three patients in the VGLB arm and 4 in the RF arm had a common PV ostium, thus 97 PVs in the VGLB arm and 96 in the RF arm were targeted for PVI. Ninety-three PVs (95.9%) in the VGLB arm and 94 (97.9%) in the RF arm could be successfully isolated (P = 0.41). The right inferior PVs could not be isolated in 2 patients in each arm because of temperature exceeding 39.5°C in the esophagus. Additionally, in 1 patient the left common ostium and in another one the right inferior PV could not be isolated in the VGLB arm because of temperature rise in the esophagus and as well as incomplete occlusion of the veins with the balloon resulting in ablation with low laser energy.

Significantly more PVs were isolated after the first encirclement in the VGLB arm than in the RF arm 80.4% (78 PVs) versus 47.9% (46 PVs), respectively; P < 0.001.

3.2 | Adenosine provocation test

All isolated PVs underwent an APT. Mean time to ATP after isolation of each PV was not different between both therapy arms (28 minutes in VGLB vs. 31.5 minutes in RF; P = 0.12). In VGLB significantly less PVs had a positive APT than in RF (10 [10.8%] vs. 29 [30.9%], P = 0.001). In VGLB significantly less PVs had a positive APT than in RF (10 [10.8%] vs. 29 [30.9%], P = 0.001). Of all the reconnected PVs, only 1 in the VGLB arm and 2 in the RF arm had a permanent reconnection. Since the rate of permanent reconnection in both groups was very low no further statistical analysis had been performed because of the irrelevance. More patients had at least one PV with reconnection in the RF arm than in the VGLB arm (n = 16 [64%] vs. n = 8 [32%], P = 0.02). In the VGLB arm, reconnection under adenosine was seen in 3 of the LSPV, in 4 of the LIPV, in 1 of the RSPV, and in 2 of the RIPV; in the RF arm in 7 of the LSPV, in 5 of the LIPV, in 1 of the left common PV, in 8 of the RPSV, and in 8 of the RIPV. There was no difference in the adenosine administration time when PVs with reconnection

TABLE 3 Comparison of reconnected and nonreconnected PVs in VGLB arm

	APT-negative (n = 83)	APT-positive (n = 10)	P-value
Time to APT, min*	28 (22.0–36)	29 (23.5–37.5)	0.71
Application time, sec	570 (454–785)	955 (485–1,053)	0.19
Number of applications	29 (24–39)	46.5 (25–52)	0.22
Mean power, Watt	10 ± 1.0	8.8 ± 1.5	0.01
Total energy, Joule	5,720 (4,490–7,232)	7,952 (4,996–10,272)	0.16
Occlusion-grade	1 (1–1)	1.5 (1–4)	0.002

Values are mean ± SD or median (IQR).
*Defined as time from the isolation of a vein to the administration of adenosine for that vein.

were compared with PVs without reconnection in each therapy arm separately.

3.3 | Differences in clinical and procedural parameters in APT positive and negative groups

Clinical characteristics of patients with or without reconnection did not differ between therapy arms (each P = n.s.). Only a minority of patients had general anesthesia (5 patients, 10%). The type of anesthesia had no influence on the reconnection rates; 4 (20%) out of 20 PVs had a positive APT in patients with general anesthesia versus 35 (21%) out of 167 PVs in patients with conscious sedation, P = 1.0. PVs with reconnection were more likely to be incompletely occluded with the laser balloon (balloon occlusion grade 1.5 vs. 1.0, respectively; P = 0.002) and to be ablated with less power (8.8 ± 1.5 W to 10 ± 1.0 W, respectively; P = 0.01) (Table 3). No significant differences in the ablation data (total energy applied 250.6 ± 67.1 kJ vs. 227.9 ± 67.8 kJ and 250.6 ± 67.1 kJ; P = 0.42; ablation time 3,611 ± 1,029 seconds vs. 3,152 ± 865 seconds; P = 0.27) and the time to ATP (31 minutes vs. 34 minutes; P = 0.0194) could be detected in the RF arm between reconnected and nonreconnected PVs.

3.4 | Reablation after positive APT

Three PVs (1 with permanent reconnection) in the VGLB arm and 14 PVs (2 with permanent reconnection) in the RF arm were reablated because of positive APT. Twenty minutes after reisolation, a second APT had been performed. In 2 of the 3 reablated PVs in the VGLB arm and in 6 of the 14 in the RF arm, no reconnection could be detected in the repeat APT. The PVs with permanent reconnection did not reconnect after reisolation with the second APT.

3.5 | Complications

Three patients in the VGLB and 1 patient in the RF arm developed a slight groin hematoma treated conservatively (P = n.s.). In 1 female patient, a pericardial tamponade occurred during placing the diagnostic catheter into the coronary sinus. Four weeks later, a successful PVI with RF was performed; the effusion was classified as procedure but not device-related complication. In a male patient, the atrial septal puncture site was not occluded after VGLB ablation resulting in implantation of an atrial septum closure device 2 months after the procedure.

4 | DISCUSSION

This is the first randomized study comparing the acute PV reconnection rate after PVI with VGLB versus RF ablation by using APT. The major finding is that PVs isolated with VGLB were significantly less prone to reconnection than those PVs isolated with RF energy. Significant more patients in the VGLB arm had no PVs reconnected than in RF arm, 68% (17) versus 36% (9), respectively; P = 0.024.

The results for the VGLB arm are concordant with a previous report from our group.[14] In that study, APT detected a PV reconnection rate of 6.7% after VGLB ablation. Thus, the low acute reconnection rate after PVI with VGLB is consistent.

Further, the current study showed similar rates of acute reconnection after RF ablation as in the first studies with APT. Arentz et al. used adenosine provocation for the first time to unmask dormant PV conduction after PVI with RF and detected a PV reconnection rate of 25%.[5] Recently, in the ADVICE study a reconnection rate of 21% was detected.[11]

The current study confirmed and expanded the apparently higher acute efficiency of VGLB over RF ablation in a randomized fashion.

Although tissue injury caused by RF as well as by laser energy is thermally mediated, there are differences.[12] Gerstenfeld et al. analyzed the lesions created with laser and with RF energy in a swine model. Histopathological examinations showed that the lesions created with laser energy were all circumferential and transmural, whereas none of the lesions by RF were transmural. Moreover, only those PVs with transmural lesions after VGLB ablation remained persistently isolated after VGLB.[13] On the other hand, all PVs in the RF arm were reconnected and all of them had nontransmural lesions.[13] Thus, transmural lesions seem to be a “must to have” for permanent isolation. Dukkipati et al. performed two studies, where the patients underwent a second LA procedure to check the PVs 3 months after the index VGLB procedure. Note that 86–90% of the PVs were still disconnected.[14,15] Opposite, a similar remapping study after the PVI with RF showed a disconnection rate of only 57%.[16]

In the light of these studies, we can assume that the VGLB ablation has the potential to create truly transmural lesions, which might be reflected by acute efficiency and therefore lower reconnection rates in APT.

The most feasible explanation for the nontransmural and noncontiguous lesion sets by RF ablation seem to be the ablation technique itself. Three-dimensional (3D) mapping systems ablation gaps are still not avoidable. The second big issue is the tissue contact of the ablation catheter, which directly determines the depth of the lesion.[17] In contrast, the strength of VGLB is the ability to place ablation lesions under direct visualization, which ensures the continuity of the lesion set. Moreover, the appearance of blood-free tissue under the balloon confirms optimal tissue contact. This is probably the reason why more PVs could be isolated after the first encirclement in the VGLB arm than in the RF arm in our study, a finding like the results of the first randomized multicenter study comparing VGLB and RF ablation.[18] Dukkipati et al. proved the noninferiority of VGLB compared to RF ablation for treatment of paroxysmal AF regarding the safety (61.1% vs. 61.7%) and the efficacy (11.8% vs. 14.5%) endpoints.[18] Although APT was not used in that trial, all PVs were examined for spontaneous reconnection after a 30-minute waiting period, which occurred significantly more often in RF than in VGLB. Interestingly, the spontaneous reconnection rate in both groups was very low compared to the reconnection rates with APT in our study, especially in the RF arm (2.7% spontaneous reconnection in the study of Dukkipati et al. vs. 30.9% in our study). This observation highlights the importance of adenosine provocation during PVI and maybe of using the adenosine test as the ultimate criterion to identify the PVs with persistent viable tissue to ablate them again before ending the procedure. There was no difference in the clinical outcome in the two treatment arms in the multicenter study at the end, but the study design allowed only in the RF arm reablation of the patients with AF recurrence in the first 80 days after PVI.[18] In the light of the current study, outcome studies should be designed comparing different ablation techniques with the use of APT.

On the other hand, there are conflicting data about the clinical significance of a positive adenosine test with repeat ablation.[11,19] In the ADVICE trial, absolute risk of recurrent atrial arrhythmias was significantly reduced by 27% in patients with paroxysmal AF, if the PV with adenosine induced reconnection had been reisolated.[11] In the UNDER-ATP, Kobori et al. found no difference in rate of arrhythmia free survival, whether they reisolated the PVs with reconnection or left them without reisolation after reconnecting under APT.[19] There were significant differences in these two studies regarding the type of AF, the adenosine administration time, and the treatment approach. Despite these conflicting results in these two studies, there is no doubt, that APT detects dormant conduction and thus predicts electrical reconnection of PVs and which could result in recurrence of AF, at least for patients with paroxysmal AF.[5,6]

The absence of a difference in the clinical and ablation variables such as duration of ablation and mean power of application in the RF arm between reconnected and nonreconnected PVs shows the unpredictably of a PV reconnection by using these variables. For example, a very poor tissue contact prevents an effective lesion formation, no matter what the power of the ablation is. Measuring the contact force during RF ablation therefore would help to predict those PVs at risk for reconnection.[20] In the VGLB arm, the reconnected PVs had lower mean applied power (8.8 W vs. 10 W) resulting from less optimal occlusion of the PV ostium with the balloon; thus, for an effective transmural lesion with a negative APT, mean ablation power of at least 10 W is needed—which also underscores the necessity of a complete occlusion of the PV ostium.

5 | LIMITATIONS

The present study was not designed and powered to evaluate the recurrence rate of AF. Thus, we could not evaluate the effects of the lower reconnection rate with the VGLB on the clinical outcome. But the study fulfilled its main purpose, namely, showing the higher acute efficiency of the VGLB. New studies with adequate power to assess the clinical significance of this finding should be designed.

Another limitation is that we did not use contact force catheters in the RF arm, which are standard in many clinics. At the start of the study we did not use contact force. The difference could be lower or diminish completely if VGLB would be compared with RF ablation with contact force measurement, since the reconnection rate with contact force catheters are lower than with the standard RF catheters (8% vs. 35%).[20] Therefore, when designing an outcome study the VGLB should be compared against contact force RF catheter.

6 | CONCLUSION

The acute reconnection rate after PVI with VGLB ablation is significantly less than after PVI with RF, which means that the lesion sets created with VGLB is more durable in the acute phase than the lesions created with RF. If this better efficiency will translate into better clinical outcomes after PVI for paroxysmal AF should be tested with adequately powered randomized studies comparing VGBL with RF.

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