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Substrate Targeted Ablation of Atrial Fibrillation Guided by High Density Voltage Mapping: Long-Term Results

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Abstract

Background: Long-term ablation results for atrial fibrillation (AF) have been disappointing, particularly for non-paroxysmal AF (NPAF). We hypothesize fibrosis in paroxysmal AF (PAF) and NPAF would be reflected in voltage fragmentation and visualized by high density mapping. Targeted ablation of discrete low voltage bridges (LVB) would eliminate endocardial fragmentation and should have a positive effect on long-term sinus rhythm (SR) survival.

Objective: To assess the efficacy of LVB ablation on SR survival in patients with PAF and NPAF, as well as, determine its impact on P wave duration (PWD) and LA volume (LAV).

Methods: 56 patients (29PAF/26NPAF) had a voltage gradient map (VGM) created, high and low voltage limits were adjusted to image LVB. Ablation was performed until no LVB were observed. Baseline PWD and LAV were obtained and reassessed 6 months' post ablation. Patients were followed for 5 years with intermittent monitors.

Results: Termination of AF in NPAF was 88%. PWD normalized in PAF and were normal in NPAF post ablation. LAV decreased significantly in NPAF. At 5 years, SR was observed in 89% of PAF and 67% of NPAF.

Conclusion: 1. LVB ablation terminates AF in NPAF 88%; 2. Both PWD and LAV were improved; 3. Maintenance of SR was observed in 89% and 67% (PAF vs NPAF); 4. The present study demonstrates efficacy of a simplified, individualized, and unified methodology for AF ablation.

Introduction

The long-termresults of atrial fibrillation ablation have been disappointing. While the initial sinus rhythm (SR) survival in patents with paroxysmal AF (PAF) is reported to be around 70-80%, multiple reports suggest that 5-year SR survival is 27-59 %[1,2,3]. In patients with persistent AF (PrAF), the success of pulmonary vein isolation (PVI) alone has not been encouraging. Recent comparison of PVI in these patients with and without ancillary ablation targets suggests no improvement in short-term outcomes despite added ablation targets[4]. Multiple methodologies have been advanced in addition to PVI, including complex fractionated atrial electrograms (CFAE), ganglion, rotors, or linear ablation. None appear to alter either initial success or long-term efficacy [5,6,7]. Several studies have evaluated low voltage regions of the LA as ablation targets[8,9,10,11]. The results have been more encouraging especially regarding PrAF. Low voltage areas have been treated byisolation (boxing), homogenation (via mass lesions), or electrogram guidedablation.

Key Words

Atrial Fibrillation, Catheter Ablation, High Density Voltage Mapping.

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In the present study, we present the long-term out come in patients undergoing ablation targeting focal low voltage bridges (LVBs) found during high density voltage mapping. We hypothesize that, by ablating these LVBs, the electrical end ocardial fragmentation seen in PAF and PrAF may be treated. This approach both simplifies atrial ablation and unifies ablation methodology for both PAF and PrAF. Further, we hypothesize that by eliminating endocardial fragmentation, long-term electrical stability may be maintained. To test this hypothesis, we evaluated the utility of VGM with LVB targeting in 54 consecutive patients undergoing initial AF ablation of PAF (29 patients) or PrAF (25patients).

Methods

Mapping Technique

Informed clinical consent was obtained from all study participants. The institutional review board of Iowa Heart Center, Des Moines, Iowa approved the study. Since this is a retrospective cohort analysis the need for informed consent for analysis was waived. 54 consecutive patients undergoing AF ablation had VGM guided substrate ablation (SA) performed. We have previously reported this methodology for visualization of the slow pathway, CTI for Atrial flutter ablation, and atrial fibrillation [12,13,14]. Utilizing the SJM Velocity 3D mapping system,

electrograms were collected with a 20-pole circular catheter (Reflection HD, SJM) and 1500- 2000 electrograms were recorded from the LA and pulmonary veins (PV). The ablation catheter was used to collect electrograms within the PVs when required. The high and low voltages settings were adjusted to image LVB which were defined as regions of higher voltage connected by a LVB. The voltage settings were based on individual patient values in order to define the LVB. The maps were generated in SR or AF. When possible, maps were created in both SR and AF. Since relative voltage was used, the absolute voltage settings varied between patients and was dependent upon the rhythm mapped (AF voltages were lower). Voltage settings were readjusted on re maps following ablation. Detection was set toabsolute peak with manual review for consistency over a 10-beat recording associated with each point. Internal projection was adjusted to 5-10 mm depending on visualizing consistent LVB with interpolation at the lowest setting creating a consistent VGM typically 10mm.

Ablation Technique

Following adjustment of the voltage settings, LVBs were identified and targeted for focal ablation. Pulmonary Vein Isolation:LVBs entering the PVs were targeted at the antrum to isolate the PV; rarely a short linear lesion was required at the PV antrum when high voltage entered the vein, or when there was a broad LVB noted. PVs were isolated in all patients and confirmed by the absence of voltage within. Absence of recorded voltage within the PV corresponded to inability to pace the LA from the PV. Figure 1 shows the impact of LVB ablation on PV isolation. As noted, an isolated PV potential is observed within the PV.

Ablation of LVB within the LA: Radiofrequency ablation was applied to the LVBs focally on the the LA roof, LA septum, anterior and posterior walls. RF was applied until there was loss of endocardial electrograms (typically <20 seconds per application). A non-irrigated 8 mm RF catheter was used (Blazer, BS). Termination of AF in patients with PrAF was recorded. Post ablation induction protocol included burst pacing from the RAA and CS at 10mV and 10ms until pacing refractoriness was achieved.No special electrogram criteria was utilized to determine LVB ablation priority. Linear lesions were only used as noted above and were not connected to anatomic or created regions of block.

Ablation Endpoints

Primary endpoints of the ablation were absence of connecting LVBs within the endocardium, and inability to induce AF or tachycardia following ablation (PrAF and PAF). A final map was createdto confirm absence of connecting LVB.

Table 1: The average voltage setting are noted before and after LVB ablation are provided

	LV Pre	LV Post	HV Pre	HV Post
PAF	0.33 + 0.18	0.17 + 0.12	1.44 + 0.36	0.95 + 0.47
NPAF	0.23 + 0.2	0.15 + 0.08	0.99 + 0.4	0.23 + 0.19
P value	NS	NS	0.003	NS

There was a significant difference between the high voltage setting between patients with PAF and NPAF. Additionally, the voltage setting were decreased post ablation in order to image residual LVB. (adopted from Bailin, etal. [12])

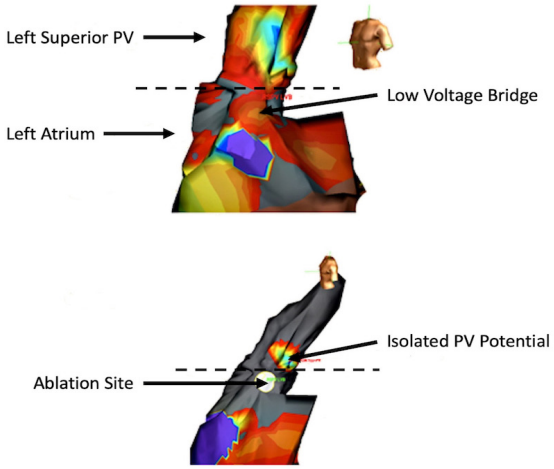

Figure 1: Pulmonary vein isolation by focal ablation of entering LVB
A low voltage bridge (LVB) is seen entering the left superior pulmonary vein from the left atrium. Ablation of the LVB electrically isolates the pulmonary vein. A spontaneous pulmonary vein potential is observed and does not enter the left atrium

Follow-up

Periodic monitors were used throughout the follow-up period to document ambient rhythms (30-day event and 48 hourholter) typically at 6 months and yearly or when there were symptomatic complaints. Patients with documented symptomatic AF or AT recurrences underwent drug therapy or repeat ablation. Failure was defined by an atrial arrhythmia > 30 seconds in duration.

Statistical analysis

In the PAF and the PrAFcohorts continuous variables were mentioned as mean (standard deviation) or median (interquartile range) depending on the normality of data distribution. Categorical variables were mentioned as number (%). Baseline and 5 year follow-up of continuous variables were compared using student't' test or Wilcoxon rank sum test depending on the normality of data distribution. Categorical variables at 5 year follow-up were compared to baseline using Chi square test. Unadjusted Kaplan-Meir survival curves were calculated for the PAF and the PrAF cohorts separately during the

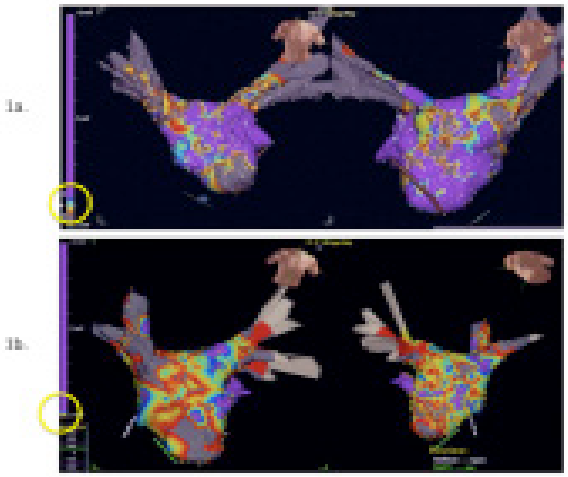

Figure 2: Overall voltage is higher in patients with PAF compared to patients with NPAF. Low voltage bridging is seen as yellow-red bands connecting regions of higher voltage which is prominent in panel b. (adopted from Bailin, etal. [12]).

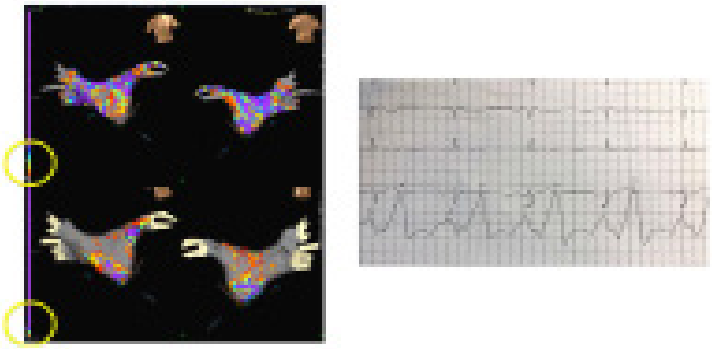

Figure 3: Baseline voltage map is seen in a. Following ablation of LVBs the endocardial voltage is markedly reduced. No further atrial arrhythmia is inducible, b. Despite loss of endocardial voltage, atrial mechanical function is preserved, as seen in the "a" wave recorded from LA pressure waveform, c.

5 year follow-up for the outcome of SR survival. All analysis were performed using STATA statistical software and a P value < 0.05 was considered statistically significant.

Results

The mean age of the total cohort was 58 years (PAF: 56 years and PrAF: 59 years). There were 48% and 41% female participants in the PAF and PrAF cohorts respectively. On an average participants in both groups had failed at least 2 antiarrhythmic medications. Both groups had normal left ventricular ejection fractions at baseline (mean 57%). Left atrial volume was 46.6 and 54.1 in the PAF and PrAF cohorts at baseline.

Figure 1(Representative figure) shows a typical VGM created with high density mapping in PAF (a) and PrAF (b). In comparison, patients with PAF had higher overall atrial voltages and less endocardial fragmentation reflected by the large areas of uniform high voltage.In PrAF patients there was severe endocardial fragmentation with large areas of low voltage containing numerous LVBs.

All patients had absence of LVBs at the end of the ablation. Inability to induce AF or tachycardia correlated to the absence of connected LVB observed on repeat mapping.Inability to induce tachycardia was observed in 95% of patients. Figure 3shows the pre (a) and post ablation (b) VGM. There was asignificant absence of voltage and endocardial fragmentation. A hemodynamic tracing (c) from a patient demonstrates atrial contraction despite the change in endocardial voltage and is consistent withpreservation of mechanical function.

Termination of PrAF with conversion to SR was observed in 88% of patients after LVB ablation.

Table 1 lists the voltage settings used in PAF and PrAF patients. In patients with PrAF, the average high voltage setting was significantly reduced compared to PAF patients, <1.0 mV vs 1.49 mV. Unlike other studies, no fixed voltage setting was used to define the low voltage area. The purpose of the voltage adjustment was to adjust the relative voltages to define LVB within the endocardium.

There was a significant difference between the high voltage setting between patients with PAF and PrAF. Additionally, the voltage setting were decreased post ablation in order to image residual LVB. (adopted from Bailin, etal. [12])

The impact of LVB ablation on surrounding endocardium may be seen in figure 4. As can be seen, ablation limited to the LVB can result in large areas of voltage loss. Targeting of the LVB is therefore efficient in altering the atrial substrate (see figures 4a,b,c).

Total RF lesions delivered ranged between 60 and 137 with an average lesion time of 20 seconds. An average of 2.8 maps were created during the case.

Overall single procedure success was 61% (33/54), with 72% single procedure success for patients with PAF compared to 48% in patients with PrAF. Average number of procedures per patient was 1.25 for PAF and 1.4 for PrAF patients. In the PAF group, most recurrences were micro re-entry atrial tachycardia, usually mitral isthmus flutter. In both groups, AF recurrence was associated with poor outcome following a second procedure (<10% success). Figure 4 details the success rates for first and second procedures in both groups.

Table 2 shows the effect of SA upon P wave duration and LA Volume. P wave duration was normalized in patients with PAF (p=0.0001) and normal in patients with PrAF (PWD 101.2 + 32.8). LA volume tended to be smaller in patients with PAF but was not significant (p=0.12),

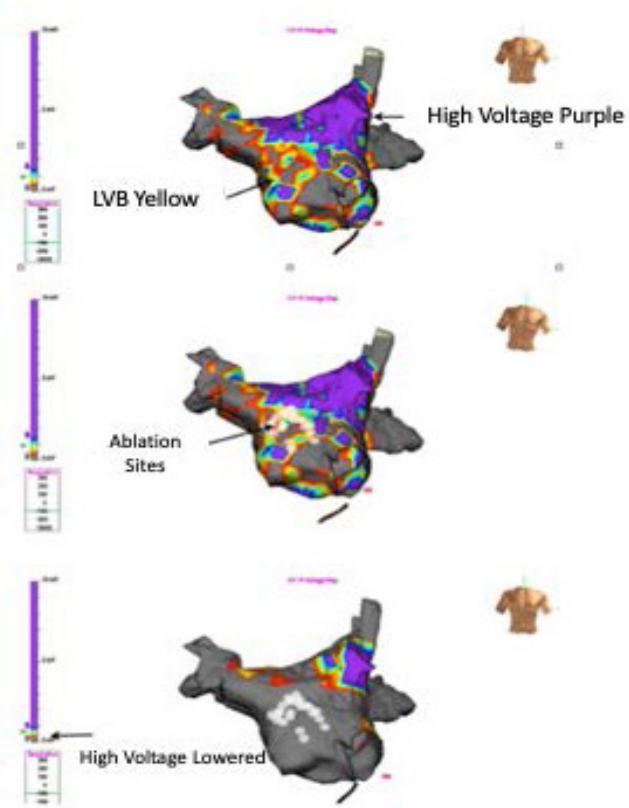

Figure 4: As can be seen, ablation limited to the LVB affects the voltage in surrounding endocardium, suggesting that the LVB provides inputs to surrounding endocardial areas. (adopted from Bailin, et al. [12]).

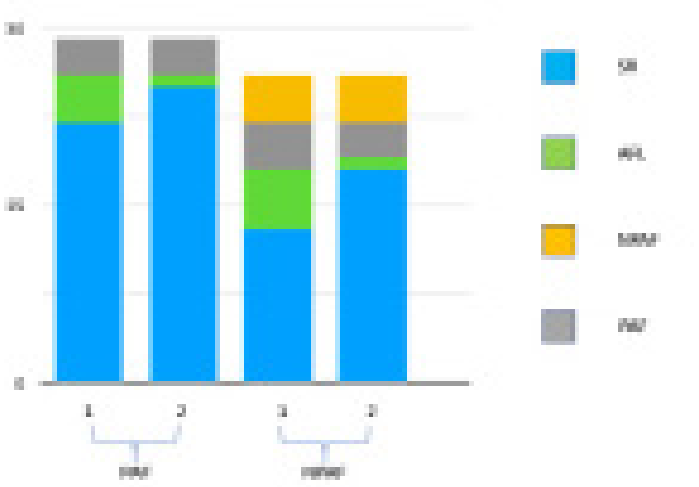

Figure 5: **Outcomes of first and second procedure. The graphs detail the outcomes of first and second procedures in our study cohort**

while LA volume was significantly decreased in patients with PrAF (p=0.029).

There was a significant decrease in PWD in patients with PAF and a normal PWD in patients with PrAF following LVB ablation. LAv tended to be smaller following LVB ablation in patients with PAF while a significant decrease in LAv was observed in patients with PrAF. These findings suggest positive electrical and mechanical remodeling following LVB ablation.

Figure6 shows the 5-year Kaplan-Meir arrhythmia free survival curve for PAF (a) and PrAF (b). Over a five-year follow-up period 89% of PAF patients and 67% of PrAF patients remained in SR. 18% of PAF and 25% of PrAFrequired antiarrhythmic therapy.

Discussion

Substrate ablation by targeting LVBs observed during VGM results in isolation of the PVs, termination of AF, and inability to induce AF or AT. Additionally, long term outcomeyields stable results. In the present study, endocardial fragmentation was eliminated by ablation of connecting LVB. In 95% of patients no AF or AT was inducible following SA. Long term, 89% of PAF and 67% of persistent AF remained in SR at 5 years which compares favorably to previous studies [1,2,3].

Following substrate modification, most recurrences of atrial arrhythmia were macro re-entry atrial flutter, especially in patients with PAF. Subsequent ablation of the mitral isthmus was successful in terminating tachycardia and prevented arrhythmia recurrence during follow-up. In the present study, ablation of the mitral isthmus during the first procedure was not routinely performed. Based on the recurrence of mitral re-entry atrial flutter, we recommend creation of mitral isthmus block during the first procedure when performing atrial substrate ablation. In patients presenting with recurrent AF following substrate ablation, repeat ablation was usually unsuccessful. We observed that in some patients, organization of the left atrium was accompanied by AF localized to the right atrium, usually within the right atrial appendage (RAA). Attempted ablation within the RAA or RAA isolation was not successful in these patients. In other patients, despite absence of endocardial fragmentation, AF persisted, suggesting the possibility of an epicardial contribution to maintenance of AF. The higher rate of AF following endocardial substrate ablation in PrAF patients, in particular, would be consistent with greater disease burden and electrical fragmentation of the epicardium analogous to that seen in the endocardium. Such an evaluation would require epicardial mapping not performed in this study.

Table 2: **The impact on P wave duration (PWD) and LA Volume (LAv) is provided.**

	PWD Pre	PWD Post	P value	LAV Pre	LAV Post	P
PAF	120 ± 5.7	96.9 ± 5.1	< 0.001	46.6 ± 9.9	39.5 ± 7.7	0.12
NPAF	NA	101.2 ± 32.8	NA	54.1 ± 11.4	41.5 ± 8	0.029

There was a significant decrease in PWD in patients with PAF and a normal PWD in patients with PrAF following LVB ablation. LAv tended to be smaller following LVB ablation in patients with PAF while a significant decrease in LAv was observed in patients with PrAF. These findings suggest positive electrical and mechanical remodeling following LVB ablation.

The importance of low voltage regions within the atrium has been reported[15,16,17]. Overall long-term outcomes are worse when there are residual low voltage regions[18]. Indeed, most studies have demonstrated a positive effect on outcome when low voltage regions are addressed by ablation. Further, because AF is a progressive disease, fibrosis and loss of gap junctions continue, leading to greater endocardial fragmentation and worsened outcomes impacting long term success in patients with PAF[19,20].

Previous studies have evaluated the link between endocardial low voltage regions and fibrosis detected by MRI or CT[21]. These studies show the stage of AF to be related to the degree of atrial fibrosis observed. The present study confirms that patients with PAF have less endocardial fragmentation than patients with PrAF as observed by VGM.

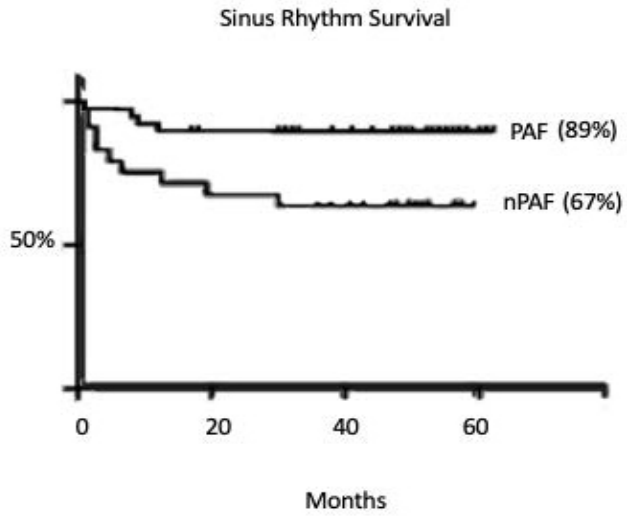

Figure 6: **Kaplan-Meier survival curves in the PAF and NPAF cohorts. Kaplan-Meier curves showing the 5 year arrhythmia free survival in patients with PAF NPAF**

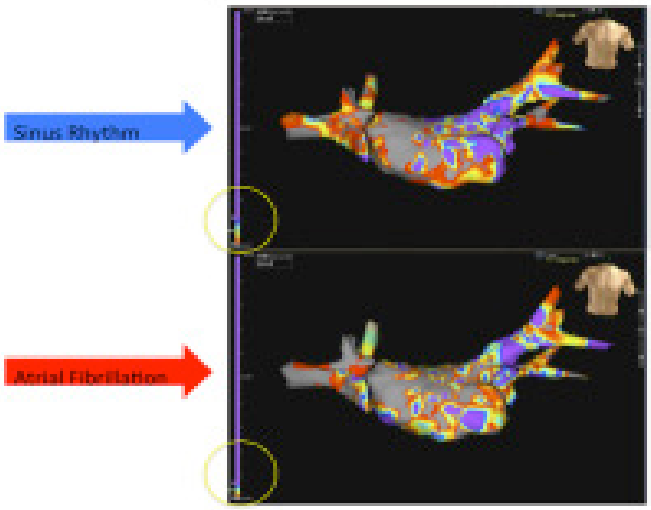

Figure 7: **Voltage maps in AF and sinus rhythm. While recorded in different rhythms, the voltage maps of AF and SR are remarkably similar. The voltage settings are lower in AF, but the voltage maps demonstrate that the substrate remains consistent**

The following evidence support the relevance of LVB to atrial substrate.

1. Because the VGM reflects the underlying endocardial substrate, we would expect that VGMs recorded during SR should be similar to VGMs recorded during AF. The primary difference being the lower voltages associated with AF. As noted in figure 6 7, a SR and AF recording are strikingly similar and supports the hypothesis that the VGM reflects underlying substrate as it is independent of the rhythm recorded.

2. Focal ablation of LVB results in significant changes to regional voltage (fig 3 4). This unexpected effect may be explained if the LVB represents points of critical input into a protected endocardial region. In this way, the atrial endocardium may be divided by selective fiber input to high voltage regions. Ablation of the critical input, renders that endocardial segment electrically silent.

3. The degree of atrial endocardial fragmentation correlates with the disease state: patients with PAF have less fragmentation and LVBs compared to patients with persistent AF [see fig 1 2 (representative figure)]. There is a clear correlation of fibrosis to the stage of AF as noted in previous trials and MRI data[19,21].

4. Absence of residual LVB and endocardial defragmentation is associated with termination of AF, and inability to induce atrial dysrhythmia acutely. It is also associated with sinus rhythm stability in the long-term. Despite the significant loss of endocardial voltage, indices of LA health were observed as evidenced by normalization of PWD; preservation of mechanical function; and normalization of LA volume.

Long-term results demonstrate the importance of substrate modification on maintenance of SR. In the present study, the 5-year SR survival rate in patients with PAF was 89%, and with67% persistent AF.In patients with PAF, elimination of potential progressive fragmentation of the atrial endocardiumis prevented compared to PVI, where ablation is limited to the regions surrounding the PVs and large areas of the endocardium is left intact. Our methodology allows individualization of AF therapy based on patient specific substrate rather than anatomic PV isolation.

Targeting LVB in PrAF similarly results in stable long-term arrhythmia free survival. The stability of this outcome supports the hypothesis that initial "endocardial defragmentation" by targeting LVBs is effective in preventing recurrent AF in both PAF and PrAF patients. Thus, we suggest that the same ablation methodology may be used for patients with PAF and patients with PrAF.

An interesting effect of substrate modification via VGM is the finding that the p wave duration invariably decreases following ablation (120 to 97 p=0.0001). LA activation is primarily an epicardial dependent phenomenon. Bachmann's bundle crosses the anterior atrial septum epicardially and then inter-digitates with fibers around the LAA and between the PV posteriorly. Thus, non-linear, focal, and potentially non-transmural lesions may be advantageous for preserving normal epicardial conduction. Additionally, evidence of positive remodeling is seen in normalization of LA volumes following SA via LVB ablation.

Recent studies have also evaluated targeting low voltage for ablation. In a paper by Hassiguirre[13], LA areas were targeted based upon electrogram characteristics. Regions of low voltage were defines as <0.5mV and ablation was applied to sites with evidence of fractionated electrical activity (>70% of AF cycle) or rotational activity. They reported a 78% termination rate which is similar to the present study. However, in the present study, the analysis of complex electrograms is not required, and offers a simplified methodology based on LVB targeting.

In the study by Rolf[8], low voltage areas defined by voltage <0.5mV were isolated by "boxing" them or placing linear lesions through them. They reported a successes rate of 70% over a 1-year period. A paper by Yamaguchi9 defined low voltage zones as voltage <0.5mV and placed lesions within the zone to homogenize the voltage. They reported a near-term success rate of 72% In PrAF. These studies show the benefit of focusing upon low voltage regions within the endocardium. In the

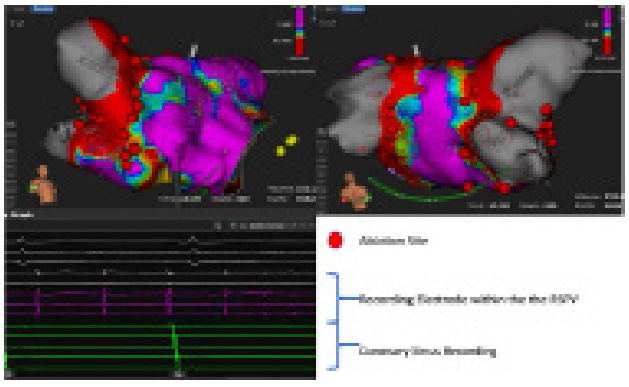

Figure 8: **While not circumferential and contiguous, ablation of LVB entering the PV results in PVI. As can be seen, SR is recorded in the CS, while within the PV, an atrial tachycardia persists. Both entrance and exit block exist.**

present study, we differ by using a relative voltage with no lower limit upon the low voltage setting. In this way, the LVB can be imaged and focally ablated. Additionally, our methodology does not require large lesion sets to be created, rather, it identifies focal areas to be ablated (LVB).

Limitations

Although encouraging, a multicenter trial duplicating these results will be important to confirm the validity of this study. Specifically, the ability to duplicate the VGM across multiple centers and a larger patient population. At present, the VGM requires manual adjustment of the high and low voltage settings. This may pose a barrier to wider adaptation. Additionally, elimination of artifact or premature atrial beats is required to validate the map and at present requires a manual review of questionable voltage points. Further, this methodologyhas only been validated in the velocity system from SJM. This methodology may not be applicable to other mapping systems.

Conclusion

Atrial fibrillation is a progressive disease of fibrosis and loss of intercellular connection. These changes are reflected in the substrate map created by VGM. As the disease persistence progresses, there is loss of atrial voltage and more importantly, an increase in atrial endocardial fragmentation. By targeting the LVB spanning these fragments, AF can be terminated in PrAF and results in inability to induce atrial dysrhythmia in all patients. Beneficial effects on PWD and LA volume were observed. Additionally, SR was maintained over a long follow-up period of 5 years in both patients with PAF and PrAF. This methodology offers a simplified and unified technique for successful ablation of AF. These results should stimulate interest in further studies of VGM guided AF ablation.

Conflict of interest

Steven Bailin, intellectual property (patent) for voltage gradient mapping. No other authors declare conflicts.

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