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Shohreh Honarbakhsh, MRCP BSc, Richard J. Schilling, MRCP MD, Michele Orini, PhD, Rui Providencia, MD, Emily Keating, BAppSc, Malcolm Finlay, MRCP PhD, Simon Sporton, FRCP MD BSc, Anthony Chow, FRCP MD, Mark J. Earley, MRCP MD, Pier D. Lambiase, FRCP PhD, Ross J. Hunter, FESC PhD.

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Shohreh Honarbakhsh* MRCP BSc, Richard J Schilling* MRCP MD, Michele Orini* PhD, Rui Providencia* MD, Emily Keating* BAppSc, Malcolm Finlay* MRCP PhD, Simon Sporton* FRCP MD BSc, Anthony Chow* FRCP MD, Mark J Earley* MRCP MD, Pier D Lambiase* FRCP PhD, Ross J Hunter* FESC PhD.

*Barts Heart Centre, Barts Health NHS Trust, London, United Kingdom

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Corresponding Author:
Dr Ross J Hunter
Consultant Electrophysiologist
Barts Heart Centre
Barts Health NHS Trust
W. Smithfield
26 EC1A 7BE

27 Email: ross.hunter@bartshealth.nhs.uk

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ABSTRACT

Background- Rate-dependent conduction velocity (CV) slowing is associated with atrial fibrillation (AF) initiation and reentry mechanisms.

Objectives- Assess the relationship between bipolar voltage, CV dynamics and AF drivers.

Methods- Patients undergoing catheter ablation for persistent AF (<24 months) were enrolled. Unipolar electrograms were recorded with a 64-pole basket catheter during atrial pacing at four pacing intervals (PIs) during sinus rhythm. CVs were measured between pole pairs along the wavefront path and correlated with underlying bipolar voltage. CV dynamics within low voltage zones (LVZs <0.5mV) were compared to those of non-LVZs (≥0.5mV) and were correlated to driver sites mapped using CARTOFINDER.

Results- Eighteen patients were included (age 62±10 yrs). Mean CV at 600ms was 1.59±0.13m/s vs. 0.98±0.23m/s, in non-LVZs and LVZs respectively (p<0.001). CV decreased incrementally over all four-PIs in LVZs whilst in non-LVZs a substantial decrease in CV was only seen between PI 300-250ms CLs (0.59±0.09m/s; p<0.001). Rate-dependent CV slowing sites measurements, defined as exhibiting a CV reduction ≥20% more than the mean CV reduction seen between PIs 600-250ms for that voltage zone were predominantly in LVZs (0.2-0.5mV, 75.6±15.5%; p<0.001). Confirmed rotational drivers were mapped to these sites in 94.1% of cases (sensitivity 94.1%, 95%CI 71.3-99.9% and specificity 77.9%, 95%CI 74.9-80.7%).
Conclusions- CV dynamics are determined largely by the extent of remodeling. Rate-dependent CV slowing sites are predominantly confined to LVZs [0.2-0.5 mV] and the resultant CV heterogeneity may promote driver formation in AF.

Keywords: Conduction velocity, atrial fibrillation, bipolar voltage, structural remodeling, drivers
INTRODUCTION

The effect of structural remodeling on human left atrial conduction velocity (CV) has been studied previously (1). Low voltage zones (LVZ) defined by bipolar voltage (1) and late gadolinium enhancement on cardiac MRI (2) have demonstrated lower local CVs, which may promote reentry. This forms the rationale for current strategies ablating LVZs for atrial fibrillation (AF) (2, 3).

A direct relationship between bipolar voltage and CV in the human left atrium (LA) has not been established. It is therefore unclear how CV changes over the spectrum of structural remodeling seen in AF. CV dynamic curves in myocardial tissue demonstrate a steep CV reduction with a decrease in pacing interval (PI) (4). With the presence of structural remodeling these curves are shifted to the right, whereby the rate-adapted CV slowing occurs at longer PIs (5). These differences in CV dynamics have been shown to contribute to reentry (4). Sites with marked slowing of CV with increasing rate, i.e. rate-dependent CV slowing, have been shown to be associated with the ability to induce AF (5) and correspond to sites of reentry initiation at AF onset (6).

We aimed to determine the interaction between remodeling through analyzing LVZs and local CVs in the human LA utilizing a 64-pole basket catheter. CV dynamics were compared across a range of voltages and the presence of rate-dependent CV slowing was evaluated. The CARTOFINDER mapping system was used to map AF (7), to assess whether abnormalities in CV dynamics are directly linked to the mechanisms sustaining AF.
METHOD

i) Study design

Patients undergoing catheter ablation for persistent AF (<24 months and no previous ablation) and in sinus rhythm at the start of the case (prior direct current cardioversion) were included. Patients provided informed consent and the study was approved by the UK Research Ethics Committee (London-Bloomsbury Research Ethics Committee, 16/LO/1379).

ii) Electrophysiological mapping

Mapping was performed with CARTOFINDER (CARTO, Biosense Webster, Inc, CA) (7, Supplemental Method).

LA geometry and high-density bipolar voltage map were created using a PentaRay® NAV catheter with 2-6-2mm electrode spacing (Biosense Webster, Inc, CA) (Supplemental Method). Voltage zones were defined as non-LVZs ≥0.5 mV, LVZs [0.2-0.5mV] and very LVZ (vLVZ) [0-0.2mV] (8). Unipolar electrograms were obtained from LabSystem Pro electrophysiological recording system (Bard Electrophysiology Division, MA) by referencing to a decapolar catheter (Biosense Webster, Inc, CA) positioned in the IVC. The filter bandwidth was 0.05-500Hz.

A 64-pole basket catheter (Constellation, Boston Scientific Ltd, Natick, MA or FIRMap, Abbott, CA, USA) was used to record unipolar signals. This was positioned in the LA to achieve the best possible atrial coverage (9).

iii) Pacing procedure
To achieve wavefront propagations in different directions, atrial pacing was performed in sinus rhythm with the ablation catheter from four sites: proximal and distal coronary sinus (CS) (endocardialy), LA roof and LA appendage. Uninterrupted pacing was performed at four PIs, 600ms, 450ms, 300ms and 250ms. For each PI, 30-seconds of unipolar electrograms were recorded at a sampling frequency of 2000Hz. A location point was also taken on CARTO to obtain 3D coordinates for each pole.

iv) Local CVs

CV was defined as the geodesic distance divided by the activation time difference and expressed in m/s (Supplemental Method).

v) CV dynamics and bipolar voltage

Using a MATLAB custom written script the position of the electrode pairs included in the analysis and bipolar voltage points taken with the PentaRay catheter was projected onto the LA geometry. The bipolar voltage points were considered within a 5mm band between the electrodes from which CV was assessed. The mean of these was taken as the local bipolar voltage along the path between each electrode pair and used to define the voltage zone along the path.

Where the distance between electrodes for measurement of CV was seen to traverse different voltage zones then measurements were excluded so as to avoid CV measurements over heterogenous tissues. CV at each PI was compared in the three voltage zones. To evaluate for heterogeneity in CV dynamics within LVZs and non-LVZs, sites of rate-dependent CV slowing were identified. These were defined as zones exhibiting a reduction in CV between PI=600ms and PI=250ms of ≥20% more than the mean CV reduction seen between these PIs for that voltage zone.
vi) CV and AF driver sites

AF was induced following the study protocol by burst atrial pacing from the CS (Supplemental Method).

CARTOFINDER maps were then created pre and post-pulmonary vein isolation (PVI) and the maps post-PVI were used to guide further ablation. A potential driver was defined as either i) focal with radial activation over ≥2 consecutive wavefronts or ii) rotational activity with ≥1.5 rotations of 360 degrees (7). Confirmed drivers were defined as sites where ablation terminated AF into an AT or sinus rhythm or slowed AF CL by ≥30ms (7).

vii) Ablation strategy

The ablation strategy used in this study has previously been defined (7, Supplemental Method).

Statistical analysis

This was performed using SPSS (SPSS Statistics, Version 24 IBM Corp, Armonk, NY, USA). Continuous variables are displayed as mean ± standard deviation (SD). Categorical variables are presented as a number and percentage. Chi-square was used for the comparison of nominal variables. The Student t-test, or its non-parametric equivalent, Mann-Whitney U test when appropriate was used for comparison of continuous variables. Spearman rank-order correlation was used to assess the strength and association between CV and bipolar voltage. Paired Student t-test was used to compare CVs obtained for each PI. One-Way ANOVA was used to compare the CV changes over the PIs between voltage zones. ROC curves were performed to
determine the diagnostic ability of different parameters in predicting driver sites. P-value <0.05 were regarded as significant.

RESULTS

Eighteen patients were included (Supplemental Table 1).

i) Bipolar voltage and CV

15,363 bipolar voltage points were taken with an average of 854±240 points per patient, of which 487±188 points were <0.5 mV (57±22%). The mean bipolar voltage was 0.43±0.18mV. LVZs were found to occur as islands or plaques each one covering a minimum of 10% of the LA surface (29±15%). LVZs predominantly affected the anterior wall (33%) (Figure 1A-B).

CV was determined over a total of 3197 electrode pairs with a mean of 45.8±8.2 pairs for each activation sequence in each patient. At a PI of 600ms mean CV was higher in non-LVZs than LVZs (Figure 2A). There was a positive correlation between the mean CV for a patient and both mean bipolar voltage ($r_s=0.95$, $p<0.001$; Figure 3A) and proportion of non-LVZs ($r_s=0.87$, $p<0.001$; Figure 3B).

ii) CV dynamics and bipolar voltage

As shown in Figure 2A and Supplemental Table 2, CV dynamics significantly differed at sites of non-LVZs, LVZs [0.2-0.5] and νLVZs [0-0.2mV]. In non-LVZs, CVs only significantly change between PIs of 300-250ms (0.59±0.09m/s; $p<0.001$) with a total average reduction of 62.9±6.9% between PIs 600-250ms whilst the activation time increased by an average of 12±5ms. In LVZs [0.2-0.5mV] there was a progressive decrease in CV between all four-PIS with a total average reduction of...
23.7±13.6% between PIs 600-250ms. The activation time increased by an average of 9±3ms. In vLVZs [0-0.2mV] there was minimal change in CV with increased pacing rate (mean change of 0.02±0.02m/s over each PI; p=0.48).

iii) Relationship between rate-dependent CV slowing sites and bipolar voltage

For each pacing site, a mean of 10.7±4.3 rate-dependent CV slowing measurements were observed per patient (24.0±11.9% of sites sampled) with a mean of 1.46±0.64 rate-dependent CV slowing sites per patient (total of 41 rate-dependent CV slowing sites in the 18 patients) which were spatially stable. The rate-dependent CV slowing site measurements were significantly more common in LVZs than non-LVZs (75.6±15.5% vs. 24.4±15.0; p<0.001; Figure 2B). In all, 14.0±4.3% of LVZs exhibited rate-dependent CV slowing compared to 7.8±4.8% of non-LVZs (p<0.001). Rate-dependent CV slowing sites were more prevalent in patients with a lower mean bipolar voltage ($r_s=-0.91$, p<0.001). Rate-dependent CV slowing sites were more commonly mapped to the anterior (37%) and posterior (24%) wall, which correlated to sites where LVZs were more frequent (Figure 1A-B).

The rate-dependent CV slowing sites in LVZs were all LVZs [0.2-0.5mV] and showed progressive decrease in CV over all four PIs (mean decrease in CV of 0.12±0.03m/s for each PI) resulting in broader curves. The rate-dependent CV slowing sites in non-LVZs showed greatest decrease in CV between PIs of 300-250ms (mean decrease in CV of 0.70±0.09m/s; p=0.001) with minimal change at longer PIs, resulting in a steeper curve.

iv) Relationship between LVZs and rate-dependent CV slowing and drivers
In the 18 AF patients, 29 possible drivers were identified using the CARTOFINDER system (1.6±0.7 drivers per patient; n=18 rotational activity and n=11 focal activity). Ablation at 25 of the 29 driver sites (n=8 focal and n=17 rotational; 86.2%) resulted in an effect that met the study criteria of a confirmed driver (Table 1). With four drivers the pre-defined ablation response was not seen on ablation (n=3 focal and n=1 rotational).

The drivers demonstrated spatial stability but temporal periodicity with a consecutive repetition of 3.8±1.1 and a recurrence rate of 8.2±4.8 times per 30-second recording.

Eighteen of the 25 confirmed AF drivers were mapped to LVZs (72.0%), which included 15 of the 17 confirmed drivers with rotational activation (88.2%) but only 3 out of 8 confirmed drivers with focal activation (37.5%; p=0.02). The mean bipolar voltage was 0.33±0.10mV at the confirmed driver sites. No drivers were identified in vLVZs.

Eighteen of the 25 confirmed drivers (72.0%) were found at rate-dependent CV slowing sites (Supplemental Figure 1 and Supplemental Table 3), which included 16 of the 17 confirmed drivers with rotational activation (94.1%) but only 2 out of 8 (25.0%) with focal activation (p=0.001). Notably 15 out of the 18 (83.3%) confirmed drivers that resulted in AF termination were mapped to rate-dependent CV slowing sites (Figure 4A-D).

v) Potential predictive factors of confirmed driver sites
LVZs predicted driver sites with a sensitivity of 72.0% (95%CI 50.4-87.1%) and specificity of 43.4% (95%CI 40.0-46.9%).
Rate-dependent CV slowing sites showed a sensitivity and specificity of 72.0% (95%CI 50.6-87.9%) and 78.1% (95%CI 75.0-80.9%), respectively, for predicting confirmed driver sites in AF and a sensitivity and specificity of 94.1% (95%CI 71.3-99.9%) and 77.9% (95%CI 74.9-80.7%) respectively for predicting drivers with rotational activity. When only including the 18 confirmed drivers mapped to LVZs, rate-dependent CV slowing sites showed a sensitivity and specificity of 83.3% (95%CI 57.7-95.6%) and 83.7% (95%CI 81.0-86.2%) respectively for predicting AF driver sites. Table 2 demonstrates the value of different factors in predicting AF drivers mapped to LVZs.

DISCUSSION

This is the first study to assess the interaction between CV dynamics and bipolar voltage in the human LA. A direct correlation between CV and bipolar voltage was observed. However, CV dynamics were not determined entirely by the presence or absence of LVZs, and not all LVZs were associated with rate-dependent CV slowing. Although CV was slowest in vLVZs [0-0.2mV], these zones did not exhibit rate-dependent CV slowing. Sites of rate-dependent CV slowing predicted the sites of rotational activity in AF with high sensitivity and specificity, supporting the hypothesis that rate-dependency of CV dynamics is mechanistically important in the development of reentrant arrhythmias.

i) CV and bipolar voltage

LVZ were clustered in relatively large regions rather than scattered throughout the myocardium. The focal nature of this remodeling process has been observed previously (9), and enabled an accurate assessment of CV dynamics within these
zones. CV at 600ms PI was reduced by around 15% in LVZ [0.2-0.5 mV] and 40% in vLVZs [0-0.2mV] compared to non-LVZs ≥0.5mV, suggesting that CV slows progressively with fibrosis. The strong correlation between mean CV and both mean bipolar voltage and proportion of non-LVZs demonstrates a strong link between structural and electrical remodeling.

ii) CV dynamics and bipolar voltage

CV dynamics curves alter with structural remodeling (4) which was consistent with the study findings. With structural remodeling there is replacement of myocardial tissue by fibrosis (6), alteration in gap junction communication (11) and coupling of myocytes with fibroblasts (12). These phenomena may contribute to the slowing of conduction and altered CV dynamics seen in LVZs.

Atrial CV dynamics curves have not previously been studied in relation to structural remodeling. Patients with persistent AF have been shown to have broader CV dynamics curves than those with paroxysmal AF (5, 13). The finding that areas of structural remodeling have broad CV dynamics curves may explain this finding, since atria in patients with persistent AF are often more dilated and scarred than those with paroxysmal AF (14).

iii) Relationship between rate-dependent CV slowing and drivers

Rate-dependent CV slowing sites were predominantly located in LVZs and their prevalence increased with the proportion of the atrium made up by LVZs. Interestingly, they were limited to LVZs [0.2-0.5mV]. This is probably because this tissue is healthy enough to be capable of near normal CV at longer PIs (600ms), but is abnormal enough to reduce CV significantly with shorter PIs (<600ms). In vLVZs [0-
0.2mV] tissue is likely to be markedly diseased, as reflected by the already very slow 
CV at a 600ms PI. This then shows little further slowing in CV at shorter PIs, i.e. 
there is no conduction reserve.

Rate-dependent CV slowing sites were also seen in non-LVZs. It is unclear why 
certain areas with no fibrosis/scar showed enhanced CV slowing with rate. It is 
possible that sites defined as non-LVZs are not truly structurally normal and there is 
presence of sub-endocardial or epicardial fibrosis that would not be identified on 
endocardial bipolar voltage maps. This could account for the heterogeneity seen in 
apparently healthy tissue. However, these sites did not correlate to the location of 
reentry causing rotational activity in AF and therefore may not play an important 
mechanistic role. It may be that structural remodeling must be transmural to 
effectively promote reentry.

In this study majority of drivers had a rotational activation (62.0%) which is 
supported by the findings of our previous work (7). It has been suggested that 
localized slow conduction is necessary to maintain rotors, or at least that rotors may 
become anchored to such areas (15). In this study 15 of the 17 confirmed drivers with 
rotational activation pattern were located in LVZs [0.2-0.5mV] with rate-dependent 
CV slowing. The 11 focal activation patterns showed no predilection to LVZs and 
rate-dependent CV slowing sites, which is consistent with previous findings (16). It 
has been shown that sites with a broad CV dynamics curve have an alteration in 
activation vector and arcing with accelerated rates which may reflect rate-dependent 
conduction block in certain directions (5). This may promote reentry (17). These data 
suggest that sites with a broad CV dynamics curve and enhanced rate-dependent CV 
slowing play an important role in the initiation and/or maintenance of reentrant
mechanisms supporting AF. It may also explain why ablation of such areas has an organizing effect without simply creating an area of fixed conduction block to which reentry might anchor. It may be that ablation reduces heterogeneity of CV by eliminating areas of rate-dependent CV slowing without the need to necessarily produce areas of continuous conduction block.

To our knowledge, CV restitution in the human atrium and its relationship to drivers mapped in AF has not previously been assessed. However, animal studies and computer modelling data investigating, ventricular fibrillation have shown that rotors are associated with a broad CV restitution curve (18). This is consistent with the study findings whereby rotational drivers mapped to areas with a broad restitution curve and rate-dependent CV slowing.

The prevalence of rate-dependent CV slowing sites in LVZs may explain the poorer short and long-term outcomes of AF catheter ablation in patients with more diseased atria (19). The study findings do point towards a potential role for a substrate modification approach to AF ablation based on LVZs and CV dynamics, since sites of rate-dependent CV slowing correlate to AF driver sites. Substrate modification based on voltage has shown promising results (2, 3). These data suggest that the targeting of scar could potentially be refined based on electrophysiological criteria.

Animal studies have elegantly shown that rotors can be functional and occur in normal tissue. We have previously demonstrated that drivers with rotational activity show a predilection for LVZs and that the amount of LVZ is predictive of the identification of rotational drivers (20). Others have demonstrated this independently using separate technologies (21). Computer modelling has suggested that fibrosis can
anchor a rotor (22). It has also been shown that CV heterogeneity can promote re-entry (4). Therefore it is possible that rotors and other re-entry mechanisms might form within or gravitate towards LVZ, in particular those with heterogeneous conduction due to rate dependent CV slowing.

**Limitations**

One of the main limitations of this study is the small patient numbers. This was overcome to some extent through assessing CV between more than a total of 3000 electrode pairs to allow regional analysis of multiple LVZs. The LA coverage achieved with the basket catheter is limited by catheter design and LA geometry and hence the number of rate-dependent CV slowing sites may be underestimated. In this study wavefront collision was not seen between electrode pairs over which CV was measured, but clearly this would impact CV measurements. Studies evaluating CV should consider this as a potential source of error and adjust the pacing site if needed.

The impact of fibre orientation and anisotropic effect on CV was not directly assessed in this study. However, sites of rate-dependent CV slowing were spatially stable and were not impacted by pacing site or the direction of wavefront propagation and hence are unlikely to be explained by anisotropy.

The study aim was to map the LA for possible AF drivers and assess for CV heterogeneity. RA mapping with the CARTOFINDER system has not demonstrated RA drivers (7) and hence the RA was not mapped in this study. It is therefore uncertain whether this relationship between CV dynamics and drivers exists in the RA.
It remains unclear what recording duration is optimal for the identification of potential drivers in AF and it is possible that a longer recording may have identified more drivers. The CARTOFINDER mapping system uses a 30-second recording similar to that used by other mapping systems (23, 24). However, the drivers identified were observed repeatedly and the response to ablation suggested they were mechanistically important. Indeed, drivers that demonstrate greater temporal stability may be more important in maintaining AF (20). The relevance of focal or rotational activity that occurs less frequently remains unclear.

In this study we focused on electrophysiological endpoints to determine the mechanistic significance of potential drivers since there is arguably no other way to verify that a driver has been mapped. Others have used termination of AF or CL prolongation as a surrogate for the interruption of mechanisms important for the maintenance of AF (25, 26). Larger multi-center studies powered to assess outcomes are currently in progress utilizing CARTOFINDER to target drivers in AF (NCT03064451).

The voltage ranges studied were those conventionally regarded as LVZ, but it is accepted that areas with voltage >0.5mV could still be abnormal. Further studies to define the lower limits of the normal range are desirable.

The current study used the ablation response to confirm the presence of drivers so as to correlate this with sites of CV heterogeneity. Further studies are needed to determine the impact of an approach targeting ablation based on local CV dynamics.

CONCLUSIONS
Structural remodeling results in heterogeneous CV dynamics which are determined largely by the degree of atrial disease. Moderately diseased tissue [0.2-0.5mV] was most likely to display rate-dependent CV slowing which showed a good correlation with rotational activation in AF. Notably not all areas with voltage <0.5mV appeared mechanistically important in this way. These data provide a potential rationale for randomized studies comparing long-term outcomes of an electrophysiological approach to substrate modification for AF based on CV dynamics to other ablation strategies.
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Increase in organization index predicts atrial fibrillation termination with
flecainide post-ablation: spectral analysis of intracardiac electrograms.
Table 1 - Mechanism of possible drivers mapped in AF and the ablation response

<table>
<thead>
<tr>
<th>AF drivers</th>
<th>29</th>
</tr>
</thead>
<tbody>
<tr>
<td>Focal activity</td>
<td>11</td>
</tr>
<tr>
<td>Rotational activity</td>
<td>18</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>AF response to ablation at driver site</th>
<th>29</th>
</tr>
</thead>
<tbody>
<tr>
<td>Termination to sinus rhythm</td>
<td>6</td>
</tr>
<tr>
<td>Organized to an AT</td>
<td>12</td>
</tr>
<tr>
<td>Cavo-tricuspid isthmus dependent flutter</td>
<td>2</td>
</tr>
<tr>
<td>Mitral-isthmus dependent flutter</td>
<td>4</td>
</tr>
<tr>
<td>Roof dependent flutter</td>
<td>5</td>
</tr>
<tr>
<td>Ligament of Marshall</td>
<td>1</td>
</tr>
<tr>
<td>CL(^\d) slowing $\geq$30ms</td>
<td>7</td>
</tr>
<tr>
<td>No effect of ablation</td>
<td>4</td>
</tr>
</tbody>
</table>

\(^\d\)CL- cycle length
Table 2- The value of different factors in predicting drivers in AF

<table>
<thead>
<tr>
<th>Each LVZ island</th>
<th>AUC</th>
<th>p-value</th>
<th>95% CI</th>
<th>Optimal</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surface area cm²</td>
<td>0.63</td>
<td>0.13</td>
<td>0.47-0.79</td>
<td>3.0</td>
<td>0.68</td>
<td>0.67</td>
</tr>
<tr>
<td>Mean bipolar voltage mV</td>
<td>0.81</td>
<td>&lt;0.001</td>
<td>0.68-0.93</td>
<td>0.28</td>
<td>0.88</td>
<td>0.63</td>
</tr>
<tr>
<td>SD of mean bipolar voltage mV</td>
<td>0.46</td>
<td>0.62</td>
<td>0.29-0.63</td>
<td>0.10</td>
<td>0.56</td>
<td>0.50</td>
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<tr>
<td>CV^ at 600ms m/s</td>
<td>0.76</td>
<td>0.002</td>
<td>0.62-0.90</td>
<td>1.17</td>
<td>0.76</td>
<td>0.71</td>
</tr>
<tr>
<td>%CV measurements demonstrating RD^ CV slowing</td>
<td>0.86</td>
<td>&lt;0.001</td>
<td>0.73-0.98</td>
<td>19.1</td>
<td>0.80</td>
<td>0.91</td>
</tr>
</tbody>
</table>

^CV- conduction velocity
^RD- rate dependent
**Figure 1A-B**- Anterior (A) and posterior (B) views of the LA demonstrating the distribution of the LVZs and rate-dependent CV slowing sites (percentage in brackets) in the patients involved in the study (Red- Septum, Green- Lateral, Blue- Anterior, Yellow-Posterior, Purple- Roof).

**Figure 2A-B**- A) Demonstrates the change in CV over the four PIs in non-LVZs $\geq 0.5$ mV (black triangle), LVZs [0.2-0.5 mV] (light grey circle) and vLVZs [0-0.2 mV] (dark grey triangle) B) Bar chart shows the percentage of the rate-dependent CV slowing sites in non-LVZs $\geq 0.5$ mV, LVZs [0.2-0.5 mV] and vLVZs [0-0.2 mV] and the proportion of non-LVZs $\geq 0.5$ mV, LVZs [0.2-0.5 mV] and vLVZs [0-0.2 mV] demonstrating rate-dependent CV slowing.

**Figure 3A-B**- Shows the relationship between the mean CV for each patient at a PI of 600ms (the average of all the CV measured between all pole pairs in each patient) and A) Mean bipolar voltage including all bipolar voltage points in each patient B) Proportion of non-LVZs in each patient.

**Figure 4A-D**- Demonstrates Ai-iv) Still CARTOFINDER map demonstrating a rotational driver at the anterior roof B) In an area of LVZ as shown on the bipolar voltage map C) Where ablation resulted in AF termination to sinus rhythm on the Bard electrograms. Di) Replicated CARTO geometry created in Matlab demonstrating site of rate-dependent CV slowing at the anterior roof in an area of LVZ [0.2-0.5] [F3-F5 electrodes- vertical] and [F4-E4 electrode-horizontal] Dii-iii) Electrograms obtained at ii) F3 and F5 electrodes during LA appendage pacing at PI 600-250ms show an increase in activation time difference of 12ms (80% increase).
between the two electrodes when reaching PI of 250ms (iii) F4 and E4 electrodes during roof pacing at PI 600-250ms show an increase in activation time difference of 13ms (163% increase).

V- far field ventricular signal
A) CV vs Bipolar Voltage

B) CV vs Proportion of non-LVZs