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Identification of Critical Slowing of Conduction Using Unipolar Atrial Voltage and Fractionation Mapping

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ABSTRACT

BACKGROUND Ablation strategies targeting fractionated or low-voltage potentials have been widely used in patients with persistent types of atrial fibrillation (AF). However, recent studies have questioned their role in effectively representing sites of conduction slowing, and thus arrhythmogenic substrates.

OBJECTIVES The authors studied the relationship between local conduction velocity (CV) and the occurrence of fractionated and/or low-voltage potentials in order to identify areas with critically slowing of conduction.

METHODS Intraoperative epicardial mapping was performed during sinus rhythm. Unipolar potentials with an amplitude <1.0 mV were initially classified as low-voltage and potentials with ≥3 deflections as fractionation. A range of thresholds were also explored. Local CV was computed using discrete velocity vectors.

RESULTS A total of 319 patients were included. Fractionated, low-voltage potentials were rare, accounting for only 0.36% (Q1-Q3: 0.15%-0.78%) of all atrial sites. Local CV at sites with fractionated, low-voltage potentials (46.0 cm/s [Q1-Q3: 22.6-72.7 cm/s]) was lowest compared with sites with either low-voltage, nonfractionated potentials (64.5 cm/s [Q1-Q3: 34.8-99.4 cm/s]) or fractionated, high-voltage potentials (65.9 cm/s [Q1-Q3: 41.7-92.8 cm/s]; $P < 0.001$). Slow conduction areas (CV <50 cm/s) could be most accurately identified by using a low voltage threshold (<1 mV) and a minimum of 3 deflections (positive predictive value: 54.2%-70.7%), although the overall sensitivity remained low (0.1%-1.9%).

CONCLUSIONS Sites with fractionated, low-voltage potentials have substantially slower local CV compared with sites with either low-voltage, nonfractionated potentials or fractionated, high-voltage potentials. However, the strong inverse relationship between the positive predictive value and sensitivity of a combined voltage and fractionation threshold for slowed conduction is likely to complicate the use of these signal-based ablation approaches in AF patients. (JACC Clin Electrophysiol. 2024;10:1971–1981) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation
BB = Bachmann's bundle
CV = conduction velocity
EGM = electrogram
LA = left atrium
PVA = pulmonary vein area
RA = right atrium
SR = sinus rhythm

In the search to improve ablation outcomes in patients with (persistent) atrial fibrillation (AF), various substrate-based ablation approaches have been introduced over the years. Among these strategies, ablation targeting fractionated potentials or low-voltage potentials is the most common.[1] The application of these strategies in AF treatment initially showed positive outcomes in mostly single-center studies but are now increasingly followed by negative outcomes in (large) randomized controlled trials.[2-4]

The reason for the lack of benefit associated with additional ablation of fractionated and/or low-voltage potentials is not well understood. Limited knowledge on the exact arrhythmogenic properties of both fractionated and low-voltage potentials underlies in part the inability to discern the additional value of modification of both parameters. While fractionation and low voltage are considered to occur at sites of conduction slowing, and therefore critical in initiation and perpetuation of AF, they can also occur due to nonpathologic reasons (eg, wavefront collisions and diffuse fiber orientation). Several studies have attempted to characterize the relationship between conduction velocity (CV) and either fractionated or low-voltage potentials.[5-12] However, these studies not only yielded in contradicting results, they also lacked the interrelationship between the 3 parameters. Small sample size, lack of high-density mapping (across both atria), and variation in recording techniques could explain the inconsistent findings among these studies.

In order to better understand the arrhythmogenic properties of fractionated and low-voltage potentials, a comprehensive assessment of both potential characteristics and the relationship with local CV is needed. Therefore, the aim of our study was to study the relationship between local CV and the occurrence of fractionated and/or low-voltage potentials in order to identify areas with critically slowing of conduction as indicator of potential arrhythmogenic substrate.

METHODS

STUDY POPULATION. Participants (≥18 years of age) who underwent elective cardiac surgery, including coronary artery bypass grafting surgery and/or mitral valve surgery, at Erasmus Medical Center Rotterdam were included. Exclusion criteria were the presence of prior ablative therapy or cardiac surgery, radiation therapy of the chest, atrial pacemaker leads, an estimated glomerular filtration rate <30 mL/min/1.73 m^2, and the need for inotropic or mechanical support at the time of surgery. This study has been approved by the Institutional Medical Ethics Committee (MEC2010-054/MEC2014-393). Written informed consent was required from all patients prior to recruitment, and the patient's baseline characteristics (eg, age, medical history, underlying heart diseases) were extracted from the patient's medical record.

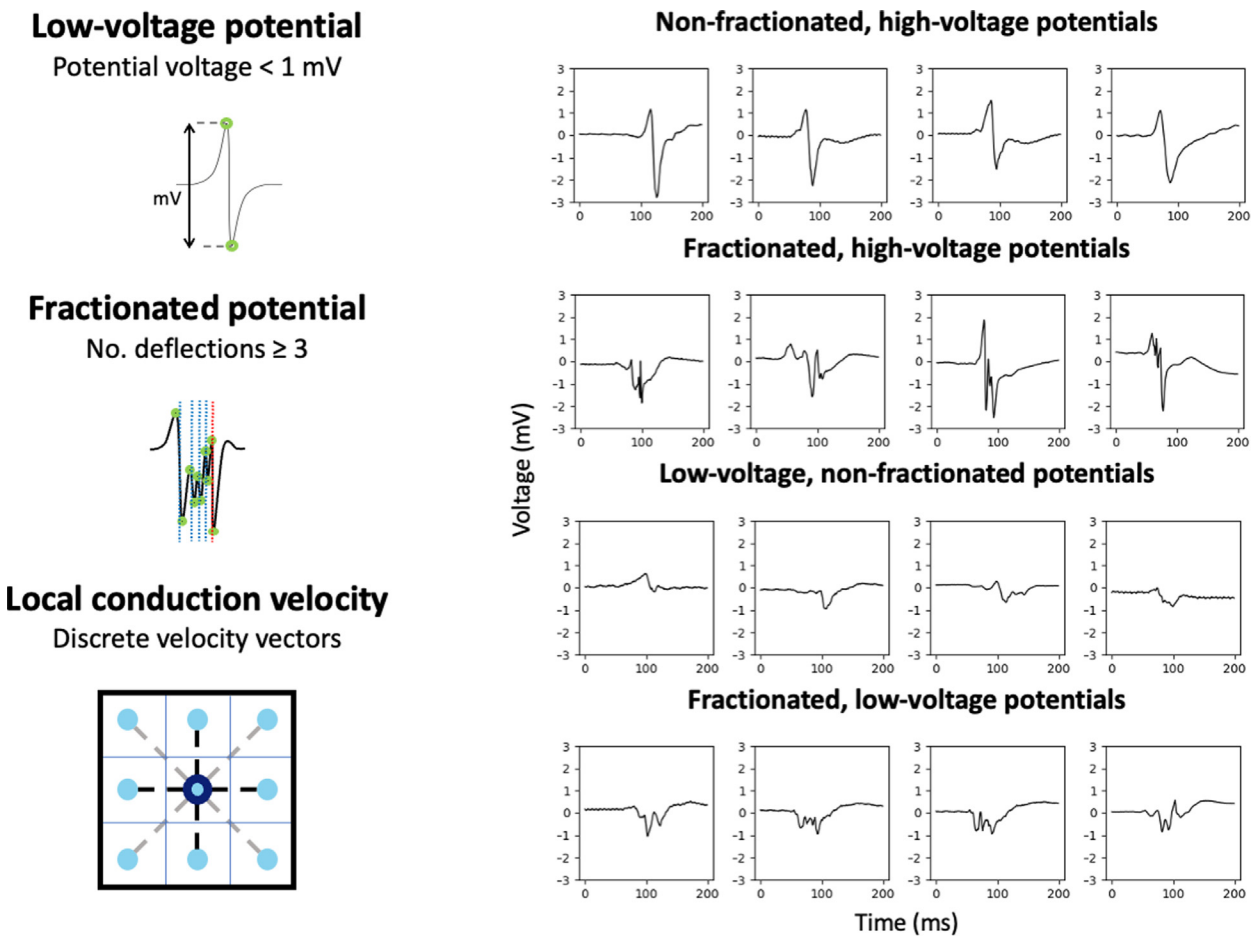
MAPPING PROCEDURE. As described previously, epicardial high-resolution mapping was performed before cardiopulmonary bypass.[13] A temporal bipolar epicardial pacemaker wire connected to the free wall of right atrium (RA) was used as reference electrode, and a steel wire attached to the subcutaneous tissue of thoracic cavity served as indifferent electrode. Epicardial mapping was performed using a 128- or 192-electrode array (electrode diameter 0.65 mm or 0.45 mm, distance 2.0 mm, respectively).

Mapping of the RA was performed from the inferior to superior caval vein perpendicular to the terminal crest. The pulmonary vein area (PVA) was mapped from the transverse sinus fold down along the margins of the left and right pulmonary veins toward the atrioventricular groove and the left atrioventricular groove from the lower margin of the left inferior pulmonary vein to the left atrial (LA) appendage. Bachmann's bundle (BB) was mapped from the border of the LA appendage, across the roof of the LA, behind the aorta toward the superior cavoatrial junction. At each mapping location, 5-second unipolar electrograms (EGMs) were recorded during sinus rhythm (SR), including an individual surface electrocardiogram lead, 2 mV and 1,000 ms calibration signal, and bipolar reference EGM. Data were amplified (gain 1,000), filtered (bandwidth 0.5-400 Hz), sampled (1 kHz), and analog-to-digital converted (16-bit) and stored on a hard disk.

DATA ANALYSIS. Customized software was used for semi-automatic analysis of EGM morphology. EGMs with ≥25% loss of recording site and atrial extrasystoles were excluded. Local activation time was defined as the steepest negative slope of a unipolar potential. All annotations were manually inspected by 2 researchers (M.S., N.G.).

Peak-to-peak amplitudes of all unipolar potentials were evaluated, as illustrated in **Figure 1**. In line with previous studies, low-voltage was defined as a potential voltage <1.0 mV.[9] A unipolar potential was classified as fractionated when it contained ≥3 deflections.[14] In line with prior studies, local effective CV was computed using discrete velocity vectors.[15] Local activation times of electrode pairs surrounding the center electrode (longitudinal, transversal, and diagonal) were used to calculate the mean

FIGURE 1 Electrogram Processing Approach and Potential Types



(Left) The definitions for low-voltage and fractionated potentials and conduction velocity. (Right) Typical examples of different unipolar potentials, including: 1) non-fractionated, high-voltage potentials; 2) fractionated, high-voltage potentials; 3) low-voltage, nonfractionated potentials; and 4) fractionated, low-voltage potentials.

velocity in horizontal (x) and vertical (y) direction. In order to increase the reliability of the CV estimate, only CVs with at least 3 estimates in both the horizontal and vertical directions were included. The magnitude of each vector was calculated to represent the CV independently of the propagation direction angle. Areas with slowed localized conduction were defined as a CV <50 cm/s.[16] Mapping areas with simultaneous activation, defined as a CV of 0 cm/s, were excluded from the analysis to avoid inclusion of far-field potentials.

A performance matrix is constructed using both the potential voltages and the number of deflections to predict whether a specific potential morphology reflects a slow conduction area. The positive predictive value represents the change that a given potential morphology actually represents a slow conduction area. The sensitivity denotes the proportion of potential morphologies that correctly indicates a slow conduction area out of all slow conduction areas.

STATISTICAL ANALYSIS. The Shapiro-Wilk test was used to inspect normality before data analysis. Normally distributed data are presented as mean ± SD and compared using independent samples *t* test or analysis of variance appropriately. Skewed data are presented as median (Q1-Q3) and difference between

TABLE 1 Baseline Characteristics of the Study Population

	Without AF History (n = 256)	With AF History (n = 63)	*P* Value
Age, y	65 ± 10	71 ± 8	<0.001
Male	208 (81.25)	38 (60.32)	0.001
BMI, kg/m^2	27.83 ± 4.27	27.05 ± 4.02	0.188
Underlying heart diseases			<0.001
CABG	213 (83.20)	23 (36.51)	
MVD	27 (10.55)	29 (46.03)	
MVD with CABG	16 (6.25)	11 (17.46)	
Type of AF			<0.001
No AF	256 (100.00)	0 (0.00)	
Paroxysmal AF	0 (0.00)	43 (68.25)	
Persistent AF	0 (0.00)	16 (25.40)	
Long-standing persistent AF	0 (0.00)	4 (6.35)	
Hypertension	144 (56.25)	35 (55.56)	1.000
Dyslipidemia	103 (40.23)	15 (23.81)	0.023
Diabetes mellitus	80 (31.25)	12 (19.05)	0.078
Myocardial infarction	112 (43.75)	17 (26.98)	0.022
Left ventricular function			0.035
Normal (EF >55%)	190 (74.22)	41 (66.13)	
Mild impairment (EF 46%-55%)	52 (20.31)	14 (22.58)	
Moderate impairment (EF 36%-45%)	13 (5.08)	4 (6.45)	
Severe impairment (EF <35%)	1 (0.39)	3 (4.84)	
Left atrial dilatation >45 mm	46 (17.97)	39 (61.90)	<0.001
ACEI/ARB/AT2 antagonist	167 (65.49)	38 (60.32)	0.534
Statin	208 (81.25)	31 (50.00)	<0.001
Class I	1 (0.39)	1 (1.59)	0.852
Class II	192 (75.00)	36 (57.14)	0.008
Class III	3 (1.17)	15 (23.81)	<0.001
Class IV	12 (4.69)	2 (3.17)	0.856
Digoxin	3 (1.17)	12 (19.05)	<0.001

Values are mean ± SD or n (%).

ACEI = angiotensin-converting enzyme inhibitor; AF = atrial fibrillation; ARB = angiotensin receptor blocker; AT2 = angiotensin type 2 receptor; BMI = body mass index; CABG = coronary artery bypass grafting; EF = ejection fraction; MVD = mitral valve disease.

groups was compared using the Kruskal-Wallis test, or the Mann-Whitney *U* test appropriately. Categorical data are presented as number and percentage and were compared using chi-square or Fisher exact test if the expected frequency was <5. A 2-sided *P* value <0.05 was considered statistically significant. Data analysis was performed using IBM SPSS statistics (version 28), RStudio (version 4.1.3), and Python (version 3.8, Python Software Foundation).

RESULTS

STUDY POPULATION. A total of 319 adult patients (mean age 66 ± 10 years, 246 [77.1%] male) were included. Sixty-three (19.8%) patients had a history of AF. The majority of patients (72.6%) had normal left ventricular function and 86 (26.7%) patients had LA dilation. Clinical characteristics of the study population are summarized in Table 1.

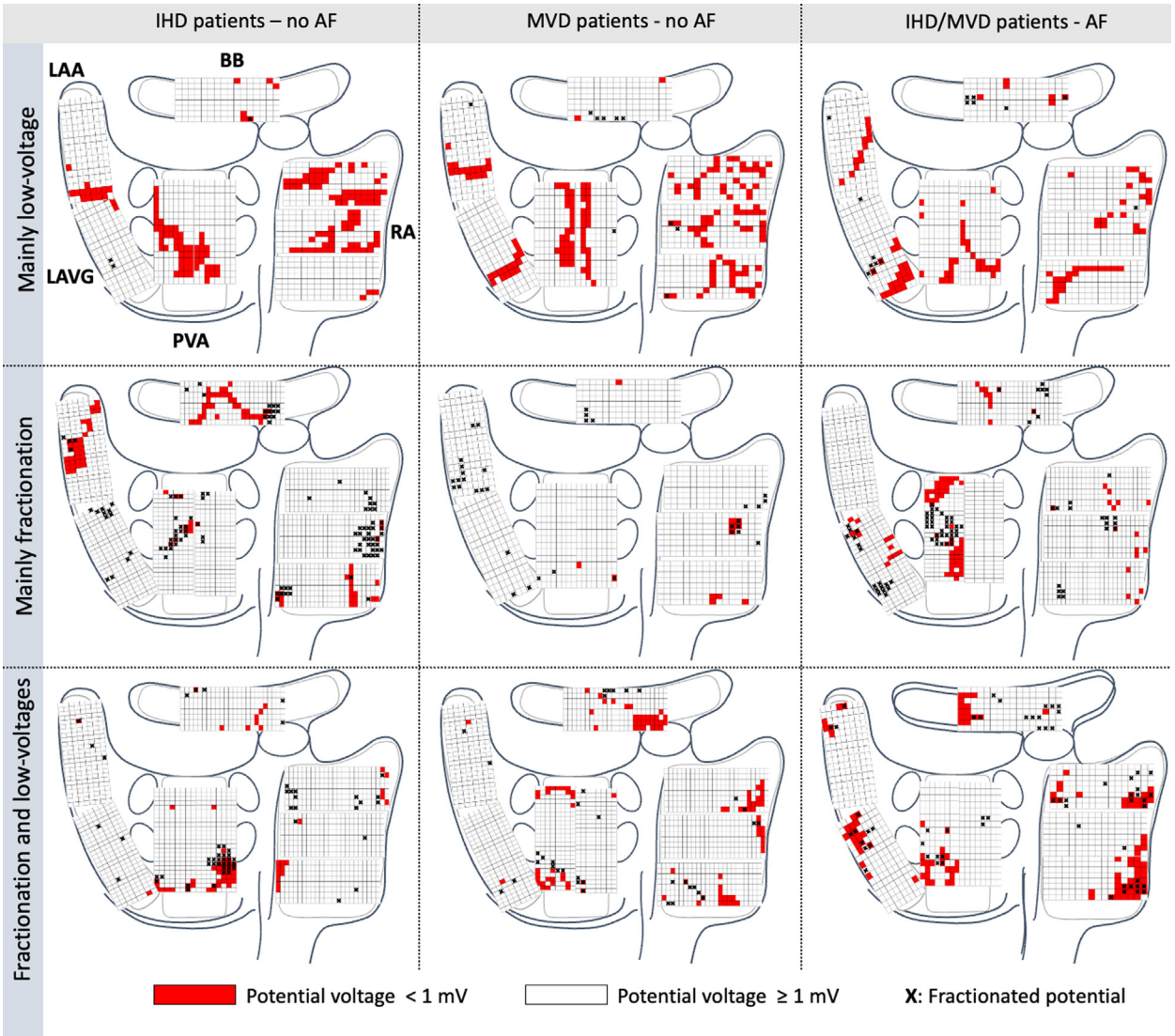
MAPPING DATA. Average SR cycle length was 874 ± 166 ms and did not differ between patients with (871 ± 162 ms) and without (875 ± 167 ms) AF ($P = 0.889$). A total of 2,943,017 atrial potentials (9,225 ± 3,051 per patient) were included for analysis. Most potentials were recorded from the RA (n = 1,390,027 [47.2%]), followed by the PVA (n = 649,852 [22.1%]) and LA (n = 572,269 [19.4%]) and BB (n = 330,869 [11.3%]).

SPATIAL DISTRIBUTION OF FRACTIONATION AND LOW-VOLTAGE POTENTIALS. Figure 2 shows the spatial distribution of fractionated and low-voltage potentials across the atria in 9 different patients. In the upper panels, patients were characterized by a high amount of low-voltage potentials without fractionation. In the middle panels, patients were characterized by mainly fractionated, high-voltage potentials. The lower panels contain examples from patients who were characterized by the presence of both low-voltage potentials with or without fractionation, and fractionated, high-voltage potentials. In all examples, only a minority of the potentials were labeled as low-voltage with fractionation. The maps reveal a substantial regional and interindividual variation in the occurrence of fractionation and low-voltage potentials.

Compared with patients without AF, fractionated potentials and low-voltage potentials were more common among patients with history of AF (1.62 [Q1-Q3: 0.84-2.56] vs 1.87 [Q1-Q3: 1.20-3.23]; $P = 0.017$; and 6.04 [Q1-Q3: 3.70-9.49] vs 9.01 [Q1-Q3: 4.43-11.52]; $P = 0.022$, respectively). Fractionated, low-voltage potentials were rare and equally common in patients with AF and patients without AF (0.37 [Q1-Q3: 0.21-0.93] vs 0.36 [Q1-Q3: 0.14-0.75]; $P = 0.195$).

REGIONAL DIFFERENCES IN PREVALENCE OF FRACTIONATION AND LOW-VOLTAGE POTENTIALS. Table 2 summarizes the regional prevalence of both fractionation and low-voltage potentials across all patients. The prevalence of fractionated potentials in the RA, BB, PVA, and LA was 1.31% (Q1-Q3: 0.41%-2.92%), 1.74% (Q1-Q3: 0.54%-4.20%), 0.74% (Q1-Q3: 0.23%-2.22%), and 1.07% (Q1-Q3: 0.35%-2.57%), respectively, whereas the prevalence of low-voltage potentials was 6.06% (Q1-Q3: 2.83%-10.72%), 2.41 (Q1-Q3: 0.62%-8.40%), 4.79% (Q1-Q3: 1.63%-12.35%), and 3.84% [Q1-Q3: 1.25%-8.92%), respectively. Fractionated, low-voltage potentials were most common at the RA (0.41% [Q1-Q3: 0.10%-0.98%]), followed by

FIGURE 2 Spatial Distribution of Fractionation and Low-Voltage Potentials



Biatrial maps, including Bachmann's bundle (BB), indicate variations in spatial distributions of fractionation and low-voltage potentials in different patient groups, including patients with ischemic heart disease (IHD) and mitral valve disease (MVD) with and without a history of atrial fibrillation. Each panel represents a unique patient. (Top row) Patients with mainly low-voltage potentials, while the middle row shows patients from whom mainly fractionated potentials were recorded. The lower row shows patients with a large number of fractionated, low-voltage potentials. LAA = left atrial appendage; LAVG = left atrioventricular groove; PVA = pulmonary vein area; RA = right atrium.

BB (0.25% [Q1-Q3: 0.00%-0.84%]), PVA (0.08% [Q1-Q3: 0.00%-0.34%]), and LA (0.05% [Q1-Q3: 0.00%-0.25%]). Patients with AF were characterized by a higher amount of fractionated potentials, low-voltage potentials, and fractionated, low-voltage potentials only at BB and PVA ($P < 0.005$).

INTERRELATIONSHIP BETWEEN FRACTIONATION, LOW VOLTAGE, AND LOCAL CV. All potentials were subdivided into 4 different groups: 1) fractionated, low-voltage potentials; 2) low-voltage, non-fractionated potentials; 3) fractionated, high-voltage potentials; and 4) nonfractionated, high-voltage

TABLE 2 Prevalence and Regional Distribution of Fractionation and Low-Voltage Potentials

	Fractionated Potentials (%)	Low-Voltage Potentials (%)	Fractionated, Low-Voltage Potentials (%)
Total population			
Entire atrium	1.72 (0.87-2.75)	6.22 (3.73-10.18)	0.36 (0.15-0.78)
RA	1.31 (0.41-2.92)	6.06 (2.83-10.72)	0.41 (0.10-0.98)
BB	1.74 (0.54-4.20)	2.41 (0.62-8.40)	0.25 (0.00-0.84)
PVA	0.74 (0.23-2.22)	4.79 (1.63-12.35)	0.08 (0.00-0.34)
LA	1.07 (0.35-2.57)	3.84 (1.25-8.92)	0.05 (0.00-0.25)
Without a history of AF			
Entire atrium	1.62 (0.84-2.56)	6.04 (3.70-9.49)	0.36 (0.14-0.75)
RA	1.39 (0.41-2.91)	5.95 (2.81-10.39)	0.46 (0.10-0.99)
BB	1.43 (0.43-3.63)	1.67 (0.47-6.19)	0.16 (0.00-0.73)
PVA	0.71 (0.20-2.04)	4.44 (1.21-11.45)	0.07 (0.00-0.25)
LA	1.07 (0.37-2.41)	3.84 (1.00-9.11)	0.04 (0.00-0.22)
With a history of AF			
Entire atrium	1.87 (1.20-3.23)[a]	9.01 (4.43-11.52)[a]	0.37 (0.21-0.93)
RA	1.04 (0.42-3.10)	6.84 (3.15-12.83)	0.29 (0.11-0.71)
BB	3.10 (1.18-5.88)[a]	7.25 (2.80-18.88)[a]	0.61 (0.10-1.83)[a]
PVA	1.07 (0.56-4.05)[a]	8.12 (3.82-14.72)[a]	0.31 (0.00-0.57)[a]
LA	1.05 (0.31-3.25)	3.82 (1.96-8.11)	0.08 (0.00-0.32)

Values are median (Q1-Q3). [a]$P < 0.05$ between patients with and without history of AF at corresponding location.
AF = atrial fibrillation; BB = Bachmann's bundle; LA = left atrium; PVA = pulmonary vein area; RA = right atrium.

potentials. The distribution of each category across the 4 atrial regions is listed in Table 3. Figure 3 illustrates the differences in local CV between the 4 categories. Local CV at sites with fractionated, low-voltage potentials (46.0 cm/s [Q1-Q3: 22.6-72.7 cm/s]) was considerably lower compared with sites with either low-voltage, nonfractionated potentials (64.5 cm/s [Q1-Q3: 34.8-99.4 cm/s]) and fractionated, high-voltage potentials (65.9 cm/s [Q1-Q3: 41.7-92.8 cm/s]) or sites with nonfractionated, high-voltage potentials (92.3 cm/s [Q1-Q3: 66.7-117.9 cm/s]; $P < 0.001$ for each comparison). A similar trend in local CV differences was also found for each atrial region separately, indicating that sites with fractionated, low-voltage potentials differ considerably from the other 3 categories, regardless of the anatomical location (Supplemental Figure 1).

TABLE 3 Distribution of Potentials per Potential Type

Locations	Nonfractionated, High-Voltage Potentials	Fractionated, High-Voltage Potentials	Low-Voltage, Nonfractionated Potentials	Fractionated, Low-Voltage Potentials
Entire atrium	2,691,366 (91.45)	45,114 (1.53)	190,758 (6.48)	15,779 (0.54)
RA	1,266,118 (91.09)	19,305 (1.39)	94,280 (6.78)	10,324 (0.74)
BB	303,261 (91.66)	7,476 (2.26)	17,900 (5.41)	2,232 (0.67)
PVA	593,312 (91.30)	8,359 (1.29)	46,347 (7.13)	1,834 (0.28)
LA	528,675 (92.39)	9,974 (1.74)	32,231 (5.63)	1,389 (0.24)

Values are n (%).
Abbreviations as in Table 2.

As demonstrated in Figure 3, slowed conduction (CV <50 cm/s) was most common at areas containing fractionated, low-voltage potentials (54.7%), followed by low-voltage, nonfractionated potentials (38.0%); fractionated, high-voltage potentials (33.5%); and nonfractionated, high-voltage potentials (14.4%).

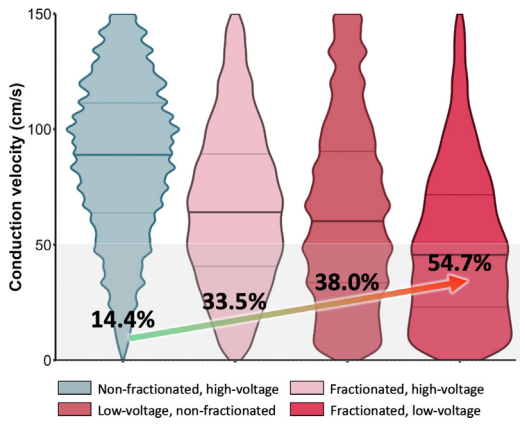
IDENTIFICATION OF SLOW CONDUCTION AREAS. The left panel of Figure 4 demonstrates the positive predictive values to identify slow conduction areas by using various voltage thresholds and a minimal number of deflections. The highest predictive values can be achieved by using a small voltage threshold (<1 mV) and a minimum of 3 deflections, which resulted in positive predictive values ranging from 54.2% to 70.7%, as illustrated in the Central Illustration. However, as demonstrated in the right panel of Figure 4, the sensitivity of these thresholds was relatively low (0.003%-1.89%). Therefore, many slow conduction areas are still missed when using these potential morphology parameters only. However, in the case when fractionated, low-voltage potentials are present, they are very likely to correspond to slow conduction.

DISCUSSION

KEY FINDINGS. In this biatrial epicardial mapping study, we report an in-depth analysis of the relationship between fractionation, low-voltage potentials and local CV during SR. Particularly fractionated, low-voltage potentials were related to a reduced CV and were linked to the largest degree of slowed conduction. These specific potentials were more common in patients with prior AF episodes, particularly at the PVA and BB. However, many areas of slowed conduction could still be missed when using solely potential voltage and fractionation as these areas also frequently occur in the presence of nonfractionated, high-voltage potentials. The strong inverse relationship between the positive predictive value and sensitivity will therefore likely complicate the use of these signal-based ablation approaches in AF patients for identifying slow conduction zones.

PREVALENCE AND REGIONAL DISTRIBUTION OF FRACTIONATION AND LOW VOLTAGE. Despite the usage of fractionation- and low voltage-guided ablation approaches, detailed understanding of substrates have been hampered by the use of nonuniform definitions, lack of high-density mapping, and

FIGURE 3 Local Conduction Velocity Distribution for Each Potential Type



Violin plots of local conduction velocities at sites with: 1) nonfractionated, high-voltage potentials; 2) fractionated, high-voltage potentials; 3) low-voltage, nonfractionated potentials; and 4) fractionated, low-voltage potentials. The numbers within the shaded area indicate the percentage of slow conduction velocity <50 cm/s.

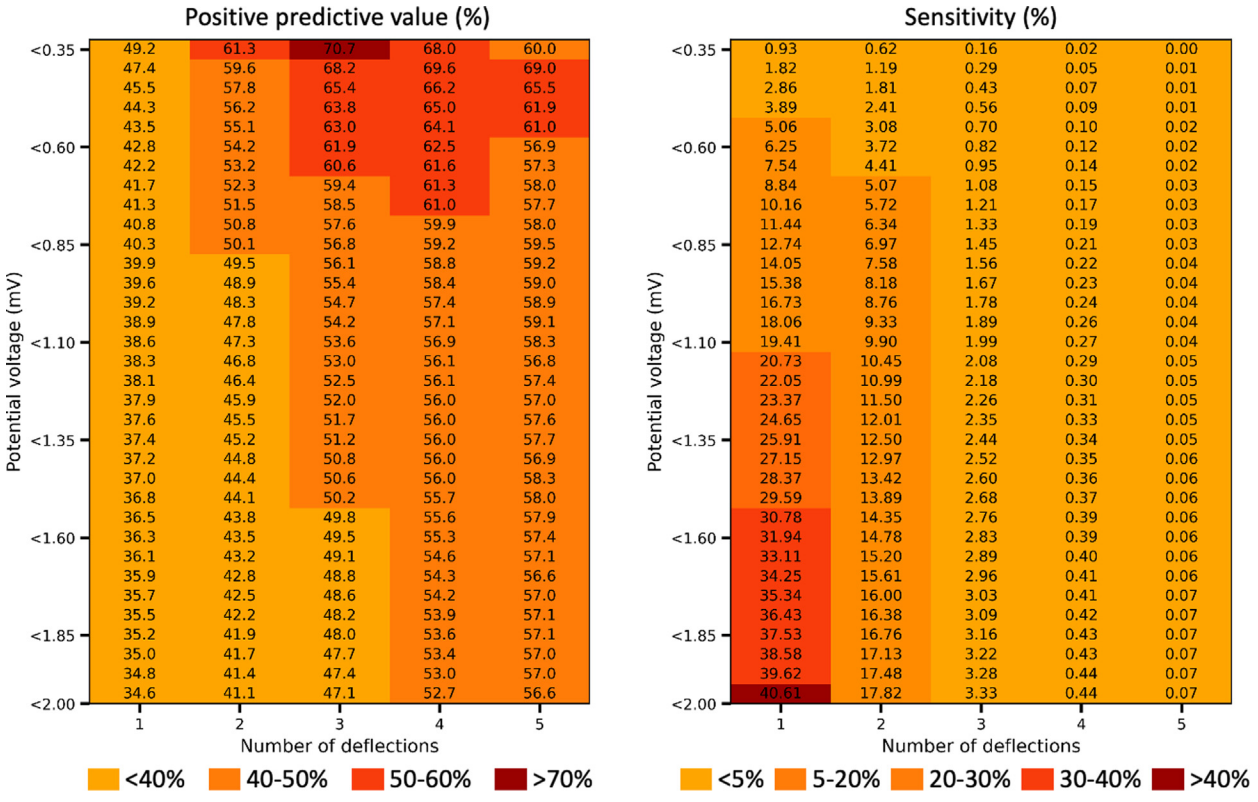
various electrogram processing technologies.[1] In the present study, we systematically examined the prevalence of fractionation and low-voltage potentials across both atria, including the BB. Where previous studies lacked exact quantification of the amount of fractionated and/or low-voltage potentials during SR,[5-12] we now demonstrate that sites with fractionated, low-voltage potentials are rare across all atrial regions but were particularly present at BB and PVA in patients with a history of AF. Moreover, fractionated, low-voltage potentials only accounted for a modest portion of either all fractionated or all low-voltage potentials, which is contrast with the general assumption that fractionation relates to low potential voltage and vice versa.[17,18]

There are numerous factors that influence atrial potential morphology, including underlying electrophysiological properties, tissue structure, and recording technology.[1] A considerable amount of fractionation, particularly those with a high potential voltage, may be caused by colliding wavefronts and diffuse fiber orientation.[19] Even in the PVA, only a minority of fractionated potentials had low-voltage components, while this area is assumed to be the preferential site for fractionation-based ablation therapy in daily practice. Pashakhanloo et al[20] examined the LA wall at a submillimeter resolution and showed a local, disorganized transmural fiber distribution. A heterogeneous transmural fiber orientation was especially observed at the posteroinferior region of the LA, which corresponds to the PVA in our study. The architecture of the LA wall may therefore explain the presence of fractionated, high-voltage potentials at these sites.

On the other hand, a large proportion of low-voltage potentials had no fractionated components. Unipolar potential voltage reflects the summation of action potentials within the recording area of 1 electrode, and its shape and amplitude are influenced by electrophysiological and structural characteristics of the myocardial tissue.[1] The myocardial architecture can attenuate unipolar voltage by atrial wall thickness and the presence of epicardial fat,[21,22] which does not necessarily result in inhomogeneous conduction. In a previous study, we also demonstrated that unipolar voltage of single potentials is mainly determined by their relative R- and S-wave morphology, which is influenced by the wavefront propagation.[23] Consequently, a large amount of low-voltage, nonfractionated potentials could also be explained by asymmetry of the relative R- and S-wave amplitudes. It is for these reasons that low-voltage potentials do not equal fractionation and that absolute low-voltage thresholds for inhomogeneous conduction remain arbitrary.

RELATION BETWEEN CV, FRACTIONATION, AND LOW VOLTAGE. Sites containing fractionation and low-voltage potentials are considered targets for substrate modification therapy, as they are indicative of slowing of conduction. The relationship between CV, fractionation, and low voltages has been described in various studies.[5-12] However, the methodology to define the 3 parameters differs considerably. First, clinical studies mostly use bipolar EGMs during the measurements, which have a considerable direction-dependent effect on potential voltages and lack a standardized definition for fractionation.[10,18] In contrast, characterization of fractionation by using unipolar EGMs is more straightforward and is therefore preferred. Second, there are many different techniques to compute CV.[15,24-27] In most studies, global CV instead of local CV is used to correlate to fractionation and low voltage.[6,7] For instance, in the study of Hansson et al,[28] the global CV was in the range of 68 ± 4 cm/s to 103 ± 3 cm/s. However, we demonstrated that the maximal value of the local CV

FIGURE 4 **Positive Predictive Values and Sensitivity for Identifying Slow Conduction Areas**



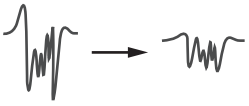
The positive predictive values (left) and sensitivity (right) for identifying slow conduction areas according to different voltage thresholds and a minimal number of deflections. The color gradients of the heat maps illustrate the performance of each metric, ranging from weak (light orange) to strong (dark red).

can reach up to even 150 cm/s. It is important to emphasize that Hansson et al[28] calculated CV using a different methodology and over a larger distance (2 × 2 cm or 2 × 4 cm), which may not accurately represent local effective CV. In contrast, our study utilized a small electrode array (interelectrode distance: 2.0 mm) to calculate CV, potentially providing a more accurate estimation of local CV. Our results align with a previous study,[29] which demonstrated that CV values can reach as high as 187 cm/s in the LA. In addition, our method of discrete velocity vectors also showed important superiority to previously used local CV techniques, such as finite differences and polynomial surface fitting.[15] These other CV estimation techniques masked local areas of conduction slowing more often due to smoothing of wavefront propagation.

To date, no study has investigated local CV while discriminating between sites with both fractionation and low voltage, or the presence of solely fractionated or low-voltage potentials. In a recent study, van Schie et al[9] demonstrated that there was no clear correlation between unipolar potential voltage and local CV, although smaller voltages were observed in areas of slowed conduction. Also, they demonstrated that unipolar potential voltages were decreased in fractionated potentials compared with potentials with 1 single deflection, showing a clear inversely proportional relationship between unipolar potential voltage and the number of deflections. In a following study, van Schie et al[10] showed that bipolar low-voltage areas were characterized by a decreased CV and more fractionation. However, it was also demonstrated that high unipolar potential voltages and CVs could still be recorded in these bipolar low-voltage areas, even by using direction-independent omnipolar EGMs. In the current study, we demonstrated the importance of differentiating between: 1) fractionated, low-voltage potentials; 2) low-voltage, nonfractionated potentials; and 3) fractionated, high-voltage potentials. Local CV at sites with fractionated, low-voltage potentials was considerably

CENTRAL ILLUSTRATION **Identification of Critical Slowing of Conduction Using Epicardial Mapping**

Epicardial mapping in 319 patients
19.8% with AF
2,943,017 unipolar potentials



Descriptive Characteristics		
Prevalence	**Morphology**	**Proportion Slowed Conduction**
91.5%	Non-fractionated, high-voltage potentials	14.4%
6.48%	Low-voltage, non-fractionated potentials	38.0%
1.53%	Fractionated, high-voltage potentials	33.5%
0.54%	Fractionated, low-voltage potentials	54.7%

Performance Matrix to Locate Slowed Conduction		
Sensitivity	**Morphology**	**Positive Predictive Value**
16.7 to 40.6%	1.0-2.0 mV and 1 deflection	34.6 to 39.6%
0.003 to 1.89%	0.03-1.0 mV and ≥3 deflection	54.2 to 70.7%

Ye Z, et al. JACC Clin Electrophysiol. 2024;10(9):1971-1981.

Local areas of slowed conduction are mainly characterized by fractionated, low-voltage potentials, although the overall prevalence remains low. With increasing complexity of unipolar potentials, the positive predictive value to identify slowed conduction increases at the expense of the sensitivity.
AF = atrial fibrillation.

lower compared with sites with either low-voltage, nonfractionated potentials and fractionated, high-voltage potentials.

Recently, Frontera et al[16] demonstrated the importance of slowing of conduction by analyzing CV during SR. Their data revealed that the number and density of slow conduction corridors, defined as discrete areas of CV <50 cm/s, increased in parallel with the progression of AF. The observed slow conduction corridors were often associated with pivot points, defined as sites characterized by a high wavefront curvature. We further expanded on identification of these slow conduction zones by showing that fractionated, low-voltage potentials most often coincide with slowed CV (<50 cm/s). However, 14.4% of all nonfractionated, high-voltage potentials had slowed CV. These findings highlight therefore the complexity of the conventional signal-based thresholds for slowed CV.

If a signal-based approach would be attempted to target slowed CV, the voltage thresholds and number of deflections will have significant impact on the positive predictive value. While high positive predictive values would result in avoidance of needless scarring, it will be accompanied by a low sensitivity (<50%). Hence, this first-time granular approach targeting slow conduction areas shows the limitations of fractionated and/or voltage based ablations. Also, this may provide in part the rational why either approach currently appears to be ineffective in improving ablation outcomes in persistent types of AF.[2-4] Future studies should therefore explore additional (non-signal based) parameters or approaches if slowed conduction is to be targeted.

STUDY LIMITATIONS. In daily clinical practice, electrophysiological studies are performed from the endocardium. Although properties of endocardial

potentials are unknown in the current study, simultaneous epicardial and endocardial mapping studies during SR demonstrated only limited differences in fractionation.[30] In addition, epicardial mapping assures better close-contact recordings than conventional endocardial mapping, thereby decreasing the chance that low voltage potentials are the result of poor contact. In the current study, we did not perform structural analysis to further provide insight in the relation between fractionation, low voltage, and CV. Histological examination and/or integration with other imaging modalities, such as late gadolinium enhancement magnetic resonance images, will aid in further characterizing the underlying (arrhythmogenic) substrate.

CONCLUSIONS

Sites with fractionated, low-voltage potentials have substantially lower local CV compared with sites with either low-voltage, nonfractionated potentials or fractionated, high-voltage potentials. However, the strong inverse relationship between the positive predictive value and sensitivity of combined voltage and fractionation threshold for slowed CV is likely to complicate the use of these signal-based ablation approaches in AF patients.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Ablation of low-voltage and fractionated potentials are 2 types of signal-based ablation approaches that are proposed in patients with recurrent AF after pulmonary vein isolation. Both potential features are related to slow conduction and therefore are considered to be interchangeable. The findings of the current study have important implications for our understanding of the complex relationship between potential features and the local CV. Low-voltage, nonfractionated potentials and fractionated, high-voltage potentials are recorded from areas with moderately slow local CV compared with areas with nonfractionated, high-voltage potentials. In contrast to these 3 potential types, local CV is substantially lower in areas with combined low-voltage, fractionated potentials. This underscores the significance of well-defined potential characteristics for substrate modification therapies. However, despite the high positive predictive value of the combined voltage and fractionation threshold for slowing of conduction, the sensitivity is extremely low due the presence of nonfractionated, high-voltage potentials in areas with slow CV. This observation indicates the complexity of signal-based ablation approaches in patients with AF.

TRANSLATIONAL OUTLOOK: In order to identify specific potential features that are accurate surrogates for slowing of conduction, different mechanisms underlying slow CV (ie, local asynchronous activation or pivot points) should also be assessed and related to tissue analysis. Furthermore, future studies should evaluate the role of conduction slowing in initiation and maintenance of AF.

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KEY WORDS **atrial fibrillation, complex fractionated electrograms, epicardial mapping, low-voltage potentials, slowing of conduction**

APPENDIX **For a supplemental figure, please see the online version of this paper.**