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Defining the substrate for ventricular tachycardia ablation: The impact of rhythm at the time of mapping

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ABSTRACT

Background: Voltage mapping is critical to define substrate during ablation. In ventricular tachycardia, abnormal potentials may be targets. However, wavefront of activation could impact local signal characteristics. This may be particularly true when comparing sinus rhythm versus paced rhythms. We sought to determine how activation wavefront impacts electrogram characteristics.
Methods: Patients with ischemic cardiomyopathy, ventricular tachycardia, and without fascicular or bundle branch block were included. Point by point mapping was done and at each point, one was obtained during an atrial paced rhythm and one during a right ventricular paced rhythm. Signals were adjudicated after ablation to define late potentials, fractionated potentials, and quantify local voltage. Areas of abnormal voltage (defined as <1.5 mV) were also determined.
Results: 9 patients were included (age 61.3 ± 9.2 years, 56% male, mean LVEF 34.9 ± 8.6%). LV endocardium was mapped with an average 375 ± 53 points/rhythm. Late potentials were more frequent during right ventricular pacing (51 ± 21 versus 32 ± 15, $p < 0.01$) while overall scar area was higher during atrial pacing (22 ± 11% vs 13 ± 7%, $p < 0.05$). In 1/9 patients, abnormal potentials were seen during a right ventricular paced rhythm that were not apparent in an atrial paced rhythm, ablation of which resulted in non-inducibility.
Conclusion: Rhythm in which mapping is performed has an impact on electrogram characteristics. Whether one rhythm is preferable to map in remains to be determined. However, it is possible defining local signals during normal conduction as well as variable paced rhythms may impart a greater likelihood of elucidating arrhythmogenic substrate.

1. Introduction

Catheter ablation is a widely accepted therapy for ventricular tachycardia (VT) refractory to drugs in structurally abnormal hearts [1,2]. Entrainment and activation mapping have been considered the gold standard to identify areas containing critical isthmuses for the VT circuit. However, in the presence of hemodynamic instability and multiple or non-inducible VTs, substrate-based approaches may be an acceptable alternative [3—5].

Substrate guided ablation involves targeting areas of local abnormal ventricular activation (LAVA), i.e., late potentials and regions of fragmented signals suggestive of local slowing of conduction, or targeting low voltage areas as traditionally defined by pre-specified cutoff values. Previous reports suggest that targeting the scar region and/or complete elimination of LAVA is associated with improved VT free survival [3,6]. However, the anatomical location of scar within ventricular myocardium has been previously described to affect signal characteristics [7]. It is further known that the direction of activation wavefront may alter the appearance of local electrograms. These rhythm associated changes could include the voltage amplitude (and thereby definition as scar versus border zone versus normal tissue), and local signal properties (including differentiation as a fractionated potential, late potential, or split potential). Such changes could, in turn, impact identification of

areas of interest for a substrate-based ablation strategy.

In this study, we sought to rigorously define how LAVA characteristics, scar region and areas of abnormal voltage are affected during an atrial paced rhythm, during which ventricular activation utilizes the His-Purkinje system, versus a right ventricular paced rhythm.

2. Methods

2.1. Study population

This study enrolled 9 ischemic cardiomyopathy patients undergoing VT ablation using a 3D electroanatomic mapping system. All patients had recurrent sustained VT refractory to anti-arrhythmic drugs resulting in implantable cardioverter defibrillator therapy. A written informed consent was obtained in all patients. The Mayo Clinic Institutional Board Review approved the study.

2.2. Electrophysiological study

All anti-arrhythmic drugs were discontinued at least 5 half-lives prior to the ablation if there was no sustained VT (one month in the case of amiodarone). ICD therapies were turned off prior to the start of the procedure. A 5 French (Fr.) quadripolar catheter was placed in the right ventricular apex and a 7 Fr. decapolar catheter was placed in the coronary sinus. The use of other diagnostic catheters was up to the discretion of the provider. The left ventricular endocardium was accessed either via retrograde aortic or transeptal approach. Epicardial mapping or ablation was only performed if clinically indicated during the study.

2.3. Electroanatomic mapping

Mapping was performed using a CARTO 3 (Biosense Webster, Diamond Bar, CA) mapping system. A detailed point-to-point map using an ablation catheter (THERMOCOOL® Biosense Webster) was created. At each location, a point would be acquired during pacing from an atrial catheter and a point would then be acquired during right ventricular pacing at the same rate. All bipolar signals were recorded between the distal electrode pair and filtered from 30 to 400 Hz and displayed at 100 mm/s.

Low voltage ventricular myocardium was defined as peak to peak bipolar voltage of <1.5 mV and a voltage of <0.5 mV with inability to capture at high output was defined as scar. Fractionated signals were defined as sharp high frequency local signals of low amplitude showing multiple components. Late signals were defined as sharp high-frequency local ventricular signals of any amplitude occurring after the onset of QRS, separated from the far-field ventricular signal by an iso-electric segment.

A complete LV map was made in both rhythms and all points were retrospectively reviewed and adjudicated by two independent operators. Maps were set to a fill threshold of 10 mm.

2.4. Radiofrequency ablation

The ablation procedure was performed independent of the results of the study. Activation and entrainment mapping were used to guide ablation where feasible. When a substrate-based approach was used, the areas targeted for ablation were at the sole discretion of the physician. All patients underwent pre- and post-ablation programmed ventricular stimulation using drive trains of 600 ms and 400 ms with single, double, and triple extra stimuli from two different sites.

2.5. Statistical analysis

All continuous variables are expressed as mean ± SD and were compared using the student t-test. Categorical variables are expressed as absolute number and percentages. All tests were two-tailed with a $p < 0.05$ considered significant.

3. Results

3.1. Demographics

Baseline characteristics of the patients are described in detail in Table-1. The average age was 61.3 ± 9.2 years with 56% male. The mean LVEF was 34.9 ± 8.6% The LV endocardium was mapped with an average of 375 ± 53 points/rhythm for each patient.

3.2. Effect of rhythm on electrogram characterization and bipolar voltage

Of all the electrograms reviewed, late potentials were noted to be more frequent during RV pacing (Table 2). There was no net effect on number of fractionated potentials seen. Low voltage points were more frequent during atrial pacing. Fig. 1 shows an example of a late

Table 2
Differences in substrate parameters based on the rhythm.

	Right atrial pacing	Right ventricular pacing	P value
Late potentials	32 ± 15	51 ± 21	P < 0.01
Fractionated potentials	97 ± 44	103 ± 42	P=NS
Low voltage sites	160 ± 90	121 ± 87	P < 0.05

Table 1
Baseline characteristics of the study population.

Patient Number	Age (years)	Sex	DM	HTN	CKD	Prior Ablation	LVEDD (mm)	LVEF (%)	Prior Infarct location	Prior revascularization	Epicardial Ablation	VT induced at the beginning of the case	VT inducible at the end of the case
1	65	F	No	Yes	Yes	Yes	62	21	Anterior	CABG	No	Yes	No
2	69	M	No	No	No	No	65	40	Inferior/Lateral	CABG	No	Yes	No
3	68	M	No	No	Yes	No	65	37	Inferior	PCI	Yes	Yes	No
4	68	M	No	Yes	No	No	64	38	Inferior	CABG/PCI	No	Yes	No
5	51	F	Yes	Yes	No	Yes	73	35	Anterior	PCI	No	Yes	No
6	71	M	Yes	No	Yes	No	75	20	Inferior	CABG	No	Yes	No
7	61	F	No	Yes	No	No	59	45	Anterior	PCI	No	Yes	No
8	45	M	Yes	Yes	No	Yes	63	38	Inferior	PCI	No	Yes	Yes
9	54	F	No	Yes	No	No	65	40	Inferior	PCI	No	Yes	No

(Abbreviations; M = Male; F = female; DM = Diabetes mellitus; HTN=Hypertension; CKD=Chronic Kidney Disease; LVEDD = Left ventricular end-diastolic diameter; LVEF = Left ventricular ejection fraction; PCI=Percutaneous Coronary Intervention; CABG=Coronary Artery Bypass Grafting).
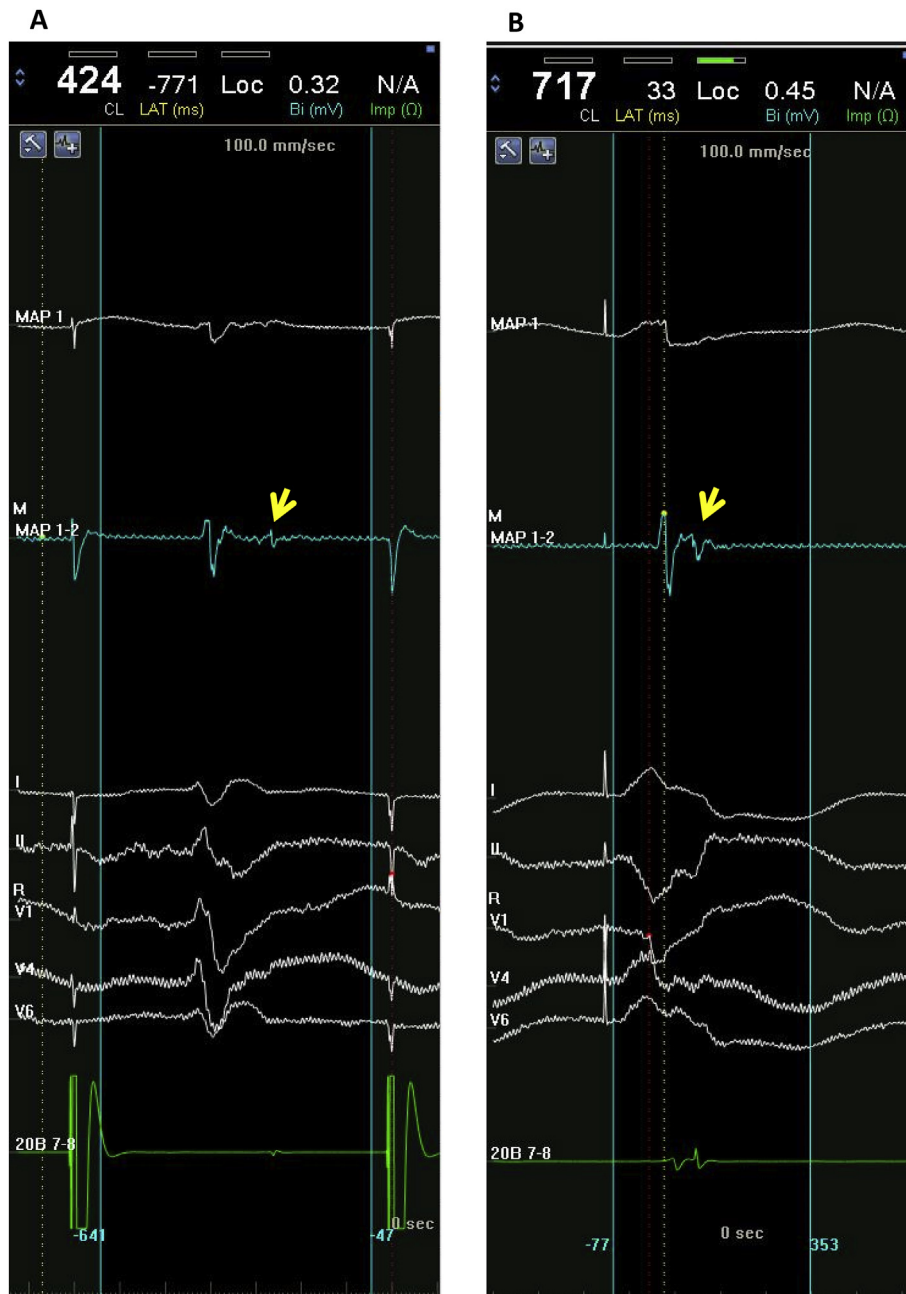
Fig. 1. Example of a change in potential during (a) atrial pacing (b) ventricular pacing. Note during atrial pacing there is a late potential that is fused during ventricular pacing to the local EGM (yellow arrow).

potential during atrial pacing that fuses during ventricular pacing. Fig. 2 shows as example of change in the voltage distribution and scar burden with change in rhythm in 1 patient. Table 3 summarizes the frequency of late versus fractionated potentials based on the scar distribution in individual patients. There was no significant difference in the frequency of late potentials in septal scars during atrial versus ventricular pacing (37 ± 12 versus 50 ± 20, p = 0.31) or in non-septal scars (29 ± 17 versus 51 ± 24, p = 0.13). Similarly, there was no significant difference in the frequency of fractionated potentials in septal scars (107 ± 42 versus 110 ± 39, p = 0.92) or in non-septal scars (90 ± 49 versus 97 ± 49, p = 0.83).

3.3. Outcomes

Amongst the 9 patients, 3 patients had at least 1 mappable VT and all patients had at least 1 unmappable VT. Thus, substrate based ablation and ablation targeted at pace mapping within the scar region were performed in all patients. Five of the patients were ablated based on substrate identified during an atrial paced rhythm and four patients were ablated based on substrate identified during a right ventricular paced rhythm. Programmed stimulation performed after ablation demonstrated non-inducibility in 3/5 atrial paced patients and 4/4 ventricular paced patients. In the 2/2 atrial paced patients who were still inducible post ablation, review of the ventricular paced map demonstrated a corresponding region where there were apparent late potentials not apparent in the atrial paced map, extending 2.5 mm beyond the margins where ablation had been performed in the latter (Fig. 3). Pace-mapping here exhibited similar morphology to the induced VT and further ablation resulted in non-inducibility in 1 though 1 patient was still inducible for a faster, non-
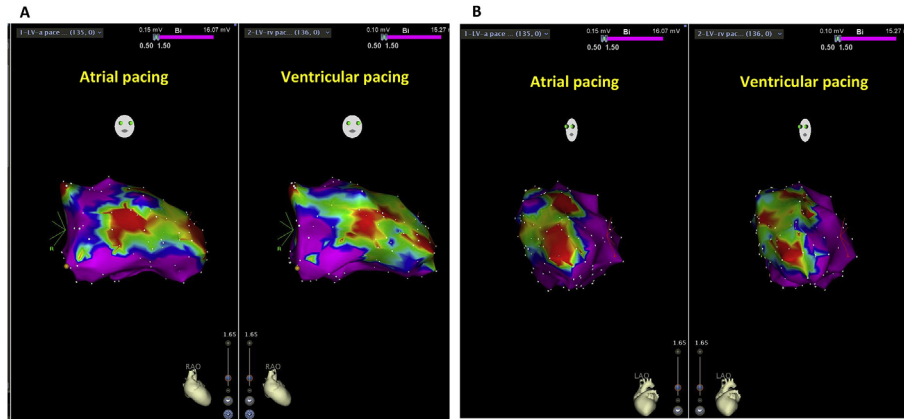
Fig. 2. Change in voltage at specific points during atrial vs. ventricular pacing (a) RAO (b) LAO.

Table 3
Scar distribution and impact of activation path on late and fractionated potentials.

Patient Number	Scar distribution	Late potentials		Fractionated potentials	
		A-pace	V-pace	A-pace	V-pace
1	Anterolateral	25	45	140	151
2	Inferior/inferolateral	43	75	113	116
3	Inferior	19	39	94	102
4	Inferior/inferoseptal	54	78	121	129
5	Septal	26	31	113	111
6	Inferior/inferolateral	49	76	94	99
7	Anteroseptal	31	45	145	143
8	Inferoseptal	37	45	47	55
9	Inferior/inferolateral	8	21	10	18

clinical VT that was not targeted. There were no adverse events during the study or as part of the ablation. Over 1 ± 0.5 year follow-up, there was no VT recurrence amongst 7 patients, 4 of whom remained on antiarrhythmic drugs (1 amiodarone, 2 sotalol) and 3 of whom discontinued antiarrhythmic drugs. The 2 patients with recurrence underwent redo ablation at 6 months and 9 months, respectively (1 was inducible at the end of the procedure). Notably, 1 of the patients had been ablated based on the atrial paced rhythm and the other based on a ventricular paced rhythm.
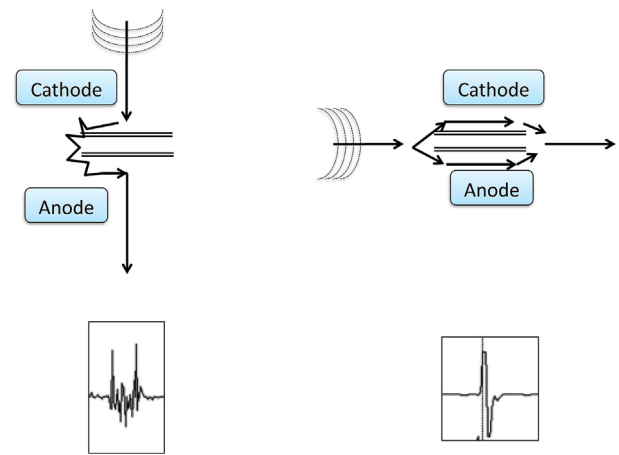

Fig. 4. Impact of wavefront directionality on electrogram. Shown is a schematic of how orientation of the wavefront to a region of myocardial abnormality may impact appearance of an electrogram. In the case of a wavefront that is perpendicular to an area of substrate, in which the wave must propagate slowly through channels in the substrate region, one may see a fractionated potential. If parallel, however, the electrogram may appear singular without fractionation if velocity is similar on both sides.
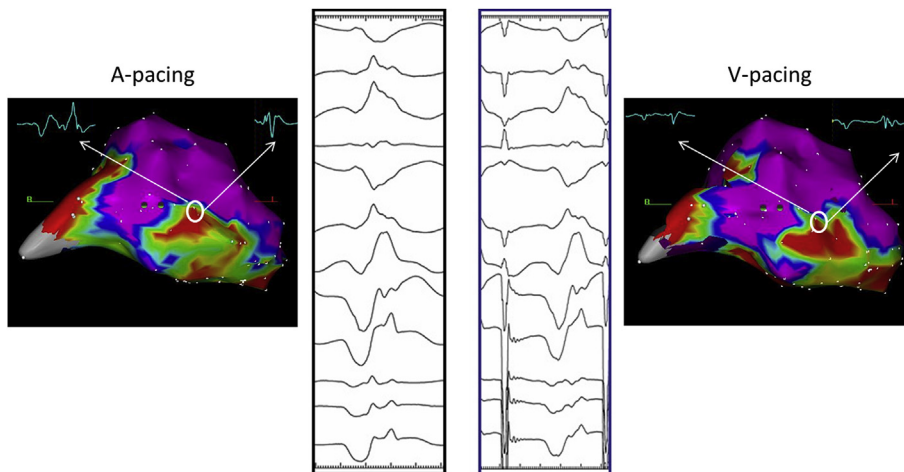

Fig. 3. Example of a case in which initial ablation was done on the atrial paced map. VT (middle left ECG) was still inducible. On the ventricular paced voltage map (right hand map) there were areas of late potentials not obvious during atrial pacing (left hand map), pacing at which showed similarity to the inducible VT. Ablation here rendered the patient subsequently non-inducible.
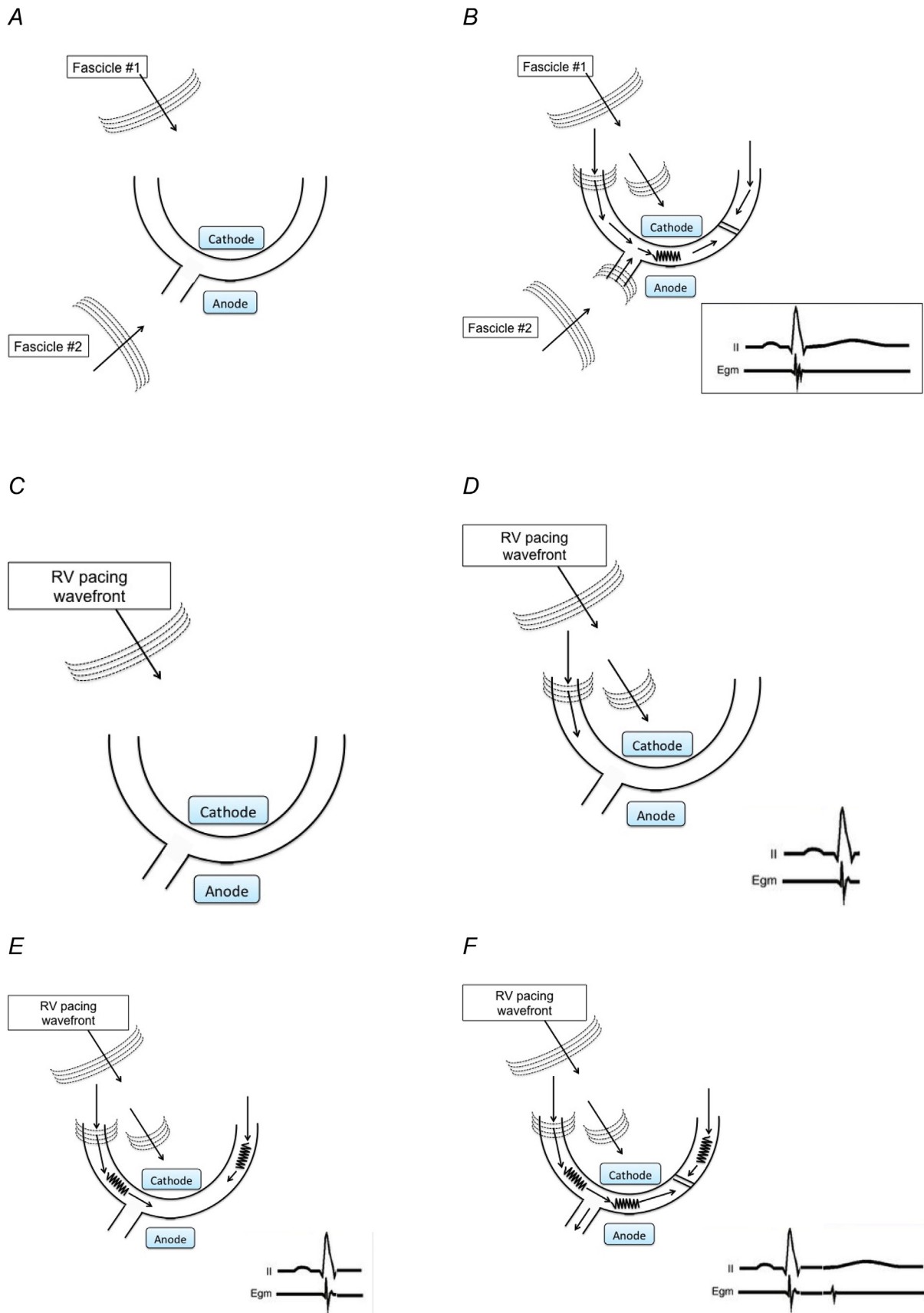
Fig. 5. Impact of normal His purkinje system conduction versus RV pacing on electrogram appearance in region of substrate. Demonstrated is one potential mechanism for why electrograms may appear different depending on the wavefront of activation. In Fig. 5A—B, there are two wavefronts from fascicular activation with entry into the substrate zone approaching the cathode from 2 angles — one through normal tissue and the other via the scar (5B). As a result, wavefronts all collide in the area of scar simultaneously resulting in appearance of a single signal. In Fig. 5C—F, there is a singular wavefront during RV pacing which results in a single electrogram as it reaches the cathode (5D). Then it slowly traverses the scar zone, eventually passing the bipolar recording electrode again resulting in a second (or late) potential.

4. Discussion

The main findings of this study are that the vector of ventricular depolarization alters the timing, amplitude, and quality of the signal during mapping. Furthermore, in one patient, the appearance of late potentials in RV pacing outside the scar area noted during atrial pacing were a target for additional ablation, resulting in non-inducibility. These findings support the critical importance of wavefront in discriminating local signals during cardiac mapping and ablation. Furthermore, as noted in Fig. 1, we demonstrate one case where a late potential visible during native conduction was not obvious during right ventricular pacing. This stands within reason as it can be assumed that a path of activation using *trans*-septal activation of the left ventricle during right ventricular pacing may similarly mask activation of certain potentials due to the activation path through a region of scar. Specifically, relative differences in path of activation and entrance into the scar zone during wavefront propagation from two different sites may alter the potential for unmasking signals suggestive of arrhythmogenicity. This principle partly underlies the reasoning of using at least two sites for stimulation during induction protocols in reentry based arrhythmias. Furthermore, the distribution of scar may impact the relevant effects of activation wavefront, with a greater effect on manifestation of late potentials with RV pacing for lateral scars than septal scars though this did not bear out in subgroup analyses in our study group.

Surviving myocardial cells in scar are a critical part of the VT circuit [8]. Sinus or atrial paced rhythm conducts via the fast Purkinje system and allowing synchronous activation of the LV in healthy and diseased myocardium [9,10]. During RV apical pacing, LV activation typically occurs *trans*-septally, though it is possible that the native conduction system could be engaged as well. For example, in some instances, part of the left ventricle during RV pacing may get activated via retrograde activation of the right bundle branch, thus resulting in different vectors of depolarization. Further, the orientation of the electrical wavefront, parallel or perpendicular, to the surviving myocardial cells may alter the temporal spacing of the recorded signals [11] (Fig. 4). Thus a late signal may become earlier in relation to the QRS complex depending on the propagation wavefront (Fig. 5). This may be the case in both cases of native conduction based ventricular activation or ventricular pacing.

In our study, there was a significant increase in LAVA points during RV pacing. This may be due to the lack of involvement of the conduction system allowing for slow conduction and better temporal resolution of the local signal. Moreover, this separation may have an effect on the amplitude of the local signal, thus changing the voltage in the area and alter the perceived "low voltage" potentials as seen in our study. Intervening areas of functional and anatomical block from scar may result in further change in the activation wavefront as has been described previously [12]. The lateness of LAVA has previously been shown to be dependent on the location of the scar [7]. This distance will also differ based on the direction of the wavefront as areas of early activation during sinus rhythm may become late during RV pacing, thus affecting LAVA characteristics and may be one of the reasons for the difference in the presented data. It is possible that consistent appearance of LAVA, irrespective of the rhythm, may be a more specific marker to identify high yield areas to target during catheter ablation. However, these inferences based on this small study are speculative at best and require more data. Furthermore, given our study was focused on the same precise spot being obtained during both pacing trains, many points were discarded for purposes of analysis and thus extrapolation of scar area due to the high amount of interpolation between a relatively smaller number of points comprising the overall map could not be done reliably.

4.1. Limitations

This is a proof-of-concept study and is best interpreted in the context of its limitations. This study did not account for disease within the conduction system, which may vary from patient to patient. We exclusively used the Carto mapping system for our study and our findings may not apply to other mapping systems due to differences in proprietary filters and algorithms. We did not assess the impact of different pacing cycle lengths as it may also alter local conduction velocity. Moreover, the clinical benefit in terms of improved outcomes of VT ablation of either approach is yet to be determined. Further, we did point to point mapping in order to ensure comparison during RV pacing and atrial pacing at *each point* dependably. Thus, the limited number of points obtained may limit extrapolation to cases of higher density mapping wherein less interpolation is needed. Finally, given the small number of patients considered, larger studies are required to determine consistency of the findings and potential role in defining ablation strategies when choosing the rhythm in which to map.

5. Conclusion

In conclusion, we here demonstrate that the rhythm at the time of mapping has a significant impact on the definition of the arrhythmic substrate of interest during ablation of VT. Future larger studies evaluating the role of each technique in overall outcomes (such as whether one rhythm is optimal over another) of the ablation procedure are needed.

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Ethical approval

The study was approved by the Mayo Clinic Institutional Review Board.

Informed consent

Informed consent was obtained from all included patients.

Declaration of competing interest

None of the authors have any conflicts of interest to disclose.

CRediT authorship contribution statement

Danesh K. Kella: Formal analysis, Writing - original draft. **Seth H. Sheldon:** Conceptualization, Data curation, Formal analysis, Writing - review & editing. **Amit Noheria:** Conceptualization, Data curation, Formal analysis, Writing - review & editing. **Deepak Padmanabhan:** Formal analysis, Investigation, Writing - review & editing. **Thomas Munger:** Investigation, Writing - review & editing. **Samuel J. Asirvatham:** Conceptualization, Methodology, Validation, Writing - review & editing. **Suraj Kapa:** Conceptualization, Methodology, Investigation, Formal analysis, Supervision, Validation, Writing - review & editing.

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