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Substrate mapping for scar-related ventricular tachycardia in patients with resynchronization therapy—the importance of the pacing mode

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Abstract

Purpose Targets for substrate-based catheter ablation of scar-related ventricular tachycardia (VT) include sites with fractionated and late potentials (LPs). We hypothesized that in patients with cardiac resynchronization therapy (CRT), the pacing mode may influence the timing of abnormal electrograms (EGMs) relative to the surface QRS complex.

Methods We assessed bipolar EGM characteristics in left ventricular low bipolar voltage areas (< 1.5 mV) from 10 patients with coronary disease and a CRT device undergoing catheter ablation for VT. EGMs at 81 sites were analyzed during three different pacing modes (biventricular (BiV), right ventricular (RV)-only, and left ventricular (LV)-only) pacing.

Results Stimulus to end of local electrogram duration (Stim-to-eEGM) depended significantly on the stimulation site (BiV, LV, or RV, $p = 0.032$). Single-chamber pacing unmasked LPs, not present during BiV pacing, in three patients. In another three patients, a concomitant increase in stimulus to end of surface QRS duration caused by single-site pacing compensated for the increase in Stim-to-eEGM duration, thereby prohibiting LP unmasking.

Conclusion The sequence of ventricular activation, as determined by the pacing site in patients with CRT devices, has a major influence on the detection of late potentials during substrate-guided ablation. Further study is warranted to define the optimal approaches, including the rhythm, for substrate mapping, but our findings suggest that BiV pacing may be most likely to obscure detection of late potentials as compared to single-site pacing.

Keywords Ventricular tachycardia · Catheter ablation · Ischemic heart disease · Substrate modification · Cardiac resynchronization therapy

1 Introduction

Monomorphic ventricular tachycardia (VT) is an important cause of morbidity and increased mortality in patients with structural heart disease [1]. Catheter ablation can reduce the burden of defibrillator shocks, can improve quality of life, and can be life saving in VT storm [2–4]. Percutaneous catheter ablation has been shown to be superior to anti-arrhythmic drugs alone in preventing VT recurrences [5].

Channels of surviving myofibers within scar tissue create the arrhythmogenic substrate for scar-related reentrant VT and are targets for catheter ablation [6]. These channels can be identified by using activation and entrainment mapping, but this approach requires mapping during tachycardia, which is often limited by non-inducibility or poor hemodynamic tolerance [7]. A substrate-based approach targeting abnormal, fractionated LPs identifiable in sinus or paced rhythm is widely employed [8]. While many definitions for LPs are described, the most reproducible definition is that of a bipolar electrogram (EGM) that is recorded after the inscription of the end of the surface QRS complex [9].

Drs. Baldinger and Kumar contributed equally to this manuscript and share first authorship.

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Pacing maneuvers may unmask abnormal EGMs by separating them from the ventricular far-field signal [10, 11]. This can be explained by an increased delay of the local EGM with faster paced cycle length or with extrastimuli but may also be influenced by changes in the direction of wavefront activation of the tissue creating the local EGM relative to the rest of the myocardium [12].

In patients with cardiac resynchronization therapy (CRT) abnormal tissue can be activated from the right ventricular (RV) or left ventricular (LV) pacing lead. We hypothesized that the pacing mode may influence the timing of EGMs relative to the surface QRS complex. In addition, biventricular (BiV) pacing, by decreasing the activation times across the heart and in surviving myofibers within scar tissue, may hide LPs (Fig. 1).

We sought to assess the timing of abnormal EGMs recorded at identical locations within bipolar low-voltage zones during BiV, LV, and RV pacing. We surmised that the mode of pacing fundamentally influences the identification of substrate-based ablation targets in patients with structural heart disease undergoing catheter ablation for scar-related VT.

2 Methods

2.1 Study population

Unselected patients with coronary artery disease and CRT devices, undergoing catheter ablation for VT between July 2014 and June 2016, were prospectively studied. Data collection was performed according to protocols approved by the Human Research Committee of Brigham and Women's Hospital. Each patient gave written informed consent for the electrophysiology procedure. During this time, 128 patients with ischemic heart disease underwent ablation for sustained monomorphic VT; of these, 36 had a CRT device and 10 were suitable for substrate mapping with pacing from multiple sites; 26 patients were excluded due to individual operator decision to begin ablation before complete substrate mapping.

2.2 Catheter mapping and ablation

Procedures were performed under either conscious sedation or general anesthesia as described previously [13]. Standard CRT device programming included a voltage safety margin

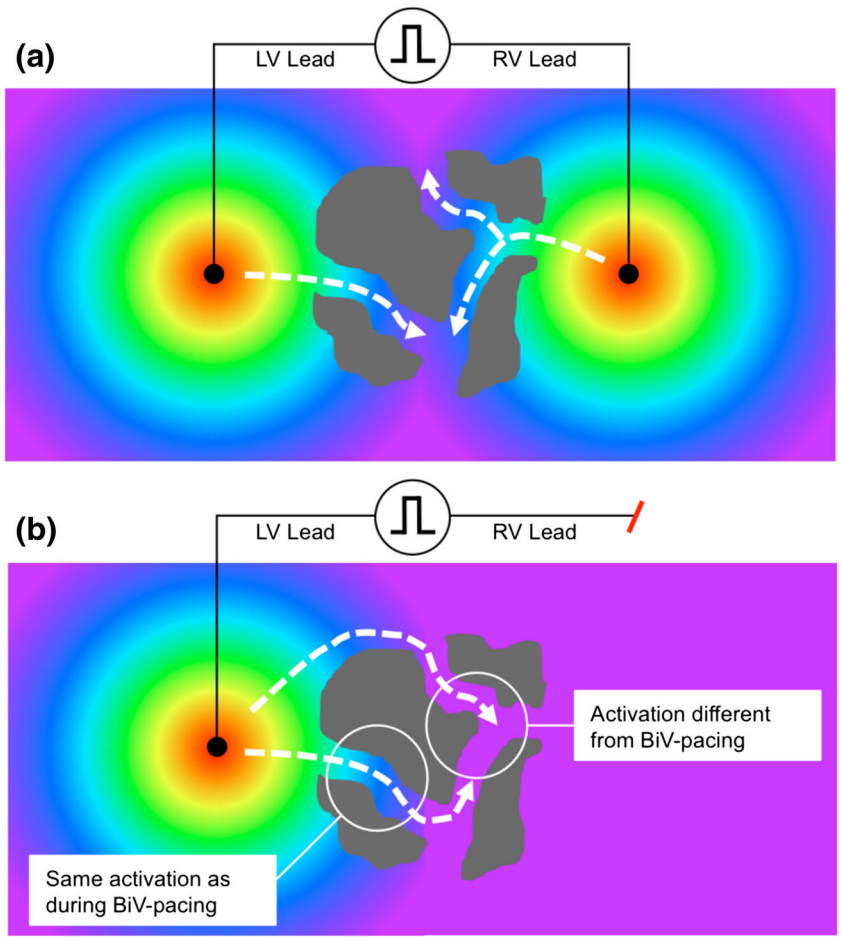

Fig. 1 The figure illustrates the theoretical activation sequence of VT channels during BiV pacing compared to single-chamber pacing. In regions activated by the RV lead during BiV pacing, the activation sequence will be the same during RV-only pacing but different during LV pacing and vice versa

Table 1 Baseline characteristics

	$n = 10$
Patient characteristics	
Age (years)	72 (66–77)
Male gender	10 (100)
Hypertension	8 (80)
Hyperlipidemia	8 (80)
Diabetes	4 (40)
Body mass index (kg/m^2)	31 (27–35)
NYHA class	2 (2–3)
Ischemic heart disease	10 (100)
CRT-D	10 (100)
Number of failed AAD	2 (1–2)
Failed treatment with amiodarone	7 (70)
Echocardiography	
Left ventricular ejection fraction (%)	20 (20–25)
Left ventricular end-diastolic diameter (mm)	66 (62–68)
Previous procedures	
Patients with prior cardiac surgery	7 (70)
Coronary artery bypass grafting	7 (70)
Other	1 (10)
Patients with prior VT ablations	4 (40)

Values are presented as median (interquartile range), or as *n* (%)

VT ventricular tachycardia, *ADDs* antiarrhythmic drugs

of at least 100% over pacing threshold. Pacing output was not changed for the procedure. Devices were programmed to VOO or DOO with a short AV delay and pacing rates between 60/min and 90/min. Programmed ventricular stimulation was performed at the beginning of the procedure to document inducible VT. At the end of the procedure, the same stimulation protocol was repeated to assess acute success. A detailed electroanatomic map was initially created during BiV pacing using an electroanatomic mapping system (CARTO3®, Biosense Webster, Diamond Bar, CA) and a multipole, multispline catheter (Pentaray® NAV; Biosense Webster). Sites of abnormal EGMs were tagged. After completion of the electroanatomical map, the multispline catheter was positioned at a stable site with abnormal EGMs, within or at the border of the scar, confirmed by 3-D mapping and fluoroscopy, and the CRT device was programmed to LV-only pacing and then to RV-only pacing. EGMs were recorded in all pacing modes from the multispline catheter maintained at the same position. Pacing rate was not changed for mapping when switching from BiV to RV- or LV-only pacing. Thus, bipolar EGMs from the multipolar catheter were recorded at identical sites during all three pacing modes (BiV, RV, and LV) at 10 sites in 10 patients. After exclusion for unstable, or absent electrograms, a total of 81 EGMs were available for analysis.

VT was then initiated with programmed stimulation, and entrainment maneuvers were performed at selected sites. Ablation was performed with a 3.5-mm-tip open-irrigated catheter (ThermoCool® SmartTouch; Biosense Webster) at putative isthmus sites. If the induced VT was hemodynamically unstable, it was terminated and ablation was continued during sinus rhythm targeting regions showing abnormal EGMs and with long-paced stimulus to QRS delays [14].

2.3 Late potential maps and stimulus to end of electrogram durations

Late potentials were defined as any bipolar EGM recorded after the inscription of the end of the surface QRS complex [9]. For every EGM recorded from the multispline catheter in the low-voltage area, the last distinct component was annotated on the electroanatomic mapping system thereby creating maps of the latest activation. For all EGMs recorded at the identical site from the multispline catheter during BiV, RV, and LV pacing, the duration from the stimulus to the end of the EGM (Stim-to-eEGM) was measured and mean values

Table 2 Scar locations and lead positions

Patient	Scar location	Pentaray location	RV lead	LV lead	Late potentials present
1	Anterior, septal, inferior	Septal scar	Apical	Anterolateral	No LPs
2	Anterior	Anterolateral scar border	Apical	Lateral	LPs during BiV and RV pacing
3	Anterior, septal	Anterior scar	Apical	Posterolateral	LPs during BiV pacing, additional LPs during RV pacing
4	Anterior, septal, apical	Apical scar	Apical	Lateral	LPs during BiV and RV pacing
5	Anterior, septal, apical	Anteroseptal scar	Apical	Posterolateral	LPs only during LV pacing
6	Inferolateral	Inferior scar border	Septal	Lateral	LPs only during BiV pacing
7	Inferior, inferoseptal	Inferior scar	Apical	Anterolateral	No LPs
8	Anterior	Anterior scar	Apical	Posterolateral	LPs during BiV and RV pacing
9	Inferoseptal, apical	Apical scar	Apical	Lateral	No LPs
10	Inferior, lateral	Inferior scar border	Septal	Posterolateral	LPs only during LV pacing

BiV biventricular, *LP* late potential, *LV* left ventricle, *RV* right ventricle

Table 3 Procedural data

	BiV pacing	RV pacing
Total mapping points	459 (286–893)	384 (297–418)
Total scar points (< 1.5 mV)	356 (243–821)	304 (274–368)
Point density (points per cm^2)	3.4 (2.6–9.9)	3.4 (2.7–4.4)

Values are presented as median (interquartile range)

were calculated for all pacing modes separately in order to compare mean EGM latest activation.

2.4 Statistical analysis

Continuous variables are presented as median (and interquartile range) and minimum and maximum values for selected variables. Median values were compared by a Friedman test or by a Wilcoxon signed-rank test as appropriate. The Bonferroni–Holm method was used to correct for multiple testing. Categorical variables are expressed as counts (percentage). Throughout all calculations, a 2-tailed p value < 0.05 was considered statistically significant. Data analysis was performed using IBM SPSS Statistics for Mac, version 22.0 Armonk, NY, and R version 3.2.1.

3 Results

A total of 10 male patients, 72 years (66–77), were studied. Median left ventricular ejection fraction was 20% (20–25). Baseline characteristics are summarized in Table 1. Scar areas were defined as regions of low bipolar voltage (< 1.5 mV). Scar locations and lead positions are shown in Table 2. The median total low-voltage area (< 1.5 mV) within the LV was 92.0 cm^2 (67–125) when assessed during BiV pacing. Mapping data are summarized in Table 3.

Median stimulus to end of QRS duration was 180 ms (164–186) during BiV pacing, 258 ms (244–281) during LV pacing, and 234 ms (222–268) during RV pacing.

At 81 selected sites, EGMs were recorded in all three different pacing modes without changing the multipolar catheter position. Variability in electrograms was frequently observed:

- At least one LP was recorded in five patients during BiV pacing.
- In five patients, BiV and RV pacing showed the same EGM activation sequence. During LV pacing, however, the activation sequence changed and the median Stim-to-eEGM duration increased (Fig. 2, blue lines).

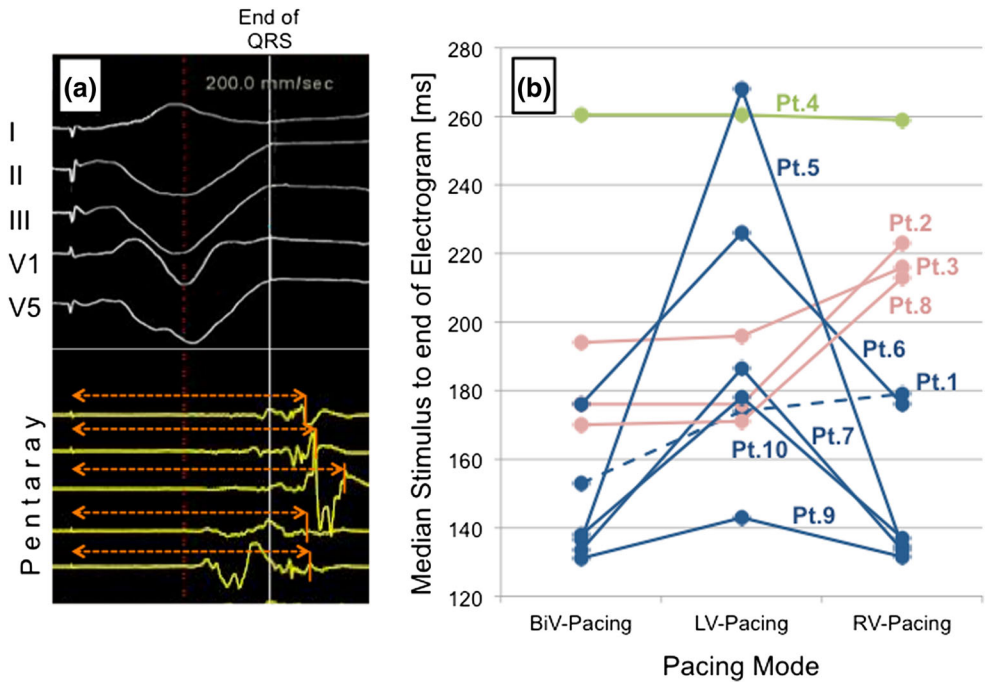

Fig. 2 **a** Example EGMs from patient 3. EGM delays were compared by calculating the median value for Stim-to-eEGM durations recorded from the multispline catheter in the low-voltage area (median of the intervals indicated by orange double arrows). **b** Shown are median Stim-to-eEGM durations for all 10 patients during different pacing modes. In five patients, BiV and RV pacing showed the same median Stim-to-eEGM duration with longer values during LV pacing (blue lines). In three patients, BiV and LV pacing showed the same median Stim-to-eEGM duration with longer values during RV pacing (red lines). In one patient, median Stim-to-eEGM duration was the same in all pacing modes (green line). In one patient, the Stim-to-eEGM duration was longer during RV and LV pacing, compared to BiV pacing (dashed blue line). LPs were unmasked by LV pacing in patients 5 and 10 and by RV pacing in patient 3

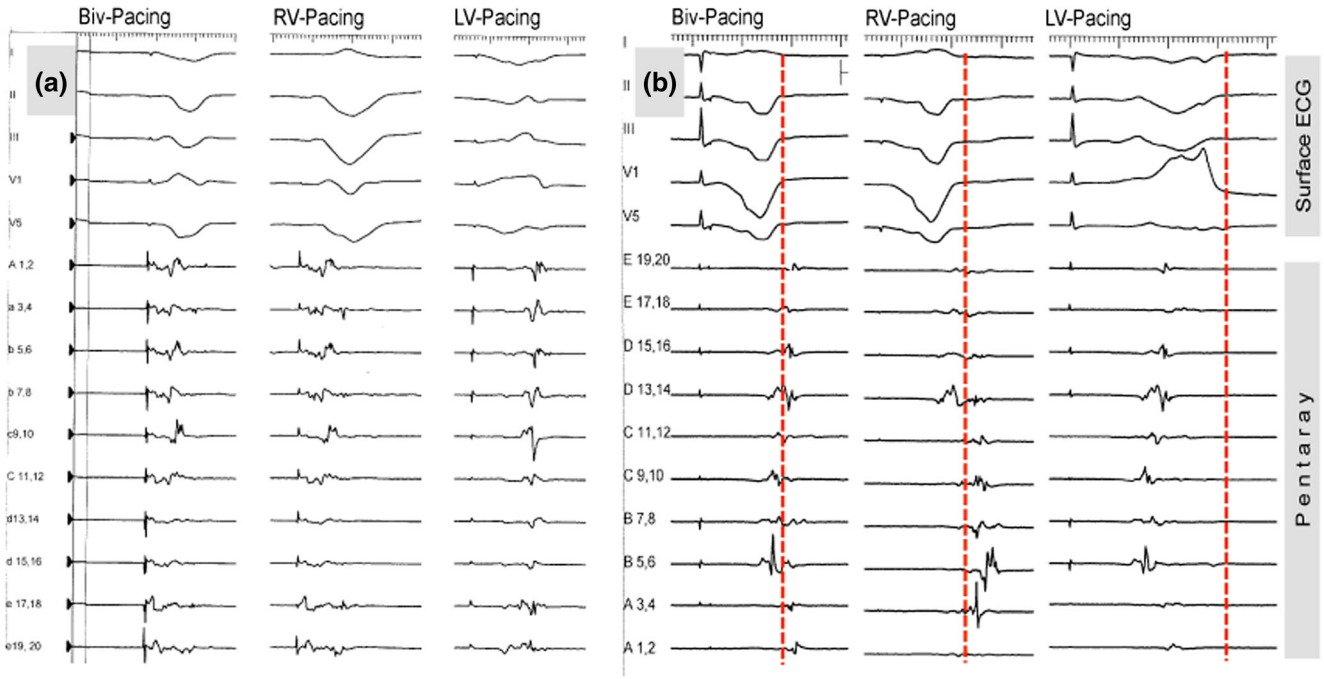

Fig. 3 Electrograms recorded at the same site during BiV, RV, and LV pacing in two different patients (**a**, **b**) are shown. **a** Example EGMs from patient 7. The activation sequence and delay of the EGMs recorded from the multispline catheter do not change between BiV and RV pacing but show a different pattern during LV pacing, however, without any EMGs recorded after the inscription of the surface QRS. **b** Example EGMs from patient 3. LPs are already present during BiV pacing. The activation sequence during RV pacing changes compared to BiV pacing resulting in multiple additional components now being recorded after the end of the surface QRS (red dotted line). The activation sequence during LV pacing is the same as during BiV pacing but the long stimulus to QRS duration and the wider QRS complex during LV pacing causes the EGMs that were recorded after the QRS complex during BiV pacing to occur prior to the end of the QRS (LPs are hidden)

- In three patients, BiV and LV pacing showed the same EGM activation sequence. During RV pacing, however, the activation sequence changed and the median Stim-to-eEGM increased (Fig. 2, red lines).
- In one patient, the EGM activation sequence was different during LV pacing compared to BiV and RV pacing but median Stim-to-eEGM duration was the same in all pacing modes (Fig. 2, green line).
- In one patient, the Stim-to-eEGM duration was longer during RV and LV pacing, compared to BiV pacing (Fig. 2, dashed blue line).

Stim-to-eEGM duration depended significantly on stimulation site (BiV, LV, or RV, $p = 0.032$). Pairwise comparisons amongst groups revealed that this was related to an increase in Stim-to-eEGM duration if patients were paced in the LV instead of BiV ($p = 0.023$). EGM examples are provided in Fig. 3.

The increase in Stim-to-eEGM duration during RV or LV pacing unmasked LPs, not present during BiV pacing, in three patients (patient 3, 5, and 10). Figure 4b, c shows an example of late potential activation maps created during BiV and RV pacing. In another three patients, the increase in stimulus to end of QRS duration caused by RV or LV pacing compensated for the increase in Stim-to-eEGM duration; thereby, although the Stim-to-EGM interval prolonged, the end of the QRS was also later and the electrogram did not fall after the QRS (Fig. 3b).

4 Discussion

LPs defined as EGMs recorded after the terminal inscription of the QRS complex have been suggested to be potential targets for catheter ablation [8]. The concept behind this approach is that LPs are recorded from poorly coupled surviving myofibers within scar tissue. However, the lateness of an EGM is not only defined by the conduction delay but also from the activation sequence of the EGM relative to the rest of the myocardium.

In this study, we show that in patients with coronary artery disease and CRT devices, the pacing mode influences the timing of abnormal EGMs relative to the pacing stimulus. The Stim-to-eEGM duration most often differs when pacing from the RV compared to the LV lead in patients with CRT devices. The distance from the pacing leads to the tissue generating abnormal EGMs and the electrical propagation properties of the tissue in-between determines the Stim-to-eEGM duration. Therefore, the lead that shows the shorter Stim-to-

eEGM duration during single-chamber pacing determines the Stim-to-eEGM duration during BiV pacing and can usually be identified by comparing BiV to LV and RV pacing.

EGMs that are recorded late during single-chamber pacing may be activated earlier by the other wavefront during BiV pacing and can therefore be hidden within the QRS complex during BiV pacing. In this situation, single-chamber pacing can unmask LPs by increasing the delay of EGMs. On the other hand, the increase of the QRS duration during single-chamber pacing (compared to BiV pacing) may compensate for this delay or even "hide" LPs.

Earlier work by Tung and coworkers showed that different activation wavefronts may influence bipolar and unipolar scar characteristics, especially in areas without any dense scar. In this study, we show that the timing of an abnormal EGM relative to the QRS complex should not be considered as an unchangeable characteristic of the tissue creating the EGM but is greatly influenced by the activation sequence. These findings suggest that the pacing mode can influence selection of ablation sites for substrate mapping, and therefore could influence the outcome of VT ablation. Additional maneuvers, such as pacing from another location or at faster rates, changing the pacing mode in CRT patients, using programmed stimulation with decremental extrastimuli or pacing from the ablation catheter to assess pace capture and the stimulus to QRS delay and pace-map QRS morphology, as suggested by Jais and coworkers, may help to target abnormal substrate more specifically [10, 11, 14, 15].

5 Limitations

This study includes a limited number of patients referred to a tertiary care center for VT ablation. Recordings at identical sites during multiple pacing modes for the entire substrate would be of interest, but were not felt to be practical and therefore were obtained only at a one site selected based on presence of an abnormality during the

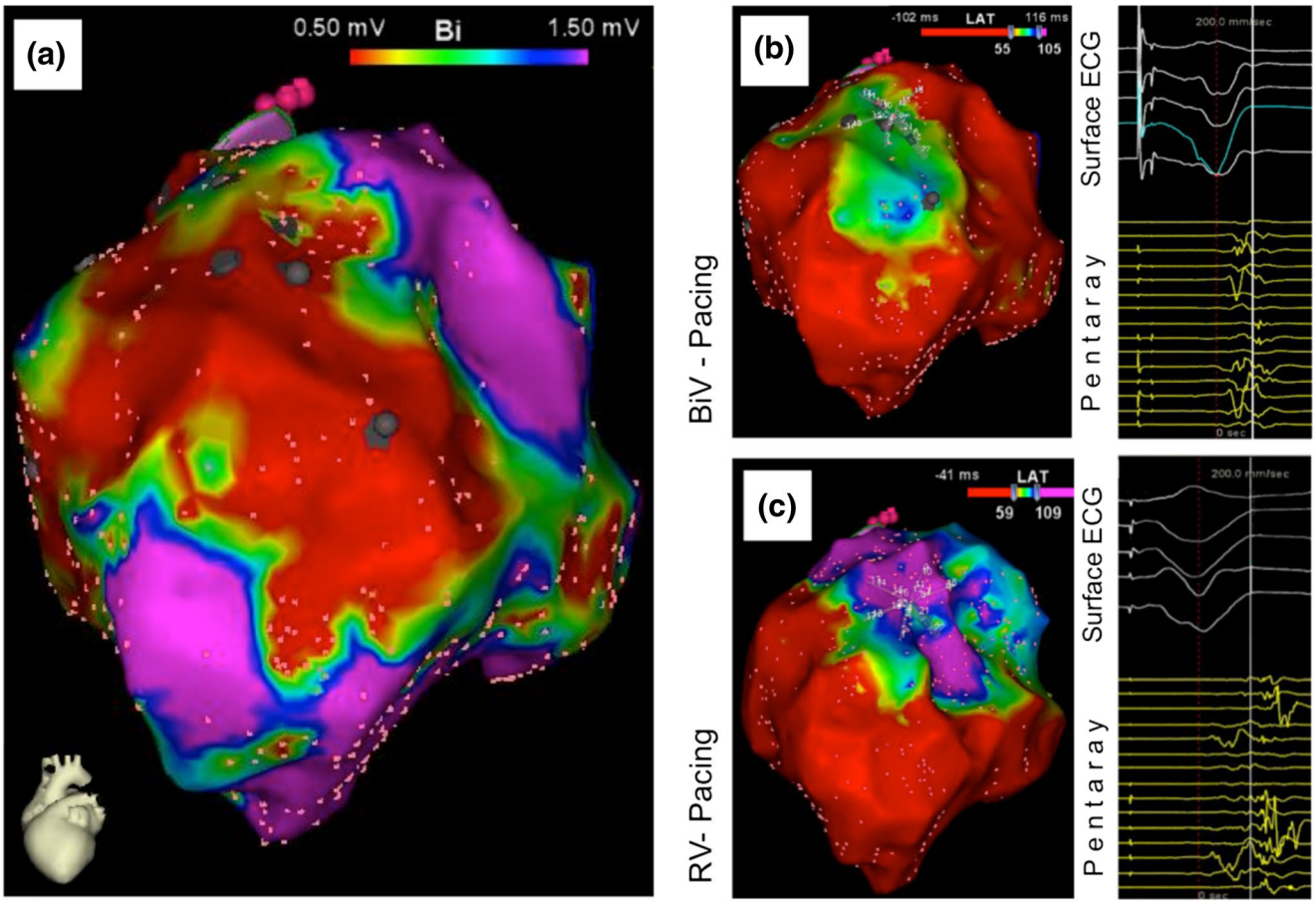

Fig. 4 Bipolar voltage map (**a**) and LP maps during BiV- (**b**) and RV-only (**c**) pacing from patient 3 with a large anteroseptal low-voltage area are shown. Areas with EGMs recorded during the QRS are in red, and areas with electrograms inscribed after the surface QRS are coded according to progressive later Stim-to-EGM interval in yellow, green, blue, and purple, with purple being the latest. The white horizontal line indicates the end of the surface QRS complex. Representative EGMs for each panel are shown in the far right hand panels during BiV (**b**) and RV only (**c**). More LPs and overall later EGMs are present during RV pacing

pacing mode being mapped for each patient. Thus, although an impact of pacing mode was observed in the majority, the precise frequency with which this occurs is not certain. The majority of patients had anterior or anteroseptal scars. Therefore, this study does not examine the effect of pacing mode specific to scar distribution or pacing lead location. Since signal filter settings and electrode spacing substantially influence signal characteristics [16], our results may be different for other recording systems, catheters, and filter settings. We were not able to relate particular LPs to specific VT circuits because mapping during VT was limited in these patients due to hemodynamic intolerance or non-inducibility. Most cases have been performed without any integration of fluoroscopic images into the 3-D mapping system. We therefore do not have any information on scar around the pacing leads that could have an influence on the stimulus-to-QRS interval and the activation wavefront.

6 Conclusions

The sequence of ventricular activation, as determined by the pacing site in patients with CRT devices, has a major influence on the detection of late and fractionated potentials during substrate guided ablation. Further study is warranted to define the optimal approaches, including the rhythm, for substrate mapping, but our findings suggest that BiV pacing may be most likely to obscure detection of late potentials as compared to single-site pacing.

Author contributions Samuel H. Baldinger: concept/design, data analysis/interpretation, drafting of manuscript
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Akira Fujii: data collection, critical revision
Andreas Haeberlin: statistics, critical revision
Jorge Romero: critical revision
Laurence M. Epstein: critical revision
Gregory F. Michaud: critical revision
Roy John: critical revision
Usha B. Tedrow: critical revision
William G. Stevenson: concept/design, data interpretation, critical revision

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Compliance with ethical standards

Data collection was performed according to protocols approved by the Human Research Committee of Brigham and Women's Hospital. Each patient gave written informed consent for the electrophysiology procedure.

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