Electrocardiographic and electrophysiological characteristics of idiopathic ventricular arrhythmias with acute successful ablation at the left ventricle basal inferoseptum near the mitral annulus

Short Title: VAs at the LV-BIS-MA

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Abstract Introduction: We sought to clarify the electrocardiographic and electrophysiological characteristics of ventricular arrhythmias (VAs), including idiopathic ventricular tachycardia (VT) and

premature ventricular contractions (PVCs), with acute successful radiofrequency catheter ablation (RFCA) at the left ventricle basal inferoseptum near the mitral annulus (LV-BIS-MA).

Methods and Results: Twenty-five patients with acute successful RFCA at the LV-BIS-MA were included in this study. The S wave amplitudes on lead III during VAs were 1.54 ± 0.38 mV, significantly larger than that on lead II (0.55 ± 0.19 mV) and aVF (1.04 ± 0.31 mV) ($P < 0.01$). Precordial R/S >1 transition before Lead V_2 and S-waves in lead V_6 were recorded in 100% and 48.0% of patients, respectively. The earliest bipolar activation preceded the QRS onset by 32.3 ± 11.5 ms. Pace mapping demonstrated perfect QRS morphology match only in 56.0% of patients. The RFCA start-to-effect time was 10.2 ± 5.8 seconds (s) in 21 patients (84.0%). In the remaining 4 patients (16.0%), the mean duration of successful RFCA was not well determined due to infrequent nature of clinical VAs during ablation. Trans-septal approach were utilized in all the 25 cases. Intra-cardiac echocardiography (ICE) showed that the ablation catheter tip was underneath the anterior leaflet of the mitral valve via the reversed C-curve technique. Early (within 3 days) and late (one-year) recurrence rates were 4.0% (one patient) and 12.0% (three patients), respectively. No complications occurred during RFCA or the one-year follow up.

CONCLUSION: LV-BIS-MA VAs are a subgroup of idiopathic VAs with distinctive ECG and EP features. RFCA via a transseptal approach using a reversed C curve technique is effective for better identification and targeting the areas of VAs origin and ICE showed that the ablation catheter tip was underneath the anterior leaflet of the mitral valve.

KEYWORDS Catheter ablation; Electrophysiology mapping; Electrograms; Ventricular arrhythmia; Mitral annulus

1 Introduction

Most idiopathic ventricular arrhythmias (VAs), including idiopathic ventricular tachycardia (VT) and

premature ventricular contractions (PVCs), have a right ventricular outflow tract (RVOT) or left ventricular outflow tract (LVOT) origin, but some may arise from other anatomical sites, including the right or left ventricular (LV) epicardial site, the aortic sinus cusps (ASCs), the aortomitral continuity (AMC), around the anterior portion of the mitral annulus and other sites.[1-3] Radiofrequency catheter ablation (RFCA) has emerged as a treatment for these idiopathic VAs and has a fairly high success rate. Recently, several cases of VAs have been reported to be successfully ablated at the left ventricle basal inferoseptum near the mitral annulus (LV-BIS-MA).[4,5] However, little is known about the prevalence, electrocardiographic (ECG) and electrophysiological (EP) characteristics, efficacy of RFCA and follow-up findings of LV-BIS-MA VAs. This study was undertaken to clarify these points.

2 Methods

2.1 Patient Selection

Among 543 consecutive patients who presented with VAs for RFCA, including idiopathic VT and PVC, between July 2010 and November 2019, 25 (4.6%) patients were found to have an acute successful RFCA of VAs at the LV-BIS-MA. None of these patients exhibited significant coronary artery disease by coronary angiography or CT coronary angiography and any structural heart disease. They failed beta-blocker or at least one anti-arrhythmic drug therapy. Monomorphic non-sustained VT (defined as three or more consecutive PVCs, was present in 2 patients, and monomorphic PVCs were seen in the remaining 23 patients. All patients were in normal sinus rhythm (SR) before RFCA. Twelve-lead ECGs and 24-h ambulatory Holter were carried out at least once before RFCA. The demographic and clinical data, including patient age, sex, height, weight, biochemical blood examination results, echocardiographic parameters and clinical arrhythmias, were collected prior to the procedure. The study protocol was reviewed and approved by the hospital's ethics committee, and all patients

provided written informed consent before undergoing RFCA.

2.2 ECG analysis

All antiarrhythmic drugs were discontinued at least 5 half-lives before the ECGs were recorded for analysis. Twelve-lead ECGs were recorded utilizing the Libang Electrical System (Libang ECG recording, Libang Medical, Shenzhen, China). The ECGs were analyzed at a paper speed of 25 mm/s, and the signals were amplified at 10 mm/mV. VAs were analyzed for the following parameters: (1) The QRS duration; (2) The QRS amplitude in the inferior leads; (3) The maximum deflection index (MDI), defined as the duration from the earliest activation to the peak of the largest amplitude deflection divided by the total QRS duration, measured in the precordial leads; (4) The S-wave in lead V_6. All parameters were measured with electronic calipers by 3 experienced investigators blinded to the site of origin. The mean values of these measurements were used for analysis. If the inter-observer difference was more than 5 ms, a final decision was adjudicated by a joint meeting of the three investigators.

2.3 Preparation and activation mapping

All antiarrhythmic drugs were discontinued at least 5 half-lives before the EP study. Intracardiac tracings were recorded utilizing a Prucka CardioLab™ electrophysiology system (General Electric Health Care System, Inc, Milwaukee, WI, USA). If the clinical VAs did not occur spontaneously and were not induced at baseline, intravenous isoproterenol (0.5 to 2.0 g/min) was administered to induce the clinical VAs. A 7.5-French, 3.5-mm-tip, irrigated ablation catheter (F-curve, NaviStar ThermoCool or Smarttouch, Biosense Webster, Diamond Bar, CA, USA) was then introduced into the right ventricle (RV) via the right femoral vein. Mapping of the left ventricle (using a transseptal approach) was initiated after mapping the RV, and intravenous heparin was administered to maintain an activated clotting time of 250 - 300 seconds. Steerable sheath (MobiCath, Biosense Webster,

Diamond Bar, CA, USA) were advanced alternately only when the non-steerable sheath (8.5F SL1, St. Jude Medical, St. Paul, MN, USA) could not advance the ablation catheter to the LV-BIS-MA.

2.4 Electrogram (EGM) collection and analysis

During an episode of spontaneous clinical VA, activation mapping was performed on at least three arrhythmic beats at a mapping site. The unipolar EGM was recorded from the distal (D) electrode of the mapping catheter and filtered at 0.5-100 Hz. The bipolar EGM was recorded from the distal (D-2) electrode pairs of the mapping catheter and filtered at 30-500 Hz. All EGM and twelve-lead ECG data were stored on the multichannel mapping system for offline analysis with a paper speed of 100 mm/s.[6] The V-QRS interval was calculated from the start of the bipolar ventricular EGM to the earliest start of QRS complex from any lead (QRS from surface leads and EGM from all intra-cardiac channels). All parameters were measured with electronic calipers by 3 experienced investigators blinded to the site of origin. We adopted the mean values of these measurements as the data. If the inter-observer difference was more than 5 ms, a final decision was adjudicated by a joint meeting of the three investigators.

2.5 Pace mapping

Pace mapping during SR was performed at the earliest activation site using the distal bipolar electrodes at a coupling interval of the VA interval and a stimulus amplitude of 1 mA greater than the late diastolic threshold (up to a maximum output of 10 mA and pulse width of 2.0 ms). If present, a perfect pace-mapping match (12/12 leads) was indicative of the site at or in close proximity to the origin of VAs; otherwise, the activation mapping result was only used for guiding RFCA.

2.6 RFCA

RFCA was applied at the site where the earliest V-QRS interval or perfect pace-mapping match on ECG was recorded. RFCA was delivered using the power-control mode at a maximum power of 35 to

40 W and a temperature of 43℃ with irrigation mode at a flow rate of 17 mL/min. If the VA was not eliminated within 30 seconds after energy delivery, the energy application was terminated, and the RFCA site was tagged as an unsuccessful site on the map. If the VA was abolished within 30 seconds, the energy application was continued for a total of 180 - 240 seconds at and around the target site, and the site was tagged as a successful site on the map.

2.7 Definition of acute successful RFCA

Acute successful RFCA was defined according to the following criteria: absence of spontaneous or induced clinical VAs, both in the absence and presence of isoproterenol infusion after RFCA with observation lasting 0.5 to 1 hour.

2.8 Definition of VAs near the LV-BIS-MA

We defined an LV-BIS-MA location as follows: 1) The catheter tip demonstrated the LV-BIS-MA location when viewed on the right and left anterior oblique fluoroscopic views at the successful RFCA site; 2) The ratio of atrial to ventricular EGMs at the RFCA site was <1, and the amplitudes of the atrial and ventricular EGMs were > 0.08 mV and 0.5 mV at the RFCA site during sinus beat, respectively;[3] 3) Acute successful VAs elimination was achieved by RFCA energy delivery at the LV-BIS-MA location; 4) Intra-cardiac echocardiography (ICE) showed that the ablation catheter tip was underneath the anterior leaflet of the mitral valve via the reversed C-curve technique using the trans-septal approach.

2.9 Observation after RFCA and at the one-year follow up

The patients were monitored for at least 3 days in the hospital after RFCA, and twelve-lead ECG and 24-hour ambulatory Holter monitoring were carried out at least once during the 3-day hospitalization after RFCA. The patients were followed up in the outpatient arrhythmia clinic for one year, and twelve-lead ECG and 24-hour ambulatory Holter monitoring were carried out at least once

every three months. Clinical success was defined as free of clinical VAs (symptomatic or asymptomatic) that were targeted during RFCA at the follow-up visit, and at least 80% reduction of VAs burden documented on post-RFCA 24-hour Holter recording as compared to pre-RFCA VAs burden.

2.10 Statistical analysis

Continuous data are given as the mean ± SD, differences among groups were compared with one-way ANOVA. A p value <0.05 was considered to indicate statistical significance.

3 RESULTS

3.1 Location and frequency of VAs

Of 543 patients referred for RFCA of idiopathic VAs, twenty-five (4.6%) patients had successful RFCA at LV-BIS-MA location. The other origins were registered as follows: RVOT, 42.5%; ASC, 29.1%; AMC, 7.9%; tricuspid annulus (TA), 6.8%; papillary muscle, 3.1%; lateral and posterior portion of the MA, 5.7%; and possible right ventricular moderate band, 0.2%. The mean age of the 25 patients with LV-BIS-MA VAs was 67 ± 7 years with 20 males and 5 females, and their clinical characteristics were summarized in **Table 1**.

3.2 ECG characteristics of LV-BIS-MA VAs

During the clinical VAs, the R_{II}, S_{II}, R_{III}, S_{III}, R_{aVF} and S_{aVF} amplitudes were 0.17 ± 0.12 mV, 0.55 ± 0.19 mV, 0.05 ± 0.06 mV, 1.54 ± 0.38 mV, 0.09 ± 0.07 mV and 1.04 ± 0.31 mV, respectively (**Table 2**). The QRS duration, MDI were 165.8 ± 27.9 ms, 0.54 ± 0.08, respectively. Precordial R/S >1 transition before lead V_2 and S-waves in lead V_6 were recorded in 100% and 48.0% of patients, respectively. QRS morphology in lead V_1 of qr, R, qs pattern were recorded in 44.0%, 40.0%, 16.0%, of patients, respectively. QRS notching in inferior leads was not seen in all 25 patients.

3.3 Activation mapping of clinical LV-BIS-MA VAs

Detailed mapping of the middle cardiac vein, coronary sinus, right and left basal ventricular septal regions were performed in all the 25 patients. In all cases, the site of earliest activation was inferior and basal to the location of the His bundle electrogram on the LV septum. Furthermore, no areas of abnormal endocardial voltage were seen in both sides of the basal ventricular septal regions. Acute successful RFCA at the LV-BIS-MA site was achieved in all 25 patients with a transseptal approach. As shown in **Table 3**, the a/v amplitude ratio at the RFCA site during SR was 0.13 ± 0.10. The mean earliest V-QRS interval was 32.3 ± 11.5 ms, and initial unipolar QS-waves were recorded in 23 patients (92.0%). With bipolar mapping, isolated pre-potential, fragmented potential, earliest V-QRS interval without isolated pre-potential or fragmented potential preceding the QRS complexes was recorded in 3 (12.0%), 6 (24.0%), 16 (64.0%) of patients, respectively. ECGs from all these cases showed precordial R/S >1 transition before Lead V_2 and superior axis on inferior leads **(Figure 1A, 2A and 3A)**. Pace mapping and activation map in **Figure 1B/1D, 2B/2D** and **3C/3E** at the successful ablation site showed near identical match and with V-QRS interval of 57 ms/ 70ms/ 28ms for bipolar recording during PVC. The LV-BIS-MA PVC location was shown in **Figure 1E/1F**, 2**E/2F and 3F/3G (**Right and left anterior oblique fluoroscopic views). **Figure 1G** showed a non-sustained VT episode during RFCA with QRS morphology similar to the clinical PVC. ICE showed that the ablation catheter tip was underneath the anterior leaflet of the mitral valve via the reversed C-curve technique using the trans-septal approach (**Figure 3F, 3G** and **3H**).

3.4 Pace mapping

Perfect (12/leads) or near perfect (11/12 leads) pace maps to the QRS morphology of the clinical VAs were obtained in 14 patients (56.0%) at the successful RFCA site. A relatively large amount of myocardium could be captured around the pacing electrodes, which might have obscured subtle

changes in the QRS morphology in 11 (44%) of these patients.

3.5 RFCA at the LV-BIS-MA location

Complete elimination of the VA could be achieved by RFCA at the site where the earliest V-QRS interval was recorded at the LV-BIS-MA location. The mean duration of successful RFCA was 10.2 ± 5.8 s in 21 patients (84.0%). In the remaining 4 patients (16.0%), the mean duration of successful RFCA was not well determined due to infrequent nature of clinical VAs during ablation. Junctional rhythm was recorded in 1 patient (4.0%) after 21 seconds of RFCA, where the ablation was carried out only intermittently and was discontinued immediately when junctional rhythm occurred. No complications including atrioventricular block, pericardial effusion occurred during the RFCA procedure.

3.6 Observations after RFCA and at the one-year follow up

No complications occurred during at least 3 days of observation after RFCA or during the one-year follow-up period. Clinical VAs could still be recorded in 1 patient (4.0%) during 3 days of in-hospital monitoring after RFCA. During the one-year follow-up period, 3/25 (12.0%) patients had clinical VAs recurrence, and one patient undergo re-do procedure. The final RFCA target was the same as the index procedure based on X-ray fluoroscopic views and CARTO3 mapping result.

4 DISCUSSION

4.1 Main findings

The current study has four major findings. First, the frequency of LV-BIS-MA VAs confirmed by successful RFCA was 4.6% in 543 consecutive patients with idiopathic VAs in a single center. Second, precordial R/S >1 transition before Lead V_2 were recorded in 100% of patients and S_{III} amplitudes were significantly larger than S_{II} and S_{aVF} amplitudes without QRS notching in inferior leads in all the 25 patients. Third, RFCA via a transseptal approach using a reversed C curve technique is effective for

the acute elimination of these VAs. Forth, ICE showed that the ablation catheter tip was underneath the anterior leaflet of the mitral valve.

4.2 ECG characteristic of VAs from LV-BIS-MA

The origin of LV-BIS-MA VAs is located in the left inferior basal portion of the LV septum, distant from the precordial electrodes and lead III. The myocardium at the RFCA site is depolarized in a direction toward the precordial electrodes and backward the lead III. This could account for the early precordial transition and concordant positive QRS pattern in leads V_1 to V_5 and significantly larger S_{III} than S_{II} and S_{aVF}. The ventricular septum is oriented nearly horizontally to the electrode of lead V_1. The myocardium during LV-BIS-MA VAs may be depolarized to or away from the lead V_1. This may account for the different QRS morphologies in lead V_1 in different patients (**Table 2**). The ventricular septum and the rest of the myocardium were depolarized simultaneously during LV-BIS-MA VAs, which may explain the absence of notching in inferior leads or the absence of an s-wave in lead V_6. An electric impulse from LV-BIS-MA region takes more time to reach the Purkinje network to depolarize myocardium than that of an electric impulse from Purkinje network, resulting in a wide QRS duration and maximum deflection index (MDI) during LV-BIS-MA VAs. Our results of LV-BIS-MA VAs are different from those of right side para-Hisian VAs reported by Sun et al on the 25 consecutive patients[7]. In para-Hisian VAs, the magnitude of the R wave in lead II is larger than that in lead III and precordial R wave transition occurred between leads V_2 and V_3 in 17 of 25 (68%) patients. Liang JJ et al reported similar ECG characteristics of VAs from 25 patients with successfully ablated at the basal inferoseptal LV endocardium (BIS-LVe) with wider QRS duration of 178.2 ± 22.4 ms and MDI of 0.49 ± 0.04.[8] In contrast, LV-BIS-MA VAs in our study showed more than half of the patients with MDI ≥0.55. Based on the QRS morphology on 12-lead electrocardiographic recordings of our 25 patients and 44

patients from the aforementioned 2 studies, we proposed a flowchart to differentiate LV-BIS-MA VAs from other VAs (**Figure 4)**.

4.3 Hypothetical mechanism of VAs genesis near the LV-BIS-MA

The isolated pre-potential or fragmented potential at successful RFCA targets suggest a focal mechanism of either automaticity or triggered activity with a slow conduction area between the VAs origin and the ventricle breakout point (**Figure 1 and 2**). However, in 16 of 25 patients (64%), earliest bipolar V-QRS interval without isolated pre-potential or fragmented potential were recorded at the successful RFCA sites. This suggests that the VAs origin may be right at the ventricular breakout point without conduction delay, or maybe located at intramyocardial or epicardial location too small to be recorded.

While the mechanism of LV-BIS-MA VAs cannot be determined in our study, an appreciation of the particular anatomical-histological evaluation of this region potentially provides some insights. Yanni et al[9] reported histologically and histochemically different AV ring-specialized tissue at the MA and TA, which may lead to arrhythmia genesis. Tawara first described the structure of the compact AV node and its left and right posterior extensions.[10] Inoue S et al[11] reported that among 21 randomly selected and basically normal hearts obtained from autopsies, 13 showed posterior extensions of AV node on both the right and left sides, 7 showed a rightward posterior extension only, and only 1 heart showed a single leftward extension. The rightward extension ran close to the TA and the leftward extension ran close to the MA. McGuire MA et al[12] reported that microelectrode recordings revealed cells with nodal-type action potentials were found within 1 to 2 mm of the tricuspid and mitral valve rings. These nodal-type cells can response to adenosine, and lack of connexin-43. Ashikaga K et al[13] reported a VT case originating from the LV-BIS-MA, which could be induced by

exercise or an isoproterenol administration, but not by pacing. Frequent PVCs with the same QRS morphology as the VT were transiently suppressed by an adenosine triphosphate injection, suggesting that the mechanism was due to cyclic-AMP mediated triggered activity. We speculate that those nodal-type cells from the left posterior extension may represent the arrhythmogenic substrate for LV-BIS-MA VAs. Anisotropy of conduction velocity and refractory period could be existed between the so called left posterior extension and its neighbourring ventricular myocardium which may potentially provide the arrhythmogenic substrates for micro-reentry, abnormal automaticity or triggered activity near the LV-BIS-MA area. It will be important to test this in the future, both in the laboratory and in the clinical study, and this is an area for further electrophysiological study.

4.4 Related studies

Several previous studies have reported the successful ablation of VAs at or near the LV-BIS-MA location, however, none has systemically determined the prevalence, ECG and EP characteristics of VAs originating from the LV-BIS-MA location and short and long-term outcomes in as many patients as in this study.[2-5] Li A et al[14] reported such VAs significantly increased with intravenous isoproterenol infusion or became more prominent during the washout phase after infusion termination, instead of inducing by programmed stimulation, suggesting triggered activity or automaticity as the potential mechanisms. Kawamura M et al[15] reported idiopathic VAs from the cardiac crux with similar electrocardiographic characteristics and ablation is effective for eliminating these VAs. Ashikaga K et al[16] reported a PVC case which was transiently suppressed by an adenosine triphosphate injection, supporting cyclic-AMP mediated triggered activity.

4.5 Transseptal approach vs the transaortic approach

Both activation map and pace map methods were useful in identifying target sites for LV-BIS-MA VAs in this study. We choose trans-septal approach in all the 25 cases. Ouyang et al[17] reported transseptal

approach using a reversed S curve was effective for ablating ventricular arrhythmias arising from the LVOT below the aortic sinus cusps. The advantage of transseptal approach over the transaortic approach is mainly for easier catheter manipulation, easier advance to the VAs origin, avoiding obstacle of the aortic valve, chordae tendineae and papillary muscle and for avoiding passing catheters through tortuous iliac or femoral artery. Venous access also had low risk of hematoma with short bed rest time.

4.6 Study limitations

There are several limitations with this retrospective study. First, while isolated pre-potential or fragmented potential preceding the QRS complexes was recorded at the RFCA site, its genesis and significance were not determined. Second, the majority of the VAs were successfully ablated despite that isolated pre-potential or fragmented potentials during VAs were not recorded. The causes for lack of recording for isolated pre-potential or fragmented potential were only speculative. Third, this was a retrospective analysis result, which needs to be validated with a prospective study with a larger sample size.

5 Conclusion

LV-BIS-MA VAs are a subgroup of idiopathic VAs with distinctive ECG and EP features. RFCA via a transseptal approach using a reversed C curve is effective for the acute elimination of these VAs. ICE showed that the ablation catheter tip was underneath the anterior leaflet of the mitral valve. Advanced knowledge of the LV-BIS-MA anatomy, ECG and EP features may be useful in planning and facilitating the RFCA procedure.

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Figure Legends

Figure 1 Premature ventricular contraction (PVC) with acute successful ablation at the left ventricle basal inferoseptum near the mitral annulus (LV-BIS-MA). **A:** Twelve-lead electrocardiographic (ECG) morphology of the QRS complex during sinus rhythm (SR) and PVC. **B:** Pace-mapping QRS complex morphology. **C:** CARTO3 mapping indicates an acute successful RFCA site at the LV-BIS-MA. **D:** Earliest isolated pre-potential with V-QRS interval of 57 ms for bipolar recording during PVC, delayed potential during SR (arrow) and an a/v amplitude ratio of 0.15 during SR (paper speed 100 mm/s). **E and F:** Right and left anterior oblique fluoroscopic views indicate a reversed C curve at the LV-BIS-MA. **G:** Ventricular tachycardia episode during RFCA with QRS morphology similar to the clinical PVC. See

the text for further details (paper speed 25 mm/s unless indicated). CS= coronary sinus; ABL=ablation catheter; MAP 1-2 = bipolar recording; MAP 1 = unipolar recording; Stim = stimulation. The same explanation as in **Figure 2** and **3** unless indicated.

Figure 2 PVC with acute successful ablation at the LV-BIS-MA. **A:** Twelve-lead ECG morphology of the QRS complex during SR and PVC. **B:** Pace-mapping QRS complex morphology. **C:** CARTO3 mapping indicates an acute successful RFCA site at the LV-BIS-MA. **D:** Earliest fragmented bipolar potential with V-QRS interval of 70 ms for bipolar recording during PVC and an a/v amplitude ratio of 0.05 during SR (paper speed 100 mm/s). **E and F:** Right and left anterior oblique fluoroscopic views indicate a reversed C curve at the LV-BIS-MA.

Figure 3 PVC with acute successful ablation at the LV-BIS-MA. **A:** Twelve-lead ECG morphology of the QRS complex during SR and PVC. **B and C:** Clinical PVC and pace-mapping QRS complex morphology (paper speed 25mm/s). **D:** CARTO3 mapping indicates an acute successful RFCA site at the LV-BIS-MA. **E:** Earliest V-QRS interval of 28 ms for bipolar recording during PVC and an a/v amplitude ratio of 0.05 during SR (paper speed 100 mm/s). **E and F:** Right and left anterior oblique fluoroscopic views indicate a reversed C curve at the LV-BIS-MA. **H:** ICE showed that the ablation catheter tip was underneath the anterior leaflet of the mitral valve (arrow). I: PVC was successfully ablated within 12.4 seconds ablation (paper speed 10mm/s). ICE= intra-cardiac echocardiography; LA= left atrium; LV= left ventricle; IVS= intra-ventricular septum; MV=mitral valve.

Figure 4 Proposed algorithm to predict the precise focus of ventricular arrhythmias (VAs) at the LV-BIS-MA based on the QRS morphology on 12-lead ECG recordings. TA: tricuspid annulus; MA: mitral

annulus.