Reviews in Cardiovascular Medicine

Rev. Cardiovasc. Med. **2022**; 23(2): 044
http://doi.org/10.31083/j.rcm2302044

Review

Right ventricular outflow tract endocardial unipolar substrate mapping: implications in risk stratification of Brugada syndrome

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Academic Editor: Peter A. McCullough
Submitted: 12 October 2021 Revised: 29 December 2021 Accepted: 8 January 2022 Published: 25 January 2022

Abstract

Brugada syndrome (BrS) is a complex arrhythmogenic disease displaying electrical and micro-structural abnormalities mainly located at the epicardium of the right ventricular outflow tract (RVOT). It is well-known that fibrosis, fatty infiltration, inflammation and reduced gap junction expression have been demonstrated at the epicardial anterior aspect of the RVOT providing the arrhythmogenic substrate for ventricular arrhythmic events in BrS. A number of models have been proposed for the risk stratification of patients with BrS. Endocardial unipolar electroanatomical mapping is an emerging tool that has been reintroduced to identify and quantify epicardial electrical abnormalities. Interestingly, current findings correlate the presence of large-sized endocardial unipolar electroanatomical abnormalities with either ventricular fibrillation inducibility during programmed ventricular stimulation or symptom status. This review aims to present existing data about the role of endocardial unipolar electroanatomical mapping for the identification of RVOT epicardial abnormalities as well as its potential clinical implications in risk stratification of BrS.

Keywords: Brugada syndrome; Electroanatomical mapping; Risk stratification

1. Introduction

Brugada syndrome (BrS), a complex arrhythmogenic disease displaying electrical and micro-structural abnormalities mainly located at the epicardium of the right ventricular outflow tract (RVOT), is characterized by J-point elevation in the right precordial leads on the 12-lead electrocardiogram (ECG) and an increased risk of sudden cardiac death (SCD) due to ventricular fibrillation (VF) [1–5]. BrS is an inherited disease that is usually transmitted in an autosomal dominant manner [6]. The BrS related mutations are mainly associated with encoding of sodium channel, calcium channels and potassium channels [7]. The most important mutation is the *SCN5A*, encoding the sodium channel α-subunit, account for 20 to 30% of patients with BrS [7,8]. Specifically, BrS has been associated with reduced INa and loss-of-function *SCN5A* gene mutations. Regarding the pathophysiological basis of BrS, abnormal depolarization, abnormal repolarization, and current-load-mismatch are the three hypotheses that have been proposed in the literature [9,10].

Fibrosis, fatty infiltration, inflammation and reduced gap junction expression have been demonstrated at the anterior aspect of the RVOT epicardium providing the arrhythmogenic substrate for sustained VF in BrS [4,5,11,12]. Epicardial substrate catheter ablation has been associated with electrocardiogram normalization and ventricular arrhythmia non-inducibility in patients with BrS supporting the current consideration of an epicardial disease [13–15]. Endocardial unipolar electroanatomical mapping (EAM) is an emerging tool that has been reintroduced into clinical practice for the identification and quantification of epicardial electrical abnormalities in specific cardiomyopathies with several clinical implications, including risk stratification for sudden cardiac death [16]. Risk stratification for BrS patients, and especially of asymptomatic ones, remains challenging [17]. Due to certain limitations of the current

risk factors predictors, including programmed ventricular stimulation (PVS), multiparametric scores have been established for risk stratification [18,19]. This review article questions the accuracy of endocardial unipolar EAM for the identification of RVOT epicardial electrical abnormalities as well as its potential clinical implications in risk stratification of BrS.

2. The arrhythmogenic substrate of Brugada syndrome is related to structural abnormalities

Accumulating data suggest that mild structural abnormalities including inflammation, fatty infiltration, and fibrosis, mainly located at the epicardial aspect of the RVOT, provide the arrhythmia substrate in BrS. Lymphocytic myocarditis has been detected in endomyocardial biopsy samples in 77% of patients with BrS without structural abnormalities assessed by imaging techniques [3]. Nademanee *et al*. [4] studied autoptic samples from BrS patients and showed an epicardial to endocardial gradient of collagen deposition, indicating a progression of the pathological process from the epicardium to endocardium, which correlated with low expression of Connexin 43 (Cx43). Interestingly, BrS has been associated with increased collagen content throughout the right and left ventricular myocardium [12]. Miles *et al*. [12] evaluated 28 whole hearts from consecutive SCD cases attributed to BrS and 29 hearts from a control group comprised of non-cardiac deaths. Cardiac tissue from BrS decedents displayed a higher amount of collagen in relation to control subjects. The highest collagen accumulation was observed at the epicardial RVOT (geometric mean area 23.7%) [12]. Pieroni *et al*. [11] performed EAM-guided endomyocardial biopsies demonstrating histopathological abnormalities, including fibrosis and lymphomononuclear infiltrates in the majority of cases. EAM abnormalities manifested as low voltage unipolar and bipolar areas correlated with myocardial inflammation. Zumhagen *et al*. [20] showed that 55% of BrS patients and normal imaging of the right ventricle (RV) display histopathologic abnormalities (fibrosis, inflammation, and fatty tissue). A similar study identified fatty tissue infiltration, interstitial fibrosis, and lymphocyte infiltration in 52% of BrS with inducible VF [21].

Imaging studies have also provided evidence that subtle cardiac structural abnormalities exist in BrS patients. Computed tomography studies demonstrated wall motion abnormalities within the RVOT in most BrS patients with cardiac arrest [22]. Mild reduction of RVOT ejection fraction, dilatation of the RV inflow tract diameter, and increased RV end-systolic volume have been reported in BrS patients by cardiac magnetic resonance imaging (MRI) [23,24]. Electromechanical substrate abnormalities during ajmaline challenge including an increase of the electrical substrate in combination with worsening of the mechanical function of the RV, particularly in the anterior free wall of RVOT, have been recently demonstrated [25].

EAM studies have consistently demonstrated the presence of abnormal substrate at the epicardium of the RVOT. In Nademanee's seminal report, abnormal electrograms characterized by low voltage ($<$1 mV), prolonged duration ($>$120 ms), and fractionated late potentials clustering in the anterior aspect of the RVOT epicardium were demonstrated [26]. Following drug challenge with ajmaline, a 2-fold increase of these areas has been noticed [13]. Of note, the arrhythmogenic substrate detected during electroanatomical mapping has been correlated with fibrosis *in vivo* tissue samples [4]. The presence of a localized region in the anterior aspect of the epicardial RVOT with conduction slowing evidenced by prolonged electrogram duration (78.79 $\pm$ 19.87 ms vs. 58.93 $\pm$ 10.11 ms in the epicardial right ventricle, and 59.87 $\pm$ 12.61 ms in the endocardial RVOT) with variable low voltage (0.97 $\pm$ 0.48 mV; median scar area 19.8 $\pm$ 25.9 cm^2) has been demonstrated in a different study [27]. In a high-density endocardial EAM study, we recorded fractionated potentials of mean duration 94.7 $\pm$ 21.2 ms in all BrS patients mainly sited within the low bipolar voltage areas at the free wall of the RVOT [28]. In addition, the mean RVOT activation time (latest endocardial activation at the sub-pulmonary valve RVOT regions) was significantly prolonged in BrS patients compared to the control group (86.4 $\pm$ 16.5 ms vs. 63.4 $\pm$ 9.7 ms). Isochronal mapping demonstrated lines of conduction slowing predominantly at the free wall of the RVOT. Interestingly, Pannone *et al*. [15] found a similar duration for low-frequency potentials of 87.1 ms $\pm$ 23.1 at the epicardium.

Lambiase *et al*. [29], using high-resolution non-contact endocardial mapping, have demonstrated significant regional conduction delays, reduction in the activation gradient, and formation of lines of functional conduction block at the anterolateral free wall of the RVOT compared to the body and the apex of the RV. Postema *et al*. [30] have shown conduction slowing and abnormal conduction velocity restitution in the RV in BrS. These data are consistent with the depolarization hypothesis regarding the pathophysiology of BrS [17]. The cardiac intercalated disc is the host of a protein interacting network, called "the connexome", where different molecules including desmosomes, fascia adherence junctions, gap junctions, and voltage-gated sodium channels interact together to control excitability, electrical coupling, and intercellular adhesion in the heart. Although BrS is considered a primary electrical disease, microstructural abnormalities may enhance the electrical heterogeneity by affecting any of the "connexome" components [31,32]. Sodium channel activity could be affected by the disruption of any "connexome" components. Cx43 expression that is required for Nav1.5 stability in the intercalated disk membrane is impaired in BrS [4].

3. Definition of the abnormal endocardial unipolar substrate of the right ventricular outflow tract

The wide "field of view" of endocardial unipolar EAM allows identifying tissue abnormalities deeper in the mid-myocardium and epicardium. Previous studies, using different methodologies (either using the 95% confidence interval in healthy patients or direct comparison of adjacent endocardial and epicardial points), have proposed different endocardial unipolar voltage cut-off values for the identification of abnormal epicardial abnormalities of the RVOT. Polin *et al*. [33] have initially suggested the 5.5 mV cut-off criterion by using the 95% confidence interval in healthy control patients. Of note, mapping was performed using a 4-mm-tip electrode ablation catheter (2-mm-ring electrode separated by 1-mm spacing), and the sampling points ranged between 105 and 164. In a high-density EAM study (1019.1 $\pm$ 171.7 points) performed with a multi-electrode catheter (2 mm-tip, 2–8–2 mm interelectrode spacing) in subjects with idiopathic RVOT ventricular arrhythmias and negative cardiac MRI, we have shown that the mean amplitude of unipolar electrograms within the RVOT segments was 7.9 $\pm$ 0.7 mV, with 95% of the recorded unipolar signals having an amplitude $>$4 mV [28]. In a combined endocardial-epicardial mapping study (3.5-mm-tip electrode ablation catheter, separated by 1-mm spacing from a 2-mm ring electrode) where each endocardial mapping point was matched to the corresponding nearest epicardial point, a 4.4 mV unipolar voltage cut-off value has been suggested for detection of epicardial abnormalities [34]. In an elegant study comparing opposing endocardial and epicardial electrograms with a 3.5 mm-tip mapping catheter, in areas with normal endocardial bipolar voltage, the optimal endocardial unipolar voltage cut-off value for the detection of an epicardial scar not caused by fat was 3.9 mV [35]. The optimal endocardial unipolar voltage cut-off value to detect fragmented electrogram and late potentials at the epicardium was 3.7 mV. Of note, the latter study provides epicardial fat information as detected by computed tomography (CT), which displays significant limitations during epicardial mapping. Chrispin *et al*. [36] have shown that when unipolar endocardial mapping is performed with a multi-electrode catheter (1-mm-tip, 4–4–4 mm interelectrode spacing) instead of the conventional 3.5-mm-tip mapping/ablation catheters, a cut-off of 3.3mV should be used to identify the presence of epicardial RV free wall abnormalities. In structurally normal hearts, the point-by-point mapping performed using a 3.5-mm irrigated-tip mapping catheter with a 1-mm tip-to-ring interelectrode distance demonstrated that 95% of unipolar electrograms exhibited a peak-to-peak voltage $>$3.8 mV in the right ventricular free wall or $>$4.5 mV in the right ventricular septum [37]. In a recent endocardial-epicardial high-density mapping study performed in BrS patients with aborted SCD using a 5-spline multielectrode catheter (20 electrodes with 2–6–2 mm interelectrode spacing), we demonstrated that the 5.3 mV criterion of unipolar endocardial signals displayed 92.4% specificity and 86.3% sensitivity for the detection of epicardial bipolar low-voltage areas $<$1 mV (Fig. 1). In addition, the previously studied 4 mV cut-off value for unipolar signals displayed 100% specificity but only 40% sensitivity for the identification of epicardial lesions [38].

The accuracy of endocardial unipolar EAM to identify distant epicardial scar is compromised by several factors, including tissue thickness, the electrode orientation with respect to the tissue, the presence of endocardial scar (low bipolar voltage areas), the electrode size of the mapping catheter, the tissue contact, and the number of sampling points (high-density) [16]. Therefore, the exact "field of view" of unipolar recordings is not completely predictable. A compact area of unipolar voltage abnormalities possibly reflects real anatomic abnormalities deeper into the endocardial layer [3]. By lowering the unipolar voltage slider bar down (from 5 to 4 or 3 mV) and still demonstrating abnormalities, an intramural and/or epicardial scar is suggested with a higher degree of certainty (Fig. 2).

4. Endocardial unipolar voltage abnormalities predict ventricular fibrillation inducibility during programmed ventricular stimulation

The prognostic significance of VF inducibility during PVS is under continuous debate. There are numerous reasons for the discrepancy of data regarding PVS [16]. First, methodological differences in the stimulation protocols, including the number of extra stimuli, the minimum coupling interval used, and the stimulation site, have a significant impact on PVS results [39]. Second, the inducibility rate may be correlated to the BrS ECG type on the day of the procedure [40]. Third, data regarding the reproducibility of PVS are very limited and do not correlate with clinical presentation [41]. Finally, a false positive VF induction cannot be ruled out.

Endocardial unipolar EAM may improve the prognostic accuracy with respect to true positive PVS results in BrS. We have initially tested the hypothesis that RVOT abnormalities detected by high-density endocardial unipolar EAM mapping predict VF inducibility during PVS [42]. The study population consisted of 17 asymptomatic probands with spontaneous type 1 BrS ECG pattern referred for risk stratification with PVS. A comprehensive evaluation including late gadolinium enhancement cardiac MRI ruled out structural heart disease in all patients. An EAM was considered abnormal in the presence of low-voltage areas $>$1.5 cm^2 including $\geq$3 adjacent points with a unipolar signal amplitude $<$4 mV. PVS induced VF in 6 patients (35%). Patients with VF inducibility demonstrated greater areas of abnormal unipolar signals (16.0 $\pm$ 3.8 cm^2 vs. 8.1 $\pm$ 4.0 cm^2) compared with those without arrhythmia induction. Receiver operating characteristics curve analysis

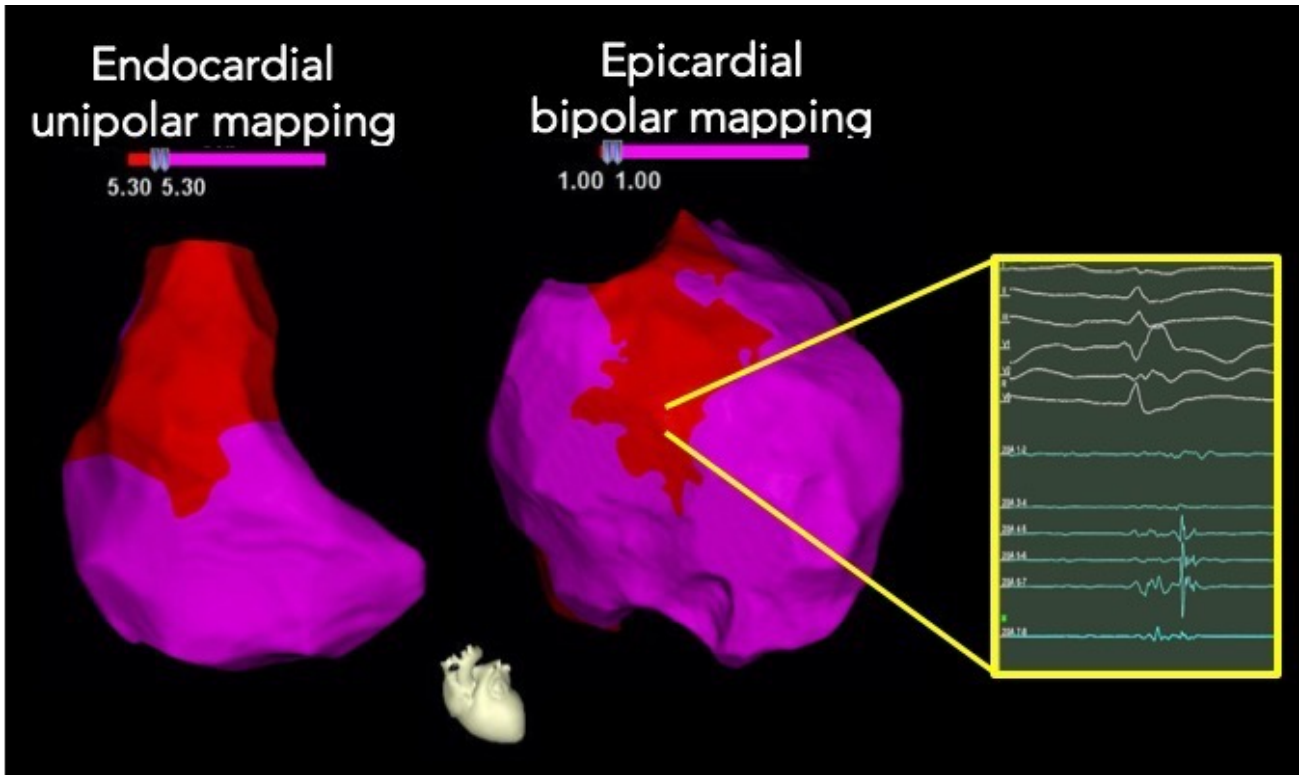

Fig. 1. Combined endocardial-epicardial RV/RVOT high density electroanatomical mapping in BrS. Endocardial unipolar voltage abnormalities (<5.3 mV) correlate with epicardial bipolar voltage abnormalities (<1 mV). Abnormal long duration fractionated bipolar electrograms are recorded at the epicardial aspect of the RVOT. Abbreviations: BrS, Brugada syndrome; EGM, electrogram; RV/RVOT, right ventricle/right ventricular outflow tract.

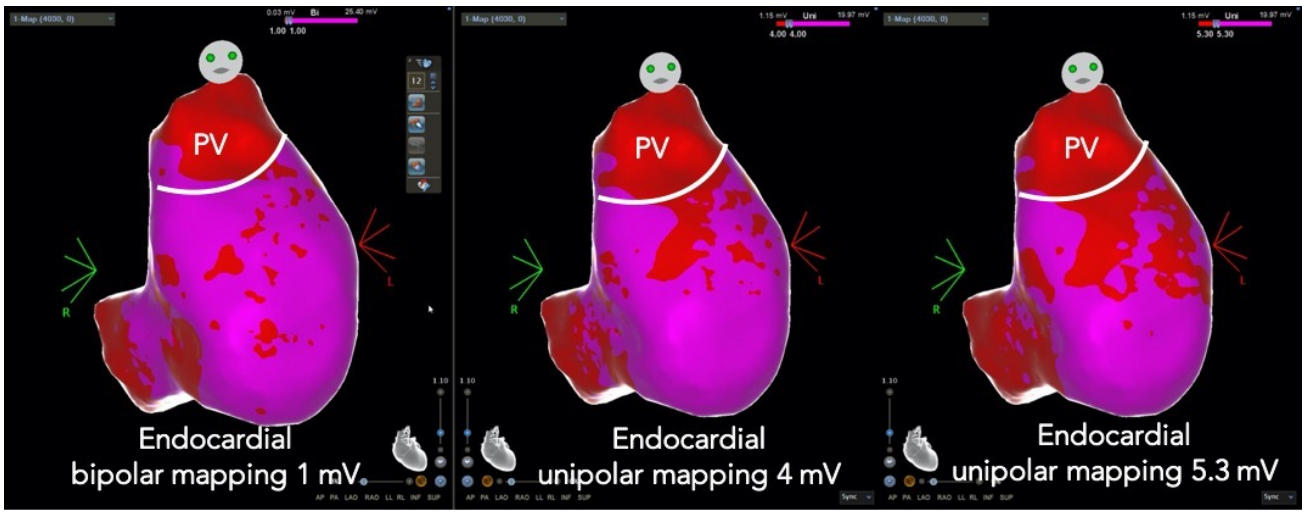

Fig. 2. High density electroanatomical mapping showing patchy areas of low-voltage bipolar signals (<1 mV) at the free wall of the RVOT (modified right anterior oblique view); Large low-voltage unipolar areas are revealed at the RVOT using different unipolar thresholds (4 and 5.3 mV). By lowering the unipolar voltage slider bar down (from 5.3 to 4 mV) and still demonstrating abnormalities, an intramural and/or epicardial scar is suggested with a higher degree of certainty. Abbreviations: RVOT, right ventricular outflow tract.

demonstrated that the presence of an area size >11 cm^2 for low-amplitude unipolar signals predict VF inducibility during PVS (sensitivity, 100%; specificity, 73%). On the contrary, subjects with normal endocardial unipolar EAM were non-inducible. Pieroni *et al.* [11] have elegantly shown that inducible patients display significantly greater endocardial

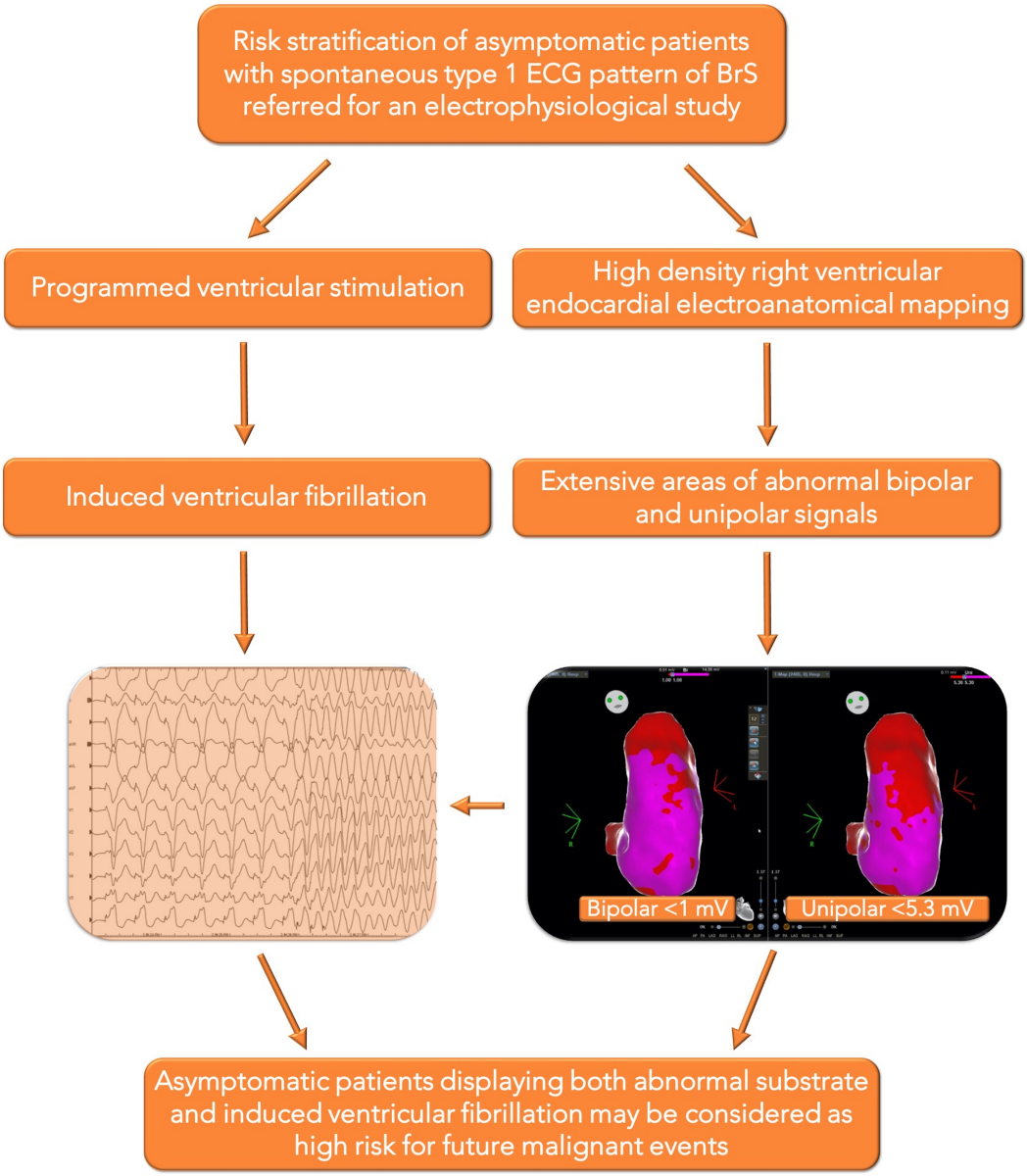

Fig. 3. Proposed workflow for risk stratification of asymptomatic individuals with BrS referred for an electrophysiological study. The presence of abnormal RVOT substrate revealed by high-density EAM predicts VF inducibility and is possibly related to symptom status. Subjects with abnormal substrate and induced VF may be at higher risk for future arrhythmic events. Abbreviations, BrS, Brugada syndrome; EAM, electroanatomical mapping; ECG, electrocardiogram; RVOT, right ventricular outflow tract; VF, ventricular fibrillation.

unipolar low-voltage areas compared with non-inducible ones. These findings have been confirmed in epicardial mapping studies. Pappone *et al.* [5] have demonstrated that wide epicardial abnormal areas with fragmented long-duration ventricular potentials are found in patients with inducible VF compared to patients without inducible arrhythmias, irrespective of clinical presentation. A substrate size of 4 cm^2 showed a good performance in identifying patients with inducible arrhythmias. Of note, patients with wider substrates became inducible with a less aggressive protocol.

5. Endocardial unipolar voltage abnormalities as a risk stratification tool in Brugada syndrome

Risk stratification of BrS patients still remains puzzling and represents a great challenge. The prognostic significance of spontaneous type-1 ECG pattern, QRS fragmentation, family history of SCD, VF inducibility during PVS, sinus node dysfunction, and even syncope merit special consideration as single risk factors before implanting an ICD [16]. Multiparametric scores, including the markers mentioned above, have been introduced into clinical prac-

tice for a better selection approach [18,19]. However, novel markers are mandatory to improve risk stratification of BrS patients, especially of asymptomatic ones.

In a recent study including 14 patients with BrS and aborted SCD in the setting of documented VF and 40 asymptomatic individuals with spontaneous type-1 ECG patterns, we evaluated the prognostic significance of RVOT electroanatomical abnormalities [38]. A combined high-density endocardial-epicardial mapping procedure was performed in all cases with aborted SCD. All symptomatic patients with aborted SCD displayed abnormal endocardial-epicardial maps. The endocardial unipolar low-voltage areas (<5.3 mV) mainly located at the anterior aspect of the RVOT were colocalized with the epicardial bipolar low-voltage areas (<1 mV) in all subjects. Patients with aborted SCD exhibited significantly wider endocardial unipolar and bipolar low-voltage areas in relation to asymptomatic patients. The presence of endocardial unipolar low-voltage areas >14.5 cm^2 discriminated symptomatic from asymptomatic individuals with a sensitivity of 92.5% and a specificity of 72.5% [38]. Using the strict 4 mV criterion for unipolar signals, the difference in unipolar low-voltage areas between symptomatic and asymptomatic individuals remained statistically significant.

In BrS, the presence of both repolarization and depolarization abnormalities constitute the functional and anatomical substrates that are possibly implicated in VF maintenance [17]. The mechanisms that maintain VF are partially clarified. The presence of arrhythmogenic substrates related to structural abnormalities is considered a key factor for sustained VF [43,44]. Fibrillatory mechanisms are strongly related to the underlying electro-architectural substrate including fibrosis patterns and the degree of abnormal gap junction coupling [44]. VF is sustained by a continuous spectrum of mechanisms ranging from organized fibrillation sustained by stable rotational activities to disorganized fibrillation without stable rotational activities [44]. Previous studies have demonstrated that rotational activities are mainly localized to areas of greater fibrosis in perfused cardiomyopathic hearts and low voltage areas during EAM [45,46]. Based on these findings, the extent of the abnormal substrate may play an essential role in VF maintenance in BrS. A proposed workflow for risk stratification of asymptomatic individuals with BrS referred for an electrophysiological study is shown in the Fig. 3. Subjects displaying both abnormal RVOT substrate and induced VF may be at higher risk for future arrhythmic events.

6. Conclusions

Preliminary findings correlate the presence of large-sized electroanatomical abnormalities with both VF inducibility during PVS and/or symptom status in patients BrS. Due to the certain limitations of PVS, the identification of microstructural alterations in BrS by different imaging modalities, including endocardial unipolar EAM, may assist in the risk stratification of patients with BrS.

Author contributions

KPL—conception of the idea, wrote the first draft, critical revisions, final approval; KV, ME, SD, PK, GT, TL, GB, PN, EP, FS, MH, AB—critical revision, final approval.

Ethics approval and consent to participate

Not applicable.

Acknowledgment

Not applicable.

Funding

This research received no external funding.

Conflict of interest

The authors declare no conflict of interest. Konstantinos P. Letsas is serving as one of the Guest editors of this journal. We declare that Konstantinos P. Letsas had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to Peter A. McCullough.

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