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ORIGINAL RESEARCH

CATHETER ABLATION - VENTRICULAR TACHYCARDIA

Substrate Mapping for Ventricular Tachycardia Ablation Through High-Density Whole-Chamber Double Extra Stimuli

The S3 Protocol

Jean-Baptiste Guichard, MD, PhD,[a,b,c,d,e] Mariona Regany-Closa, MSc,[a] Sara Vázquez-Calvo, MD,[a] Blanca Zazu, MSc,[a] Berta Pellicer Sendra, BEng,[a] Jaume Serrano-Campaner, BEng,[a] Sílvia Molero-Pereira, BEng,[a] Roger Borràs, MSc,[a,f] José Tomás Ortiz, MD, PhD, MSc,[a,b] Pasquale Valerio Falzone, MD,[a,b] Frida Eulogio, MD,[a] Jana Reventos-Presmanes, BEng,[a,g] Paz Garre, MSc,[a] Elena Arbelo, MD, PhD,[a,b,c] Till F. Althoff, MD,[a] Eduard Guasch, MD, PhD,[a,c] Jose María Tolosana, MD, PhD,[a,b] Josep Brugada, MD, PhD,[a] Lluís Mont, MD, PhD,[a,b,c] Andreu Porta-Sánchez, MD, PhD,[a] Ivo Roca-Luque, MD, PhD[a,b]

ABSTRACT

BACKGROUND A partial delineation of targets for ablation of ventricular tachycardia (VT) during a stable rhythm is likely responsible for a suboptimal success rate. The abnormal low-voltage near-field functional components may be hidden within the high-amplitude far-field signal.

OBJECTIVES The aim of this study was to evaluate the benefit and feasibility of functional substrate mapping using a full-ventricle S3 protocol and to assess its colocalization with arrhythmogenic conducting channels (CCs) on late gadolinium enhancement cardiac magnetic resonance.

METHODS An S3 mapping protocol with a drive train of S1 followed by S2 (effective refractory period + 30 ms) and S3 (effective refractory period + 50 ms) from the right ventricular apex was performed in 40 consecutive patients undergoing scar-related VT ablation. Deceleration zones (DZs) and areas of late potentials (LPs) were identified for all maps. A preprocedural noninvasive substrate assessment was done using late gadolinium enhancement cardiac magnetic resonance and postprocessing with automated CC identification.

RESULTS The S3 protocol was completed in 34 of the 40 procedures (85.0%). The S3 protocol enhanced the identification of VT isthmus on the basis of DZ (89% vs 62%; $P < 0.01$) and LP (93% vs 78%; $P = 0.04$) assessment. The percentage of CCs unmasked by DZs and LPs using S3 maps was significantly higher than the ones using S2 and S1 maps (78%, 65%, and 48% [$P < 0.001$] and 88%, 81%, and 68% [$P < 0.01$], respectively). The functional substrate identified during S3 activation mapping was significantly more extensive than the one identified using S2 and S1, including a greater number of DZs (2.94, 2.47, and 1.82, respectively; $P < 0.001$) and a wider area of LPs (44.1, 38.2, and 29.4 cm^2, respectively; $P < 0.001$). After VT ablation, 77.9% of patients have been VT free during a median follow-up period of 13.6 months.

CONCLUSIONS The S3 protocol was feasible in 85% of patients, allows a better identification of targets for ablation, and might improve VT ablation results. (JACC Clin Electrophysiol 2024;10:1534–1547) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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Catheter ablation is the cornerstone therapeutic strategy for treating scar-related ventricular tachycardia (VT).[1,2] But long-term success rates are suboptimal,[3] possibly because of the incomplete identification of ablation targets involved in all possible VTs. Various methods of substrate mapping have been proposed,[4] such as the identification of low-voltage areas,[5] late potentials (LPs),[6] local abnormal ventricular activities (LAVAs),[7] and deceleration zones (DZs) on the basis of isochronal late activation mapping (ILAM).[8] But these diagnostic strategies might face difficulties in assessing the arrhythmogenic substrate. For instance, the pathologic near-field signal can be concealed within the far-field signal during sinus rhythm or right ventricular (RV) pacing,[9] and bipolar voltage may vary significantly depending on the pacing site.[10,11] Additionally, the interpretation of the signals is somewhat subjective, and DZs could occur during the main ventricular activation rather than late, potentially leading to their being overlooked. To improve the identification of relevant substrate, approaches involving 1 or more extrastimuli to a baseline rhythm have been proposed,[12] providing increased specificity for the detection of VT isthmuses.[13] However, the potential benefit of high-density mapping on the basis of a whole-chamber double-extrastimuli protocol has not been studied so far. Furthermore, late gadolinium enhancement (LGE) cardiac magnetic resonance (CMR) has demonstrated high accuracy in identifying arrhythmogenic conducting channels (CCs) that colocalize with ILAM-defined DZs.[14] However, some of the CCs were identified only after the initial ablation set. We hypothesized that a whole-chamber, systematic, high-density map (a so-called S3 map) with double ventricular close-coupled stimuli (S3 protocol) could lead to the identification of more CCs and better depict the arrhythmogenic substrate.

Therefore, the objectives of this study were as follows: 1) to evaluate the benefits and feasibility of an S3 map compared with the standard S1 and S2 maps in assessing the arrhythmogenic substrate; and 2) to assess the correlation between the detected functional substrate and the structural substrate on the basis of CCs detected on LGE CMR.

METHODS

STUDY SAMPLE. From November 2021 to December 2022, a total of 44 patients who underwent catheter ablation for scar-related VT at Hospital Clínic de Barcelona were consecutively screened for eligibility in this study. The inclusion criteria were the presence of structural heart disease and age >18 years. Demographic and clinical data were collected at the time of patient inclusion. The presence of ischemic cardiac disease was defined as a history of a coronary stenosis accompanied by focal wall motion defect and/or previous coronary intervention. The study adhered to the principles of the Declaration of Helsinki, and all patients provided written informed consent. The study protocol was approved by the ethics committee of our institution. The data supporting the findings of the study are available from the corresponding author upon reasonable request.

MAPPING OF THE FUNCTIONAL SUBSTRATE. All procedures were conducted under general anesthesia. Endocardial access to the left ventricle was achieved using either a transseptal or a retrograde aortic approach, depending on the physician's discretion. Epicardial mapping was performed if there was clinical suspicion of an epicardial substrate, subepicardial fibrosis and epicardial CCs on the basis of LGE CMR assessment, or previous failed endocardial-only ablation. From the RV apex, the ventricular effective refractory period (ERP) was determined after a stimulation train using a fixed cycle length of 600 ms. After that, the ERP after S2 was determined and the maps were obtained using S2 = ERP + 30 ms and S3 = ERP after S2 + 50 ms. An S3 protocol was systematically used in the entire chamber of interest to assess the functional substrate. A

ABBREVIATIONS AND ACRONYMS

BZ = border zone
CC = arrhythmogenic conducting channel
CMR = cardiac magnetic resonance
DZ = deceleration zone
ERP = effective refractory period
ICD = implantable cardioverter-defibrillator
ILAM = isochronal late activation mapping
LAVA = local abnormal ventricular activity
LGE = late gadolinium enhancement
LP = late potential
RV = right ventricle/ventricular
VT = ventricular tachycardia

From [a]Institut Clínic Cardiovascular, Hospital Clínic, Universitat de Barcelona, Barcelona, Spain; [b]Institut d'Investigacions Biomèdiques August Pi i Sunyer, Barcelona, Spain; [c]Centro de Investigación Biomédica en Red de Enfermedades Cardiovasculares, Madrid, Spain; [d]INSERM, SAINBIOSE U1059, University Hospital of Saint-Étienne, Saint-Étienne, France; [e]Cardiology Department, University Hospital of Saint-Étienne, Saint-Étienne, France; [f]Centro de Investigación Biomédica en Red e Salud Mental, Instituto de Salud Carlos III, Madrid, Spain; and the [g]ITACA Institute, Universitat Politècnica de València, Valencia, Spain.
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minimum resting period of 2 seconds was required between pacing sequences. The instant assessment of the functional substrate was based on the electroanatomic map obtained from the second extrastimulus (S3 map), while the S1 and S2 electroanatomic maps were postprocessed using TurboMap (Abbott Cardiovascular) after the case. For procedures using the CARTO 3 navigation system (Biosense Webster), the different maps were created simultaneously using the PARALLEL MAP tool. The S3 map was the one visualized all the time. The window of interest was consistently set until the next pacing extrastimulus for the S1 and S2 maps and for a duration of 500 ms for the S3 map. All maps were acquired using a multielectrode catheter: the PENTARAY (Biosense Webster) for CARTO 3 cases and the HD Grid (Abbott Cardiovascular) for EnSite X (Abbott Cardiovascular) cases. The local activation time was automatically determined as the latest deflection of the electrogram recorded using the EnSite X system and the last deflection algorithm, as well as using the wave front algorithm (Biosense Webster). A manual reannotation of the local activation times was conducted during postprocessing to identify any LPs that may have been missed during the automatic annotation for the S1, S2, and S3 activation maps. Local activation time outliers were identified and corrected if necessary.

ANALYSIS OF ELECTROANATOMICAL MAPS. A comprehensive multiparametric evaluation of the functional substrate was systematically conducted for the S1, S2, and S3 maps in the entire study cohort. The identification of abnormal and/or delayed near-field signal was based on the assessment of LPs and LAVAs, using previously established definitions.[6,7] The areas containing LPs or LAVAs were manually delineated, creating a boundary between the signals with abnormal components and those without. The total surface area of LPs and LAVAs was then calculated by adding the areas of the different identified zones. Maps of DZs were established using ILAM, following a previously described methodology.[8] In brief, the entire activation window was divided into 8 equally timed isochrones. DZs were identified on the basis of the presence of at least 3 isochrones within a 1-cm radius, indicating isochronal crowding. The area of a DZ was determined by drawing a border line 5 mm outside the zone of isochronal crowding. The total surface area encompassing the different DZs was then measured. The number of color-coded isochrones involved in the crowding area was assessed. The duration of an isochrone was calculated as the total local activation time window duration divided by 8, representing 12.5% of the overall activation time. To estimate the duration of a DZ, the number of colors was multiplied by the isochrone time. The maximal number of colors and duration of a DZ were systematically recorded.

ASSESSMENT OF THE STRUCTURAL SUBSTRATE BY LGE CMR. Preprocedural LGE CMR was performed in 26 patients (76.5%) within the entire cohort, of whom 2 (7.7%) did not have implantable cardioverter-defibrillators (ICDs) during imaging acquisition, receiving ICDs after ablation. There were no significant differences regarding clinical and procedural features between patients who underwent LGE CMR and those who did not. For patients without ICDs, 3-T scans were used, whereas patients with ICDs underwent 1.5-T scans with a dedicated wideband sequence to mitigate artifacts that has shown reproducible and consistent results for VT substrate analysis.[15] A semiautomated segmentation of the left ventricle and a quantitative assessment of the intramural hypersignal areas on the basis of a standardized protocol were conducted using postprocessing ADAS 3D software (ADAS 3D). Subsequently, 9-layer 3-dimensional maps were automatically generated, providing LGE maps from the endocardium to the epicardium.[16] The LGE pixel signal intensity maps obtained from the LGE CMR sequence were projected onto the corresponding layer using a trilinear interpolation algorithm and color-coded using lower and upper thresholds of 40% ± 5% and 60% ± 5% of the maximum intensity, respectively. The core area of the scar was depicted in red, healthy tissue in blue, and the border zones (BZs) in intermediate colors. CCs, defined as continuous corridors of BZ tissue surrounded by dense fibrotic tissue or anatomical barriers that connect 2 areas of healthy tissue, were automatically identified.[16] CCs with lengths exceeding 10 mm were then singled out, as they are associated with higher arrhythmogenicity,[14] and they can be readily available in the ADAS 3D software output. The postprocessed 3-dimensional LGE CMR map, including CCs, was then merged to the electroanatomic map in the EnSite X system. Fiducials from the trunk and the main branches of the pulmonary artery, as well as the apical part of the left ventricle, were selected to ensure accurate merging of the 2 maps. For each map of the S3 protocol (S1, S2, and S3 maps), the number of CCs with areas of DZs or LPs was assessed. The number of DZs matching with CCs was also recorded, and the ratio of DZs matching with CCs was calculated.

IDENTIFICATION OF THE CRITICAL SITE OF THE VT. The assessment of the protected isthmus was

systematically conducted in cases of sustained VT if hemodynamically tolerated. The induction protocol involved drive cycles of 600, 500, and 430 ms, with up to triple extrastimuli delivered until refractoriness or 200 ms. Induction was performed after evaluating the ventricular functional substrate and before the ablation procedure. In cases in which hemodynamically tolerated arrhythmias were present, focused activation mapping of the area deemed most likely to be critical on the basis of the substrate mapping was performed. The aim of this mapping was to identify diastolic and presystolic activities,[17] without the possibility of using entrainment maneuvers. For arrhythmias that were poorly tolerated, a high-density pace map was performed, and the critical site of the re-entry was defined as the transition zone between the area associated with the best pace map (score >90%) with a prolonged stimulus-QRS interval and the area with a modest pace map zone as previously described.[18] An analysis was subsequently conducted to examine the correlation between the functional substrate zones, including both LP and LAVA zones and DZ zones, and the critical isthmus of the VT.

ABLATION PROCEDURE. A consistent ablation strategy was systematically used during the procedure. Initially, the site deemed critical for the arrhythmia was targeted (on the basis of pace mapping and/or activation mapping), and radiofrequency lesions were delivered using an externally irrigated 3.5-mm-tip ablation catheter that allowed contact-force assessment (TactiCath SE [Abbott Cardiovascular] or ThermoCool SmartTouch [Biosense Webster]). The temperature control was set at 45°C, with a power range of 30 to 50 W depending on catheter contact, impedance drop, and wall thickness of the region and an irrigation rate of 26 to 30 mL/min. Following the targeting and ablation of the critical site, the entire extent of the DZs identified by the S3 protocol was then targeted and ablated.

PROCEDURAL OUTCOMES AND CLINICAL FOLLOW-UP. The first procedural endpoint of the ablation procedure was the abolition of DZs, LAVAs, and LPs. Following the initial ablation phase, a systematic S3 protocol remap was performed. Additional ablation was conducted if persistent and/or new areas of functional substrate were identified. The number of remaps refers to the number of S3 protocols needed after the initial ablation set to eradicate the entire functional substrate.

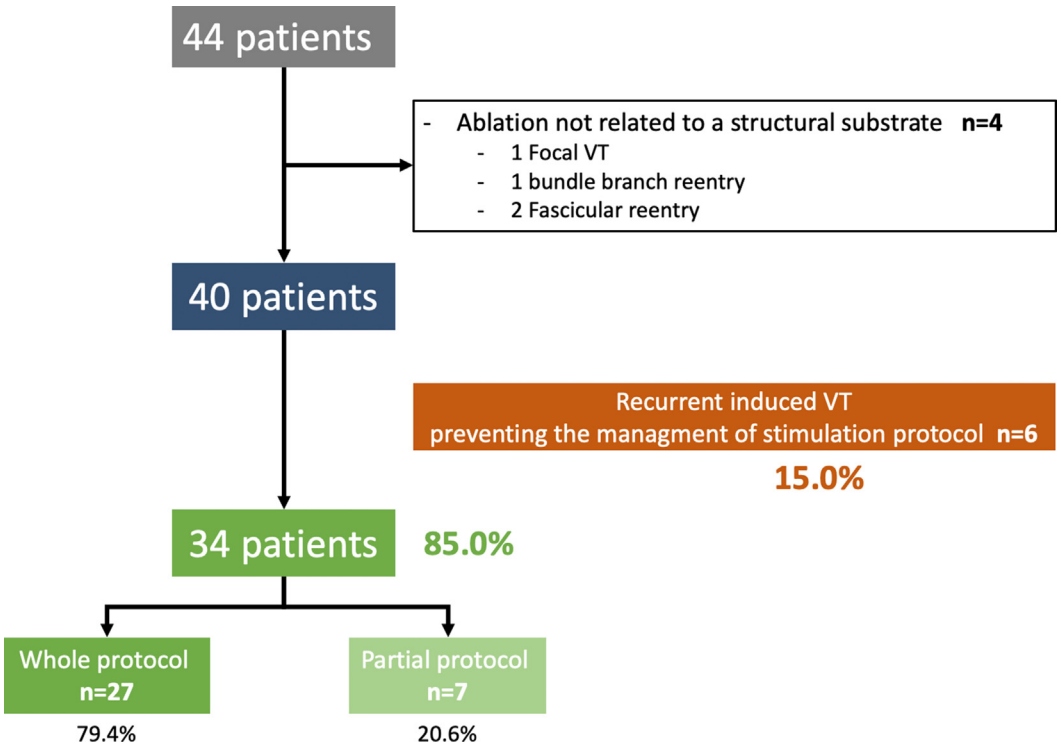
The second procedural outcome was VT noninducibility with train cycles of 600, 500, and 430 ms associated with up to triple extrastimuli until refractoriness and/or 200 ms from the RV apex. The induction of a sustained monomorphic VT was considered as VT inducibility.

The safety of the S3 protocol was also assessed. If 3 or more sustained ventricular arrhythmias occurred, requiring electrical cardioversion or overdrive pacing for termination, the protocol was discontinued, the S3 was removed, and S1-S2 mapping was performed.

Antiarrhythmic drugs were discontinued before hospital discharge if VT noninducibility was achieved at the end of the procedure. Systematic clinical follow-up, including clinical history, physical examination, and ICD interrogation, was conducted at 3, 6, and 12 months after the ablation procedure. Remote ICD follow-up was performed to assess the recurrence of sustained ventricular arrhythmia during the follow-up period. The recurrence of ventricular arrhythmia was defined as a ventricular arrhythmia lasting more than 30 seconds and/or a history of appropriate therapy, either antitachycardia pacing or shock. Patients who were lost to follow-up were censored, and mortality was confirmed using medical records.

STATISTICAL ANALYSIS. Continuous variables are presented as mean ± SD or median (Q1-Q3) as appropriate. Categorical variables are expressed as total numbers and percentages. To evaluate the differential diagnostic capacity of the different maps of the S3 protocol (S1, S2, and S3 maps), an analysis using generalized multilevel mixed effects models for repeated measures was conducted. For every outcome, the normality assumption for residuals was tested. If a statistically significant global difference was found, a post hoc comparison between the different maps was then performed using Tukey's adjustment strategy. For the survival analysis, patients who were lost to follow-up were censored at the time of their last follow-up assessments. Time to event for ventricular arrhythmia recurrence and all-cause mortality was estimated using the Kaplan-Meier method, and between-group comparisons were conducted using the unadjusted log-rank test. HRs and corresponding 95% CIs were calculated. All statistical tests used a 2-sided type I error of 5%, and a P value <0.05 was considered to indicate statistical significance. generalized multilevel mixed effects models were fitted using the library Lme4 version 1.1-31, and statistical estimations and comparisons were done using emmeans version 1.8.5. R software for Windows version 4.2.1 (R Project for Statistical Computing) was used for statistical analysis.

FIGURE 1 Flowchart of the Study



Among 44 consecutive patients undergoing an ablation for ventricular tachycardia (VT), 40 patients met the inclusion criteria. A partial or complete S3 protocol was realized in 85% of the patients, while the use of the novel diagnostic protocol was aborted because of the recurrent induction of sustained VT.

RESULTS

STUDY SAMPLE AND BASELINE ENDOCAVITY PROCEDURE. The flowchart of patients is presented in Figure 1. Within the global cohort, 4 VTs were not scar related, and the whole-chamber S3 protocol was not feasible in 6 patients (15.0%) because of recurrent induced VTs. Among the 34 patients who consecutively underwent the S3 protocol, the whole S3 protocol was performed in 27 patients (79.4%), while an S2 protocol was used in 7 patients because of excessive arrhythmogenicity caused by S3. The entire study sample of 34 patients, including those who underwent the S2 and S3 protocols, was included in the final analysis. The baseline characteristics of the patients included in the S3-VT-FREE cohort are presented in Table 1. In summary, the patients had an average age of 69 years, were predominantly men (91.2%), had ischemic cardiac disease (79.4%), and were treated with beta-blockers (91.2%) and amiodarone (88.2%). The patients in the cohort had severe left ventricular systolic dysfunction (median left ventricular ejection fraction 30.5%), and LGE CMR revealed 8.1% ± 2.8% scar tissue, 18.7% ± 6.5% BZ, and an average of 2 CCs. Catheter ablation was carried out in response to an electrical storm in 6 patients (18.2%), which hindered the implementation of an S3 protocol in the majority (n = 5 [83.3%]). An epicardial approach was used in 4 patients (11.8%). Following the stimulation train (S1) at 600 ms, a first extrastimulus (S2) of 326 ± 33 ms cycle length was provided and followed by a second extrastimulus (S3) of 338 ± 28 ms.

CORRELATION BETWEEN THE IDENTIFIED FUNCTIONAL SUBSTRATE, THE STRUCTURAL SUBSTRATE, AND THE ISTHMUS OF THE VT. Compared with the ventricular structural substrate assessed noninvasively by LGE CMR, the S3 protocol (Central Illustration) improved the delineation of CMR CCs, as illustrated in Figures 2 and 3 and detailed in Table 2 and Supplemental Table 1. As depicted in Figure 4D, the number of DZs located in a CMR CC was significantly increased by the S3 protocol, from 1.32 (95% CI: 0.87-1.77) in the S1

TABLE 1 Baseline Characteristics of the Patients (N = 34)

Age, y	69.0 (61.5-76.0)
Male	31 (91.2)
Cardiovascular risk factors	
Hypertension	25 (73.5)
Diabetes mellitus	16 (47.1)
Dyslipidemia	22 (64.7)
Tobacco use	15 (44.1)
COPD	9 (26.5)
Chronic kidney disease	6 (17.6)
Characteristics of structural heart disease	
Ischemic cardiac disease	27 (79.4)
Anterior and lateral location	12
Apical location	5
Inferior location	10
Left ventricular ejection fraction, %	32.0 ± 11.0
NYHA functional class	
I	5 (14.7)
II	23 (67.6)
III	6 (17.6)
Core of the scar, %	8.1 ± 2.8
Border zone of the scar, %	18.7 ± 6.5
Number of conduction channels	3 (2-4)
Number of conduction channels >10 mm	2 (2-4)
Arrhythmia characteristics	
Antiarrhythmic drugs	
Amiodarone	30 (88.2)
Class I	5 (14.7)
Beta-blockers	31 (91.2)
Electrical storm indicating VT ablation	6 (18.2)

Values are median (Q1-Q3), n (%), or mean ± SD.
COPD = chronic obstructive pulmonary disease; VT = ventricular tachycardia.

map to 2.40 (95% CI: 1.92-2.388) in the S3 map ($P < 0.001$). By focusing on the delineation of CMR CCs through the assessment of the functional substrate, the S3 protocol improved the diagnostic capacity of invasive electroanatomical mapping. The percentage of CMR CCs identified by the assessment of DZs and LPs was significantly increased during S2 mapping (65% [42%-88%] and 81% [95% CI: 60%-102%], respectively) and S3 mapping (78% [95% CI: 55%-102%] and 88% [67%-110%], respectively) compared with S1 mapping (45% [95% CI: 21%-68%] and 68% [95% CI: 47%-89%], respectively; $P < 0.001$). Although a significant proportion of the VT isthmus area was identified by the assessment of DZs and LPs during S1 mapping (62% [95% CI: 45%-79%] and 78% [95% CI: 64%-92%], respectively), the S3 protocol enhanced the identification of the area of interest for the clinical VT (89% [95% CI: 72%-107%; $P < 0.01$] vs S1 and 93% [95% CI: 78%-108%; $P = 0.04$] vs S1, respectively) (**Figures 4A and 4B**). Interestingly, S2 mapping did not yield any benefit in enhancing the detection of VT isthmuses through LP and DZ assessment. Additionally, no interaction was observed between the type of cardiomyopathy and the efficacy of the S3 protocol in revealing functional ventricular substrate (Supplemental Table 1).

BENEFIT OF THE SYSTEMATIC S3 PROTOCOL IN UNMASKING THE ARRHYTHMOGENIC SUBSTRATE. As shown in **Table 3**, the timing of the latest activation time was delayed from 167 ms during S1 to 203 ms during S2 and 218 ms during S3. Using ILAM, the number of DZs identified increased from the S1 to S2 and S3 maps (1.82 [95% CI: 1.41-2.24], 2.47 [95% CI: 2.06-2.88], and 2.94 [95% CI: 2.49-3.38], respectively; $P < 0.001$). An example of the benefit of the S3 protocol in unmasking the functional substrate is illustrated in **Figures 2 and 3**. As shown in **Table 2**, detailed in Supplemental Table 2, and depicted in **Figure 4C**, the S3 protocol resulted in an expansion of the total surface area of the DZs and the mean duration involved in a DZ ($P < 0.001$ and $P < 0.01$, respectively). Regarding the assessment of areas displaying LPs and LAVAs, the S3 protocol led to an increase of in the area of LPs and LAVAs from 29.4 cm^2 (95% CI: 22.1-36.6 cm^2) in the S1 map to 38.2 cm^2 (95% CI: 30.9-45.5 cm^2) in the S2 map and 44.1 cm^2 (95% CI: 36.6-51.5 cm^2) in the S3 map ($P < 0.001$).

PROCEDURAL OUTCOMES AND LONG-TERM FOLLOW-UP. The total procedure time was 258 ± 49 minutes, and the radiofrequency duration was 42 ± 16 minutes (**Table 3**). There were no differences in procedural duration between the 2 mapping systems used. The median number of remaps required until the complete elimination of the functional ventricular substrate was 1.0 (95% CI: 1.0-2.0). In other words, 19 patients (55.9%) were free of any functional substrate on the basis of the S3 protocol during the first remap after ablation. At the end of the procedure, 4 patients (11.8%) remained inducible (mean VT cycle length 232 ± 28 ms). One patient (2.9%) experienced a mild complication related to the procedure (groin hematoma that did not require surgical intervention). During a median follow-up period of 13.6 months (95% CI: 7.9-17.1 months), the overall survival rate was 93.3% ± 6.4%, while the VT-free survival rate was 77.9% ± 10.5%. As shown in **Figure 5**, the recurrence of VT and the all-cause mortality burden after the index procedure did not differ on the basis of the presence of ischemic or nonischemic structural heart disease.

DISCUSSION

MAIN FINDINGS. The S3-VT-FREE study emphasizes that the S3 protocol was effective for the vast majority

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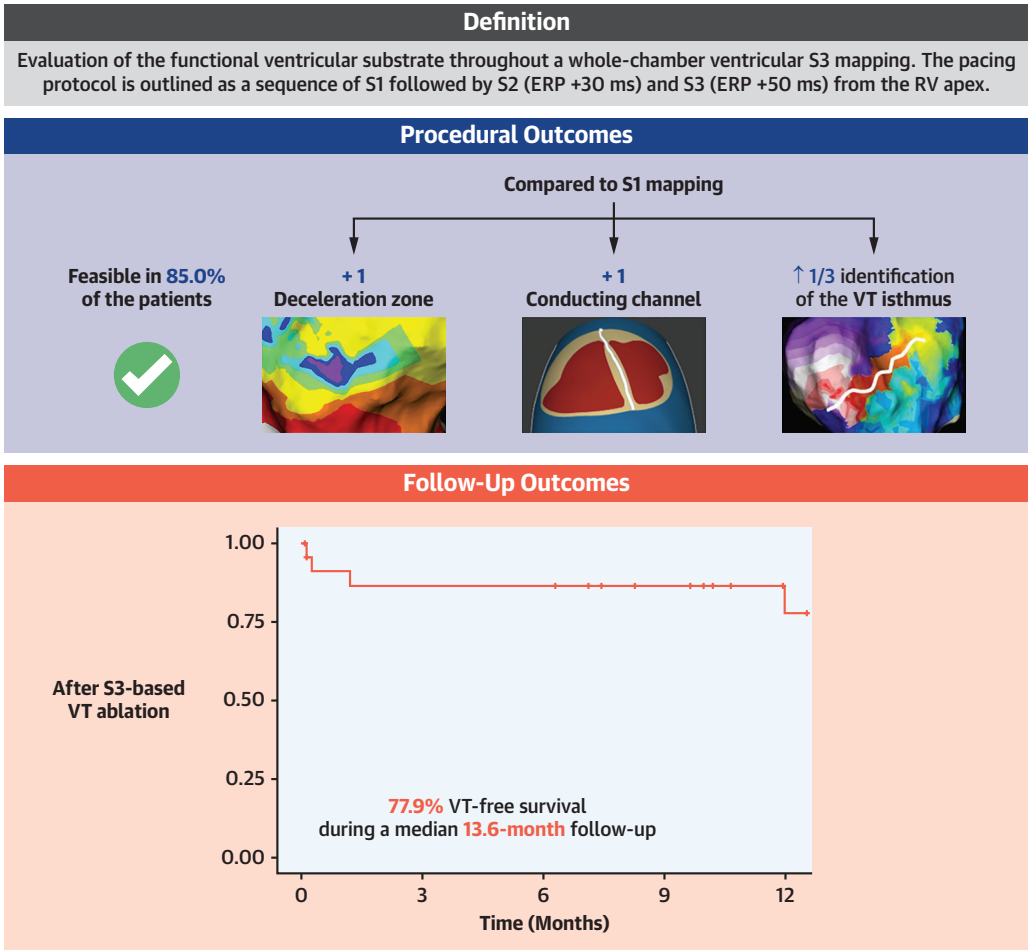
CENTRAL ILLUSTRATION **S3 Protocol for Scar-Related VT Ablation**



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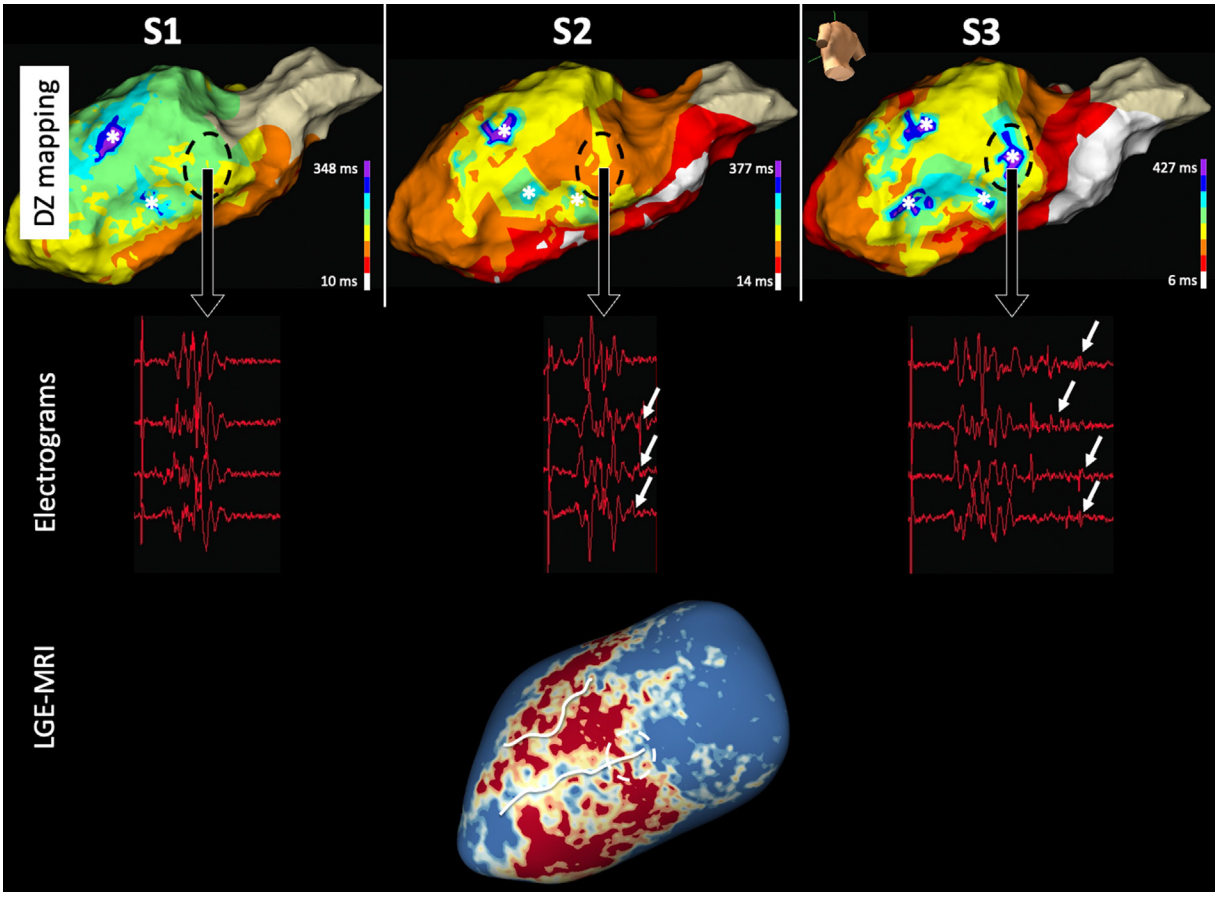
ERP = effective refractory period; RV = right ventricular; VT = ventricular tachycardia.

of patients (85.0%) who underwent catheter ablation for scar-related VT. The S3 protocol, a whole-chamber high-density mapping based on double ventricular extrastimuli, led to an enhanced delineation of the ventricular functional substrate, resulting in improved identification of DZs and an increased overall area of both DZs and LPs or LAVAs. Additionally, this approach identified novel CCs as determined by LGE CMR and bolstered the localization of the VT isthmus via electroanatomic mapping. After 1-year follow-up, 77.9% of patients remained free of VT recurrence, irrespective of the underlying structural heart disease, with an overall survival rate of 93.3%.

SIGNIFICANT ROLE OF DECREMENTAL PROPERTIES TO IMPROVE THE ASSESSMENT OF THE ARRHYTHMOGENIC SUBSTRATE. The decremental property of myocardial tissue involved in macro-re-entry, acting as a critical isthmus, plays a crucial role in initiating and maintaining scar-related VT in patients with structural heart disease. Leveraging the decremental properties of abnormal tissue could unmask the functional substrate involved in scar-related VT. Compared with assessing LPs during sinus rhythm or a fixed pacing train from the RV apex (S1 mapping), the addition of an extrastimulus (S2 mapping) improves the diagnostic capabilities for delineating the diastolic zone during VT.[19] Recently, Chrispin and Tandri[10] demonstrated that using an S2 protocol for detecting the latest activation significantly enhances the identification of the VT isthmus compared with RV pacing and sinus rhythm. In fact, the inclusion of an extrastimulus increases sensitivity, negative

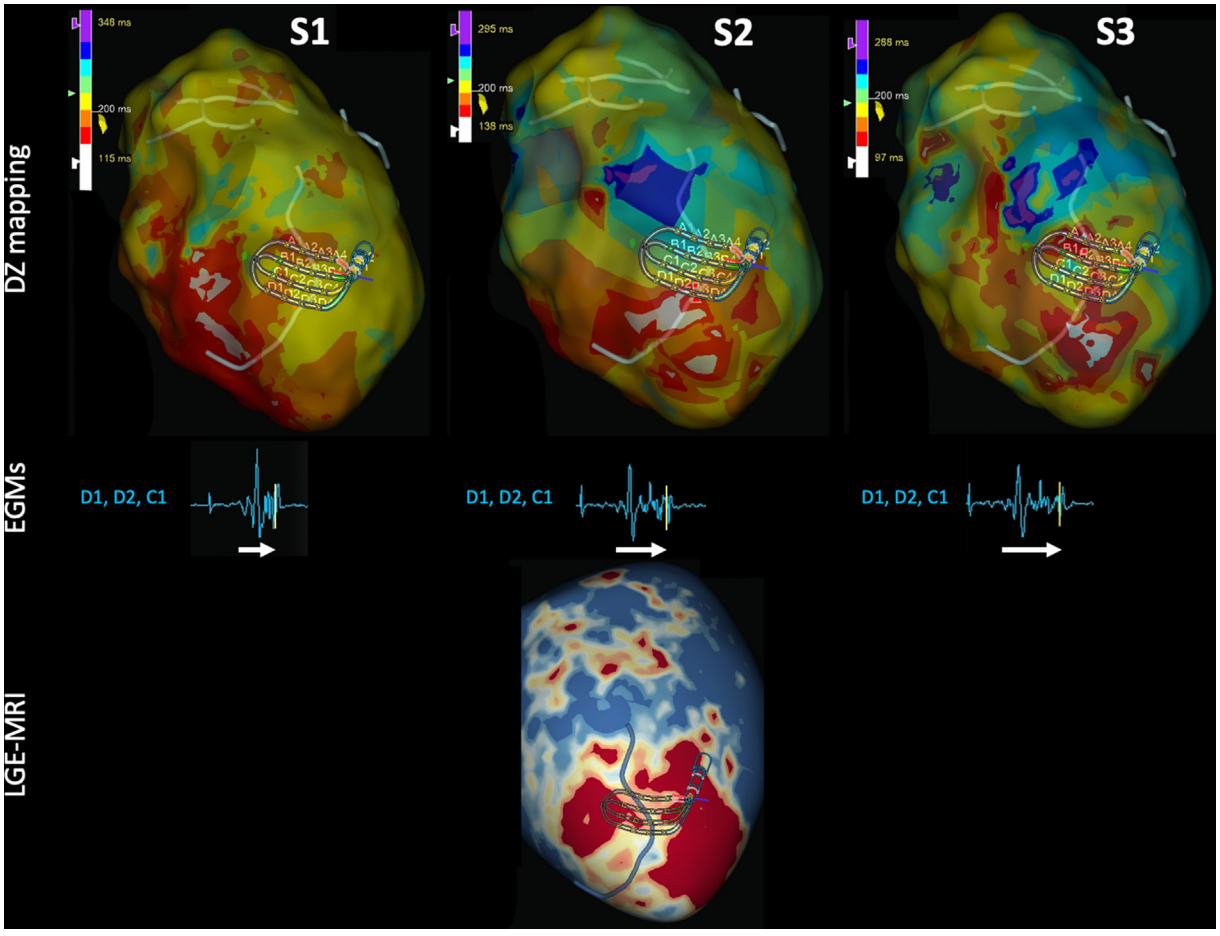
FIGURE 2 Graphical Example of the Substantial Benefit of the S3 Protocol Regarding the Delineation of the Functional Substrate and the Match With the Structural Substrate



The different activation mappings identify deceleration zones (asterisk) matching with a conducting channel on late gadolinium enhancement (LGE) magnetic resonance imaging (MRI). The S3 protocol unmasks abnormal electrograms (white arrows) hidden in the S1 map. The S2 and S3 activation mappings unmask novel deceleration zones (DZs) leading to a more accurate assessment of a second conducting channel compared with the S1 activation mapping.

predictive value, and positive predictive value while maintaining specificity.[19] To the best of our knowledge, our study is the first to show a comprehensive assessment of the entire ventricular substrate with double extrastimulation. Acosta et al[13] showed that occasionally adding a double-extrastimulus protocol to the standard approach in areas that were considered close to the BZ with suspected abnormal electrograms led to a reduction in radiofrequency time and improved noninducibility rates at the end of the procedure. Our S3-VT-FREE study suggests that the S3 protocol presents substantial benefits when performed systematically across the whole chamber and, as it is performed systematically, avoids the subjectivity linked to other protocols that deliver the second extrastimuli only in areas with electrograms that, according operator, could have hidden abnormal potentials. The S3 protocol reveals areas of interest that are distant from those identified using the conventional S1 protocol by highlighting regions that correlate with CCs assessed using LGE CMR. The diagnosis of functional substrate is based on identifying regions with decreased conduction velocity due to source-sink mismatch and nonuniform anisotropic propagation.[20] Currently, no standardized stimulation protocol has been established to evaluate the functional substrate. The identification of functional substrate depends on the stimulation site,[21] scar zone size, and CC morphology.[22] The S3 protocol may overcome these factors that prevent the detection of the functional substrate. The use of decremental properties of the scar zone of interest has been used to achieve 2 distinct objectives. First, it focuses the ablation strategy on decremental zones, as in the

FIGURE 3 Graphical Example of the Substantial Benefit of the S3 Protocol Regarding the Delineation of the Functional Substrate and the Match With the Structural Substrate



The S3 protocol unmasks abnormal electrograms (EGMs) (yellow bar) hidden in the S1 map. The S2 and S3 activation mappings unmask novel DZs, leading to a more accurate assessment of the conducting channel depicted in the different merged maps (in white) compared with the S1 activation mapping. Abbreviations as in Figure 2.

decrement-evoked potential mapping,[12] to increase the specificity of the region responsible for ventricular arrhythmogenicity.[23] Second, it uncovers areas of the functional substrate by differentiating the near-field potential from the far-field electrogram. Thus, the target zone for ablation expands with the addition of an extrastimulus, encompassing a greater area of LP[24] and LAVA[25] signals. Our study illustrates the advantages of the systematic and whole-chamber S3 protocol in comprehensively assessing the functional substrate by improving the identification of the protected isthmus and detecting additional CCs compared with the standard S1 protocol.

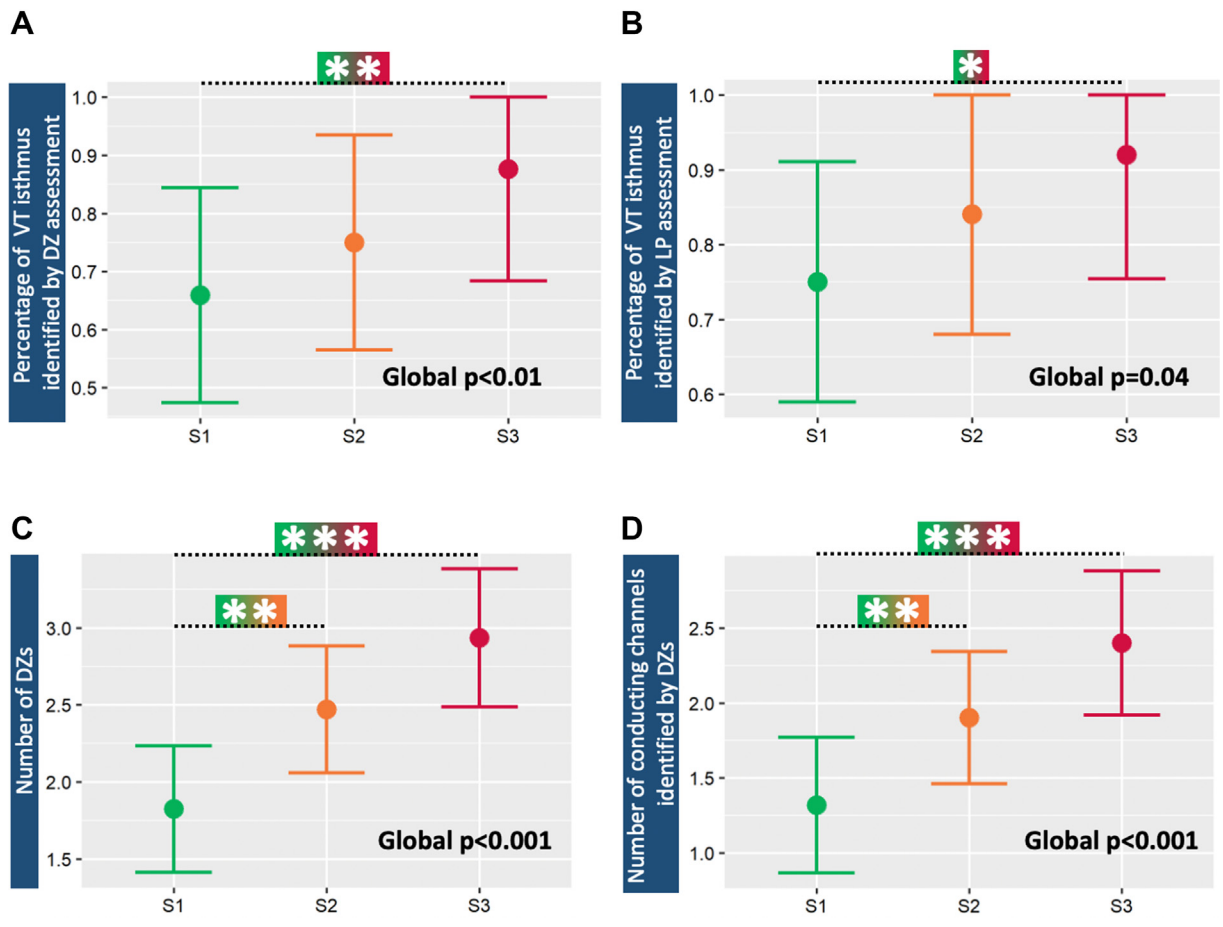
DELINEATING FUNCTIONAL AND STRUCTURAL SUBSTRATE IN ABLATION FOR VT. The diagnosis of ventricular functional substrate during sinus rhythm is a preferred strategy in catheter ablation for VT. However, there is currently no standardized diagnostic protocol for identifying areas of interest in VT secondary to scar and structural heart disease.[26] The diagnostic capacities of the various proposed methods do not appear to be optimal. For instance, there is a significant number of CCs identified by LGE CMR that are not located in areas of low voltage and LPs on electroanatomical maps.[27] Reducing the number of collateral channels due to VT ablation is associated with a lower risk for VT recurrence,[28] underscoring the importance of screening collateral channels to enhance the lesion set during VT ablation. In our study, the S3 protocol allowed the identification of expanded target areas, including an increased number of DZs and a larger surface area of LPs and DZs, which could improve the sensitivity of

TABLE 2 Differential Capacity of S1, S2, and S3 Mapping in Targeting the Isthmus of the Scar-Related VT and Highlighting the Functional and Structural Substrate

				P Value			
	S1	S2	S3	Global	S1-S3	S1-S2	S2-S3
Correlation between functional substrate and VT isthmus							
Percentage of VT isthmus detected by DZ assessment	0.62 (0.45-0.79)	0.78 (0.61-0.95)	0.89 (0.72-1.00)	**<0.01**	**<0.01**	0.14	0.41
Percentage of VT isthmus detected by assessment of LP area	0.78 (0.64-0.92)	0.86 (0.72-1.00)	0.93 (0.78-1.00)	**0.04**	**0.04**	0.36	0.50
Correlation between functional and structural substrate							
Percentage of conducting channels detected by DZ assessment	0.45 (0.21-0.68)	0.65 (0.42-0.88)	0.78 (0.55-1.00)	**<0.001**	**<0.001**	**<0.01**	0.09
Percentage of conducting channel detected by assessment of LP area	0.68 (0.47-0.89)	0.81 (0.60-1.02)	0.88 (0.67-1.00)	**<0.01**	**0.01**	0.06	0.46
Assessment of the deceleration zones							
Number of DZs	1.82 (1.41-2.24)	2.47 (2.06-2.88)	2.94 (2.49-3.38)	**<0.001**	**<0.001**	**0.01**	0.12
Total surface of deceleration zones, cm^2	7.75 (5.55-9.95)	12.69 (10.49-14.88)	15.26 (12.89-17.62)	**<0.001**	**<0.001**	**<0.001**	0.08
Assessment of the areas of LPs							
Total area of LPs, cm^2	29.4 (22.1-36.6)	38.2 (30.9-45.5)	44.1 (36.6-51.5)	**<0.001**	**<0.001**	**<0.001**	**0.01**

If a global statistical difference between the different maps was found (global $P < 0.05$), a detailed analysis was performed among the different groups. *P* values in **bold** denote statistical significance ($P < 0.05$).
DZ = deceleration zone; LP = late potential; S1 = pacing protocol from the apex of the right ventricle with 6 stimuli; S2 = first extrastimulus; S3 = second extrastimulus; VT = ventricular tachycardia.

FIGURE 4 Graphical Representation of the Main Benefits of the S3 Protocol to Unmask Arrhythmogenic Substrate



(A) Number of VT isthmuses identified by the assessment of the DZs depending on the different activation maps of the S3 protocol. (B) Number of VT isthmuses detected by the assessment of the late potentials (LPs) among the different VT activation maps or high-density pace maps of the S3 protocol. (C) Number of DZs assessed during the S3 protocol. (D) Number of conducting channels detected by the assessment of the DZs depending on the different activation maps of the S3 protocol. Interestingly, the detection of VT isthmuses was enhanced through LP and DZ assessment with S3 mapping, whereas S2 mapping did not yield any benefit. The *P* value of the global analysis of variance is reported in the right bottom corner of each panel. * $P < 0.05$, ** $P < 0.01$, and *** $P < 0.001$ between the different groups. Abbreviations as in Figures 1 and 2.

TABLE 3 Characteristics of the Ablation Procedure for Scar-Related Ventricular Tachycardia (N = 34)

Procedure features	
Procedure approach	
Transseptal approach	32 (94.1)
Arterial approach	2 (5.9)
Epicardial approach	4 (11.8)
Procedure duration, min	258 ± 49
Radiofrequency duration, min	41.9 ± 16.0
Number of initial induced VT	1.0 (1.0-2.0)
Mean cycle length of the induced VT, ms	349 (284-419)
Methods used to identify VT isthmus	
Activation mapping	20 (58.8)
Pace mapping	10 (29.4)
Characteristics of the S3 protocol	
Number of acquired points	
S1	2,734 (1,813-3,537)
S2	1,642 (1,202-1,911)
S3	1,623 (1,229-2,083)
Pacing cycle lengths	
Effective refractory period, ms	281 ± 27
Cycle length of S1	596 ± 19
Cycle length of S2	326 ± 33
Cycle length of S3	338 ± 28
Width of the LAT window, ms	
S1	167 (141-218)
S2	203 (153-251)
S3	218 (163-292)
Intraprocedural outcomes	
Number of remaps	1.0 (1.0-2.0)
Noninducibility of VT at the end of ablation procedure	29 (85.3)
Intraprocedural complications	1 (2.9)

Values are n (%), mean ± SD, or median (Q1-Q3).
LAT = local activation time; other abbreviations as in Table 2.

diagnosing the functional substrate. However, the identification of abnormal electrograms, whether through LPs or LAVAs, results in an expanded target area but lacks specificity.[29] The lower specificity of LP and LAVA diagnostic methods is confirmed in the S3-VT-FREE study, as the surface area of abnormal electrograms is nearly 3 times larger than that of DZs.[8] A high correlation between DZs and CCs identified by LGE CMR was previously observed and confirmed in this study.[30,31] Interestingly, the S3 protocol improves the diagnosis of the target substrate by identifying new CCs, increasing the number of channels from roughly 1 with the S1 map to 2 with the S3 map. The involvement of additional functional substrate identified by the S3 protocol in VT re-entry may be questioned. Although an important proportion of clinical VT isthmuses can be identified with a simple stimulation train (S1) from the RV apex, the S3 protocol significantly improves the diagnosis of the VT isthmus zone. Moreover, it has already been demonstrated that complete ablation of the functional substrate, in addition to noninducibility, is a major prognostic factor for long-term VT recurrence-free survival.[32]

STUDY LIMITATIONS. First, no control group was available for comparing the S3 protocol with the conventional protocol. Despite the lack of a control group, we proved the benefits and feasibility of the S3 protocol in delineating the functional substrate compared with the conventional S1 protocol within the same patient in all analyzed parameters (VT isthmus, DZs, LPs, and CMR CCs).

Another potential limitation is the lower density of points acquired points for S2 and S3 compared with the S1 map. However, this fact would underscore the relevance of S2 and S3 maps, as the number of DZs and their surface area might have been underestimated in the context of S2 and S3 maps, given that the quality of ILAM is significantly influenced by the definition and acquired point density of the mapping. In this sense, this lower density of S3 does not seem to be a real limitation to evaluate its benefit.

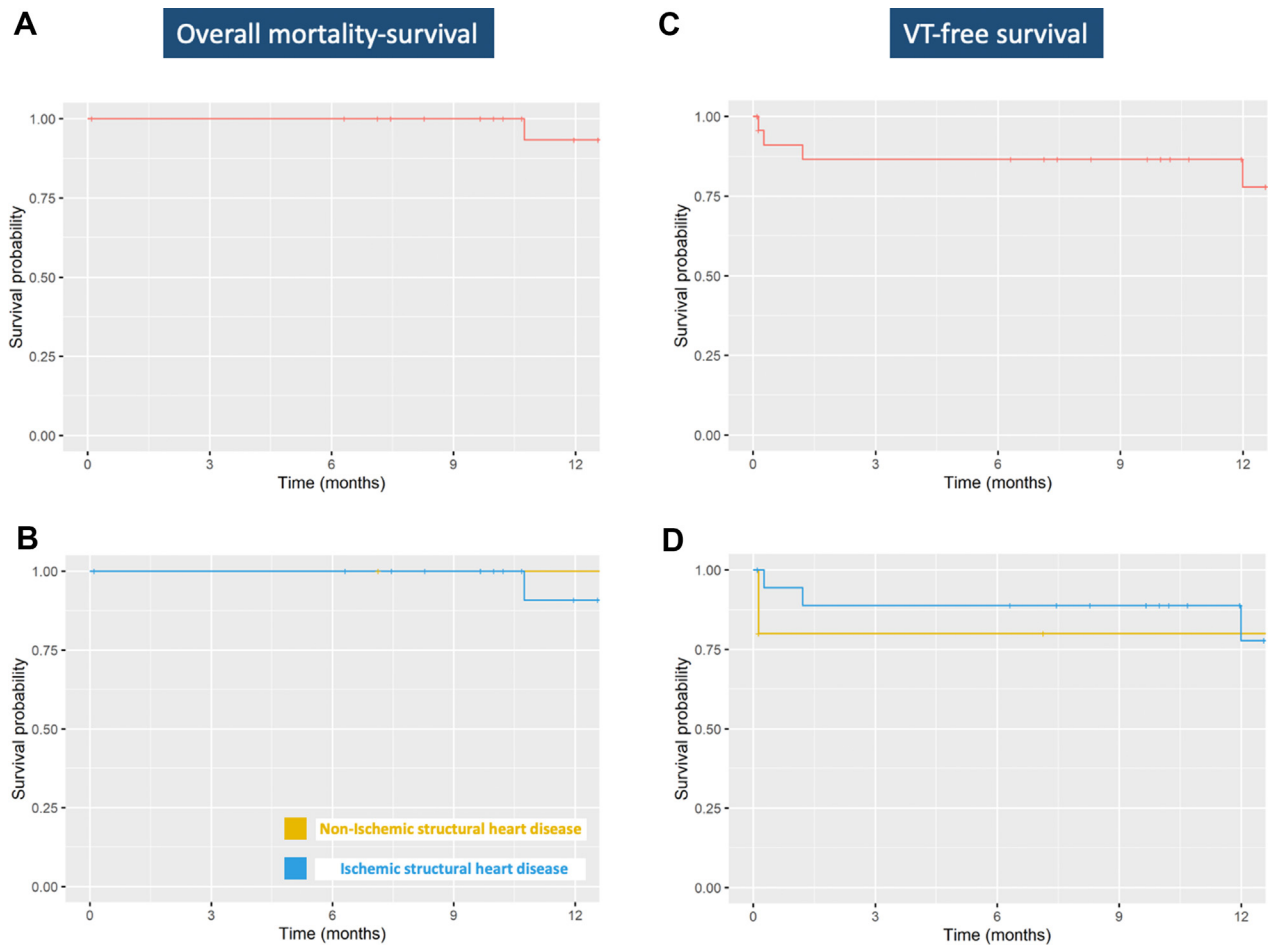
We acknowledge also that the use of different navigation systems and annotation algorithms may have an impact on the results. However, the methodology used was designed to mitigate any bias by performing a systematic annotation and correction, and more important, the use of 2 different navigation systems enhances the generalizability of the results.

A feasibility limitation must be noted. Among patients who underwent VT ablation for VT storm, the S3 protocol was not feasible in many instances, thus limiting its application in this specific population.

Finally, the clinical benefits in terms of a decreased recurrence rate in this study need to be assessed through longer term follow-up and additional randomized trials.

CLINICAL PERSPECTIVES. The S3-VT-FREE study validates the clinical relevance, feasibility, and safety of the novel S3 protocol, consisting of a high-density whole-chamber mapping based on double extrastimuli for delineating the functional substrate in cases of scar-based VT. The implementation of the S3 protocol is feasible in the vast majority of patients, with 15% of cases experiencing hindrance because of repeated induction of ventricular arrhythmias. The assessment of the functional ventricular substrate using the S3 protocol expands the area of interest for catheter ablation. It effectively detects DZs and enlarges the surface area of DZs and LPs or LAVAs. Additionally, the S3 protocol helps identify on average 1 additional arrhythmogenic DZ and increases the identification

FIGURE 5 Graphical Representation of Survival Analysis Showing Freedom From Recurrent VT and Overall Mortality in the Global Cohort and by Etiology of Cardiomyopathy



(A) Overall survival in the whole cohort. (B) Differential overall mortality-survival in patients with nonischemic and ischemic structural heart disease. (C) Overall ventricular tachycardia (VT)–free survival in the whole cohort. (D) Differential overall VT-free survival in patients with nonischemic and ischemic structural heart disease. The graphical representations of overall mortality and VT-free survival were created using the Kaplan-Meier method.

of the VT critical sites and CMR-detected CCs. The S3 protocol procedural times and radiofrequency times are in keeping with the latest literature and do not seem to be linked to extended procedural times. Additionally, a slight majority of patients (56%) were free of functional substrate after the first remapping, eliminating the need for time-consuming repetitive remapping and ablation sets to address the arrhythmogenic substrate. Various 3-dimensional mapping systems facilitate the acquisition and editing of multiple activation maps. enabling the analysis of S1, S2, and S3 maps during the procedure. Nevertheless, a controlled and randomized trial would be ideal to compare these findings with other ablation strategies.

CONCLUSIONS

The novel S3 whole-chamber protocol for assessing the ventricular functional substrate is feasible in the majority of patients and enables improved identification of ablation targets. This protocol has the potential to facilitate VT ablation and to improve patient prognosis following the procedure.

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ADDRESS FOR CORRESPONDENCE: Dr Ivo Roca-Luque, Unitat d'Arítmies, Hospital Clínic de Barcelona, Carrer Villarroel, 170, 08036 Barcelona, Spain. E-mail: iroca@clinic.cat.

PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: This study underscores the advantages of using a high-density, whole-chamber double-extrastimuli (S3) protocol to enhance the delineation of functional substrate mapping during VT ablation procedures. It demonstrates that using an S3 protocol results in improved delineation of the ventricular functional substrate, leading to enhanced identification of DZs and areas of LPs. Furthermore, this approach facilitates the identification of novel CCs as determined by CMR imaging and strengthens the localization of the VT isthmus.

TRANSLATIONAL OUTLOOK: Understanding the decremental properties of cardiomyocytes involved as a substrate for VT in patients with structural cardiomyopathy is valuable for identifying the target zone in catheter ablation procedures.

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KEY WORDS **catheter ablation, decremental property, functional substrate, structural remodeling, ventricular tachycardia**

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