Cardiovascular Magnetic Resonance Determinants of Ventricular Arrhythmic Events After Myocardial Infarction

Brief Title: *CMR Determinants of Scar Arrhythmogenicity*

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ABSTRACT

Aims: To noninvasively characterize, by means of late gadolinium enhancement cardiac magnetic resonance (LGE-CMR), scar differences and potential variables associated with VT occurrence in chronic post-MI patients.

Methods: A case-control study was designed through retrospective LGE-CMR data analysis of chronic post-MI patients i) consecutively referred for VT substrate ablation after a first VT episode (n=66), and ii) from a control group (n=84) with no arrhythmia evidence. The myocardium was characterized differentiating core, border zone (BZ) and BZ channels (BZC) using the ADAS 3D post-processing imaging platform. Clinical and scar characteristics, including a novel parameter, the BZC mass, were compared between both groups.

Results: 150 post-MI patients were included. Four multivariable Cox proportional hazards regression models were created for total scar mass, BZ mass, core mass, and BZC mass, adjusting them by age, sex, and LVEF. A cut-off of 5.15 g of BZC mass identified the cases with 92.4% sensitivity and 86.9% specificity [AUC 0.93 (0.89 – 0.97); $p < 0.001$], with a significant increase in the AUC compared to other scar parameters ($p < 0.001$ for all pairwise comparisons). Adding BZC mass to LVEF allowed to reclassify 33.3% of the cases and 39.3% of the controls [NRI = 0.73 (0.71 – 0.74)].

Conclusions: The mass of BZC is the strongest independent variable associated with the occurrence of SMVT in post-MI patients after adjustment for age, sex, and LVEF. BZC mass measurement could permit a more accurate VT risk stratification than LVEF in chronic post-MI patients.

KEYWORDS

Myocardial infarction; arrhythmogenic substrate; scar arrhythmogenicity; cardiac magnetic resonance; border zone channels; ventricular arrhythmias.

WHAT'S NEW?

- This is the first report describing the border zone channel (BZC) mass as a powerful non-invasive, CMR-derived parameter that may improve arrhythmia risk stratification in chronic post-MI patients.
- BZC mass is the strongest independent scar-derived variable associated with the appearance of clinical sustained monomorphic VTs in chronic post-MI patients after covariate adjustment for age, sex, and LVEF.
- Adding the information of CMR-derived BZC mass to LVEF could improve the accuracy of VT risk stratification in chronic post-MI patients.
- The BZC mass is intrinsically linked to the qualitative structure of the scar, its heterogeneity and spatial distribution, and is related to the presence and amount of slow conducting channels within the scar.

INTRODUCTION

The presence of viable strands of cardiomyocytes embedded within fibrotic tissue is known to be the substrate for the appearance of scar-related reentrant ventricular arrhythmias (VA) in chronic ischemic cardiomyopathy (ICM).(1) Late gadolinium enhancement cardiac magnetic resonance (LGE-CMR) has proven to be a useful technique in the non-invasive characterization of the scarred tissue and the underlying arrhythmogenic substrate.(2) Previous studies identified the CMR-derived infarct mass as a better predictor of sustained monomorphic ventricular tachycardia (SMVT) inducibility during an electrophysiologic study (EPS), when compared to left ventricular ejection fraction (LVEF).(3) In fact, the presence of significant scarring (>5% of the LV mass) is an independent predictor of adverse outcome in patients being considered for implantable cardioverter-defibrillator (ICD) placement.(4) On the other hand, in inducible patients for SMVT during EPS, more heterogeneous scars (i.e. with greater border zone mass) can be found.(5) Similarly, the presence of heterogeneous tissue channels, which correlate with voltage channels after endocardial voltage mapping of the scar, can be more frequently observed in patients suffering from SMVT than in matched controls for age, sex, infarct location, and LVEF.(6) However, the lack of solid evidence and randomized trials makes LVEF still the main decision parameter when assessing suitability for ICD implantation in primary prevention.(7,8) In the present study, we sought to characterize scar differences and potential variables associated with arrhythmogenicity in post-myocardial infarction (MI) patients using a commercially available, post-processing imaging platform with FDA 510(k) Clearance and CE Mark approval.

METHODS

Study population

Figure 1 shows the flow diagram of the study population. A case-control study was designed through retrospective LGE-CMR data analysis from our imaging database. In brief, cases were recruited from: i) a prospective cohort of post-MI patients referred for VT substrate ablation after a first SMVT episode, and ii) an additional prospective cohort of post-MI patients who underwent ICD implantation in primary prevention and had any documented episode of SMVT thereafter. All the cases had undergone a CMR study right before substrate ablation or before ICD implantation (which is regular practice in our institution).

On the other hand, controls were selected from: i) a cohort of consecutive post-MI patients with no arrhythmia evidence, either in terms of standard clinical follow-up for those with LVEF > 35%, or after periodic ICD interrogations (at least once per year) for those with ICD in primary prevention (LVEF ≤ 35%); and ii) a prospective cohort of post-MI patients undergoing ICD implantation in primary prevention, with no documented SMVT episodes thereafter. All the controls had to have a CMR study performed at least 4 years after the MI (which is regular practice in our institution), or right before the ICD implantation, when indicated.

All patients were treated according to clinical guidelines, and none of them had been pre-treated with antiarrhythmic drugs. SMVT was defined as any ventricular rhythm faster than 100 beats per minute, lasting ≥ 30 s or requiring termination due to hemodynamic instability or by antitachycardia pacing (ATP) or shocks. The study complied with the Declaration of Helsinki, and the local ethics committee approved the study protocol.

LGE-CMR processing

LGE-CMR tests were performed using a 3-Tesla scanner (MAGNETOM Trio, Siemens Healthcare, Erlangen, Germany), or 1.5-Tesla scanners (ACHIEVA, Philips, The Netherlands; and MAGNETOM Aera, Siemens Healthcare, Erlangen, Germany). In patients previously implanted with an ICD, LGE-CMR was performed using a specific wide-band sequence to avoid device artefacts. Image acquisition protocol is summarized in the Supplementary Methods. All LGE-CMR images were analyzed using a previously described protocol.(9) A full left ventricular (LV) volume was reconstructed in the axial orientation, and the resulting images were processed with ADAS 3D LV software (ADAS3D Medical, Barcelona, Spain). Ten concentric surface layers (from 10% to 90%) were created automatically from endocardium to epicardium of the LV wall thickness, obtaining a 3D shell for each layer. Color-coded pixel signal intensity (PSI) maps based on LGE-CMR images were projected to each shell, following a trilinear interpolation algorithm. A PSI-based algorithm was applied to characterize the hyperenhanced area as core zone, border zone (BZ) or healthy tissue using 40% ± 5% and 60% ± 5% of the maximum PSI as thresholds.(9)

Myocardial scar characterization

The total scar mass, BZ mass, and core mass in each shell were automatically measured using the ADAS 3D LV software. BZ channels (BZCs) were defined as continuous corridors of BZ surrounded by scar core or an anatomical barrier (i.e. mitral annulus) connecting two areas of healthy tissue. The BZC mass, defined as grams of BZ tissue that make up BZC, was obtained by multiplying the number of image voxels within the identified BZC by the voxel volume and a myocardial density of 1.05 g/cm^3 (see Supplementary Methods for rationale and calculation method), using a full-automated tool embedded within the ADAS 3D LV software.

Statistical analysis

Continuous variables are given as mean ± standard deviation or median (interquartile range, IQR), as appropriate. Categorical variables are given as total number and percentages. To compare the means of 2 variables, the Student t-test or Wilcoxon test were used, when applicable. Proportions were compared using the χ^2 or Fisher exact test, as fitted. Time-dependent receiver-operating characteristic (ROC) curve analyses were used to evaluate the optimal cut-off value of BZC mass for predicting occurrence of VT. Comparisons of AUCs were performed using the De Long's test. Kaplan-Meier curves and the log-rank test were used to assess cumulative survival. Cox proportional hazard models were used to assess relative risks. The overall discriminatory capacity of the Cox models was assessed by using the Harrell concordance index (C-index), which was validated by bootstrapping with 1000 replications. Propensity scores (PS) were calculated for cases and controls using a multivariable regression model that included the following clinical variables: age, sex, and LVEF. Pairing was performed using a greedy protocol 1:1 (caliper 0.01), with no replacement, and adequate goodness of fit was assumed if standardized differences were < 10%. Predictive capabilities were further evaluated using continuous net reclassification improvement (NRI), and integrated discrimination improvement (IDI). $P < 0.05$ was considered of statistical significance. Statistical analysis was performed using IBM SPSS Statistics, version 26.0 (IBM Corp. Released 2019; Armonk, NY: IBM Corp.), MedCalc Statistical Software version 16.4.3 (MedCalc Software bv, Ostend, Belgium), and SAS 9.3 (SAS Institute, Inc., Cary, NC).

RESULTS

Patient population

One hundred and fifty chronic post-MI patients were included for analysis (figure 1). There were 66 cases; 59/66 (89%) were patients referred for VT substrate ablation after a first documented SMVT, and 7/66 (11%) had any documented SMVT episode after ICD implantation in primary prevention. The median time from MI until the first VT episode was 72 (IQR 22 – 151, range 13 – 404) months, whereas the median time from MI until the CMR acquisition in this group was 37 (22 – 131) months. Among those referred for VT ablation, 37/59 (63%) had a previously implanted ICD. From them, 23/37 (62%) underwent a 3-Tesla CMR before the ICD implantation, and 14/37 (38%) underwent a 1.5-Tesla CMR before ablation using a wideband sequence to avoid ICD artifacts.

There were 84 controls; 38/84 (45%) were patients with no arrhythmia evidence, and 46/84 (55%) were ICD carriers in primary prevention with no arrhythmia evidence after a median follow-up of 31 (IQR 12 – 64) months post-implantation (figure 1). The median time from MI until study inclusion was 57 (IQR 51 – 115, range 48 – 408) months ($p = 0.89$ for the comparison with cases, table 1). For the controls, all the CMR studies were performed at least 4 years after the MI.

Baseline characteristics and scar characterization

Baseline characteristics of the total population can be found in table 1. Mean LVEF was 36 ± 13%, being similar between cases and controls (34 ± 10 vs. 38 ± 14%; $p = 0.07$). Compared to controls, cases were significantly older (67 ± 9 vs. 62 ± 11 years; $p = 0.007$), had more cardiovascular risk factors and were more frequently male (96% vs. 83%, $p = 0.02$) (table 1). Regarding scar characteristics, cases had a greater scar mass (33.5 ± 15.5 vs. 20.9 ± 16.1 g; $p < 0.001$), BZ mass (20.9 ± 9.5 vs. 11.7 ± 10.1 g; $p < 0.001$), core mas (12.4 ± 8.3 vs. 9.2 ± 8.8

g; p = 0.03), and BZC mass (9.7 ± 4.1 vs. 2.8 ± 3.4 g; p < 0.001) (table 1). These differences were also found in a propensity score-adjusted population (n = 132; 66 cases and 66 controls), controlling for relevant clinical covariates (age, sex, and LVEF) (supplementary table 1). There was only a slight negative linear correlation between scar mass and LVEF (r^2 0.18; p < 0.001), suggesting that not only the scar mass but also remodeling of the remote myocardium is contributing to the decrease in LVEF after MI. On the contrary, there was a strong positive linear association between scar mass and BZ mass (r^2 0.80; p < 0.001), and a mild positive linear association between scar mass and BZC mass (r^2 0.37; p < 0.001), suggesting a different spatial distribution of BZ tissue in scars with the same total scar mass.

Scar variables associated with VT events

Four multivariable Cox proportional hazards regression models were created for total scar mass (model 1), BZ mass (model 2), core mass (model 3), and BZC mass (model 4). All of them were adjusted by age, sex, and LVEF (table 2). In the corresponding models, only total scar mass, BZ mass, core mass, and BZC mass were independent variables associated with the development of VT, with similar findings after a doubly robust estimation weighting for the calculated propensity scores (table 2). Supplementary figure 1 shows the distribution of calculated BZC mass values between cases and controls. The overall diagnostic performance of BZC mass to differentiate cases and controls was excellent, with an area under the ROC curve (AUC) of 0.93 [95% CI 0.89 to 0.97; p < 0.001). From De Long's test, all pairwise comparisons of AUCs between BZC mass and total scar mass, BZ mass, and core mass showed statistical significance (p < 0.001). Time-dependent ROC curves for all the scar parameters analyzed are shown in figure 2. For BZC mass, a cut-off point of > 5.15 g showed 92% sensitivity and 87% specificity values for the identification of patients with documented

VT. A visual example of the scar characteristics and differences between cases and controls is shown in figure 3.

Interestingly, 49/66 (74%) of the cases had transmural scars, as opposed to only 48/84 (57%) of the controls ($p = 0.03$) (supplementary figure 2). Total scar mass, BZ mass, core mass, and BZC mass were significantly higher for transmural substrates as compared to non-transmural scars ($p < 0.001$ for all comparisons) (supplementary table 2).

BZC mass vs. LVEF for prediction of VT events

Out of 67 (45%) patients having a LVEF > 35%, 29 (43%) had a BZC mass > 5.15 g. Of them, 26 (90%) were cases. On the contrary, out of 83 (55%) patients with LVEF ≤ 35%, 40 (48%) had a BZC mass < 5.15 g and, from them, 36 (90%) were controls. Cumulative survival curves from MI until first documented SMVT episode according to the used LVEF and BZC mass cut-off points are shown in figure 4.

A LVEF ≤ 35% would have classified at a significant arrhythmia risk only 39/66 (59%) of the cases. Conversely, a LVEF > 35% would not have identified 44/84 (52%) of the controls. Patients fulfilling the combined criterium of LVEF > 35% and BZC mass ≤ 5.15 g (n = 38) were mostly controls (37/38, 93%). Adding BZC mass to LVEF to stratify the VT occurrence risk allowed to reclassify 33.3% of the cases and 39.3% of the controls. The NRI was 0.73 (95% CI 0.71 to 0.74), which amounted to 36.7% of all cases being reclassified (figure 5). Compared with a VT risk stratification purely based on LVEF [c-index = 0.55 (95% CI 0.46 to 0.63)], there was a significant improvement in discrimination by using the BZC mass, confirmed by a c-index difference of 0.39 (95% CI 0.29 to 0.48; $p < 0.001$). The diagnostic performance of LVEF [AUC = 0.46 (95% CI 0.36 to 0.55)] was significantly improved by combining it with the BZC mass (IDI = 0.62, $p < 0.001$). Combined diagnostic performance

of LVEF and BZC mass for predicting the occurrence of SMVT episodes in the study population is shown on table 3.

DISCUSSION

Main findings

This study is the first report describing the BZC mass as a powerful noninvasive, CMR-derived parameter that can be easily quantified and may improve arrhythmia risk stratification in chronic post-MI patients. It is also the first clinical study to report the feasibility of calculating the BZC mass in an automated way, using a commercially available cardiac imaging post-processing platform with FDA 510(k) Clearance and CE Mark approval.

The BZC mass is intrinsically linked to the qualitative structure of the scar, its heterogeneity and spatial distribution, and is related to the presence and amount of slow conducting channels within the scar. (6,10) In a previous prospective study on CRT patients (the GAUDI study), (11) the dichotomic presence of BZC had already a similar positive predictive value for arrhythmia events (24-25%) to that of an increased BZ (not BZC) mass (> 5.35 g in that study). Although the presence of BZC and BZ mass showed a better diagnostic performance than total scar mass, in the present study the quantitative BZC mass has shown to be the most accurate parameter above all.

On the other hand, the relative higher proportion of VA among patients with severely depressed LVEF may be explained because, the greater the scar, the higher the probability of LV systolic dysfunction, although this correlation is weak. (12) Similarly, the greater the scar, the higher the probability of having a greater mass of BZ and BZC. The BZC mass was, among all the scar determinants analyzed, the variable most highly associated with VT occurrence, after covariate adjustment for age, sex, and LVEF. Most likely, the BZC mass constitutes the characteristic that gets closer to the true histological substrate that gives rise to post-MI scar-related reentrant VTs, that is, the basis of scar arrhythmogenicity.

The major findings of the study can be summarized as the following:

i. Among all the scar parameters analyzed, BZC mass was the strongest independent variable associated with the appearance of clinical SMVT in chronic post-MI patients after covariate adjustment for age, sex, and LVEF. The overall diagnostic performance of BZC mass to identify post-MI patients with SMVT was very high (sensitivity 92.4% and specificity 86.9% for the cut-off value of > 5.15 g).

ii. Adding the information of CMR-derived BZC mass to LVEF could improve the accuracy of VT risk stratification in chronic post-MI patients, as shown by significant increases in AUC with respect to other scar determinants, IDI, and NRI.

Rationale for the quantitative evaluation of the BZC mass

LGE-CMR is recognized as the gold standard technique to determine the location and extent of myocardial scar.(13) The CMR-defined scar has a good correlation with low-voltage areas in the electroanatomical maps (EAM).(10,14) Moreover, the size and heterogeneity of the post-MI scar, as evaluated with CMR, are variables that, unlike LVEF, have been associated with VT inducibility,(3,5) arrhythmia events, and even mortality.(2,4,15) In a recently published, retrospective study, the presence of 'grey zone'13 fibrosis (i.e. BZ mass) > 5.0 g showed an 84% sensitivity and 72% specificity to predict the occurrence of sudden cardiac death (SCD) in chronic post-MI patients.(16) Moreover, post-MI patients with documented SMVT had more conducting channels, as evaluated during EAM, when compared to controls.(17) CMR permits to identify BZC that correlate well with the EAM conducting channels within the scar.(10) In fact, the presence of BZC has been associated (11) with a higher risk of VA/SCD, and could help deciding whether to implant an ICD in candidates for cardiac resynchronization therapy. In addition, CMR-guided VT substrate ablation approaches, which are based on the ablation of BZC identified on CMR, have shown improvement in arrhythmia-free survival during follow-up.(18) The assessment of the clinical

value of BZC mass quantification in the present study has been the necessary next step to set up future prospective studies to confirm the role of CMR in improving risk stratification for VA and SCD in post-MI patients.

Clinical implications for SCD risk stratification

In chronic post-MI patients, VA causing SCD are mostly reentrant SMVT. Therefore, identification of scars with arrhythmogenic characteristics could help better identify patients at a higher risk of SCD. In previous reports, LVEF has shown low-specificity in differentiating the risk of SCD from risk of death associated with comorbidities or the evolution of heart failure.(15) With the current, LVEF-based decision algorithms used for primary prevention of SCD with ICDs, the contemporary rate of appropriated therapies is very low, inferior than in classical ICD implantation trials that provided the evidence for current recommendations. Therefore, a more accurate identification of patients at risk is urgently needed. Upon further validation, the use of BZC mass may help improving the selection of post-MI patients for ICD implantation (i.e., in cardiac resynchronization therapy candidates), (11) or contribute to decide closer monitoring or to carry out additional screening tests (i.e. electrophysiological studies) in those patients at higher arrhythmic risk, regardless of their LVEF.(11) Yet, it shall be reminded that most cases of SCD in post-MI patients occur with normal or moderately reduced LVEF.(19) Larger cohort studies would be necessary to prospectively evaluate the use of BZC mass and its predictive accuracy for the appearance of VA and SCD.

Study limitations

Despite the inherent limitations of a case-control design, it can be acceptable to propose new variables to be tested when a low event rate is observed. However, the generated risk and

effect of the scar variables analyzed could have been overestimated. On the other hand, post-MI scar may suffer structural changes in the long-term, (20) being therefore unknown which would be the best timing for a BZC mass screening. VT screening capacity was limited for those patients who were not ICD carriers, as no continuous monitoring was available. Finally, optimal CMR quality should be a requisite to obtain reliable BZC mass measurements. Medical decision-making based on the BZC mass should be supported by external clinical validation in prospective studies. Lastly, it shall be reminded that SCD in post-MI patients may not be always due to SMVT degenerating into VF.

Conclusions

The mass of BZC is the strongest independent variable associated with the occurrence of SMVT in post-MI patients after adjustment for sex, LVEF, and total scar mass. The determination of BZC could be used to assess the risk of having SMVT, although it is still unclear its precise role in estimating the global risk of SCD.

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CONFLICTS OF INTEREST

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REFERENCES

1. De Bakker JMT, Van Capelle FJL, Janse MJ, Wilde AAM, Coronel R, Becker AE, et al. Reentry as a cause of ventricular tachycardia in patients with chronic ischemic heart disease: Electrophysiology and anatomic correlation. Circulation. 1988;77(3):589–606.
2. Yan AT, Shayne AJ, Brown KA, Gupta SN, Chan CW, Luu TM, et al. Characterization of the peri-infarct zone by contrast-enhanced cardiac magnetic resonance imaging is a powerful predictor of post-myocardial infarction mortality. Circulation. 2006;114(1):32–9.
3. Bello D, Fieno DS, Kim RJ, Pereles FS, Passman R, Song G, et al. Infarct morphology identifies patients with substrate for sustained ventricular tachycardia. J Am Coll Cardiol. 2005;45(7):1104–8.
4. Klem I, Weinsaft JW, Bahnson TD, Hegland D, Kim HW, Hayes B, et al. Assessment of myocardial scarring improves risk stratification in patients evaluated for cardiac defibrillator implantation. J Am Coll Cardiol. 2012;60(5):408–20.
5. Schmidt A, Azevedo CF, Cheng A, Gupta SN, Bluemke DA, Foo TK, et al. Infarct tissue heterogeneity by magnetic resonance imaging identifies enhanced cardiac arrhythmia susceptibility in patients with left ventricular dysfunction. Circulation. 2007;115(15):2006–14.
6. Perez-David E, Arenal Á, Rubio-Guivernau JL, Del Castillo R, Atea L, Arbelo E, et al. Noninvasive identification of ventricular tachycardia-related conducting channels using contrast-enhanced magnetic resonance imaging in patients with chronic myocardial infarction: Comparison of signal intensity scar mapping and endocardial voltage mappin. J Am Coll Cardiol. 2011;57(2):184–94.
7. Moss AJ, Zareba W, Hall WJ, Klein H, Wilber DJ, Cannom DS, et al. Prophylactic Implantation of a Defibrillator in Patients with Myocardial Infarction and Reduced

Ejection Fraction. N Engl J Med. 2002;346(12):877–83.

8. Bardy GH, Lee KL, Mark DB, Poole JE, Packer DL, Boineau R, et al. Amiodarone or an Implantable Cardioverter–Defibrillator for Congestive Heart Failure. N Engl J Med. 2005;352(3):225–37.

9. Andreu D, Ortiz-Pérez JT, Fernández-Armenta J, Guiu E, Acosta J, Prat-González S, et al. 3D delayed-enhanced magnetic resonance sequences improve conducting channel delineation prior to ventricular tachycardia ablation. Europace. 2015;17(6):938–45.

10. Fernández-Armenta J, Berruezo A, Andreu D, Camara O, Silva E, Serra L, et al. Three-dimensional architecture of scar and conducting channels based on high resolution ce-CMR: Insights for ventricular tachycardia ablation. Circ Arrhythmia Electrophysiol. 2013;6(3):528–37.

11. Acosta J, Fernández-Armenta J, Borràs R, Anguera I, Bisbal F, Martí-Almor J, et al. Scar Characterization to Predict Life-Threatening Arrhythmic Events and Sudden Cardiac Death in Patients With Cardiac Resynchronization Therapy: The GAUDI-CRT Study. JACC Cardiovasc Imaging. 2018;11(4):561–72.

12. Palazzuoli A, Beltrami M, Gennari L, Dastidar AG, Nuti R, McAlindon E, et al. The impact of infarct size on regional and global left ventricular systolic function: a cardiac magnetic resonance imaging study. Int J Cardiovasc Imaging. 2015;31(5):1037–44.

13. Cronin EM, Bogun FM, Maury P, Peichl P, Chen M, Namboodiri N, et al. 2019 HRS/EHRA/APHRS/LAHRS expert consensus statement on catheter ablation of ventricular arrhythmias. Hear Rhythm. 2020;17(1):e2–154.

14. Gupta S, Desjardins B, Baman T, Ilg K, Good E, Crawford T, et al. Delayed-enhanced MR scar imaging and intraprocedural registration into an electroanatomical mapping system in post-infarction patients. JACC: Cardiovascular Imaging. 2012;5(2):207–10.

15. Disertori M, Rigoni M, Pace N, Casolo G, Masè M, Gonzini L, et al. Myocardial

Fibrosis Assessment by LGE Is a Powerful Predictor of Ventricular Tachyarrhythmias in Ischemic and Nonischemic LV Dysfunction: A Meta-Analysis. JACC Cardiovasc Imaging. 2016;9(9):1046–55.

16. Abbasin Z, Osita O, Joseph de B, Manish K, Mauro L, Howard M, et al. Myocardial Fibrosis as a Predictor of Sudden Death in Patients With Coronary Artery Disease. J Am Coll Cardiol. 2021;77(1):29–41.

17. Haqqani HM, Kalman JM, Roberts-Thomson KC, Balasubramaniam RN, Rosso R, Snowdon RL, et al. Fundamental Differences in Electrophysiologic and Electroanatomic Substrate Between Ischemic Cardiomyopathy Patients With and Without Clinical Ventricular Tachycardia. J Am Coll Cardiol. 2009;54(2):166–73.

18. Soto-Iglesias D, Penela D, Jáuregui B, Acosta J, Fernández-Armenta J, Linhart M, et al. Cardiac Magnetic Resonance-Guided Ventricular Tachycardia Substrate Ablation. JACC Clin Electrophysiol. 2020;6(4):436–47.

19. Huikuri H V., Castellanos A, Myerburg RJ. Sudden Death Due to Cardiac Arrhythmias. N Engl J Med. 2001;345(20):1473–82.

20. Jáuregui B, Soto-Iglesias D, Penela D, Acosta J, Fernández-Armenta J, Linhart M, et al. Follow-Up After Myocardial Infarction to Explore the Stability of Arrhythmogenic Substrate: The Footprint Study. JACC Clin Electrophysiol. 2020;6(2):207–18.

FIGURE LEGENDS

Graphical Abstract. Main findings of the study. CMR permits to identify and characterize the components of the myocardial scar after a MI. Using a dedicated software, post-processed CMR images allow to quantify the mass (in grams) of the different scar components. A BZC mass > 5.15 g has shown to be strongly associated with the occurrence of VT events (survival curve). Examples of scars with and without critical BZC mass are shown.

Figure 1. Flow chart of the study population.

Figure 2. Time-dependent ROC curves for different scar determinants. Increased diagnostic performance is constantly noted at different time-points after MI when using BZC mass as compared to other scar variables. $P < 0.001$ applied for all ROC curves.

Figure 3. Example of the scar differences between cases and controls. From top left to bottom right in each panel, the 10%, 30%, 50%, and 90% myocardial layers are visualized. Core is color-coded in red, BZ in green, and healthy myocardium in pink. *Green panel*: CMR images of an asymptomatic patient (*control*) with anterior MI 5 years before the CMR acquisition; his LVEF was 42%, scar mass 21.31 g and BZC mass 0 g. *Red panel:* CMR images of a patient with incessant, sustained monomorphic VT (*case*), and an inferolateral MI 6 years before the CMR acquisition; his LVEF was 45%, scar mass 29.55 g and BZC mass 10.56 g. *White lines* delimit the identified BZC.

Figure 4. Kaplan-Meier survival curves for SMVT occurrence after MI. VT-free survival according to the amount of BZC mass within the scar (*panel A*), and LVEF (*panel B*). P-values for log-rank tests are shown in each curve.

Figure 5. Reclassification analysis. Proportion of patients correctly reclassified as cases or controls using BZC mass, as compared to LVEF.

TABLES

Table 1. Clinical and scar characteristics of the patient population.

	TOTAL (n = 150)	**CASES (n = 66)**	**CONTROLS (n = 84)**	**p**
Age (years)	64 ± 11	67 ± 9	62 ± 11	0.007*
Male sex	133 (89%)	63 (96%)	70 (83%)	0.02*
Hypertension	89 (65%)	46 (78%)	43 (54%)	0.004*
Diabetes mellitus	41 (30%)	21 (36%)	20 (25%)	0.14
Dyslipidemia	81 (59%)	44 (75%)	37 (47%)	0.001*
Smoker	27 (20%)	5 (9%)	22 (28%)	0.005*
Atrial fibrillation	6 (4%)	1 (2%)	5 (6%)	0.20
LVEF (%)	36 ± 13	34 ± 10	38 ± 14	0.07
MI location (anterior)	65 (44%)	26 (40%)	39 (46%)	0.46
Time since MI (months)	58 (31 – 120)	72 (22 – 151)	57 (51 – 115)	0.89
Betablockers	112 (81%)	43 (73%)	69 (87%)	0.03*
ACEI/ARB	97 (70%)	37 (63%)	60 (76%)	0.08
Diuretics	64 (46%)	29 (49%)	35 (44%)	0.54
MRA	72 (52%)	36 (61%)	36 (46%)	0.07
Statins	130 (94%)	58 (98%)	72 (91%)	0.07
Total scar mass (g)	26.4 ± 17.0	33.5 ± 15.5	20.9 ± 16.1	< 0.001*
BZ mass (g)	15.7 ± 10.9	20.9 ± 9.5	11.7 ± 10.1	< 0.001*
Core mass (g)	10.6 ± 8.7	12.4 ± 8.3	9.2 ± 8.8	0.03*
BZC mass (g)	5.8 ± 5.1	9.7 ± 4.2	3.4 ± 2.8	< 0.001*

*MI: Myocardial infarction; LVEF: left ventricular ejection fraction; ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; MRA: mineralocorticoid-receptor antagonists; BZ: border zone; BZC: border zone channel. * Statistically significant differences (p < 0.05).*

Table 2. Multivariable Cox proportional hazards regression models to identify independent variables associated with VT events in the study population.

MULTIVARIABLE MODEL 1					
	Covariate adjustment			**PS as covariate "doubly robust"**	
	HR (95% CI)	**p**	**c-statistic**	**HR (95% CI)**	**p**
Age (years)	1.02 (0.99 – 1.06)	0.13	0.69	1.06 (1.01 – 1.12)	0.02*
Male sex	1.07 (0.32 – 3.59)	0.92		1.06 (0.31 – 3.60)	0.50
LVEF (%)	1.00 (0.98 – 1.03)	0.83		1.00 (0.97 – 1.03)	0.93
Total scar mass (g)	1.03 (1.02 – 1.05)	< 0.001*		1.03 (1.02 – 1.05)	< 0.001*
MULTIVARIABLE MODEL 2					
	Covariate adjustment			**PS as covariate "doubly robust"**	
	HR (95% CI)	**p**	**c-statistic**	**HR (95% CI)**	**p**
Age (years)	1.02 (0.99 – 1.05)	0.23	0.73	1.05 (1.00 – 1.11)	0.047*
Male sex	0.85 (0.25 – 2.91)	0.80		0.85 (0.24 – 2.92)	0.57
LVEF (%)	0.99 (0.97 – 1.02)	0.56		0.99 (0.96 – 1.02)	0.32
BZ mass (g)	1.06 (1.04 – 1.09)	< 0.001*		1.06 (1.04 – 1.09)	< 0.001*
MULTIVARIABLE MODEL 3					
	Covariate adjustment			**PS as covariate "doubly robust"**	
	HR (95% CI)	**p**	**c-statistic**	**HR (95% CI)**	**p**

Age (years)	1.03 (1.00 – 1.06)	0.05	0.61	1.02 (0.99 – 1.05)	0.31
Male sex	1.53 (0.47 – 4.99)	0.48		1.53 (0.47 – 4.99)	0.40
LVEF (%)	0.99 (0.96 – 1.01)	0.24		0.98 (0.96 – 1.01)	0.26
Core mass (g)	1.00 (0.97 – 1.03)	0.94		1.00 (0.97 – 1.04)	0.85
MULTIVARIABLE MODEL 4					
	Covariate adjustment			**PS as covariate "doubly robust"**	
	HR (95% CI)	**p**	**c-statistic**	**HR (95% CI)**	**p**
Age (years)	1.02 (0.99 – 1.05)	0.31	0.77	1.04 (0.99 – 1.09)	0.13
Male sex	0.94 (0.28 – 3.18)	0.92		0.94 (0.27 – 3.18)	0.51
LVEF (%)	0.99 (0.97 – 1.02)	0.58		0.99 (0.96 – 1.02)	0.54
BZC mass (g)	1.12 (1.07 – 1.17)	< 0.001*		1.11 (1.07 – 1.16)	< 0.001*

*LVEF: left ventricular ejection fraction; BZ: border zone; BZC: border zone channel; HR: hazard ratio; CI: confidence interval; PS: propensity score. *Statistically significant differences (p < 0.05).*

Table 3. Diagnostic performance of LVEF, BZC mass and a combination of both for predicting the occurrence of SMVT episodes in the study population.

LVEF performance	**CASE**	**CONTROL**	**TOTAL**
LVEF ≤ 35% (high risk)	39	44	83
LVEF > 35% (low risk)	27	40	67
TOTAL	66	84	150
Se = 59.1%; Sp 47.6%			
BZC mass performance	**CASE**	**CONTROL**	**TOTAL**
BZC mass > 5.15 g (high risk)	61	11	72
BZC mass ≤ 5.15 g (low risk)	5	73	78
TOTAL	66	84	150
Se = 92.4%; Sp = 86.9%			
Combined performance (LVEF + BZC mass)	**CASE**	**CONTROL**	**TOTAL**
LVEF ≤ 35% and BZC mass > 5.15 g (high risk)	35	8	43
LVEF > 35% and BZC mass ≤ 5.15 g (low risk)	1	37	38
TOTAL	36	45	81
Se = 97.2%; Sp = 82.2%			

LVEF: Left ventricular ejection fraction; BZC: border zone channel; Se: Sensitivity; Sp: specificity.