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Abstract	Abnormal propagation of cardiac electrical impulses in hearts with fibrosis developed post-infarction often lead to rapid ventricular tachycardia (VT) and sudden cardiac death, a major cause of mortality. Certain values of ejection fraction (e.g. EF < 35%) are used clinically to refer scar-related VT patients for ICD implantation; however, these values are not an indication of VT severity (i.e., how fast is the heart rate in VT). Our aim here is to use a preclinical model of chronic fibrosis to determine whether the extent of fibrosis defined by MRI correlates better than EF with the heart rate during VT (a measure known as *VT cycle length*). Specifically, n = 10 pigs with prior infarct underwent MR imaging (i.e., cine scans to calculate EF, and high resolution late gadolinium enhancement (LGE) to measure the extent of fibrosis, followed by an X-ray guided VT inducibility study to determine VT cycle length. The total infarct size in LGE images was given by the extent of dense scar plus that of *gray zone,* GZ (a mixture of viable muscle and collagen fibers, located at the scar periphery), as defined by two clinically accepted segmentation thresholding methods: 5SD (standard deviation) and FWHM (full-width at half maximum), respectively. Overall, LGE-defined scar/GZ corresponded well to infarct heterogeneities observed in collagen-sensitive histological stains. Our quantitative results showed that the amount of LGE-defined fibrosis (relative to the left ventricular volume) correlated well with VTCL (R ~ 0.78), suggesting that it could be a potential clinical predictor of dangerous VT.

Keywords (separated by '-')	myocardial infarct - MR imaging - late gadolinium enhancement LGE - heterogeneous fibrosis - ventricular tachycardia substrate

The Extent of LGE-Defined Fibrosis Predicts Ventricular Arrhythmia Severity: Insights from a Preclinical Model of Chronic Infarction

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Abstract. Abnormal propagation of cardiac electrical impulses in hearts with fibrosis developed post-infarction often lead to rapid ventricular tachycardia (VT) and sudden cardiac death, a major cause of mortality. Certain values of ejection fraction (e.g. EF < 35%) are used clinically to refer scar-related VT patients for ICD implantation; however, these values are not an indication of VT severity (i.e., how fast is the heart rate in VT). Our aim here is to use a preclinical model of chronic fibrosis to determine whether the extent of fibrosis defined by MRI correlates better than EF with the heart rate during VT (a measure known as *VT cycle length*). Specifically, n = 10 pigs with prior infarct underwent MR imaging (i.e., cine scans to calculate EF, and high resolution late gadolinium enhancement (LGE) to measure the extent of fibrosis, followed by an X-ray guided VT inducibility study to determine VT cycle length. The total infarct size in LGE images was given by the extent of dense scar plus that of *gray zone,* GZ (a mixture of viable muscle and collagen fibers, located at the scar periphery), as defined by two clinically accepted segmentation thresholding methods: 5SD (standard deviation) and FWHM (full-width at half maximum), respectively. Overall, LGE-defined scar/GZ corresponded well to infarct heterogeneities observed in collagen-sensitive histological stains. Our quantitative results showed that the amount of LGE-defined fibrosis (relative to the left ventricular volume) correlated well with VTCL (R ~ 0.78), suggesting that it could be a potential clinical predictor of dangerous VT.

Keywords: myocardial infarct · MR imaging · late gadolinium enhancement LGE · heterogeneous fibrosis · ventricular tachycardia substrate

1 Introduction

Abnormally high heart rhythms (tachyarrhythmias) are often associated with structural heart disease, such as myocardial infarction. In particular, scar-related ventricular tachycardia (VT) is a major cause of sudden cardiac death (SCD) [1]. The VT substrate (a mixture of viable myocytes and collagen bundles) allows the electrical impulse to traverse dense scars through these viable paths and to loop around the dense scars with a

O. Bernard et al. (Eds.): FIMH 2023, LNCS 13958, pp. 1–10, 2023.
https://doi.org/10.1007/978-3-031-35302-4_71

VT cycle length (VTCL) depending directly on the scar size [2]. The geometrical configuration of unexcitable dense scars encasing viable paths (i.e., critical channels with reduced conduction velocity of the electrical impulse), forms a reentry circuit (Fig. 1) that facilitates a VT wave to repeatedly enter from one side of the circuit and exit from the opposite side, overriding the normal sinus node-driven heart rhythm [3].

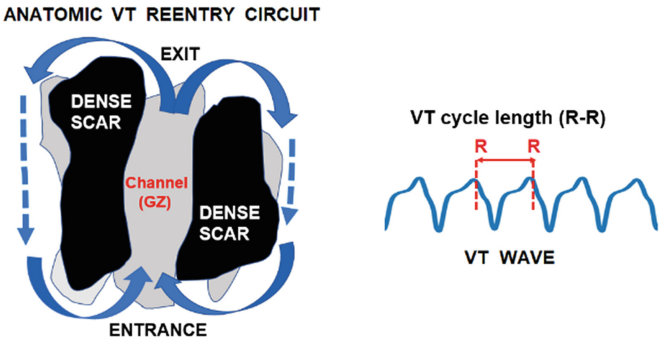

Fig. 1. Reentry circuit in scar-related VT and its associated wave, where the VTCL is determined from consecutive R-R intervals.

In practice, a VT episode can be terminated either by an implantable defibrillator device (ICD) or by an RF ablation procedure that interrupts the circuit by thermally ablating the critical channels. Thus, accurate localization of infarct heterogeneities is critical for VT diagnosis [4]. Moreover, prior to ICD implantation or RF ablation procedures, VT is evaluated in the EP lab during an invasive test inducing VT through rapid pacing.

Several studies have shown that cardiac MR imaging can identify the location and extent of the scar and VT substrate using late gadolinium enhanced (LGE) imaging. Due to its intermediate MR signal intensity (between the signal intensity of healthy myocardium and dense scar), the VT substrate is usually called *gray zone* (GZ). The amounts of scar and GZ are useful clinical predictors of mortality rates [5] or arrhythmia events (as demonstrated by the VT/VF episodes recorded by ICDs) [6]. Unfortunately, most clinical MR imaging exams use 2D LGE methods with spatial resolution limited to ~ 8–10 mm slice thickness, leading to partial volume effects and inadequate quantification of scar and GZ. This also affects the sudden cardiac death (SCD) risk stratification as well as the selection of candidates for ICDs. With respect to scar/GZ quantification from LGE images, several semi-automatic algorithms have been developed, including: standard-deviation (n-SD); full-width-at-half-maximum (FWHM); graph cut/continuous max-flow; and, gaussian-mixture clustering [7]. However, among them, FWHM and n-SD approaches remain the most clinically accepted methods.

In this study, we hypothesized that LGE-derived fibrosis is a better predictor of the VT severity (indicated by VTCL), than the ejection fraction (EF). Specifically, here we aimed to use a high-resolution free breathing 3D LGE method (at 1.4 mm isotropic spatial resolution), in order to identify and adequately quantify the infarct location and size (i.e., amount of dense scar and GZ). To achieve this, we proposed to use a pig model of

chronic infarction, and to correlate the amount of LGE-derived fibrotic infarct with the VTCLs recorded during VT inducibility tests performed under x-ray guidance. Additionally, we also correlated the recorded VTCLs with the EF values derived from cine MR imaging scans, and then studied which MRI-based biomarker is a better predictor of fast (dangerous) VTs.

2 Methodology

In this section we describe all experimental procedures, along with the analysis performed in order to correlate the amount of infarcted tissue and EF, respectively, with the severity of VT (i.e., cycle length measured during the VT induced by standard clinical protocols). A diagram of the study workflow is illustrated in Fig. 2.

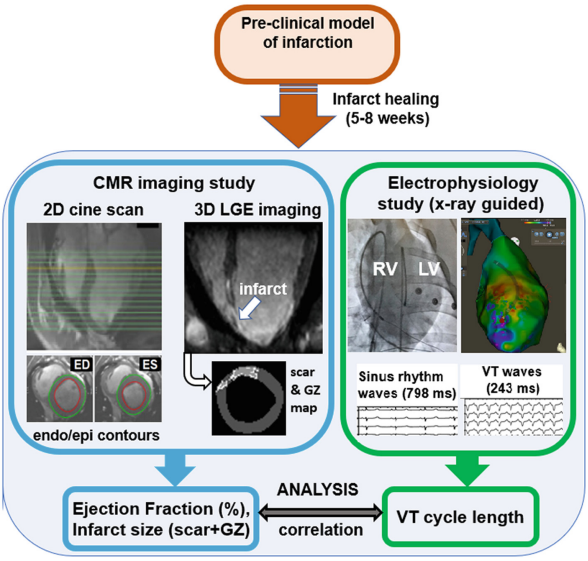

Fig. 2. Schematic diagram of the MR-EP studies and analysis performed in pigs with chronic infarction, to correlate the left ventricular EF and infarct size with VTCL

2.1 Preclinical Model of Infarction

This study included n = 10 swine (each weighing ~30kg prior to the infarct creation). All procedures (i.e., infarct creation, MRI scans, and x-ray guided arrhythmia studies) were conducted with approval from the Animal Care Committee at Sunnybrook Research Institute, Toronto (Canada). During each procedure, the pigs were placed under a cocktail anesthesia (0.05 mg/kg atropine and 33 mg/kg ketamine), maintained by 1–5% isoflurane delivered via a mechanical ventilator. In order to create heterogeneous infarctions comprised of dense scar and GZ (i.e., VT foci), the pigs underwent a left anterior descending

artery occlusion via balloon inflation for 90–100 min, followed by reperfusion, as in [8, 9]. The infarcted animals were allowed to heal during the following 5–8 weeks. Note that the infarct heterogeneity was verified by histological examination in select samples, at the completion of MR-EP studies.

2.2 MR Imaging and Associated Image Analysis

All MR scans were performed on a 3T MR750 scanner (GE Healthcare, Waukesha, Wisconsin) using an 8-channel cardiac coil. Amiodarone was injected to avoid spontaneous arrhythmia occurrence and to stabilize the heart rate during the scans.

a) *Cardiac function* was evaluated using a 2D steady-state-free-precession (SSFP) sequence in cine mode. Approximately 18 short-axis slices were prescribed per animal to fully cover the heart ventricles. The following MR imaging parameters were used: 8 views/segment, 20 phases per slice, TR = 4ms, TE = 1.7 ms, flip angle = 45°, FOV = 24 × 21.6 cm, matrix = 224 × 160 and slice thickness = 5 mm.

   The cine SSFP images were analyzed using the *CVI42* software (Circle Cardiovascular Imaging, Calgary, CA). Specifically, we manually draw the endocardial and epicardial contours of the left ventricle at *end systole* (ES) and *end diastole* (ED) phases, which allowed us to compute the ejection fraction, EF, using the formula: EF (%) = (EDV-ESV)/EDV, where EDV and ESV are the blood volumes corresponding to ED and ES phases, respectively.

b) For *infarct imaging,* a bolus of Gd-DTPA (0.2 mmol/kg, Magnevist) was intravenously administered and imaging started ~ 10min after the contrast agent injection. For the LGE scan, we used a free-breathing high resolution 3D inversion recovery (IR) prepared spoiled gradient echo (SPGR) sequence with respiratory navigation. The following MR imaging parameters were used: TE = 1.5 ms, TR = 3.5 ms, flip angle = 15°, BW = 100 kHz, optimized inversion TI ~ 250 ms (to maximize the contrast between the infarcted area and healthy tissue), and voxel size = 1.4 × 1.4 × 1.4mm^3.

In this work we focused only on the left ventricle (LV) analysis, for which we first manually delineated the epicardial and endocardial contours. We then characterized infarct heterogeneities and computed *tissue maps* by defining 3 classes: dense scar; grey zone (GZ); and, healthy myocardium. For this, we performed a thresholding of the signal intensity in the LGE images using the two widely used segmentation approaches: standard deviation (n-SD) method and FWHM method, respectively.

i) For the n-SD method, we used the mean and standard deviation (SD) of the signal intensity (SI). For each LGE slice, an ROI was drawn in the remote/healthy myocardium zone. The mean (mean_remote), peak (peak_remote), and standard deviation (SD_remote) of the SI within the selected remote ROI were calculated. To obtain the aforementioned classes (scar, GZ and healthy tissue) in the resulting *tissue map*, we used cut-off thresholds of the SI as per clinical guidelines [10]:

$$SI\_scar > mean\_remote + 5 * SD\_remote \quad (1)$$

$$mean\_remote + 2 * SD\_remote < SI\_gz < mean\_remote + 5 * SD\_remote \quad (2)$$

where SI_scar is the SI of a pixel classified as dense scar (i.e., infarct core), and SI_gz is the SI of a pixel classified as gray zone. Henceforth, the n-SD method will be referred as the 5SD method.

ii) The second method was based on the full-width half-maximum (FWHM) approach [11], using a 50% threshold and the following definitions:

$$SI\_scar > 0.5 * peak\_scar \tag{3}$$

$$peak\_remote < SI\_gz < 0.5 * peak\_scar \tag{4}$$

where peak_scar is the peak of signal intensity of all fibrotic (infarcted) pixels.

The entire analysis pipeline including all processing steps and both semi-automatic segmentation algorithms is presented in Fig. 3. It employed in-house written scripts and was implemented in Matlab using the *image processing toolbox* and a GUI interface. Notably, approximately 600 LGE images acquired in the 10 pigs were segmented by each method. The LV binary masks were used to calculate the LV volume, per heart.

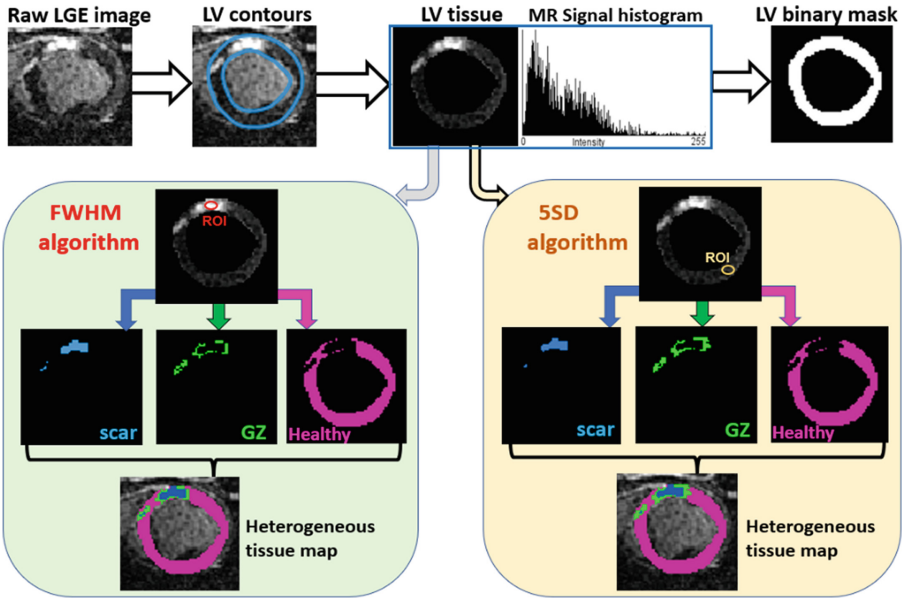

Fig. 3. Image analysis pipeline presented using an exemplary LGE image in short-axis and the associated pixel-wise *tissue maps* obtained by the 5SD and FWHM methods (pink = healthy myocardium, green = GZ, blue = scar).

2.3 Electrophysiology Study and VT Inducibility Protocol

All pigs underwent x-ray guided EP studies the day after the MR scans, to ensure that amiodarone was effectively out of the body and did not impede VT inducibility. All EP studies were carried out under X-ray guidance, using a C-arm Toshiba INFINIX VF-I/SP-S. For the VT inducibility tests, we inserted an SF Thermocool catheter (Biosense Webster Inc., Irvine, CA, USA) into the right ventricle (RV) of each pig, and then performed rapid pacing, mimicking the clinical diagnostic protocols. Specifically, we started with a train of 8 × S1 pacing stimuli at 400–600 ms, followed by S2-S3 extra-stimuli with reduced coupling interval, until VT was induced. The VT waves were recorded and VTCL was calculated from the R-R intervals (peak-to-peak).

2.4 Histology

Select samples (4 mm thickness) from hearts were cut to align with the short-axis view of LGE images and embedded in paraffin. Thin slices (4 μm) were cut from each paraffin block, fixed on large glass slides and stained with collagen-sensitive Masson Trichrome stain. The stained slides were matched to their corresponding short-axis LGE images using anatomical markers (RV/LV insertion point, papillary muscle), and were used for a qualitative comparison with the LGE-derived tissue maps.

2.5 Statistical Analysis

For the quantitative analysis, linear fits were performed in order to derive the correlation between VTCL and % fibrosis (scar + GZ) relative to LV volume, as well as between VTCL and EF (%). In addition, the Bland–Altman analysis was used to evaluate bias and the two-tailed *P* value was used to statistically compare the amount of fibrosis (scar + GZ) determined by the 5SD method vs. the FWHM method.

3 Results

Figure 4 shows exemplary outputs of the scar/GZ segmentations (note: in the raw LGE image the infarct is indicated by a hyperenhanced area). Both *tissue maps* identified similar infarct patterns and extent (although the 5SD-defined dense scar was slightly smaller), as well as surviving sub-endocardial GZ pixels and healthy pixels. Qualitatively, the infarct heterogeneities corresponded well to those identified in the histology stain (see white rectangles in tissue maps and magnified area in MT slide).

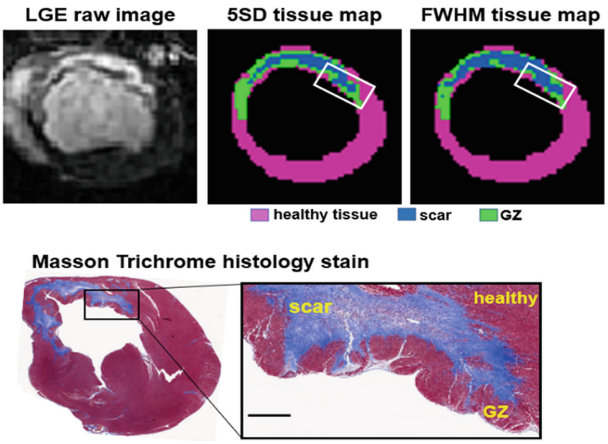

Fig. 4. Qualitative example of the segmentation comparison: *(upper row)* a raw LGE image and resulted pixel-wise tissue maps obtained using 5SD and FWHM methods (pink = healthy myocardium, green = GZ, blue = scar); *(bottom row)* corresponding histology MT slide (collagenous fibrosis stained blue and healthy tissue in dark red). (Color figure online)

Figure 5a presents the results obtained in all animals, relating the VTCL and % fibrosis (scar + GZ) calculated relative to LV volume. We observed that smaller amounts of fibrosis clearly related to faster VT rates (i.e., more dangerous arrhythmia events).

The linear fits yielded good correlations between the VTCL and the % fibrosis defined by either segmentation method ($R > 0.78$). Furthermore, there was no bias between the two segmentation methods, as indicated by the Bland-Altman plot (see Fig. 5b). In addition, the difference in % fibrosis derived by the two segmentation methods was not statistically significant ($P < 0.05$), with a correlation coefficient close to unity.

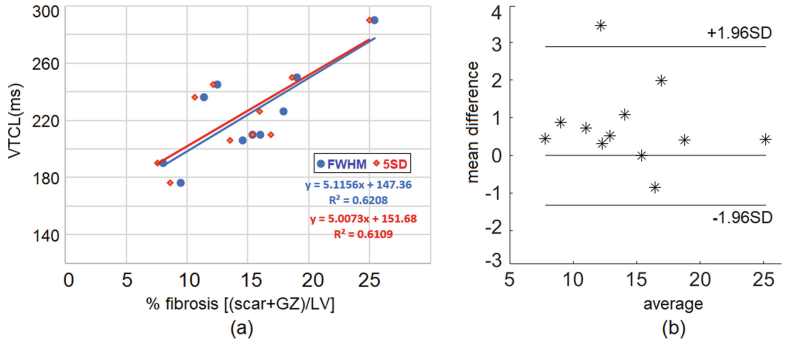

Fig. 5. Results from quantitative analysis: (a) linear fitting of VTCL vs % fibrosis defined by 5SD and FWHM methods; (b) Bland-Altman plot (overall bias ± 95% limits of agreement) showing no bias between the 5SD and FWHM segmentation methods.

Figure 6 shows results from the correlation analysis between the VTCL (ms) and the measured EF values (%) of the left ventricle. Overall, the linear fit yielded a rather

poor correlation (R = 0.13) between these two measurements, suggesting that EF is not a good indicator of how fast the VT rate might be in a given post-infarction case.

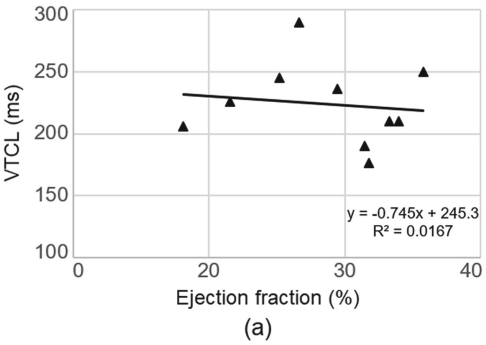

Fig. 6. Linear fitting demonstrating a poor correlation between VTCL (ms) and EF (%).

4 Discussion

Accurate prediction of ventricular arrhythmia in post-infarction patients is a clinical burden. Especially, the prediction of how fast the heart rate might be in the settings of scar-related VT is of paramount importance. With this respect, contrast-enhanced MR imaging represents an exquisite tool for the evaluation of fibrotic infarct heterogeneity and the identification of GZ, where the substrate of potentially lethal VT is harboured.

First, the work presented in this study successfully demonstrated the capability of a high resolution 3D LGE method (with isotropic voxel size) to distinguish dense scar from GZ in a pig model of chronic infarction. This allowed us to accurately assess the extent of fibrosis by two segmentation methods based on SI thresholding (i.e., 5SD and FWHM), both methods yielding similar results. Our preclinical model mimicked the human pathophysiology of scar-related VT, thus highlighting its translational aspect and the potential clinical utility of the 3D LGE method in predicting the severity of VT episodes. As noted in Fig. 4, the ischemic GZ had fibrotic bundles intermingled with viable myocytes (salvaged by reperfusion), while in the dense scar most necrotic areas were replaced by mature collagenous fibrosis. This heterogenous pattern (as revealed by the MR signal intensity enhancement within the infarcted area) likely favoured the VT inducibility. Typically, the VT waves rotate around unexcitable patches (scars).

Second, our results showed that the correlation between VT cycle length and the amount of heterogeneous infarct (scar + GZ), was superior to the correlation between VTCL and EF. To the best of our knowledge this is the first quantitative study suggesting that the amount of LGE-defined fibrosis might be a better predictor (than EF) of the severity of VT. Previous preclinical and clinical studies have suggested only the utility of MRI-defined scar and GZ, respectively, as predictors of mortality (based on SCD evidence) [5], or predictors of possible occurrence of arrhythmia (shown by recorded VT/VF episodes in patients with implantable defibrillator devices) [6]. The negative

slope obtained in our correlation analysis between VTCL and EF, could be explained by the fact that longer VTCLs correspond to larger infarcts, which are usually associated with reduced EF values. However, in the clinics, many patients present with preserved EF; thus, we suggest that a correlation between VTCL and EF might not be clinically useful.

One limitation of our data-driven predictive study is that the image analysis was performed for the LV only. In some of the hearts, the infarcted area also had RV involvement; thus, the total amount of fibrosis within the entire heart (LV + RV) might slightly change the correlation with VTCL. Furthermore, conventional LGE imaging is known to have several technical limitations, such as: optimal inversion time TI is found through trial-end-error tests (prolonging the scan time); MR signal intensity depends on the gadolinium wash-in and wash-out kinetics; difficult differentiation of sub-endocardial scar/GZ from the bright blood pool; and, the manual selection of ROI is operator-dependent. These issues could be avoided by using for instance robust T1/T1* imaging mapping methods [8, 9] instead of LGE.

In this work we specifically correlated the total amount of infarct (scar + GZ), since the VT wave around dense (unexcitable) patches propagates through both healthy tissue and slow conduction GZ areas (located at the periphery of dense scar). As per the simplified VT circuit illustrated in Fig. 1, the reentry wave will have different speeds in different tissue segments, each contributing to the final cycle length of one complete rotation. Moreover, the main channels often traverse large scars (partitioning them into smaller dense patches that define the VT pattern), while some circuits present with secondary channels [2] that can alter the VT morphology and CL during the inducibility procedure. Thus, VTCL cannot exactly correlate with the total scar circumference; instead, the length of each circuit component needs to be measured. For these reasons, we also did not expect to obtain a perfect correlation in Fig. 5. Additionally, while the amount of GZ is an independent predictor of the arrhythmia [5, 6], the GZ size alone would not have a strong correlation with VTCL.

Considering these complex aspects, our future work will focus on reconstructing the 3D geometry of the circuits, as such knowledge is critical in planning the RF ablation procedures [4, 12] in order to successfully terminate VT. We also plan to further employ biophysical modelling tools to accurately predict the electrical wave propagation and VT inducibility per individual heart. Such virtual 3D heart models can integrate image-defined scar/GZ areas [13, 14], from which one will be able to precisely compute the CL of dangerously fast (potentially lethal) VTs via *in silico* computer simulations.

5 Conclusion

Our preclinical study suggests that the LGE-defined extent of infarct is a better predictor of VTCL than the ejection fraction, which was poorly correlated with VTCL. Although Gd-DTPA is not a collagen-specific contrast-agent, it can be used with confidence to evaluate the extent of fibrosis (scar + GZ) in remodelled chronic infarcts by both 5SD and FWHM standard methods, as they yielded similar results in segmenting the infarct heterogeneities such as dense scar and GZ (where the VT substrate resides).

Acknowledgements. The authors would like to thank: Mr. Adebayo Adeeko for processing the explanted hearts and for staining the histology slides; Ms. Melissa Larsen for help with the animal preparation during the MRI-VT studies; and, Dr. Xiuling Qi and Mr. Venkat Ramanan for help with MR imaging. This research was funded by the Canadian Institutes of Health Research (CIHR): Project grant PJT-153212 awarded to Dr Mihaela Pop and Project grant PJT-178299 awarded to Dr. Graham Wright.

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