

# Measuring the Degree of Fibrosity of Myocardial Scars from Late Gadolinium-Enhanced Cardiovascular Magnetic Resonance Images

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## Abstract

*We seek to define and measure the degree of fibrosity of the scars in myocardial infarction (MI) patients, and to see if it helps in separating a group of MI patients who have had episodes of ventricular tachycardia (VT) after the infarction from a group of MI patients who have not.*

*Late gadolinium-enhanced cardiovascular magnetic resonance images of 20 MI patients with VT and 34 without were taken, and the scars demarcated by cardiologists. Various fibrosity measures were defined through weighting the normalised signal intensity distributions of the scars. The fibrosity measures were used as input to a classifier together with the left ventricular ejection fraction (LVEF) and the relative scar size. The classification problem being separating the two patient groups and done in a leave-one-out fashion.*

*At a sensitivity of 90%, combining the best fibrosity measure with LVEF gave a specificity of 91% (with 95% confidence interval (CI) 76-98%), whereas LVEF combined with relative scar size yielded 85% (CI: 69-94%) and LVEF alone 82% (CI: 66-92%).*

*Capturing the degree of fibrosity of myocardial scars through weighting the scars' normalised signal intensity distributions might be of assistance in evaluating the risk of MI patients getting VT.*

## 1. Introduction

Myocardial infarction (MI) is a major contributor to morbidity and mortality worldwide. Following MI there is a replacement of dead (necrotic) myocardium by fibrotic tissue, so-called fibrotic replacement. The amount of fibrotic replacement varies greatly, depending upon the initial extent and severity of myocardial necrosis and upon the healing process. The severity of fibrosis is directly related to subsequent risk of premature death and morbidity. Some of the deaths are caused by ventricular tachycardia (VT). An implantable cardioverter-

defibrillator (ICD) [1] or radiofrequency ablation [2] can help prevent fatal arrhythmias. It is therefore important to predict who will get VT. The most commonly used predictor is the left ventricular ejection fraction (LVEF) [1]. The scar size (relative to the ventricle size) has also been identified as an additional risk factor for VT [3]. Other reported risk factors are transmuralty [4] and various image-based texture measures [5,6].

Both the extension and the degree of myocardial fibrosis can be assessed in late gadolinium-enhanced cardiovascular magnetic resonance (LGE-CMR) images. Gadolinium-based contrast agents are retained in fibrotic tissue, causing an increase in signal intensity in regions of tissue with increased fibrosis, for example in the myocardial scar area. The scar is normally measured *quantitatively* by its size (relative to the ventricle size), using manual demarcation or various types of thresholding schemes [7]. Sometimes, this is taken one step further, yielding two scar quantities, by dividing the scar into two types of tissue: core and grey zone, with the core being the most fibrotic tissue and the grey zone denoting an intermediate level of fibrosity [8]. Such approaches are categorical and consider a voxel as fibrous, semi-fibrous or not fibrous at all. This naturally leads to the question of whether a *qualitative* measure describing *the degree* of myocardial fibrosis by taking into account the continuous varying levels of signal intensity within the scar could have clinical value, complementing the quantitative measures.

We address this question by defining a family of qualitative measures of myocardial scars, based on weighting the normalised signal intensity distributions of the (manually demarcated) scars. We refer to these measures as fibrosity measures. In order to test the clinical value, we studied the discriminative power of the fibrosity measures in two groups of MI patients - one of which with VT episodes, the other without.

## 2. Materials and methods

## 2.1. Study population

The study population consisted of two patient groups with acute MI in their history. The first group consisted of 20 patients who had had episodes of VT in the years following the MI. The LGE-CMR images of these patients were taken many years after the MI (varied from patient to patient). More details on this group are given in [9]. The other group consisted of 34 patients for which there were no observed episodes of VT in the first year following the MI. The LGE-CMR images of these patients were taken 1 year after the MI. The study was approved by the Regional Ethics Committee, and informed consent was obtained from all patients.

## 2.2. Image acquisition

For each patient, the LGE-CMR images were acquired as follows: First, the gadolinium-based contrast agent Omniscan® was administered intravenously at a dosage of 0.25 mmol/kg body weight. Then, 10-15 minutes later, an image sequence of short-axis slices was taken, covering the whole left ventricle. The slices were 10 mm thick, without overlap. The images had  $512 \times 512$  pixels, with each pixel covering  $0.82 \times 0.82 \text{ mm}^2$ . The image bit depth was 12. The images were taken by a 1.5-tesla magnetic resonance scanner (Philips Intera 1.5T; Philips Medical Systems, Best, the Netherlands), using an inversion-recovery-prepared,  $T_1$ -weighted gradient-echo sequence with 1.3 ms echo time and 4.1 ms repetition time. The inversion time was individually adapted, aiming to null normal myocardium (typically 200–300 ms).

## 2.3. Image analysis

First, the myocardial and scars were demarcated by two cardiologists, as illustrated in Figure 1. Then, the scars voxel values were analysed in the spatial domain, without considering neighbour relations. In the following, the word frequency is thus used as in statistics (i.e. counting occurrences of voxel values), and the term fibrosis refers to voxels with high signal intensity values - not to texture.

Let  $m$  denote the 99th percentile of the frequency distribution of the voxel values in a patient's scar (note: all scar tissue from all slices merged together). First, every voxel value larger than  $m$  was set to  $m$ , to diminish the effect of outliers. Second, the scar was normalised by dividing every voxel value by  $m$ , to make it comparable with the scars of other patients. The resulting scar thus had voxel values in the set

$$\mathcal{D} = \left\{0, \frac{1}{m}, \dots, 1\right\}.$$

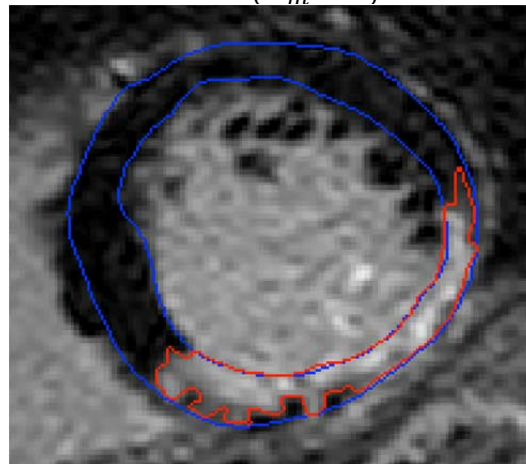


Figure 1. Cropped LGE-CMR image with cardiologists' demarcation of myocardium (blue) and scar (red).

Let

$$P(x): \mathcal{D} \rightarrow [0, 1]$$

denote the relative frequency distribution of the voxel values of the resulting scar. Let

$$w(x): [0, 1] \rightarrow [0, 1]$$

be a monotonically increasing weighting function with  $w(1) = 1$ . The fibrosity of the scar was defined as

$$\mathcal{F}_w = \sum_{x \in \mathcal{D}} w(x)P(x).$$

(Remark:  $\mathcal{F}_w$  is approximately the same as  $\int_0^1 w(x)p(x)dx$  for a density function  $p(x)$  fitted to  $P(x)$ .)

Various fibrosity measures were calculated from  $P(x)$  as above, using the following families of piecewise linear and exponential functions as weighting functions:

$$L_\alpha(x) = \begin{cases} \frac{1}{1-\alpha}x - \frac{\alpha}{1-\alpha} & \text{if } x \geq \alpha \\ 0 & \text{if } x < \alpha \end{cases}, \text{ where } \alpha \in [0, 1],$$

$$E_\beta(x) = e^{\beta(x-1)}, \text{ where } \beta \in [0, \infty).$$

The parameters used were  $\alpha = 0, 0.35, 0.5, 0.65, 0.8$  for  $L_\alpha(x)$  and  $\beta = 1, 4, \dots, 16$  for  $E_\beta(x)$ , as shown in Figure 2 and Figure 3, respectively.

Figure 4 shows the effects of the weighting function  $E_7(x)$  on a density function  $p(x)$  fitted to the relative frequency distribution  $P(x)$  of a scar. (The density function for illustrational purposes.) The fibrosity  $\mathcal{F}_{E_7} = \sum_{x \in \mathcal{D}} E_7(x)P(x)$  of the scar is approximately equal to  $\int_0^1 E_7(x)p(x)dx$ , which is the area enclosed by the  $x$ -axis and the curve  $y = E_7(x)p(x)$  on the interval  $[0, 1]$ . It is seen that  $E_7(x)$  gives much influence to high relative signal intensities, leading to high fibrosity for scars with left-skewed (left-tailed) signal distributions.

Since the tail of  $P(x)$  might indicate how fibrotic the

scar is, the Fisher-Pearson coefficient  $g_1$  of sample skewness of each scar was also calculated to use as a fibrosity measure. The sample skewness is defined as  $g_1 = \frac{\frac{1}{n} \sum_{i=1}^n (x_i - \bar{x})^3}{\left(\frac{1}{n} \sum_{i=1}^n (x_i - \bar{x})^2\right)^{3/2}}$ , where  $n$  is the number of voxels,  $x_i$  the voxel values, and  $\bar{x}$  the average voxel value.

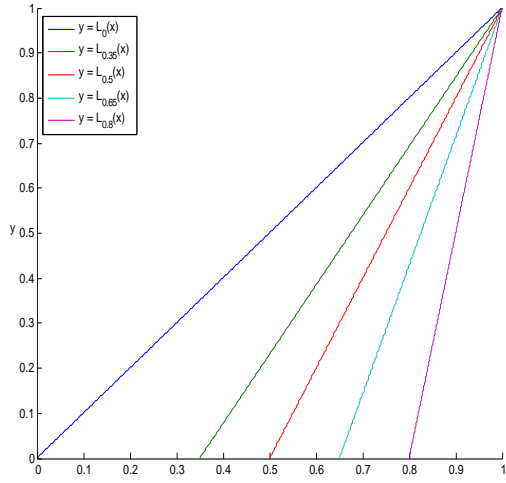


Figure 2. Linear weighting functions  $L_\alpha(x)$  used in the fibrosity measures  $\mathcal{F}_{L_\alpha}$ .

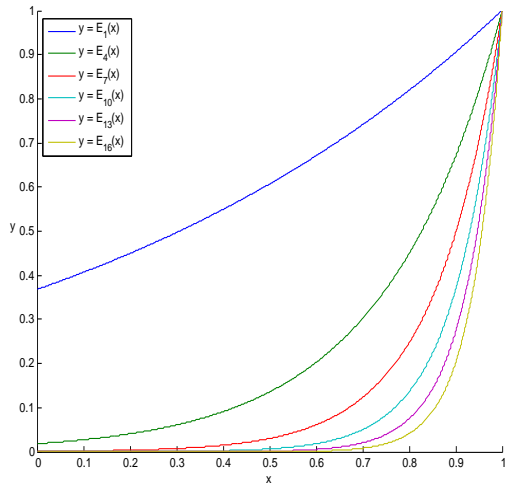


Figure 3. Exponential weighting functions  $E_\beta(x)$  used in the fibrosity measures  $\mathcal{F}_{E_\beta}$ .

## 2.4. Classification

The classification problem we sought to improve was separating the patients who had had incidents of VT after

the MI from those who had not. The fibrosity measures were used as input to a feedforward neural network classifier together with the LVEF and the relative scar size, denoted  $\mathcal{S}$ . All experiments were done using leave-one-out cross-validation. The neural network had one hidden layer, with  $\left\lfloor \frac{\#features}{2} \right\rfloor + 1$  sigmoid nodes.

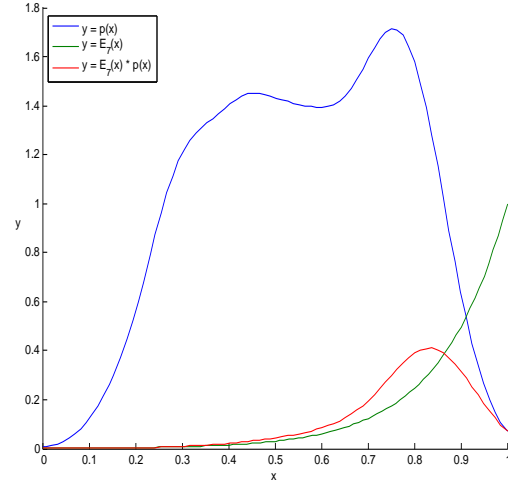


Figure 4. The effects of the weighting function  $E_7(x)$  on a density function  $p(x)$  fitted to the relative frequency distribution  $P(x)$  of a scar. The fibrosity of the scar is  $\mathcal{F}_{E_7} = \sum_{x \in \mathcal{D}} E_7(x) P(x) \approx \int_0^1 E_7(x) p(x) dx$ , the latter being the area enclosed by the x-axis and the curve  $y = E_7(x)p(x)$  on the interval  $[0, 1]$ .

## 3. Results

The classification results at a sensitivity of 90% are shown in Table 1.

Using LVEF alone gave a specificity of 82.4%. Combining LVEF with any of the fibrosity measures, except  $\mathcal{F}_{L_0}$  and  $\mathcal{F}_{E_1}$ , improved upon using LVEF alone. The fibrosity measures  $\mathcal{F}_{E_\beta}$  performed better than the  $\mathcal{F}_{L_\alpha}$  ones. The best among  $\mathcal{F}_{E_\beta}$  were the cases  $\beta = 10$  and  $\beta = 16$ , with a specificity of 91.2%, whereas the best among  $\mathcal{F}_{L_\alpha}$  were the cases  $\alpha = 0.5$  and  $\alpha = 0.65$ , with a specificity of 88.2%. The skewness  $g_1$  in conjunction with LVEF performed slightly better (85.3%) than LVEF alone.

Adding the relative scar size  $\mathcal{S}$  to LVEF improved the specificity to 85.3%. Adding any of the fibrosity measures  $\mathcal{F}_{L_\alpha}$  to LVEF and  $\mathcal{S}$  gave the same or higher specificity: The larger  $\alpha$ , the higher specificity, the best being 91.2% for  $\alpha = 0.5$  and  $\alpha = 0.65$ . Combining  $\mathcal{F}_{E_\beta}$  with LVEF and  $\mathcal{S}$  improved the specificity to 91.2% for

$\beta = 13$ , whereas it got worse for  $\beta = 10$ . The skewness  $g_1$  did not change the specificity when added to LVEF and  $\mathcal{S}$ .

Table 1. Specificity with 95% Agresti-Coull confidence interval (CI) for various feature combinations. The sensitivity was set to 90% in all cases. The relative scar size is denoted by  $\mathcal{S}$ .

	Specificity (95% CI in parentheses)	
	LVEF	LVEF, $\mathcal{S}$
	82.4% (66.1-92.0%)	85.3% (69.4-94.0%)
$g_1$	85.3% (69.4-94.0%)	85.3% (69.4-94.0%)
$\mathcal{F}_{L_0}$	76.5% (59.8-88.8%)	85.3% (69.4-94.0%)
$\mathcal{F}_{L_{0.35}}$	85.3% (69.4-94.0%)	85.3% (69.4-94.0%)
$\mathcal{F}_{L_{0.5}}$	88.2% (72.8-95.9%)	88.2% (72.8-95.9%)
$\mathcal{F}_{L_{0.65}}$	88.2% (72.8-95.9%)	91.2% (76.3-97.7%)
$\mathcal{F}_{L_{0.8}}$	85.3% (69.4-94.0%)	91.2% (76.3-97.7%)
$\mathcal{F}_{E_1}$	82.4% (66.1-92.0%)	85.3% (69.4-94.0%)
$\mathcal{F}_{E_4}$	88.2% (72.8-95.9%)	88.2% (72.8-95.9%)
$\mathcal{F}_{E_7}$	88.2% (72.8-95.9%)	88.2% (72.8-95.9%)
$\mathcal{F}_{E_{10}}$	91.2% (76.3-97.7%)	82.4% (66.1-92.0%)
$\mathcal{F}_{E_{13}}$	88.2% (72.8-95.9%)	91.2% (76.3-97.7%)
$\mathcal{F}_{E_{16}}$	91.2% (76.3-97.7%)	88.2% (72.8-95.9%)

#### 4. Discussion

There are two obvious limitations in the definitions of the fibrosity measures. The first one is the manual demarcation of the scars, which could suffer from both intra- and interobserver variability. The other is the normalisation scheme, since it is based on the implicit assumption that a voxel value equal to the 99th percentile of the signal distribution in one patient can be considered as denoting the same level of fibrosity as the corresponding voxel value in another patient.

The empirical study suffers from a small population. Furthermore, the images of the patients with VT episodes were taken an arbitrarily long time after the MI, whereas the images of those without VT episodes were taken one year after the MI.

#### 5. Conclusion

Some of the fibrosity measures improved the discriminative power of the LVEF and scar size in predicting which MI patients would get VT, thus demonstrating a potential clinical value. This should be further evaluated in a large-scale study, for those who have access to such data. We also hypothesise that some of the fibrosity measures have a universal application in the assessment of myocardial scars, and hence could be

used in other types of MI studies.

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