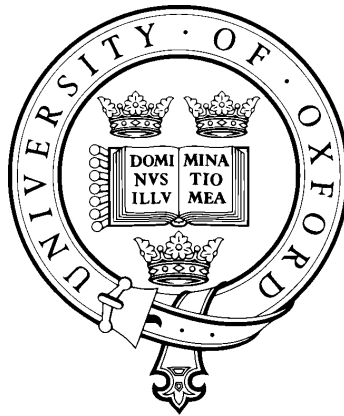


Assessing the Effect of Tissue Structural Changes during Cardiac Deformation using Magnetic Resonance Imaging Techniques



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I dedicate this Thesis to my mother Monica, my father Sorin, and my partner Benjamin who have supported and encouraged me to pursue the dream of becoming a researcher. I am most grateful to all three of you. Without your loving support and encouragement, none of this would have been possible.

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Statement of Originality

I hereby declare that this thesis is entirely my own work and, except where otherwise stated, describes my own research. This work was performed under the supervision of Professor Vicente Grau within the Institute of Biomedical Engineering, Department of Engineering and Science, University of Oxford and Cardiologist Dr Erica Dall'Armellina of Leeds Cardiovascular Research Organization, University of Leeds, Leeds, UK and Department of Cardiovascular Medicine, Acute Vascular Imaging Centre, University of Oxford, UK.

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Abstract

Global assessment of the myocardial tissue wall motion from cine MRI (Magnetic Resonance Imaging) is widely used in clinical practice, however, the estimation is done, in the majority of cases, visually rather than quantitatively. This doctoral thesis proposes steps forward in the local assessment of the left ventricular (LV) function in order to provide a better estimation of the damage post acute myocardial infarction (MI). Accurate post acute MI tissue damage estimation from cine MR tracking might help clinicians to perform, better, more personalised, revascularisation treatments. This thesis makes three technical contributions.

The first technical contribution focuses on LV scar segmentation from Late Gadolinium Enhancement (LGE) using supervoxels. LGE represents the gold standard for assessing the viability of the heart muscle. However, considerable user input is needed in order to correctly segment the scar. A global intensity threshold is used, and a further, remote, area of "healthy myocardium" also needs to be segmented. Furthermore, an additional number of corrections are required to remove false positive areas of enhancement. We found that by using a strong regulariser such as a modified version of the Single Linear Iterative Clustering (SLIC) supervoxels, we can eliminate the false positive enhancement areas. Furthermore, there is no need for a remote "healthy myocardium" area to be contoured.

The second technical contribution is to provide a 4D map of supervoxels (voxels clustered together based on local similarity) computed using similarity in strain curves. Our study found that while LGE performs extremely well in highlighting the area where scarring occurs, at the same time it underestimates the area of affected myocardium when compared with strain analysis. Here we investigated various registration methods, based on optical flow deformable registration, in order to evaluate the accuracy of computing the displacement curves, and subsequently validated the registration method against manually placed landmarks in the LV.

The third technical contribution is a modification to the maskSLIC algorithm to generate six cluster centers in each short axis, basal and mid-ventricular slice, equally distributed at 60° from each other in order to mimic the AHA 16 segments model used in clinical practice.

Considering clinical perspectives centered approach, these technical advances will contribute to the field of regional assessment of the cardiac function, therefore potentially improving patient outcome.

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Chapter 1

Introduction

1.1 Research motivation and aim of this work

Coronary heart disease (CHD) represents one of the biggest killers in modern society. Coronary heart disease was responsible for nearly 70,000 deaths in UK in 2016, with an average of 190 people per day, or one every eight minutes, according to the 2016 British Heart Foundation cardiovascular diseases (CVD) Statistics Report [16]. The total annual cost on the National Health Service (NHS) relating to cardiovascular disease is estimated to approximately 11 billion pounds each year. According to the same report, most deaths from CVD are caused by heart attacks. The number of prescriptions for lipid-lowering drugs have risen more than six times since 2000, with a significant increase in number of prescriptions for antihypertensive and heart failure drugs. Hypertension and high levels of low-density lipoprotein (LDL) cholesterol are the two most important risk factors that can lead to myocardial infarction [203]. Other risk factors include smoking, diabetes and obesity [111] - more than 1 in 6 adults in the UK are smokers, 27% of adults in the UK are obese and 39% of adults don't meet physical activity recommendations. There are an estimated 7 million people living with CVD in the UK. Furthermore, an ageing population, as well as, improved survivor rates from cardiovascular events, could raise these numbers further. Clearly a better solution must be sought to tackle these pathologies in a more personalised way, and imaging can help.

By understanding the biomechanics of the cardiac function [216] as well as, the electrical conductivity patterns of the heart [30], as an example of the impact, we could optimise the number of implantable cardioverter defibrillators (ICD) implanted world wide at the moment [8] to a specific number of patients who would benefit from them, rather than a large number of patients being implanted with ICDs but ending up never using the device or even worse, developing infections and having to undergo a second surgical intervention in order to remove the device [109].

At present, a poorly personalised treatment does not allow for patient specific assessment to be used in clinical practice. This can be improved by longitudinal monitoring of the scarred tissue remodelling post myocardial infarction. Longitudinal monitoring as well as accurate assessment could potentially lead to a better personalised investigation of the conditions that lead to heart failure. Conditions such as cardiac remodelling are poorly understood at the moment, not only in pathologies such as myocardial infarction, but also hypertrophic cardiomyopathy (HCM) or the thickening of the heart muscle.

A key goal of our work is to analyse patient specific strain patterns and discern between healthy and pathological myocardial tissue functionality. In the case of patients who have suffered one or multiple myocardial infarctions, the goal is to identify and track the tissue structural changes longitudinally by looking at how the biomechanical remodelling of the scarred tissue affects the overall function of the heart. Left ventricular remodelling post myocardial infarction is an important stage in the evolution of cardiac disease. The first stage of the scar evolution is the inflammatory phase [167]. Usually this remodelling translates into an overall increase in volume and wall mass [31, 191]. Of special interest is the long term remodelling [73] of the adjacent tissue to the affected area [119]. The adjacent tissue of the scar is difficult to visualise using the Late Gadolinium Enhancement (LGE) technique. The affected, but viable tissue [185], surrounding the scar, does not present Gadolinium accumulations, as in the case of fibrotic tissue [37]. In the

case of HCM it has been proved that concentric HCM is less dangerous than eccentric HCM [140]. In a similar fashion, a heart that has been affected by a large myocardial infarction, presents an eccentric contraction pattern [58]. However, at the moment we are just scratching the surface, due to limited knowledge of the affected tissue biomechanics in vivo. Therefore a better methodology should be developed in order to help clinicians make more accurate diagnostics.

1.2 Thesis structure

This thesis is structured in seven chapters, where explanations have been given to keep informed both medical and engineering audiences.

Chapter 1 provides an **introduction** to the field of anatomy and physiology of the heart. Subsequently it outlines the aim of this research and the contributions to the field. This chapter also outlines the structure of the rest of the thesis, as well as, the contributions of this doctoral research. A clinical context of the scar assessment in the heart is also provided in this chapter.

Chapter 2 describes the estimation of cardiac scar extent using a novel method for performing localised analysis: **maskSLIC supervoxels on late Gadolinium enhancement (LGE) images**. This is a step used pre-analysis of wall motion abnormalities in order to validate the work in Chapters 5 and 6. The clinical way of segmenting the scar from Late Gadolinium Enhancement (LGE) images, is manual and time consuming, therefore this chapter could prove useful for the automation of LGE segmentation as well. In this chapter we use a novel implementation of the conventional Simple Linear Iterative Clustering (SLIC) called maskSLIC, where we generate the centres of the clusters in a mask, rather than on a rectangular grid. This makes the algorithm more appropriate for medical imaging applications, where a segmentation into subregions of an already segmented area is often required.

Chapter 3 describes the technical aspects of **cardiac wall displacement quan-**

tification using image registration methods. The calculation of myocardial tissue strains is based on the computation of displacement curves for individual voxels using initially the Bruhn-Weickert combined local-global optical flow registration algorithm [19] and subsequently an optimised diffeomorphic log Demons algorithm [107] framework.

Chapter 4 introduces the clinical and technical problem of estimating **cardiac tissue strain**. In our case this is done relying entirely on indirect measurement techniques, i.e. MRI images. In imaging there are multiple ways of computing the strain, which will be explained in detail, in this chapter. Also in this chapter, we develop a framework for the calculation of the strain curves by dividing the left ventricle into sixteen segments, in accordance to the American Heart Association (AHA) model, as presented by M. Cerqueira [26], and computing the corresponding mean strain curves for each of these segments. This research is needed in clinical practice for multiple reasons, such as enabling clinicians to assist the function of the myocardial muscle in a dynamic way, but also localised enough to accurately estimate the extent of the pathology (damaged tissue). At present in clinical practice cardiac strains can be calculated using echo Doppler speckle tracking [112], tagged MRI [84], and feature tracking from cine MRI [213]. With newer techniques such as tissue tracking [178] emerging. However, except the echo Doppler speckle tracking, the above methods are not routinely used in clinical practice and have limitations in accuracy and robustness, as well as, consistency across manufacturers for normal ranges.

Cine MRI is already widely used in clinical practice for evaluating global cardiac function as ejection fraction, however, not for analysing local viability of the tissue, based on patient specific strain patterns. Calculating the strains from cine MRI sequences means that no additional imaging sequences are needed, which translates in less costs for the NHS and other governmental healthcare systems.

Chapter 5 consolidates the **supervoxel parcellation method by applying**

it to the left ventricle, based on local similarities in strain patterns. This chapter investigates the development of a clustering based segmentation method. We have noticed that voxels present clearly distinctive motion patterns in accordance to the corresponding anatomical structure. We believe there is a possibility of being able to distinguish between healthy and pathological tissue by clustering these voxels together using clustering methods based on local similarity. We can do this by using fuzzy c-means or k-means clustering. We reduce the dimensionality of features by using a principal component analysis (PCA) approach, as presented by Irving et al in [86]. Irving et al in [90] have implemented a way to detect airway shapes in the lungs using PCA, and trained the algorithm to detect abnormalities in the case of paediatric tuberculosis, proving that PCA can be used for the detection of complex geometries. In terms of voxel clustering, we cluster voxels corresponding to the left ventricle in three regions, with the aim to distinguish between healthy and pathological tissue.

We use a modified supervoxel approach, maskSLIC, to look at these clusters, combined with PCA and adapted for cardiac strains, in a machine learning approach, and subsequently compare with pathologies visually highlighted by clinicians. We believe this would be a more localised way to detect pathology, rather than using only the AHA six segments division in short axis. We could then use the mean strain per supervoxel as opposed to mean strain per segmental region. This could lead to a significant noise reduction, would be simpler to analyse, and grouped according to similarity rather than general anatomy.

Chapter 6 proposes the development of a **myocardial tissue parcellation into 16 segments using the maskSLIC method.** The aim of this chapter is to replicate the clinical approach in dividing the left ventricle into segments based on the AHA model, however, not based on equal degrees segments, $6 \times 60^\circ$ but based on tissue strain pattern similarities. The cluster centres are computed automatically after the left to right (or anterior) insertion point is placed manually by an expert

annotator, where each cluster centre is placed within the AHA corresponding annulus sector centroid, and subsequently six supervoxels are generated in short axis view, based on local similarity in strain.

Chapter 7 provides **overall conclusion and future work**. This chapter provides conclusion on the techniques used for this doctoral research, and puts into context all the contributions of this thesis. For immediate future work, one of the first steps would be the introduction of information from the coronary territory. For this purpose we are investigating the possibility of access to a database of 50 participants with mapped coronary territory and corresponding cine and T1 maps from the University of Oxford Radcliffe Department of Medicine. Combining wall motion abnormality with coronary territory is of clinical relevance, because it has the potential to eliminate the use of contrast agents. Subsequent work will be using a large database called UK Biobank of approximately 100,000 participants, where cine MRI images as well as quantitative maps are provided, together with the corresponding contours, as well as segmental scores. This will be done by using a deep neural network approach in the attempt to learn normal strain curve patterns, as well as investigate inter subject variability.

1.3 Contributions

This thesis has three chapters of technical contributions, **Chapters 2, 5, and 6**. Also as part of this work we applied and tested methods for calculating strain from image sequences described in **Chapters 3 and 4**.

- In **Chapter 2** we present our first main contribution: a novel method for the quantification of infarcted region that, different to current state of the art, does not require any user interaction and provides compact, accurate estimations of the infarcted area. We have used the maskSLIC algorithm for the first time in cardiac imaging.

- Our second main contribution is presented in **Chapter 5**: the first voxel-wise method applied to cardiac imaging and the first voxel-wise method using tissue similarity in strains to assess the extent of damaged tissue post myocardial infarction.
- In **Chapter 6** we present our third main contribution: a ventricular division method based on a clinical segmental model using the maskSLIC superpixel algorithm to divide the left ventricle into regions based on similarity in tissue dynamics. We present the first model for ventricular division based on tissue characteristic strains but also constrained by the clinical left ventricular division model.

The main aims are: to investigate the parcellation of the myocardial tissue (tissue of the heart) based on local similarity, both in a 4D (3D+time) fashion, investigating similarity in motion patterns, as well as in 2D, looking at accurately segmenting the extent of positive Late Gadolinium Enhancement (LGE) areas. For the later, in order to segment, the cardiologist needs to place another region of remote myocardium to then compute an intensity threshold, and highlight the LGE area based on this threshold. Using the proposed Chapter 2 method, the need of having to segment such areas is eliminated, as well as the need of correcting for false positive enhancements. As far as strain analysis is concerned, in clinical practice a model (AHA 16 segments model) is used to divide the myocardium into regions. The trouble is that this regions are not a single block of moving tissue, and the very complex motion cannot therefore be accurately determined using this method. What this thesis is proposing in Chapter 5, is using an approach that allows clustering together small parts of tissue that have similar motion patterns. However, since the AHA model is a well established model in clinical cardiology, and therefore cardiologists are very familiar using it, a combination of the two is proposed in Chapter 6, in order to allow segmental analysis, while increasing the sensitivity in detecting pathological

tissue borders.

1.4 Anatomy and physiology of the heart

1.4.1 Overview

The heart is a muscular organ used to circulate the blood in the body. It has a conical shape and it weighs about 225 g in women and about 310 g in men [1, 45]. The heart is located in the thoracic cavity, between the lungs, tilted to the left side of the body, and it has four chambers (as seen in Figure 1.1) two atria that have a main function to receive the blood, and two ventricles that have a main function to pump the blood out of the heart. The heart wall comprises of three layers of tissue: epicardium, myocardium (middle layer) and endocardium (or the interior layer). The heart is surrounded by a sac called pericardium.

The pericardium is a membrane composed of two layers, the serous layer and the fibrous layer [210]. A single layer of flattened epithelial cells can be found within the serous layer. This layer is responsible for secreting the fluid that allows smooth movement between layers during cardiac motion. In healthy controls the two layers are located in the proximity of each other, however in pathology there is a liquid accumulation between these two layers, which leads to oedema, also known as pericarditis [220]. The pericardium is of great importance in biomechanics because it allows the myocardium to rotate freely by sliding against it, thanks to the presence of fluid [114, 233]. The outer layer of the myocardial muscle, the epicardium, contains a network of vessels that run on the surface of the heart and are responsible for supplying the myocardium with blood.

The myocardium is composed of a specialised type of muscular tissue, called cardiac striated muscle. The myocardium is responsible for the pumping action of the heart, it is also the thickest layer of the heart wall (about 95%) [202]. The orientation of the myocytes (also known as fibre orientation) is a double helical structure

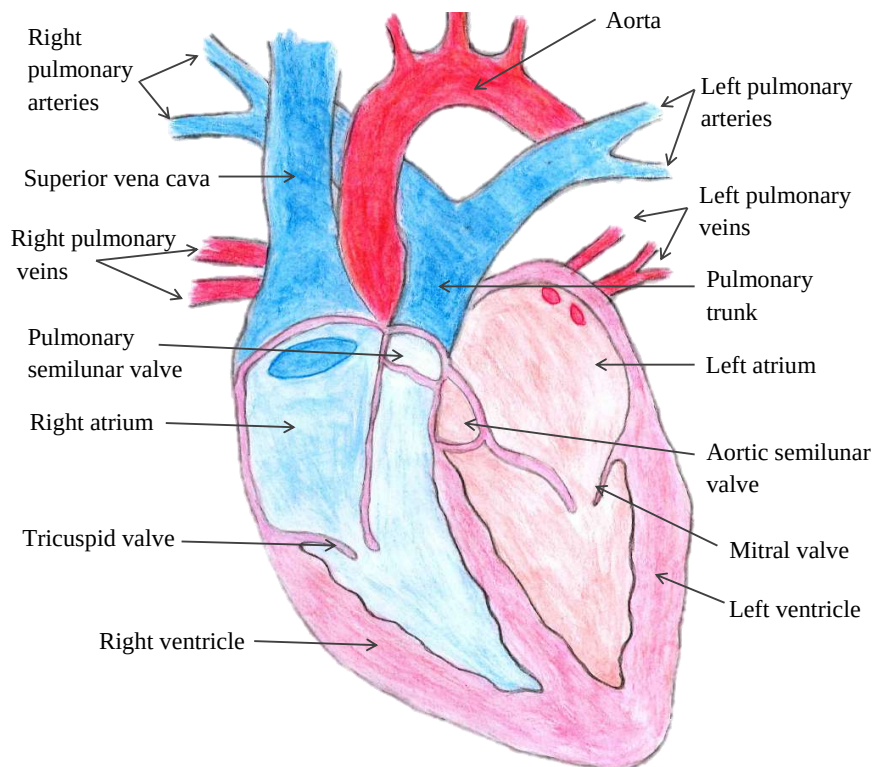


Figure 1.1: Schematic drawing of heart anatomy. Original hand-drawn by Iulia Popescu. All rights reserved. In blue is the venous blood, and in red the arterial blood (or oxygenated blood). This drawing is purely for informative purpose on the general anatomy of the heart.

[172, 163]. The combined effect of their contraction is a shortening in the chambers in the longitudinal direction as well as rotation/torsion in the circumferential direction and thickening in the radial direction. Even though the two ventricles act as two pumps that simultaneously pump blood, the left ventricle is significantly thicker than the right ventricle. This is because unlike the right ventricle which only pumps blood to the lungs, the left ventricle pumps blood to all the organs in body, needing higher pressure to fulfil the task and therefore applying higher forces on the tissue during contraction [202].

1.4.2 Structure of the cardiac muscle tissue

In this section the structure of the cardiac muscle will be explained briefly in order to set the context for tissue analysis using Magnetic Resonance Imaging (MRI). Same as the skeletal muscle, the cardiac muscle is of striated type. Unlike the skeletal muscle, the myocardial muscle contraction is involuntary. The texture of the cardiac muscle is of striated type, although the pattern is not as ordered as in skeletal muscle [162]. Also known as myocardium, the cardiac muscle forms a thick layer between the outer layer of the heart (epicardium), and inner layer of the heart (endocardium). Cardiac muscle cells are called cardiomyocytes, and are of mononuclear type. Unlike skeletal muscle, cardiac muscle fibres are shorter in length and experience branching [180]. The cardiomyocytes connect among themselves by intercalated disks. The intercalated discs are crucial in the contraction of the heart because they support the synchronised contraction of myocardium [100]. They are formed of desmosomes - which provide a commune structure between neighbouring fibres, and gap junctions - which allow action potential to conduct from one fibre to another. Gap junctions enable the myocardium to contract as one unit [202].

1.4.3 Electrical activity of the heart

Unlike the skeletal muscle, the cardiac muscle does not have the capacity to contract voluntarily. Therefore a rhythmical electrical activation system is in place to perform the task. This system is formed by a network of nodes that generate and propagate respectively the electrical signals across the myocardium, making the heart contract in a coordinated manner, and therefore making it efficient in its pumping function. The electrical signal is propagated across the myocardium by a network of autorhythmic fibres - self-excitable specialised cardiac muscle fibres [202]. As shown in Figure 1.2, on the ECG wave the T wave marks the beginning of the repolarisation (or relaxation stage), the QRS complex corresponds to depolarisation of the left and right ventricle, while the P wave represents the atrial depolarisation. However, in case of pathology, the electrical conduction patterns can be significantly modified, such in the case of arrhythmias - or irregular heart beat patterns. One of the most dangerous cardiac arrhythmias are due to reentrant waves [51]. Reentrant waves are electrical waves that loop repeatedly throughout the tissue at a higher frequency [32] than the normal waves produced by the sinoatrial node. These occurrences are very dangerous and can be life-threatening, especially ventricular arrhythmias [29].

1.4.4 Changes in pressure and volume over a cardiac cycle

The heart acts as a natural pump for the blood to be circulated in the body. The atria and ventricles contract and relax alternatively, therefore forcing the blood to move from high pressure - in contraction (systole), to lower pressure - in relaxation (diastole). Atrial systole contributes to about 25% of the total volume of blood already existing in each ventricle [130]. During ventricular systole ventricles start to contract and at the same time atria start to relax, a process called atrial diastole. Ventricular contraction is an isovolumetric contraction of the ventricular muscle, meaning that the overall volume of the ventricles remains the same over the con-

traction stage [60], and when the blood pressure inside the left ventricle surpasses the aortic pressure, the aortic valve opens and the ejection phase begins [216].

In clinical practice, the most widely used metric to assess the pumping function of the myocardium is the left ventricular ejection fraction. The ejection fraction quantifies the fraction of blood pumped out of the ventricles with each contraction. The ejection fraction is computed using the formula in Equation 1.1, which uses the difference in volume between the end systolic (ESV) and end diastolic (EDV) phases.

$$E_f(\%) = \frac{SV}{EDV} \times 100 \quad (1.1)$$

where the stroke volume (SV) is:

$$SV = EDV - ESV \quad (1.2)$$

Approximately 50% to 70% of blood pumped out on every heart beat represents a normal ejection fraction [159, 158], while lower values than 40% represents evidence of heart failure [136].

However, ejection fraction values within the normal range do not necessarily indicate a healthy heart. Approximately 30% to 40% of myocardial infarction patients have a preserved ejection fraction [63]. The physiopathology of heart failure patients with preserved ejection fraction is complex, but increased left ventricular diastolic stiffness is believed to play an important role in many cases [146]. While the ejection fraction represents a good metric for the assessment of cardiac function, it is not always the most accurate one, since the cardiac disfunction can be either regional [219], or global [223]. Therefore, a more accurate metric is necessary in order to investigate the regional aspect of cardiac disfunction. This will be discussed further in detail in the next chapters of this doctoral research.

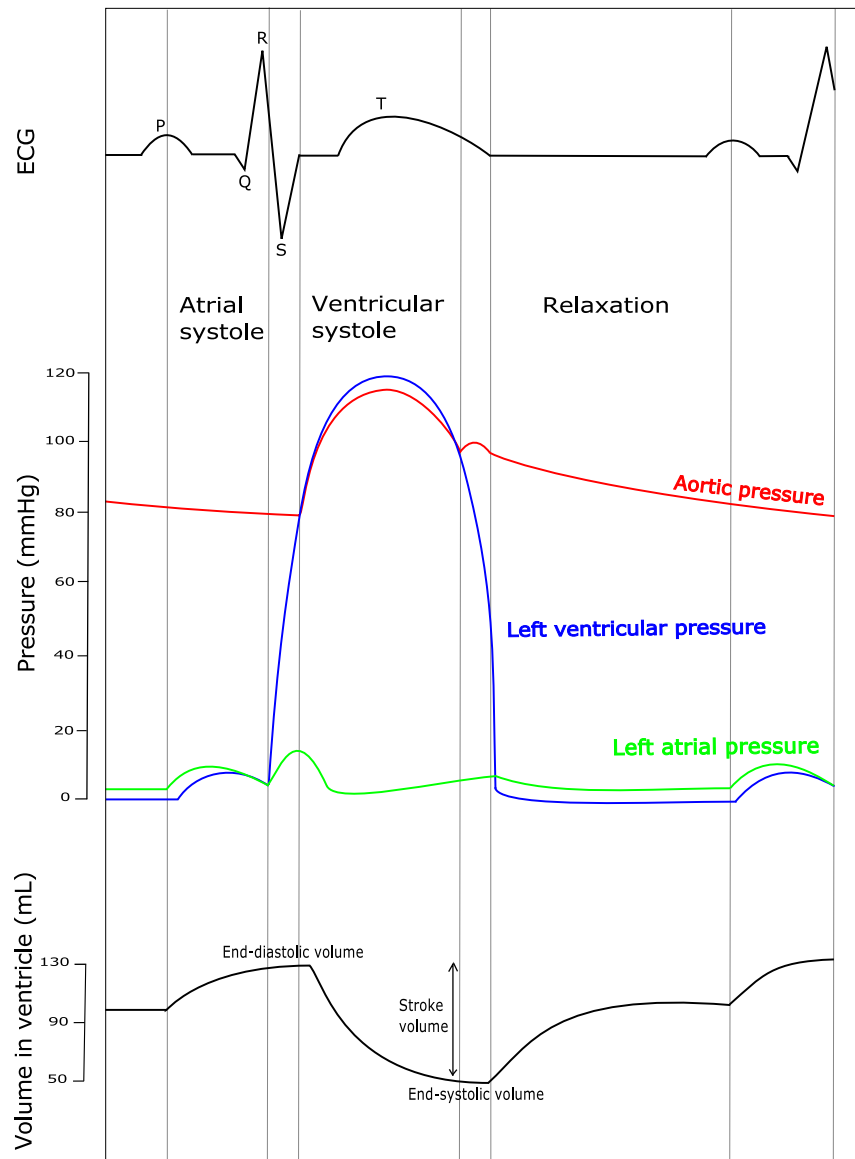


Figure 1.2: Phases of the cardiac cycle. From top to bottom: ECG wave, Changes in atrial, ventricular, and aortic pressure, and Changes in ventricular volume.

1.4.5 Cardiac output

The electrical potential of the heart is activated by autorhythmic fibres that allow it to beat in a controlled and highly efficient way, however, it's performance as an organ is dependent of whole body factors, such as exercise [22], or diet [103]. Cardiac cells must receive a relatively large amount of oxygen, compared to skeletal muscle cells, and nutrients from the blood to ensure proper function. These cells are highly active metabolically, and therefore, if deprivation of blood is present, they will get damaged and eventually die, forming a scar in the myocardial tissue. Within the scar the cardiac tissue is usually replaced initially by fibrotic tissue, which has no contractile properties. Subsequently this tissue can be replaced by fat, in old myocardial scars. Nevertheless, these types of tissue are non-contractile, meaning greater strain is put on the surrounding tissue to compensate for the loss. This leads to a general decreased function of the myocardium. Furthermore, depending on its size and location a scar might influence the electrical conduction patterns [202, 27], potentially causing sudden death.

1.5 Myocardial scar assessment - Clinical state of the art

Late gadolinium enhancement (LGE) represents the gold standard for the quantification of the extent of scarred tissue, post myocardial infarction. The administration of Gadolinium-based contrast agents is an invasive procedure, sometimes with side effects, that have only started to be investigated [46, 199]. The concept is that in the presence of fibrotic tissue, the contrast agent remains in the intercellular space [139], translating into an increase in intensity when imaged. Patients who have suffered a myocardial infarction develop scars within the myocardium. Depending on the extent of the scar, the treatment plan is designed so that the cardiac function is recovered as much as possible [124, 179]. Within these scars the tissue

loses its ability to contract. However, the tissue surrounding the scar is affected (hypo-contractile tissue) but viable, and could therefore be salvaged sometimes, if assessed accurately. Patients with affected, but viable tissue, may benefit from reperfusion and revascularisation therapies, where necessary and beneficial. Two of the revascularisation techniques most widely used in clinical practice are Percutaneous Coronary Intervention (PCI) and Coronary Artery Bypass Grafting (CABG). However, with present techniques and technology, it is not always clear who should benefit from revascularisation therapy, and who would experience no benefit.

To assess the extent of the scar a wall motion assessment is required, as well as LGE imaging, to highlight the amount of fibrotic tissue [83]. Clinical myocardial wall motion assessment using Cardiac Magnetic Resonance (CMR) techniques can be considered rather subjective. The motion is visually assessed, using a five category scale: 'akinesis', 'hypokinesis', 'normokinesis', 'hyperkinesis', and 'dyskinesis' and the 17 segments American Heart Association (AHA), Writing Group on Myocardial Segmentation and Registration for Cardiac Imaging, model [25] for standardised left ventricular division. A visual representation of the AHA 17 segments model can be seen in Figure 1.3.

One of the limitations of the clinically available software for scar segmentation is that it requires a significant amount of user input in terms of manual segmentation. When using LGE images, first the endocardial and epicardial contours are defined, second an area of normal or remote myocardium is segmented with the mean and standard deviation of its intensities calculated [56]. These are used to calculate a threshold that differentiates healthy from scarred myocardium, which is usually calculated as the mean plus three to five standard deviations. Finally, areas corresponding to false positives (i.e. large intensities that arise from image artefacts rather than fibrosis) are visually identified and removed. This process generates sometimes a high quantity of false positives, that need subsequent manual removal.

We believe that both scar segmentation from LGE images as well as wall motion

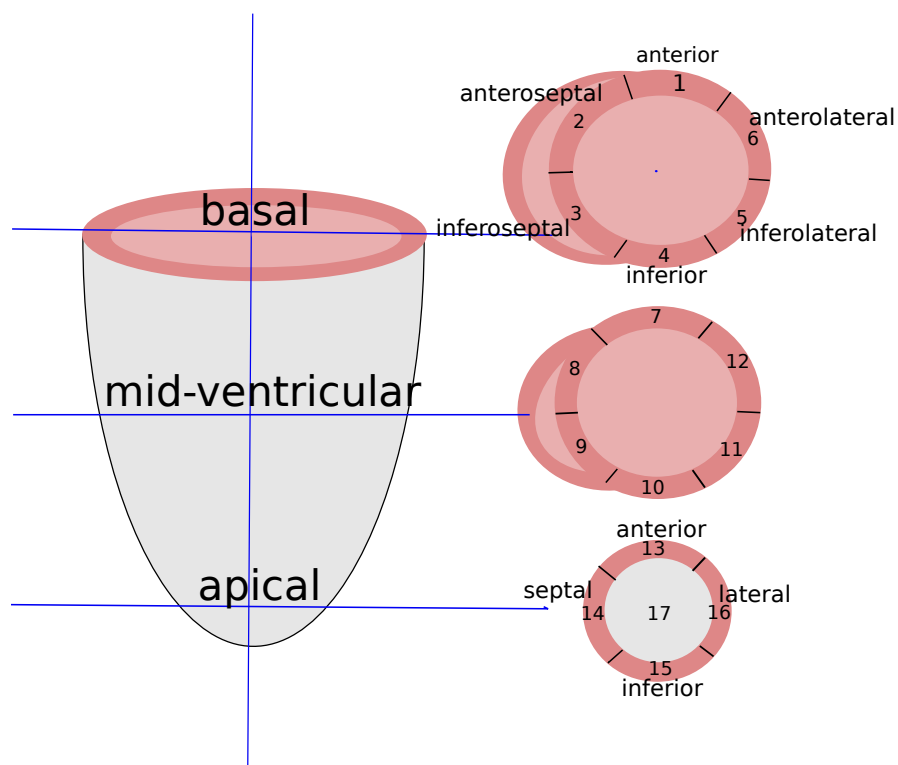


Figure 1.3: The AHA 17 segments model for left ventricular division according to Cerqueira et al. [26]. Where the apex of the heart is represented by segment 17.

assessment can be performed in a more accurate, personalised and quantitative way, and in this thesis we embark in a journey to investigate the current limitations, and develop more automated, reproducible tools.

Chapter 2

LGE myocardial scar segmentation using maskSLIC supervoxels

Iulia A. Popescu, Alessadra Borlotti, Erica Dall’Armellina and Vicente Grau. Automated LGE myocardial scar segmentation using maskSLIC supervoxels - Replicating the clinical method. Medical Imaging Understanding and Analysis (MIUA), 2017.

2.1 Introduction

In this Chapter we propose a semi-automated segmentation framework for the enhanced areas of myocardial scar from Late Gadolinium Enhancement (LGE) Magnetic Resonance Imaging. Accurate estimation of the extent of the scar can potentially lead to a better patient risk stratification and treatment. However, in clinical practice the process is laborious with high inter- and intra- user variability.

2.2 Late Gadolinium Enhancement

Delayed enhancement cardiac magnetic resonance (DE-CMR) imaging is used to identify the location and extent of myocardial scar (dense myocardial fibrosis) due to ischaemic and non-ischaemic heart disease [207]. The technique is also known as Late Gadolinium Enhancement and it is an MRI imaging technique used for displaying

the presence of a gadolinium based contrast agent (GBCA) in the extracellular space in the tissue. In its free state, gadolinium is a toxic element, which is why all contrast agents used in clinical routine, as well as clinical research, are made of a chemical bond between gadolinium ion and a carrier molecule. The carrier molecule is called a chelating agent. This carrier molecule modifies the distribution of gadolinium within the body to overcome its toxicity while maintaining its contrast properties [46, 169]. Due to their size, the molecules are not able to enter the extracellular space. Most contrast agents are excreted by the kidneys, and until recently it was believed that the contrast agent would be completely cleared out of the blood stream over 24 hours. Contrast agents have been considered safe for years, however we now know that gadolinium can cause a severe disease called nephrogenic systemic sclerosis (NSF), mainly seen in patients with reduced kidney function or on dialysis [176], and for this reason GBCA imaging is contraindicated in kidney disease patients. Furthermore, more recently, evidence is shown in published reports regarding deposition of the contrast agent in the brain, such as in the case of repeated scans for patients where disease progression needs to be constantly monitored and which require a series of MRI scans using GBCA imaging [69, 70]. Furthermore, GBCA imaging is used routinely in clinical practice as clinical diagnosis tools for obtaining the extent of the scar post myocardial infarction.

Late Gadolinium Enhancement (LGE) is a technique based on the delayed wash-in wash-out effect [101] of a intravenously administrated GBCA. DE-CMR is typically obtained using an inversion recovery gradient recalled echo sequence (IR-GRE) with breath-holds [207]. Gadolinium is a paramagnetic agent that changes the magnetic properties of tissues in which it collects, therefore causing enhancement of the structure on MRI (brighter image) [131]. Within the myocardium, in the infarcted region, the myocardial tissue is replaced by fibrotic tissue produced by fibroblasts and myofibroblasts [192]. Within this fibrotic region the extracellular space becomes much larger than in healthy tissue. After the administration of the contrast agent,

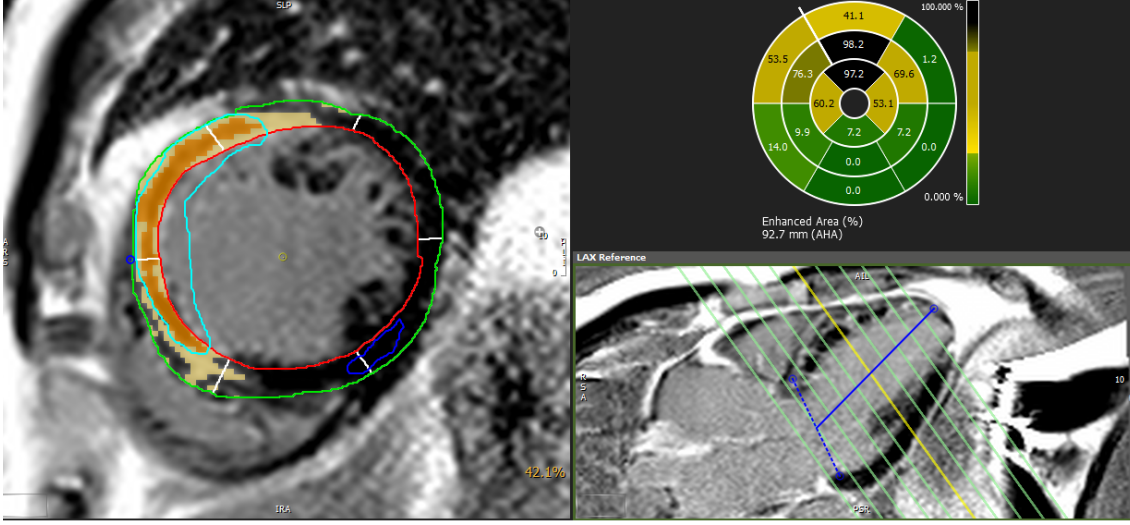


Figure 2.1: Screen caption from cvi⁴² (Circle Cardiovascular Imaging, Calgary, Alberta, Canada) clinical software. Used here, is the LGE scar segmentation module for the quantification of the extent of damage in the tissue, post myocardial infarction. In blue is a "remote myocardium" manually segmented region. Mean+3 to 5 STD of this region is used to threshold the intensity in the LV mask. Regions of false-positive are manually removed using a provided tool.

a set of MR images are acquired, usually 5 to 15 minutes after the administration. The fibrotic region appears brighter in the MR image than the non-affected tissue, due to temporary deposition of contrast agent within the extracellular space. LGE is a technique used routinely in cardiology to highlight the changes in acute and chronic ischaemia. However, the process of quantifying the extent of scarred tissue is mostly manual and involves multiple steps in adjusting the contoured areas.

The current gold standard in clinical practice for scar segmentation involves significant user input. The contouring process is laborious [65] and includes a multitude of manual steps in obtaining the segmentation of the enhanced area. The clinician or the image analyst, has to manually segment contours such as a control region of unaffected myocardium called 'remote myocardium' and usually located opposite to the scarred tissue, and subsequently apply a global intensity threshold to segment the scar areas. An example using the commercially available software cvi⁴²(Circle Cardiovascular Imaging, Calgary, Alberta, Canada) can be seen in Figure 2.1. Of-

ten, additional steps, such as including areas that have not been enhanced as scar, but are part of it, are required. Furthermore the method is prone to false positives, due to incorrect left-ventricular mask segmentation (allowing voxels from the pericardium to be included in the mask). This process is not only time consuming, but also has a high intra- and inter-user variability.

2.3 Semi-automated and automated segmentation from LGE images

Automated segmentation of the scar is of clinical importance, as it provides valuable estimation of the extent of the damage and subsequently the decision of the treatment plan. Changes in acute ischaemia are both complex and dynamic [39] and therefore accurately segmenting the enhanced areas is not a trivial task. Since LGE represents the gold standard for the assessment of scarred tissue in myocardial infarction patients, automated scar segmentation from LGE images is a highly desired tool for the clinical world. However, so far the only methods that have made it into clinical practice are those that involve global thresholding. As before mentioned, the clinical approach for myocardial scar segmentation from late gadolinium enhancement is still very much manual, and involves manually selecting a healthy region (remote myocardium), calculating the mean and standard deviation of its intensity values and setting a threshold at this mean plus three to five standard deviations. This approach is based on the work by Flett et al [55] which use a fixed model where intensities are thresholded to a fixed number of standard deviation to the mean intensity of the remote myocardium. A second common fixed model approach is the full-width-half-maximum (FWHM) [4], where half of the maximum intensity of a user selected region of hyper-enhancement (LGE positive) is selected as a fixed threshold. The segmented region, after applying final manual corrections (e.g. to eliminate small high intensity artefacts that do not correspond to scar), is considered scar.

Extensive work has been done in developing semi-automated and automated methods for segmenting the scar in LGE images. One of these methods uses Rician distributions to model the intensities of homogenous tissue in LGE, where an expectation maximisation algorithm is used to fit the data [77]. Work by Densky et al proposes adding features maps from steady state and $T1^*$ [42], which correlates well with the FWHM method. Other methods proposed in the literature suggest using a completely automated pipeline for segmenting the myocardium as well as the scar. One of these methods used Graph-cuts to classify the myocardium into infarcted and non-infarcted [222, 93] areas. Another research approach suggested using Graph-cuts [122] to semi automatically segment the scar, however, manual corrections were still needed for about 49% of the cases, according to the authors. Edge detection, combined with Otsu thresholding [168], conditional random fields [96], or Gaussian mixed models [24] are other proposed research methods. Fully automated segmentation pipelines [194, 226] have also been proposed in the literature as a way to reduce inter-user variability and overall increase the automation of the segmentation process. Initiatives to benchmark some of the algorithms before mentioned were proposed in the literature [94]. This work used the Dice similarity metric as a performance metric. Within this framework, the medians of these individual Dice overlaps, between manual consensus and the proposed algorithms, were reported as follows: Otsu [94] = 73, Graph-cuts [93] = 74, Conditional random fields [96] = 85, Expectation Maximisation algorithm [77] = 44. Within the same framework, fixed model approaches for segmenting the scar were also compared with ground truth: 2SDs [55] = 47, 3SDs [55] = 54, 4SDs [55] = 55, 5SDs [55] = 62, 6SDs [55] = 64, and FWHM [4] = 78. The relative low performance of some of these methods, limits their usability in medical image analysis, while for others the complicated implementation and lengthy processing time make their deployment to clinical practice difficult.

More recent approaches [227, 141] proposed using deep-learning based frame-

works for performing the segmentation of the scar, this time in the atrium. However, by not providing the community with the trained network, this approach is still a draw-back from a clinical point of view. Intensity based thresholding and spatial constraints have been reported previously in the literature [193]. At the time of writing this doctoral research, to our best knowledge a supervoxel approach was not used for cardiac scar segmentation tasks. However at a similar time a framework using a combination of atlas based left atrial segmentation and supervoxel clustering was proposed in the literature [226].

Previous work in semi-automated LGE scar segmentation that include adding an additional clustering step, where in [138] conventional k-means clustering is used to segment the scar, are proposed in previously published research, however by itself k-means does not assure spatial connectivity. Another semi-automated method [81] for scar segmentation involves enforcing spatial constraints, however even though the authors claim the algorithm contains a component for identifying subendocardial scarring, the results they present are on significantly large transmural scars. Furthermore, our approach differs from [193] in that we first enforce spatial connectivity - to remove the noise, and subsequently apply the thresholding to segment the scar. The images are subsequently offline post processed to identify the existence, and if positive, extent of the scar.

In the next sections of this chapter we will explain in detail the proposed semi-automated pipeline for scar segmentation from LGE MR images using local clustering in a combination with a thresholding approach, in order to semi-automatically segment the myocardial scar without the need of contouring a remote myocardium area.

2.4 SLIC and maskSLIC supervoxels - Clustering based on local similarities in intensity

A supervoxel based approach was used for several reasons. Firstly, the spatial regularisation removes the occurrence of false-positive enhancement areas - that do not belong to the scar region. This is important because the false-positive enhancement areas have to be manually segmented out by the MR analyst, which means more time spent per case. Secondly, it provides meaningful regions for visual assessment and quantification of the extent of scarred tissue.

In the following sections of this chapter the concepts of supervoxel, as well as, the thresholding based on intensity histogram peak separation will be explained in detail.

2.4.1 SLIC supervoxels

Simple linear iterative clustering (SLIC) [3] is a local clustering method that performs a k-means clustering based on local similarity. SLIC was originally created to segment natural images, however, in the last couple of years it has become increasingly popular in medical image analysis. Conventional SLIC starts by placing a grid over the image to be segmented, and subsequently assigns equally spaced clusters centres for each element of the grid. A local k-means is applied in order to assign each voxel to a cluster centre. A distance function (d) is used in the clustering to combine the spatial and the feature similarity, as shown in Equation 2.1.

$$d = \sqrt{(d_f)^2 + \left(\frac{d_s}{S}\right)^2} \quad (2.1)$$

where d_f is the feature distance as a normalised score derived from the data, d_s is the spatial distance, and S is the maximum spatial distance expected within a given superpixel (equal to the sampling interval).

2.4.1.1 Supervoxel compactness

To explain the relationship between S and the compactness [175] of the superpixel let us take A_S as the area and L_S as the perimeter of the superpixel S . The circle with the same perimeter as the superpixel has the radius $r = L_S/2\pi$. Let A_C be the area of a circle with the radius r . Given this, the isoperimetric quotient is described by Equation 2.2.

$$Q_S = \frac{A_S}{A_C} = \frac{4\pi A_S}{L_S^2} \quad (2.2)$$

Based on the isoperimetric quotient, a metric is proposed in the work by Schick et al [175], to assess the compactness (c) of a superpixel segmentation. For a given segmentation, the sum over the isoperimetric quotients of each superpixel normalised by the fraction of the superpixel's size (S) over the whole image is computed. Let ξ be the sum of superpixels from a segmented image I . The compactness of the segmentation can be then defined as:

$$c = \sum_{S \in \xi} Q_S \frac{|S|}{|I|} \quad (2.3)$$

The work on superpixel compactness in this doctoral research it is based on the implementation by Schick et al [175].

While the conventional SLIC method is useful for segmenting from natural images, in our case, it fails to find the myocardium, thus manual contouring is called for, and given the manual contour it is appropriate to then adopt the maskSLIC approach. MaskSLIC [89] is an algorithm that was developed for the purpose of segmenting a previously segmented region (e.g. the left ventricular mask into locally similar regions). One of the main limitations of the conventional SLIC method in particular for cardiac imaging is due to soft edges in the LGE MRI image compared with sharp edges in the case of natural images. MaskSLIC was developed to overcome this limitation, by defining the centres of the supervoxels within the

myocardial mask. The centres of the supervoxels are placed by using the Euclidean distance between two consecutive centres and the borders of the mask, and a predefined number of supervoxels centres.

2.4.2 Left ventricle parcellation - maskSLIC supervoxels

The maskSLIC [89] algorithm is a novel implementation of the Simple Linear Iterative Clustering (SLIC) method, where the supervoxels are generated within a predefined mask, compared with the conventional SLIC method, where supervoxels are generated in a rectangular grid. MaskSLIC algorithm is more suitable for when defining subregions inside a mask, where is unlikely to have regular regions of interest (ROI) to segment and analyse.

The conventional SLIC algorithm divides the ROI into locally similar regions, called superpixels, using a modified k-means clustering method, where a distance metric is used as a weight between pixel intensity and spatial similarity [3]. In conventional SLIC the cluster centres are generated using a grid, and placed equidistantly in the image, while in maskSLIC the cluster centres are generated within a mask using seed points. The position of the seeds is subsequently recomputed based on the distance transform in respect to the mask boundary. This method allows for the supervoxels to be generated only within the mask and therefore eliminates the possibility for supervoxels belonging only partially to the region of interest. The source code was made available to encourage reimplementations.¹

The maskSLIC algorithm [89] has a three step implementation. The first two steps are used to generate points (cluster centres) initialisation in the mask. Once these points are initialised, the third step is to limit the clustering to voxels inside the mask.

As the first step, the Euclidean distance is used to iteratively place seed points spaced at a maximum distance from the boundaries and from each other. The

¹URL: <https://github.com/benjaminirving/maskSLIC>

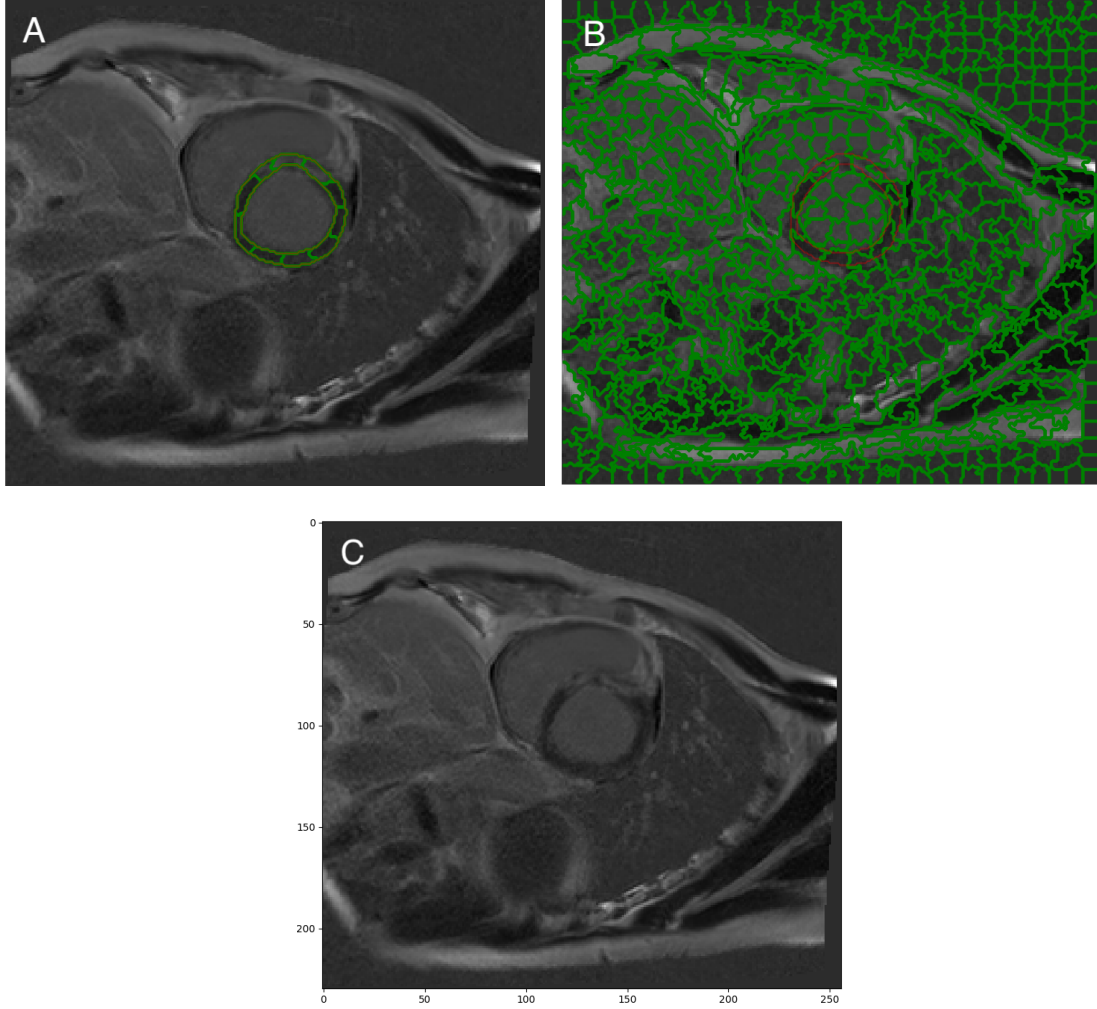


Figure 2.2: MaskSLIC (A) and SLIC (B) supervoxels in short axis view for the OxAMI021 v1, using the same number of supervoxels for the myocardial area. Presented with the LGE image (C) for comparison of the position of the scar.

distance transform to compute the points location is $D(x)$, at location x is given by Eq 2.4.

$$D(x) = \min_{y \in L} \left(\sum_i^n (x_i - y_i) \right)^{\frac{1}{2}} \quad (2.4)$$

where n represents the number of spatial dimensions of the image, L is a vector containing the background (B) and labelled points (P), x_i and y_i are the coordinates of each supervoxel centre.

The furthest distance, p^* is found:

$$p^* = \arg_x \max D(x) \quad (2.5)$$

In the second step, SLIC is applied to the seed points (P) with only the distance feature (d_S). The cluster centres are recomputed M times. This step is to optimise the location of the seeds within the mask.

Finally, in step three, SLIC is applied to the voxels that are defined inside the mask.

2.5 Otsu Thresholding - dividing the myocardium into scar and background

Otsu thresholding is a method used to classify the region of interest in two classes: background and foreground pixels. The method computes the threshold t that separates the two classes using Equation 2.6.

$$\sigma_w^2(t) = \omega_0(t)\sigma_0^2(t) + \omega_1(t)\sigma_1^2(t) \quad (2.6)$$

where ω_0 and ω_1 weights represent the probabilities of the two classes that will be separated by a threshold t , and σ_0^2 and σ_1^2 represent the variances of these two classes.

where class probability $\omega_{0,1}$ (Equation 2.7 and 2.8) are computed from the L bins of the histogram:

$$\omega_0(t) = \sum_{i=0}^{t-1} (p(i)) \quad (2.7)$$

$$\omega_1(t) = \sum_{i=t}^{L-1} (p(i)) \quad (2.8)$$

The number of pixels at level i is represented by n_i and the total number of pixels by $N = n_1 + n_2 + n_3 + \dots + n_L$. The probability distribution is defined as:

$$p(i) = n_i/N, p(i) \geq 0, \sum_{i=0}^{L-1} (p(i)) = 1 \quad (2.9)$$

Even though other more sophisticated methods might be available, here the focus was on using a simple method that is widely accepted and easy to interpret by the clinicians.

In the following sections of this chapter, we present **a novel method for the automated segmentation of the myocardial scar from LGE MR images using maskSLIC supervoxels**. Specific contributions include: **a)** The development of a parcellation method for dividing the left ventricle into locally similar regions based on intensity, which has the potential of automate the LGE scar segmentation from MR images. **b)** Automated scar segmentation that excludes the false-positive enhancement regions, without user interference.

A correct assessment of the extent of the scar can lead to a more accurate patient assessment and potentially a better outcome.

2.6 Materials

The images used for this study are part of the OxAMI (Oxford Acute Myocardial Infarction) clinical study. The data was provided by the University of Oxford Centre for Clinical Magnetic Resonance Research at the John Radcliffe Hospital,

Oxford. The images were acquired on a 3.0T Siemens TIM-Trio whole-body MRI scanner, where LGE-CMR was performed with a T1-weighted segmented inversion-recovery gradient echo-phase sensitive-inversion recovery (GRE-PSIR) sequence 5 to 10 minutes after the administration of 0.1 mmol/kg contrast agent (Gadodiamide, OmniscanTM, GE Healthcare, Amersham, UK). The segmentation of the left ventricle (LV) and the LGE remote areas segmentation was done manually by an expert cardiologist. Full explanations on the dataset used can be found in the Appendix A.2 of this doctoral research.

2.7 Methods for scar segmentation using maskSLIC supervoxels and Otsu thresholding

2.7.1 Determining supervoxel compactness

One of the debates in the field of computer vision, when using SLIC supervoxels, is the number and compactness of the supervoxels [187]. Besides an appealing visual appearance, there are practical reasons why compact supervoxels are advantageous. Compact supervoxels can capture spatially coherent information, as well as, less complicated boundary relationship with neighbouring supervoxels [175].

In order to investigate the robustness of the method for our application, we performed an analysis, and present two cases in Table 2.1 for exemplification, where the number (N) (10, 30, 60 and 100) and compactness (c) (0.001, 0.01 and 0.1) of the supervoxels was varied, in order to determine the optimal number and level of compactness for this specific task, namely, left ventricular parcellation based on local similarities in intensity.

2.7.2 Segmenting the scar from LGE images

Our working hypothesis is that by automating this process, we are not only minimising the time, but also decreasing the intra- and inter-user variability. For this purpose we propose a novel method to automatically segment the scar from

LGE images using the maskSLIC [89] algorithm. maskSLIC is more robust and less user-depended than the segmentation approach used at present in clinical practice. We eliminate the need of manually segmenting the normal area and subsequently manually removing areas of false positive enhancement.

As a first preprocessing step, the LGE images are normalised using $n_i = (p_i - p_{i\min})/p_{i\max}$ to reduce the noise and possible artefacts. Where n_i is the normalised pixel value, the p_i is the pixel value before normalisation, and $p_{i\min}$ and $p_{i\max}$ and the minimum and maximum pre normalisation pixel values, respectively.

We use the output of the maskSLIC supervoxels to take the mean value of intensity per supervoxel and subsequently build a histogram of intensities from these mean values per supervoxel. We classify the myocardium into two regions based on this histogram using the Otsu threshold. Otsu method is a binarisation algorithm that takes as an input an image assuming that it has two classes and builds a bimodal histogram of foreground and background pixels, and subsequently calculates the optimum threshold to separate the two classes so that the variability within each class is minimal [183].

Otsu threshold has been previously used in segmenting the scar from LGE MR images, however to our best knowledge it has never been used in conjunction with a supervoxels based method. By using the maskSLIC [87] supervoxels approach prior to classification, we enforce spatial consistency and therefore overcome the previous limitations reported in the literature [94].

Mean intensity value per supervoxel is used to binarise the image. For the purpose of image binarisation we propose using the Otsu thresholding method.

The results were compared with the clinically reported results (Appendix Table A.3 and Appendix Table A.4) using manual segmentation as explained in the introduction section of this Chapter, and using three to five standard deviations. The delineation is performed using the clinical software cmr⁴² (Circle Cardiovascular Imaging, Calgary, Alberta, Canada). Here the analysis was performed using the

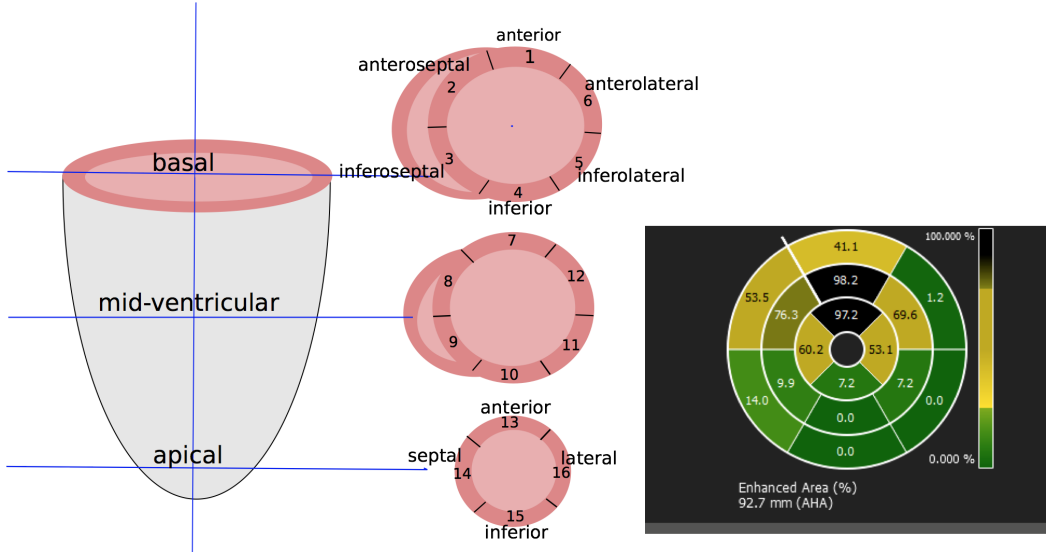


Figure 2.3: Visual representation of the AHA 16 segments model for left ventricular division, proposed by Cerqueira and et al [26] and used conventionally in clinical practice for localised (segmental) analysis of the left ventricle. Presented alongside with a screen caption from the cmr⁴² (Circle Cardiovascular Imaging, Calgary, Alberta, Canada) of a bullseye diagram for a patient. Bullseye is the conventional way of visual assessment of the extent of scarring, post myocardial infarction. Here, 100% means completely damaged tissue (LGE positive) and 0% means healthy tissue.

16 Segments AHA Model for left ventricular segmentation [26], at 24 hours post myocardial infarction and, subsequently, at the six months follow-up scan. A visual representation of the 16 segments model is presented in Figure 2.3. For the purpose of validating the proposed method, we use the Dice overlap metric between the conventionally segmented scar and our proposed method. Dice is a similarity metric used to measure spatial overlap [234], in this case between two segmentations.

Some of the earliest proposed methods for scar segmentation from LGE images used voxelwise intensity based global threshold [95]. However, these methods suffer from spatial discontinuity, resulting in areas that are not part of the scar being classified as scar, when in fact they are just pericardium or artefacts. A common way to compute this threshold is taking three to five standard deviations above the mean value of a region that is considered normal within the myocardium. This approach is still used in clinical practice at present. An example can be seen in

Figure 2.4, for patient OXAMI21 for both acute visit and six months follow-up scan.

To assess the accuracy of the proposed method a sensitivity specificity test is performed. The accuracy analysis is performed in the myocardial mask because the the analysis using maskSLIC and Otsu thresholding is performed in the myocardial mask.

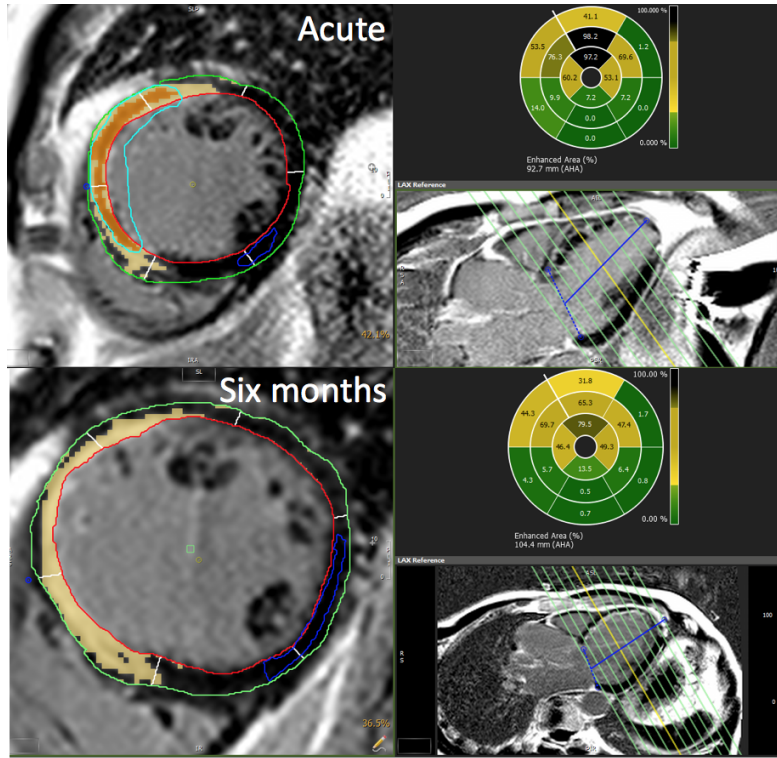


Figure 2.4: Visual assessment of the extent of the scar in patient OXAMI21 for both acute stage of myocardial infarction and six months follow-up. Presented alongside with bullseye representation of 16AHA segments model, to evaluate the extent of the damage, post myocardial infarction - Screen caption from cmr⁴² (Circle Cardiovascular Imaging, Calgary, Alberta, Canada).

The results are compared with the method used at present in clinical practice. This involves manually segmenting a region considered normal - or remote in respect to the enhancement region, and subsequently calculating the threshold, $t = \text{mean}(\text{normal myocardium region}) + 5\text{std}(\text{normal myocardium region})$, in order to obtain the desired threshold for segmenting the scarred area. Where remote repre-

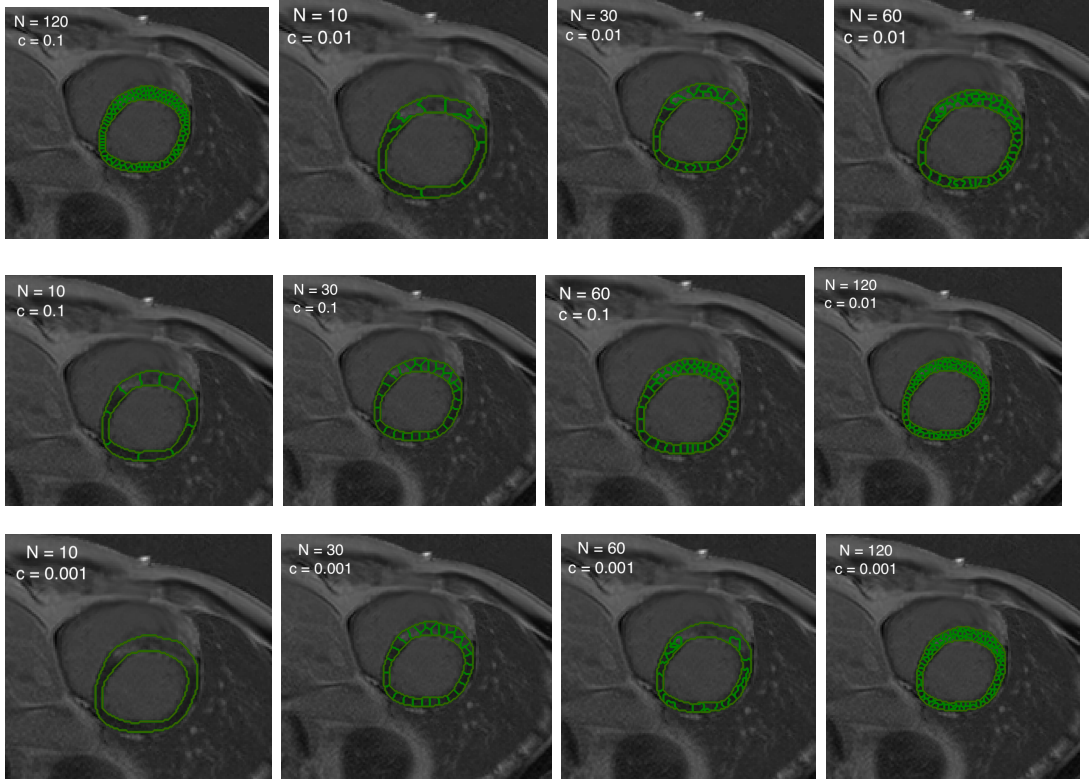


Figure 2.5: MaskSLIC parameter variation. One case where the number of supervoxels and compactness has been varied in order to determine the best parameter fit for segmenting the myocardial scar from LGE images. Where N represents the number of supervoxels centres and c represents the compactness.

sents the healthy myocardium and std represents the standard deviation.

2.8 Results

After performing a parameter search, we determine that the number of supervoxels (N) equals to 60 and the compactness (c) equals to 0.01 is optimal for our application, as it was found that this combination provides the highest Dice Similarity Metric (DCS) overlap with the manual ground truth (mean DSC = 0.9205). The results can be visualised in Table 2.1. The results are presented for the OxAMI21 patient, at the acute visit, in Figure 2.5 for visualisation purposes.

The set of experiments was performed on ten myocardial infarction patients using

OxAMI21 - acute stage	number of supervoxels			
compactness	10	30	60	120
0.1	0.9276	0.9496	0.9407	0.6433
0.01	0.9397	0.9293	0.9302	0.9087
0.001	0.7269	0.8262	0.8457	0.8956
OxAMI53 - acute stage	number of supervoxels			
compactness	10	30	60	120
0.1	0.9272	0.9005	0.8970	0.8944
0.01	0.8298	0.9061	0.9108	0.8939
0.001	0.7010	0.7554	0.8452	0.8777

Table 2.1: Dice similarity coefficient between gold standard and maskSLIC clustering based segmentation. Parameter optimisation for maskSLIC by varying the number of supervoxels and compactness. Presented here for two cases (OxAMI21 and OxAMI53), with the purpose of segmenting the scar post myocardial infarction from LGE images using maskSLIC.

late gadolinium enhancement MR images. The cmr⁴² clinical software was used - on the same images, to determine the position and dimension of the scarred tissue in order to evaluate the performance of the proposed method. The evaluation of the scar volume predicted using the proposed method correlates well with the clinical state-of-the-art, mean DSC = 0.867 (min DSC = 0.73, max DSC = 0.93). This is higher than the best performing algorithm in work by Karim et al [94] algorithm benchmarking, Conditional random fields (DSC = 0.85) [96] for the same task of myocardial scar segmentation from LGE images.

It is worth mentioning that in clinical practice the scars obtained are not directly segmented, but computed using a healthy myocardium area. The LGE images were acquired 24 hours after the myocardial infarction patient was presented at the emergency care unit - considered the acute stage post infarction. Also the stage at which, if assessed accurately, the extent of the scar can lead to a more accurate treatment plan.

The supervoxels are generated in the 2D left ventricular mask for each slice, and subsequently the corresponding Otsu threshold is computed. The Otsu threshold is not a global threshold in this case, but a local parameter, which changes with

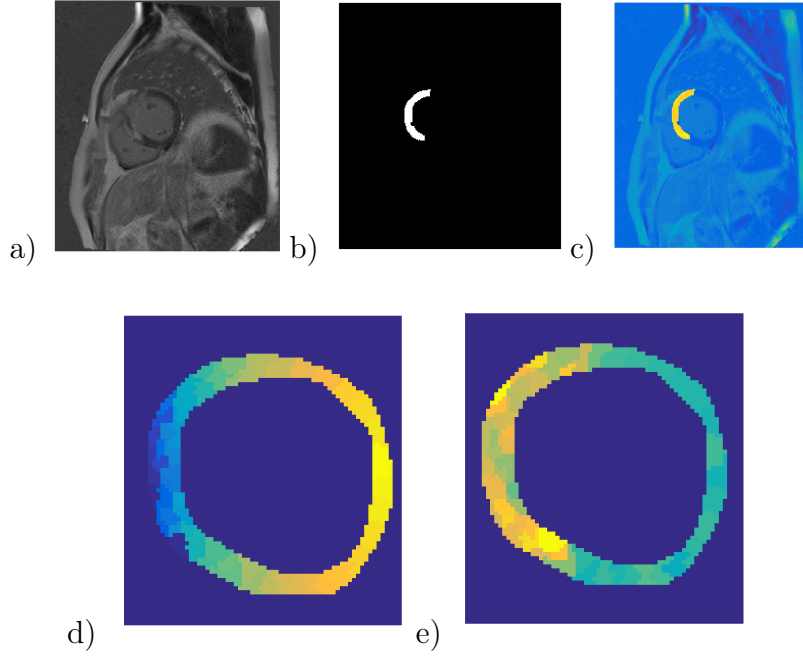


Figure 2.6: a) Late gadolinium enhancement (LGE) for myocardial infarction patient, case1. b) maskSLIC and Otsu thresholding generated scar enhancement. c) maskSLIC supervoxels and Otsu thresholding over corresponding LGE image. d) maskSLIC supervoxels e) maskSLIC mean value of intensity per supervoxel.

each slice, and it has a local significance in accordance with the 2D distribution of intensities.

In Figure 2.6 b) we present the final mask of the enhanced region using maskSLIC supervoxels and Otsu thresholding to separate the background and foreground pixels for one of the cases. In Figure 2.6 d) we show how these supervoxels were generated based on local similarities in intensity, and subsequently the mean intensity value per supervoxel (Figure 2.6 e)). It can be seen that variations in intensity are higher in the enhanced areas (yellow and orange) than in the normal ones (in blue and green).

Using the maskSLIC approach, we eliminate the possibility of supervoxels being generated outside the myocardial mask or across the border of the myocardial mask, therefore increasing the accuracy of the segmentation method. In Figure 2.7 we present four cases with the scars segmented using the conventional clinical method

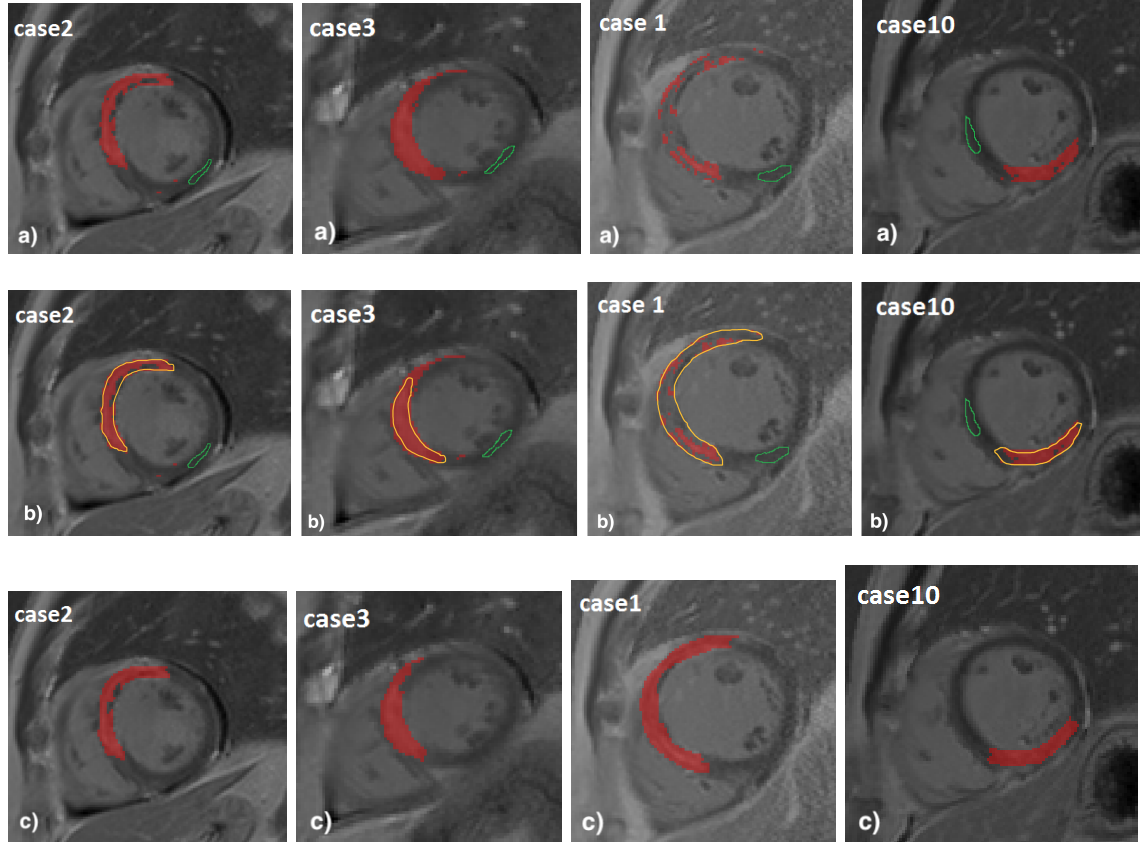


Figure 2.7: Four cases with panel a) representing the scars generated using mean plus 5 standard deviations of the healthy myocardium, panel b) represents the final result after manual correction - in yellow, and panel c) is generated using maskSLIC plus Otsu thresholding on the left ventricular mask respectively.

initial global thresholding (a), final segmentation after manual correction (b), and using the proposed maskSLIC and Otsu thresholding method (c).

The supervoxels output is used to compute the mean value of intensity per supervoxel, from which we subsequently build a histogram of intensities.

Otsu thresholding is then used to separate background and foreground pixels and segment the myocardial scar. In Figure 2.8 a) we present the Otsu thresholding method on a normalised LGE, where the stem histogram represents the distribution of mean intensities per supervoxel within the myocardial border.

We use the Dice similarity coefficient as a validation metric between the proposed method and the scars generated in clinical context. The results are presented in

Figure 2.8 b) for all the ten cases of the myocardial infarction patients.

The post-processing is done using Matlab and Python. The average processing times using a Intel i5, 32GB (RAM) and 64-bit Ubuntu operating system is 2.4 seconds per case.

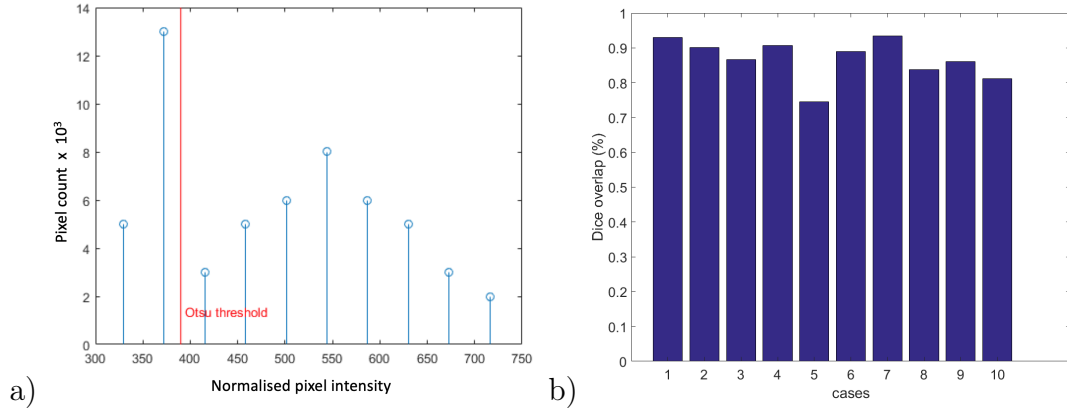


Figure 2.8: a) Otsu method - Intensities distribution for the myocardial area in an infarcted patient, case1. b) maskSLIC and Otsu thresholding LGE scar enhancement results for all the 10 analysed patients.

		Actual values		
		Positive (1)	Negative (0)	
Predicted values	Positive (1)	TP	FP	$Sp = \frac{TN}{TN + FN}$ $Sn = \frac{TP}{TP + FP}$
	Negative (0)	FN	TN	

Figure 2.9: Confusion matrix schematic representation for actual (manual contouring) and predicted (using maskSLIC+Otsu thresholding) values of pixels corresponding to the scar within the myocardial mask.

To assess the discrepancies arising from true and false positive or negative scar identification we performed a sensitivity specificity accuracy analysis (Figure 2.9). The accuracy was computed as $AC = (TP + TN)/(TP + FP + TN + FN)$. The results are presented in Table 2.2. The average accuracy for the study is $AC = 88\%$.

Oxford Acute Myocardial Infarction (OxAMI) clinical trial - acute								
	No	SN(%)	SP(%)	TP	FP	TN	FN	AC(%)
OXAMI0021	1	100	67	501	159	329	0	84
OXAMI0070	2	98	95	304	23	442	7	96
OXAMI0073	3	88	100	205	0	195	27	94
OXAMI0092	4	97	75	187	148	438	5	80
OXAMI0094	5	100	66	253	102	201	1	82
OXAMI0095	6	96	91	269	14	150	11	94
OXAMI0097	7	99	85	171	45	251	2	90
OXAMI0104	8	100	90	117	84	750	0	91
OXAMI0108	9	80	98	135	4	188	33	90
OXAMI0126	10	100	70	172	135	312	0	78
OXAMI0131	11	80	99	162	3	351	41	92

Table 2.2: Confusion matrix - results between ground truth scar segmented clinically (mean+5SDs of the remote myocardium) with additional manual correction steps and the proposed method using maskSLIC and Otsu thresholding, done in the myocardial mask.

The sensitivity (SN) and specificity (SP) for each individual cases can be observed in the Table 2.2.

2.9 Discussion

The proposed method has the potential to automate the LGE scar segmentation process. At present, considerable user input is required in order to correctly estimate the extent of the myocardial scar in a clinical setting. Firstly, because the clinical used approach does not enforce spatial constraints, meaning that subsequent exclusion areas need to be hand-drawn in order to eliminate the false-positive enhancement areas. Secondly, no global thresholding formula can be applied without having to reposition the remote myocardium area (manually segmented), until the best match is achieved. This can be time consuming and obviously subjective to intra- and inter-user variability.

Our method does not involve the need of manually segmenting the remote area of the myocardium, as well as having to manually exclude false positive enhancements,

as the maskSLIC supervoxels approach represents an excellent regulariser within the region of interest.

It is perhaps worth mentioning that Dice overlap similarity metric can be biased in this case, as we compare against a ground truth that has not been generated by manual contouring, but by using a remote area to extract the mean intensity value from and subsequently highlight every pixel that is more than 5 standard deviations from this mean. We therefore argue that the proposed method might perform better than the one used at present in clinical practice.

In order to assess the limitations in using the Dice coefficient as a main assessment metric we compared it against the sensitivity specificity analysis on identifying the scarred tissue. The decision was to use the myocardial mask instead of the whole image. Conventionally in machine learning the confusion matrix is used on the whole image, but in our case, the region of interest, the scar segmentation, is small when compared to the background, and therefore that would make our analysis biased towards the background. The sensitivity and specificity analysis shows the method is highly sensitive in detecting the myocardial scar, however the specificity of the method is average. It was observed that blood pool was sometimes included (a couple of voxels) in the ground truth myocardial mask, this resulting is a source of error for the proposed method. Thus, voxels belonging to the blood pool will also be classified as scar using the proposed method. Therefore in the near future an automated segmentation method to delineate the myocardium will be investigated.

Furthermore some slices did not have manual contours, either due to artefacts or due to incorrect blood pool nulling. Even if the proposed method performed a segmentation of the scar for these slices, the results are probably not of clinical relevance. In the future methods to automatically exclude these slices will be considered.

We also consider including erosion to the masks obtained using the proposed method, in order to better match the steps performed in clinical practice. Adjusting

the Otsu thresholding is also one of the immediate next steps, in order to maintain the high sensitivity, while increasing the specificity.

In order to replicate the clinical method as much as possible, we suggest an additional step, where a region can be selected by simply selecting one of supervoxels in the remote area and compute the threshold value above five standard deviations of the average intensity of that supervoxel. However, this is not necessary for the method to perform, as presented in this work the method achieves comparable results with the clinical method.

2.10 Limitations

In this Chapter we saw that it is possible to segment the scar from the left ventricular mask without the need of manually segmenting additional healthy regions. However, within the proposed method, the myocardium still needs to be segmented manually. Manually segmented myocardial masks are a limitation of the method, because of the prevalence of including voxels from the blood pool. In the near future, automated methods for myocardial segmentation will be investigated. In order to eliminate this need, we are planning in the near future to use deep learning automated segmentation methods to automatically segment the left ventricle.

Another limitation of the proposed method is in using the DICE overlap as the main metric for comparison. As the scar segmented in clinical practice is not a true ground truth (being generated using global thresholding and additional manual correction steps) - was not generated by manual contouring.

2.11 Conclusion

MaskSLIC plus Otsu thresholding can be used to segment the post myocardial infarction scar without the need to delineate regions of healthy myocardium and subsequently clean false positive enhancement areas.

Chapter 3

Quantification of the displacements - Image registration methods

3.1 Introduction

This chapter covers the imaging registration frameworks used in this doctoral research, as well as, it provides an overview on image registration in medical imaging. First, we implemented an optical flow image registration framework, based on a combined local global registration framework called Bruhn-Weickert. Subsequently, we moved towards using a diffeomorphic Log Demons optimised implementation. We used these two frameworks to perform the calculation of the displacements curves from volumetric (isotropic voxel size) cine Magnetic Resonance Imaging (MRI). The emphasis of this chapter will be on the registration algorithms themselves, while the subsequent chapter, **Chapter 4** will present more in detail how these 4D (3D+time) displacement curves are then used to compute the cardiac strains. The 4D cardiac strain curves will then be implemented in the analysis of regional wall motion of the human cardiac muscle in **Chapter 5** and **Chapter 6** of this doctoral research.

3.2 Clinical motivation: cine MRI images - from global cardiac function to regional tissue analysis

Cinematic MRI (cineMRI) represents the gold standard for the assessment of global cardiac function in clinical routine practice [76, 53], however more recently its use for indirect tissue characterisation from motion patterns has also been investigated [61]. While at present cine MRI enables the global assessment of the cardiac function through ejection fraction measurements, as well as local function measurements using a segmental model [26], mass estimation, its capability to record motion over time has enabled the analysis of motion patterns over the cardiac cycle. In the recent years, of particular interest has been the regional analysis of the myocardial tissue. At present, the ejection fraction is the parameter of choice in clinical practice in the assessment of pumping capacity of the heart. The ejection fraction is defined as the change in volume of blood between diastole and systole (full details can be seen in Chapter 1, Section 1.4.4 of this doctoral research) and it is generally accepted to correlate well with patient clinical outcome. However, recent research shows that patients can have a preserved ejection fraction, and still have a very poor clinical outcome, sometimes degenerating into heart failure [166]. Therefore it is becoming quite clear that a more regional analysis, using a deformable model, is needed in order to accurately quantify the extent of the damage within the myocardial muscle. In general many such deformable models have been proposed for medical imaging applications [184].

In order to quantify the motion within the myocardium using images, a registration framework is required. Non parametric registration methods, like fluid [142] or demons [198] are widely used for non-rigid registration of medical images. The general principle is to estimate a dense motion field between two images by minimising a cost function. Usually this function includes an intensity based term and

a regularisation term. Parametric image registration uses a mesh of fixed points and interpolates the deformation between them using cubic B-splines. In this Thesis we focus on non parametric image registration frameworks. Some of the most popular approaches in cardiac tissue motion analysis include tissue tracking using non parametric optical flow registration algorithms [218]. More recently, an incompressibility criteria has been investigated, where a mask is placed on the myocardium and the condition is super-imposed on the corresponding tissue under the mask. One of these implementations is the iLogDemons registration algorithm [126]. B-splines, a parametric registration approach, initially developed for oncologic image analysis applications [171], but subsequently used in a large number of medical image analysis applications, may provide a more natural quantification of tissue displacement than optical flow thanks to its use of smooth base functions [121]. More recently the field has experienced a shift towards a more local analysis of motion patterns. Bai et al., presents an approach of dividing the left ventricle into similar patches using hierarchical clustering [11] on the displacement curves over time. The method defines the number of clusters to be equal to the number of segments proposed in the American Heart Association Writing Group on Myocardial Segmentation and Registration for Cardiac Imaging (AHA) 16 segments model [26] plus the apex of the heart.

3.3 Medical image registration

Image registration is the process of determining a correspondence of features between two or more images [34]. The image registration can be intensity based or feature based. As a typical registration framework, one image is considered moving or source while the other image is considered fixed, or target. In the registration process, the source image is deformed to align with the target image. The fixed image is named reference image, while all the other images are deformed to match the

reference image. This spatial transformation is retained and it is called displacement of a pixel over time. Intensity based methods use a similarity metric to compare intensities between two images at the same pixel level, while feature based image registration are based on identifying correspondences in terms of locating similar features between the moving and the fixed image. Knowing these correspondences, a geometrical transformation can then be determined between the target image and the reference image. This establishes a pixel by pixel correspondence between the target and the reference image.

Image registration plays a critical role in medical imaging in enabling comparison or integration of data obtained from different measurements, either using a single imaging modality or multi-modality imaging [98]. This doctoral research focuses on single modality imaging and multi-modality imaging, within MRI, with the purpose of computing spatial transforms over the cardiac cycle, as well as, matching LGE images to cine MR images with the purpose of locating the scar formed post-myocardial infarction.

Within this context, in this Chapter we investigate two intensity based image registration techniques: the optical flow registration method, with applications and limitations, as well as, the log Demons registration algorithm. These two methods are used to compute the displacement curves from which we then calculate the strain components presented in detail in Chapter 4 of this doctoral research.

3.4 Optical flow based registration

Optical flow is a motion tracking technique, first proposed in computer vision [18] and further on, widely used in the estimation of motion in medical images. The fundamental assumption in optical flow, is that image intensity remains constant along a motion trajectory (Equation 3.1). However, alternative metrics, such as phase based optical flow registration [62] have also been proposed. Phase based reg-

istration frameworks are generally recommended for multi-modal image registration, in particular cine MRI to Late Gadolinium Enhancement (LGE) images, where the intensity differences are beyond the capacity of the intensity based methods to perform the registration. For a 3D + time volume, a voxel location (x,y,z) and intensity $f(x,y,z,t)$, the movement between two volumes is given by Equation 3.1.

$$f(x + dx, y + dy, z + dz, t + dt) = f(x, y, z, t) \quad (3.1)$$

where the displacement field $(dx, dy, dz)^T(x, y, z, t)$ is called optical flow. For small displacements, the optical flow content is approximated by the first order Taylor expansion (Equation 3.2) of the Equation 3.1.

$$f_x u_x + f_y u_y + f_z u_z + f_t t = 0 \quad (3.2)$$

where u_x, u_y, u_z represent the unknown deformation fields between two images. Evidently, one equation is not enough to compute all three u_x, u_y, u_z unknowns. This is a well known ill-posed problem referred to as the *aperture problem*. Many methods have addressed this matter, both from a local, and global description. The registration framework investigated in this Chapter, uses a combination of local [123] and global [80] optical flow methods. The method is called Combined Local-Global optical flow registration method (*Bruhn-Weickert*) [18].

3.4.1 Bruhn-Weickert combined local global optical flow registration algorithm

In this section we explain first the concept of local optical flow, together with its limitations. Subsequently we touch on the concept of global optical flow, and explain the limitations, and how it was a natural step to combine the two for the purpose of investigating medical imaging applications. The explanations below arise from the work in [18].

Lucas-Kanade [123] is a local optical flow method which assumes that the un-

known optical flow vector is constant within a neighbourhood of size ρ . In this case is possible to determine the three unknowns u_x, u_y, u_z at a certain location (x, y, z, t) , using a weighted least square fit to minimise the energy function (Equation 3.3).

$$E_{LK}(u_x, u_y, u_z) = K_\rho * ((f_x u_x + f_y u_y + f_z u_z + f_t)^2) \quad (3.3)$$

where the standard deviation ρ of the Gaussian smoothing kernel K_ρ serves as an integration scale over which the least square fit is computed. The solution is locally dependent due to the introduction of Gaussian kernel. A solution for u_x, u_y, u_z can be obtained by setting the differentials of the energy function E to zero. The result is a linear system (Equation 3.4).

$$\begin{pmatrix} K_\rho * (f_x)^2 & K_\rho * (f_x f_y) & K_\rho * (f_x f_z) \\ K_\rho * (f_y f_x) & K_\rho * (f_y)^2 & K_\rho * (f_y f_z) \\ K_\rho * (f_z f_x) & K_\rho * (f_z f_y) & K_\rho * (f_z)^2 \end{pmatrix} \begin{pmatrix} u_x \\ u_y \\ u_z \end{pmatrix} = \begin{pmatrix} -K_\rho * (f_x f_t) \\ -K_\rho * (f_y f_t) \\ -K_\rho * (f_z f_t) \end{pmatrix} \quad (3.4)$$

The matrix equation (Equation 3.4) cannot be solved for flat image regions, where the image gradients are not constant over time, or in regions where the eigenvalues of the matrix system are close to zero. Therefore, the aperture problem still remains. This constitutes the most severe limitation of the method making it impossible to provide the dense flow estimation needed in medical image analysis. This limitation is not seen in global optical flow measurements. Here the regularisation term will approximate (where is not possible to be computed directly) the flow field, based on nearest neighbourhood method. One of these methods is *Horn-Schunck*, which embeds the optical flow constant into a regularisation framework. *Horn-Schunck* [80] determinates the unknown functions $u_x(x, y, z, t)$, $u_y(x, y, z, t)$, and $u_z(x, y, z, t)$ as minimisers of the global energy function (Equation 3.5).

$$E_{HS}(u_x, u_y, u_z) = \int_{\Omega} ((f_x u + f_y u + f_z u + f_t)^2 + \alpha(|\nabla u_x|^2 + |\nabla u_y|^2 + |\nabla u_z|^2)) d_x d_y d_z \quad (3.5)$$

where the smoothness parameter α ($\alpha > 0$), determines the weight of the regularisation term.

However, one of the limitations of the method is its susceptibility to noise, which is higher than in local optical flow measurements. It is therefore desired to combine the two methods (local and global) of optical flow, into a hybrid method [18], that preserves the main advantages from each method – the robustness of the local method, and the density of flow field of the global approach.

Lucas-Kanade minimises the quadratic form of the energy function while the *Horn-Schunck* method minimises the functional of the energy function. This suggests a way to extend the *Horn-Schunck* method to a combined local-global (CLG) function [18]. The new combined energy function is shown in Equation 3.6:

$$E_{CLG}(W) = \int_{\Omega} (W^T J_{\rho}(\nabla_3 f) W + \alpha |\nabla W|^2) d_x d_y d_z \quad (3.6)$$

where:

$$W = (u_x, u_y, u_z, 1)^T$$

$$|\nabla W|^2 = |\nabla u_x|^2 + |\nabla u_y|^2 + |\nabla u_z|^2$$

$$J_{\rho}(\nabla_3 f) = K_{\rho} * (\nabla_3 f \nabla_3 f^T)$$

$$\nabla_3 f = (f_x, f_y, f_z, f_t)^T$$

Optical flow based registration methods were chosen for their availability for open source code, which facilitated reimplementation, as well as, the large pool of evidence in the literature about their applicability and utility to medical image registration [33, 113, 74, 78, 67] applications.

Except for the effect of blood perfusion (which will slightly alter the overall myocardial volume), the myocardium is nearly incompressible [206]. The common assumption regarding myocardial volume change is that the difference in volume between systole and diastole is no greater than 4% [7]. One of the first medical applications of the assumption that the myocardial tissue is nearly incompressible, was to construct 3D velocity fields inside the heart using 3D CT data [15]. The tissue incompressibility criteria will be further explained in the context of a deformable model in Chapter 4 of this doctoral research.

3.4.2 Optical flow registration framework - Implementation

A combined local global optical flow deformable registration framework, Bruhn-Weickert, is utilised here to recover the motion of the left ventricle from cine MRI, based on the assumptions that the myocardium is almost incompressible. In this section, the deformation was modelled using the displacement between a reference frame and each consecutive frame, in a multistep approach.

The displacement curve for each voxel is computed in a multistep process, in order to minimise the propagation of cumulative errors. **Step 1:** register the consecutive frames to each other (from first to last). **Step 2:** register all frames to first frame (forwards) using the previously recorded (Step 2) consecutive frames displacement. **Step 3:** register the consecutive frames to each other (from last to first). **Step 4:** Register all frames to first (backwards) using the previously recorded (Step 3) consecutive frames displacement. The final result is weighted displacement. The final result is the same as registering all the frames to the first frame, with the difference of final voxel position being closer to the initial voxel position, compared with direct all to one registration.

Prior to the computation of displacement and strain curves, we correct for slice misalignment by using intensity based matching normalised cross correlation and reconstruct the 3D volume of the left ventricle using linear interpolation. Furthermore,

Alpha (α)	Mean LV Ecc (Circumferential Strain)	Mean LV Err (Ra- dial Strain)
$1 * 10^6$	$-0.1734 \pm 6.7412e-04$	$0.5204 \pm 7.7481e-04$
$1 * 10^5$	-0.1731 ± 0.0072	0.5206 ± 0.0075
$1 * 10^4$	-0.1729 ± 0.0414	0.5236 ± 0.0527
$1 * 10^3$	-0.1761 ± 0.1160	0.5293 ± 0.1768
$1 * 10^2$	-0.1875 ± 0.2527	0.5414 ± 0.3480
1	-0.2115 ± 0.5215	0.5823 ± 0.8270

Table 3.1: Alpha (α) regularisation parameter optimisation within a range of 1 and 1×10^6 , varied logarithmically. Influence of changing α in the measured values of the circumferential and radial strain.

we introduce the long axis slices in the volume reconstruction of the left ventricle to obtain extra information for the basal and apical areas in particular - where the short axis slices alone do not have sufficient information for the computation of the displacement curves. By introducing the long axis slices we are able to capture the sliding and twisting motion of the heart and improve the calculation of the displacement and implicitly the strain curves. However, differences in intensity between long and short axis slices can potentially introduce artefacts. The aim of this work was to overcome this limitation by correcting for intensity differences between the long and the short axis. This was done by applying an approximate scaling and additive correction factor, based on a method presented by Zhen et al. in [232].

In order to optimise the computation time, as well as, to ensure convergence, we performed a parameter search for optimising alpha (α). Alpha represents the regularisation term, or blending factor, in the energy minimisation function, explained in detail in Section 3.3.1 of this chapter. Currently it can be said from the published evidence, that there is a lack of automatic parameter optimisation [154]. However a couple of optimisation-based frameworks have been proposed in previously published work. Just to give a few examples, Bayesian optimisation [106], stochastic optimisation [115] are among the most popular methods proposed. Also multi-objective approach for parameter estimation [41] and metaheuristic optimisa-

tion algorithms [155] were proposed. There is a lot of debate in the field regarding parameter optimisation in optical flow, but the general consensus seems to be that the optimisation is not universally applicable, and that it is highly dependent on the registration task itself [154]. The α parameter, allows a trade-off in computation time while preserving the image features necessary for the task, in our case the task is to preserve the geometry of the strain curves. Work also sustained by evidence published on the topic [28]. The strain computation will be explained in detail in Section 4.4 of Chapter 4 of this doctoral research.

In this work we took a heuristic approach to alpha optimisation based on practical observations. Alpha was varied logarithmically between 1 and 10^6 in accordance with literature evidence for small [154] and large [17] deformations. The results are presented in Table 3.1. An alpha value of $\alpha = 100$ was chosen as a tradeoff between smoothness and displacement information in order to ensure convergence while maintaining the computation time relatively fast. This is in accordance with the original Horn-Schunck approach, where $\alpha = 105$ [18]. Within this framework, we present the results for the circumferential strain (Ecc) and radial strain (Err), with further details on how these two strain components are calculated, being presented in Chapter 4 of this doctoral research. $E_{cc} = -0.1735 \pm 0.4760$, $E_{rr} = 0.5204 \pm 0.4760$, and determinant of the Jacobian of the deformation = 0.9912 ± 0.0933 . This is a diffeomorphic deformation where the determinant of the Jacobian of the deformation was within the accepted limits for incompressibility criteria, $J=1$ [190].

The average processing time for a typically contoured 25 frames, 3D, data set using a Intel(R) Core(TM) i7-3370 CPU, 3.49GHz, 16GB (RAM) and 64-bit operating system, is: tracking end temporal fitting = 0.3 second; calculating strain from displacement curves = 0.1 second.

One of the limitations of using velocity based optical flow registration is that errors propagate from one frame to another, influencing the displacement curves and ultimately the calculation of the tissue strain. We have overcome this limitation

by introducing a novel method of calculating the displacement of individual voxels from one frame to another. This novel method involves a multiple step registration process, where the final motion field is calculated by aligning consecutive frames together plus aligning all the frames to a reference one, doing the alignment both in the forward and backwards directions, and calculating the average motion. This process provides a more accurate method to quantify the displacement. When the tracking is performed from frame to frame, the likelihood of errors propagation is significantly decreased.

However, one of the limitations of this algorithm, shared with many other iterative optimisation algorithms in medical image analysis, is its tendency to get stuck in local minima, therefore, we propose to follow a framework that involves using an algorithm that is less sensitive to local minima [67]. This algorithm is called Diffeomorphic log Demons and it is explained in the section below.

3.5 Diffeomorphic log Demons registration algorithm

Diffeomorphic log Demons is a non-parametric, non-rigid, image registration algorithm based on Thirion’s registration algorithm first proposed in 1998, with the added benefit of enforcing diffeomorphic transformations [209]. Diffeomorphic transformations are a requirement in the field of computational anatomy. Diffeomorphisms are important, as they preserve the topology of the object, therefore preventing the occurrence of folding, which is physiologically impossible in the myocardium, and would therefore represent an artefact in the motion field, introducing inherent errors of measurement. The original Demons registration algorithm as it was proposed by Thirion [198], back in 1998, defines demons as local forces that push according to local characteristics of the image. These forces are inspired from optical flow equations and are computed in an alternating fashion with regularisation steps by Gaussian smoothing.

To explain the concept, let us take a fixed image (f), and a moving image (m), the non-parametric image registration is an optimisation problem, where the displacement of each pixel/voxel is computed with the aim of getting an alignment of the two images. Each pixel from the moving image is modeled to best match a corresponding pixel/voxel in the fixed image. This non-parametric spatial transform is called displacement field (Equation 3.7).

$$u = \frac{(m - f)\nabla f}{|\nabla f|^2 + (m - f)^2} \quad (3.7)$$

Where u is the estimated displacement or velocity and ∇f is the gradient of the fixed image f . ∇f is a internal, edge based force, $(m-f)$ is an external force, and m represents the moving image. *He Wang* et al. [217] adds to this equation the edge forces of the moving image, therefore improving the original convergence speed and stability (Equation 3.8).

$$u = \frac{(m - f)\nabla f}{|\nabla f|^2 + \alpha^2(m - f)^2} + \frac{(m - f)\nabla m}{|\nabla m|^2 + \alpha^2(m - f)^2} \quad (3.8)$$

where α is a normalisation constant, to adjust the strength of the force.

Most registration algorithms are based on a standard energy minimisation framework. Energy minimisation frameworks (E) are composed of a smoothness term and a data term: $E = E_{smooth}(f) + E_{data}(f)$. Where the smoothness term penalises those configurations that are inconsistent with the spatial smoothness, and the data term penalises the configurations that are inconsistent with the observed data [99].

The Demons algorithm implementation by Vercauteren et al. [209] uses a similarity metric to minimise the energy function. Squared pixel distance is used as a similarity metric and squared gradient of the velocity field as smoothness regularisation. Gradient descent is the basic solver for $argmin_x(E(x))$. Mutual information is frequently used as a similarity metric in multi-modal image registration. The concept of using mutual information in image registration relies on the fact that both the static and the moving image have regions of relatively uniform intensities, that

are separated by edges. In the process of trying to match the two images, iteratively, as corresponding regions overlap more and more, the peaks in the joint histogram increase. Kroon et al. [107] proposed to use this joint histogram to enable Demons algorithm to work with multi-modal images, however, we observed that this optimisation scheme works in improving the speed of the registration for same modality image registration of a moving object (the heart, in our case). Furthermore, the method proposed by Kroon et al. is less prone to local minima. The optimised registration algorithm is represented by Equations 3.9 and 3.10.

$$E = \frac{1}{2} \|F_T - M \circ (S + U)\|^2 + \frac{1}{2} \|F - M_T \circ (S + U)\|^2 + \frac{\sigma_i^2}{\sigma_x^2} \|U^2\| \quad (3.9)$$

$$\nabla E = (M_T \circ S - F) \left(\frac{\nabla F}{|\nabla F|^2 + \alpha^2 (M_T \circ S - F)^2} \right) + (M \circ S - F_T) \left(\frac{\nabla M}{|\nabla M|^2 + \alpha^2 (M \circ S - F_T)^2} \right) \quad (3.10)$$

E represents the registration error that we want to minimise, M_T and F_T represent the modality transformed images (static and moving), S is the transformation field, U is the iterative update of the transformation field.

Kroon et al. [107] proposes using a scale space approach. Scale-space approach, is a method used to exploit the information from images at different scales and/or focus at the most relevant scales for a particular task. In medical image analysis, scale space or multiresolution approaches have been used to improve algorithm robustness by reducing the likelihood of getting stuck in local minima. Other similar applications include image registration for vessel reconstruction [75]. The framework proposed by Kroon et al. [107] takes the original image size, and scales it to 8×8 pixels, computes a deformation and then uses the result as initial guess for the next 16×16 pixels image, and so on, until the full resolution of the original image is reached.

3.5.1 Log Demons registration algorithm - Implementation

The validation of the displacement curves was performed using a set of healthy controls [200] available through the Cardiac Atlas Project and by emailing the lead author Catalina Tobon-Gomez for additional segmentations. The dataset is comprised of ultrasound, tagging MR, and cine MR in human volunteers, as well as, a phantom data. All available data has manually placed landmarks in the basal, mid-ventricular and apical areas of the left ventricle. Full 3D volume reconstruction of the left ventricle is provided, where the corresponding meshes (as seen in Figure 3.1) are provided as well. The 3D meshes had to be voxelised, as they were provided as a VTK structure. In order to voxelise the meshes, we used the ITK-Snap [228] software. The corresponding landmarks coordinate system was used to reposition the voxelised mask in the same coordinate system as the landmarks. A full description of the data used for this section can be found in the Appendix A.1 of this doctoral research.

The Diffeomorphic Log Demons deformable registration algorithm was used to compute the displacements and it is compared against benchmarked algorithms [201] using the above mentioned dataset. The corresponding voxel position was chosen to be at the same xyz location as the manually placed landmark. A visual representation is shown in Figure 3.2, where in red is the position of the corresponding voxel location with each landmark coordinates, and in green the landmark position (manually placed) for each frame. To validate the registration algorithm, a parameter search was performed, by varying α , σ_i and σ_x parameters. α is a constant used to reduce the influence of edges (and noise), or a regulariser. σ_i is the standard deviation of the gaussian smoothing kernel for pixel velocity field, a form of fluid regularization. σ_x is the sigma for smoothing the transformation field, a form of diffusion-like regularization. σ_x , which is not part of the original demon registration, was introduced by Kroon et al. in order to optimise the registration framework.

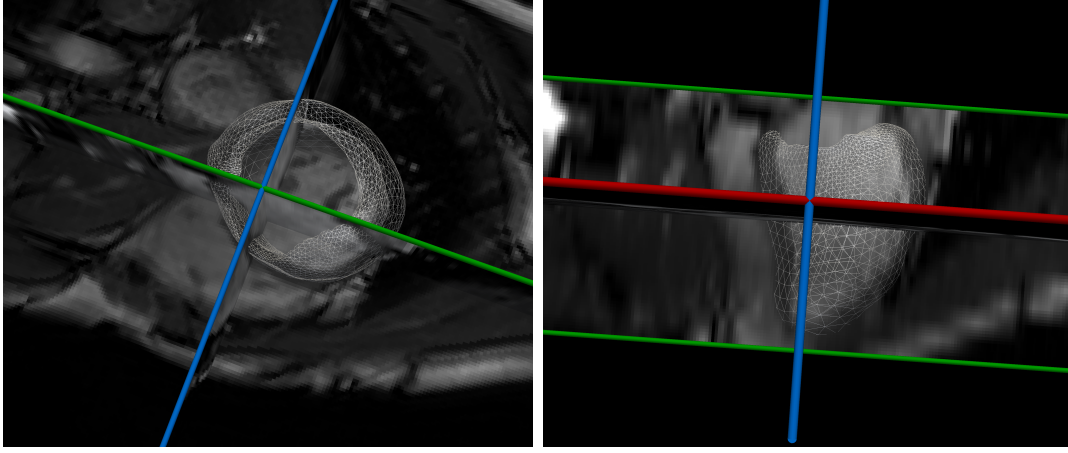


Figure 3.1: 3D mesh of the left ventricle (LV) from the validation dataset, visualised using the Medical Imaging Interaction Toolkit (MITK) (Copyright (c) German Cancer Research Center), open-source software system.

	test0	test1	test2	test3	test4	test5	test6	test7	test8	test9
σ_i fluid	8	10	12	12	10	14	16	21	16	21
σ_x diffusion	1.5	2	2	1	1	1	1	1	1	1
α	5	5	6	5	5	5	5	5	8	8
ES (mm)	4.38	-	-	3.09	3.52	2.69	3.11	2.19	1.86	0.98
FF (mm)	1.33	-	-	1.19	1.12	1.07	0.83	0.89	0.76	0.53

Table 3.2: Sigma fluid (σ_i), sigma diffusion (σ_x) and alpha (α) parameter search for the optimisation of the Diffeomorphic Log Demons registration algorithm presented here together with the outputs of the parameter search: the first to end systolic frame (ES) error, and the first to final frame (FF) error between the ground truth landmarks and corresponding voxel position using the Diffeomorphic Log Demons registration algorithm.

The results can be seen in Table 3.2. The default values of the α parameter is 4, σ_x is 1, and σ_i is 4, as implemented by Kroon et al. [107] and available via MathWorks code. This version of the algorithm was used in this Thesis.

The displacement curves are computed in a multistep framework, as explained in Section 3.3 of this Chapter. The results of the parameter search for the optimisation of the Demons registration framework are presented in Table 3.2, together with the graphical representation of the landmarks both manually placed and corresponding voxel location, in Figure 3.2.

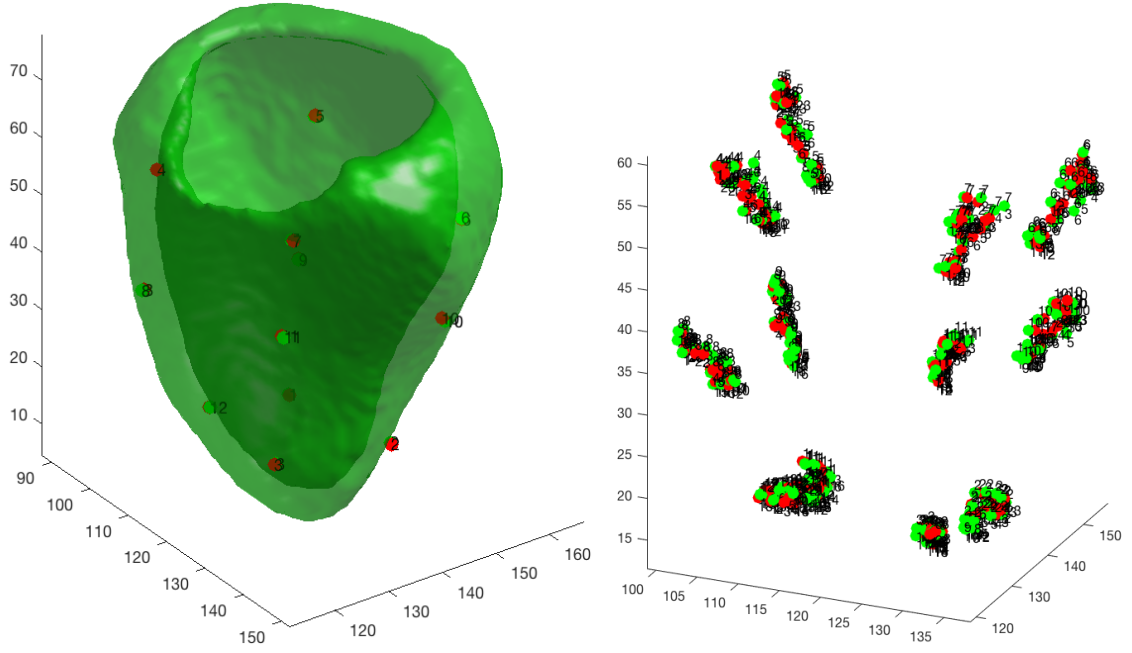


Figure 3.2: 3D representation of the left ventricle (LV) and manually placed landmarks (for all stages of the cardiac cycle), in green, together with output of the registration landmarks at same voxel location, in red. Presented alongside with full displacement curves for all 25 frames of the cardiac cycle, for the validation dataset.

During parameter search it could be observed that in the basal area some of the landmark Euclidian distance is relatively large, this is believed to be because of the landmarks being placed too high and caught in the LV outflow tract, during cardiac motion. Also, in the apical area, some of the landmarks at end systolic frame were not as close as desired to the manually placed ones. This is believed to be due to partial volume effects.

A graphical representation of the displacement vectors for each voxel can be observed in Figure 3.3 and Figure 3.4 for the region of interest (ROI), as well as for the voxels corresponding to the myocardium.

3.6 Conclusion

Non-parametric registration algorithms such as optical flow and Diffeomorphic Log Demons applied to cardiac cine MR can accurately quantify the voxel displace-

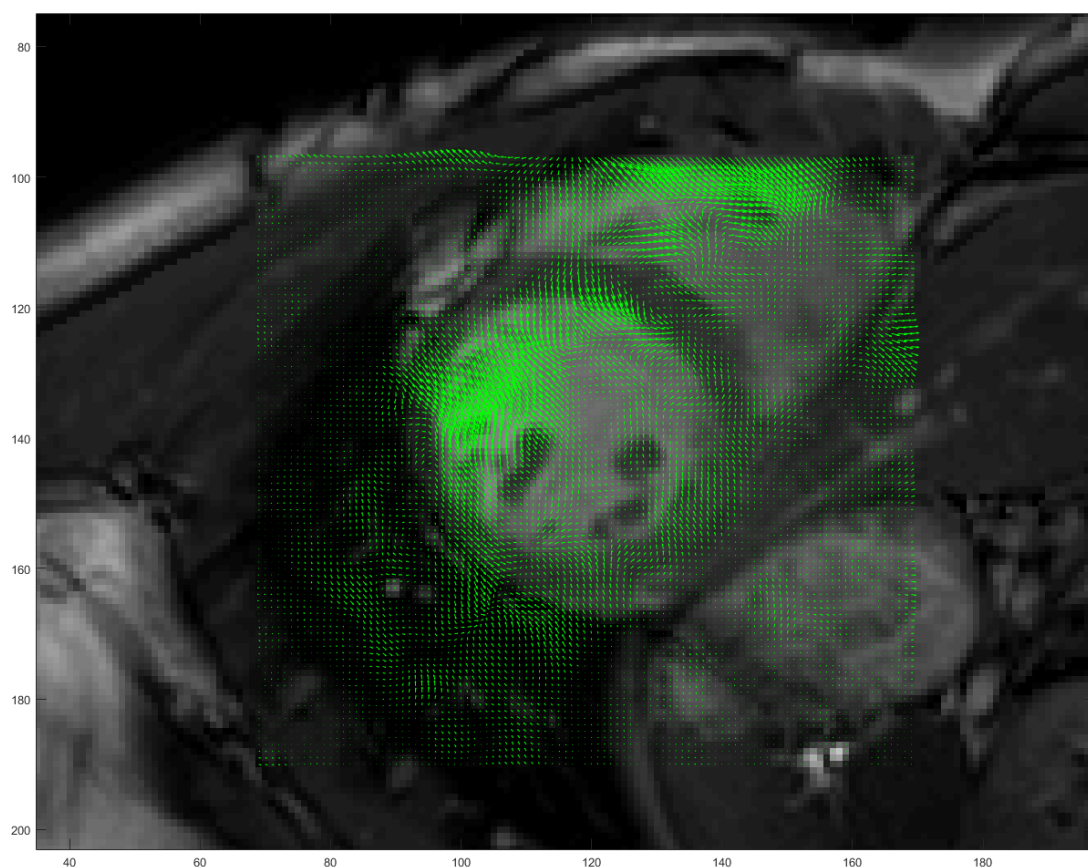


Figure 3.3: Quiver plot of the displacement vectors presented for the whole ROI, as per registration process, using Diffeomorphic Log Demons deformable registration algorithm.

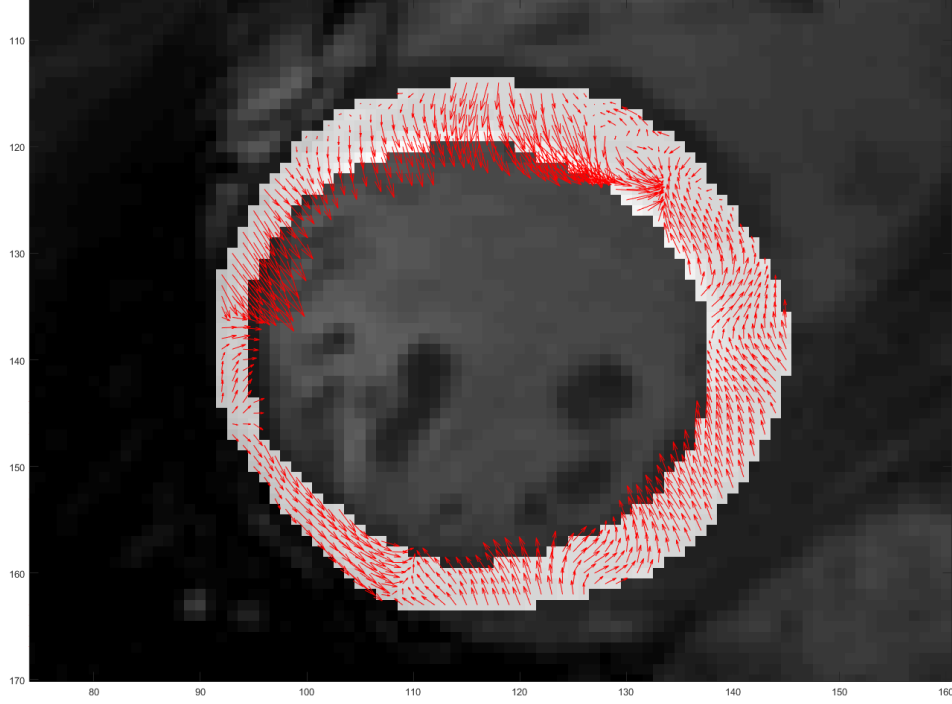


Figure 3.4: Displacement vectors for each voxel corresponding to the myocardium, presented from end diastolic to end systolic frame.

ment over the cardiac cycle. However, parameters optimisation can be a subjective process, which is task dependent and therefore will need to be tailored for each application. In this Chapter we optimised the registration algorithms used to quantify the cardiac muscle motion over time using cine MR images. We found that an alpha regulariser $\alpha = 100$ ensures the fastest convergence while preserving the 3D features of the displacement curve over time. We also found that increasing the regularisation parameters as a batch within the Log Demons Diffeomorphic registration algorithm lead to a decrease of the registration error between registered voxels and ground truth manually placed markers, however it also lead to image smoothness and implicitly to loss of features in the displacement curves. Therefore, we decided not to use these ES and FF as metrics for parameter optimisation. In the next chapter of this doctoral research we will explain in detail how these displacement curves are then used to compute the cardiac strains.

Chapter 4

Myocardial regional strain analysis

4.1 Introduction

Importance: An accurate quantification of the myocardial strain can lead to a more personalised treatment and a better clinical outcome for the cardiac patients. Extensive work has been done in quantifying the functionality of the tissue from CMR images, using strain as an indicator of pathology, however, they are not widely used in clinical practice. This is perhaps due to variability in the results depending on which registration method was used, reproducibility and consistency across healthy controls, as well as, ranges for different categories of diseases. This is about to change with the ever more present commercial products available, referred to as feature tracking software [48]. This chapter takes an overview on the current work in tissue strain analysis and explains the continuum mechanics strain theory, as well as, its applications to cardiac MRI image analysis.

4.2 Cardiac strain assessment using imaging techniques

Strain is a quantification method of the percentage of displacement relative to a reference length (a visual example of 4D (3D+time) displacements can be seen in Figure 4.1) over time [195]. In the case of cardiac muscle the strain measurement can be used as an indicator of a disease. Given contraction is an active mechanism (in

this case the cardiac cells), different strains can indicate a combination of mechanical properties and differences in contraction. There are two types of strain quantification that can be used in the assessment of cardiac tissue functionality, Lagrangian and Eulerian strain (Figure 4.2). Eulerian strain - also known as natural strain, or instantaneous strain [105], quantifies the instantaneous change related to elasticity and therefore can only be computed between two consecutive frames. Eulerian strain was the first to be used in cardiac applications [148, 173]. However, to quantify the shortening and lengthening of the myocardial tissue, an initial measurement of length is required, which might not be obtained accurately by measuring natural strain during contraction [129]. Therefore the Lagrangian strain became more popular for cardiac applications. The Lagrangian strain quantifies the change over time, allowing us to compute differences between extreme (systolic and diastolic phases) frames in the cardiac cycle. The cardiac cycle begins with the diastolic phase (near complete relaxation of the muscle - the cardiac muscle is never fully relaxed, there is a residual stress even in diastole [2]), followed by the start of contraction - the blood gets ejected, followed by the systolic phase - where the heart is fully contracted, and subsequently the relaxation of the muscle (diastole) follows.

4.2.1 Strain delay - a marker for the quantification of the pumping dysfunction of the heart

In heart failure patients ventricular dyssynchrony is a common cause of decreased volume of blood pumped in the body. To correct this dysfunction a device, called biventricular pacemaker is implanted with the purpose of generating electric signals that correct for the abnormally generated ones and ultimately resynchronise the two ventricles of the heart. A prolonged QRS duration is used as clinical indicator to identify dyssynchrony, however recent studies [117, 118] argue that a prolonged QRS segment is not enough to define if a patient has dyssynchrony or not. A more complex analysis is required in order to achieve resynchronisation. Another life

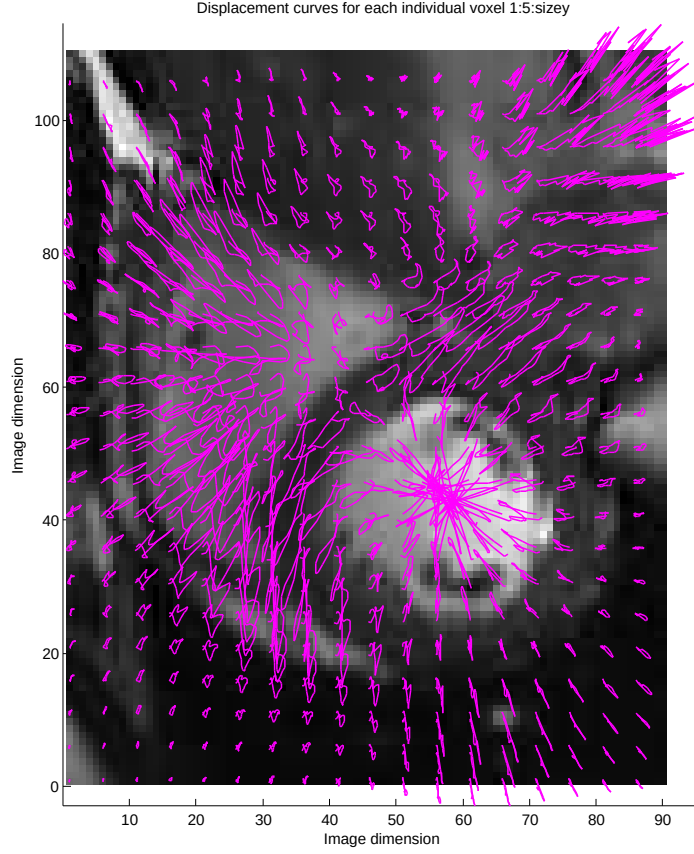


Figure 4.1: 4D (3D+time) displacement curves plotted here for one in five voxels overlaying the corresponding cardiac MR region of interest around the myocardium.

threatening situation for cardiac patients is represented by sudden death. Individuals considered to be at an increased risk of sudden cardiac death are implanted with Implantable Cardioverter Defibrillators (ICDs). Mounting evidence introduces the strain index as a marker of response in ICD implanted patients [117, 72]. A large scale report, published in 2011, presented world wide data accounting for over 80 % of the total implanted ICD devices [143]. The number of ICD implanted patients were at an all-time high (latest available data), with virtually every country (a total number of 61 countries) investigated having an increase in the number of implanted devices. Since then, the trend is the same ascending order, with one of the latest clinical reports confirming that the number of ICDs was still at an all-time high [59]. The ICDs inevitably carry the risk of complications, with one in twenty patients suffering complications after the surgical intervention [49]. Only a small number of implanted IDCs are reported as ever needing to provide an electrical shock during their implantation time [165]. Furthermore, no treatment has been

proved successful in patients with preserved ejection fraction [133]. More recent studies quantified the myocardial stiffness as an important factor for classification and monitoring of heart failure patients [144]. The effect of peak strain delay can be observed in Figure 4.6, both for a healthy control as well as a myocardial infarction patient.

The most widely used metric of assessing the myocardial function in clinical practice is the ejection fraction (EF). The EF has been explained in detail in Chapter 1 of this doctoral research. However, as previously mentioned, a decrease of the EF is not necessarily an indicative of disease. This is can be particularly prevalent in systolic heart failure, where 30-40% of patients have preserved EF as shown in one of the seminal work on the topic [149]. More recent data puts this figure to 50%, while emphasising the limitations and the erroneous character of the metric in measuring myocardial contractility [102]. With newly published clinical guidelines suggesting moving beyond the ejection fraction and towards a more regional assessment of the myocardial function [205].

Strain analysis enables us to perform a regional assessment of the myocardium, which is essential in early disease detection. The most common method for myocardial strain analysis is echocardiography, however relatively low spatial resolution as well as angular dependence of tissue velocity measurements and difficulty in imaging both ventricles at the same time, significantly limit its usability [40]. Cardiac MRI techniques provide a much better spatial resolution for this application. Tagged MRI represents the most commonly used technique for quantifying myocardial motion. Tagging MRI is a sequence that uses saturation pulses to place a grid on the image and subsequently follow the tissue over time, during contraction and relaxation [134]. Despite the fact that tagged MRI represents the gold standard for quantifying myocardial tissue dynamics, the method has never made it to routine clinical practice, due to its high user input, as well as, lengthy acquisition time [197].

The two established methods for assessing the deformation (strain), Eulerian

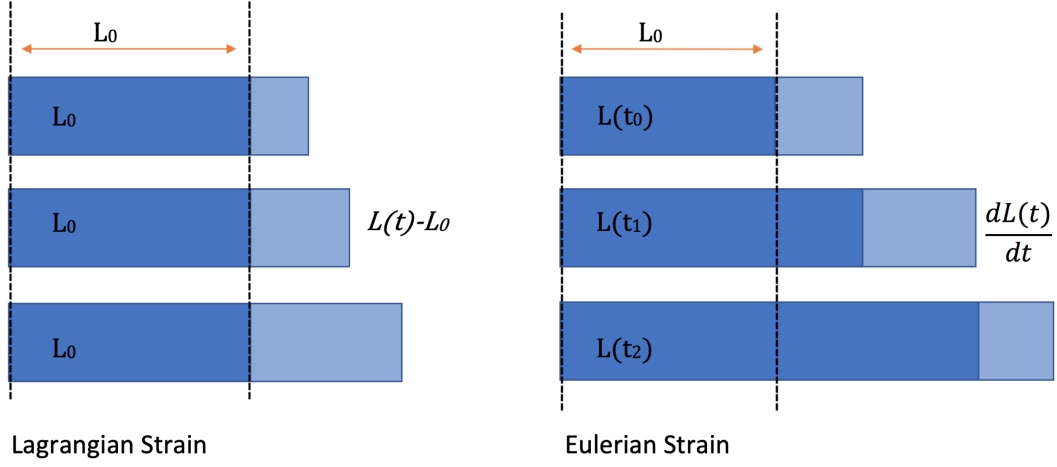


Figure 4.2: Graphical representation of the two types of strains estimations used in cardiac image analysis for strain computation. Left, Lagrangian strain. Right, Eulerian, or natural, strain. Modified from Voigt and et al. [215].

and Lagrangian strain, will be explained in detail in this chapter. In order to better understand the differences between Eulerian and Lagrangian strain, let us also consider the strain rate (SR). SR describes the rate of deformation, and together with the Eulerian and Lagrangian strains it is needed in clinical practice using dedicated software to assess the regional wall motion. However, at present, the Lagrangian strain is most often used in cardiac strain assessment using tissue tracking techniques

The Lagrangian strain [43] uses a reference length (L_0) and it is calculated using the formula below:

$$S_L(t) = \frac{L(t) - L_0}{L_0} \quad (4.1)$$

where $L(t)$ represents the length at time t and L_0 represents the reference length at time t_0 (Figure 4.2). For cardiac strain assessment, this is usually at end-diastole in the cardiac cycle.

The Lagrangian strain rate represents the first derivative of the Lagrangian strain (Equation 4.2).

$$SR_L(t) = \frac{dS_L(t)}{dt} = \frac{1}{L_0} \frac{dL(t)}{dt} \quad (4.2)$$

Eulerian strain, also known as natural strain, quantifies the deformation from one time point to consecutive time point and therefore provides information about instantaneous change in length. For medical image analysis purposes, the Eulerian strain is used mostly in tagged MRI (for the quantification of natural displacement of a nodes grid over the cardiac cycle) [151], but also in echocardiography tissue Doppler imaging, and cardiac computed tomography (CT).

The Eulerian (natural) strain $S_E(t)$ uses a dynamic reference length, that changes with each step of the deformation. This type of strain therefore provides information about the instantaneous change in length of an object. The Eulerian strain rate (SR_E) is the temporal derivative of the Eulerian strain and describes the instantaneous rate of length change (Equation 4.3).

$$SR_E(t) = \frac{dS_E(t)}{dt} = \frac{1}{L(t)} \frac{dL(t)}{dt} \quad (4.3)$$

It is important mention that Eulerian strain rate (Equation 4.3) differs from the Lagrangian strain rate (Equation 4.2) in that the denominator changes over time. The Eulerian strain can be calculated by the integration of Equation 4.3.

$$S_E(t) = \int_{t_0}^t SR_E(t)dt = \int_{t_0}^t \frac{1}{L(t)} \frac{dL(t)}{dt} dt \quad (4.4)$$

Note that the reference length (L_0) used in the calculation of the Lagrangian strain (Equation 4.1) it is always constant, while the reference length, $L(t)$, used in the calculation of the Eulerian strain (Equation 4.4) varies at each time point. A graphical representation of the Lagrangian and Eulerian strain can be visualised in Figure 4.2.

4.3 Hyperelastic biomechanical model for cardiac strain estimation

The displacement curves computed using image registration and described in detail in Chapter 3 of this doctoral research, provide useful information of the moving (salient) features, such as the cardiac boundaries. However in order to address the quantification of the wall motion a deformable model is needed. For the cardiac tissue which undergoes large deformation, a hyperelastic material model can be used to define the biomechanical deformable model [181, 68]. One such hyperelastic material model is the Saint-Venant-Kirchhoff model [145]. This model defines the material, in our case, the cardiac tissue, as nearly incompressible and isotropic (Equation 4.5).

$$\Psi = \frac{1}{2}\lambda(tr(E))^2 + \mu E : E \quad (4.5)$$

where Ψ represents the strain energy density, λ and μ are the Lamé constants. tr is the sum of the diagonal elements of the matrix. In order to quantify the deformation, in this doctoral research we will use the Green-Lagrange strain tensor (E). The Green-Lagrange strain tensor represents the isovolumetric part of the Saint-Venant-Kirchhoff model, and it is defined as follows:

$$E = \frac{1}{2}(F^T \cdot F - I) \quad (4.6)$$

where I is the identity matrix and F represents the gradient of the deformation. For the work presented in this doctoral research, we used the Green-Lagrange strain tensor, which will be further explained in the following section.

As previously mentioned, the hyperelastic material model used needs to retain the constraint that the cardiac tissue is nearly incompressible material [79], in accordance to the consensus statement by the European Association of Cardiovascular Imaging, the American Society of Echocardiography, and the Industry Task force

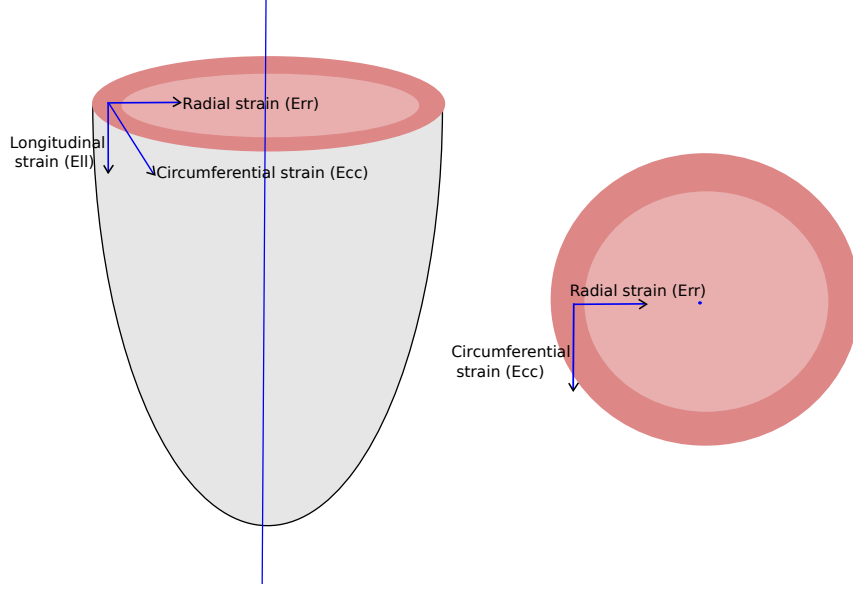


Figure 4.3: Cardiac strains - main components: Radial, Circumferential and Longitudinal strains. Visualised here both in 3D as well as 2D.

guidelines, which defines the cardiac tissue as nearly incompressible [215]. For the criteria of incompressibility to be satisfied, the Jacobian of the deformation (Equation 4.14) needs to be as close as possible to 1. A graphical representation of the Jacobian of the deformation can be seen in Figure 4.4.

4.3.1 Multistep strain curves computation - practical implementation

The strain-time curves are mapped using frame-to-frame tracking of the voxel centre, which is geometrically fixed with respect to a reference frame. If all myocardial voxel centres are tracked at t_1 , the strain can be calculated at a spatial resolution approximately equal to the voxel size. The proposed method uses a deformation gradient tensor $F = I + \nabla u$, where ∇ represents the gradient operator defined as $\delta u_i / \delta u_j$, or in Cartesian components $F_{ik} = \delta_{ik} + \frac{\delta u_i}{\delta u_k}$, to quantify the change in shape. Where I is the identity tensor with components described by the Kronecker delta symbol (Equation 4.7):

$$\delta_{ik} = \begin{cases} 1 & \text{if } n = k \\ 0 & \text{if } n \neq k \end{cases} \quad (4.7)$$

The concept of deformation gradient is introduced to quantify the change in shape of infinitesimal line elements in a solid body, and it can be visualised in Figure 4.2. To explain the concept let us take a straight, infinitely small, line, d_x , on an undeformed configuration of a solid. Now let us map the same infinitely small line on the deformed same solid configuration, the new line will be therefore d_y . The infinitesimal segments d_x and d_y are related by:

$d_y = F * d_x$. Using d_x and d_y , the deformation can be decomposed into a translation and a rotation.

Written as a matrix expression the deformation would be (Equation 4.8):

$$\begin{bmatrix} dy_1 \\ dy_2 \\ dy_3 \end{bmatrix} = \begin{bmatrix} 1 + \frac{\partial u_1}{\partial x_1} & \frac{\partial u_1}{\partial x_2} & \frac{\partial u_1}{\partial x_3} \\ \frac{\partial u_2}{\partial x_1} & 1 + \frac{\partial u_2}{\partial x_2} & \frac{\partial u_2}{\partial x_3} \\ \frac{\partial u_3}{\partial x_1} & \frac{\partial u_3}{\partial x_2} & 1 + \frac{\partial u_3}{\partial x_3} \end{bmatrix} \begin{bmatrix} dx_1 \\ dx_2 \\ dx_3 \end{bmatrix} \quad (4.8)$$

expanded as a Taylor series (Equation 4.9) the result is:

$$dy_i = (\delta_{ik} + \frac{\partial u_i}{\partial x_k}) dx_k \quad (4.9)$$

where $\delta_{ik} + \frac{\partial u_i}{\partial x_k}$ represents the deformation gradient tensor.

As described in the introduction, cardiovascular diseases affect the structure of the myocardial tissue, therefore resulting into abnormalities in the contractile capability of the tissue. In this study, the quantification of the contractile function is performed using 3D Lagrangian Strain Tensor analysis, E , where $E = 1/2(F^T F - I)$, to analyse the proprieties of the tissue.

The 3D Lagrangian strain tensor quantifies the changes in length of a bundle of fibres with respect to their initial configuration. Analysis of the Lagrangian strain tensor E provides a direct estimation of the magnitude of the deformation through six indices: E_{xx} , E_{yy} , E_{zz} , $E_{xy} = E_{yx}$, $E_{xz} = E_{zx}$, $E_{yz} = E_{zy}$.

In order to quantify the behaviour of myocardial tissue, it is more useful anatomically to express the strain in terms of radial, circumferential and longitudinal coordinates. For this purpose, the Green-Lagrange strain tensor can be transformed from a cartesian basis into cylindrical. The Green-Lagrange strain tensor is translated from Cartesian basis into Cylindrical Polar Coordinates bases using Equation 4.10. The centre of the LV blood pool was chosen as a centre of rotation for the Cylindrical Polar coordinate system, with r being the radius of external myocardium, and θ the rotation angle. The Cartesian and Cylindrical Polar sets of components are related by:

$$\begin{bmatrix} E_{rr} & E_{r\theta} & E_{rz} \\ E_{\theta r} & E_{\theta\theta} & E_{\theta z} \\ E_{zr} & E_{z\theta} & E_{zz} \end{bmatrix} = R \begin{bmatrix} E_{xx} & E_{xy} & E_{xz} \\ E_{yx} & E_{yy} & E_{yz} \\ E_{zx} & E_{zy} & E_{zz} \end{bmatrix} R^T \quad (4.10)$$

$$R = \begin{bmatrix} \cos \theta & -\sin \theta & 0 \\ \sin \theta & \cos \theta & 0 \\ 0 & 0 & 1 \end{bmatrix} \quad (4.11)$$

where R is the rotation matrix, r is the radial coordinate and θ is the rotation angle.

E_{rr} and $E_{\theta\theta}$ (E_{cc}) represent the *radial* respectively the *circumferential* strain components. Changes in tissue elastic proprieties are mostly visible in the radial and circumferential components of the Green-Lagrange strain tensor. The relationship between Cartesian and Polar coordinates for the radial and circumferential strain are given by Equation 4.12 and Equation 4.13:

$$E_{rr} = E_{xx} \cos^2 \theta + \sin \theta \cos \theta (E_{yx} + E_{xy}) + E_{yy} \sin^2 \theta \quad (4.12)$$

$$E_{cc} = E_{\theta\theta} = E_{xx} \sin^2 \theta - \sin \theta \cos \theta (E_{yx} + E_{xy}) + E_{yy} \cos^2 \theta \quad (4.13)$$

A physiologically relevant parameter in analysing the tissue displacement is the determinant of the Jacobian of the deformation, which provides a measure of quantification the change in volume. The Jacobian matrix is in fact an extension of

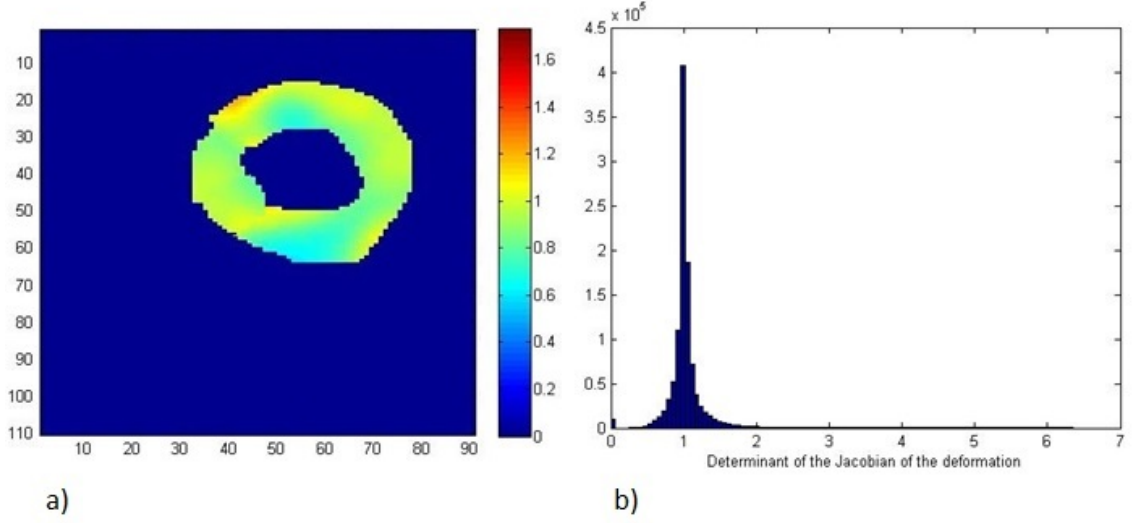


Figure 4.4: The Jacobian of the deformation in the left ventricle (a), presented for one of the patients, at frame 5 in the cineMR images, indicating no folds of the tissues due to errors in the registration and supporting the assumption that tissue is incompressible by having most of the values close to one (b).

the deformation gradient tensor F ($J = \det(F)$), defining differential expansion or contraction (Equation 4.14).

$$J = \det \begin{bmatrix} 1 + \frac{\partial u_1}{\partial x_1} & \frac{\partial u_1}{\partial x_2} & \frac{\partial u_1}{\partial x_3} \\ \frac{\partial u_2}{\partial x_1} & 1 + \frac{\partial u_2}{\partial x_2} & \frac{\partial u_2}{\partial x_3} \\ \frac{\partial u_3}{\partial x_1} & \frac{\partial u_3}{\partial x_2} & 1 + \frac{\partial u_3}{\partial x_3} \end{bmatrix} \quad (4.14)$$

The determinant of the Jacobian (Equation 4.14) ranges between 0 and ∞ . Values greater than 1 represent expansion, while values smaller than 1 represent compression. A Jacobian of 1 corresponds to zero volume change. Negative values of the Jacobian represent tissue folding, and are most likely to represent errors in the registration process. In Figure 4.4 the Jacobian of the deformation is shown for a sample patient, being computed from cine MRI images over the cardiac cycle.

4.4 Cardiac strain using CMR

Cardiac strain using cardiac magnetic resonance imaging has been intensively investigated in the last decade [174, 6] and is finally making its way to clinical prac-

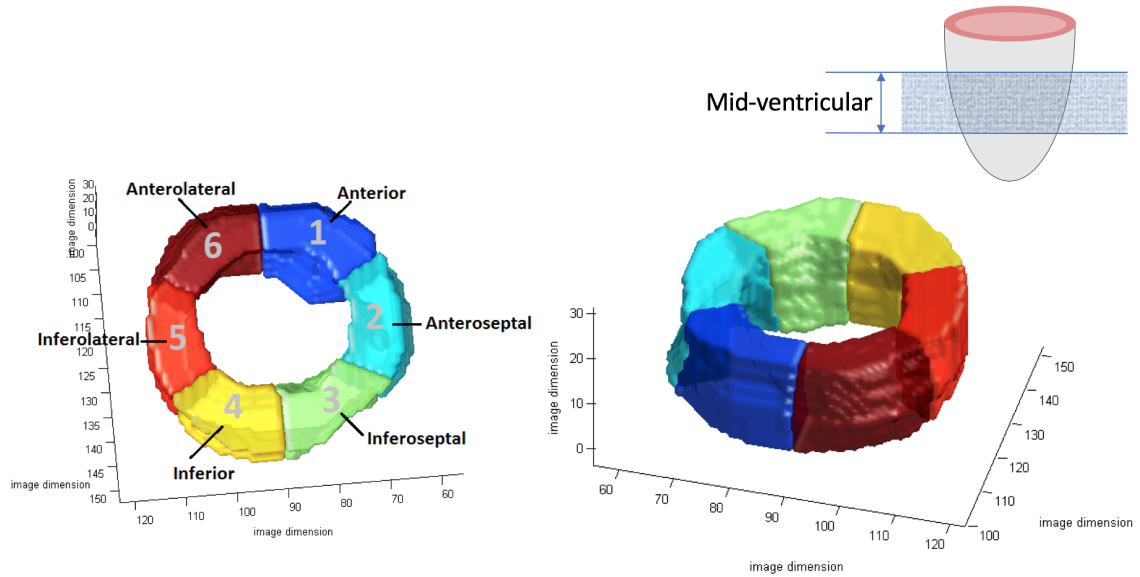


Figure 4.5: Mid-ventricular division using the 16 segments AHA model and tri-linear interpolation to reconstruct a 3D volume from 2D slices. Presented together with the standardised segmental numbering and whole left ventricle volume for better localisation.

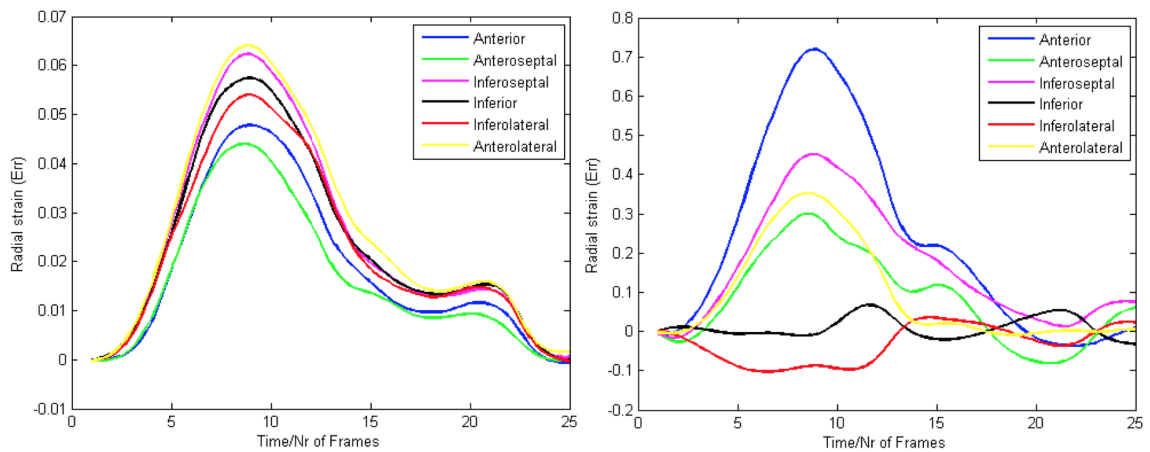


Figure 4.6: Mid-ventricular radial strain 4D (3D+time) curves for a healthy control (left) and an infarcted patient (acute stage - 24 hours after hospital admission) (right). Colour coded corresponding to segments in Figure 4.5.

tice [177]. One of the limitations of clinical application of CMR strain analysis is represented by the wide range of values reported, using various image registration methods, however, recent efforts have been made into standardising the range of healthy controls. A relatively recent literature review [213] aimed to overcome these limitations by suggesting ranges for normal healthy subjects for radial, circumferential and longitudinal strain. This has already been done in echocardiography, through consensus papers [215] and scientific task forces, with the target of standardising deformation imaging and therefore implicitly the strain values. For example myocardial strain analysis can prove very useful in assessing diffuse pathologies, such as, diffuse fibrosis seen in patients suffering from amyloidosis [92], or abnormal accumulation of protein fibres in the heart, called amyloid proteins. These accumulations lead to a serious decrease in function of the myocardium [44]. This pathology is very difficult to image using conventional LGE as sometimes gadolinium does not get deposited in the tissue, therefore making it very difficult to diagnose. Making strain CMR measurements more consistent across the field, would therefore make them more applicable in clinical practice, with potential added value to the patients outcome.

4.4.1 Patient data cohort - pre-processing

To assess the myocardial regional wall motion abnormality, a patient cohort was used, which is described in details in the Appendix A.1 and A.2 of this doctoral research. From this data the cine MR images were used, and for the patient cohort, both the acute visit and the 6 months follow-up scan. The results will be presented in details in Chapters 5 and 6.

Before embarking in the wall motion assessment using local similarity in strain, it is important to mention the pre-processing steps that were taken to allow the data processing.

First the data were cropped around the myocardium, matrix size 56x56 in order

to reduce the computation time for the Demons registration method. The Demons registration method was explained in detail in Chapter 3 of this doctoral research.

A short axis stack (SAX) was used (usually 9 -10 slices), with a voxel resolution typically of 1.5-1.8 mm² and through-plane resolution of typically 8 mm, together with a horizontal long axis (HLA) and vertical long axis (VLA) slices. The three orientations were co-registered using the method proposed by Villard et al, which was shown to reduce the misalignment due to respiratory motion from 2.19 mm to 1.63 mm [212].

To reconstruct the 3D volume, trilinear interpolation was performed to build an isotropic voxel with a typical size of 1.5-1.8 mm³. A visual representation of the 3D volume can be visualised in Figure 4.5 for mid-ventricular volume reconstruction. For the purpose of visual validation, one dataset of a healthy control was used from the Cardiac Atlas Model dataset. Details about the healthy cohort used for this doctoral research can be found in the Appendix A.1.

The strain analysis was performed segmentally, where the AHA 17 segments model was used to divide the left ventricle into segments based on the general geometry of the coronary territory. These concepts will be further explained in Chapters 5 and 6, but are presented here for illustrative purposes (Figure 4.6) for a healthy control (left) and a patient (right).

4.5 Conclusion

In this Chapter we showed that based on the work described in the literature it is possible to extract strain information from cine MRI using image registration methods. This work will be applied in the Chapters 5 and 6 of this doctoral research to investigate the cardiac regional assessment of the wall motion, including the quantification of wall motion abnormalities.

Chapter 5

Myocardial wall motion - assessment based on local similarity in strain

Iulia A. Popescu, Benjamin Irving, Alessandra Borlotti, Erica Dall’Armellina, and Vicente Grau. Myocardial Scar Quantification Using SLIC Supervoxels - Parcellation Based on Tissue Characteristic Strains, pages 182-190. Medical Image Computing and Computer Assisted Intervention (MICCAI) - Statistical Atlases and Computational Modelling of the Heart (STACOM), 2017

Iulia A. Popescu, Christopher Kelly, Alessandra Borlotti, Keith M Channon, Stefan Piechnik, Vicente Grau, and Erica Dall’Armellina. Method for objective automatic assessment of wall motion abnormality from cine MR images, pages 1095-1096. Journal of Cardiovascular Magnetic Resonance (JCMR), Conference Abstract, 2018

5.1 Introduction

This Chapter investigates the assessment of myocardial tissue structural changes during cardiac contraction in patients who have suffered a myocardial infarction, or heart attack. Our working hypothesis is that local wall motion assessment of the left ventricle can provide a more accurate estimate of the extent of tissue damage compared with the conventional AHA model. The longer term aim is to develop non-invasive, advanced cardiac magnetic resonance imaging (MRI) post-processing techniques to characterise the heart in detail, to allow personalised patient treat-

ment and improvement in the clinical outcomes. After a heart attack, accurate assessment of the tissue surrounding the scar is vital to determine the amount and type of damage, which can be used as an indicator of the risk of developing potentially life-threatening arrhythmias or heart failure. At present, in clinical practice the wall motion of the heart using MRI is assessed visually making the decision on the normality rather subjective and open to interpretation. While certain aspects, such as the failure to contract in the infarcted area, can be easily appreciated, other abnormalities, such as areas at risk where the tissue is damaged but potentially salvageable, are more subjective and difficult to assess. Therefore in this Chapter we investigate the possibility of quantifying the wall motion objectively, as well as propose a novel method for voxel-wise tissue functionality estimation based on local similarity in strains. We will first analyse the techniques proposed in the literature for the assessment of the wall motion from MRI images and subsequently the proposed techniques for the quantification of strains and their potential impact on the clinical outcome. To the authors best knowledge, this work is the first to investigate a voxel-wise analysis for the assessment of left ventricular tissue functionality. Regional wall motion assessment and scar quantification from cine images respectively, it is of great interest at present for the field, with recently published work [110, 50] proposing using deep learning structures and optical flow based framework to assess regional wall motion abnormalities and delineate scarred tissue in the left ventricle.

5.2 Myocardial wall motion assessment

Accurate quantification of abnormal wall motion of the heart can potentially lead to a better clinical outcome for cardiac patients. The gold standard is represented by tagged MRI, however its relatively low distribution in clinical practice restricts the method only to research centres [125]. Cine MRI is the gold standard for the quantification of the global function of the myocardium. However, its vast presence

in clinical practice, as well as good spatial resolution, makes it a good candidate for objectively assessing wall motion.

At present the assessment of wall motion from cine MRI is done in a rather subjective way, by visually assessing the degree of motion and assigning tissue to one of the following categories: 'akinesis', 'hypokinesis', 'normokinesis', 'hyperkinesis', and 'dyskinesis'. Despite the myriad methods being developed in the research community, from semi-automated wall motion assessment [189], to dictionary approaches [135] very little has made it to clinical practice, leaving this particular area of the field in much need for a method that can be translated into clinical practice. Accurate assessment of wall motion from cine images can lead to enabling the assessment for tissue at risk without the need of using contrast agents, such as Gadolinium to image the scars formed post myocardial infarction.

Extensive time was spent during this research, investigating methods of quantifying wall motion exclusively from cine MRI images. First, tagged MRI was investigated for this task, but quickly we ran into limitations of the technique, such as considerable user input in post-processing, as well as the long scanning time and limited availability of the imaging method in clinical setting. Even if tagged MRI is the current gold standard for quantification of wall motion in clinical practice, cine MRI has the potential to change that. Cine MRI is the gold standard for tissue characterisation at present, however, extensive work in the field reported methods for using cine MRI in quantifying tissue deformation [127][126][11]. In the next section we will focus on such methods and propose a novel framework for the local assessment of the wall function based on locally similar strain patterns.

Cardiac strain can be used to summarise tissue deformation and is thus directly related to structural properties of the tissue. Spottiswoode et al. [186] use cine DENSE MRI to compute the radial and circumferential strains. Mansi et al. [127] use Physically Constrained Diffeomorphic Demons to estimate the circumferential and radial strains from cine MRI.

5.3 Myocardial scar quantification

From strain based techniques to quantitative tissue mapping using tissue specific magnetisation recovery times, several techniques have been proposed with the goal of shifting from contrast agent based techniques to fully non-invasive approaches.

Post myocardial infarction scars form within the myocardial tissue. It is of critical importance that the extent of this scar is assessed as accurately as possible. This assessment could impact subsequently the treatment plan, including if reperfusion therapy is appropriate or not, to each specific patient. At present Gadolinium is injected and subsequently the extracellular space enlarged within the dead tissue can be visualised as gadolinium accumulates in this type of fibrotic tissue (explained in detail in Chapter 2, Section 2.2). In the last couple of years emerging techniques such as T1 mapping have made possible the assessment of the extent of fibrotic tissue [20], as well as, tissue remodelling [14], completely contrast agent free. One limitation of the most well known T1 mapping technique Modified Look-Looker inversion recovery (MOLLI) [137] was the acquisition time of 17 heart beats breah-hold, and furthermore it is heart rate dependent, making it prone to artefacts at high heart rates. These are significant limitations in using the MOLLI method in clinical practice. Since then, an emerging variant of MOLLI called Short Modified look-looker or ShMOLLI [160] has overcome this limitation while also providing robust validation and a tight range [161] of normal controls myocardial native T1 values, therefore making T1 mapping possible in patients. The combination of a voxel-wise assessment for the extent of tissue damage using cine MRI, and tissue characterisation using T1 mapping, could translate into a powerful tissue biomarker, to assess the myocardial tissue structure and function in order to improve patient risk stratification. For example the initial triage of patients, allowing those with more rare diseases, such as amyloidosis, iron deposition, or hypertrophic cardiomyopathy to be investigated in a more personalised way.

5.4 Myocardial scar quantification and wall motion assessment using maskSLIC supervoxels

Accurate assessment of the extent of the scar has the potential to improve revascularisation therapies and therefore directly translate into an improved clinical outcome for cardiac patients. One of the major advantages of using LGE is the assessment of scar within the myocardium, post myocardial infarction, however recent studies show that gadolinium could have potential side effects previously unknown, such as deposition in the brain [132] while exposed to repeated doses of gadolinium. Furthermore, in patients with impaired renal function gadolinium is contraindicated [169].

Abnormal myocardial motion occurs in many cardiac pathologies, though it manifests in different ways, depending on the disease, some of which can result in negative clinical outcomes. Therefore, a better understanding of the contractile capability of the tissue is crucial in providing an improved and patient-specific clinical outcome [38]. Cardiovascular Magnetic Resonance Imaging (CMR) is considered the gold standard for the assessment of cardiac function and has the potential to also be used for routine tissue strain analysis because of its high availability in clinical practice. In this study we estimate the local strain in myocardial tissue over a cardiac cycle using cine MRI imaging to perform the analysis. To quantify the tissue displacement, we use the diffeomorphic log Demons registration algorithm [209] in a multi-step 3D registration, for the minimisation of cumulative errors propagation. Using the displacement gradient of the deformation, individual voxel strain curves are computed. We present a novel method for parcellating the myocardium into regions based on the strain behaviour of clusters of voxels. We define the supervoxels using the Simple Linear Iterative Clustering (SLIC) algorithm [3] inside a predefined mask. The results are consistent with late gadolinium enhancement scar identification.

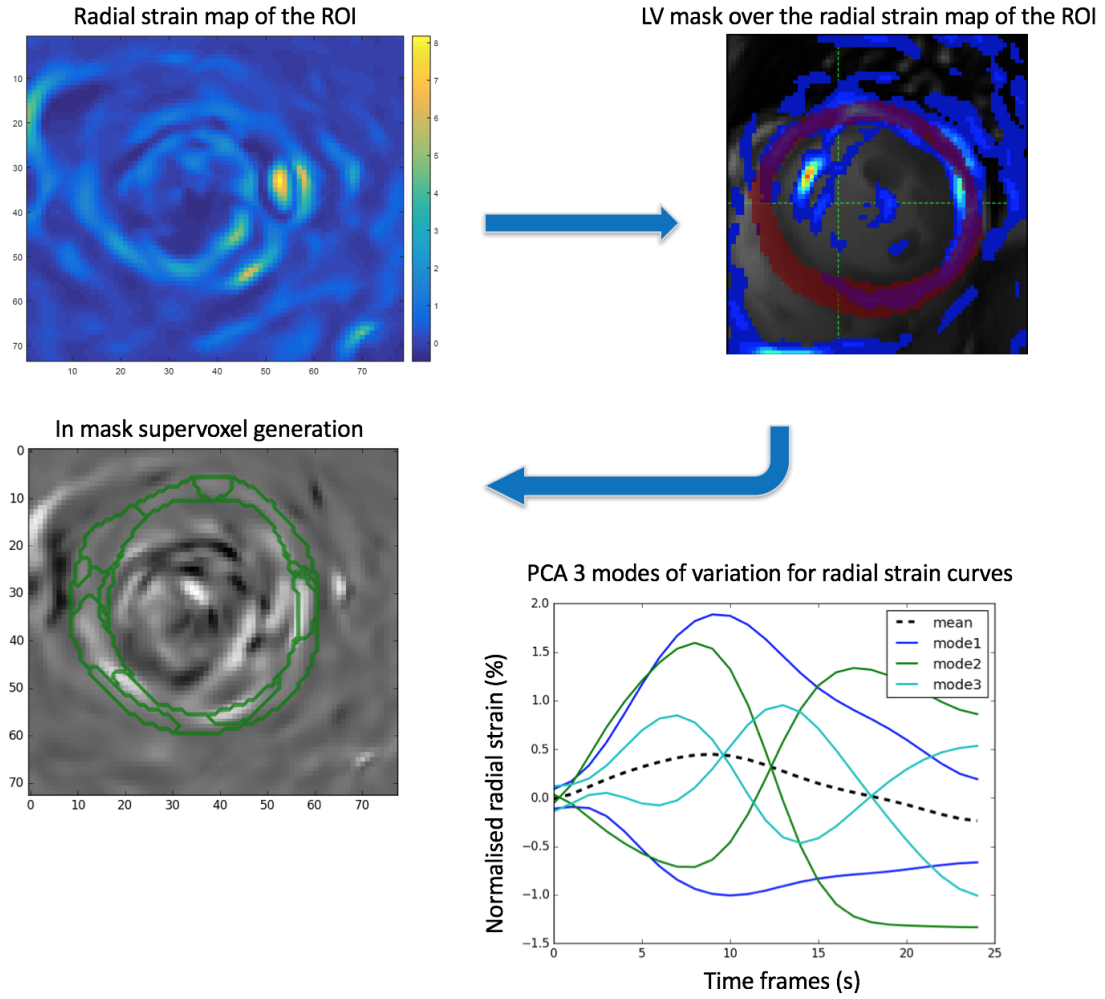


Figure 5.1: Overview of the method presented in this Chapter. We use the left ventricular mask to assess the function of tissue contractility. We quantify this by computing the strain for each voxel belonging to the myocardium. We select these voxels by applying a binary mask over the data. We use a modified SLIC supervoxels method to cluster voxels together based on similarity of strain patterns and using PCA to reduce the dimensionality of the curves.

5.4.1 Voxel-wise assessment of the left ventricle using local strain similarity

Accurate quantification of myocardial contraction and relaxation is fundamental for a comprehensive analysis of cardiac health. One of the earliest methods for tracking myocardial motion was based on the implantation of radiopaque fiducial markers, however due to its invasive nature, this method is not practical for large scale clinical use [91]. Echocardiography, either using Tissue Doppler or speckle tracking (STE), can be used to estimate myocardial motion and strain. However, the angular dependence of tissue velocity measurements, the low spatial resolution of the images, as well as the difficulty to image both ventricles at the same time, significantly limit its usability. Furthermore, a significant percentage of cardiac patients have poor acoustic windows due to either body size or previous surgical procedures [178]. MRI imaging overcomes these limitations. Excellent temporal resolution of STE is an advantage over CMR, however, developments in signal to noise ratio makes CMR feature tracking potentially superior to STE [150].

Tagged MRI is generally accepted as the current gold standard for quantification of myocardial motion in the clinical setting [221]. The method uses spin tagging prepulses to produce a magnetised rigid grid on the image [10], and subsequently the grid deformation is tracked over a cardiac cycle. However, some of the main limitations of the method are the acquisition time (the acquisition requires significantly more time in the scanner compared to cine MRI), a complex sequence, and the need for substantial user interaction in post processing of the images.

Cine MRI is considered the gold standard in clinical practice for tissue characterisation. However, its use for the quantification of tissue deformation and strain has also been explored. Previous methods include tissue tracking using a diffeomorphic registration algorithms with a superimposed incompressibility criteria for volume preservation [126], or with physical constraints such as divergence free deformations and myocardium elasticity modelling [127] to extract the strain curves. More re-

cently, Bai et al [11] have investigated the division of left ventricle based on tissue displacements using a hierarchical clustering method, where the number of clusters were set to be equivalent to the number of segments in the 17 segments model. The method proposed in this Chapter differs from [11] in that we identify the region or regions that have been affected by pathology. While the concept of local division, or parcellation, is not new to biomedical image analysis, being extensively used in brain applications, it is only recently that has been proposed in cardiac applications.

The standard clinical method for the quantification of scarred tissue - post myocardial infarction, is late gadolinium enhancement (LGE). The concept was explained in detail in chapter 2 of this doctoral research. While LGE provides critical information for patient diagnosis and management, its combination with motion analysis provides a more complete picture of structure-function relationship in cardiac disease. More recently, imaging methods for scar quantification have been proposed based on motion patterns [156] and quantification of the myocardial deformation [47], where the aim is to replace the need to use contrast enhancement agents, like in the case of conventional LGE.

In this work we present **a novel method for the quantification of myocardial strain from cine MRI sequences using individual voxel strain curves**, grouped using a supervoxel algorithm. Our main contribution is the development of a parcellation method for the division of the left ventricle into regions based on tissue characteristic radial strain, which has the potential to improve tissue strain analysis. For this purpose we also present a method for spatial tracking of discrete material points (voxels) of the myocardium during myocardial motion, and subsequently build strain curves of the tracked voxels over a cardiac cycle. We provide initial validation by comparing results with LGE images.

5.4.2 Materials

The data set used for this work is part of the OxAMI (Oxford Acute Myocardial Infarction) clinical study, which was provided by the University of Oxford Centre for Clinical Magnetic Resonance Research at the John Radcliffe Hospital, Oxford. A cohort of 20 patients with acute myocardial infarction were acquired on a 3.0T Siemens TIM-Trio whole-body MRI scanner, using steady-state free precession (SSFP) for cine imaging, and were gated to the vector ECG. Both cine MRI and LGE images were acquired in the same visit, typically 24 hours after myocardial infarction patient was presented at the emergency care unit. Each of cases has the following image characteristics: 25 time frames per slice, with a typical voxel size of $1.56 \times 1.56 \text{ mm}^2$ and a slice thickness of 8mm. Further information on the data can be seen in the Appendix A.2 of this doctoral research.

The segmentation of the left ventricle (LV) was done manually by an expert cardiologist, where for each time frame the endocardium and epicardium is segmented using the cmr⁴² software (Circle Cardiovascular Imaging, Calgary, Alberta, Canada). This segmentation was used as a LV mask.

5.4.3 Methods

For each patient, we use a cine 4D volume with isotropic voxel size of $1.56 \times 1.56 \times 1.56 \text{ mm}^3$. Details on how this volume was generated can be found in chapter 4, section 4.4.1 of this doctoral research. From the 4D registered volume we extracted the displacement curves over a cardiac cycle for the ROI, explained in detail in Section 5.5.1. Subsequently the left ventricular mask is applied, and the supervoxels are generated inside the mask using as a feature the voxel individual strain curves.

We use k-means clustering to separate the labeled supervoxels into three classes in the attempt to have a class for each of the following possibility of tissue being healthy, damaged, or affected but viable. However, this being only preliminary work, extra clinical validation is needed in order to assign names to classes.

First we run a cohort-wide PCA modes of variation to capture the inter-patient variability (Figure 5.4). Secondly we run a PCA modes of variation within individual cases (Figure 5.3) because the dynamics of the pathological hearts are different, and therefore it would be interesting to also investigate this intra-patient variability. For the second analysis, we show a 3D rendering for this analysis in Figure 5.5.

The validation of the proposed method is performed against LGE identified scar regions. For the purpose of validating the proposed method, we performed a quantitative assessment of the overlap of the scar using the proposed method, compared with Late Gadolinium Enhancement (LGE) which will be explained in detail in the following sections of this chapter.

5.5 Identification of the scar location in cine MRI images

This section was done in partnership with Christopher Kelly, where Christopher Kelly was responsible for performing the registration of the cine MRI images to the Late Gadolinium Enhancement (LGE) images. Since this is a multimodal image registration and the intensities of the two images are structurally different, an intensity based registration approach was not suitable for the task.

Even if both cine and LGE images are acquired in the same scan, there are still spatial differences in some cases, where the patient can move slightly during the scan or during the 'breath in - breath out' instructions they do not stop breathing while in fully exhaled phase. Among others, these factors can lead to a spatial disagreement (misalignments) between LGE and cine images.

In order to overcome this limitation, in this section we propose using a phase based registration framework. Unlike intensity, local phase is constant to image brightness and contrast, making it a descriptor of multimodal image structures. Here we use a combined local-global registration method previously described in Section 3.2.2, however this time we use the phase of the signal instead of the intensity. We

perform this in a 2D LGE to cine framework, and subsequently we perform linear interpolation in the z direction in order to reconstruct the 3D volume of the scar from the LGE images. The 3D LGE scar is then overlapped on the cine volume and compared against the local parcellation based on strain similarities, explained in detail in Chapter 5 of this Thesis.

An alternative way of validating the registration algorithm for our application, was to perform a comparative analysis on tagged MRI image sequences and cine MRI image sequences of a patient diagnosed with myocardial infarction. Both sequences were acquired on the same visit, in acute stage and four weeks after the myocardial infarction episode. The strain curves from the tagged sequence were obtained by using the CIM software (CIMTag2D v.7, Auckland MRI Research Group, New Zealand). The 2D contours were manually delineated by an expert image analyst for end-systolic and end-diastolic time points, and subsequently, propagated for the rest of the cardiac cycle points. However, tagging MRI can only compute the 2D strains, and in this case at three different locations in the left ventricle short axis view: basal, mid-ventricular, and apical slice. One of the limitations of tagged MRI is that in the case of a small myocardial infarction, due to the localised nature of the pathology, the abnormal wall motion can be missed. In the case of using full 4D (3D+time) reconstructed left ventricle with the computation of voxel-individual displacement curves, and subsequently the calculation of voxel-individual strain curves, we are able to provide a more accurate assessment tool for cardiac patient outcome.

5.5.1 Diffeomorphic log Demons image registration algorithm

The Diffeomorphic Demons registration algorithm is a non-parametric, non-rigid, image registration algorithm. The algorithm consists of two terms: a similarity criteria, and a regularisation term (a Gaussian smoothing filter in this case) (full details about the Log Demons algorithm can be found on Chapter 3 of this doctoral research). The displacement of each voxel is calculated using the intensity similarities

between a static (reference) and a moving image. For this Chapter we use an implementation developed by Dirk-Jan Kroon [107]. Our method applies this algorithm within a multiple step registration process, designed to minimise accumulation of errors. The final motion field is computed as follows: **First pass:** a) Consecutive frames are aligned to each other in an descending order; b) Pre-aligned frames are aligned to the reference frame (last); **Second pass:** a) Consecutive frames are aligned to each other in an ascending order; b) Pre-aligned frames are aligned to the reference frame (first). Both deformation fields are then combined, using a weighting function, according to the distance between each frame and the reference frame. While an incompressible version, iLog Demons, is available, the lack of an open-source implementation and the good results obtained by Log Demons made us choose the latter.

5.5.2 4D strain estimation for maskSLIC supervoxels

To quantify the contractile function of the tissue, we compute the 3D Lagrangian strain tensor E . Here $E = 1/2(F^T F - I)$, with I representing the identity matrix. The 3D Lagrangian strain tensor is explained in detail in Chapter 4, Section 4.3.1.

The 3D Lagrangian strain tensor quantifies the changes in shape of a piece of tissue with respect to its original configuration. The analysis of the Lagrangian strain tensor provides a direct estimation of the magnitude of the deformation through six indices: 3 normal strains: radial, circumferential, and longitudinal and 3 pairs of shear strains. In this work we use the radial strain as a proof of concept.

5.5.3 Left ventricle parcellation - maskSLIC supervoxels

Simple Linear Iterative Clustering (SLIC) is a segmentation algorithm that divides an image into small clusters of pixels, called superpixels [3]. The SLIC algorithm is explained in detail in Chapter 2, Section 2.4.1. Because the superpixel/supervoxel segmentation is a method for dividing an image into a set of regions,

based on local similarity, in our case, this approach can provide a more natural set of subregions for analysis. In conventional SLIC [3], k initial cluster centres are sampled on a rectangular grid. In this work we use a 3D + time adaptation of the SLIC algorithm, called the maskSLIC algorithm [88], to generate the supervoxels in a segmented region. The source code is available to facilitate reimplementa-tion.¹ The key novelty is that we use shape characteristics of the strain curves to define each supervoxel region.

We used PCA modes of variation for dimensionality reduction [90], instead of all the available time points, in order to remove as much noise as possible from the strain curves. As an additional step, the PCA modes of variation are identified from the whole cohort. PCA is first applied to strain curves calculated for each voxel corresponding to myocardial tissue. The first three modes of variation from PCA are selected. By definition of PCA, the first mode will represent the largest variation, and every subsequent mode would represent a smaller variation [88]. The PCA values were subsequently used to generate the supervoxels. Within the maskSLIC, the voxels are assigned to the nearest cluster centre using k-means clustering, with a 2S X 2S X 2S distance of each cluster, with a modified distance metric to include a feature distance term, using principal component analysis to extract these features [88]. An additional adaptation is that the supervoxel calculation is only performed within the mask. This is done by placing equidistant seed points within the mask to initialise the SLIC using a distance transform derived method [85].

A supervoxel based step was used for a number of reasons, first the spatial regularisation reduces noise in the images and allows more robust features from each region, second, it provides meaningful regions for visual assessment, and finally it reduces the computational complexity of the analysis.

¹URL: <https://github.com/benjaminirving/perfusion-slic>

5.5.4 Dividing the tissue according to similar patterns in radial strain curves

Once the supervoxels have been calculated, based on local similarity in strains for each voxel corresponding to the myocardium of each patient, we use the supervoxels to obtain a division of the left ventricle into classes of tissue based on local tissue functionality, as an alternative to the standard left ventricular division using the AHA 17 segment model.

5.5.5 Results

For this study we used a set of 20 myocardial infarction patients. The Late Gadolinium Enhancement images (Figure 5.2 a) and b)) were used to visually estimate the position and dimension of the scarred tissue. The corresponding slices, cine MRI (Figure 5.2 c) and d)) were the only ones used to compute the radial strain in the left ventricle.

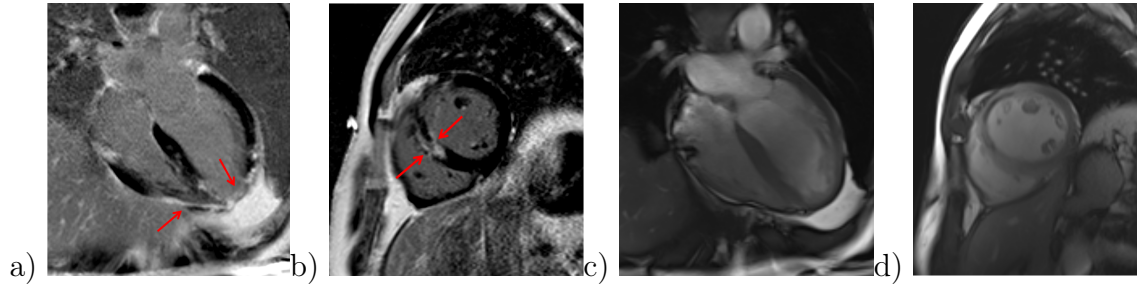


Figure 5.2: Late gadolinium enhancement for myocardial infarction patient, case1 (a) and b)) and cine MRI matching slices for the same case, c) and d). One mention is that the LGE images are for only one time point, beginning of systolic phase.

A 3D rendering of the supervoxels distribution, as well as the three clusters built using tissue characteristic radial strain, can be seen in Figures 5.5 and 5.7, for Case I (a) and Case IV (b). Figure 5.5 was interpreted by a consultant cardiologist which found that the two patients had the same ejection fraction (EF) $EF = 35$ (low) at acute presentation. Correlation with ejection fraction (EF) was made highlighting

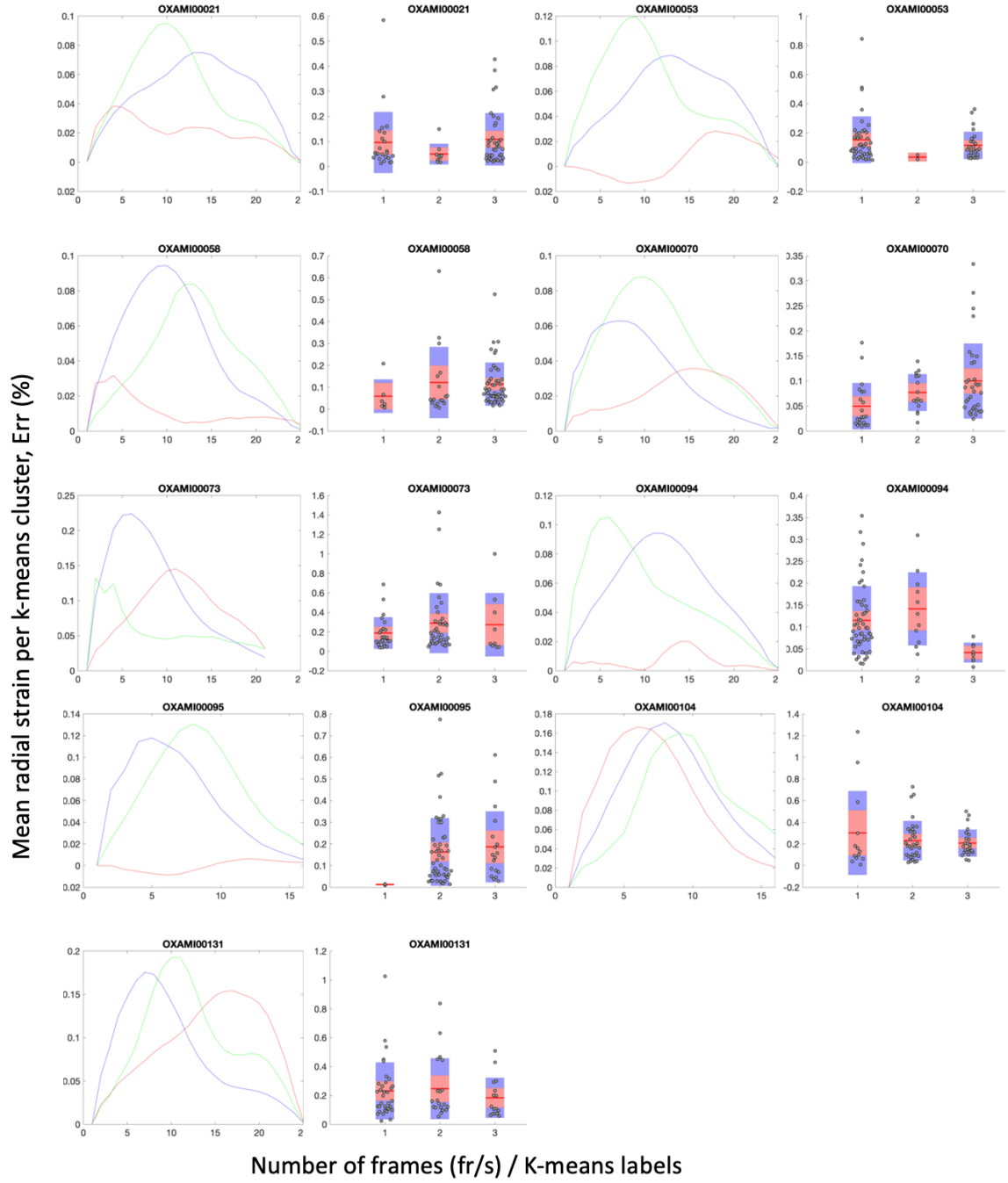


Figure 5.3: Cohort-wide trained PCA. Mean strain curves of the k-means classes for each of these cases presented for the 4D (3D+time) radial strain curves at the acute visit (usually within 24 hours from the Emergency and Accidents (EA) presentation). Presented alongside box plots with the number of supervoxels for each k-means cluster.

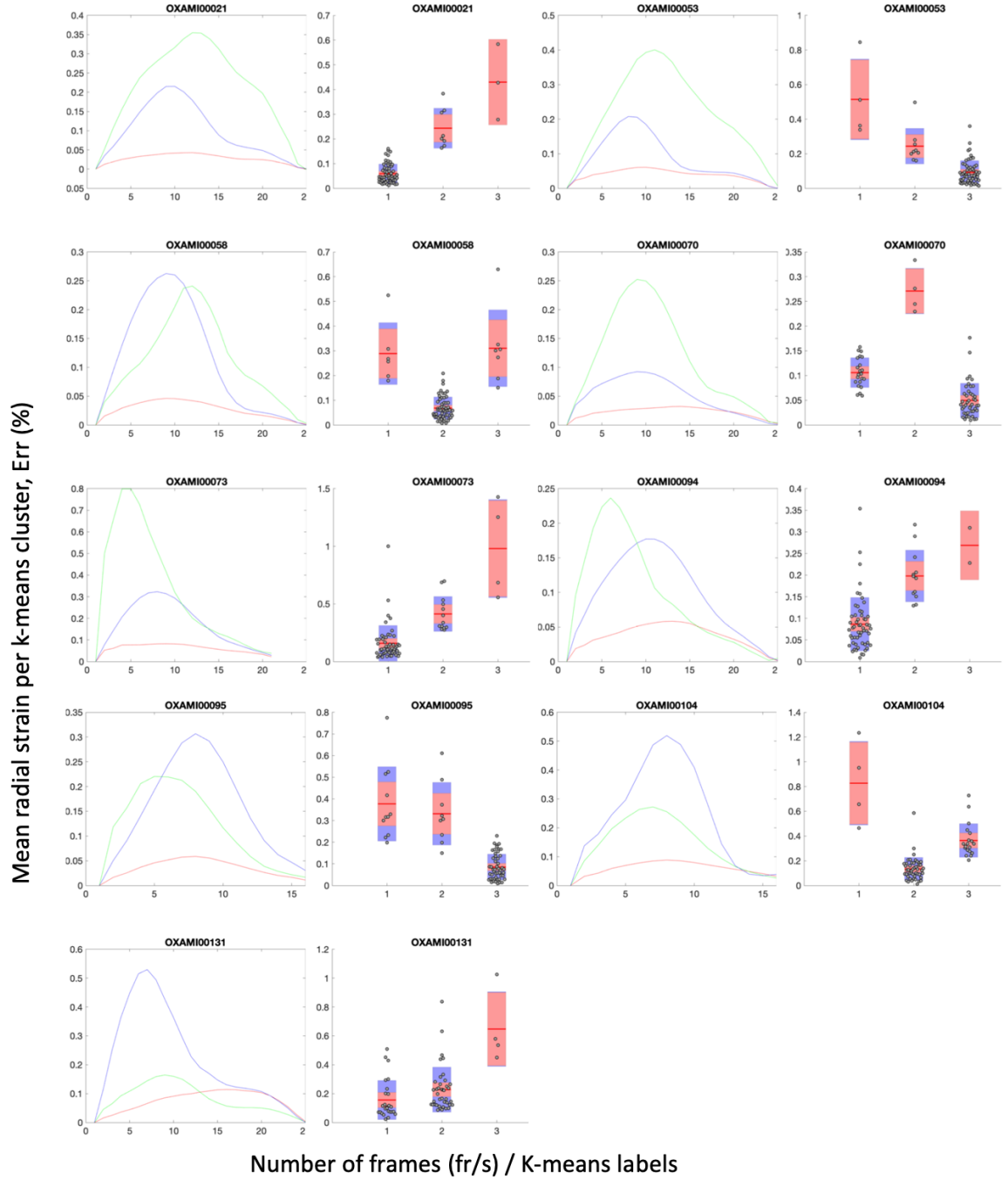


Figure 5.4: Individually trained PCA. Mean radial strain curves for each k-means labels. Each case is presented for the 4D (3D+time) radial strain curve at acute presentation (usually within 24 hours from the Emergency and Accidents (EA)). The radial strain curves are presented alongside box plots of variation for each label, and the number of supervoxels belonging to each k-means class.

that both cases had a EF of 35 at first visit, while at second visit it can be observed that one of the cases (Case IV) recovered pumping function better than the other (Case I at six months follow-up EF = 38, Case IV at six months follow-up EF = 47). The segmental extent of the scarring for these two cases can be seen in the Appendix of this doctoral research, Table A.3 (acute) and Table A.4 (at six months). The proposed method identified the case that recovered better as having higher peak strain, as seen in Table 5.1. It is worth noting that for both patients the EDV and ESV were abnormal, when compared against charts for normal values in healthy population [23], indicating cardiac problems beyond the myocardial infarction.

For Case OxAMI00021, we found that the radial strain curves have a range of peak values between 39% and 97% as shown in Figure 5.3, where the lower value is believed to be caused by pathology. Cases OxAMI00040, OxAMI00069, OxAMI00092, and OxAMI00126 were excluded due to severe slice misalignment, detected in visual assessment. For these four cases, the registration algorithm failed to converge, therefore the strain analysis was not performed. For visualisation purposes, a set of nine cases are presented in Figure 5.3 for the cohort-wide generated PCA and Figure 5.4 for individually generated PCA, summarising the mean strain curves for each cluster, as well as k-means labels for each case.

The post-processing was done using Matlab and Python. The average processing times using a Intel i7, 16GB (RAM) and 64-bit Windows operating system, for 25 volumes of a typical dataset are: complete cardiac cycle displacement curves - approx 1h; complete cardiac cycle strains computation per 25 volumes - approx 134s.

A segmental distribution can be seen in the Table 5.2, for each of the OxAMI cases. In some of the cases the left ventricular masks were not segmented at each slice, furthermore, for one of the cases, OxAMI0015 the LV mask was not there at all. Therefore this case was excluded from the study.

All patients had a positive LGE with a LV% $28 \pm 14\%$ with ejection fraction (EF) of $46 \pm 8\%$. Using the proposed method, the average percentage per patient

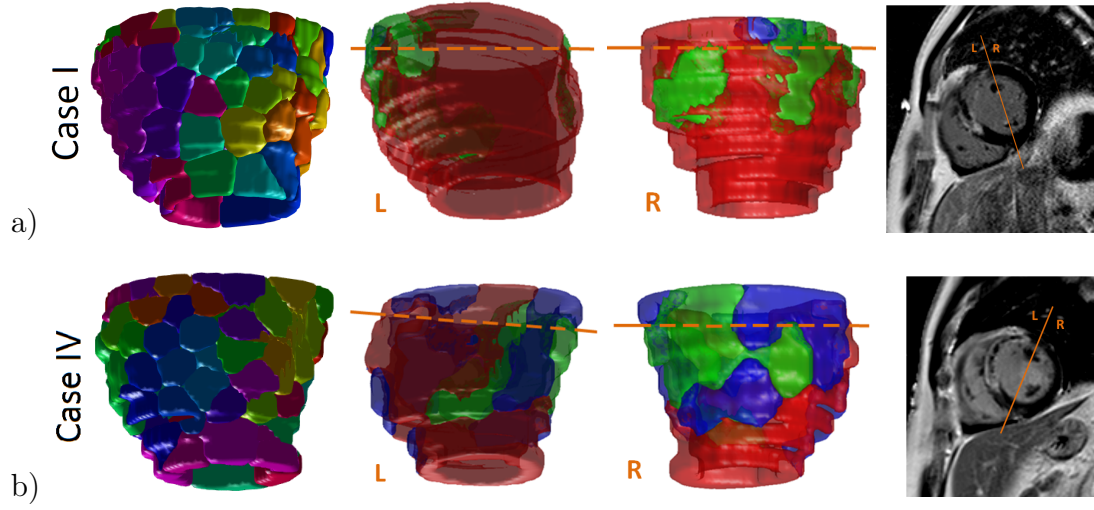


Figure 5.5: 3D rendering of a) Case I (OxAMI00021 acute) and b) Case IV(OxAMI00070 acute): From left to right: Left ventricle supervoxels generated using the first three PCA modes of variation on individual strain curves. Tissue clustered into three clusters using k-means, septal view (L=left). Tissue clustered into three clusters using k-means, lateral view (R=right). Corresponding LGE image.

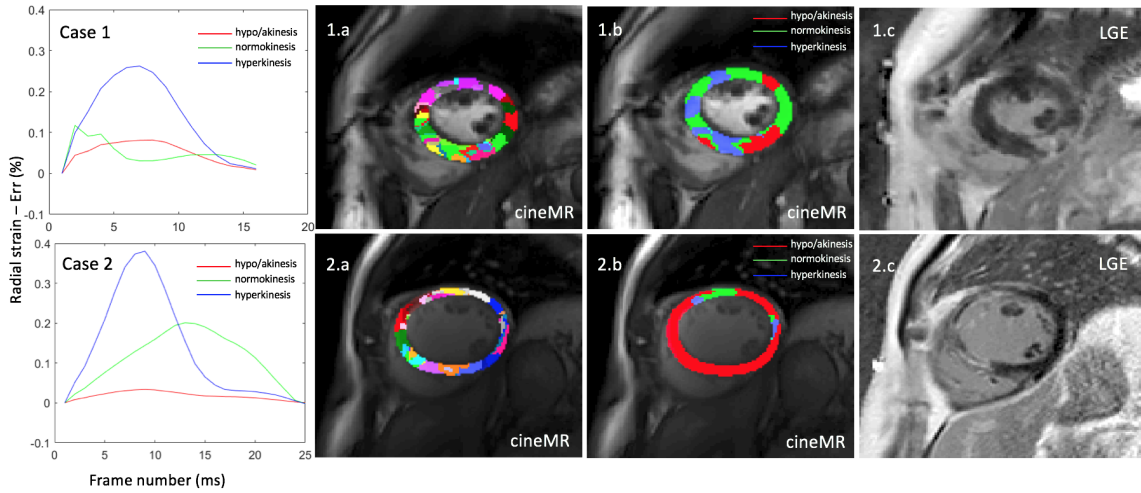


Figure 5.6: ROI based assessment of wall motion abnormalities using maskSLIC clustering method: Exemplary cases. From left to right: Panels Case 1. and Case 2. mean radial strain curve per cluster; Panels 1.a and 2.a colour coded map showing regions of myocardium with similar values of radial strain (Err) as assessed from cine images; Panels 1.b and 2.b: colour coded mask showing the final division of the myocardium in normokinetic (green), hyperkinetic=blue and hypo/akinetic=red regions of interest, based on differences in Err in local regions; Panels 1.c and 2.c corresponding LGE images.

Study	minErr	midErr	maxErr
oxami00004	0.04	0.27	0.35
oxami00006	0.05	0.015	0.25
oxami00015	0.05	0.57	0.99
oxami00016	0.01	0.1	0.11
oxami00021	0.03	0.2	0.38
oxami00040	rejected - bad slice missalignment		
oxami00053	0.02	0.19	0.28
oxami00058	0.03	0.15	0.29
oxami00064	0.04	0.14	0.35
oxami00069	0.02	0.11	0.36
oxami00070	0.01	0.11	0.74
oxami00073	0.08	1.14	2.18
oxami00092	0.06	0.67	1.08
oxami00094	0.03	0.16	0.59
oxami00095	0.03	0.24	0.31
oxami00097	0.07	0.33	1
oxami00104	0.08	0.12	0.26
oxami00108	0.11	0.37	0.74
oxami00126	0.06	0.17	0.4
oxami00131	0.07	0.36	0.48
Study average	0.059333	0.361	0.742667

Table 5.1: Radial strain (Err) for each of the three clusters. Presented here for all the 20 patients at first visit, the acute stage of the myocardial infarction. Cases OxAMI0015, OxAMI0073, OxAMI0092 are where the registration algorithm failed to compute the displacement curves, due to slice misalignment. The LV mask was also not completely segmented for there cases. Case OxAMI0040 was rejected from the study due to severe slice misalignment.

Study	Radial strain															
	Segment number - mask	SLIC tissue representation (% of kines)	normokinesis - hyperkinesis - hypokinesis													
AHA segments	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
oxami00004	0-0-100	0-20-80	3-35-62	0-0-100	4-36-60	0-12-88	0-6-94	0-2-98	0-2-98	0-12-88	0-19-81	0-16-84	9/22/69	4-35-61	0-4-96	0-0-100
oxami00006	82-8-10	no mask	100-0-0	70-15-15	48-10-42	94-6-0	57-0-43	88-0-12	100-0-0	86-14-0	97-3-0	78-0-22	82-0-18	100-0-0	100-0-0	85-0-15
oxami00015								mask not complete								
oxami00016	14-57-29	58-42-0	0-98-2	46-54-0	42-32-26	22-53-25	54-9-37	56-38-6	0-92-8	0-68-32	5-77-18	0-56-44	29-71-0	6-67-27	0-83-17	0-75-25
oxami00021	4-22-74	0-79-21	0-100-0	0-100-0	41-59-0	0-73-27	16-65-19	0-100-0	0-100-0	0-100-0	24-68-8	0-58-42	0-100-0	0-100-0	1-99-0	0-100-0
oxami00040							rejected from study due to bad slice									
oxami00053	98-0-2	81-0-19	100-0-0	100-0-0	73-0-27	65-26-9	67-0-33	100-0-0	100-0-0	84-0-16	90-0-10	67-0-33	100-0-0	100-0-0	100-0-0	89-11-0
oxami00058	71-4-25	69-7-24	83-7-10	80-0-20	82-14-4	52-18-30	96-1-2	99-0-1	98-0-2	93-0-7	100-0-0	41-51-8	100-0-0	81-0-19	90-0-10	89-0-11
oxami00064	100-0-0	29-71-0	56-44-0	99-1-0	100-0-0	79-0-21	96-0-4	88-12-0	100-0-0	54-46-0	90-10-0	83-0-17	100-0-0	100-0-0	39-61-0	54-46-0
oxami00069	0-0-100	38-0-62	0-0-100	0-0-100	24-0-76	52-0-48	51-0-49	42-2-56	0-0-100	5-0-95	25-0-75	27-0-73	60-0-40	8-0-92	0-0-100	13-0-87
oxami00070	80-8-12	100-0-0	61-39-0	91-9-0	94-6-0	100-0-0	100-0-0	65-35-0	50-50-0	76-24-0	26-74-0	83-17-0	100-0-0	91-9-0	98-2-0	100-0-0
oxami00073	100-0-0	100-0-0	100-0-0	100-0-0	100-0-0	100-0-0	100-0-0	100-0-0	100-0-0	100-0-0	100-0-0	100-0-0	100-0-0	88-0-12	100-0-0	100-0-0
oxami00092	83-17-0	97-3-0	58-42-0	100-0-0	100-0-0	100-0-0	59-41-0	100-0-0	91-9-0	100-0-0	100-0-0	94-6-0	100-0-0	100-0-0	100-0-0	100-0-0
oxami00094	19-80-1	50-40-10	15-84-1	32-68-0	4-96-0	47-54-0	18-82-0	40-60-0	43-57-0	10-90-0	23-77-0	28-72-0	7-93-0	22-49-29	0-100-0	40-60-0
oxami00095	93-0-7	100-0-0	70-0-30	100-0-0	32-0-68	72-23-5	100-0-0	100-0-0	100-0-0	94-0-6	70-0-30	98-2-0	100-0-0	100-0-0	72-0-28	93-0-7
oxami00097	0-100-0	0-100-0	0-100-0	0-79-21	0-100-0	0-100-0	0-100-0	0-100-0	0-90-10	0-100-0	0-78-22	0-100-0		no mask		
oxami00104	43-20-37	35-29-36	30-0-70	63-17-20	57-8-35	50-10-40	57-43-0	53-47-0	32-55-13	18-22-60	77-0-23	63-0-37	54-46-0	94-6-0	100-0-0	90-4-6
oxami00108	0-0-100	0-0-100	11-11-78	5-0-95	0-0-100	0-0-100	0-0-100	0-0-100	17-8-75	0-0-100	0-0-100	0-0-100	0-0-100	0-0-100	0-0-100	0-0-100
oxami00126	74-26-0	77-20-3	76-24-0	100-0-0	71-29-0	100-0-0	85-0-15	32-4-64	98-2-0	100-0-0	100-0-0	100-0-0	46-44-10	100-0-0	100-0-0	100-0-0
oxami00131	100-0-0	57-40-3	78-7-15	100-0-0	82-0-18	100-0-0	100-0-0	67-14-19	100-0-0	100-0-0	100-0-0	100-0-0	100-0-0	100-0-0	100-0-0	100-0-0

Table 5.2: Segmental representation of the distribution of classes (%) for each k-means cluster for the OxAMI acute myocardial infarction and six months follow-up patient study. Cases in yellow did not have complete masks manually segmented by an image analyst. The case in orange was excluded from the study for severe slice misalignment.

of myocardium with decreased radial strain (Err) was $84 \pm 11\%$ and significantly larger than the LGE extent ($p=0.00013$ using the Wilcoxon Signed rank test). The radial strain concept was presented in detail in Chapter 3. The regions of reduced contractility were co-localised with LGE positive regions (degree of concordance: 87%) (Figure 5.6). The Err in regions with different degrees of LGE segmental damage fraction are: $Err = 8 \pm 4\%$ in segments with $\leq 50\%$ LGE, $Err = 6 \pm 4\%$ in segments with $51\% < LGE \leq 75\%$ and $Err = 3 \pm 3\%$ with $LGE > 75\%$.

We found that the peak radial strains for each k-means labels, for each patient (represented by symbols) varied between frame 4 and frame 14, while the end systolic frames (shown in grey) were frame 8 to frame 10. This is an indicator of pathology, as confirmed with LGE, and it can be seen in Figure 5.8.

5.5.6 Discussion

The rationale for choosing LGE to confirm the location of the scar identified using the proposed method is that at the moment LGE represents the gold standard in scar identification using MRI. However, this approach is not a one to one validation of the scar tissue identification using the proposed method. While a direct correlation can be observed using the proposed method and LGE imaging, we observed that using the proposed method, the strain prediction encompasses the LGE scar region. This is in accordance with published reports showing that LGE displays limited agreement with endocardial and epicardial scars [230, 208], where its strength relies in the detection of transmural scars. In the same work [230] it was shown that quantitative strain analysis has higher sensitivity and accuracy than qualitative wall motion assessment done by visual assessment consensus. Using the proposed method there were no regions of false positive (identified as scar using maskSLIC on the strain curves) when compared with LGE. All LGE positive regions corresponded to a decrease in strains. Furthermore we observed areas of hyperkinesia directly opposite to the location of the scars in the acute presentation, indicating perhaps

that those areas may be compensating for the loss of contractility [54], however further investigation is required.

We believe that assessing the intra-patient variability provides a more personalised way of assessing individual dynamics of the pathological heart.

We argue that while the 17 segments AHA model is very useful for the anatomical localisation of the infarction, this approach can introduce errors by not taking into consideration features like time to peak, or peak strain value for individual voxels, or averaging curves with different peak times into a low peak strain curve, which might or might not be indicated by the total average of the segment. Time to peak can be a powerful marker to quantify the LV dyssynchrony [182], with one potential application being in quantifying the dyssynchrony to predict risk of ventricular arrhythmias [108]. Using a parcellation approach, like 3D modified SLIC, gives us the possibility to investigate individual voxels behaviour and subsequently group them according to similar motion patterns. Regional assessment of the wall motion and implicitly the estimation of the scar extent is becoming a trend in the CMR field, with substantial work on the subject being proposed recently [224, 214]. On the clinical side, tissue tracking is becoming a popular method of assessing wall motion [48, 174], gaining popularity over tagging MR, due to its availability as well as the fact that it can be computed from cine MR images, without the need to acquire new sequences for the purpose of strain analysis.

In healthy individuals it is known that the peak radial strain should correspond with the end of systole. For our cohort, as an indicator of pathology confirmed with scar in LGE images, the peak radial strain is either earlier or later than end of systole, indicating overload or late contraction for some of the tissue regions (Figure 5.8).

For this work we used radial strain, however, in the future we consider introducing both radial and circumferential, as well as longitudinal strain in the classifier to generate the supervoxels. This would then lead to a more comprehensive quantifi-

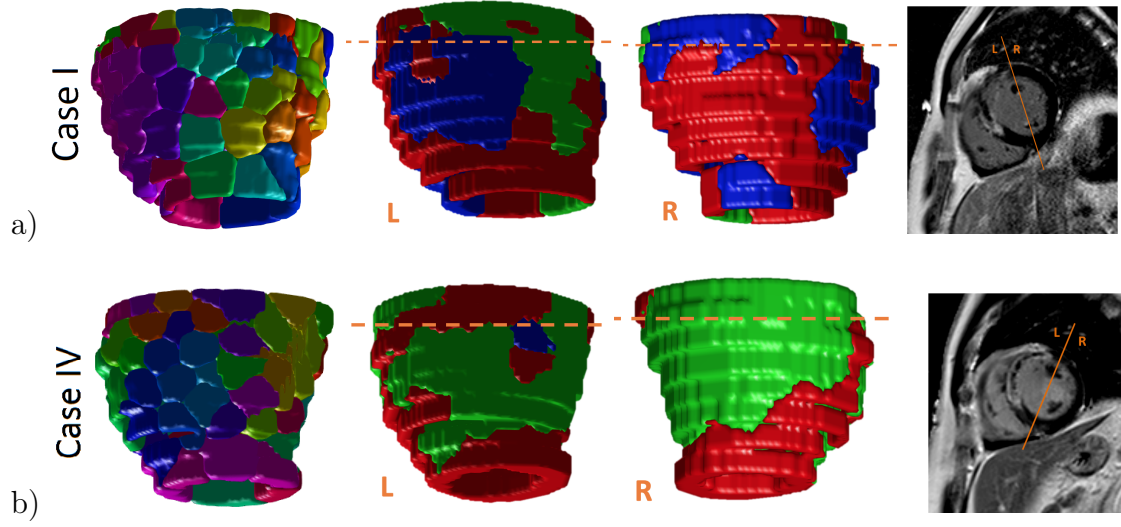


Figure 5.7: 3D rendering of a) Case I (OxAMI00021 acute) and b) Case IV (OxAMI00070 acute): From left to right: Left ventricle supervoxels generated using the first three cohort-wide PCA modes of variation on individual strain curves. Tissue clustered into three clusters using k-means, septal view (L=left). Tissue clustered into three clusters using k-means, lateral view (R=right). Corresponding LGE image.

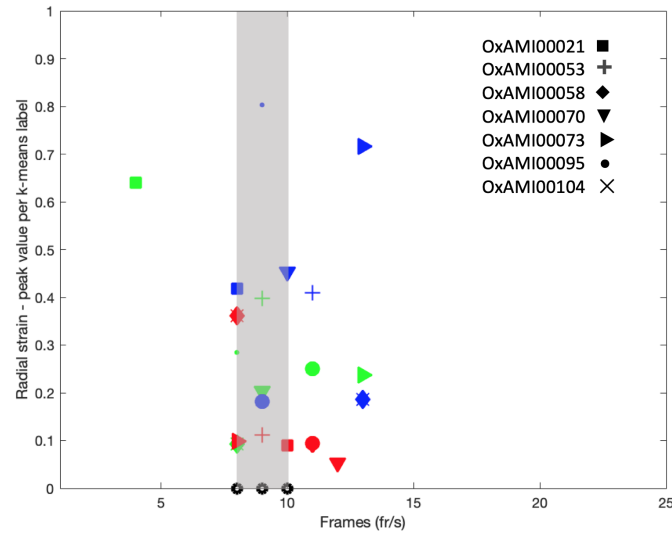


Figure 5.8: Radial peak strain for each k-means label for each patient. In grey is the range of end systolic frames for the cohort. For healthy controls it would be expected that the radial peak systolic strain would fall within the grey area, but for pathology it is expected to happen before end systole, indicating an early overload or late contraction for areas of tissue within the myocardium,

cation of the subtle wall motion abnormalities. For example, mid-wall fibres mostly contribute to circumferential strain, the presence of mid-wall fibrosis in non-ischemic heart disease (NIHD) has shown to affect circumferential strain, while longitudinal and radial strains seem to be normal [196], making circumferential strain a marker for detecting NIHD. Furthermore, the interventricular septum accounts for a significant part of global right ventricular (RV) function, mainly through its longitudinal shortening. Therefore making longitudinal strain a potential early detection marker of the RV pumping function [104]. The left ventricle was chosen for this study due to relatively easy segmentation compared to the RV, however, we consider extending the method to the RV in the future.

This work has the potential to become a semi-automated tool, where clinicians could interact with the regions of supervoxels, and even perhaps use the same regions over time to quantify change.

Strain calculation methods previously reported in the literature do not always agree on maximum peak strain. However, they report similar order of magnitude strains, with consistent strain curves shape morphology across methods. Maximum peak strain can vary depending on the registration algorithm used, whether the algorithm has a regularisation term or not, as explained in previous work [201]. Registration algorithms that have no regularisation term tend to show higher maximum peak strain values, while registration algorithms that have a regularisation term tend to underestimate the radial strain in particular.

The proposed method is suitable for segmentation applications where quantification of tissue properties within a ROI is required. Local clustering provides an objective and robust metric for assessing localised changes in the myocardium, overcoming the averaging effects of segmental analysis, as in the case of 16 AHA segments model and hence it could potentially be a more accurate assessment tool for the extent of damage post myocardial infarction, including the extent of area at risk and clinical improvements post treatments.

5.5.7 Limitations

K-means clustering represents a limitation at the moment, due to a predefined number of clusters. In future, there is potential for considering more features to characterise the strain curves. Once we have acquired clinical delineations of the infarcted regions we can extend this approach to supervised learning, however there is uncertainty in the clinical delineation in LGE, therefore, region-based cine MRI analysis offers an alternative. Also, a comparison of our method with other existing methods for scar quantification, will be considered.

In the absence of a true validation metric, LGE was chosen to confirm the location of the scar when using the proposed method. It is however a limitation of the methodology since it is known from previous research that while the scar is contained within the region classified as damaged (low tissue strain compared with normal), it is not limited to the LGE positive. Therefore a better assessment metric needs to be considered in the future, such as histology or ex-vivo mechanical assessment in animal studies.

5.5.8 Conclusion

Cine MRI is the most commonly used MRI imaging sequence in cardiac MRI imaging. Although currently used for the assessment of the global heart function and anatomy, it presents a great potential in the assessment of cardiac tissue structural changes. One of the advantages over techniques like tagged MRI, is the general availability, limited need for user interaction as well as the reduction of study time. However, low resolution in the z direction and limited texture analysis inside the myocardium, could potentially become limitations in using the cine MRI sequence for the computation of the strains. Furthermore, building a visualisation colourmap, can help provide a more straight forward representation of the extent of pathology [97], rather than segmental representation. This can potentially be of more accurate usage in treatment planning then the currently used AHA segmental method.

Chapter 6

Myocardial tissue parcellation into 16 segments using maskSLIC - replicating the clinical AHA 16 segments model

Iulia A. Popescu, Benjamin Irving, Christopher Kelly, Alessandra Borlotti, Keith M Channon, Erica Dall’Armellina, Vanessa Ferreira, Stefan Piechnik and Vicente Grau. Left ventricular division based on local similarity in strain, using maskSLIC supervoxels - Replicating the clinical AHA 16 segments model approach. Journal of Medical Image Analysis (MIA), in preparation for peer review, November 2019

6.1 Introduction

This Chapter consolidates the idea of using a pixel based analysis to investigate the cardiac wall motion abnormalities. In this section, we propose using the maskSLIC framework, explained in **Chapter 4**, in a structure that allows us to replicate the clinical division of the left ventricle (LV) into 16 segments, in accordance with the AHA LV division model, and therefore accounting in the strain quantification model for the coronary territory as well.

6.2 Importance

An accurate assessment of the myocardial injury either post myocardial infarction or due to other pathologies, such in the case of hypertrophic cardiomyopathy (HCM), is crucial in improving the long term outcome of the cardiac patients. An accurate estimation of the scar size or diffuse fibrosis extent is crucial in improving patient risk stratification. Used in conjunction with clinical measurements, such as the left ventricular ejection fraction and end-systolic volume index, this framework can potentially provide a powerful evaluation metric of the mortality risk after hospital discharge [21]. This is now a well known fact in the clinical world and well tested on large patient groups follow-ups.

The left ventricle represents the most muscular chamber of the heart, that pumps the blood with oxygen to the body through the aortic artery. In order to improve the clinical outcome of cardiac patients, it is vital to salvage as much of the left ventricular myocardium as possible. Sixteen years ago a model was proposed by the American Heart Association Writing Group on Myocardial Segmentation and Registration for Cardiac Imaging [26] named AHA 16 segments model for standardised myocardial segmentation, to divide the left ventricle into regions based on the coronary territories. The coronary arteries are the vessels that lay on the surface of the heart and perfuse the heart muscle with blood. Most individuals have three coronary main arteries: the right coronary artery (RCA), the left circumflex artery (LCX), and the left anterior descending artery (LAD). They arise from two stems: one for the LAD and LCX and one for the RCA branch [211]. In this Chapter we explain what the AHA model is, together with its limitations, and propose a novel approach in dividing the left ventricle into locally similar regions using this model, but based on patient specific local similarity in strains, rather than a geometrical division based on general anatomy.

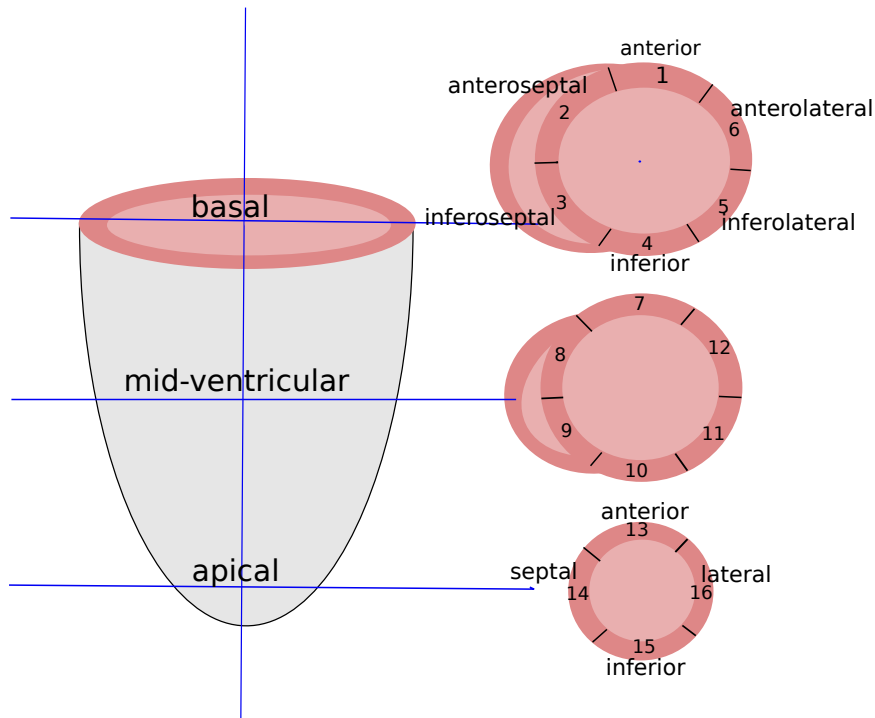


Figure 6.1: The AHA 16 segments model for left ventricular division according to Cerqueira and et al. [26].

6.3 AHA 16 segments model from a clinical perspective and its limitations

The American Heart Association (AHA) 16 segment model [26] represents the gold standard for dividing the left ventricle into regions, or segments, for clinical assessment. A graphical representation of the AHA model can be seen in Figure 6.1. The guidelines for dividing the left ventricle were originally published to standardise the division of the left ventricle. However, it can be argued that general geometrical division over a relatively large area is perhaps not the best, most accurate, approach for accurately assessing the extent of tissue damage and tissue remodelling due to myocardial injury, mechanical overload, or a combination of the two [170].

The AHA 16 segments model was originally designed to be associated with coronary territories, however, as it was demonstrated in a large study using contrast

agent administration, only 67% of the total segments assessed could be associated with a coronary territory [157]. A subsequent study [147] performed on 93 subjects in acute stage of myocardial infarction and imaged after percutaneous coronary intervention were able to match 76% of the segments with coronary territories. When compared with hyperenhancement (HE) patterns in late gadolinium images, the highest match was achieved for the LAD, followed by RCA. The LCX territory had the worst match with HE (57%). According to infarct related artery (IRA), 49.5 % of the LCX segments were found to be not corresponding to the AHA assignment. Particularly low correspondence was found for the mid-anterolateral (segment 12) and apical lateral (segment 16) segments, 20% and 29.6%, respectively [147].

In practice the anatomy of the coronary vessels varies between patients, and that is recognised to be the biggest limitation of the the AHA model, with a study finding large disagreements in mid-anterolateral (12) and apical lateral (16) segments, originally assigned to the LCX artery as well as the inferoapical segment originally attributed to the RCA. [229].

6.4 Local strain similarity guided AHA 16 segments left ventricular division

In this section we propose a modification to the maskSLIC clustering algorithm, as it was explained in Chapter 2, Section 2.4.2 of this Thesis, from using the Euclidean distance to place the supervoxels centres as far as possible from the boundaries and from each other, to using the 16 segments AHA model to generate the cluster centres. We then generate the supervoxels based on local similarity in radial strain. We present an average value per segment based on radial strain similarity rather than averaging over an annulus sector. This approach can potentially lead to a more patient specific assessment for the quantification of the extent of tissue damage post myocardial infarction.

In short axis view, the centres of each supervoxel are defined using the 6 AHA

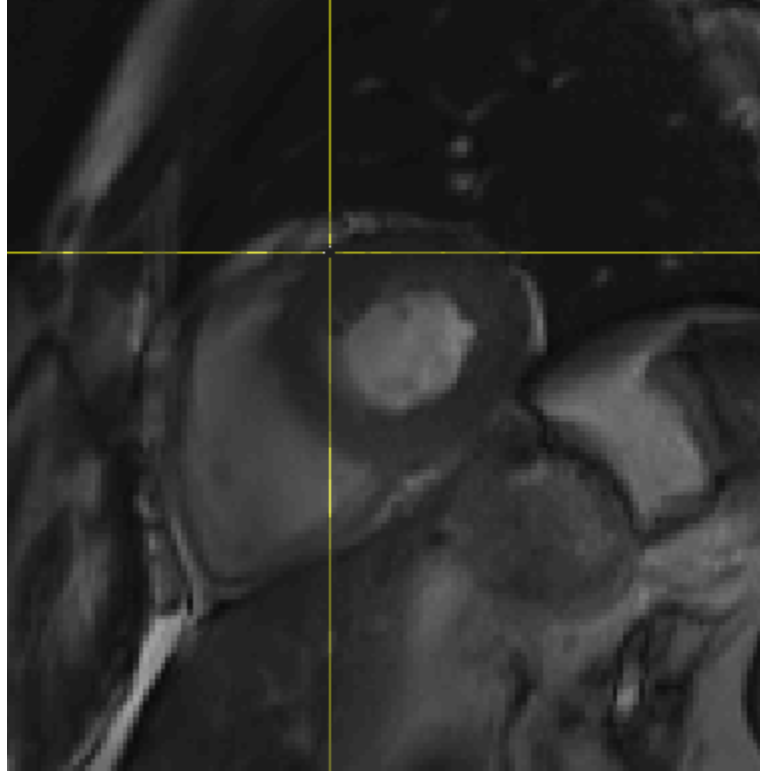


Figure 6.2: Left to right ventricle anterior insertion point has been manually set and used subsequently to decide the start point of the AHA segment division, alongside with the centre of the left ventricular blood pool.

segments (for basal and mid-ventricular slices), at 60° starting from the left to right ventricular anterior insertion point and the centre of the left ventricular blood pool. The anterior insertion point, as well as the left ventricular mask has been placed and drawn manually (as seen in Figure 6.2 and Figure 6.3) and the centre of the blood pool was computed using the average x and y voxel coordinates corresponding to the left ventricular mask.

To compute the centroid for the myocardial ring, let us take x_i and y_i coordinates of each in-plane voxel $v(x_i, y_i)$ corresponding to the myocardial mask. Therefore the centre of the blood pool can be defined as:

$$\begin{aligned} x_{bpc} &= \frac{\sum (x_i)}{n} \\ y_{bpc} &= \frac{\sum (y_i)}{n} \end{aligned} \tag{6.1}$$

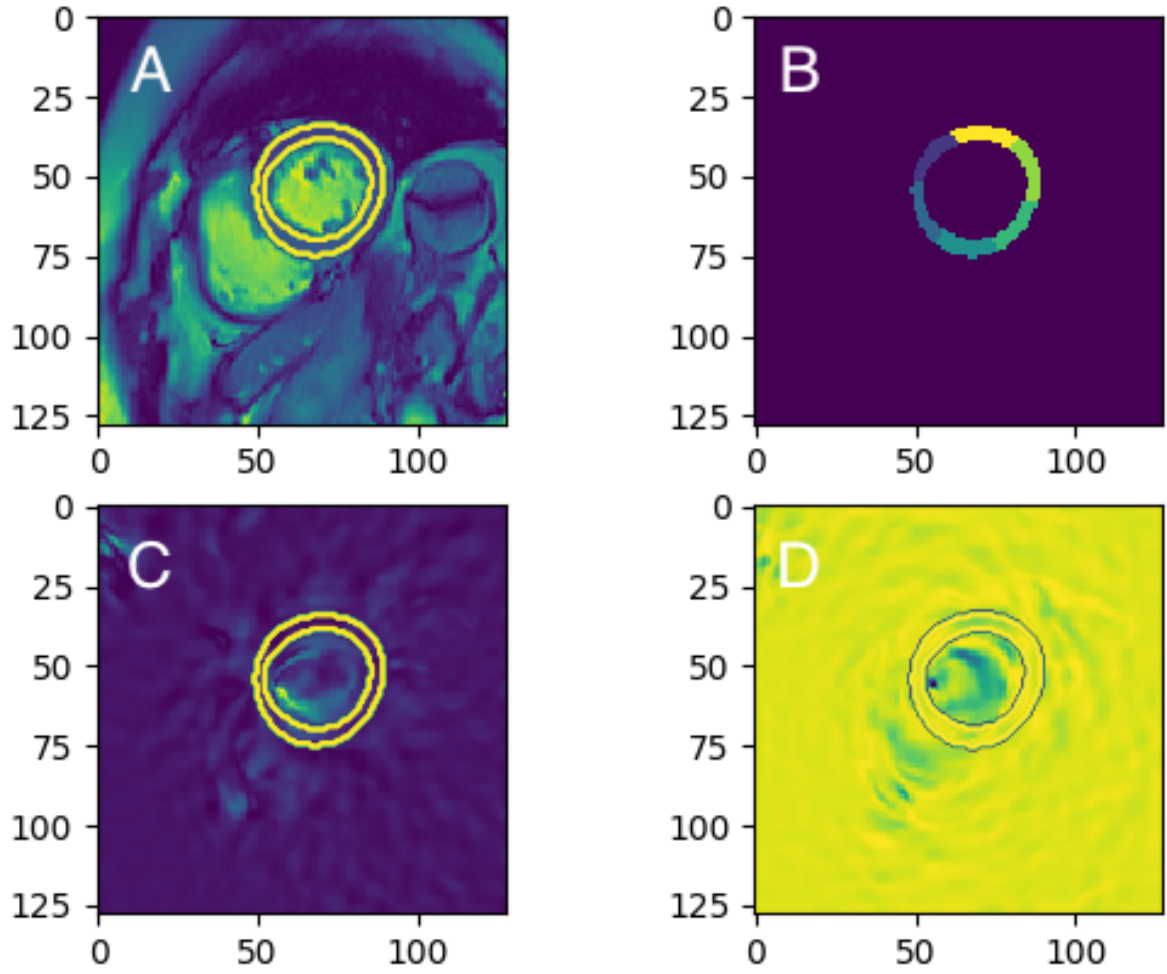


Figure 6.3: Left ventricular mask over the corresponding ROI in short axis slice (A). The original AHA segments model (B). The left ventricular mask over the radial strain field corresponding to the data ROI (C). The left ventricular mask over the circumferential strain field corresponding to the data ROI (D).

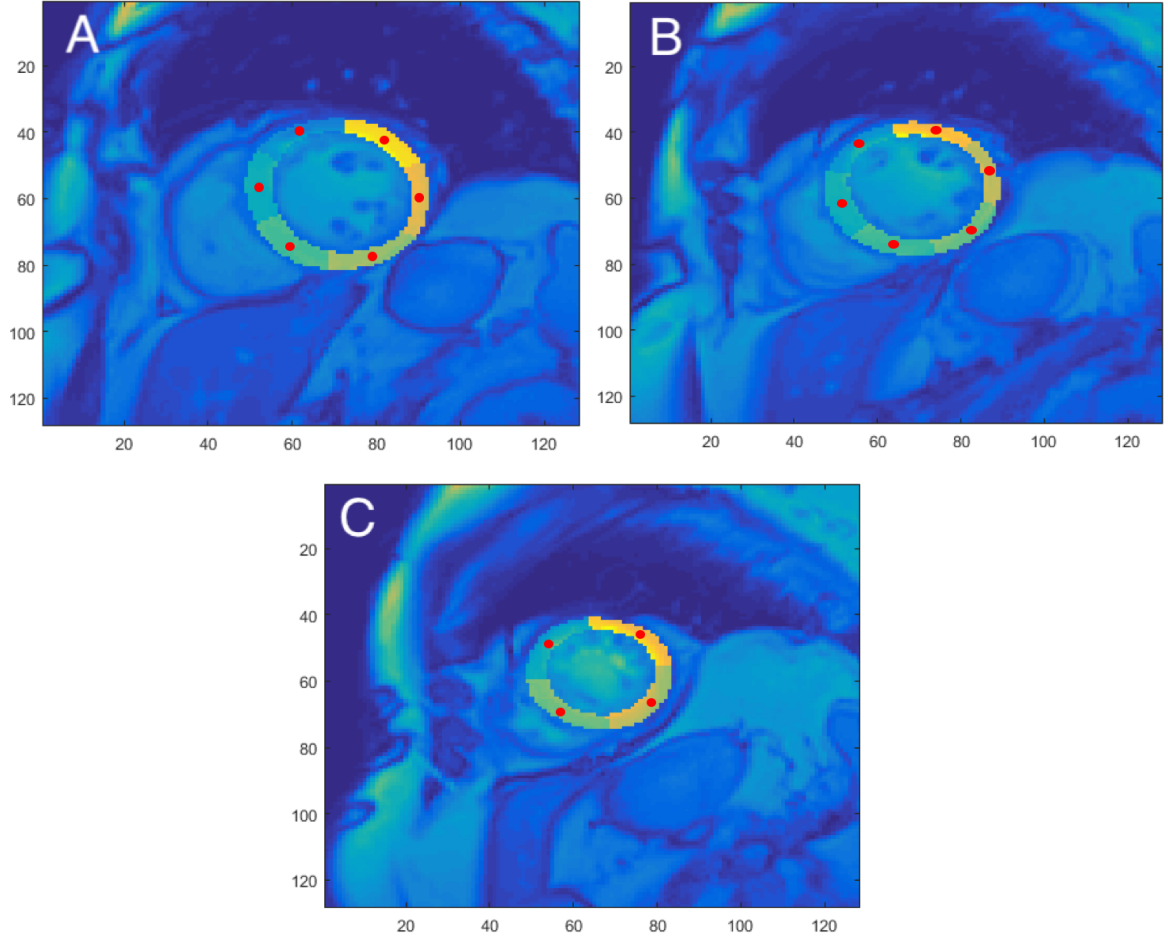


Figure 6.4: Two dimensional representation of the AHA 16 segments model for basal (A), mid-ventricular (B), and apical (C) slices. Represented together with cluster centres attribution using the maskSLIC algorithm. This is a manual contouring of the left ventricle and a manual setting of the left to right anterior insertion point. The centre of the blood pool is computed by averaging the in plane coordinates of the left ventricular mask.

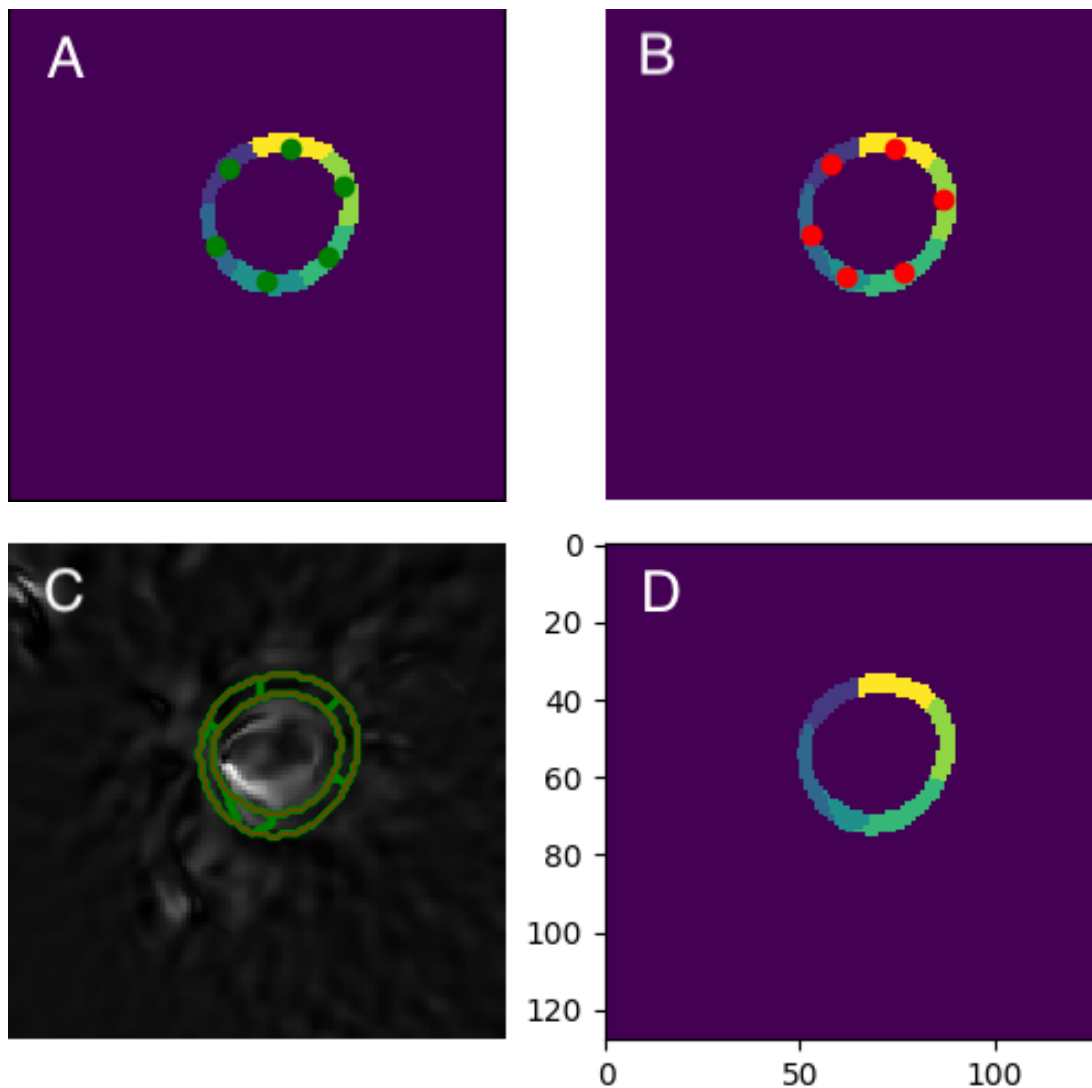


Figure 6.5: Original AHA 6 segments division in short axis view and placement of the centres of the supervoxels (A). Proposed maskSLIC for segmental division centres of the supervoxels (B). Proposed segmental maskSLIC over the radial strain field (C). Proposed maskSLIC segments (D).

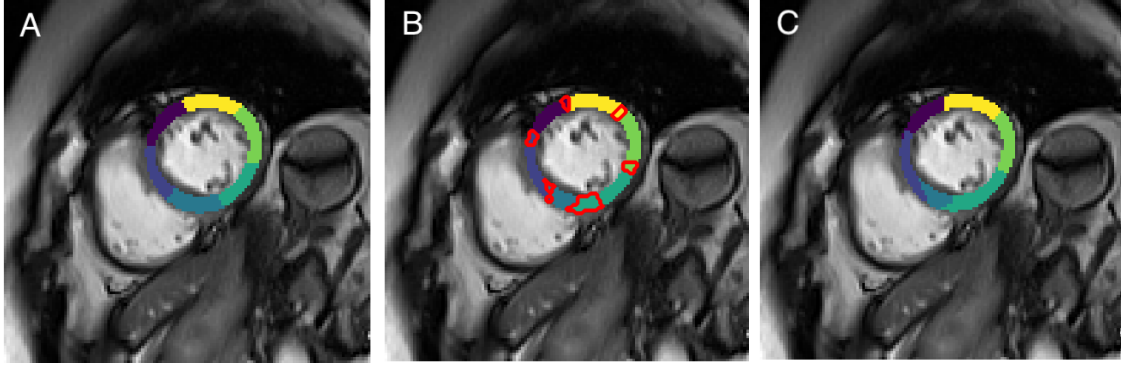


Figure 6.6: AHA 6 segments division in short axis view overlap with corresponding data ROI (A). Overlap between the original AHA segments and the proposed maskSLIC segments, and non-overlapping areas between the two highlighted in red (B). Proposed segmental maskSLIC over the corresponding short axis view for data ROI (C).

where x_{bpc} and y_{bpc} are the x_i and y_i coordinates of the voxel corresponding to the centre of the blood pool, and n represents the total number of voxels corresponding to the myocardial mask.

As an additional step, x_{bpc} and y_{bpc} are rounded to the nearest integer.

The centroid of the myocardial ring and the left to right ventricular anterior insertion point are used to determine the start position of the second AHA segment in short axis view. The end of the second segment is represented by $\theta = 60^\circ$. Subsequent segments are defined at every $\theta = 60^\circ$ in counter clockwise direction.

The centroid (x_{sector}, y_{sector}) for each annulus sector (AHA segment) is used to generate the centre of each maskSLIC segment supervoxel and it is computed as follows:

$$\begin{aligned} x_{sector}(j) &= \frac{\sum (x_j MyoSect)}{n_j} \\ y_{sector}(j) &= \frac{\sum (y_j MyoSect)}{n_j} \end{aligned} \quad (6.2)$$

where i represents the respective annulus sector, $x_j MyoSect$ and $y_j MyoSect$ represent the in plane x and y coordinates of each voxel corresponding to sector j

and n_j is the number of voxels corresponding to sector j , $j \in [1, 16]$.

6.4.1 Materials

In this Chapter we use the OxAMI dataset, as presented in the Materials Section 5.4.2 of Chapter 5 of this doctoral research. The full details on the dataset used for this chapter, can be found in the Appendix A.2 of this doctoral research. For the work in this chapter, we use both the cineMRI images, as well as, Late Gadolinium Enhancement (LGE) images, in short axis (SA) view.

6.4.2 Methods

For this Chapter we used 4D radial strain volumes, as explained in detail in the Methods Section 5.4.3 of Chapter 5, in a supervoxel framework to cluster the left ventricle into locally similar regions, based on similarity in strains, and using a number of 6 regions in each 2D slice, for the basal and the mid-ventricular cine MRI short axis slices, and 4 regions for the apical slice. The left ventricular mask was manually segmented as explained in the Methods section of Chapter 5 of this Thesis. The segmental division using the AHA segmental model was performed in MATLAB using the anterior insertion point of the left ventricle.

We performed a paired t-test to provide a comparison of the quantitative strain metric within the comparable segments generated using the AHA segmental model and the maskSLIC segmental division proposed method. We used the mean radial strain curves for each segment with the full 25 time points (full cardiac cycle).

6.4.3 Results

The Dice overlap between the maskSLIC proposed method and the original AHA segmental model are presented in Table 6.1, for visualisation purposes at mid-ventricular short axis view for each of the short axis six segments. A correlation with segmental clinical late gadolinium enhancement (LGE) assessment presented

Oxford Acute Myocardial Infarction (OxAMI) clinical trial - acute stage						
	Segment 7	Segment 8	Segment 9	Segment 10	Segment 11	Segment 12
OXAMI0006	0.85	0.84	0.61	0.66	0.84	0.88
OXAMI0021	0.90	0.73	0.57	0.74	0.75	0.85
OXAMI0053	0.86	0.73	0.76	0.83	0.63	0.66
OXAMI0064	0.92	0.99	0.97	0.93	0.83	0.80
OXAMI0095	0.97	0.97	0.99	0.98	0.97	0.97
OXAMI0104	1.00	0.99	0.99	1.00	1.00	0.99

Table 6.1: Dice overlap (%) using the maskSLIC segments proposed method for left ventricular division based on local similarity in radial strains and the original AHA six segments at mid-ventricle, short axis view.

in Table A.3 from Chapter 4, Section 4.3. e.g. for case OXAMI0006 segments 9 and 10 appear to have lower Dice overlap with the original AHA segments, using the proposed method, while for LGE segments 8 and 9 seem to have the highest percentage enhancement using LGE. Therefore the proposed method shows some evidence that pathology may be found at the intersection of the two, in segment 9. In Figure 6.5 it can be seen that segments 8 and 10 move their borders towards the segment, where the pathology is located.

The paired t-test between comparable segments (six segments short axis view) was performed using the AHA segmental model and the maskSLIC segmental division proposed method on six patients, mid-ventricular slices. The results can be visualised in Table 6.2. A graphical representation for all the cases presented, can be seen in Figure 6.7 for all the segments generated. The segments are presented at mid-ventricular level. We found that the segments identified using the proposed method were significantly different ($p \leq 0.05$) than the ones generated using the AHA segmental division.

6.4.4 Discussion

It is important to mention that the proposed method using DICE as a similarity metric informs us when the strain based segmentation differs from the standard

	Segment 7	Segment 8	Segment 9	Segment 10	Segment 11	Segment 12
OXAMI0006	p≤0.05	p≤0.05	p≤0.05	p>0.05	p>0.05	p≤0.05
OXAMI0021	p≤0.05	p≤0.05	p>0.05	p≤0.05	p>0.05	p≤0.05
OXAMI0053	p≤0.05	p≤0.05	p≤0.05	p≤0.05	p>0.05	p>0.05
OXAMI0064	p>0.05	p≤0.05	p>0.05	p≤0.05	p≤0.05	p≤0.05
OXAMI0095	p>0.05	p>0.05	p≤0.05	p≤0.05	p≤0.05	p≤0.05
OXAMI0104	p>0.05	p>0.05	p≤0.05	p≤0.05	p≤0.05	p≤0.05

Table 6.2: Paired t-test analysis for the mean radial strain curve for each segment within the AHA model at mid-ventricular level and the corresponding maskSLIC segmental model using local similarities in radial strain.

AHA.

The method was however validated on a small dataset. With additional validation, the correlation of AHA segments with wall motion quantification using the proposed modified version of the maskSLIC algorithm can potentially provide a more accurate parcellation of the left ventricle, based on patient specific LV dynamics, rather than general geometrical divide.

Furthermore, potential combination of the proposed method with quantitative T1 and stress perfusion imaging can improve the quantification into the extent of the damage post myocardial infarction, and therefore potentially enable the pathway towards a better understanding of the mechanisms that lead to heart failure. This approach can be more relevant to clinical practice than Bai et al. [11], where a number of 17 clusters were chosen using a hierarchical clustering method, however, these clusters have no correlation with anatomical structures.

While in clinical practice the AHA 16 segments model continues to be used, there is great interest in automating the contouring process and segmental analysis, with previous work in this area proposing an automated segmental division by using landmark detection in a combination with a right ventricular mask [82], to determine the left to right ventricle insertion points. Therefore, one of the immediate next steps would be to include these automated landmark detection and LV contouring

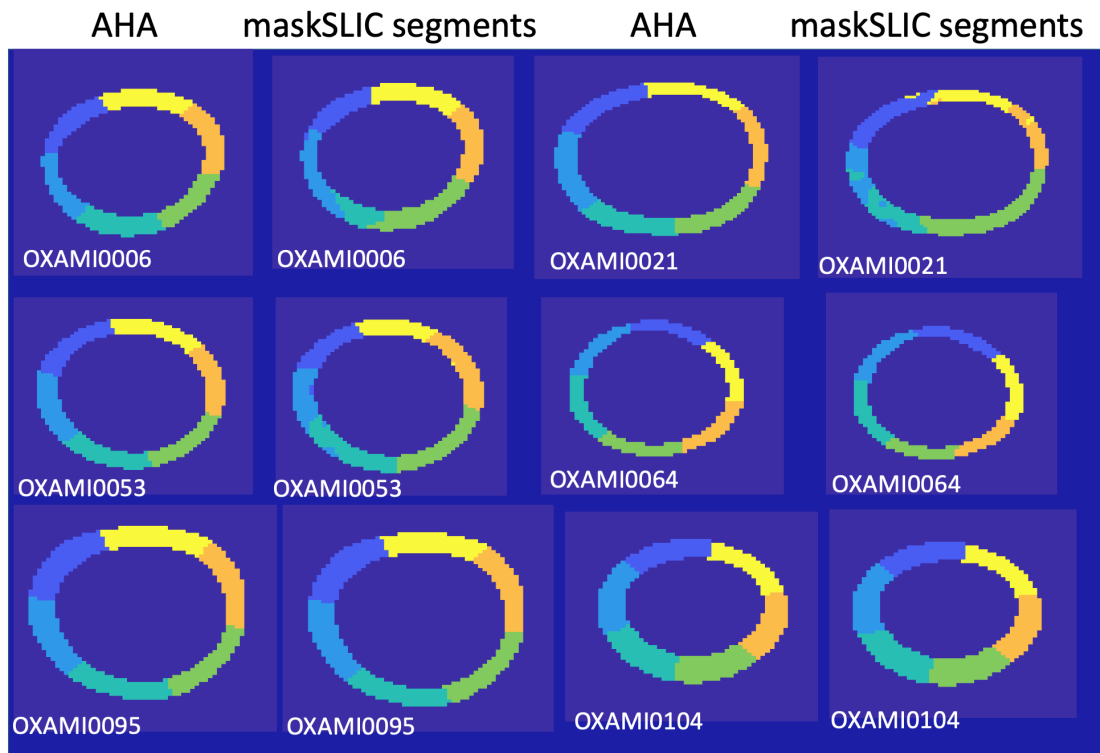


Figure 6.7: Segmental division at mid-ventricular level using the AHA segmental model and the proposed maskSLIC 16 segments model. Each case is presented for both the AHA division and the maskSLIC 16 segments division based on local similarity in radial strain. If the segments generated using the two methods look very similar, no scar it is present at that level.

methods into the pipeline to speed up the process as well as to decrease the inter-user variability inherently seen in manual segmentation approaches.

Future work will include the validation process of the proposed method using a quantitative metric between the new segmentations of the scar area, and the correspondent scar area from LGE imaging.

6.4.5 Limitations

One of the limitations of the method is that it was not tested in healthy controls, however it was observed that in myocardial infarction patients, in the absence of scar there is minimal difference ($p > 0.05$) between the proposed method and the conventional AHA segmental model used in clinical practice.

Not all the patient cohort data was available at the time of this analysis, due to data migration from MATLAB to Python for the AHA segments. This aspect is a limitation of the maskSLIC AHA segments generation segmentation pipeline. In the future we plan to extend the analysis to the whole cohort, using a different way of importing the segments directly from cvi42, without the need to generate them in MATLAB using the anterior insertion point.

Small pathologies, such as small subendocardial infarctions, might still be difficult to quantify based purely on cine MR images, and subsequent additional imaging techniques such as T1 quantitative mapping might be used in order to get as much complementary information as possible. Multi modality assessment might help tackling the size of the injury problem. However, for this problem to be addressed a dataset of tissue viability patients needs to be considered.

6.4.6 Conclusion

16 segments model generated based on local similarity in strain has the potential to improve the clinical analysis of wall motion displacement, by making it more quantitative as well as based on local similarity on tissue displacement properties,

rather than the current clinical standard, which is based on visual assessment. This can be a powerful tool for early detection of ventricular dysfunction, and eventually patient risk stratification. Patient risk stratification is of particular importance in hypertrophic cardiomyopathy where patients are exposed to increased risk of cardiac failure as well as sudden death [128]. Therefore a better understanding of the wall motion abnormalities can lead to a better, more personalised treatment for cardiac patients.

Chapter 7

Conclusion and future directions

This chapter provides conclusions of the work presented in this doctoral research, as well as, sets the context for future research and implementation steps required to transfer the proposed work to clinical practice. The chapter then looks at potential directions of research where the work presented in this thesis can be integrated to help clinicians improve patient diagnostic. We envisage that imaging tools for diagnosis and treatment personalisation, using data fusion (imaging and non-imaging biomarkers) and moving beyond the use of Gadolinium Based Contrast Agents (GBCA), will improve patient outcome and will be one of the key areas the field will focus on in the near future and beyond.

7.1 Thesis conclusion

In clinical practice Late Gadolinium Enhancement LGE scar quantification that is fast, reliable, and reproducible, is paramount. It is desirable that the contouring of the enhanced areas is consistent and free of false positive enhancements. In **Chapter 2**, of this doctoral research we took steps in providing a consistent approach to segment the scar from LGE images by removing the need of manual contouring a remote myocardium area and the necessity of manually remove areas of false positive enhancements thereafter.

One of the limitations of the proposed method is that it requires the Left Ventric-

ular (LV) contour. Manually segmented LV mask can include pixels corresponding to the blood pool, as well as, it can introduce intra- and inter-observer variabilities. Another limitation of the proposed method is the use of DICE as an evaluation metric. As we compare against a ground truth that has not been generated by manual contouring, but by using a remote area to extract the mean intensity value from and subsequently highlight every pixel that is more than five standard deviations from this mean. In the lack of a true ground truth this contour from clinical practice was used. However, in the future we plan to obtain manually generated contours of the scar in order to do an additional validation to the method. Independent testing of the method on a large patient cohort it is another step that will be taken in the near future. With steps taken in the direction of automated LV contouring and independent testing and validating on a large patient cohort, the method will be ready to be applied to clinical practice to provide a robust segmentation that will not be affected by intra- and inter-observer variability.

Registration plays a very important role in quantifying the motion of the myocardium over the cardiac cycle as shown in **Chapter 3** of this doctoral research. The multi step registration framework proposed in this chapter was found to provide an accurate estimate of the displacement curve corresponding to myocardial voxels. The proposed method was validated using manually placed markers on the cine images. We found that sometimes it can take a significant amount of time (up to 6 hours) to register a full 4D (3D+time) volume (interpolated in the z-direction using trilinear interpolation). Therefore one of the limitations of the proposed framework at the moment is the lack of optimisation enabling 4D registration to be performed in seconds or minutes. This would then make the method feasible for use in routine clinical practice. We see that with the advance of deep-learning based registration frameworks, the computation time requirement for such clinical practice applications will become feasible in the near future.

An accurate registration algorithm for this purpose can translate into a more

accurate assessment of the tissue functionality at a macro level. Obviously, aspects such as microvasculature obstruction are not taken into account here, however if combined with techniques such as quantitative T1 mapping, the proposed methods for assessing tissue functionality can potentially become a powerful tool towards patient specific myocardial tissue damage assessment.

Strain quantification is not currently used in clinical practice. However, in research centres Tagging MRI, and more recently feature tracking from cine MRI, are used to quantify the strain deformations. **Chapter 4** of this doctoral research introduces the theoretical concept of strain quantification and it's application to cardiac image analysis. Strain analysis can potentially play an important role in the assessment of cardiac mechanics and therefore may improve the diagnosis of left ventricular diastolic dysfunction.

A more accurate quantification of the myocardial tissue can potentially lead to a better, more personalised, treatment and patient outcome. The aim of this work was to take steps towards regional quantification of the extent of tissue damage post-myocardial infarction to enable a more patient specific assessment.

Clustering based on local similarity in strains can potentially become a powerful marker for the assessment of ventricular dysfunction without the need of administering contrast agents, as shown in **Chapter 5** of this Thesis. This statement is further supported by initial proof of concept presented in **Chapter 6**, as well as a great body of evidence reported in the literature. Currently, the pixel based dynamics of the heart, is not well examined. This Thesis took steps to address the limitation by proposing a 4D (3D+time) pixel based map to quantify the motion of the left ventricle. Some of the limitations of the proposed method are the lack of actual ground truth, in which case LGE was used to confirm the location of the scar. However the size of the damaged tissue could not be quantitatively validated. While it was observed that the scar detected using LGE imaging, was contained within the region classified as damaged using the proposed method, the actual borders of

damaged tissue could not be validated.

DICOM data is difficult to read in a way that the data and the segmentations always overlap, therefore for some of the cases it was needed to do further rotation translation transformations, prior to the volume registration, in order to properly match the data volume (cine MRI) with the manual segmentations. 3D myocardial mask rendering from 2D DICOMs can sometimes be difficult in Matlab, therefore a more dedicated 3D rendering platform it is recommended in order to speed up the process and perhaps even use the proposed method at the time of scan. Once steps will be taken towards integrating commercially used modules to generate the 3D rendering of the myocardium, and additional validation of the proposed method will be performed independently on a large patient cohort, the method will be ready for clinical application.

An accurate regional analysis can provide a very powerful tool in patient risk stratification and therefore significantly improve the patient outcome as well as reducing the costs for the national health care services. Treatment based on individualised characterisation of the left ventricle for a particular patient may allow risk-stratification of heart attack patients into multiple, accurately defined, risk groups, with tailored treatment to achieve the best outcomes for that particular patient. Myocardial strain quantification is a sensitive biomarker that can be used for early detection of left ventricular impairment, and therefore can be a valuable biomarker for patient phenotyping and patient risk stratification.

Apart from the already well known localised pathologies such as myocardial infarction, it is now known that many diffuse pathologies, such as coronary artery disease (ischemic), hypertrophic cardiomyopathy (non-ischemic), and others, do not affect the cardiac function uniformly, but rather locally [64].

7.2 Future directions

The future of cardiac imaging looks bright, especially with the newly established large population studies such as the UK BioBank [188] health resource, which provide unparalleled opportunities for research. Within the UK BioBank database, an imaging subcohort of 100,000 volunteers with no apparent health or well-being problems are being scanned. Several other pieces of data (from questionnaires, blood samples, etc.) are also being collected simultaneously. The results obtained from these and other large studies may lead to better disease prevention and personalised treatments.

7.2.1 Short term

One immediate next step would be the quantitative validation on a larger dataset for the proposed method in Chapter 6. A subsequent step would be the quantification of the sliding motion [152] in the registration algorithm, and compare the results with the Log Demons algorithm used in this Thesis and the results presented in Chapter 3. Accurate quantification of the sliding motion is essential in the accurate quantification of the longitudinal strain. The longitudinal strain is emerging as an important biomarker for the evaluation of microvasculature obstruction [13], as well as in patients with suspected heart failure and normal ejection fraction [153], and cardiotoxicity prediction in patients with breast cancer [66].

One of the first subsequent short term goals is to investigate the myocardial scar heterogeneity using neural networks. One limitation here would be the lack of ground truth needed for validation. However, recent work [224, 225] shows a trend in the direction of scar contouring using neural networks, on a deep learning based framework.

Taking coronary territory into account using angiographic data [231], can provide a more accurate way of assessing ischemia in the absence of gadolinium enhancement.

Furthermore expanding the investigation into chronic infarction patients, as opposed to acute infarction patients such as the OxAMI dataset, can help shedding some light into the complex mechanisms of heart failure to improve patient risk stratification.

Further automation of the pipeline can speed up the post processing, helping translate this method into clinical practice. Using a deep learning approach to segment the myocardium, identify the left to right ventricle anterior insertion point, and place the segmental model automatically, will decrease considerably the inter- and intra- user variability and allow for large multi centre studies.

7.2.2 Mid and long term

It is clear that machine learning approaches, such as using Deep Learning is the key to a more accurate pattern recognition in strain clustering, which is why, once the standardisation of strain values is decided by the research and clinical communities, we plan using U-nets to train, test and validate clustering methods to determine wall motion within the left ventricle. With the advance of MRI image acquisition, smaller structures, such as left atrium or the right ventricle, will also be possible to analyse, using strain quantification methods to assess wall motion abnormalities. Artificial intelligence machine learning approaches already play an increasingly important role in cardiac image segmentation [204, 116]. A combination of deep learning and a deformable model of the heart [9], has already been proved to be efficient in segmentation tasks. By using cardiac models [12] in combination with deep learning frameworks, we can potentially predict more accurately the risk of cardiac patients to develop cardiac failure or sudden heart death. Furthermore, by using patient history information from clinical records [164], the personalisation of cardiac treatment can further improved.

For example, the leads of the implantable cardioverter defibrillators (ICD's) could be placed more accurately, if a patient specific approach is taken instead of 'one fits all' approach used at present in clinical practice.

Disease progression for early detection [52, 5] of pathologies is becoming an increasingly popular area of research. Using imaging as well as non imaging, such as biomarkers and genetic sequencing, the data are fused together, to provide a very complex phenotype of individual patients. One of the applications using imaging to investigate early detection of drug induced toxicity, is cancer therapy induced cardiotoxicity [120]. Important task force groups have been put together to provide consensus [71] for tackling early detection of myocardial and pericardial diseases.

Appendices

Appendix A

Data description

A.1 Healthy controls cohort

The healthy controls cohort used for this thesis is part of the *Cardiac Atlas Project* [57] and it can be found under the *Challenges* menu, *Motion Tracking*¹. The data was acquired at the Division of Imaging Sciences and Biomedical Engineering, King’s College London, United Kingdom, and the Department of Internal Medicine II -Cardiology, University of Ulm, Germany.

The dataset is comprised of 16 healthy volunteers without a history of cardiac disease (3 female, aged 28 ± 5 years). One volunteer acquisition was incomplete (V3) and therefore discarded. The MR dataset were acquired using a 3T Philips Achieva System (Philips Healthcare, Best, The Netherlands). The MR sequences are cine Steady State Free Precession (SSFP) and 3D tagged Magnetic Resonance (3DTAG). SSFP datasets were scanned in multiple views (TR = 2.9 ms, TE = 1.5 ms, flip angle = 40°). All images were acquired during breath-holds of approximately 15s and were gated to the vector ECG. 3DTAG datasets were obtained using three sequential breath-hold acquisitions in each orthogonal direction (TR = 7.0 ms, TE = 3.2 ms, flip angle = 19° – 25° , tag distance = 7 mm). Images were acquired with reduced field-of-view around the left ventricle. A respiratory navigator was used to compensate for possible respiratory miss-alignment during sequential acquisitions.

¹<https://www.cardiacatlas.org/challenges/motion-tracking-challenge/>

The spatial resolution of the MR data was between 1.15 mm and 1.25 mm in plane resolution and 8mm slice thickness. The number of frames acquired comprising the cardiac cycle was 30.

A full left ventricular 4D (3D+time) reconstructed mesh is provided from the SSFP and 3DTAG data in VTK and NIFTI formats. The meshes are generated using anatomical information from the SSFP data-sets as follows: (1) short-axis SSFP frame with closest trigger time to the end diastolic 3DTAG frame was selected; (2) the left ventricle (LV) was segmented from the selected short-axis dataset by manually deforming a left ventricular model; (3) the segmented LV mesh was registered to the 3DTAG coordinates using the information from the DICOM header. For this thesis, the VTK voxelised volumes of the meshes used were provided on request from the *Motion Tracking Challenge* co-authors.

The ground-truth landmarks were generated from the 3DTAG datasets. A total of 12 landmarks per volunteer were extracted, as follows: one landmark per wall (anterior, lateral, posterior, septal), per short axis slice at basal, mid-ventricular, and apical planning. Each landmark was placed on the intersection of the tag lines on the three orthogonal visualisation planes. These landmarks were used as initialisation points and manually tracked by two observers. In order to achieve real 4D tracking of the landmarks, the process was done one landmark at a time. That is, the following time frame was visualised and the landmark was manually displaced to follow the tag marks on the three orthogonal planes. This process was repeated until the landmark was tracked over the whole cardiac cycle.

The ultrasound datasets were acquired using an iE33 3D echo-cardiography system (Philips Healthcare, Best, The Netherlands) with a 3D X3-1 matrix array transducer. The in-plane resolution of the data was between 0.77 - 0.96 mm with a through plane resolution 0.58 - 0.96 mm. The number of cardiac phases required varied between 13 and 24 [201].

All data in this study are provided in anonymised DICOM format. The data are

provided with open access policy by attribution [201].

The data used for this doctoral research is comprised of cine MR images and the manually annotated landmarks corresponding to the cine images.

A.2 The OxAMI dataset - acute myocardial infarction patient cohort

A.2.1 Study - overview

The Oxford Acute Myocardial Infarction (OxAMI) study is a study in patients who present at the John Radcliffe hospital in Oxford with symptomatic coronary artery disease. Most of these patients can be categorised into an ST elevation myocardial infarction (STEMI) or a non ST elevation myocardial infarction (NSTEMI) or angina. The remainder may have non-obstructive coronary arteries with alternative pathological explanations for their symptoms and signs (e.g. myocarditis). The aim of this study is to investigate in more detail heart disease in patients admitted for emergency treatment. Patients recruited in the OxAMI study are assessed using a combination of invasive and non-invasive investigations and followed up for up to 10 years. OxAMI is funded by the NIHR Oxford Biomedical Research Centre. The study Principal Investigator is Professor Keith Channon.

The OxAMI study aims to recruit 800 patients with symptomatic coronary artery disease.

From the time of admission to the hospital and after obtaining the patient consent, a number of investigations are carried, that are additional to the standard care pathway.

Patients arriving with acute myocardial infarction are approached by the OXAMI investigator (usually the caring cardiologist) whilst in the emergency catheter lab. A process called ‘assenting’ takes place, whereby the investigator describes to the patient about study and asks their permission to enrol them in it. An advocate, who

is an independent member of the clinical team, witnesses this. The study complies with the Declaration of Helsinki and was approved by local ethics committee (REC: 10/H0408/24).

During the coronary angiogram and percutaneous coronary intervention (PCI), blood samples are drawn from the coronary artery, aorta, coronary sinus and a peripheral vein (10ml each) as well as the coronary physiology (coronary flow, pressure and resistance) is measured before and after PCI.

After the patient has been treated and stabilised on the ward, an OXAMI investigator provides them with a patient information leaflet and formally consents them for further participation in the study. During the patient's stay in hospital, they will undergo a CMR scan between 24-48 hours after the PCI and a blood sampling from a peripheral vein at 6, 24 and 48 hours. The clinical data including past medical history, the initial presentation, blood test results and discharge medications are captured ². At the time of writing this doctoral research there was no published report describing the OxAMI study, such in the case of the healthy cohort used for this doctoral research. Therefore we provided a link to the webpage of the OxAMI study.

The patient returns to hospital at 6 months after the discharge for a CMR scan, a blood sampling from a peripheral vein and health questionnaire.

All blood samples are spun down in a centrifuge machine immediately and the serum and plasma are stored in multiple vials in a -80C freezer.

Scientists who seek to answer a specific question in patients with acute myocardial infarction can apply to utilise these samples (bio-bank) and correlate it with many clinical parameters including coronary flow, Index of Microcirculatory Resistance (IMR) and infarct size as measured on CMR [36, 35].

All patients are followed up annually for 10 years to have their clinical outcomes mapped. This will help ascertain the prognostic implications of all research and

²<https://oxami.org.uk/about-oxami/>

clinical parameters acquired during the index visit and at 6 months.

A.2.2 MRI component of the OxAMI study

During the initial percutaneous coronary intervention, the coronary blood flow and pressure is measured invasively, by introducing an additional catheter into the artery. Intravascular imaging may be used to acquire images from inside the heart vessels. The first MRI scan of the heart at 24-48 hours after admission (acutely). Additionally, blood samples are collected at five time points: upon arrival, immediately after the initial procedure and at 6, 24 and 48 hours afterwards. Participants are asked to come back for research follow-up visits to monitor their recovery.

Post percutaneous coronary intervention (PCI), the patients underwent 3T MRI scans acutely and at 6 months. The MRI protocol includes cine imaging, T2-weighted oedema imaging, pre-contrast T1 mapping (native), rest first-pass perfusion, and late gadolinium enhancement (LGE) imaging.

The patients underwent a 3T MRI scan (either MAGNETOM TIM Trio or MAGNETOM Verio, Siemens Healthcare, Erlangen, Germany) at 2 time points: acutely (24-48 hours post PPCI) and at 6 months. A full stack of cine short axis slices (SAX) covering the left ventricle is acquired, together with corresponding horizontal long axis (HLA) and vertical long axis (VLA) views. Matching short axis slices covering the left ventricle (LV) were acquired using an established CMR protocol including cine, native T1-mapping using the Shortened Modified Look-Locker Inversion recovery (ShMOLLI), and Late Gadolinium Enhancement (LGE). ShMOLLI T1 maps were generated from 5 to 7 SSFP images with variable inversion preparation time. Typical acquisition parameters were: TE = 1.07 ms, TR = 2.14 ms, flip angle (FA) = 35°, FOV = 340 × 255 mm, matrix size = 192 × 144, 107 phase encoding steps, typical voxel size = 1.6 × 1.6 × 8 mm, for the ShMOLLI sequence the interpolated reconstructed voxel size = 0.9 × 0.9 × 8 mm, GRAPPA = 2, 24 reference lines, cardiac delay time TD = S2 500 ms and 206 ms acquisition time for

Oxford Acute Myocardial Infarction (OxAMI) clinical trial - acute stage					
	Age	Gender	EDV(ml)	ESV(ml)	EF(%)
OXAMI0004	47	M	201	127	37
OXAMI0006	68	F	87	42	51
OXAMI0015	69	M	156	77	51
OXAMI0016	76	F	106	56	47
OXAMI0021	55	M	275	178	35
OXAMI0053	55	M	151	89	41
OXAMI0058	60	F	159	82	48
OXAMI0064	49	M	142	87	39
OXAMI0069	50	M	200	115	43
OXAMI0070	53	M	170	111	35
OXAMI0073	72	M	93	39	58
OXAMI0092	64	M	157	91	42
OXAMI0094	57	F	103	61	41
OXAMI0095	40	M	201	111	45
OXAMI0097	71	M	208	142	32
OXAMI0104	78	F	100	36	64
OXAMI0108	64	F	131	58	56
OXAMI0126	49	M	170	93	46
OXAMI0131	65	M	186	104	44

Table A.1: Table of clinical presentation for OxAMI patients in acute stage of myocardial infarction - recorded usually 24 hours after presentation to EA room.

single image. LGE was performed with a T1-weighted segmented inversion recovery gradient echo-phase sensitive-inversion recovery (GREPSIR) sequence (TE = 2.5ms, TR = 5ms, voxel size $1.8 \times 1.4 \times 8$ mm, FA = 20°). LGE were collected 10 to 15 minutes after the administration of 0.1 mmol/kg contrast agent (Gadodiamide, Omniscan TM, GE Healthcare, Amersham, UK). For the LGE sequence, the inversion time was adjusted for optimal nulling of the remote normal myocardium. SSFP cine images were acquired using retrospective gating (TE = 1.4 ms, TR = 3.2 ms, FA = 50°, typical voxel size: $1.6 \times 1.6 \times 8$ mm). Two to three-fold accelerated parallel imaging (GRAPPA) was used to shorten the breath-hold on LGE imaging.

For this doctoral research we used a subset of 20 STEMI patients, with two MRI visits: acute (24-48 hours after admission) and at 6 months presentation. From the full dataset, we used the cine MR and the LGE images respectively.

Oxford Acute Myocardial Infarction (OxAMI) clinical trial - 6 months					
	Age	Gender	EDV(ml)	ESV(ml)	EF(%)
OXAMI0004	47/48	M	209	101	52
OXAMI0006	68/69	F	108	39	64
OXAMI0015	69/70	M	192	94	51
OXAMI0016	76/77	F	109	45	58
OXAMI0021	55/56	M	274	170	38
OXAMI0053	55/56	M	180	74	59
OXAMI0058	60/61	F	161	68	58
OXAMI0064	49/50	M	146	65	55
OXAMI0069	50/51	M	172	67	61
OXAMI0070	53/54	M	164	88	47
OXAMI0073	72/73	M	122	43	65
OXAMI0092	64/65	M	177	63	57
OXAMI0094	57/58	F	147	68	54
OXAMI0095	40/41	M	214	130	39
OXAMI0097	71/72	M	214	114	47
OXAMI0104	78/79	F	149	56	62
OXAMI0108	64/65	F	139	61	56
OXAMI0126	49/50	M	183	91	50
OXAMI0131	65/66	M	166	95	43

Table A.2: Table of clinical presentation for OxAMI patients six months post myocardial infarction.

Oxford Acute Myocardial Infarction (OxAMI) clinical trial - Percentage of scarred tissue (%) - Visit I																
Segment number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
OXAMI0004	0.00	0.00	0.00	0.00	0.00	0.00	30.75	70.33	23.39	0.00	0.00	26.96	58.91	22.83	4.5	40.44
OXAMI0006	0.00	0.00	0.00	0.00	0.00	0.00	2.58	26.54	22.18	0.31	0.00	0.00	44.68	73.51	21.00	16.96
OXAMI0015	0.00	0.00	29.11	83.29	44.31	0.03	0.00	1.38	35.23	28.45	2.76	0.02	1.96	53.45	57.57	0.00
OXAMI0016	0.00	0.55	15.76	16.34	0.44	0.00	0.00	0.00	0.00	16.40	13.08	0.00	6.60	3.41	38.26	56.33
OXAMI0021	60.62	92.10	8.63	0.00	0.00	0.31	97.29	98.33	21.50	0.04	1.77	60.80	87.04	87.28	14.65	49.22
OXAMI0053	33.40	88.01	30.99	0.00	0.00	0.00	87.16	80.96	15.27	0.18	0.00	23.82	39.53	33.98	30.72	20.93
OXAMI0058	5.10	5.17	0.00	0.00	0.00	0.00	73.70	61.04	30.74	9.35	0.00	9.25	84.79	84.93	36.54	12.85
OXAMI0064	0.41	0.00	0.00	22.88	33.62	18.49	0.34	0.00	4.36	16.10	18.25	7.10	0.83	25.17	55.02	24.02
OXAMI0069	36.16	0.00	11.83	4.38	2.72	37.35	5.66	0.38	40.19	17.97	18.01	24.45	0.00	0.00	0.00	0.00
OXAMI0070	44.54	95.05	35.74	0.87	0.07	0.61	97.74	95.80	26.81	3.73	16.81	40.69	94.85	93.63	70.08	79.97
OXAMI0073	15.37	71.27	18.78	0.00	0.00	0.00	17.42	95.80	88.80	22.82	0.02	0.06	79.33	99.12	25.77	10.21
OXAMI0092	0.00	0.00	42.11	84.81	52.57	0.00	0.00	0.00	37.47	76.29	36.36	0.15	1.76	20.61	46.70	18.62
OXAMI0094	81.07	55.50	1.80	0.00	0.00	8.57	93.24	88.38	23.96	3.79	11.02	53.13	86.76	79.47	42.78	85.28
OXAMI0095	1.60	42.82	8.39	0.33	0.00	0.00	93.46	95.22	40.07	0.03	0.03	61.88	93.73	71.97	15.01	53.78
OXAMI0097	44.72	92.27	33.83	0.00	45.49	56.18	93.80	97.41	38.09	2.42	59.59	67.93	98.08	75.78	23.46	83.68
OXAMI0104	0.37	0.00	42.65	94.30	24.64	0.19	0.48	0.00	38.34	24.06	3.08	0.22	0.00	0.00	0.35	0.15
OXAMI0108	0.00	0.00	14.44	29.15	32.43	0.00	0.00	0.00	2.08	51.40	50.75	1.14	0.09	5.29	26.85	15.83
OXAMI0126	3.97	0.00	26.99	57.47	76.62	0.11	0.72	0.53	16.46	74.91	33.18	0.02	0.02	10.22	16.65	0.02
OXAMI0131	9.24	28.62	14.19	0.00	0.00	0.00	66.99	37.53	1.55	0.00	0.01	32.37	21.02	0.00	0.00	12.81

Table A.3: Table of AHA Segmental Analysis using cmr⁴² clinical software for patients from the clinical trial OxAMI, visit I - 24 hours after myocardial infarction. Percentage of scarred tissue per segment using LGE images and threshold type Mean 5SDs of the remote myocardium.

Oxford Acute Myocardial Infarction (OxAMI) clinical trial - Percentage of scarred tissue (%) - Visit IV																
Segment number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
OXAMI0004	0.00	0.00	0.00	0.00	0.00	0.00	22.30	8.14	0.00	0.00	0.24	0.03	28.50	6.62	1.23	18.13
OXAMI0006	0.00	0.00	0.00	0.00	0.00	0.00	0.48	9.85	1.55	0.52	0.96	0.02	46.66	22.45	8.96	30.33
OXAMI0015	0.00	0.00	1.03	29.65	34.54	0.81	0.00	0.17	10.69	29.59	26.84	0.19	0.05	12.23	13.56	0.70
OXAMI0016	0.00	0.01	0.00	0.00	0.86	0.00	0.46	0.29	10.60	16.44	2.50	0.28	11.45	9.72	64.96	68.65
OXAMI0021	31.77	44.26	4.26	0.69	0.77	1.74	65.28	69.68	5.75	0.52	6.41	47.43	79.45	46.37	13.54	49.29
OXAMI0053	1.67	61.58	18.91	0.01	0.01	0.00	76.34	81.25	16.02	0.16	0.19	1.82	94.64	83.16	64.02	67.34
OXAMI0058	4.68	3.30	0.00	0.00	0.00	0.01	76.16	60.84	35.94	19.85	0.00	9.32	87.87	77.31	28.26	31.94
OXAMI0064	0.00	0.00	0.00	8.86	0.05	0.00	0.00	0.00	0.24	7.44	1.30	0.34	1.55	0.18	9.70	16.61
OXAMI0069	18.75	0.62	25.58	1.79	1.77	23.59	3.57	0.65	55.13	14.05	9.40	33.49	0.91	7.48	2.95	3.63
OXAMI0070	21.17	85.10	28.80	1.29	1.19	0.27	77.78	77.87	26.60	0.19	0.40	27.54	63.66	40.87	15.90	28.21
OXAMI0073	12.89	45.99	1.55	0.00	0.12	0.29	8.98	77.41	29.31	3.71	3.69	0.02	60.14	91.45	38.20	1.05
OXAMI0092	0.00	0.50	22.90	54.19	38.23	0.63	0.52	0.58	30.64	64.21	26.76	0.22	0.00	17.16	31.60	0.00
OXAMI0094	83.39	39.33	0.58	0.00	1.68	3.63	82.70	47.37	10.61	1.29	4.68	48.89	81.05	49.27	16.50	46.61
OXAMI0095	32.59	54.52	17.23	0.00	0.00	4.52	89.94	92.24	48.32	0.46	2.33	38.26	89.97	95.52	17.53	20.84
OXAMI0097	16.77	67.51	23.31	0.00	42.46	17.98	85.28	81.11	8.47	0.01	37.19	52.10	88.76	32.60	3.93	51.69
OXAMI0104	0.00	0.00	24.71	66.42	7.45	0.00	0.00	0.00	1.88	55.07	1.37	0.00	0.00	0.00	0.00	0.00
OXAMI0108	0.00	0.01	0.32	2.20	1.74	0.00	0.00	0.42	3.00	44.76	38.29	0.50	0.24	0.25	5.72	17.37
OXAMI0126	1.76	2.02	17.40	39.41	51.72	1.43	1.09	0.39	18.15	71.28	33.62	32.34	37.67	9.38	59.86	98.96
OXAMI0131	28.37	46.15	32.28	0.12	0.00	0.00	15.55	8.89	0.80	0.13	0.00	18.16	4.32	0.04	0.01	5.44

Table A.4: Table of AHA Segmental Analysis using cmr⁴² clinical software for patients from the clinical trial OxAMI, visit IV - 6 months after myocardial infarction. Percentage of scarred tissue per segment using LGE images and threshold type Mean 5SDs of the remote myocardium.

Bibliography

- [1] The normal size of the heart muscle weight. *Acta Medica Scandinavica*, 139(S257):15–19, 1951.
- [2] Hiroyuki Abé, Satoru Goto, Teruo Kimura, Hidetsugu Kushibiki, and Shigeru Arai. *Residual Stress in the Left Ventricle*, pages 77–91. Springer Japan, Tokyo, 1996.
- [3] Radhakrishna Achanta, Appu Shaji, Kevin Smith, Aurelien Lucchi, Pascal Fua, and Sabine Süsstrunk. SLIC superpixels compared to state-of-the-art superpixel methods. *IEEE Transactions on Pattern Analysis and Machine Intelligence*, 34(11):2274–2281, 2012.
- [4] Luciano C. Amado, Bernhard L. Gerber, Sandeep N. Gupta, Dan W. Rettmann, Gilberto Szarf, Robert Schock, Khurram Nasir, Dara L. Kraitchman, and João A.C. Lima. Accurate and objective infarct sizing by contrast-enhanced magnetic resonance imaging in a canine myocardial infarction model. *Journal of the American College of Cardiology*, 44(12):2383–2389, 2004.
- [5] Myriam Amsallem, Toshinobu Saito, Yuko Tada, Rajesh Dash, and Michael V. McConnell. Magnetic Resonance Imaging and Positron Emission Tomography Approaches to Imaging Vascular and Cardiac Inflammation. *Circulation Journal*, 80(6):1269–1277, 2016.
- [6] M. S. Amzulescu, M. De Craene, H. Langet, A. Pasquet, D. Vancraeynest, A. C. Pouleur, J. L. Vanoverschelde, and B. L. Gerber. Myocardial strain

- imaging: review of general principles, validation, and sources of discrepancies. *European heart journal cardiovascular Imaging*, 20(6):605–619, 2019.
- [7] H. Ashikaga, B. A. Coppola, K. G. Yamazaki, F. J. Villarreal, J. H. Omens, and J. W. Covell. Changes in regional myocardial volume during the cardiac cycle: implications for transmural blood flow and cardiac structure. *AJP: Heart and Circulatory Physiology*, 295(2):H610–H618, 2008.
- [8] Daniel A. Auger, Kenneth C. Bilchick, Jorge A. Gonzalez, Sophia X. Cui, Jeffrey W. Holmes, Christopher M. Kramer, Michael Salerno, and Frederick H. Epstein. Imaging left-ventricular mechanical activation in heart failure patients using cine DENSE MRI: Validation and implications for cardiac resynchronization therapy. *Journal of Magnetic Resonance Imaging*, 46(3):887–896, 2017.
- [9] M. R. Avendi, Arash Kheradvar, and Hamid Jafarkhani. A combined deep-learning and deformable-model approach to fully automatic segmentation of the left ventricle in cardiac MRI. *Medical Image Analysis*, 30:108–119, 2016.
- [10] L. Axel, A. Montillo, and D. Kim. Tagged magnetic resonance imaging of the heart a survey. *Medical Image Analysis*, 9:376–393, 2005.
- [11] Wenjia Bai, Devis Peressutti, Sarah Parisot, Ozan Oktay, Martin Rajchl, Declan O’Regan, Stuart Cook, Andrew King, and Daniel Rueckert. Beyond the AHA 17-segment model: Motion-driven parcellation of the left ventricle. *STACOM, LNCS*, 9534(Lv):13–20, 2015.
- [12] J Bestel, F Clément, and M Sorine. A Biomechanical Model of Muscle Contraction. *Medical Image Computing and Computer-Assisted Intervention - MICCAI 2001*, 2208(2):1159–1161, 2001.

- [13] Loïc Bière, Erwan Donal, Gwenola Terrien, Gaëlle Kervio, Serge Willoteaux, Alain Furber, and Fabrice Prunier. Longitudinal strain is a marker of microvascular obstruction and infarct size in patients with acute ST-segment elevation myocardial infarction. *PLoS ONE*, 9(1):1–9, 2014.
- [14] Stefan Biesbroek, Raquel Amier, Lourens Robbers, Paul Teunissen, Aernout Beek, Albert van Rossum, Mark Hofman, Niels Van Royen, and Robin Nijveldt. Remote Myocardial Tissue Changes After Acute Myocardial Infarction and Its Role in Cardiac Remodeling: a Cmr T1-Mapping Study. *Journal of the American College of Cardiology*, 67(13):1695, 2016.
- [15] A. Bistoquet, J. Oshinski, and O. Skrinjar. Left ventricular deformation recovery from cine mri using an incompressible model. *IEEE Transactions in Medical Imaging*, 26:1136–1153, 2007.
- [16] British Heart Foundation. CVD Statistics - BHF UK Factsheet. (Cvd), 2016.
- [17] Thomas Brox, Christoph Bregler, and Jitendra Malik. Large displacement optical flow. *2009 IEEE Computer Society Conference on Computer Vision and Pattern Recognition Workshops, CVPR Workshops 2009*, 2009 IEEE Computer Society Conference on Computer Vision and Pattern Recognition:41–48, 2009.
- [18] A. Bruhn, J. Weickert, and C. Schnorr. Lucas kanade meets horn schunck: Combining local and global optic flow methods. *International Journal of Computer Vision*, 61:211–231, 2005.
- [19] Andrés Bruhn, Joachim Weickert, and Christoph Schnörr. Lucas/Kanade meets Horn/Schunck: Combining local and global optic flow methods. *International Journal of Computer Vision*, 61(3):1–21, 2005.

- [20] Heerajnarain Bulluck, Steven K. White, Stefania Rosmini, Anish Bhuva, Thomas A. Treibel, Marianna Fontana, Amna Abdel-Gadir, Anna Herrey, Charlotte Manisty, Simon M. Y. Wan, Ashley Groves, Leon Menezes, James C. Moon, and Derek J. Hausenloy. T1 mapping and T2 mapping at 3T for quantifying the area-at-risk in reperfused STEMI patients. *Journal of Cardiovascular Magnetic Resonance*, 17(1):73, 2015.
- [21] Robert J. Burns, Raymond J. Gibbons, Qilong Yi, Robin S. Roberts, Todd D. Miller, Gary L. Schaer, Jeffrey L. Anderson, and Salim Yusuf. The relationships of left ventricular ejection fraction, end-systolic volume index and infarct size to six-month mortality after hospital discharge following myocardial infarction treated by thrombolysis. *Journal of the American College of Cardiology*, 39(1):30–36, 2002.
- [22] Deborah Anne Burton, Keith Stokes, and George M Hall. Physiological effects of exercise. *Continuing Education in Anaesthesia, Critical Care & Pain*, 4(6):185–188, 2004.
- [23] Peter A. Cain, Ragnhild Ahl, Erik Hedstrom, Martin Ugander, Ase Allansdotter-Johnsson, Peter Friberg, and Hakan Arheden. Age and gender specific normal values of left ventricular mass, volume and function for gradient echo magnetic resonance imaging: A cross sectional study. *BMC Medical Imaging*, 9, 2009.
- [24] M.C. Carminati, C. Boniotti, M. Pepi, and E.G. Caiani. Quantification of myocardial viability in late Gadolinium enhancement Cardiac MRI. *Computing in Cardiology*, 42:97–100, 2015.
- [25] Manuel D. Cerqueira, Neil J. Weissman, Vasken Dilsizian, Alice K. Jacobs, Sanjiv Kaul, Warren K. Laskey, Dudley J. Pennell, John a. Rumberger, Thomas Ryan, and Mario S. Verani. Standardized myocardial segmentation

- and nomenclature for tomographic imaging of the heart: A Statement for Healthcare Professionals from the Cardiac Imaging Committee of the Council on Clinical Cardiology of the American Heart Association. *Circulation*, 105(4):539–542, 2002.
- [26] MD. Cerqueira, NJ Weissman, V. Dilsizian, AJ. Jacobs, S. Kaul, WK Pennell DJ. Laskey, JA. Rumberger, T. Ryan, and MS. Verani. Standardized myocardial segmentation and nomenclature for tomographic imaging of the heart. *AHA Scientific Statement*, 105:539–542, 2002.
- [27] Michael Chappell and Stephen Payne. *Physiology for engineers : applying engineering methods to physiological systems*. Biosystems & biorobotics. Springer, Cham, 2016.
- [28] Teodora Chitiboi and Leon Axel. Magnetic resonance imaging of myocardial strain: A review of current approaches. *Journal of Magnetic Resonance Imaging*, 46(5):1263–1280, 2017.
- [29] D J Christini, K M Stein, S M Markowitz, S Mittal, D J Slotwiner, M A Scheiner, S Iwai, and B B Lerman. Nonlinear-dynamical arrhythmia control in humans. *Proceedings of the National Academy of Sciences of the United States of America*, 98(10):5827–32, 2001.
- [30] Vincent M. Christoffels and Antoon F.M. Moorman. Development of the cardiac conduction system why are some regions of the heart more arrhythmogenic than others? *Circulation: Arrhythmia and Electrophysiology*, 2(2):195–207, 2009.
- [31] Jay N Cohn, Roberto Ferrari, and Norman Sharpe. Cardiac remodeling—concepts and clinical implications: a consensus paper from an international forum on cardiac remodeling. *Journal of the American College of Cardiology*, 35(3):569 – 582, 2000.

- [32] P. Comtois, J. Kneller, and Stanley Nattel. Of circles and spirals: Bridging the gap between the leading circle and spiral wave concepts of cardiac reentry. *Europace*, 7(SUPPL. 2):10–20, 2005.
- [33] J. R. Cooper and N. Ritter. Optical flow for validating medical image registration. *Proceedings of the IASTED International Conference on Signal and Image Processing*, 5:502–506, 2003.
- [34] W. R. Crum, T. Hartkens, and Derek L.G. Hill. Non-rigid image registration: Theory and practice. *British Journal of Radiology*, 77(SPEC. ISS. 2), 2004.
- [35] Florim Cuculi, Erica Dall’Armellina, Cedric Manlhiot, Alberto R. De Caterina, Sharon Colyer, Vanessa Ferreira, Alireza Morovat, Bernard D. Prendergast, J. Colin Forfar, Nicholas J. Alp, Robin P. Choudhury, Stefan Neubauer, Keith M. Channon, Adrian P. Banning, and Rajesh K. Kharbanda. Early change in invasive measures of microvascular function can predict myocardial recovery following PCI for ST-elevation myocardial infarction. *European Heart Journal*, 35(29):1971–1980, 10 2013.
- [36] Florim Cuculi, Neil Herring, Alberto R De Caterina, Adrian P Banning, Bernard D Prendergast, John C Forfar, Robin P Choudhury, Keith M Channon, and Rajesh K Kharbanda. Relationship of plasma neuropeptide Y with angiographic, electrocardiographic and coronary physiology indices of reperfusion during ST elevation myocardial infarction. *Heart*, 99(16):1198–1203, 2013.
- [37] Michael P. Czubryt. Common threads in cardiac fibrosis, infarct scar formation, and wound healing. *Fibrogenesis and Tissue Repair*, 5(1):1, 2012.
- [38] Erica Dall’Armellina and Robin P. Choudhury. The Role of Cardiovascular Magnetic Resonance in Patients With Acute Coronary Syndromes. *Progress in Cardiovascular Diseases*, 54(3):230–239, 2011.

- [39] Erica Dall’Armellina, Nina Karia, Alistair C. Lindsay, Theodoros D. Karamitsos, Vanessa Ferreira, Matthew D. Robson, Peter Kellman, Jane M. Francis, Colin Fofar, Bernard D. Prendergast, Adrian P. Banning, Keith M. Channon, Rajesh K. Kharbanda, Stefan Neubauer, and Robin P. Choudhury. Dynamic changes of edema and late gadolinium enhancement after acute myocardial infarction and their relationship to functional recovery and salvage index. *Circulation: Cardiovascular Imaging*, 4(3):228–236, 2011.
- [40] M Dandel, H Lehmkuhl, C Knosalla, N Suramelashvili, and R Hetzer. Strain and strain rate imaging by echocardiography - basic concepts and clinical applicability. *Curr Cardiol Rev*, 5(2):133–148, 2009.
- [41] Jose Delpiano, Luis Pizarro, Rodrigo Verschae, and Javier Ruiz-del Solar. Multi-objective optimization for parameter selection and characterization of optical flow methods. *Applied Soft Computing Journal*, 46:1067–1078, 2016.
- [42] Jay S. Detsky, Gideon Paul, Alexander J. Dick, and Graham A. Wright. Reproducible classification of infarct heterogeneity using fuzzy clustering on multi-contrast delayed enhancement magnetic resonance images. *IEEE Transactions on Medical Imaging*, 28(10):1606–1614, 2009.
- [43] J D’Hooge, A. Heimdal, F Jamal, T Kukulski, B Bijnens, F Rademakers, L Hatle, P Suetens, and G R Sutherland. Regional Strain and Strain Rate Measurements by Cardiac Ultrasound: Principles, Implementation and Limitations. *European Journal of Echocardiography*, 1(3):154–170, 2000.
- [44] Gianluca Di Bella, Fausto Pizzino, Fabio Minutoli, Concetta Zito, Rocco Donato, Giuseppe Dattilo, Giuseppe Oreto, Sergio Baldari, Giuseppe Vita, Bijoy K. Khandheria, and Scipione Carerj. The mosaic of the cardiac amyloidosis diagnosis: role of imaging in subtypes and stages of the disease. *European Heart Journal - Cardiovascular Imaging*, 15(12):1307–1315, 2014.

- [45] Harold T. Dodge and William A. Baxley. Left ventricular volume and mass and their significance in heart disease. *The American Journal of Cardiology*, 23(4):528–537, 1969.
- [46] Adelina Doltra, Brage Amundsen, Rolf Gebker, Eckart Fleck, and Sebastian Kelle. Emerging Concepts for Myocardial Late Gadolinium Enhancement MRI. *Current Cardiology Reviews*, 9(3):185–190, 2013.
- [47] Nicholas Duchateau and Maxime Sermesant. Prediction of Infarct Localization from Myocardial Deformation. *STACOM, LNCS*, 9534:51–59, 2015.
- [48] Ingo Eitel, Thomas Stiermaier, Torben Lange, Karl Philipp Rommel, Alexander Koschalka, Johannes T. Kowallick, Joachim Lotz, Shelby Kutty, Matthias Gutberlet, Gerd Hasenfuß, Holger Thiele, and Andreas Schuster. Cardiac Magnetic Resonance Myocardial Feature Tracking for Optimized Prediction of Cardiovascular Events Following Myocardial Infarction. *JACC: Cardiovascular Imaging*, 2018.
- [49] Vivienne A Ezzat, Victor Lee, Syed Ahsan, Anthony W Chow, Oliver Segal, Edward Rowland, Martin D Lowe, and Pier D Lambiase. A systematic review of icd complications in randomised controlled trials versus registries: is our ‘real-world’ data an underestimation? *Open Heart*, 2(1), 2015.
- [50] Ahmed S. Fahmy, Ulf Neisius, Raymond H. Chan, Ethan J. Rowin, Warren J. Manning, Martin S. Maron, and Reza Nezafat. Three-dimensional deep convolutional neural networks for automated myocardial scar quantification in hypertrophic cardiomyopathy: A multicenter multivendor study. *Radiology*, 2019.
- [51] Flavio H. Fenton, Elizabeth M. Cherry, Harold M. Hastings, and Steven J. Evans. Multiple mechanisms of spiral wave breakup in a model of cardiac electrical activity. *Chaos*, 12(3):852–892, 2002.

- [52] L Fernandez-Friera, A Garcia-Alvarez, and B Ibanez. Imagining the future of diagnostic imaging. *Rev Esp Cardiol (Engl Ed)*, 66(2):134–143, 2013.
- [53] Vanessa M. Ferreira, Stefan K. Piechnik, Matthew D. Robson, Stefan Neubauer, and Theodoros D. Karamitsos. Myocardial tissue characterization by magnetic resonance imaging: Novel applications of T1 and T2 mapping. *Journal of Thoracic Imaging*, 29(3):147–154, 2014.
- [54] Frank A. Flachskampf, Michael Schmid, Christian Rost, Stephan Achenbach, Anthony N. Demaria, and Werner G. Daniel. Cardiac imaging after myocardial infarction. *European Heart Journal*, 32(3):272–283, 2011.
- [55] Andrew S. Flett, Jonathan Hasleton, Christopher Cook, Derek Hausenloy, Giovanni Quarta, Cono Ariti, Vivek Muthurangu, and James C. Moon. Evaluation of techniques for the quantification of myocardial scar of differing etiology using cardiac magnetic resonance. *JACC: Cardiovascular Imaging*, 4(2):150–156, 2011.
- [56] James R.J. Foley, David A. Broadbent, Graham J. Fent, Pankaj Garg, Louise A.E. Brown, Pei G. Chew, Laura E. Dobson, Peter P. Swoboda, Sven Plein, David M. Higgins, and John P. Greenwood. Clinical evaluation of two dark blood methods of late gadolinium quantification of ischemic scar. *Journal of Magnetic Resonance Imaging*, 50(1):146–152, 2019.
- [57] Carissa G. Fonseca, Michael Backhaus, David A. Bluemke, Randall D. Britten, Jae Do Chung, Brett R. Cowan, Ivo D. Dinov, J. Paul Finn, Peter J. Hunter, Alan H. Kadish, Daniel C. Lee, Joao A.C. Lima, Pau Medrano-Gracia, Kalyanam Shivkumar, Avan Suinesiaputra, Wenchao Tao, and Alistair A. Young. The cardiac Atlas Project-an imaging database for computational modeling and statistical atlases of the heart. *Bioinformatics*, 27(16):2288–2295, 2011.

- [58] Brent A. French and Christopher M. Kramer. Mechanisms of postinfarct left ventricular remodeling. *Drug Discovery Today: Disease Mechanisms*, 4(3):185–196, 2007.
- [59] Daniel J. Friedman, Craig S. Parzynski, Paul D. Varosy, Jordan M. Prutkin, Kristen K. Patton, Ali Mithani, Andrea M. Russo, Jephtha P. Curtis, and Sana M. Al-Khatib. Trends and In-Hospital Outcomes Associated With Adoption of the Subcutaneous Implantable Cardioverter Defibrillator in the United States. *JAMA Cardiology*, 1(8):900, 2016.
- [60] Hidekatsu Fukuta and William C. Little. The Cardiac Cycle and the Physiologic Basis of Left Ventricular Contraction, Ejection, Relaxation, and Filling. *Heart Failure Clinics*, 4(1):1–11, 2008.
- [61] Bin Gao, Wanyu Liu, Liang Wang, Zhengjun Liu, Pierre Croisille, Philippe Delachartre, and Patrick Clarysse. Estimation of cardiac motion in cine-mri sequences by correlation transform optical flow of monogenic features distance. *Physics in Medicine and Biology*, 61(24):8640, 2016.
- [62] T Gautama and M a Van Hulle. A phase-based approach to the estimation of the optical flow field using spatial filtering. *IEEE Transactions on Neural Networks*, 13(5):1127–1136, 2002.
- [63] Yariv Gerber, Susan A. Weston, Cecilia Berardi, Sheila M. McNallan, Ruoxiang Jiang, Margaret M. Redfield, and Véronique L. Roger. Contemporary trends in heart failure with reduced and preserved ejection fraction after myocardial infarction: A community study. *American Journal of Epidemiology*, 178(8):1272–1280, 2013.
- [64] Bernard J. Gersh, Barry J. Maron, Robert O. Bonow, Joseph A. Dearani, Michael A. Fifer, Mark S. Link, Srihari S. Naidu, Rick A. Nishimura, Steve R.

- Ommen, Harry Rakowski, Christine E. Seidman, Jeffrey A. Towbin, James E. Udelson, and Clyde W. Yancy. 2011 ACCF/AHA guideline for the diagnosis and treatment of hypertrophic cardiomyopathy: A report of the American College of cardiology foundation/American heart association task force on practice guidelines. *Circulation*, 124(24), 2011.
- [65] Archontis Giannakidis, Eva Nyktari, Jennifer Keegan, Iain Pierce, Irina Suman Horduna, Shouvik Haldar, Dudley J. Pennell, Raad Mohiaddin, Tom Wong, and David N. Firmin. Rapid automatic segmentation of abnormal tissue in late gadolinium enhancement cardiovascular magnetic resonance images for improved management of long-standing persistent atrial fibrillation. *BioMedical Engineering Online*, 14(1):1–20, 2015.
- [66] Eliza de Almeida Gripp, Gabriela Escudini de Oliveira, Luiz Augusto Feijó, Marcelo Iorio Garcia, Sergio Salles Xavier, and Andréa Silvestre de Sousa. Global Longitudinal Strain Accuracy for Cardiotoxicity Prediction in a Cohort of Breast Cancer Patients During Anthracycline and/or Trastuzumab Treatment. *Arquivos brasileiros de cardiologia*, 110(2):140–150, 2018.
- [67] Xuejun Gu, Hubert Pan, Yun Liang, and Richard Castillo. Implementation and evaluation of various demons deformable image registration algorithms Implementation and evaluation of various demons deformable image registration algorithms on a GPU. 207:1–16, 2010.
- [68] Julius M. Guccione and Andrew D. McCulloch. Finite Element Modeling of Ventricular Mechanics. *Theory of Heart*, pages 121–144, 1991.
- [69] Vikas Gulani, Fernando Calamante, Frank G. Shellock, Emanuel Kanal, and Scott B. Reeder. Gadolinium deposition in the brain: summary of evidence and recommendations. *The Lancet Neurology*, 16(7):564–570, 2017.

- [70] Bang J. Guo, Zhen L. Yang, and Long J. Zhang. Gadolinium Deposition in Brain: Current Scientific Evidence and Future Perspectives. *Frontiers in Molecular Neuroscience*, 11(September):1–12, 2018.
- [71] Gilbert Habib, Chiara Bucciarelli-Ducci, Alida L.P. Caforio, Nuno Cardim, Philippe Charron, Bernard Cosyns, Aurélie Dehaene, Genevieve Derumeaux, Erwan Donal, Marc R. Dweck, Thor Edvardsen, Paola Anna Erba, Laura Ernande, Oliver Gaemperli, Maurizio Galderisi, Julia Grapsa, Alexis Jacquier, Karin Klingel, Patrizio Lancellotti, Danilo Neglia, Alessia Pepe, Pasquale Perrone-Filardi, Steffen E. Petersen, Sven Plein, Bogdan A. Popescu, Patricia Reant, L. Elif Sade, Erwan Salaun, Riemer H.J.A. Slart, Christophe Tribouilloy, Jose Zamorano, Victoria Delgado, Kristina Haugaa, and G. Vijayaraghavan. Multimodality Imaging in Restrictive Cardiomyopathies: An EACVI expert consensus document In collaboration with the "Working Group on myocardial and pericardial diseases" of the European Society of Cardiology Endorsed by The Indian Academy of Echocardiography. *European Heart Journal Cardiovascular Imaging*, 18(10):1090–1091, 2017.
- [72] Nina E. Hasselberg, Kristina H. Haugaa, Anne Bernard, Margareth P. Ribe, Erik Kongsgaard, Erwan Donal, and Thor Edvardsen. Left ventricular markers of mortality and ventricular arrhythmias in heart failure patients with cardiac resynchronization therapy. *European Heart Journal Cardiovascular Imaging*, 17(3):343–350, 2016.
- [73] Mariella ECJ Hassell, Wieneke Vlastra, Lourens Robbers, Alexander Hirsch, Robin Nijveldt, Jan GP Tijssen, Albert C van Rossum, Felix Zijlstra, Jan J Piek, and Ronak Delewi. Long-term left ventricular remodelling after revascularisation for st-segment elevation myocardial infarction as assessed by cardiac magnetic resonance imaging. *Open Heart*, 4(1), 2017.

- [74] M.P. Heinrich, J. Schnabel, and F.V. Gleeson. Non-rigid multimodal medical image registration using optical flow and gradient orientation. *Proc. Medical Image Understanding and Analysis*, pages 1–5, 2010.
- [75] Stefan Heldmann and Nils Papenberg. A Scale-Space Approach for Image Registration of Vessel Structures. *Bildverarbeitung für die Medizin*, pages 137–141, 2009.
- [76] Robert C Hendel, Manesh R Patel, Christopher M Kramer, Michael Poon, James C Carr, Nancy a Gerstad, Linda D Gillam, John McB Hodgson, Raymond J Kim, John R Lesser, Edward T Martin, Joseph V Messer, Rita F Redberg, Geoffrey D Rubin, John S Rumsfeld, Allen J Taylor, Wm Guy Weigold, Pamela K Woodard, Ralph G Brindis, Pamela S Douglas, Eric D Peterson, Michael J Wolk, and Joseph M Allen. ACCF/ACR/SCCT/SCMR/ASNC/NASCI/SCAI/SIR 2006 appropriateness criteria for cardiac computed tomography and cardiac magnetic resonance imaging: A Report of the American College of Cardiology Foundation Quality Strategic Directions Committee Appropriateness C. *Journal of the American College of Cardiology*, 48(7):1475–97, 2006.
- [77] Anja Hennemuth, Achim Seeger, Ola Friman, Stephan Miller, Bernhard Klumpp, Steffen Oeltze, and Heinz Otto Peitgen. A comprehensive approach to the analysis of contrast enhanced cardiac MR images. *IEEE Transactions on Medical Imaging*, 27(11):1592–1610, 2008.
- [78] Simon Hermann and René Werner. High accuracy optical flow for 3d medical image registration using the census cost function, 2014.
- [79] Gerhard A. Holzapfel. Nonlinear solid mechanics: A continuum approach for engineering science. *Meccanica*, 37(4):489–490, Jul 2002.

- [80] B. Horn and B. Schunck. Determining optical flow. *Artificial Intelligence*, 17:185–203, 1981.
- [81] Li Yueh Hsu, W. Patricia Ingkanisorn, Peter Kellman, Anthony H. Aletras, and Andrew E. Arai. Quantitative myocardial infarction on delayed enhancement MRI. Part II: Clinical application of an automated feature analysis and combined thresholding infarct sizing algorithm. *Journal of Magnetic Resonance Imaging*, 23(3):309–314, 2006.
- [82] Hsiao Hui Huang, Chun Yu Huang, Chiao Ning Chen, Yun Wen Wang, and Teng Yi Huang. Automatic regional analysis of myocardial native T1 values: left ventricle segmentation and AHA parcellations. *International Journal of Cardiovascular Imaging*, 34(1):131–140, 2018.
- [83] W. Gregory Hundley, David Bluemke, Jan G. Bogaert, Matthias G. Friedrich, Charles B. Higgins, Mark A. Lawson, Michael V. McConnell, Subha V. Raman, Albert C. Van Rossum, Scott Flamm, Christopher M. Kramer, Eike Nagel, and Stefan Neubauer. Society for Cardiovascular Magnetic Resonance guidelines for reporting cardiovascular magnetic resonance examinations. *Journal of Cardiovascular Magnetic Resonance*, 11(1):1–11, 2009.
- [84] El Sayed H. Ibrahim. Myocardial tagging by cardiovascular magnetic resonance: evolution of techniques—pulse sequences, analysis algorithms, and applications. *Journal of cardiovascular magnetic resonance : official journal of the Society for Cardiovascular Magnetic Resonance*, 13(1):36, 2011.
- [85] Benjamin Irving. SLIC in a defined mask with applications to medical imaging. pages 1–5, 2016.
- [86] Benjamin Irving, Amalia Cifor, Bartłomiej W Papież, Jamie Franklin, Ewan M Anderson, Sir Michael Brady, and Julia A Schnabel. Automated Colorectal

- Tumour Segmentation in DCE-MRI Using Supervoxel Neighbourhood Contrast Characteristics. *MICCAI*, pages 609–616, 2014.
- [87] Benjamin Irving and et al. maskSLIC: Regional Superpixel Generation with Application to Local Pathology Characterisation in Medical Images. pages 1–7, 2016.
- [88] Benjamin Irving, James M. Franklin, Bartłomiej W. Papiez, Ewan M. Anderson, Ricky A. Sharma, Fergus V. Gleeson, Sir Michael Brady, and Julia A. Schnabel. Pieces-of-parts for supervoxel segmentation with global context: Application to DCE-MRI tumour delineation. *Medical Image Analysis*, 32:69–83, 2016.
- [89] Benjamin Irving, Iulia A. Popescu, Russell Bates, P. Danny Allen, Ana L. Gomes, Pavitra Kannan, Paul Kinchesh, Stuart Gilchrist, Veerle Kersemans, Sean Smart, Julia A. Schnabel, Sir J. Michael Brady, and Michael A. Chappell. maskSLIC: Regional Superpixel Generation with Application to Local Pathology Characterisation in Medical Images. pages 1–7, 2016.
- [90] Benjamin J. Irving, Pierre Goussard, Savvas Andronikou, Robert Gie, Tania S. Douglas, Andrew Todd-Pokropek, and Paul Taylor. Computer assisted detection of abnormal airway variation in CT scans related to paediatric tuberculosis. *Medical Image Analysis*, 18(7):963–976, 2014.
- [91] Kai Jiang and Xin Yu. Quantification of regional myocardial wall motion by cardiovascular magnetic resonance. *Quantitative imaging in medicine and surgery*, 4(5):345–57, 2014.
- [92] Theodoros D. Karamitsos, Stefan K. Piechnik, Sanjay M. Banypersad, Marianna Fontana, Ntobeko B. Ntusi, Vanessa M. Ferreira, Carol J. Whelan, Saul G. Myerson, Matthew D. Robson, Philip N. Hawkins, Stefan Neubauer,

- and James C. Moon. Noncontrast t1 mapping for the diagnosis of cardiac amyloidosis. *JACC: Cardiovascular Imaging*, 6(4):488 – 497, 2013.
- [93] Rashed Karim, Aruna Arujuna, Richard James Housden, Jaspal Gill, Hannah Cliffe, Kavir Matharu, Jaswinder Gill, Christopher Aldo Rindaldi, Mark O’Neill, Daniel Rueckert, Reza Razavi, Tobias Schaeffter, and Kawal Rhode. A method to standardize quantification of left atrial scar from delayed-enhancement MR images. *IEEE Journal of Translational Engineering in Health and Medicine*, 2(1):1–15, 2014.
- [94] Rashed Karim, Pranav Bhagirath, Piet Claus, R. James Housden, Zhong Chen, Zahra Karimaghaloo, Hyon Mok Sohn, Laura Lara Rodríguez, Sergio Vera, Xènia Albà, Anja Hennemuth, Heinz Otto Peitgen, Tal Arbel, Miguel A. González Ballester, Alejandro F. Frangi, Marco Götte, Reza Razavi, Tobias Schaeffter, and Kawal Rhode. Evaluation of state-of-the-art segmentation algorithms for left ventricle infarct from late Gadolinium enhancement MR images. *Medical Image Analysis*, 30:95–107, 2016.
- [95] Rashed Karim, R James Housden, Mayuragoban Balasubramaniam, Zhong Chen, Daniel Perry, Ayesha Uddin, Yosra Al-Beyatti, Ebrahim Palkhi, Prince Acheampong, Samantha Obom, Anja Hennemuth, Yingli Lu, Wenjia Bai, Wenzhe Shi, Yi Gao, Heinz-Otto Peitgen, Perry Radau, Reza Razavi, Allen Tannenbaum, Daniel Rueckert, Josh Cates, Tobias Schaeffter, Dana Peters, Rob MacLeod, and Kawal Rhode. Evaluation of current algorithms for segmentation of scar tissue from late gadolinium enhancement cardiovascular magnetic resonance of the left atrium: an open-access grand challenge. *Journal of cardiovascular magnetic resonance : official journal of the Society for Cardiovascular Magnetic Resonance*, 15:105, 2013.

- [96] Zahra Karimaghloo, Mohak Shah, Simon J. Francis, Douglas L. Arnold, D. Louis Collins, and Tal Arbel. Automatic detection of gadolinium-enhancing multiple sclerosis lesions in brain MRI using conditional random fields. *IEEE Transactions on Medical Imaging*, 31(6):1181–1194, 2012.
- [97] Jakob Nikolas Kather, Anja Weidner, Ulrike Attenberger, Yannick Bukschat, Cleo Aron Weis, Meike Weis, Lothar R. Schad, and Frank Gerrit Zöllner. Color-coded visualization of magnetic resonance imaging multiparametric maps. *Scientific Reports*, 7:1–11, 2017.
- [98] Azira Khalil, Siew Cheok Ng, Yih Miin Liew, and Khin Wee Lai. An Overview on Image Registration Techniques for Cardiac Diagnosis and Treatment. *Cardiology Research and Practice*, 2018, 2018.
- [99] Junhwan Kim, Vladimir Kolmogorov, and Ramin Zabih. Visual Correspondence Using Energy Minimization and Mutual Information. *Proceedings of the Ninth IEEE International Conference on Computer Vision*, pages 1033–1040, 2003.
- [100] Andre G Kleber and Jeffrey E Saffitz. Role of the intercalated disc in cardiac propagation and arrhythmogenesis. *Frontiers in Physiology*, 5:1–9, 2014.
- [101] Christoph Klein, Thaiz R. Schmal, Stephan G. Nekolla, Bernhard Schnackenburg, Eckart Fleck, and Eike Nagel. Mechanism of late gadolinium enhancement in patients with acute myocardial infarction. *Journal of Cardiovascular Magnetic Resonance*, 9(4):653–658, 2007. PMID: 17578720.
- [102] Marvin A. Konstam and François M. Abboud. Ejection Fraction: Misunderstood and Overrated (Changing the Paradigm in Categorizing Heart Failure). *Circulation*, 135(8):717–719, 2017.

- [103] Christophe Kosinski and François R. Jornayvaz. Effects of ketogenic diets on cardiovascular risk factors: Evidence from animal and human studies. *Nutrients*, 9(5):1–16, 2017.
- [104] Attila Kovács, Bálint Lakatos, Márton Tokodi, and Béla Merkely. Right ventricular mechanical pattern in health and disease: beyond longitudinal shortening. *Heart Failure Reviews*, pages 511–520, 2019.
- [105] Mirosław Kowalski, Tomasz Kukulski, Fadi Jamal, Jan D’hooge, Frank Weidemann, Frank Rademakers, Bart Bijmens, Liv Hatle, and George R. Sutherland. Can natural strain and strain rate quantify regional myocardial deformation? A study in healthy subjects. *Ultrasound in Medicine and Biology*, 27(8):1087–1097, 2001.
- [106] Kai Krajsek and Rudolf Mester. Bayesian Model Selection for Optical Flow Estimation. *Pattern Recognition*, pages 142–151, 2007.
- [107] Dirk-Jan Kroon and Cornelis H. Slump. Mri modalitiy transformation in demon registration. In *Proceedings of the Sixth IEEE International Conference on Symposium on Biomedical Imaging: From Nano to Macro*, ISBI’09, pages 963–966, Piscataway, NJ, USA, 2009. IEEE Press.
- [108] Vineet Kumar. Dyssynchrony: a risk marker for ventricular arrhythmias? *Journal of Nuclear Cardiology*, 25(2):570–571, 2018.
- [109] Fred M. Kusumoto, Kent R. Bailey, Ahmad Sami Chaouki, Abhishek J. Deshmukh, Sandeep Gautam, Robert J. Kim, Daniel B. Kramer, Litsa K. Lambrakos, Naseer H. Nasser, and Dan Sorajja. Systematic review for the 2017 AHA/ACC/HRS guideline for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: A Report of the American College of Cardiology/American Heart Association Task Force on

- Clinical Practice Guidelines and the Heart Rhythm Society. *Heart Rhythm*, 15(10):e253–e274, 2018.
- [110] Kenya Kusunose, Takashi Abe, Akihiro Haga, Daiju Fukuda, Hirotsugu Yamada, Masafumi Harada, and Masataka Sata. A Deep Learning Approach for Assessment of Regional Wall Motion Abnormality From Echocardiographic Images. *JACC: Cardiovascular Imaging*, 2019.
- [111] Ben Lacey, William G. Herrington, David Preiss, Sarah Lewington, and Jane Armitage. The Role of Emerging Risk Factors in Cardiovascular Outcomes. *Current Atherosclerosis Reports*, 19(6), 2017.
- [112] Roberto M. Lang, Luigi P. Badano, Victor Mor-Avi, Jonathan Afilalo, Anderson Armstrong, Laura Ernande, Frank A. Flachskampf, Elyse Foster, Steven A. Goldstein, Tatiana Kuznetsova, Patrizio Lancellotti, Denisa Muraru, Michael H. Picard, Ernst R. Rietzschel, Lawrence Rudski, Kirk T. Spencer, Wendy Tsang, and Jens Uwe Voigt. Recommendations for cardiac chamber quantification by echocardiography in adults: An update from the American society of echocardiography and the European association of cardiovascular imaging. *European Heart Journal Cardiovascular Imaging*, 16(3):233–271, 2015.
- [113] Huai Ping Lee, Ming C. Lin, and Mark Foskey. Physically-based validation of deformable medical image registration. *Lecture Notes in Computer Science (including subseries Lecture Notes in Artificial Intelligence and Lecture Notes in Bioinformatics)*, 5242 LNCS(PART 2):830–838, 2008.
- [114] J. M. Lee and D. R. Boughner. Mechanical properties of human pericardium. Differences in viscoelastic response when compared with canine pericardium. *Circulation Research*, 57(3):475–481, 1985.

- [115] Yunpeng Li and Daniel P. Huttenlocher. Learning for optical flow using stochastic optimization. *Computer Vision – ECCV 2008*, pages 379–391, 2008.
- [116] Jesse Lieman-Sifry, Matthieu Le, Felix Lau, Sean Sall, and Daniel Golden. Fastventricle: Cardiac segmentation with ENet. *Lecture Notes in Computer Science (including subseries Lecture Notes in Artificial Intelligence and Lecture Notes in Bioinformatics)*, 10263 LNCS:127–138, 2017.
- [117] Pascal Lim, Adisai Buakhamsri, Zoran B. Popovic, Neil L. Greenberg, Dimpri Patel, ThomasJames D., and Richard A. Grimm. Longitudinal strain delay index by speckle tracking imaging: A new marker of response to cardiac resynchronization therapy. *Circulation*, 118(11):1130–1137, 2008.
- [118] Pascal Lim, Erwan Donal, Stphane Lafitte, Genevieve Derumeaux, Gilbert Habib, Patricia Rant, Sophie Thivolet, Nicolas Lellouche, Richard A. Grimm, and Pascal Gueret. Multicentre study using strain delay index for predicting response to cardiac resynchronization therapy (MUSIC study). *European Journal of Heart Failure*, 13(9):984–991, 2011.
- [119] Dan Liu, Alessandra Borlotti, Dafne Viliani, Michael Jerosch-Herold, Mohammad Alkhalil, Giovanni Luigi De Maria, Gregor Fahrni, Sam Dawkins, Rohan Wijesurendra, Jane Francis, Vanessa Ferreira, Stefan Piechnik, Matthew D. Robson, Adrian Banning, Robin Choudhury, Stefan Neubauer, Keith Channon, Rajesh Kharbanda, and Erica Dall’Armellina. CMR Native T1 Mapping Allows Differentiation of Reversible Versus Irreversible Myocardial Damage in ST-Segment-Elevation Myocardial Infarction: An OxAMI Study (Oxford Acute Myocardial Infarction). *Circulation. Cardiovascular imaging*, 10(8):2–11, 2017.
- [120] Teresa López-Fernández and Paaladinesh Thavendiranathan. Review article: Emerging cardiac imaging modalities for the early detection of cardiotoxicity

due to anticancer therapies. *Nuevas técnicas de imagen cardiaca en la detección precoz de cardiotoxicidad secundaria a tratamientos oncológicos*, 70(6):487–495, 2017.

- [121] Xuesong Lu, Rongqian Yang, Qinlan Xie, Shanxing Ou, Yunfei Zha, and Defeng Wang. Nonrigid registration with corresponding points constraint for automatic segmentation of cardiac DSCT images. *BioMedical Engineering Online*, 16(1):1–15, 2017.
- [122] Yingli Lu, Yuesong Yang, Kim A Connelly, Graham A Wright, and Perry E Radau. Automated quantification of myocardial infarction using graph cuts on contrast delayed enhanced magnetic resonance images. *Quantitative imaging in medicine and surgery*, 2(2):81–6, 2012.
- [123] B. Lucas and T. Kanade. An iterative image registration technique with an application to stereo vision. *Proceedings of Imaging Understanding Workshop*, 1:121–130, 1981.
- [124] Gunnar K. Lund, Alexander Stork, Maythem Saeed, Martin P. Bansmann, Jann H. Gerken, Vika Müller, Janos Mester, Charles B. Higgins, Gerhard Adam, and Thomas Meinertz. Acute Myocardial Infarction: Evaluation with First-Pass Enhancement and Delayed Enhancement MR Imaging Compared ²⁰¹ Tl SPECT Imaging. *Radiology*, 232(1):49–57, 2004.
- [125] Kenneth Mangion, Christie McComb, Daniel A. Auger, Frederick H. Epstein, and Colin Berry. Magnetic resonance imaging of myocardial strain after acute st-segment-elevation myocardial infarction a systematic review. *Circulation: Cardiovascular Imaging*, 10(8):1–10, 2017.
- [126] Tommaso Mansi, Xavier Pennec, Maxime Sermesant, Hervé Delingette, and Nicholas Ayache. ILogDemos: A demons-based registration algorithm for

- tracking incompressible elastic biological tissues. *International Journal of Computer Vision*, 92(1):92–111, 2011.
- [127] Tommaso Mansi, Jean Marc Peyrat, Maxime Sermesant, Hervé Delingette, Julie Blanc, Younes Boudjemline, and Nicholas Ayache. Physically-constrained diffeomorphic demons for the estimation of 3d myocardium strain from cine-mri. *Lecture Notes in Computer Science (including subseries Lecture Notes in Artificial Intelligence and Lecture Notes in Bioinformatics)*, 5528:201–210, 2009.
- [128] S. Marrakchi, I. Kammoun, E. Bennour, L. Laroussi, and S. Kachboura. Risk stratification in hypertrophic cardiomyopathy. *Herz*, Apr 2018.
- [129] Thomas H. Marwick. Measurement of strain and strain rate by echocardiography: Ready for prime time? *Journal of the American College of Cardiology*, 47(7):1313–1327, 2006.
- [130] Yasuo Matsuda, Yoichi Toma, Masunori Matsuzaki, Kohshiro Moritani, Akira Satoh, Kohtaro Shiomi, Nozomu Ohtani, Michihiro Kohno, Takashi Fujii, Kazuhiro Katayama, Masako Matsuda, and Reizo Kusukawa. Change of left atrial systolic pressure waveform in relation to left ventricular end-diastolic pressure. *Circulation*, 82(5):1659–1667, 1990.
- [131] Marcel M. Maya and Barry D. Pressman. Chapter 20 - Pituitary Imaging. *The Pituitary (Third Edition)*, pages 677–702, 2011.
- [132] Robert J. McDonald, Jennifer S. McDonald, David F. Kallmes, Mark E. Jentoft, David L. Murray, Kent R. Thielen, Eric E. Williamson, and Laurence J. Eckel. Intracranial Gadolinium Deposition after Contrast-enhanced MR Imaging. *Radiology*, 275(3):772–782, 2015.

- [133] J J McMurray and et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart. *Eur J Heart Fail*, 14(8):803–869, 2012.
- [134] Elliot R. McVeigh and Ergin Atalar. Cardiac Tagging with Breath-Hold Cine MRI. *Magnetic Resonance in Medicine*, 28(2):318–327, 1992.
- [135] Pau Medrano-Gracia, Avan Suinesiaputra, Brett Cowan, David Bluemke, Alejandro Frangi, Daniel Lee, João Lima, and Alistair Young. An atlas for cardiac MRI regional wall motion and infarct scoring. *Lecture Notes in Computer Science (including subseries Lecture Notes in Artificial Intelligence and Lecture Notes in Bioinformatics)*, 7746 LNCS:188–197, 2013.
- [136] Authors/Task Force Members, John J.V. McMurray, Stamatis Adamopoulos, Stefan D. Anker, Angelo Auricchio, Michael Böhm, Kenneth Dickstein, Volkmar Falk, Gerasimos Filippatos, Cândida Fonseca, Miguel Angel Gomez-Sanchez, Tiny Jaarsma, Lars Køber, Gregory Y.H. Lip, Aldo Pietro Maggioni, Alexander Parkhomenko, Burkert M. Pieske, Bogdan A. Popescu, Per K. Rønnevik, Frans H. Rutten, Juerg Schwitter, Petar Seferovic, Janina Stepinska, Pedro T. Trindade, Adriaan A. Voors, Faiez Zannad, Andreas Zeiher, ESC Committee for Practice Guidelines (CPG), Jeroen J. Bax, Helmut Baumgartner, Claudio Ceconi, Veronica Dean, Christi Deaton, Robert Fagard, Christian Funck-Brentano, David Hasdai, Arno Hoes, Paulus Kirchhof, Juhani Knuuti, Philippe Kolh, Theresa McDonagh, Cyril Moulin, Bogdan A. Popescu, Željko Reiner, Udo Sechtem, Per Anton Sirnes, Michal Tendera, Adam Torbicki, Alec Vahanian, Stephan Windecker, Document Reviewers, Theresa McDonagh, Udo Sechtem, Luis Almenar Bonet, Panayiotis Avraamides, Hisham A. Ben Lamin, Michele Brignole, Antonio Coca,

Peter Cowburn, Henry Dargie, Perry Elliott, Frank Arnold Flachskampf, Guido Francesco Guida, Suzanna Hardman, Bernard Iung, Bela Merkely, Christian Mueller, John N. Nanas, Olav Wendelboe Nielsen, Stein Ørn, John T. Parissis, and Piotr Ponikowski. Esc guidelines for the diagnosis and treatment of acute and chronic heart failure 2012the task force for the diagnosis and treatment of acute and chronic heart failure 2012 of the european society of cardiology. developed in collaboration with the heart failure association (hfa) of the esc. *European Heart Journal*, 33(14):1787–1847, 2012.

- [137] Daniel R. Messroghli, Aleksandra Radjenovic, Sebastian Kozerke, David M. Higgins, Mohan U. Sivananthan, and John P. Ridgway. Modified look-locker inversion recovery (MOLLI) for high-resolution T 1 mapping of the heart. *Magnetic Resonance in Medicine*, 52(1):141–146, 2004.
- [138] Mohamed K Metwally, Neamat El-gayar, and Nael F Osman. Improved Technique to Detect the Infarction in Delayed Enhancement Image Using K-Mean Method. *Prog. Imag. Anal. Recognit.*, LNCS-6112:108–119, 2010.
- [139] Nathan Mewton, Chia Ying Liu, Pierre Croisille, David Bluemke, and Joo A C Lima. Assessment of myocardial fibrosis with cardiovascular magnetic resonance. *Journal of the American College of Cardiology*, 57(8):891–903, 2011.
- [140] C. Muhl, W. R.M. Dassen, and H. Kuipers. Cardiac remodelling: Concentric versus eccentric hypertrophy in strength and endurance athletes. *Netherlands Heart Journal*, 16(4):129–133, 2008.
- [141] Sara Moccia, Riccardo Banali, Chiara Martini, Giuseppe Muscogiuri, Gianluca Pontone, Mauro Pepi, and Enrico Gianluca Caiani. Development and testing of a deep learning-based strategy for scar segmentation on cmr-lge images.

Magnetic Resonance Materials in Physics, Biology and Medicine, 32(2):187–195, Apr 2019.

- [142] Jan Modersitzki. *Numerical Methods for Image Registration*. Oxford University Press, 2003.
- [143] Harry G. Mond and Alessandro Proclemmer. The 11th world survey of cardiac pacing and implantable cardioverter-defibrillators: Calendar year 2009 - A world society of Arrhythmia’s project. *PACE - Pacing and Clinical Electrophysiology*, 34(8):1013–1027, 2011.
- [144] Anastasia Nasopoulou, Anoop Shetty, Jack Lee, David Nordsletten, C. Aldo Rinaldi, Pablo Lamata, and Steven Niederer. Improved identifiability of myocardial material parameters by an energy-based cost function. *Biomechanics and Modeling in Mechanobiology*, 2017.
- [145] Siamak Niroomandi, Icíar Alfaro, Elías Cueto, Francisco Chinesta, Siamak Niroomandi, Icíar Alfaro, Elías Cueto, and Francisco Chinesta. Model order reduction for hyperelastic materials. *International Journal for Numerical Methods in Engineering*, 81(9):1180–1206, 2010.
- [146] Tomohito Ohtani, Selma F. Mohammed, Kazuhiro Yamamoto, Shannon M. Dunlay, Susan A. Weston, Yasushi Sakata, Richard J. Rodeheffer, Veronique L. Roger, and Margaret M. Redfield. Diastolic stiffness as assessed by diastolic wall strain is associated with adverse remodelling and poor outcomes in heart failure with preserved ejection fraction. *European heart journal*, 33(14):1742–1749, 2012.
- [147] José T. Ortiz-Pérez, José Rodríguez, Sheridan N. Meyers, Daniel C. Lee, Charles Davidson, and Edwin Wu. Correspondence Between the 17-Segment Model and Coronary Arterial Anatomy Using Contrast-Enhanced Cardiac

- Magnetic Resonance Imaging. *JACC: Cardiovascular Imaging*, 1(3):282–293, 2008.
- [148] Nael F Osman, Smita Sampath, Ergin Atalar, and Jerry L Prince. Imaging Longitudinal Cardiac Strain on Short-Axis Images Using Strain-Encoded MRI. 334(July 2000):324–334, 2001.
- [149] Theophilus E. Owan, David O. Hodge, Regina M. Herges, Steven J. Jacobsen, Veronique L. Roger, and Margaret M. Redfield. Trends in prevalence and outcome of heart failure with preserved ejection fraction. *New England Journal of Medicine*, 355(3):251–259, 2006. PMID: 16855265.
- [150] Asif Padiyath, Paul Gribben, Joseph R. Abraham, Ling Li, Sheela Rangamani, Andreas Schuster, David A. Danford, Gianni Pedrizzetti, and Shelby Kutty. Echocardiography and cardiac magnetic resonance-based feature tracking in the assessment of myocardial mechanics in tetralogy of fallot: An intermodality comparison. *Echocardiography*, 30(2):203–210, 2013.
- [151] Mahsa Paknezhad, Michael S. Brown, and Stephanie Marchesseau. Improved tagged cardiac MRI myocardium strain analysis by leveraging cine segmentation. *Computer Methods and Programs in Biomedicine*, 184, 2020.
- [152] Bartłomiej W. Papiez, Mattias P. Heinrich, Jérôme Fehrenbach, Laurent Risser, and Julia A. Schnabel. An implicit sliding-motion preserving regularisation via bilateral filtering for deformable image registration. *Medical Image Analysis*, 18(8):1299–1311, 2014.
- [153] Pierpaolo Pellicori, Anna Kallvikbacka-Bennett, Olga Khaleva, Valentina Carubelli, Pierluigi Costanzo, Teresa Castiello, Kenneth Wong, Jufen Zhang, John G F Cleland, and Andrew L. Clark. Global longitudinal strain in patients with suspected heart failure and a normal ejection fraction: Does it improve

- diagnosis and risk stratification? *International Journal of Cardiovascular Imaging*, 30(1):69–79, 2014.
- [154] Danilo R. Pereira, José Delpiano, and João P. Papa. On the optical flow model selection through metaheuristics. *Eurasip Journal on Image and Video Processing*, 2015(1), 2015.
- [155] Danilo Roberto Pereira, José Delpiano, and João Paulo Papa. Evolutionary optimization applied for fine-tuning parameter estimation in optical flow-based environments. *Brazilian Symposium of Computer Graphic and Image Processing*, (August):125–132, 2014.
- [156] Devis Peressutti, Wenjia Bai, Wenzhe Shi, Catalina Tobon-Gomez, Thomas Jackson, Manav Sohal, Aldo Rinaldi, Daniel Rueckert, and King Andrew. Towards Left Ventricular Scar Localisation Using Local Motion Descriptors. *STACOM, LNCS*, 9534:30–39, 2015.
- [157] Osvaldo Pereztol-Valdés, Jaume Candell-Riera, César Santana-Boado, Juan Angel, Santiago Aguadé-Bruix, Joan Castell-Conesa, Ernest V. Garcia, and Jordi Soler-Soler. Correspondence between left ventricular 17 myocardial segments and coronary arteries. *European Heart Journal*, 26(24):2637–2643, 2005.
- [158] Steffen E. Petersen, Nay Aung, Mihir M. Sanghvi, Filip Zemrak, Kenneth Fung, Jose Miguel Paiva, Jane M. Francis, Mohammed Y. Khanji, Elena Lukaschuk, Aaron M. Lee, Valentina Carapella, Young Jin Kim, Paul Leeson, Stefan K. Piechnik, and Stefan Neubauer. Reference ranges for cardiac structure and function using cardiovascular magnetic resonance (CMR) in Caucasians from the UK Biobank population cohort. *Journal of Cardiovascular Magnetic Resonance*, 19(1):1–19, 2017.

- [159] M. E. Pfisterer, A. Battler, and B. L. Zaret. Range of normal values for left and right ventricular ejection fraction at rest and during exercise assessed by radionuclide angiocardiology. *European Heart Journal*, 6(8):647–655, 1985.
- [160] Stefan K Piechnik, Vanessa M Ferreira, Erica Dall Armellina, Lowri E Cochlin, Andreas Greiser, Stefan Neubauer, and Matthew D Robson. Shortened Modified Look-Locker Inversion recovery (ShMOLLI) for clinical myocardial T1-mapping at 1 . 5 and 3 T within a 9 heartbeat breathhold. pages 1–11, 2010.
- [161] Stefan K. Piechnik, Vanessa M. Ferreira, Adam J. Lewandowski, Ntobeko Ab Ntusi, Rajarshi Banerjee, Cameron Holloway, Mark Bm Hofman, Daniel M. Sado, Viviana Maestrini, Steven K. White, Merzaka Lazdam, Theodoros Karamitsos, James C. Moon, Stefan Neubauer, Paul Leeson, and Matthew D. Robson. Normal variation of magnetic resonance T1 relaxation times in the human population at 1.5 T using ShMOLLI. *Journal of Cardiovascular Magnetic Resonance*, 15(1):1–11, 2013.
- [162] Jeremy Pinnell, Simon Turner, and Simon Howell. Cardiac muscle physiology. *Continuing Education in Anaesthesia, Critical Care and Pain*, 7(3):85–88, 2007.
- [163] Ferran Poveda, Debora Gil, Enric Martí, Albert Andaluz, Manel Ballester, and Francesc Carreras. Helical Structure of the Cardiac Ventricular Anatomy Assessed by Diffusion Tensor Magnetic Resonance Imaging With Multiresolution Tractography. *Revista Española de Cardiología (English Edition)*, 66(10):782–790, 2013.
- [164] Esther Puyol-Anton, Bram Ruijsink, Helene Langet, Mathieu De Craene, Paolo Piro, Julia A. Schnabel, and Andrew P. King. Learning associations between clinical information and motion-based descriptors using a large scale MR-derived cardiac motion atlas. (Lv), 2018.

- [165] M. J. Pekka Raatikainen, David O. Arnar, Katja Zeppenfeld, Jose Luis Merino, Francisco Levy, Gerhardt Hindriks, and Karl Heinz Kuck. Statistics on the use of cardiac electronic devices and electrophysiological procedures in the European Society of Cardiology countries: 2014 report from the European Heart Rhythm Association. *Europace*, 17:i1–i75, 2015.
- [166] Margaret M. Redfield. Heart failure with preserved ejection fraction. *New England Journal of Medicine*, 375(19):1868–1877, 2016. PMID: 27959663.
- [167] W J Richardson, S A Clarke, T A Quinn, and J W Holmes. Physiological Implications of Myocardial Scar Structure. *Comprehensive Physiology*, 5(4):1877–1909, oct 2015.
- [168] Jordan Ringenberg, Makarand Deo, Vijay Devabhaktuni, David Filgueiras-Rama, Gonzalo Pizarro, Borja Ibañez, Omer Berenfeld, Pamela Boyers, and Jeffrey Gold. Automated segmentation and reconstruction of patient-specific cardiac anatomy and pathology from in vivo MRI. *Measurement Science and Technology*, 23(12), 2012.
- [169] Moshe Rogosnitzky and Stacy Branch. Gadolinium-based contrast agent toxicity: a review of known and proposed mechanisms. *BioMetals*, 29(3):365–376, 2016.
- [170] Bryan A. Ross, Ron Wald, Marc B. Goldstein, Darren A. Yuen, Jonathon Leipsic, Mercedeh Kiaii, Andrea Rathe, Djeven P. Deva, Anish Kirpalani, Olugbenga O. Bello, John J. Graham, Howard Leong-Poi, Kim A. Connelly, and Andrew T. Yan. Relationships Between Left Ventricular Structure and Function According to Cardiac MRI and Cardiac Biomarkers in End-Stage Renal Disease. *Canadian Journal of Cardiology*, 33(4):501–507, 2017.

- [171] Daniel Rueckert, Luke I. Sonoda, Carmel Hayes, Derek LG Hill, Martin O. Leach, and David J. Hawkes. Nonrigid registration using free-form deformations: application to breast MR images. *Tmi*, 18(8):712–21, 1999.
- [172] Robert Rushmer. *Cardiovascular Dynamics*. W. B. Saunders Company, 2th edition, 1961.
- [173] Smita Sampath, J. Andrew Derbyshire, Ergin Atalar, Nael F. Osman, and Jerry L. Prince. Real-time imaging of two-dimensional cardiac strain using a harmonic phase magnetic resonance imaging (HARP-MRI) pulse sequence. *Magnetic Resonance in Medicine*, 50(1):154–163, 2003.
- [174] A. Scatteia, A. Baritussio, and C. Bucciarelli-Ducci. Strain imaging using cardiac magnetic resonance. *Heart Failure Reviews*, 22(4):465–476, 2017.
- [175] Alexander Schick, Mika Fischer, and Rainer Stiefelhagen. Measuring and evaluating the compactness of superpixels. *Proceedings - International Conference on Pattern Recognition*, (ICPR):930–934, 2012.
- [176] Brian J Schietinger, Glenn M Brammer, Hongkun Wang, M John, Katherine W Kwon, Amy J Mangrum, J Michael Mangrum, and Christopher M Kramer. NIH Public Access. 1(4):450–456, 2010.
- [177] A. Schuster, V. C. Stahnke, C. Unterberg-Buchwald, J. T. Kowallick, P. Lamata, M. Steinmetz, S. Kutty, M. Fasshauer, W. Staab, J. M. Sohns, B. Bigalke, C. Ritter, G. Hasenfuß, P. Beerbaum, and J. Lotz. Cardiovascular magnetic resonance feature-tracking assessment of myocardial mechanics: Intervendor agreement and considerations regarding reproducibility. *Clinical Radiology*, 70(9):989–998, 2015.
- [178] Andreas Schuster, Kan N. Hor, Johannes T. Kowallick, Philipp Beerbaum, and Shelby Kutty. Cardiovascular Magnetic Resonance Myocardial Feature

- Tracking: Concepts and Clinical Applications. *Circulation: Cardiovascular Imaging*, 9(4):1–9, 2016.
- [179] Randolph M. Setser, Daniel G. Bexell, Thomas P. O’Donnell, Arthur E. Stillman, Michael L. Lieber, Paul Schoenhagen, and Richard D. White. Quantitative assessment of myocardial scar in delayed enhancement magnetic resonance imaging. *Journal of Magnetic Resonance Imaging*, 18(4):434–441, 2003.
- [180] N J Severs. The cardiac muscle cell. *BioEssays : news and reviews in molecular, cellular and developmental biology*, 22(2):188–199, 2000.
- [181] Bruce Smaill and Peter Hunter. Structure and Function of the Diastolic Heart: Material Properties of Passive Myocardium. *Theory of Heart*, pages 1–29, 1991.
- [182] Otto A. Smiseth, Hans Torp, Anders Opdahl, Kristina H. Haugaa, and Stig Urheim. Myocardial strain imaging: How useful is it in clinical decision making? *European Heart Journal*, 37(15):1196–1207b, 2016.
- [183] P Smith, D B Reid, Cluttered Environment, Lockheed Palo, Palo Alto, and P L Smith. Otsu, A threshold selection method, 1979. 20(1):62–66, 1979.
- [184] A. Sotiras, C. Davatzikos, and N. Paragios. Deformable medical image registration: A survey. *IEEE Transactions on Medical Imaging*, 32(7):1153–1190, July 2013.
- [185] Ana Luiza Mansur Souto, Rafael Mansur Souto, Isabella Cristina Resende Teixeira, and Marcelo Souto Nacif. Myocardial Viability on Cardiac Magnetic Resonance. *Arquivos Brasileiros de Cardiologia*, pages 458–469, 2017.
- [186] B. S. Spottiswoode, X. Zhong, A. T. Hess, C. M. Kramer, E. M. Meintjes, B. M. Mayosi, and Frederick H. Epstein. Tracking myocardial motion from

- cine DENSE images using spatiotemporal phase unwrapping and temporal fitting. *IEEE Transactions on Medical Imaging*, 26(1):15–30, 2007.
- [187] David Stutz, Alexander Hermans, and Bastian Leibe. Superpixels: An evaluation of the state-of-the-art. *Computer Vision and Image Understanding*, 166:1–27, 2018.
 - [188] Cathie Sudlow, John Gallacher, Naomi Allen, Valerie Beral, Paul Burton, John Danesh, Paul Downey, Paul Elliott, Jane Green, Martin Landray, Bette Liu, Paul Matthews, Giok Ong, Jill Pell, Alan Silman, Alan Young, Tim Sprosen, Tim Peakman, and Rory Collins. UK Biobank: An Open Access Resource for Identifying the Causes of a Wide Range of Complex Diseases of Middle and Old Age. *PLoS Medicine*, 12(3):1–10, 2015.
 - [189] Avan Suinesiaputra, Alejandro F. Frangi, Theodorus A M Kaandorp, Hildo J. Lamb, Jeroen J. Bax, Johan H C Reiber, and Boudewijn P F Lelieveldt. Automated regional wall motion abnormality detection by combining rest and stress cardiac MRI: Correlation with contrast-enhanced MRI. *Journal of Magnetic Resonance Imaging*, 34(2):270–278, 2011.
 - [190] Wei Sun, Elliot L Chaikof, and Marc E Levenston. Numerical approximation of tangent moduli for finite element implementations of nonlinear hyperelastic material models. *Journal of biomechanical engineering*, 130(6):61003, dec 2008.
 - [191] Yao Sun. Myocardial repair/remodelling following infarction: roles of local factors. *Cardiovascular Research*, 81(3):482–490, 2009.
 - [192] Virpi Talman and Heikki Ruskoaho. Cardiac fibrosis in myocardial infarction—from repair and remodeling to regeneration. *Cell and Tissue Research*, 365(3):563–581, 2016.

- [193] Qian Tao, Julien Milles, Katja Zeppenfeld, Hildo J. Lamb, Jeroen J. Bax, Johan H C Reiber, and Rob J. Van Der Geest. Automated segmentation of myocardial scar in late enhancement MRI using combined intensity and spatial information. *Magnetic Resonance in Medicine*, 64(2):586–594, 2010.
- [194] Qian Tao, Sebastiaan R D Piers, Hildo J. Lamb, and Rob J. Van Der Geest. Automated left ventricle segmentation in late gadolinium-enhanced MRI for objective myocardial scar assessment. *Journal of Magnetic Resonance Imaging*, 42(2):390–399, 2015.
- [195] Robin J. Taylor, William E. Moody, Fraz Umar, Nicola C. Edwards, Tiffany J. Taylor, Berthold Stegemann, John N. Townend, Kan N. Hor, Richard P. Steeds, Wojciech Mazur, and Francisco Leyva. Myocardial strain measurement with feature-tracking cardiovascular magnetic resonance: Normal values. *European Heart Journal Cardiovascular Imaging*, 16(8):871–881, 2015.
- [196] Robin J. Taylor, Fraz Umar, Erica L.S. Lin, Amar Ahmed, William E. Moody, Wojciech Mazur, Berthold Stegemann, Jonathan N. Townend, Richard P. Steeds, and Francisco Leyva. Mechanical effects of left ventricular midwall fibrosis in non-ischemic cardiomyopathy. *Journal of Cardiovascular Magnetic Resonance*, 18(1):1–8, 2016.
- [197] Michael Tee, J. Alison Noble, and David A Bluemke. Imaging techniques for cardiac strain and deformation: comparison of echocardiography, cardiac magnetic resonance and cardiac computed tomography. *Expert Review of Cardiovascular Therapy*, 11(2):221–231, 2013.
- [198] J P Thirion. Image matching as a diffusion process: an analogy with Maxwell’s demons. *Medical image analysis*, 2(3):243–260, 1998.

- [199] Henrik S. Thomsen, Peter Marckmann, and Vibeke B. Logager. Nephrogenic systemic fibrosis (NSF): A late adverse reaction to some of the gadolinium based contrast agents. *Cancer Imaging*, 7(1):130–137, 2007.
- [200] Catalina Tobon-Gomez, Mathieu De Craene, Annette Dahl, Stam Kapetanakis, Gerry Carr-White, Anja Lutz, Volker Rasche, Patrick Etyngier, Sebastian Kozerke, Tobias Schaeffter, Chiara Riccobene, Yves Martelli, Oscar Camara, Alejandro Frangi, and Kawal Rhode. A Multimodal Database for the 1st Cardiac Motion Analysis Challenge. *Statistical Atlases and Computational Models of the Heart. Imaging and Modelling Challenges*, 7085:33–44, 2012.
- [201] Catalina Tobon-Gomez and et al. Benchmarking framework for myocardial tracking and deformation algorithms : An open access database. *Medical Image Analysis*, 17(6):632–648, 2013.
- [202] Gerard J Tortora and Bryan Derrickson. *Principles of anatomy & physiology*. Wiley, Danvers, MA, 14th edition, 2014.
- [203] N Townsend, J Williams, P Bhatnagar, K Wickramasinghe, and M Rayner. *Cardiovascular Disease Statistics*. 2014.
- [204] Phi Vu Tran. A Fully Convolutional Neural Network for Cardiac Segmentation in Short-Axis MRI. pages 1–21, 2016.
- [205] Filippos Triposkiadis, Javed Butler, Francois M Abboud, Paul W Armstrong, Stamatis Adamopoulos, John J Atherton, Johannes Backs, Johann Bauersachs, Daniel Burkhoff, Robert O Bonow, Vijay K Chopra, Rudolf A de Boer, Leon de Windt, Nazha Hamdani, Gerd Hasenfuss, Stephane Heymans, Jean-Sébastien Hulot, Marvin Konstam, Richard T Lee, Wolfgang A Linke, Ida G Lunde, Alexander R Lyon, Christoph Maack, Douglas L Mann, Alexandre Mebazaa, Robert J Mentz, Petros Nihoyannopoulos, Zoltan Papp, John Parisi, Thierry Pedrazzini, Giuseppe Rosano, Jean Rouleau, Petar M Seferovic,

- Ajay M Shah, Randall C Starling, Carlo G Tocchetti, Jean-Noel Trochu, Thomas Thum, Faiez Zannad, Dirk L Brutsaert, Vincent F Segers, and Gilles W De Keulenaer. The continuous heart failure spectrum: moving beyond an ejection fraction classification. *European Heart Journal*, 40(26):2155–2163, 2019.
- [206] KAI TSUIKI and ERIK L. RITMAN. Direct evidence that left ventricular myocardium is incompressible throughout systole and diastole. *The Tohoku Journal of Experimental Medicine*, 132(1):119–120, 1980.
- [207] E. B. Turkbey, M. S. Nacif, R. A. Noureldin, C. T. Sibley, S. Liu, J. A C Lima, and D. A. Bluemke. Differentiation of myocardial scar from potential pitfalls and artefacts in delayed enhancement MRI. *British Journal of Radiology*, 85(1019), 2012.
- [208] Hans Thijs van den Broek, Steven Wenker, Rutger van de Leur, Pieter A. Doevendans, Steven A.J. Chamuleau, Frebus J. van Slochteren, and René van Es. 3D Myocardial Scar Prediction Model Derived from Multimodality Analysis of Electromechanical Mapping and Magnetic Resonance Imaging. *Journal of Cardiovascular Translational Research*, 2019.
- [209] Tom Vercauteren, Xavier Pennec, Aymeric Perchant, and Nicholas Ayache. Diffeomorphic demons: efficient non-parametric image registration. *NeuroImage*, 45(1 Suppl):S61–S72, 2009.
- [210] TM Vesely and DR Cahill. Cross-sectional anatomy of the pericardial sinuses, recesses, and adjacent structures. *Surgical and Radiologic Anatomy*, 8(4):221–227, Dec 1986.
- [211] Adriana Dm Villa, Eva Sammut, Arjun Nair, Ronak Rajani, Rodolfo Bonamini, and Amedeo Chiribiri. Coronary artery anomalies overview: The normal and the abnormal. *World journal of radiology*, 8(6):537–55, 2016.

- [212] Benjamin Villard, Ernesto Zacur, Erica Dall’Armellina, and Vicente Grau. Correction of slice misalignment in multi-breath-hold cardiac MRI scans. *Lecture Notes in Computer Science (including subseries Lecture Notes in Artificial Intelligence and Lecture Notes in Bioinformatics)*, 10124 LNCS:30–38, 2017.
- [213] Ha Q. Vo, Thomas H. Marwick, and Kazuaki Negishi. MRI-Derived Myocardial Strain Measures in Normal Subjects. *JACC: Cardiovascular Imaging*, 11(2), 2016.
- [214] Ha Q. Vo, Thomas H. Marwick, and Kazuaki Negishi. MRI-Derived Myocardial Strain Measures in Normal Subjects. *JACC: Cardiovascular Imaging*, 11(2P1):196–205, 2018.
- [215] Jens Uwe Voigt, Gianni Pedrizzetti, Peter Lysyansky, Tom H. Marwick, Helen Houle, Rolf Baumann, Stefano Pedri, Yasuhiro Ito, Yasuhiko Abe, Stephen Metz, Joo H.yun Song, Jamie Hamilton, Partho P. Sengupta, Theodore J. Koliass, Jan D’Hooge, Gerard P. Aurigemma, James D. Thomas, and Luigi P.aolo Badano. Definitions for a common standard for 2D speckle tracking echocardiography: consensus document of the EACVI/ASE/Industry Task Force to standardize deformation imaging. *European heart journal cardiovascular Imaging*, 16(1):1–11, 2015.
- [216] Andrew P. Voorhees and Hai-Chao Han. Biomechanics of Cardiac Function. *Compr Physiol*, 91(2):165–171, 2015.
- [217] He Wang, Lei Dong, Jennifer O’Daniel, Radhe Mohan, Adam S Garden, K Kian Ang, Deborah A Kuban, Mark Bonnen, Joe Y Chang, and Rex Cheung. Validation of an accelerated ’demons’ algorithm for deformable image registration in radiation therapy. *Physics in Medicine and Biology*, 50(12):2887, 2005.

- [218] Monan Wang and Pengcheng Li. A Review of Deformation Models in Medical Image Registration. *Journal of Medical and Biological Engineering*, 6(0123456789), 2018.
- [219] Na Wang, Chung-Lieh Hung, Sung-Hee Shin, Brian Claggett, Hicham Skali, Jens Jakob Thune, Lars Køber, Amil Shah, John J.V. McMurray, Marc A. Pfeffer, and Scott D. Solomon. Regional cardiac dysfunction and outcome in patients with left ventricular dysfunction, heart failure, or both after myocardial infarction. *European Heart Journal*, 37(5):466–472, 2016.
- [220] Anne Waugh, Allison Grant, and Janet S Ross. *Ross and Wilson anatomy and physiology in health and illness*. Churchill Livingstone Elsevier, Edinburgh, 11th edition, 2010.
- [221] Jessica Webb, Lauren Fovargue, Kristin Tøndel, Bradley Porter, Benjamin Sieniewicz, Justin Gould, Christopher Aldo Rinaldi, Tevfik Ismail, Amedeo Chiribiri, and Gerald Carr-White. The Emerging Role of Cardiac Magnetic Resonance Imaging in the Evaluation of Patients with HFpEF. *Current Heart Failure Reports*, 15(1):1–9, 2018.
- [222] Dong Wei, Ying Sun, Sim-heng Ong, Ping Chai, Lynette L Teo, and Adrian F Low. A Comprehensive 3-D Framework for Automatic Quantification of Late Gadolinium Enhanced Cardiac Magnetic Resonance Images. *IEEE Transactions on Medical Imaging*, 60(6):1499–1508, 2013.
- [223] L. M. Wu, D. A.L. An, Q. Y. Yao, Y. R.Z. Ou, Q. Lu, M. Jiang, and J. R. Xu. Hypertrophic cardiomyopathy and left ventricular hypertrophy in hypertensive heart disease with mildly reduced or preserved ejection fraction: insight from altered mechanics and native T1 mapping. *Clinical Radiology*, 72(10):835–843, 2017.

- [224] Chenchu Xu, Lei Xu, Gary Brahm, Heye Zhang, and Shuo Li. Segmentation and Quantification of Infarction without Contrast Agents via Spatiotemporal Generative. *MICCAI*, pages 1–11, 2018.
- [225] Chenchu Xu, Lei Xu, Zhifan Gao, Shen Zhao, Heye Zhang, Yanping Zhang, Xiuquan Du, Shu Zhao, Dhanjoo Ghista, Huafeng Liu, and Shuo Li. Direct delineation of myocardial infarction without contrast agents using a joint motion feature learning architecture. *Medical Image Analysis*, 50:82–94, 2018.
- [226] Guang Yang, Xiahai Zhuang, Habib Khan, Shouvik Haldar, Eva Nyktari, Lei Li, Ricardo Wage, Xujiong Ye, Greg Slabaugh, Raad Mohiaddin, Tom Wong, Jennifer Keegan, and David Firmin. Fully automatic segmentation and objective assessment of atrial scars for long-standing persistent atrial fibrillation patients using late gadolinium-enhanced MRI. *Medical Physics*, 45(4):1562–1576, 2018.
- [227] Guang Yang, Xiahai Zhuang, Habib Khan, Shouvik Haldar, Eva Nyktari, Xujiong Ye, Greg Slabaugh, Tom Wong, Raad Mohiaddin, Jennifer Keegan, and David Firmin. Segmenting atrial fibrosis from late gadolinium-enhanced cardiac MRI by deep-learned features with stacked sparse auto-encoders. *Communications in Computer and Information Science*, 723:195–206, 2017.
- [228] Paul A. Yushkevich, Joseph Piven, Heather Cody Hazlett, Rachel Gimpel Smith, Sean Ho, James C. Gee, and Guido Gerig. User-guided 3D active contour segmentation of anatomical structures: Significantly improved efficiency and reliability. *Neuroimage*, 31(3):1116–1128, 2006.
- [229] Constantine Zakkaroff, John D. Biglands, John P. Greenwood, Sven Plein, Roger D. Boyle, Aleksandra Radjenovic, and Derek R. Magee. Patient-specific coronary blood supply territories for quantitative perfusion analysis. *Computer*

Methods in Biomechanics and Biomedical Engineering: Imaging and Visualization, 6(2):137–154, 2018.

- [230] Tarek Zghaib, Mounes Aliyari Ghasabeh, Fabrizio R. Assis, Jonathan Chrispin, Ali Keramati, Satish Misra, Ronald Berger, Hugh Calkins, Ihab Kamel, Saman Nazarian, Stefan Zimmerman, and Harikrishna Tandri. Regional Strain by Cardiac Magnetic Resonance Imaging Improves Detection of Right Ventricular Scar Compared With Late Gadolinium Enhancement on a Multimodality Scar Evaluation in Patients With Arrhythmogenic Right Ventricular Cardiomyopathy. *Circulation. Cardiovascular imaging*, 11(9):e007546, 2018.
- [231] Lijun Zhang, Xiantao Song, Li Dong, Jianan Li, Ruiyu Dou, Zhanming Fan, Jing An, and Debiao Li. Additive value of 3T cardiovascular magnetic resonance coronary angiography for detecting coronary artery disease. *Journal of Cardiovascular Magnetic Resonance*, 20(1):1–8, 2018.
- [232] X Zhen, H Yan, X Gu, L Zhou, X Jia, and S Jiang. CT to Cone-Beam CT Deformable Registration With Simultaneous Intensity Correction. *Medical Physics*, 39(6):3960, 2012.
- [233] Tiffany Christina Zigras. Biomechanics of human pericardium: a comparative study of fresh and fixed tissue. 2007.
- [234] Kelly H. Zou, Simon K. Warfield, Aditya Bharatha, Clare M.C. Tempany, Michael R. Kaus, Steven J. Haker, William M. Wells, Ferenc A. Jolesz, and Ron Kikinis. Statistical Validation of Image Segmentation Quality Based on a Spatial Overlap Index. *Academic Radiology*, 11(2):178–189, 2004.