



UNIVERSITÀ
DEGLI STUDI
DI PADOVA

Head Office: Università degli Studi di Padova

DEPARTMENT OF CARDIAC THORACIC AND VASCULAR SCIENCES

Ph.D. COURSE:

Medicina Specialistica "G.B. Morgagni"

CURRICULUM: Cardiac Thoracic and Vascular Sciences

SERIES 30°

**NON-TRAUMATIC OUT OF HOSPITAL CARDIAC ARREST:
DIAGNOSTIC AND PROGNOSTIC ROLE
OF CARDIOVASCULAR MAGNETIC RESONANCE**

Coordinator: Prof Annalisa Angelini

Supervisor: Prof Martina Perazzolo-Marra

Co-Supervisor: Prof Chiara Bucciarelli-Ducci

PhD Student: Dr ssa Anna Baritussio

INDEX

Abstract	6
Abbreviations	8
Chapter 1. Non-traumatic out of hospital cardiac arrest	11
1.1 Aetiology	12
1.1.1 Ischemic heart disease	12
1.1.2 Non-ischemic heart disease	14
1.1.3 Idiopathic ventricular fibrillation	15
1.2 Diagnosis	16
1.2.1 Urgent coronary angiography	16
1.2.2 Cardiac Imaging	17
1.2.2.1 Trans-thoracic Echocardiogram	18
1.2.2.2 Cardiovascular Magnetic Resonance	19
1.2.2.3 Cardiac nuclear imaging	20
1.3 Management and early treatment	21
1.3.1 Post resuscitation care	21
1.3.2 Prevention of recurrences	22
Chapter 2. Cardiovascular Magnetic Resonance	24
2.1 Basic CMR physics	24
2.2 Cardiac function	29
2.3 Tissue characterisation	29
2.4 Myocardial deformation analysis	33
2.5 Contraindications to CMR	36

Chapter 3. Background. Impact of cardiovascular magnetic resonance on clinical management and decision-making in out of hospital cardiac arrest survivors with inconclusive coronary angiogram	38
3.1 Background	38
3.2 Materials and methods	39
3.3 Statistical analysis	40
3.4 Results	41
3.5 Discussion	51
3.6 Conclusions	54
Chapter 4 Aims	55
Chapter 5 Materials and Methods	57
5.1 CMR acquisition	57
5.2 CMR analysis	58
5.3 Statistical analysis	60
Chapter 6. Results	62
6.1 Clinical characteristics	62
6.2 CMR findings	63
6.3 Patients with structurally normal hearts	67
6.4 Outcome	67
6.5 Outcome in patients wearing ICD	72
Chapter 7. Discussion	74
7.1 Late gadolinium enhancement	74
7.2 Myocardial strain	76
7.3 Predictors of recurrent adverse events	78
7.4 Limitations	82
Chapter 8. Conclusions	84

8.1	Future directions	84
References		85
Acknowledgments		104

Abstract

Background Cardiovascular Magnetic Resonance (CMR) plays an important role in out of hospital cardiac arrest survivors, not only as a diagnostic tool, but also as a guide to clinical decision-making and to patients' management: CMR has shown to have a clinical impact in a considerable proportion of patients surviving both tachy-arrhythmic cardiac arrest and pulseless electrical activity. There is also growing evidence of the predictive role of CMR, especially in the setting of ventricular arrhythmias. In patients surviving ventricular fibrillation (VF) cardiac arrest, recurrence of Major Cardiovascular Adverse Events (MACE) is not rare. We sought to identify CMR-derived structural and functional myocardial predictors of MACE recurrence in VF cardiac arrest survivors.

Material and Methods We retrospectively analysed our CMR registry to enrol VF cardiac arrest survivors. All patients underwent a 1.5 T CMR, comprehensive of long and short-axis cine and late gadolinium enhancement (LGE) sequences. LGE was quantified with semi-automated software using the full width at half maximum method (cvi42, Circle Cardiovascular Imaging). Tissue tracking analysis software was used to assess myocardial deformation (cvi42, Circle Cardiovascular Imaging). Primary end-points were all-cause mortality and appropriate ICD discharge/anti-tachycardia pacing.

Results We enrolled 121 patients [82% male, 62 years (IQR 53-70)]. CMR was performed within 13 days (IQR 6-42) from VF arrest. Left ventricular (LV) systolic function was mildly impaired [LVEF 54 (41-64)%], right ventricular systolic function was preserved [RVEF 60 (53-65)%]. LGE was found in 71% of patients, median mass was 6.2 (0-15)% of the left ventricle. Myocardial deformation was overall impaired [global longitudinal strain, -15.5 (-18.9- -12.3)%; global radial strain, 34.2 (25.2-45.2)%; global circumferential strain, -

15.5 (-20.3- -11.9)%]. There was a significant correlation between LGE mass and myocardial deformation ($p < 0.001$). On CMR, 75 patients (62%) were diagnosed with ischemic heart disease (IHD) and 20 (17%) with non-ischemic heart disease (NIHD); a structural normal heart was found in 26 (21%). Fifty-two per cent of patients were implanted with an ICD. After a median follow-up of 24 months (IQR 6-41), 22 patients (18%) were lost to follow-up. Primary end-point was met in 24 patients (14 deaths, 10 appropriate ICD discharge). LVEF did not differ between patients with and without end-point ($p = 0.128$), while RVEF was significantly lower in those meeting the end-point (58% vs 61%, $p = 0.03$). LGE prevalence did not differ between patients with and without end-point ($p = 0.075$) but its extent was significantly greater in patients experiencing adverse events (LGE mass 8.6% of LV vs 4.1%, $p = 0.02$). Myocardial deformation did not differ between patients with and without end-point. Patients with LGE mass $> 4.3\%$ represented a subgroup at a higher risk of adverse events ($p = 0.0048$).

Conclusions In a population of VF cardiac arrest survivors, CMR was able to identify a pathological substrate of the cardiac arrest in 79% of cases. While CMR-derived myocardial deformation assessment was not able to differentiate patients experiencing adverse events from those event-free, an LGE mass $> 4.3\%$ of LV myocardium identified a subgroup of patients at a higher risk of developing adverse events. Further studies, in larger populations, are warranted to expand the findings on the role of CMR as risk stratification tool in this group of patients.

Abbreviations

ACS - Acute Coronary Syndromes

ARVC - Arrhythmogenic Right Ventricular Cardiomyopathy

ATP - Anti-Tachycardia Pacing

CAD - Coronary Artery Disease

CMR - Cardiovascular Magnetic Resonance

CPR - Cardio-Pulmonary Resuscitation

CPVT - Catecholaminergic Polymorphic Ventricular Tachycardia

DCM - Dilated Cardiomyopathy

ECG - Electrocardiogram

GCS - Global Circumferential Strain

GLS - Global Longitudinal Strain

GRS - Global Radial Strain

HCM - Hypertrophic Cardiomyopathy

ICD - Implantable Cardioverter Defibrillator

IHD - Ischemic Heart Disease

IQR - Interquartile Range

IVF - Idiopathic Ventricular Fibrillation

LGE - Late Gadolinium Enhancement

LQTS - Long QT Syndrome

LVEF - Left Ventricular Ejection Fraction

LVIEDV - Indexed Left Ventricular End-Diastolic Volume

LVIESV - Indexed Left Ventricular End-Systolic Volume

MACE - Major Cardiovascular Adverse Events

MI - Myocardial Infarction

MINOCA - Myocardial Infarction With Non-Obstructive Coronary Arteries

NIHD - Non-Ischemic Heart Disease

NSF - Nephrogenic Systemic Fibrosis

NSTEMI - Non ST-Segment Elevation Myocardial Infarction

OHCA - Out Of Hospital Cardiac Arrest

PCI - Percutaneous Coronary Intervention

PEA - Pulseless Electrical Activity

POC - Point-of-care

RF - Radiofrequency

ROSC - Recovery Of Spontaneous Circulation

RVEF - Right Ventricular Ejection Fraction

RViEDV - Indexed Right Ventricular End-Diastolic Volume

RViESV - Indexed Right Ventricular End-Systolic Volume

SCAD - Stable Obstructive Coronary Artery Disease

SCD - Sudden Cardiac Death

SNH - Structurally Normal Heart

SpTE - Speckle Tracking Echocardiography

SQTS - Short QT Syndrome

STE - ST segment Elevation

STEMI - ST Segment Elevation Myocardial Infarction

STIR - Short Tau Inversion Recovery

TE - Echo Time

TR - Repetition Time

TTE - Trans-Thoracic Echocardiogram

TTC - Tako-Tsubo Cardiomyopathy

TTM - Target Temperature Management

VF - Ventricular Fibrillation

VT - Ventricular Tachycardia

WMA - Wall Motion Abnormality

Chapter 1. Non-traumatic out of hospital cardiac arrest

Non-traumatic out of hospital cardiac arrest (OHCA) is the leading cause of death worldwide (1), being responsible for more than 350,000 deaths in the United States of America, only in 2014 (2). The real incidence of OHCA is difficult to establish, as OHCA definition, management and outcome recording vary widely across different countries' registries (3)(4)(5)(6). In 1990 a group of experts provided a unified classification of OHCA, called the "Utstein style", which aimed at providing criteria for the definition of OHCA and its outcome (3) (7); these criteria, which have been modified through the years, in order to make it easier to report OHCA events, were finally approved in 2012 (6). Based on these "revised Utstein style" criteria, a recent multi-centre one-month study conducted in Europe (EuReCa ONE) showed an incidence rate of 84 per 100.000 (8). Incidence of OHCA increases with age, and is more frequently associated with male gender and background of coronary artery disease (CAD) (7)(9). Although a positive history of CAD is found in 80% of cases (10), OHCA is the first manifestation of an underlying cardiac disease in up to 20-40% of cases (9), even more so now that incidence of CAD has progressively decreased; this led to a change in the at-risk population, which is now mainly represented by patients with no pre-existing cardiac diseases, and that would not meet indications for primary prevention implantable cardiac defibrillator (ICD) implantation (11). The incidence of OHCA varies considerably when considering different risk sub-groups: patients with high coronary risk profile have 0.1–0.2 per 1000 per year incidence of sudden cardiac death (SCD), those with prior coronary event have 0.5 per 1000 per year incidence, patients with heart failure and reduced ejection fraction have 1.5 per 1000 per year

incidence, while patients surviving a cardiac arrest have an incidence of 2.5 per 1000 per year (12). A progressive decrease in the incidence of shockable rhythms (ventricular fibrillation (VF)/ventricular tachycardia (VT)) has also been recently reported (8)(11)(13), mainly as a consequence of increased use of beta-blockers and of ICDs. However, survival rates have not improved over the years and remain still quite unsatisfactory, with an overall estimated rate of 10% (8)(14). Effective cardio-pulmonary resuscitation (CPR) and early defibrillation have been shown to be the most important rings of the chain of survival, playing a pivotal role in increasing survival rate: one of the most successful public health strategies has been indeed the training of laypersons to perform CPR and use automated external defibrillators (15).

1.1 Aetiology

Almost half of all sudden deaths have a cardiovascular origin (14)(16), attributable to underlying CAD or ischemic heart disease (IHD) in up to 80% of cases (14)(17), and to non-ischemic heart disease (NIHD) in 15% of cases (18). An underlying cardiomyopathy is usually identified in 90% of patients surviving OHCA, but no cause is clearly identifiable in approximately 5-10% of cases (19)(20).

1.1.1 Ischemic Heart Disease

Despite the progressive decrease in CAD prevalence (1)(9)(15), IHD still represents the leading cause of death worldwide, and CAD alone explains up to 50% of all deaths (17). When looking at how OHCA manifests in this cohort of patients, it appears that cardiac arrest is the first manifestation in a considerable

proportion of patients (40-60%)(1), frequently occurring in those with known CAD but considered to be at low risk for major cardiovascular events (MACE), while it affects less than 25% of high-risk patients (prior myocardial infarction, MI, prior ventricular arrhythmias or history of heart failure); the remaining cases are represented by acute coronary syndromes (ACS) (10)(17), which explain approximately 50% of sudden ischemic deaths (21).

A tachyarrhythmia (VT/VF) is the most common presenting rhythm in this group of patients, and is based on two major mechanisms: 1) acute ischemia, both transient or prolonged, secondary to abrupt plaque rupture determining <50% lumen patency, and 2) re-entrant electrical circuit in the context of myocardial scar (17)(22); recent studies performed with Cardiovascular Magnetic Resonance (CMR) imaging have shown that these two entities, acute ischemia and myocardial scar, can co-exist as causes of OHCA (23). The different pathogenic mechanisms explain the at-risk populations features: on one hand, patients with acute ischemia usually have neither previous history of CAD nor symptoms preceding the index event, preserved left ventricular ejection fraction (LVEF) and a higher incidence of acute coronary thrombosis in a single vessel; on the other hand, patients with scar-related OHCA tend to have a background of MI, impaired left ventricular ejection fraction (LVEF) and multi-vessel disease on coronary angiogram.

Cardiac arrest is four to six times more frequent in patients who had a myocardial infarction, with an annual incidence of 2-4%, and the risk is significantly higher in the first 30 days post-MI and exponentially decreases over the months to reach a steady state two years after the event (22).

1.1.2 Non-ischemic heart disease

Non-ischemic heart disease (NIHD) is responsible of OHCA in approximately 15-20% of cases (18)(19)(24). NIHD patients experiencing OHCA are usually young (≤ 35 years), fit, and otherwise well; the impact of life-years lost due to SCD in the young is greater than those due to cancer (25), with an SCD incidence in the 1-40 years population of 1.3-8.5 per 100,000 person-years.

The mechanism underlying OHCA in this group of patients is either genetically determined or secondary to the presence of myocardial scar. Most data on SCD occurring in this group of patients came from studies on SCD among young competitive athletes (≤ 35 years) (26)(27)(28): a large population study conducted in the Veneto region, in Italy, found a considerable prevalence, of approximately 2.3 per 100,000 athletes-year (26). Among non-ischemic cardiomyopathies, hypertrophic cardiomyopathy (HCM) accounts for one third of all OHCA cases (29)(30), followed by arrhythmogenic right ventricular cardiomyopathy (ARVC) and anomalous coronary arteries, that account for 15% of cases (24), while all the remaining cardiomyopathies (dilated cardiomyopathy, DCM, myocarditis, sarcoidosis) account for approximately 6% of cases (31)(32)(33). Anomalous coronary arteries, though found in only 1% of the population, are the commonest congenital heart disease in grown-up cardiac arrest survivors and represent the second most common cause of SCD in the young; cardiac arrest is secondary to haemodynamic instability due to a “malignant” artery course (i.e. inter-arterial course between the aortic root and the pulmonary artery) (24). Myocarditis accounts for approximately 5-10% of all cases of cardiac arrest and is generally secondary to fatal ventricular arrhythmias precipitated by inflammatory myocardial foci that do not alter LVEF or resting electrocardiogram (18)(25). Despite an overall annual risk of death of

0.1% in this young population, cardiomyopathies, such as HCM, DCM and ARVC, imply an annual risk of death of 2-4% (34).

1.1.3 Idiopathic ventricular fibrillation

The absence of an underlying cause of a tachyarrhythmia-induced OHCA, which is referred to as idiopathic ventricular fibrillation (IVF), is encountered in 5-10% of patients, and represents a great challenge, not only from a diagnostic perspective, but mainly from a prognostic one, as adverse arrhythmic events can recur in up to 30% of cases (20). IVF diagnosis is only possible once an extensive work-up has excluded all the possible structural heart diseases, both ischemic and non-ischemic, hence it is quite challenging, and that is why its incidence and pathogenesis are not yet completely understood. In order to improve the understanding and characterisation of this entity, two international registries, based in the United States (Idiopathic Ventricular Fibrillation Registry of the United States, IVF-US) and Europe (Unexplained Cardiac Arrest Registry in Europe, UCARE), respectively, were started in the 90's and are still on going. Recent studies showed that up to 30% of unexplained OHCA cases at autopsy in young subjects (<15 years of age) can be explained by channelopathies, such as Brugada syndrome, long (LQTS) and short (SQTS) QT syndrome and catecholaminergic polymorphic ventricular tachycardia (CPVT) (35). A new structural substrate has been recently described for the first time in association to OHCA, occurring especially in young adult women: myocardial fibrosis of the papillary muscle and basal inferolateral wall have been described as the structural hallmark in mitral valve prolapse patients experiencing SCD (36).

Post-mortem studies have also shown a correlation between OHCA and some non-specific anatomical and functional findings, in apparently normal hearts,

that are still under debate (18)(19): mild left ventricular hypertrophy in the absence of hypertension, atrial fibrillation, mild conduction system disease and the presence of interstitial myocardial fibrosis.

1.2 Diagnosis

1.2.1 Urgent coronary angiography

Secondary to the high prevalence of atherosclerotic lesions among OHCA survivors and at post-mortem studies of patients experiencing SCD (15), the European guidelines recommend to perform urgent coronary angiogram in view of primary percutaneous coronary intervention (PCI) in patients with resuscitated cardiac arrest with evidence of ST segment elevation (STE) on the first electrocardiogram (ECG) post recovery of spontaneous circulation (ROSC) (class I, level of evidence B) (37). However, it has been shown that obstructive or thrombotic “acute coronary syndrome” lesions can be found in 25%-58% of cardiac arrest cases with no evidence of ST elevation myocardial infarction (STEMI) on the first post-ROSC ECG (38). To strengthen the relation between CAD and OHCA, the latest 2017 ESC guidelines on STEMI have once again confirmed the indication to perform urgent coronary angiogram also in OHCA patients without diagnostic ST segment elevation, but with a high clinical suspicion of on-going infarction (class IIa, level of evidence C) (37).

Coronary angiography in OHCA survivors shows three different scenarios: 1) typical “ACS” culprit lesion, 2) obstructive CAD with stable appearance and 3) unobstructed coronary arteries (38). When a clear “ACS” culprit lesion is identified on urgent angiography, immediate PCI with flow restoration is the best strategy to improve the haemodynamic status, to reduce infarct size and cardiac

arrest recurrence, and to improve patient's survival; less clear is the relation between OHCA and stable CAD, as this might be due to transient ischemia on stable obstructive CAD (coronary spasm, plaque thrombosis with spontaneous recanalization) or it may just represent bystander disease. Nevertheless, although primary PCI and early revascularisation, respectively, significantly reduce SCD in STEMI and non-STEMI (NSTEMI) patients, sudden death early after MI, mainly secondary to mechanical complications, significantly impacts on overall deaths in this population (22). Finally, increasing attention is paid to myocardial infarction with non-obstructive coronary arteries (MINOCA), which has been shown to be involved in 1-14% of all MIs (37)(39); although an atherothrombotic cause can still be involved, other causes have to be encountered, such as myocarditis, Tako-Tsubo cardiomyopathy (TTC), and cardio-toxicity. Correct diagnosis in this subgroup of patients is of pivotal importance, as it implies different management and treatment strategy; non-invasive imaging, as will be discussed in detail later, plays an increasing and fundamental role in this setting.

1.2.2 Cardiac imaging

Current resuscitation guidelines do not recommend routine use of imaging, as they primarily aim at the resuscitation, peri- and post-resuscitation care of patients (40). However, multi-modality cardiac imaging is an important step in the correct diagnosis of OHCA causes, especially in patients without evidence of a culprit coronary lesion, and is determinant in guiding subsequent management and treatment.

1.2.2.1 Trans-thoracic echocardiogram

Trans-thoracic echocardiogram (TTE) can be useful in the identification of reversible causes of OHCA, such as cardiac tamponade or pulmonary embolism (non-cardiac cause of cardiac arrest, usually presenting as pulseless electrical activity) (41) and it successfully establishes the lack of cardiac activity during cardiac arrest. Focused TTE is recommended by the American Society of Echocardiography and by the American College of Emergency Physicians in order to identify the presence/absence of cardiac activity, assess biventricular function, identify the presence of pericardial effusion/tamponade in order to guide pericardiocentesis, and to confirm transvenous pacing wire placement (42)(43); comprehensive TTE or other imaging modalities are strongly recommended in cases of discordance between clinical presentation and findings on focused TTE. The guidelines strengthen the intrinsic limitations of TTE during resuscitation (technical difficulties related to on-going CPR, air in the stomach from bag-ventilation, presence of defibrillation pads) and recommend that TTE performance should never delay resuscitation manoeuvres or defibrillation; actually, it has been shown that focused TTE in pulseless electrical activity (PEA) cardiac arrest improves outcome by decreasing time to treatment (as a consequence of identification of underlying cause) and to ROSC. In order to avoid any delay in resuscitation manoeuvres, point-of-care (POC) focused echocardiography, which is performed during pulse-check intervals, has been proposed with the aim of diagnosing reversible causes of cardiac arrest, such as hypovolemia, cardiac tamponade and pulmonary embolism (44)(45), without interfering with resuscitation manoeuvres. POC TTE has shown to be a poor predictor of survival, but the identification of ventricular wall motion has shown to increase the likelihood of

ROSC from 2.4% to 51.6% (44). A recent meta-analysis on more than 1500 patients has shown that POC is mainly used to predict resuscitation outcome (only guiding decision to terminate resuscitation manoeuvres) and to identify reversible causes of cardiac arrest (45); however, it is limited by operator-dependency and by the need of a learning curve to perform focused TTE in non-ideal, emergency conditions; performing focused TTE during cardiac arrest is recognised as a core skill by many professional organisations (44). A comprehensive TTE once haemodynamic stability has been achieved is however the first line imaging technique for the assessment of global cardiac function, for differential diagnosis of the underlying causes of OHCA and also for in hospital follow-up of clinical improvement.

1.2.2.2 Cardiovascular Magnetic Resonance

Despite not being the first line imaging technique, the role of cardiovascular magnetic resonance (CMR) in the diagnostic assessment of patients surviving OHCA has increased over the past few years (46). As it will be discussed in details in the following chapter, the diagnostic role of CMR primarily relies on its ability to provide unique tissue characterisation, after administration of gadolinium-chelate contrast media: the presence, extent and distribution pattern of late gadolinium enhancement (LGE) allow the precise definition and differential diagnosis between IHD and NIHD (47). CMR was able to identify the underlying cause of cardiac arrest in more than two thirds of cases among 50% of OHCA survivors that had no clear diagnosis after a comprehensive clinical, electrocardiographic and imaging assessment (coronary angiogram and TTE) (48). Further evidence was provided by a similar study on OHCA survivors referred to CMR because of the absence of a clear diagnosis after a

comprehensive clinical, ECG and imaging assessment, which showed that CMR could identify a structural substrate for the cardiac arrest in 76% of patients (49). Finally, as previously described, MINOCA represent a non-negligible proportion of OHCA causes; in this setting CMR has an incomparable role, secondary to its ability to characterise both acute (i.e. oedema) and chronic myocardial damage, and the use of CMR within 2 weeks from the index event has been recently recommended for the diagnosis of the underlying cause (37)(50). Of course, the performance of a CMR scan requires the patient to be haemodynamically stable and, preferably, in spontaneous breathing, and this is way CMR is often postponed or, worse, not routinely performed in OHCA survivors. Moreover, patients surviving out of hospital cardiac arrest are often implanted with an ICD; as it will be further discussed in the next chapter, this usually requires waiting 6 weeks after endo-cavitary placement of the electrical leads in order to safely scan the patients, even in the case of MR-conditional devices.

1.2.2.3 Cardiac nuclear imaging

Cardiac nuclear imaging may also play a complimentary role in the assessment of cardiac arrest survivors, especially when it comes to defining arrhythmic risk, both in ischemic and non-ischemic cardiomyopathies (33). Single photon emission computed tomography and positron emission tomography play a role in the identification and quantification of myocardial scar, which is displayed as areas of fixed perfusion defects. The main role of these imaging modalities in the setting of ischemic cardiomyopathies comes from the identification of myocardial innervation-perfusion mismatch: nerve terminals are more susceptible to ischemia than cardiomyocytes, so that as a consequence of

myocardial infarction, viable myocardium may have impaired denervation; studies with nuclear medicine have shown that the greater the extent of myocardial denervation, the higher the number of ICD shocks at follow-up. Finally, positron emission tomography combines information on myocardial perfusion and inflammation, thus playing a pivotal role in the assessment of disease activity in sarcoidosis: a pattern of active inflammation on positron emission tomography was associated with a considerable increase in ventricular arrhythmias and death as compared to a normal study (33).

1.3 Management and early treatment

1.3.1 Post resuscitation care

The post resuscitation care is at least as important as the resuscitation phase, and big effort has been put in the identification of the best clinical practice aiming at increasing patients' survival after OHCA and prevent recurrences.

The latest European Resuscitation Council (ERC) guidelines (51) first emphasized, as one of the major post-resuscitation care, the importance of an urgent coronary angiogram in view to primary PCI in all OHCA survivors with suspected ischemic cause, as per the latest ESC guidelines previously described. The post-cardiac arrest syndrome mainly encounters brain injury and myocardial dysfunction, which mostly affect patients' survival after aborted SCD: myocardial dysfunction, which is common after OHCA and usually starts recovering within 2-3 days, is mostly responsible of early deaths (within the first 3 days), while brain injury is the leading cause of later deaths.

Fever has been proven to be one of the strongest predictors of poor outcome (51) and that is why therapeutic hypothermia has been for long time recognised

as the best practice to reduce neurological injury after OHCA, by reducing both brain metabolism and exposure to toxins. However, the Targeted Temperature Management (TTM) Trial has recently shown no difference in outcome (death and neurological outcome) in OHCA survivors of a cardiac cause treated at a temperature of 33°C vs 36°C (52).

1.3.2 Prevention of recurrences

Prognosis of OHCA survivors varies significantly according to first rhythm, with survival rates ranging from 7.4% after PEA arrest, to 27.1% after VF arrest (53). Many trials have tested the benefit of secondary prevention ICD implantation in patients surviving OHCA, showing markedly reduced adverse events rate among patients treated with ICD as compared to maximal anti-arrhythmic treatment. European guidelines recommend ICD implantation in patients with documented VF or haemodynamically non-tolerated VT in the absence of reversible causes (IA); ICD implantation should also be considered (IIaC) in patients with recurrent sustained VT (not within 48 hours from MI) who are receiving optimal medical therapy (54). Patients surviving OHCA are exposed at a higher risk of recurrent arrhythmic events: a small study on 18 patients with IVF (Brugada syndrome and the other channelopathies were systematically excluded from the study) showed a recurrence rate of VF, appropriately treated by ICD, of 39% with a mean time to first event of 12±9 months (55). Data on recurrence of adverse events after the first cardiac arrest vary significantly among different registries, with 51% ICD discharge within the first year in the Antiarrhythmic versus implantable defibrillators (AVID) trial, which enrolled patients surviving VF arrest or presenting with sustained VT and reduced LVEF, to 30% adverse events in primary prevention in the Sudden Cardiac Death in

Heart Failure (SCD-HeFT) trial within the first three years of follow-up. The vast heterogeneity in ICD discharge rate in OHCA survivors is at least in part explained by the different ICD programming: longer detection intervals have now been proven to be effective in reducing ICD therapies without increasing risk of adverse events, and are expected to change recurrence rates if systematically applied in clinical practice.

Chapter 2. Cardiovascular Magnetic Resonance

Cardiovascular magnetic resonance (CMR) is a multi-parametric, multi-planar, non-invasive imaging modality, which does not require the use of ionising radiation. Due to its higher spatial resolution, higher blood pool-epicardium contrast and superior tissue characterisation, it is an increasingly used imaging technique, also in daily clinical practice. CMR scanners commonly used in clinical practice have 1.5T or 3T field strength, which equals respectively 30000 and 60000 times the magnetic field of the Earth. A CMR scanner consists of the main static magnetic coil (B_0), the gradient coils and the radiofrequency transmitter coil.

2.1 Basic CMR physics

The physics of CMR exploits a basic concept, that 90% of human body is made of water. Looking at the nuclei, hydrogen protons are positively charged and they continuously move around an axis, they spin. As for physics principle, electrical charges in motion generate a magnetic field; when protons are put into a magnetic field (i.e. the magnetic field of a CMR scanner, B_0), they can either align along the direction of the magnetic field, or align in the opposite direction, but given that less energy is required to align along the direction of the external magnetic field, an excess of protons will align along the direction of the external magnetic field B_0 , generating a net magnetic moment (M_z , longitudinal magnetisation). The protons put into an external magnetic field B_0 will continue to move (precess), with a frequency, which is proportional to the intensity of the external magnetic field B_0 ; this is described by the *Larmor equation*: $\omega_0 = \gamma B_0$ (ω_0 is the precession frequency, expressed in Hz or MHz, γ is the gyro-

magnetic ratio, that is 42.5 MHz/T for protons, and B_0 is the external magnetic field). If a patient is put inside a 1.5T CMR scanner, the protons will align along the direction of the external magnetic field B_0 and will start precessing, but it is not possible to measure the magnetic field generated and a radiofrequency (RF) pulse has to be sent to alter the equilibrium. As it is easier to exchange energy between molecules that share similar properties, in order for the RF pulse to be able to exchange energy with the protons, the RF needs to have a specific frequency, similar to those of the protons. As the RF pulse is sent, the protons pick up energy (this process is called “resonance”) and by doing so some of the protons will go from a lower to a higher level of energy, and some will align in the direction opposite to that of the external magnetic field B_0 , so that overall the longitudinal magnetisation M_z will decrease; however, the RF pulse will make the protons precess synchronously, in phase, generating another magnetic field, pointing to the side to which the protons precess, which is called transversal magnetisation (M_{xy}) (**Figure 1**).

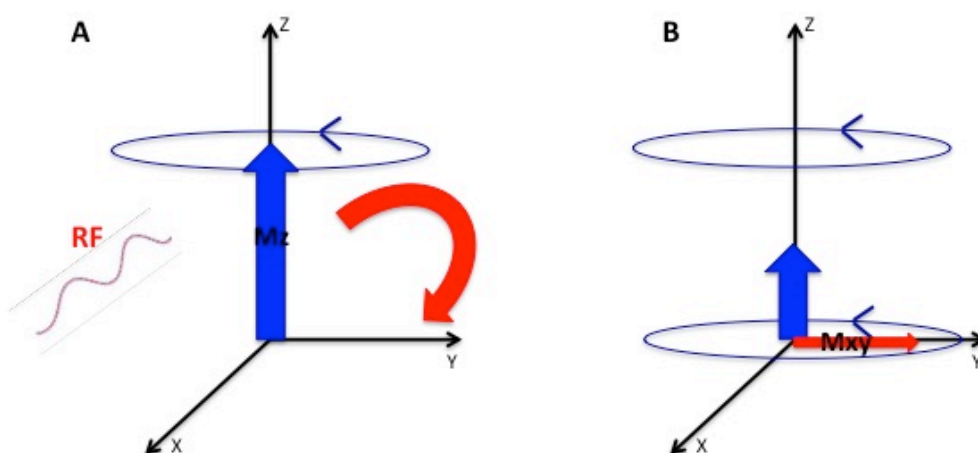


Figure 1. Longitudinal and transversal magnetisation. A) After the radiofrequency (RF) pulse is sent, protons pick up energy and change their

alignment along the external magnetic field; as a result, longitudinal magnetisation (M_z) decreases. B) The RF pulse, however, makes the protons precess in phase so that a new, transversal, magnetisation (M_{xy}) is generated.

When the RF pulse stops, the protons go back to their initial state and hand over their energy to the surroundings: the longitudinal magnetisation builds up again and the time needed to recover 63% of the original longitudinal magnetisation M_0 is described by the T1 relaxation or longitudinal (spin to lattice) relaxation; this depends on the field strength and on the tissue in which the relaxing protons are. The RF pulse had the role to make the protons precess in phase, so when the RF pulse stops, the protons do not precess in phase anymore, there is a loss of coherence and the transversal magnetisation decreases: the T2 relaxation or transversal (spin to spin) relaxation describes the time needed for the signal to decay to 37% of its original value. The magnetic field is per se inhomogeneous, and when this inhomogeneity is combined with T2 relaxation, this is called T2* relaxation (56). Different tissues have different T1 and T2 relaxation times (**Figure 2**), and this is at the basis of the tissue characterisation provided by CMR. Generally, T1 is longer than T2 (300-2000 msec vs 30-150 msec). T1 depends on tissue composition and on the surroundings. Water molecules, for example, are small and move quite rapidly, so energy handover is difficult and takes longer: fluids have long T1 relaxation; moreover, by moving fast, their local magnetic fields fluctuate fast and there is not a big difference in magnetic field: fluids have long T2. The carbon bonds at the end of lipids molecules have precession frequency very close to Larmor frequency, so that the exchange of energy is quick: T1 of fat is short. T1 relaxation can be altered by contrast administration: gadolinium-

chelate contrast agents shorten T1 relaxation time, and this is at the basis of T1 weighted post-contrast imaging.

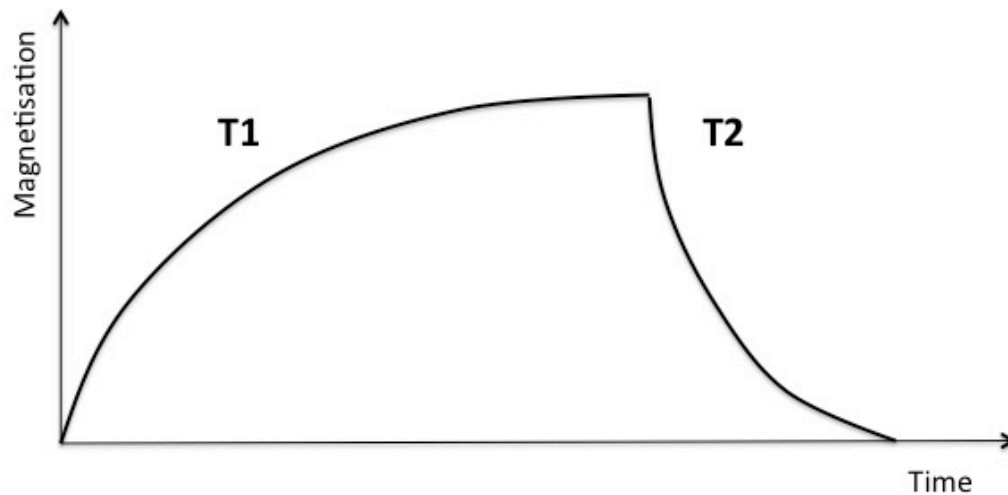


Figure 2. Coupling of the T1 and T2 relaxation curves. T1 relaxation is normally longer than T2 relaxation.

Contrast-weighting imaging is the key component of the clinical application of CMR, as it is responsible of the superior tissue characterisation provided by this technique. Contrast-weighting imaging is based on different timing parameters: repetition time (TR), which is the time between two RF pulses, and echo time (TE), which is the time between the RF pulse and the signal acquisition. The greatest difference in T1 relaxation of different tissues is at the beginning of the recovery of longitudinal magnetisation, so right after the RF pulse has been sent in: T1 weighting is greater with short TR (i.e. 500 msec); this is however at the expense of signal, which is low, as magnetisation has not recovered enough yet. Nevertheless, when image is acquired with long T1 (i.e. 1500 msec) longitudinal magnetisation has fully recovered, so signal is high, but at the expense of very small differences in T1 relaxation of different tissues, and thus

T1 weighting is very modest. Once RF pulse is stopped (i.e. with short TE, 30 msec), the transversal magnetisation is at the maximum value, so signal is high, but there is no difference in T2 relaxation of different tissues, so that T2 weighting is very modest. Transversal magnetisation then starts decreasing, and the more time passes by, the more the decay in T2 relaxation and the greatest the difference in T2 weighting between different tissues: T2 weighting is characterised by long TE (i.e. 80 msec). Short TR and short TE are used to obtain T1 weighting, while long TR and long TE are used for T2 weighting.

The energy handed over by the protons to the surroundings, once the RF pulse stops, is measured and post-processed to create an image. All MR signals acquired need to have a precise location in space, and this is achieved on CMR in different steps. First of all, a selected range of RF is usually sent in, to exchange energy only with protons with a specific Larmor frequency, so that the wider the range of RF pulses, the thicker the slice of the body imaged. A frequency-encoding gradient is then applied on the y-axis: the different magnetic field values correspond to different precession frequencies. Finally, a phase encoding gradient is applied on the x-axis, to enhance protons with the same precession frequency, but with different phases. By applying multiple phase encoding and frequency-encoding gradients it is possible to precisely localise every single MR signal; time-dependent MR signals are then expressed as different frequency components through a mathematical process (the Fourier transform), so that it is possible to know exactly how much MR signal of a specific frequency and phase is coming out of each point in space. All digitized MR signal data are then stored into the k-space, which is a data matrix; the matrix of the k-space equals in size the matrix of the field of view of the image.

2.2 Cardiac function

Cardiovascular magnetic resonance is the gold standard for the assessment of biventricular volumes and function (57)(58) and its main advantage over 2D echocardiography is based on its independence on any geometrical assumption. Volumes and systolic function assessment on CMR are based on 3D whole heart coverage, which is guaranteed by short axis cine imaging, from the mitral valve plane to the cardiac apex. The endocardium and epicardium of each short axis slice are contoured in end-diastole (image with the largest blood volume) and end-systole (image with the smallest blood volume) on each slice, in order to provide global ventricular volumes and ejection fraction, both for the left and right ventricle. As per the standardized image interpretation and post-processing in CMR of the Society for Cardiovascular magnetic Resonance (SCMR) Board of Trustee Task Force recommendations (59) the LV outflow tract is included as part of the LV blood volume and attention should be paid when drawing contours of the most basal slices, in order to omit slices containing atrial blood volume; papillary muscles are myocardial tissue and should ideally be included with the myocardium, but their exclusion is acceptable.

2.3 Tissue characterisation

The key property of CMR is its ability to provide a detailed tissue characterisation, to a level superior to any other imaging modality: this is based on the different weighting of the images, which allows the detection and differentiation of tissue components, such as fibrosis and oedema.

CMR uses gadolinium-chelate contrast agents, which are administered intravenous, but have an extra-vascular distribution: gadolinium-chelate contrast

agents are quickly washed out by normal myocardium, but accumulate in the extra-cellular space, even more so in those conditions where extra-cellular space is pathologically increased; this can be due to myocardial membrane rupture secondary to acute damage, or to collagen deposition in the context of chronic myocardial scar. Myocardial fibrosis can be seen on CMR as infarct, replacement fibrosis or diffuse fibrosis, which have been shown to represent a continuum of myocardial damage in patients with IHD: 70% of myocardial fibrosis in IHD is represented by diffuse and replacement fibrosis, while only 30% is represented by infarct (60). Gadolinium-chelate contrast agents shorten T1 relaxation and areas of contrast accumulation appear bright (white) on T1 weighting imaging, performed 10-15 minutes after contrast injection (late gadolinium enhancement, LGE). The widest application of CMR has been in the assessment of ischemic cardiomyopathy (61)(62) and its ability to detect myocardial fibrosis has been validated against histology: myocardial fibrosis seen on CMR faithfully reproduced the infarcted areas seen on pathologic specimen on animal models (63). CMR has also been shown to be superior to SPECT in the assessment of infarcted areas, especially those of small size and with non-anterior location (64).

Based on the distribution pattern of LGE, it is possible to clearly distinguish cardiomyopathy of ischemic or non-ischemic origin (47). Following the ischemic wave-front phenomenon, which proceeds from the subendocardium to the entire wall thickness, an ischemic distribution of LGE involves the subendocardium, from which it can extend within the wall thickness, to become transmural; ischemic LGE is also located along the territory of distribution of a coronary vessel. On the other hand, non-ischemic processes neither follow the ischemic wave-front phenomenon, nor the territory of distribution of a coronary

vessel, and usually present as epicardial, mid-wall or a combination of both.

The most recent CMR software not only allows the identification of LGE (presence/absence) but also provide its quantification, in absolute terms (grams of fibrosis) and as percentage of the LV mass. Quantification is based on signal intensity, which means that myocardial fibrosis is identified as a signal intensity deviating from that of the remote (normal) myocardium. Different studies have tested different thresholds of signal intensity (2 standard deviations, SD, 3SD, 5SD, 6SD) in order to correctly identify myocardial scar; most of them identified the cut-off for abnormal signal intensity at 5SD above that of remote myocardium, but recently the full width at half maximum (FWHM) technique, which uses half the maximal signal intensity within the scar as threshold, has been shown to be the most accurate and reproducible, irrespective of the underlying structural disease (65).

As previously mentioned, fluids have long T1 and T2 and appear bright (white) on T2 weighted images, thus allowing depiction of myocardial oedema. CMR can detect myocardial oedema as early as 30 minutes after chest pain onset and although there is no agreement on the actual mean persistence of myocardial oedema after an acute event, it can usually be seen for a couple of weeks up to a couple of months, persisting also once cardiac biomarkers have normalised (66).

Assessment of myocardial oedema has important implications both in ischemic and non-ischemic cardiomyopathies. Approximately one third of ACS patients do not have a culprit lesion on angiogram (67); myocardial oedema sequences help identify the “infarct-related” artery, as an area of increased signal intensity along the territory of distribution of the culprit coronary artery. Quantification of myocardial oedema after an acute MI allows the identification of the area at risk

(the area that would become necrotic if the infarcted artery was not to be treated) and the myocardial salvage (expressed as the difference between the area at risk and the LGE area) which represents the amount of myocardium “rescued” after treatment of the infarct related artery: the presence of an area at risk identifies patients that will benefit from an early invasive treatment (68), also considering that myocardial oedema has been linked to adverse cardiovascular events, irrespective of revascularisation (69)(70). Both the assessment of the area at risk and of the myocardial salvage have been validated, versus the gold standard fluorescence microsphere (71) and versus SPECT, respectively (66). Analysis of oedema sequences has gained an increasing role in the setting of MINOCA (50)(72). Plaque rupture, coronary vasospasm and embolization, that can appear on angiogram as non-flow limiting stenosis or as unobstructed arteries, can still be responsible of acute myocardial damage. This can be easily identified on CMR, especially if performed within two weeks from the index event (50)(67)(73): on T2 weighted images, myocardial oedema has an ischemic, often transmural, pattern, along the territory of distribution of a coronary artery (74). A meta-analysis on 500 patients presenting with MINOCA showed that up to a third have findings consistent with myocarditis (75), and CMR has been recently recommended by European guidelines as first line imaging technique, in stable patients with suspected myocarditis, prior to endomyocardial biopsy (76): Lake Louise criteria on CMR (myocardial oedema on the T2 weighted images, hyperemia on the early gadolinium enhancement and LGE on the post contrast images) closely resemble histologic criteria for myocarditis (77).

2.4 Myocardial deformation analysis

Myocardial architecture is very complex and is organised in three layers: the subendocardial layer, where fibres are oriented obliquely from base to apex (right-handed helix), the mid-wall layer, where fibres are circumferentially oriented, and the epicardial layer, where fibres are still oriented obliquely, but from apex to base (left-handed helix). As a consequence of this complex structure, during systole, the LV deforms along different directions, shortening in the circumferential and longitudinal direction, and thickening in the radial direction. Myocardial deformation imaging assesses the complex changes of LV myocardium during contraction, by measuring the degree of deformation of myocardial segments from the initial length (in end-diastole) to the maximum length (usually in end-systole), which is known as myocardial strain, and expressed as percentage (78)(79)(80). Myocardial strain can be measured along the three directions of LV deformation, longitudinal, radial and circumferential. The global longitudinal strain (GLS) represents myocardial shortening along the longitudinal direction, from base to apex, and has negative values; global radial strain (GRS) represents myocardial thickening along the radial direction, and has positive values; global circumferential strain (GCS) represents myocardial shortening along the circular perimeter (observed on a short-axis view), and has negative values. Different CMR sequences have been developed over the years in order to quantify myocardial deformation, from the earliest tagging sequences to the latest feature and tissue tracking (81)(82)(83)(84). Feature and tissue tracking technology is the latest strain analysis technique and is a post-processing method that tracks myocardial features on different cardiac phases on the cine sequences; post-processing software identify a myocardial feature in one cardiac frame and then the “as

much as possible similar” feature in the next frame (84)(85). Feature and tissue tracking software rely on the tracing of endocardial and epicardial borders, in two long axes and in the short axis cine stack, at end-diastole: features traced are then automatically tracked throughout the cardiac cycle (**Figure 3**). Different studies have shown a good agreement between CMR-derived strain and speckle tracking echocardiography (SpTE) (86)(87); however, SpTE-derived longitudinal strain has shown to be more accurate than feature tracking CMR, which in turn shows more reproducible measurement of circumferential strain (84). Some technical issues affect myocardial strain assessment repeatability: the global estimation of strain is more reliable and more reproducible than the segmental analysis (84), which suffers of through-plane motion, both on SpTE and CMR (88). Analysis of myocardial deformation is increasingly used in clinical practice, also because it has been shown to impair prior to the reduction of ejection fraction, thus representing an early disease marker; the earlier impairment of longitudinal strain as compared to LVEF has been attributed to higher sensibility of subendocardium to different sort of injuries (89). The ability of longitudinal strain to detect early LV dysfunction has shown to be very useful for example in HCM, where LVEF is usually normal or supra-normal but LV function is impaired: in these patients, despite a normal LVEF, longitudinal strain appears abnormal (89). In a meta-analysis on more than 5000 patients with different cardiac conditions, global longitudinal strain was the stronger predictor of all-cause mortality when compared with LVEF, with a strength of effect for the HR per standard deviation for global longitudinal strain 1.19 times greater than that of LVEF (90). As myocardial strain reflects the complex layered myocardial structure, it has shown to be particularly useful in layer-specific cardiomyopathies: circumferential strain has been shown to be

significantly different in normal myocardium as compared to areas with subendocardial or transmural MI (91)(92). The capability of some strain analysis software to assess layer-specific strain values (endocardial vs epicardial) allows the differentiation of myocardial segments with subendocardial or transmural MI, as both endocardial and epicardial strain decrease with the increase in LGE transmural extent (91). Regional variations in myocardial strain, although less reproducible, correlate with regional LGE in post-MI patients (93), and myocardial strain impairment has shown close correlation to the presence of myocardial LGE, in a way that is proportional to its size and transmural extent (94)(95). Similarly, a strong association has been found between impairment of circumferential shortening in DCM patients with mid-wall fibrosis (96), as mid-wall fibres are those responsible of circumferential shortening. Myocardial strain appears to be a very sensible detector of subtle myocardial dysfunction, as shown in HCM patients, where impaired strain goes beyond hypertrophied segments (97).

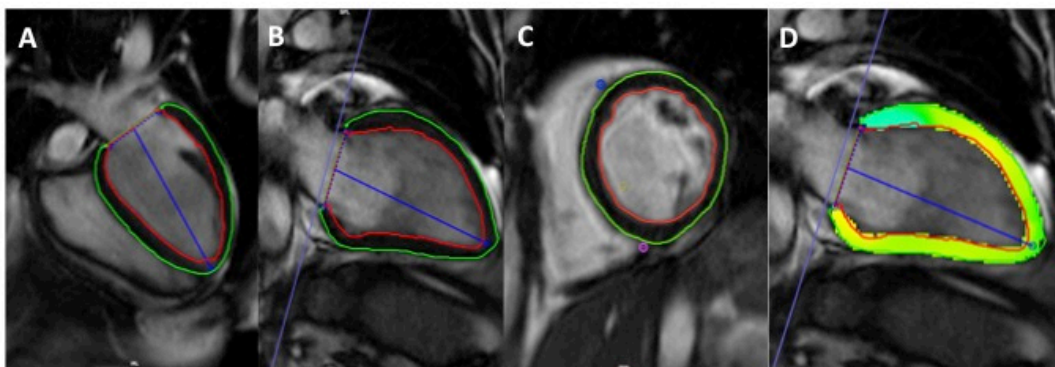


Figure 3. Myocardial strain analysis by tissue tracking. Endocardial (red) and epicardial (green) contours are traced in two long axes cine (A, B) and in the short axis cine stack images (a mid-cavity slice is shown in C). The software

tracks the features traced throughout the cardiac cycle and displays myocardial deformation (longitudinal strain is shown in D).

2.5 Contraindications to CMR

Contraindications to CMR are related to the three main components of the CMR imaging, the static magnetic field, the gradient fields and the RF pulses.

Secondary to the static magnetic field, any ferromagnetic material accelerates towards the magnetic core, with the risk of projectile injury any time a ferromagnetic material is introduced in the room where the CMR scanner is located. The gradient magnetic field is responsible of the noise (>90 dB), with consequent potential auditory damage (patients do however always wear headphones), and mainly of promoting current induction and device malfunction of medical devices. RF pulses are mainly responsible of heating effects of any medical implant.

Absolute contraindications to CMR include: ferromagnetic cerebral aneurysm clips/ocular implants, foreign ocular metallic bodies, cochlear implants, neurostimulators; CMR should also not be performed in the first trimester of pregnancy, in patients with severe renal impairment ($\text{GFR} < 30 \text{ ml/min/1.73 m}^2$) and in patients with severe claustrophobia. An important consideration with regards to MR-safety has to be made about cardiac implantable devices, such as ICD and pace-makers, as MR-conditional, and more recently MR-safe, cardiac implantable devices can be safely scanned following manufacturers instructions (conventional cardiac devices can also be scanned with low risk if appropriate precautions are taken, i.e. programming asynchronous pacing in pace-maker-dependent patients); if leads are not matured (<6 weeks after implantation), broken or abandoned a cardiac MR should not be performed

given the risk of dislodgement. Nephrogenic systemic fibrosis (NSF) is a rare condition presenting with dermal lesions and involvement of internal organs, which can be lethal; it is most likely related to the contrast agent used, but it appears to manifest only in patients with severe renal failure ($\text{GFR} < 30 \text{ ml/min/1.73 m}^2$). However, it has been shown that the risk of NSF approximates zero in patients receiving a contrast dose according to the labelling (i.e. Gadobutrol 0.1 mmol/kg), irrespective of renal function (98).

Chapter 3. Background

Impact of cardiovascular magnetic resonance on clinical management and decision-making in out of hospital cardiac arrest survivors with inconclusive coronary angiogram (99)

Reprinted from (99) Resuscitation 116 (2017), A. Baritussio, A. Zorzi, A. Ghosh Dastidar, A. Susana, G. Mattesi, J.C.L. Rodrigues, G. Biglino, A. Scatteia, E. De Garate, J. Strange, L. Cacciavillani, S. Iliceto, A. Nisbet, G.D. Angelini, D. Corrado, M. Perazzolo Marra, C. Bucciarelli-Ducci, Out of hospital cardiac arrest survivors with inconclusive coronary angiogram: Impact of cardiovascular magnetic resonance on clinical management and decision-making, Pages No. 91–97, Copyright (2017), with permission from Elsevier.

3.1. Background

Urgent angiography with view to primary percutaneous coronary intervention is a class IB recommendation in patients with resuscitated cardiac arrest whose electrocardiogram (ECG) shows STEMI. Given the high incidence of underlying CAD in this group of patients, European guidelines extended the recommendation to incorporate patients without diagnostic STE, but with high suspicion of on-going infarction (class IIaC). However non-ischemic cardiomyopathy accounts for up to 15% of OHCA and a structurally normal heart can be found in up to 10–20% of cases (99). While evidence of culprit lesion on angiogram supports acute ischemia as the cause of OHCA, diagnosis and clinical management of OHCA survivors with inconclusive coronary angiogram (either non-identifiable culprit lesion or unobstructed coronary arteries) is challenging. Cardiovascular magnetic resonance is a non-invasive imaging technique providing accurate diagnosis based on its superior spatial resolution and unique non-invasive tissue characterization.

3.2 Materials and methods

The CMR registries from two tertiary centres (Bristol, South West of England and Padua, Veneto Region, Italy) were analysed to identify OHCA survivors who underwent urgent coronary angiogram followed by CMR (October 2009–November 2015). The study focused on the analysis of patients with an “inconclusive angiogram”, defined as evidence of stable obstructive CAD (SCAD) with no culprit lesion or unobstructed coronaries (normal coronaries/non-obstructive CAD). Culprit lesion was defined as obstructive ($\geq 70\%$) CAD with TIMI 0/1 flow with abrupt closure, or TIMI 2/3 flow with features suggestive of thrombus/ulcerated plaques, ST segment-T wave changes in the corresponding ECG location, and evidence of matching regional wall motion abnormality on left ventriculogram or echocardiogram (37)(101).

CMR was performed on a 1.5T scanner (Avanto, Siemens Health-care, Germany) with a protocol including long and short axis cine sequences and post-contrast imaging, performed ten minutes after intravenous administration of 0.1 mmol/Kg of Gadobutrol (Gadovist 1.0 mmol/ml, Bayer-Schering, Berlin, Germany) in identical planes to cine images. Additional sequences for the assessment of myocardial oedema (T2-short tau inversion recovery, T2-STIR) or myocardial ischemia (stress perfusion with 140–210 ug/Kg/min adenosine) were performed when indicated, based on clinical and angiographic findings. Ventricular function was assessed with dedicated software (Circle Cardiovascular Imaging, Calgary, Canada), by tracing endo- and epicardial borders on each short axis cine slice in end-diastole and end-systole. All volumes were indexed to body surface area. The localization, extent and distribution pattern of late gadolinium enhancement (LGE) were assessed by using short- and long-axis views and confirmed only if detectable in two

orthogonal planes. The pattern of LGE distribution was defined as ischemic, subendocardial or transmural, if involving <50% or ≥50% of wall thickness, respectively, and as mid-wall/epicardial if patchy/spotty intra-mural or sub-epicardial enhancement was detected. The presence of LGE at the right ventricle/left ventricle insertion points, in the absence of other distribution patterns, was defined as non-specific findings, as its diagnostic and prognostic meaning is still unclear. All the analyses were carried out in accordance with the recommendation of the Society for Cardiovascular Magnetic Resonance (59). The study was reviewed by the local Institutional Research and Innovation Department and in view of the retrospective design, formal ethical approval was waived off. All patients gave written informed consent.

Clinical, ECG and echocardiographic data were collected and independently analysed by two clinicians blinded to CMR findings. A diagnosis was made based on clinical and imaging data available prior to CMR. According to previously used definitions (102), “clinical impact” of CMR was defined as change in diagnosis, compared to the composite pre-CMR diagnosis, or change in management. A change in management was defined as CMR findings either leading to change in medication, to an invasive procedure (i.e. repeat angiogram, myocardial revascularization, ICD implantation) or to the avoidance of such invasive procedures. Patients with a change both in diagnosis and management were only counted once.

3.3 Statistical Analysis

Continuous and categorical variables were expressed as mean±SD or median (IQR), and n (%), respectively. Categorical variables were compared by using the chi-square or Fisher exact test, as appropriate. Continuous data were

compared by using the 2-tailed unpaired t test (for normally distributed data sets) or by using the Mann-Whitney U test. Inter-rater agreement for categorical variables was assessed by Cohen's kappa coefficient. A p-value of <0.05 was considered statistically significant. Data were analysed with SPSS® version 23 (IBM®).

3.4 Results

Clinical characteristics

Out of 174 consecutive OHCA survivors referred to CMR after coronary angiogram (performed on same day of admission, IQR 0-2 days), 110 patients (63%, 84 male, age 58 years, IQR 46–68) had an inconclusive angiogram and were enrolled in the study: 37 patients (34%) had evidence of SCAD with no culprit lesion and 73 patients (66%) showed unobstructed coronaries. The first registered rhythm was ventricular tachycardia (VT)/ventricular fibrillation (VF) in 104 patients (95%) and pulseless electrical activity (PEA) in 6 patients (5%). The first ECG was available in 86 patients (78%): non-ST elevation (non-STE) was reported in 68 patients (79%), STE in 18 (21%). SCAD patients with no culprit lesion were more frequently men ($p=0.006$) and significantly older compared to patients with unobstructed coronaries ($p<0.001$); risk factors were similar, except for hypertension ($p=0.001$) and known CAD ($p<0.001$), which were more frequent among SCAD patients with no culprit lesion. STE was more common among SCAD patients with no culprit ($p=0.002$). Patients' characteristics are listed in **Table 1**.

Table 1. Clinical characteristics

		SCAD	Unobstructed	
	Total Cohort	No Culprit	Coronaries	p-value
	n=110	n=37	n=73	
Male	84 (76)	34 (92)	50 (68)	0.006
Age, years	58 (46-68)	65 (58-75)	52 (40-63)	<0.001
Hypertension	36/100 (36)	20/35 (57)	16/65 (25)	0.001
Diabetes	13/100 (13)	7/35 (20)	6/65 (9)	0.127
Active smoking	25/100 (25)	11/35 (31)	14/65 (22)	0.276
Hyperlipidaemia	20/100 (20)	10/35 (29)	10/65 (15)	0.116
Family history CAD	9/100 (9)	4/35 (11)	5/65 (8)	0.533
Family history SCD	2/100 (2)	0/35 (0)	2/65 (3)	0.295
Previous CAD	24/100 (24)	17/35 (49)	7/65 (11)	<0.001
Previous NIHD	5/100 (5)	1/35 (3)	4/65 (6)	0.471
VT/VF	104/110 (95)	34/37 (92)	70/73 (96)	0.383
PEA	6/110 (5)	3/37 (8)	3/73 (4)	0.382
ECG post ROSC, STE	18/86 (21)	11/27 (41)	7/59 (12)	0.002
ECG post ROSC, non-STE	68/86 (79)	16/27 (59)	52/59 (88)	0.002

Values are expressed as n (%) and median (IQR). SCAD, stable CAD with no culprit lesion; CAD, coronary artery disease; SCD, sudden cardiac death; NIHD, non-ischemic heart disease; VT, ventricular tachycardia; VF, ventricular fibrillation; PEA, pulseless electrical activity; ROSC, recovery of spontaneous circulation; STE, ST segment elevation.

CMR findings

Among patients with inconclusive angiogram, CMR was performed within 2 weeks from the index event (median 1.4 weeks, IQR 0.9-2.4, no difference between centres, p=0.588). Time to CMR was significantly shorter among patients with inconclusive angiogram, as compared to patients found to have an

acute coronary event on angiogram ($p=0.001$). Median left ventricular ejection fraction (LVEF) was 57% (IQR 44–64), median indexed left ventricular end-diastolic volume (LVIEDV) and end-systolic volume (LVIESV) was 87 ml/m² (IQR 73–110) and 38 ml/m² (IQR 27–56), respectively. LVEF was significantly higher among patients with unobstructed coronaries ($p<0.001$). Wall motion abnormality was reported in 55 patients (50%), with regional or diffuse pattern in 38 (35%) and 17 patients (15%), respectively (**Table 2**).

On post-contrast sequences LGE was found in 72/110 patients (65%), and it was significantly more common among SCAD patients with no culprit lesion (33/37 vs. 39/73, $p<0.001$). Analysis of LGE distribution pattern showed subendocardial LGE in 15 patients (14%), mid-wall/epicardial in 26 patients (24%), and transmural LGE in 27 patients (25%). More than one distribution pattern was reported in 4 patients (3%). No LGE was found in 38 patients (34%). T2-STIR sequences for myocardial oedema were performed in 58 patients (53%), more frequently in patients with unobstructed coronaries ($p=0.001$); myocardial oedema was found in 18 patients (31%). Presence of myocardial oedema was not significantly associated with the timing of CMR; however, there was a trend towards a higher prevalence of myocardial oedema among patients undergoing CMR within one week from index event ($p=0.064$). There was no difference in prevalence of myocardial oedema between the two groups.

Table 2. CMR Findings

		SCAD	Unobstructed	
	Total Cohort	No culprit	Coronaries	p-value
	n=110	n=37	n=73	
LVEF, %	57 (44-64)	44 (34-55)	60 (52-65)	<0.001
LViEDV, ml/m ²	87 (73-110)	94 (76-120)	86 (72-103)	0.132
LViESV, ml/m ²	38 (27-56)	48 (38-82)	35 (24-48)	<0.001
Regional WMA	38 (35)	23 (62)	15 (21)	<0.001
Diffuse WMA	17 (15)	7 (19)	10 (14)	0.474
Myocardial oedema	18/58 (31)	5/11 (45)	13/47 (28)	0.251
LGE	72 (65)	33 (89)	39 (53)	<0.001

Values are expressed as n (%) and median (IQR). LVEF, left ventricular ejection fraction; LViEDV, indexed left ventricular end-diastolic volume; LViESV, indexed left ventricular end-sistolic volume; WMA, wall motion abnormality; LGE, late gadolinium enhancement.

Overall, CMR identified a pathologic substrate in 69% of the population: IHD was the final diagnosis in 45 patients (41%) and non-ischemic heart disease (NIHD) in 31 (28%). Non-specific findings were found in 9 patients (8%) and a structurally normal heart in 25 (23%)(**Table 3**). CMR findings between the two subgroups differed significantly ($p<0.001$) (**Figure 4**).

Table 3. CMR findings.

CMR Diagnosis	n = 110
IHD	45 (41)
NIHD	31 (28)
- myocarditis	7 (6)
- DCM	6 (5)
- HCM	3 (3)
- ARVC	3 (3)
- TTC	3 (3)
- cardiac amyloidosis	1 (1)
- hypertensive heart disease	2 (2)
- LVNC	1 (1)
- HFpEF	1 (1)
- MVP	4 (3)
Structurally normal heart	25 (23)
Non-specific findings	9 (8)

Variables are n (%). IHD, ischemic heart disease; NIHD, non-ischemic heart disease; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; ARVC, arrhythmogenic right ventricular cardiomyopathy; TTC, Tako-Tsubo cardiomyopathy; LVNC, left ventricular non compaction; HFpEF, heart failure with preserved ejection fraction; MVP, mitral valve prolapse.

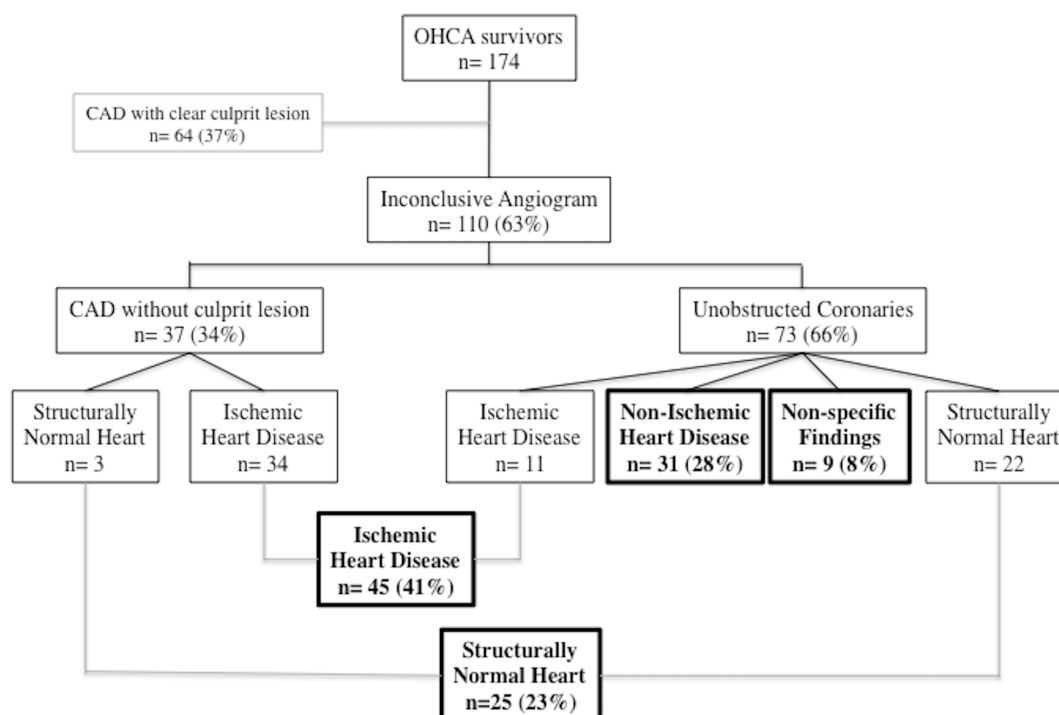


Figure 4. CMR findings in OHCA survivors with inconclusive angiogram. Final CMR findings, according to coronary angiogram data, in OHCA survivors with inconclusive angiogram. Boxes in bold show the final CMR findings in the overall cohort of OHCA survivors with inconclusive angiogram. SCAD, stable coronary artery disease.

Stable obstructive CAD with no culprit lesion

Thirty-four patients (92%) were found to have IHD, a structurally normal heart (no myocardial oedema, late enhancement or inducible ischemia) was found in 3 (8%). On T2-STIR sequences, performed in 11 patients (30%), myocardial oedema was found in a single coronary artery territory in 5 (45%), helping to localise the culprit lesion. Stress perfusion CMR was performed in 15 patients (41%): inducible ischemia was reported in 10 patients (67%) (single coronary artery territory in 7 patients and multi-vessel territory in 3), 90% of whom

received percutaneous/surgical revascularization. A viability study was performed in the remaining 22 (59%) to guide treatment (revascularization/optimization of medical therapy); CMR showed findings consistent with viable myocardium in 15 patients (68%), of which 12 (80%) underwent revascularization.

Unobstructed coronaries

IHD was diagnosed in 11 patients (15%) and NIHD in 31 (43%), with myocarditis (23%) and dilated cardiomyopathy (DCM) (10%) being the most common, followed by congenital and acquired cardiomyopathies (**Table 3**). A structurally normal heart was found in 22 patients (30%) and non-specific findings in 9 (12%)(**Figure 5**). On T2-STIR sequences, performed in 64% of patients, the presence of myocardial oedema in 13 (28%) identified an acute, reversible, cause of OHCA in 3 IHD patients and in those diagnosed with myocarditis and Tako-Tsubo cardiomyopathy (TTC). LGE was found in 53%.

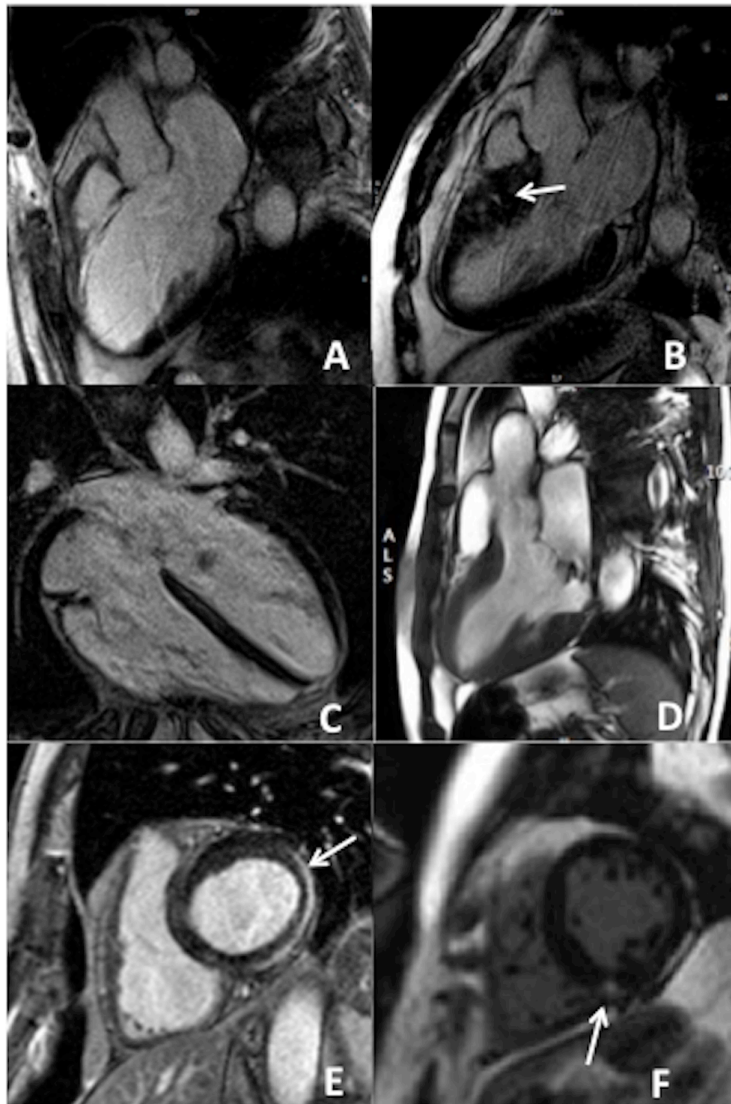


Figure 5. CMR findings. Post-contrast 3 chamber long-axis view showing transmural myocardial infarction (A). Post-contrast 3 chamber long-axis view of a patient with hypertrophic cardiomyopathy (HCM) and replacement fibrosis of the hypertrophied septum (B, arrow). Post-contrast 4 chamber long axis view of a patient with biventricular arrhythmogenic right ventricular cardiomyopathy (ARVC) (C). 3 chamber long axis cine showing prolapse of the posterior mitral leaflet at end-systole (D). Post-contrast short axis view showing epicardial enhancement of the basal lateral wall in a patient with healed myocarditis (E, F).

arrow). Post-contrast short axis view showing non-specific late enhancement of the inferior insertion point (F, arrow).

Comparison between CMR and trans-thoracic echocardiogram

A trans-thoracic echocardiogram (TTE) performed within 1 week from CMR was available in 92 patients (84%). Median LVEF by TTE was lower compared to CMR (50% vs 57%, $p < 0.001$). TTE identified a pathologic substrate in 50/92 patients (54% vs 69% by CMR, $p = 0.018$): the final diagnosis was IHD in 26/92 patients (28%) and NIHD in 24/92 patients (26%). A structurally normal heart was found in 20/92 patients (22%) and non-specific findings (structural and functional abnormalities not attributable to a conclusive diagnosis) in 22 (24%). CMR and TTE provided the same diagnosis in 51/92 patients (55%) (**Table 4**). There was a moderate agreement between CMR and TTE with regards to IHD, which was confirmed on CMR in 22/26 patients (85%) (Cohen's kappa 0.50), and to structurally normal heart, confirmed on CMR in 11/20 patients (55%) (Cohen's kappa 0.43). There was a fair agreement with regards to NIHD, which was confirmed on CMR in 15/24 patients (63%) (Cohen's kappa 0.21); based on tissue characterization CMR identified 7 patients with an ischemic distribution pattern of LGE. CMR provided a diagnosis in 14/22 (64%) patients with non-specific findings on TTE, identifying 6 patients with IHD and 8 patients with NIHD. The ability of CMR to be more definite regarding the underlying cardiac abnormalities was mainly based on LGE.

Table 4. Diagnostic agreement between CMR and TTE

	CMR				Total
	IHD	NIHD	SNH	Non-specific Findings	
IHD	22	1	3	-	26
NIHD	7	15	1	1	24
TTE Structurally Normal Heart	3	4	11	2	20
Non-specific Findings	6	8	5	3	22
Total	38	28	20	6	92

Boxes in bold represent patients receiving the same diagnosis based on both CMR and TTE findings. IHD, ischemic heart disease; NIHD, non-ischemic heart disease; SNH, structurally normal heart.

Clinical impact of CMR

CMR provided a clinical impact in 77/110 patients (70%), leading to change in diagnosis in 27 patients (25%), in management in 32 (29%), and both in diagnosis and management in 18 patients (16%). An entirely new diagnosis was found in 25% of patients, most commonly structurally normal heart (11%) and NIHD (10%). CMR led to an invasive procedure in 32 (29%) patients, namely myocardial revascularization in 21 (19%) and ICD implantation in 11 (10%). Based on CMR findings, an invasive procedure was avoided in 15 (14%) patients. CMR had greater clinical impact in SCAD patients with no culprit lesion ($p=0.002$), more frequently experiencing a change in management (86% vs. 25% unobstructed coronaries, $p<0.001$); a change in diagnosis occurred more frequently among patients with unobstructed coronaries (58% vs. 8% SCAD patients, $p<0.001$).

3.5 Discussion

The main findings of our study were that: 1) 2/3 of OHCA survivors referred to CMR have inconclusive findings on angiogram; 2) CMR identified a pathologic substrate in 69% of the population and a structurally normal heart in 23%; 3) CMR had a clinical impact in more than two thirds of patients. Acute coronary syndromes account for more than two thirds of OHCA (10,17,21,22) mainly secondary to acute coronary thrombosis or ruptured plaque (100,102) as confirmed by autopsy series. International guidelines recommend urgent angiography in OHCA survivors with STE (37) or whenever there is high suspicion of on-going infarction, irrespective of ECG (37). However, only a minority of cases (30–40%) shows angiographic and clinical evidence of ACS (37), a figure similar to that (37%) in our study. Causes other than acute ischemia are reported in up to 30% of cases. When acute ischemia is the obvious cause of OHCA, fewer patients are referred to CMR, mainly to assess the extent of myocardial scarring and the functional significance of bystander CAD. On the other hand, an inconclusive angiogram poses a diagnostic dilemma requiring further investigation, and to the best of our knowledge this is the first study looking at the role and clinical impact of CMR in OHCA survivors with this angiographic finding. Identifying OHCA aetiology is often challenging in the acute setting, as clinical data are often lacking and ECG and echocardiographic interpretation might be affected by resuscitation manoeuvres or external defibrillation (41)(100). However, correct identification of the underlying cause, especially if reversible, plays a determinant role for appropriate treatment strategy and long-term prognosis. CMR has a well-established diagnostic role, both in the ischemic and non- ischemic scenario, based on its

superior tissue characterization properties. In our study, CMR could identify an underlying pathologic substrate in 69% of the population, as compared to 54% by TTE ($p=0.018$), and this was mainly due to LGE analysis. This superior diagnostic ability carried additional value and clinical impact over TEE in the management of these patients; for example, non-specific findings were more frequently reported by TTE (24% vs 8%), but CMR was able to identify a pathologic substrate in two thirds of them. We found a high prevalence of LGE among OHCA survivors (65%), in keeping with that recently reported by Neilan (71%) in OHCA survivors referred to CMR because of an unclear diagnosis (after clinical and diagnostic assessment) (49). The aim of their study was to identify the role of LGE as an arrhythmic substrate and as a predictor of adverse cardiovascular events. They found that LGE presence and extent are the strongest predictors of adverse arrhythmic outcome, further confirming the relationship between myocardial damage and major arrhythmias, and strengthening the association between tissue characterization and arrhythmic risk, independent of the ejection fraction, as reported by many studies on cardiovascular outcome (99). White et al. (48) showed that CMR-based imaging had a pick-up diagnostic rate of 74% in identifying the myocardial substrate of ventricular arrhythmias vs. 51% based on non-CMR imaging (i.e. diagnosis of MI missed in one third of patients on non-CMR imaging). In our study, CMR identified ischemic myocardial damage in 11 patients (15%) with unobstructed coronaries on angiogram; TTE diagnosed IHD in only one of them. Among 88 patients with no label of prior MI, Neilan (49) found ischemic LGE in 49, thus supporting the hypothesis that the presence of LGE in patients with unobstructed coronaries identifies a subgroup of patients at increased risk of arrhythmic events. Compared to Neilan, our study explored the comparative

value of CMR vs TTE, as well as the clinical impact of CMR in this patients' cohort. As already confirmed in different populations, such as in heart failure [26], we found that CMR changed both diagnosis and management in a considerable proportion of OHCA survivors (70%). Of interest, CMR showed a clinical impact both in patients with unobstructed coronaries, mainly by providing a change in diagnosis, and in SCAD patients with no culprit lesion, mainly by a change in management. An entirely new diagnosis was identified in 25% of cases, mainly based on tissue characterization: a structurally normal heart was found in 11% of patients, based on the absence of LGE, and NIHD was diagnosed in 10%. Stress perfusion CMR has a well-established role not only in detecting CAD and guiding sub-sequent treatment strategy, but also in the identification of patients at increased risk of major adverse cardiovascular events (99). Stress perfusion CMR, performed in nearly half of SCAD patients with no culprit lesion, found inducible ischemia in 67% of patients, guiding myocardial revascularization in nearly all of them. It is well established that CMR has a role, over and above TTE, in re-classifying patients with regards to primary prevention ICD eligibility based on LVEF criteria, as it is the gold standard for LV function (57). The ability of CMR to detect reversible myocardial damage could play a role in guiding secondary prevention ICD implantation. In our patient population of OHCA survivors, CMR identified acute reversible myocardial injury (acute myocarditis and acute ischemia), thus avoiding secondary ICD implantation, as per guidelines, in 6% of patients. The main limitation of this study is the retrospective design. However, conducting a prospective trial in OHCA survivors might be difficult due to high mortality rate, variable downtime and consent. Sequences for myocardial oedema were available for analysis in half of the population, thus the clinical impact of

oedema analysis might have been higher if performed in all patients. A structurally “normal” heart by TTE and CMR reflects the absence of gross ischemic or non-ischemic underlying conditions, but it cannot exclude ultra-structural abnormalities. Although endomyocardial biopsy is the gold standard to assess myocardial abnormalities, it is an invasive technique, not widely performed clinically and not performed in our patients; therefore some more subtle histological and cellular abnormalities cannot be excluded. With all the above limitations, this is a real world study that reflects clinical practice in most centres. Our study only analysed the presence of focal fibrosis, although it is increasingly evident that the presence of diffuse fibrosis has a prognostic role, detecting patients at higher risk of fatal arrhythmias. The use of the most recent T1 mapping technique might help further understand the pathologic substrate in this group of patients.

3.6 Conclusions

Although ACS account for the majority of OHCA, 63% of the survivors in our cohort had an inconclusive angiogram. CMR proved to be superior to TEE in the identification of a pathologic substrate for the event in this cohort (69% vs 54%, $p = 0.018$) and its findings had a clinical impact in 70% of patients, providing a significant change both in diagnosis and in management. CMR showed a promising role in the clinical and diagnostic work-up of OHCA survivors with inconclusive angiogram and its wider use should be considered. Further prospective studies are warranted to confirm these results in a larger population.

Chapter 4. Aims

Our preliminary study showed that CMR carries an additional role in the diagnostic process of OHCA survivors with no evidence of an acute ischemic cause on urgent angiogram, and that it has direct clinical implications in patients' management and decision-making (99). This confirmed prior data showing that CMR is able to identify a structural substrate for OHCA in up to two thirds of patients, for whom an extensive clinical, electrocardiographic and echocardiographic assessment was not able to identify a diagnosis (46)(49).

There is growing evidence of the prognostic role of CMR, especially in the setting of ventricular arrhythmias, which are characterised by a complex, multifactorial pathogenesis. Myocardial scarring has been shown to be a strong predictor of adverse outcome (death, ventricular arrhythmias, ICD discharge), both in the ischemic and non-ischemic setting (104)(105), and it has been shown to extend also over LV ejection fraction, which was long considered the key determinant of an unfavourable outcome. Less than 20% of patients experiencing SCD actually have severe left ventricular systolic dysfunction ($LVEF \leq 35\%$), and CMR studies have shown that a scar mass $>5\%$ in patients with $LVEF > 30\%$ implies a higher risk of death and ICD discharge as compared to patients with $LVEF \leq 30\%$, but with scar size $<5\%$ (106).

Ventricular arrhythmias are the consequence of a trigger (i.e. acute ischemia, hypokalemia, etc.) superimposed to a favourable substrate, usually represented by inhomogeneous myocardial tissue, namely presence of viable myocytes interspersed within fibrous tissue; recent CMR software allow the detection of infarct tissue heterogeneity (i.e. the scar itself and the peri-infarct zone), and different studies have shown that an increased tissue and scar heterogeneity

not only increases arrhythmias inducibility (107), but also increases susceptibility to ventricular arrhythmias in patients with impaired LV function (108)(109). More recently, the development of new CMR software that allow the analysis of myocardial deformation from cine images, with very limited post-processing, have prompted the evaluation of CMR-derived myocardial strain as a predictor of adverse arrhythmic outcome. Myocardial strain not only has been shown to be a good predictor of adverse arrhythmic outcome in different cardiomyopathy groups, but has also shown to be a predictor of adverse outcome, irrespective of LVEF and LGE (110)(111).

Among ventricular arrhythmias, the most severe and extreme form, leading to cardiac arrest, is ventricular fibrillation. It has been demonstrated that ventricular fibrillation, especially the idiopathic form (IVF), can recur in up to 30% of cases (55), and this obviously carries important clinical implications on patients' survival and quality of life, and on their clinical management. Being able to better stratify patients, who've already experienced OHCA, in order to offer the best and tailored treatment strategies, is very important.

Aims of the study were:

- 1) To assess a) the prevalence and extent of myocardial scar and b) myocardial deformation in VF cardiac arrest survivors
- 2) To identify CMR-derived structural and mechanical predictors of recurrent major adverse cardiovascular events in VF cardiac arrest survivors

Chapter 5. Materials and Methods

We retrospectively analysed the CMR registry of the Bristol Heart Institute CMR centre (Bristol, United Kingdom) to enrol consecutive patients surviving a ventricular fibrillation out of hospital cardiac arrest. Patients were retrospectively followed-up to record a composite end-point of all-cause mortality, and appropriate ICD discharge or anti-tachycardia pacing (ATP) on VT or VF. Patients experiencing more than one end-point were only counted once: as the aim of the study was to identify structural and mechanical predictors of recurrent adverse events and given that the presence of myocardial scar is an established predictor of ventricular arrhythmias, in patients experiencing both ICD discharge and death, the ICD discharge was given more importance and counted as the only end-point. Mortality was assessed by electronic chart review; patients were followed-up at 3-6 month intervals via clinic/pacing visits. Duration of follow-up was determined from the date of the VF cardiac arrest, to the occurrence of the end-point. Patients' follow-up was recorded by a clinician blinded to CMR findings. The study was reviewed by the local Institutional Research and Innovation Department and in view of the retrospective design of the study, formal ethical approval was waived off; the study was however approved as a service evaluation (SE102).

5.1 CMR acquisition

All patients were scanned in a 1.5T CMR scanner (Avanto, Siemens Healthcare, Germany), with a protocol comprehensive of long and short axis cine images, and post-contrast (LGE) images. Steady state free precession sequences were performed to acquire the long and short axis cine images;

typical parameters were TR 38 ms, TE 1.07 ms, flip angle 80°, slice-thickness 8 mm, inter-slice gap 0 mm, bandwidth 930 Hz/Px, voxel size 1.6x1.6x8.0 mm and temporal resolution ≤45 ms between phases. For LGE imaging, a standard inversion recovery gradient-echo sequence was adopted. The LGE images were acquired 10-15 minutes after intravenous injection of 0.1 mmol/Kg of body weight of gadolinium-chelate contrast agent (Gadovist 1.0 mmol/ml, Bayer-Schering, Berlin, Germany) in identical short-axis planes to cine images, using an inversion recovery prepared breath-hold gradient-echo technique. Typical image parameters were TR 745 ms, TE 3.22 ms; flip angle 25°; slice thickness 8.0 mm, no interslice gap, bandwidth 140 Hz/Px and voxel size 1.6 × 1.2 × 8.0 mm. The inversion time was progressively optimized to null normal myocardium (typical values, 250–350 ms). Each slice was obtained during a breath-hold of 10–15 s depending on the patient's heart rate.

5.2 CMR analysis

Ventricular function was assessed with dedicated software (cvi^{42®}, Circle Cardiovascular Imaging, Calgary, Canada), by tracing endo- and epicardial borders on each short axis cine slice in end-diastole and end-systole. All volumes measurements were indexed to body surface area.

Myocardial deformation was assessed using the tissue tracking post-processing software (cvi^{42®}, Circle Cardiovascular Imaging, Calgary, Canada), by contouring the left ventricular endocardial and epicardial border in two long-axis cine images (two and four chamber view) and in the short-axis cine stack (blood pool and papillary muscles excluded), with the initial contour set at end-diastole. Regional tissue tracking features in the three directions (longitudinal, radial and circumferential) were automatically computed on a 16 segment model and

averaged to provide global peak radial strain (GRS), global peak circumferential strain (GCS), and global peak longitudinal strain (GLS) (112). Accuracy of endocardial and epicardial contouring throughout the cardiac cycle was checked in order to ensure appropriate strain measurement (**Figure 6**). A single observer (A.B., European Association of Cardiovascular Imaging Level 3 certified in Cardiovascular Magnetic Resonance) analysed all CMR data and intra-observer agreement was derived from the repetition of the analysis after 6 months. The presence/absence, localization, and distribution pattern of LGE were assessed visually by using short- and long-axis views and defined as present only if detectable in two orthogonal planes; LGE distribution pattern was defined as subendocardial or transmural, if involving <50% or ≥50% of wall thickness, respectively, and as mid-wall/epicardial if patchy/spotty intra-mural or sub-epicardial enhancement was detected. The extent of LGE was quantified by using the full width at half maximum software (FWHM) (cvi^{42®}, Circle Cardiovascular Imaging, Calgary, Canada), which uses half the maximal signal intensity within the scar as the threshold (65), and expressed as LGE mass, both in absolute terms (grams) and as percentage of the left ventricle. Ischemic heart disease (IHD) was defined as the presence of regional wall motion abnormality and subendocardial/transmural LGE consistent with coronary artery distribution territory; non-ischemic heart disease (NIHD) was defined as LGE with a mid-wall and/or epicardial pattern (59). A structurally normal heart (SNH) on CMR was defined as normal biventricular systolic function with no evidence of LGE. All the analysis was carried out in accordance with the recommendation of the Society for Cardiovascular Magnetic Resonance (59).

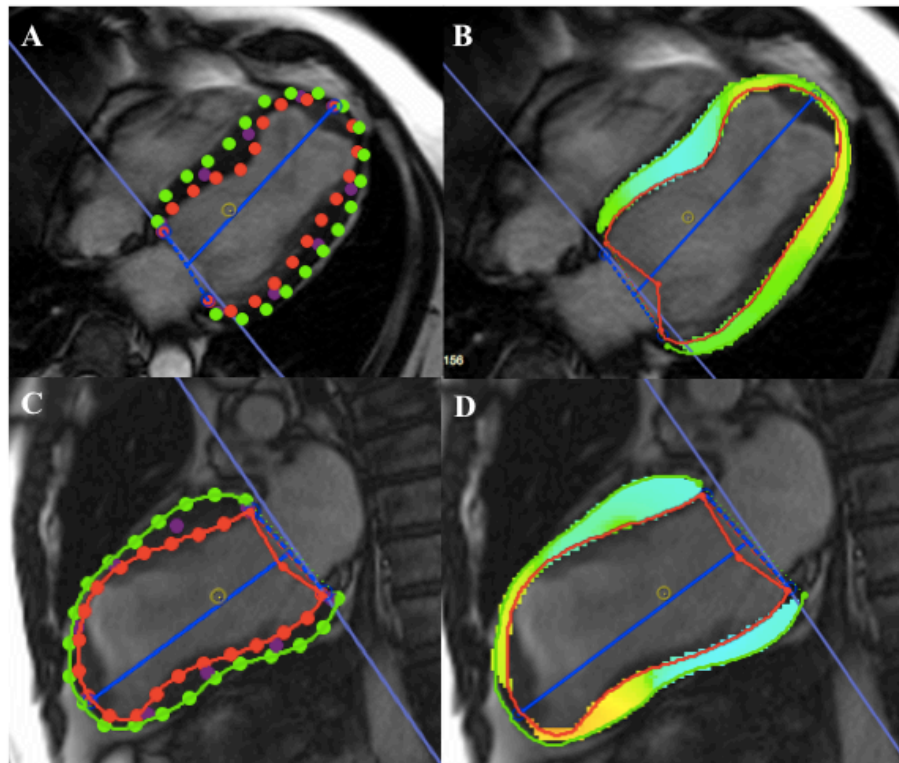


Figure 6. Quality assessment during myocardial strain analysis. Once the endocardial and epicardial contours have been traced, the software tracks the same features throughout the cardiac cycle and derives strain measurement in the three directions (longitudinal, radial, and circumferential). The software displays boundaries points (A-C, endocardial and epicardial boundaries points in the 4 and 2 chamber, respectively) that can be followed throughout the cardiac cycle to check the accuracy of endocardial and epicardial contouring and ensure the accuracy of the derived strain measurements (B-D, global longitudinal strain in the 4 and 2 chamber, respectively).

5.3 Statistical analysis

Continuous and categorical variables are expressed as mean $\pm$ SD or median (IQR), and n (%), respectively. Continuous data were compared by using the 2-tailed unpaired t test (for normally distributed data sets) or by using the Mann-

Whitney U test. Multiple comparisons were performed using the Kruskal-Wallis test. To assess intra-observer reliability of myocardial deformation analysis, myocardial strain assessment was performed by the same operator (A.B.) 6 months after the first assessment on 29 randomly selected patients (24% of total population) and the intra-class correlation coefficient (ICC) was calculated. End-point predictors were tested at the univariate analysis and variables with a significant association with the end-point ($p < 0.05$) were also tested in a multivariate model. Survival analysis was performed for the composite end-point. A receiver-operating characteristic (ROC) curve was constructed to determine the optimal value with the maximum sensitivity and specificity for LGE extent as a predictor of adverse cardio-vascular events. A p-value of < 0.05 was considered statistically significant, unless when adjusted for multiple comparisons (Bonferroni correction, $p < 0.05/n$, where n is the number of comparisons). Data were analysed in Stata (Stata v. 13, StataCorp, College Station, TX: StataCorp LP.).

Chapter 6. Results

6.1 Clinical characteristics

We consecutively enrolled 121 patients [82% male, 62 years (53-70)] surviving VF cardiac arrest. Approximately one third of patients had a history of hypertension (36%) and active smoking (27%), 21% of patients had hyperlipidemia, 14% were diabetic. The first ECG after ROSC, available in 107 patients (88%), showed STE in 39 patients (36%) and NSTE in 68 (64%). All patients received an urgent angiogram on the day of admission: 74 patients (61%) had evidence of obstructive CAD, with a culprit lesion found in 50 patients (41%); 47 patients (39%) had evidence of unobstructed coronary arteries. Clinical and demographic characteristics are summarized in **Table 5**.

Table 5. Clinical and demographic characteristics

	n=121
Gender, male	99 (82)
Age, years	62 (53-70)
Hypertension	43 (36)
Diabetes	17 (14)
Smoking	33 (27)
Hyperlipidemia	25 (21)
FHx CAD	9 (7)
FHx SCD	1 (1)
Previous CAD	26 (21)
Findings on urgent angiogram	
- Non-obstructed Coronaries	47 (39)
- CAD	74 (61)
- Culprit identified	50 (41)
- PCI performed	42 (35)
Therapy at discharge	
- Aspirin	64/99 (65)
- P2Y12 inhibitors	52/99 (53)
- ACE inhibitors	60/99 (61)
- Beta-blockers	76/99 (77)

Values are expressed as n (%) and median (IQR). CAD, coronary artery disease; SCD, sudden cardiac death; ROSC, recovery of spontaneous

circulation; STE, ST elevation; NSTE, non-ST elevation; PPCI, primary percutaneous coronary intervention.

6.2 CMR findings

Cardiovascular magnetic resonance was performed within two weeks from OHCA [13 days (6-42)]. Left ventricular systolic function was overall mildly impaired and indexed volumes were mildly increased: LVEF 54% (IQR 41-64%), LViEDV 89 ml/m² (IQR 73-109 ml/m²), LViESV 42 ml/m² (IQR 23-66 ml/m²); 68 patients (56%) had evidence of regional left ventricular wall motion abnormality (WMA), while 12 (10%) had evidence of diffuse WMA. Right ventricular systolic function and indexed volumes were within normal range: RVEF 60% (IQR 53-65 %), RViEDV 72 ml/m² (IQR 60-84 ml/m²), RViESV 28 ml/m² (IQR 21-39 ml/m²). On post-contrast images, LGE was found in 86 patients (71%): an ischemic pattern was found in 75 patients (62%), with subendocardial and transmural extent in 36 and 39 patients, respectively; a non-ischemic pattern was noted in 11 patients (9%). No LGE was found in 35 patients (29%). In a 16-segment model (excluding the apical cap), the median number of segments with LGE was 2 (IQR 0-6). Scar quantification showed a median scar mass of 3.8 grams (IQR 0-11 grams) (mean 7.8±10.8 grams), corresponding to 6.2 % (IQR 0-15%) of the left ventricle (mean LGE mass 10.7±13.4% of the left ventricle). Ischemic heart disease was diagnosed on CMR in 75 patients (62%) and NIHD in 20 (17%); a structurally normal heart (SNH) was reported in 26 patients (21%). Among patients with NIHD, the most common diagnoses were DCM (n=5) and myocarditis (n=5), followed by HCM (n=3), TTC (n=2), ARVC (n=2), left ventricular non compaction (n=1), hypertensive heart disease (n=1), mitral valve prolapse (n=1). Patients with IHD

had bigger left ventricular volumes and lower systolic function ($p<0.001$), while there was no difference in right ventricular volumes and function between IHD, NIHD and SNH. Myocardial LGE extent was significantly greater in IHD as compared to NIHD patients, both in terms of LGE mass (10.6% vs 1.6%, $p<0.001$) and number of myocardial segments affected by LGE (5 vs 0.5, $p<0.001$). Myocardial deformation was overall impaired: GLS -15.5 % (IQR -18.9- -12.3 %), GRS 34.2 % (IQR 25.2-45.2 %), GCS -15.5 % (IQR -20.3- -11.9 %). Myocardial strain differed significantly between IHD, NIHD and SNH patients ($p<0.001$ for all myocardial strain components). Circumferential and radial myocardial strain was more impaired in IHD patients, while longitudinal strain was more impaired in NIHD patients. Intra-observer variability for myocardial deformation assessment was tested on 29 patients and showed excellent agreement for all myocardial strain components: GLS ICC=0.92 (95% CI 0.82-0.96), GRS ICC=0.94 (95% CI 0.87-0.97), GCS ICC=0.85 (95% CI 0.70-0.93). CMR findings are summarised in **Table 6**.

Table 6. CMR findings

	All n=121	IHD n=75	NIHD n=20	SNH n=26	p-value
Age, years	62 (53-70)	65 (57-71)	55 (41-68)	53 (41-63)	0.003
Days to CMR	13 (6-42)	18 (7-55)	8 (6-11)	15 (5-42)	0.014
LViEDV, ml/m2	89 (73-109)	95 (81-118)	92 (84-105)	76 (63-89)	<0.001
LViESV, ml/m2	42 (27-66)	48 (35-78)	42 (33-55)	27 (19-35)	<0.001
LVEF, %	54 (41-64)	47 (35-60)	55 (43-67)	64 (62-69)	<0.001
LV mass, g/m2	66 (55-82)	69 (59-84)	69 (56-83)	56 (48-66)	0.003
RViEDV, ml/m2	72 (60-84)	66 (59-82)	76 (52-98)	76 (67-86)	0.232
RViESV, ml/m2	28 (21-39)	27 (21-40)	31 (25-39)	29 (21-37)	0.435
RVEF, %	60 (53-65)	59 (51-65)	61 (50-66)	60 (57-66)	0.235
LGE	86 (71)	75 (100)	11 (55)	0	<0.001
LGE mass, g	3.8 (0-11)	7.5 (3.5-17.35)	1.2 (0-6.0)	0	<0.001
LGE mass, %	6.2 (0-15)	10.6 (5.6-21.9)	1.6 (0-9.5)	0	<0.001
Segm. with LGE	2 (0-6)	5 (2-8)	0.5 (0-2)	0	<0.001
GLS, %	-15.5 (-18.9 -12.32)	-14.7 (-18.2 -11.9)	-13.3 (-18.2 -7.9)	-18.6 (-22.2 -15.8)	<0.001
GRS, %	34.2 (25.2-45.2)	27.9 (21.8-39.1)	35.9 (25.2-45.9)	44.6 (36.8-53.2)	<0.001
GCS, %	-15.5 (-20.33 -11.9)	-13.6 (-18.4 -10.9)	-14.9 (-20.7 -10.5)	-20.4 (-22.9 -18.1)	<0.001

Values are expressed as n (%) and median (IQR). IHD, ischemic heart disease;

NIHD, non-ischemic heart disease; SNH, structurally normal heart; LViEDV, indexed left ventricular end-diastolic volume; LViESV, indexed left ventricular end-systolic volumes; LVEF, left ventricular ejection fraction; RViEDV, indexed right ventricular end-diastolic volume; RViESV, indexed left ventricular end-systolic volume; RVEF, right ventricular ejection fraction; LGE, late gadolinium enhancement; GLS, global longitudinal strain; GRS, global radial strain; GCS, global circumferential strain. Significant p-value after Bonferroni correction was 0.017.

There was a linear correlation between all myocardial strain components and both the presence of LGE, the number of segments affected by LGE and LGE extent (% of LV) (Table 7 and Figure 7).

Table 7. Correlation between LGE and myocardial deformation

	LGE presence			Segm with LGE			LGE mass (% of LV)		
	B Coeff	p-value	95% CI	B Coeff	p-value	95% CI	B Coeff	p-value	95% CI
GLS	2.56	0.012	0.57-4.56	0.63	<0.001	0.43-0.84	0.14	<0.001	0.07-0.20
GRS	-9.20	0.001	-14.3- -4.1	-1.91	<0.001	-2.43- -1.39	-0.40	<0.001	-0.57- -0.23
GCS	3.70	0.001	1.63-5.77	0.75	<0.001	0.53-0.96	0.19	<0.001	0.14-0.26

LGE, late gadolinium enhancement; GLS, global longitudinal strain; GRS, global radial strain; GCS, global circumferential strain.

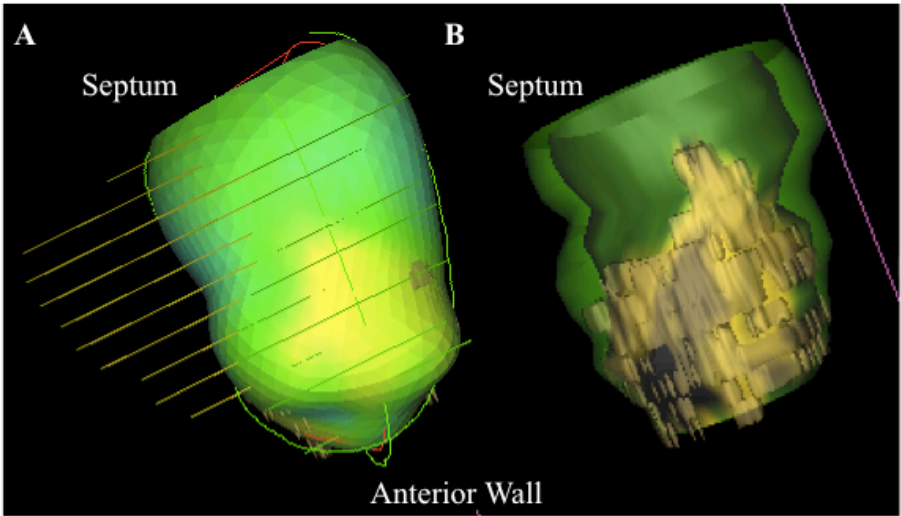


Figure 7. 3D representation of longitudinal myocardial strain (A) showing an area of impaired strain in the mid-cavity to apical anterior wall (displayed in yellow), corresponding to an area of extensive LGE of the mid-cavity to apical anterior wall in a patient with ischemic heart disease (B, normal myocardium is displayed in green, LGE is displayed in yellow/black).

6.3 Patients with structurally normal heart on CMR

Amongst patients with structurally normal heart on CMR, 6 underwent Ajmaline test, which allowed a diagnosis of Brugada syndrome in 2 patients. Three patients underwent exercise test to exclude catecholaminergic polymorphic ventricular tachycardia, which was ruled out in all. Wolf-Parkinson-White syndrome was diagnosed in 2 patients based on resting ECG, and one patient had ECG findings consistent with early repolarisation syndrome.

Patients with structurally normal heart on CMR were matched with 26 healthy volunteers, of same age, gender and LVEF (all factors known to affect myocardial strain). There was no difference in myocardial deformation between VF cardiac arrest survivors and healthy controls matched for age, gender and LVEF: GLS -18.6% vs -19.9% ($p=0.249$), GRS 44.6% vs 42.4% ($p=0.51$), GCS -20.4% vs -21.0% ($p=0.661$).

6.4 Outcome

Outcome data were available in 99 patients (82%). Twenty-two patients (18%) were lost to follow-up, as they were referred to CMR in our centre from district hospitals, but were not taken care of by our local Clinical Care Team. Median follow-up was 24 months (IQR 6-41 months). Fifty-two patients (52%) were implanted with an ICD as secondary prevention, and they were followed-up at 3-6 months interval at the local outpatient pacing clinic; the median number of pacing clinic visits (in order to obtain regular ICD interrogation) was 8 (IQR 5-11). The composite end-point was met in 24 patients (24%): 14 patients had appropriate ICD discharge/ATP (6 had multiple appropriate shocks for recurrent VF episodes; 4 patients died) and 10 patients died; all but one death was of cardiac origin. The median time from VF cardiac arrest to the first end-point was

18 months (IQR 3-25 months). There was no difference in clinical and demographic characteristics of patients meeting and not meeting the end-point (**Table 8**), and therapy at discharge did not differ between the two groups (aspirin $p=0.174$; P2Y12 inhibitors $p=0.905$; ACE inhibitors $p=0.982$; beta-blockers $p=0.432$). Amongst patients meeting the end-point, 15 were found to have IHD on CMR, 5 had NIHD and 4 had SNH. Patients meeting the end-point had bigger LV volumes (LVIEDV 111 ml/m² vs 89 ml/m², $p=0.006$, LVIESV 66 ml/m² vs 40 ml/m², $p=0.039$), but similar LVEF as compared to patients not meeting the end-point (45% vs 40%, $p=0.128$); when considering LVEF, 7 patients experiencing recurrent adverse events had LVEF $\leq$ 35%, while 17 patients experiencing recurrent adverse events had LVEF>35%. Right ventricular ejection fraction was significantly lower in patients meeting the end-point (58% vs 61%, $p=0.03$). Late gadolinium enhancement was more commonly seen in patients meeting the end-point (83% vs 64%), but without reaching statistical significance ($p=0.075$). Four adverse events occurred in patients with no evidence of LGE on CMR, as opposed to 20 adverse events occurring in patients found to have LGE on CMR; no death occurred in the LGE negative group, and all recurrent events consisted of successful ATP on VT ($n=3$), and ICD shock on VF ($n=1$). In the LGE positive group, 10 patients experienced appropriate ICD discharge (9 patients had appropriate shock on VT, 1 had ATP on VT) and 10 patients died; of the 10 patients with appropriate ICD discharge, 4 died later on during follow-up. Extent of LGE was significantly greater in patients meeting the end-point (8.6% vs 4.1%, $p=0.022$), which also had a significantly higher number of myocardial segments affected by LGE (4 vs 2, $p=0.041$). There was no difference in myocardial deformation between

patients with and without the end-point (GLS $p=0.369$, GRS $p=0.498$, GCS $p=0.319$).

Table 8. Clinical characteristics and CMR findings according to outcome

	End-point n=24	No End-point n=75	p-value
Gender, male	22 (92)	60 (80)	0.187
Age, years	67 (53-74)	62 (53-69)	0.270
Hypertension	12 (50)	27 (36)	0.222
Diabetes	5 (21)	10 (13)	0.372
Smoking	8 (33)	20 (27)	0.528
Previous CAD	6 (25)	9 (12)	0.122
LVIEDV, ml/m2	111 (86-135)	89 (71-105)	0.006
LVIESV, ml/m2	66 (34-84)	40 (25-53)	0.039
LVEF, %	40 (25-53)	45 (31-64)	0.128
LV mass, g/m2	70 (57-98)	63 (53-80)	0.104
RVIEDV, ml/m2	77 (62-96)	69 (60-85)	0.259
RVIESV, ml/m2	35 (25-41)	26 (21-37)	0.037
RVEF, %	58 (49-63)	61 (55-66)	0.030
LGE	20 (83)	48 (64)	0.075
LGE mass, g	7.3 (3.9-16.7)	2.5 (0-8.8)	0.008
LGE mass, %	8.6 (4.4-28.2)	4.1 (0-13.8)	0.022
Segm. with LGE	4 (2-8)	2 (0-5)	0.041
Transmural LGE	0 (0-3)	0 (0)	0.126
GLS, %	-12.9 (-20.9- -9.8)	-15.9 (-18.7- -12.8)	0.369
GRS, %	29.5 (21.2-47.1)	34.4 (25.8-44.7)	0.498
GCS, %	-14.1 (-20.4- -10.1)	-16.6 (-20.6- -12.5)	0.319

Values are expressed as n (%) and median (IQR). CAD, coronary artery

disease; LVIEDV, indexed left ventricular end-diastolic volume; LVIESV, indexed left ventricular end-systolic volumes; LVEF, left ventricular ejection fraction; RVIEDV, indexed right ventricular end-diastolic volume; RVIESV, indexed right ventricular end-systolic volume; RVEF, right ventricular ejection fraction; LGE, late gadolinium enhancement; GLS, global longitudinal strain; GRS, global radial strain; GCS, global circumferential strain.

The following variables were tested on univariate analysis as predictors of recurrent adverse events: LV volumes and systolic function, RV systolic function, presence and extent of LGE and myocardial deformation (GLS, GRS

and GCS). Associations with a p-value <0.05 were included in a multivariate model. Variables associated with adverse outcome on univariate analysis were LV volumes (LVIEDV p=0.009; LVIESV p=0.010), RVEF (p=0.044) and LGE mass (% of the LV)(p=0.013). In a multivariate model, LGE extent was the only variable retaining a trend towards an association with adverse outcome, although statistical significance was not reached (p=0.059) (**Table 9**).

Table 9. Predictors of recurrent adverse events

	Univariate			Multivariate		
	B Coeff	p-value	95%CI	B Coeff	p-value	95%CI
LVIEDV	0.02	0.009	0.005-0.03	0.02	0.263	-0.02-0.06
LVIESV	0.02	0.010	0.004-0.03	-0.01	0.595	-0.05-0.03
LVEF	-0.03	0.090	-0.06-0.004	-	-	-
RVEF	-0.05	0.044	-0.10- -0.001	-0.03	0.261	-0.09-0.02
LGE	1.03	0.084	-0.14-2.21	-	-	-
Segm. with LGE	0.10	0.068	-0.008-0.214	-	-	-
LGE mass, %	0.05	0.013	0.009-0.08	0.04	0.059	-0.002-0.08
GLS	0.03	0.492	-0.55-0.12	-	-	-
GRS	-0.01	0.478	-0.05-0.02	-	-	-
GCS	0.05	0.292	-0.04-0.13	-	-	-

Associations with a p-value <0.05 on univariate analysis were tested on a multivariate model. LVIEDV, indexed left ventricular end-diastolic volume; LVIESV, indexed left ventricular end-systolic volumes; LVEF, left ventricular ejection fraction; RVIEDV, indexed right ventricular end-diastolic volume; RVIESV, indexed left ventricular end-systolic volume; RVEF, right ventricular ejection fraction; LGE, late gadolinium enhancement; GLS, global longitudinal strain; GRS, global radial strain; GCS, global circumferential strain.

A ROC curve was created to determine what LGE extent could help identify a group of patients, among those with LGE, at increased risk of adverse events. ROC curve analysis showed that LGE mass of 4.3% of the LV could yield maximum values of sensitivity and specificity to predict adverse events (area under the curve 0.65; sensitivity 75%; specificity 53%) (**Figure 8**).

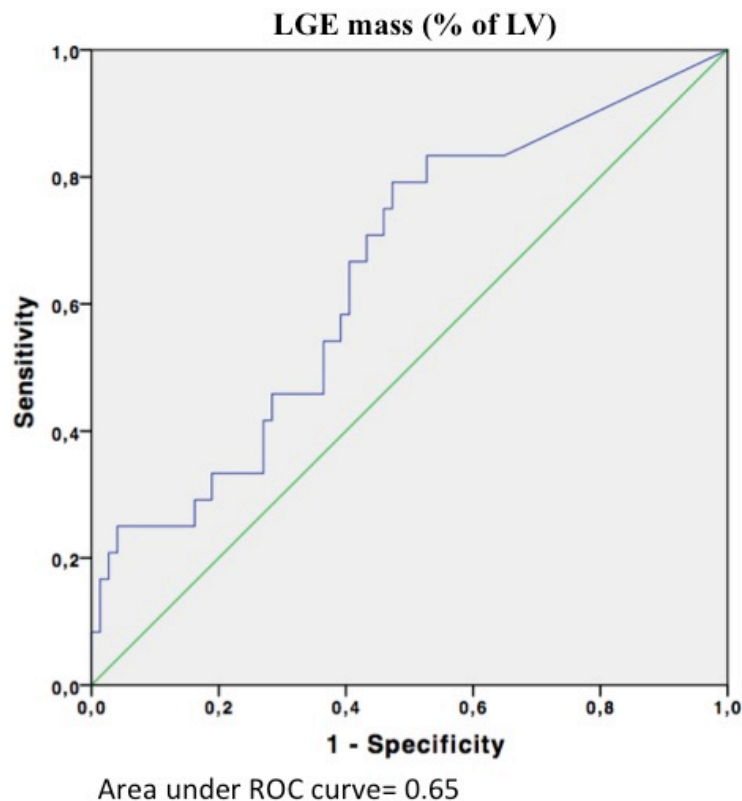


Figure 8. Receiver-operating curve (ROC) testing LGE mass (% of LV) as a predictor of recurrent adverse events. Analysis revealed that LGE mass $\geq 4.3\%$ of LV provided the maximal combination of sensitivity and specificity.

Kaplan-Meier curves were created for event-free survival using both LGE presence/absence and LGE extent (% of LV, cut-off value of $>4.3\%$) (**Figure 9**). Patients with LGE extent $>4.3\%$ of the LV were found to represent a subgroup at higher risk of recurrent adverse events ($p=0.0048$): 18 adverse events were

encountered among patients with LGE extent >4.3%, as compared to 6 adverse events among patients with LGE extent <4.3% of LV.

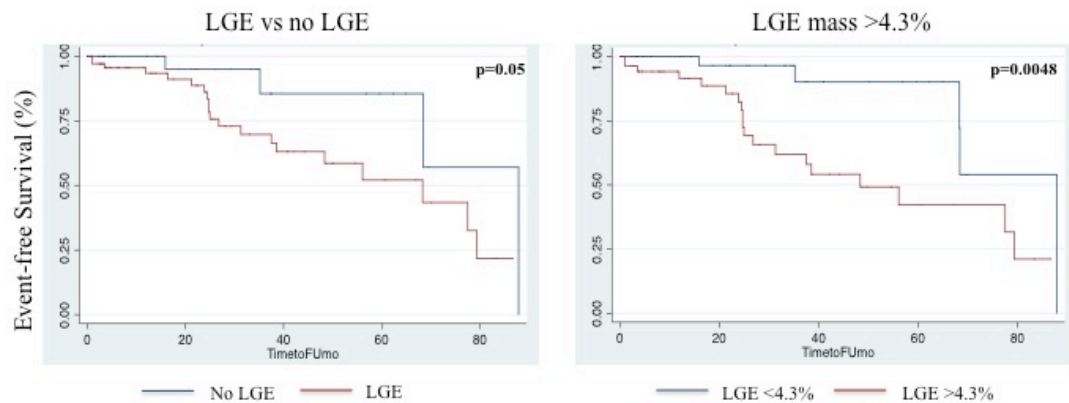


Figure 9. Kaplan-Meier curves displaying event-free survival according to presence/absence of LGE and according to LGE cut-off >4.3%.

6.5 Outcome in patients wearing ICD

Fifty-two patients (52%) were implanted with an ICD for secondary prevention. Patients implanted with an ICD tended to be younger, although the difference was not statistically significant (58 years vs 63 years, $p=0.06$). There was no difference in biventricular volumes (LVIEDV 91 ml/m² vs 92 ml/m², $p=0.486$, LVIESV 42 ml/m² vs 39 ml/m², $p=0.260$; RVIEDV 73 ml/m² vs 70 ml/m², $p=0.232$, RVIESV 28 ml/m² vs 28 ml/m², $p=0.525$) and function (LVEF 50% vs 58% $p=0.122$, RVEF 60% vs 60%, $p=0.981$) between patients who received or did not receive an ICD; there was also no difference in LGE extent (5.5% of LV vs 6.2%, $p=0.369$). Myocardial strain was more impaired in patients who received an ICD (GLS -13.3% vs -17.3, $p=0.003$; GRS 27.5% vs 36.9%, $p=0.017$; GCS -13.2% vs -16.9%, $p=0.028$). Among patients implanted with an ICD, 16 met the end-point (31%). Left ventricular volumes and function did not

differ between patients meeting or not meeting the end-point (**Table 10**), while RViESV (36 ml/m² vs 25 ml/m², p=0.022) and RVEF (55% vs 61%, p=0.024) were respectively bigger and lower in patients meeting the end-point. There was a trend towards a higher prevalence of LGE amongst patients meeting the end-point, but statistical significance was not reached (75% vs 50%, p=0.092). Only one patient had an inappropriate shock on atrial tachycardia; 4 ICDs were extracted and replaced (3 secondary to pocket infection and 1 secondary to malfunction) and 4 patients needed atrial or ventricular lead replacement secondary to dislodgement.

Table 10. Outcome in patients implanted with an ICD

	End-point n=16	No End-point n=36	p-value
LVIEDV, ml/m ²	98 (76-141)	91 (76-108)	0.201
LVIESV, ml/m ²	39 (27-96)	42 (29-63)	0.565
LVEF, %	50 (32-68)	52 (37-64)	0.889
LV mass, g/m ²	80 (52-98)	70 (58-84)	0.471
RVIEDV, ml/m ²	75 (60-109)	63 (53-85)	0.273
RVIESV, ml/m ²	36 (24-52)	25 (18-36)	0.022
RVEF, %	55 (48-63)	61 (53-70)	0.024
LGE	12 (75)	18 (50)	0.092
LGE mass, g	5.4 (0.9-12.1)	0.7 (0-11.6)	0.187
LGE mass, %	6.9 (0.9-12.8)	0.9 (0-15.4)	0.224
Segm. with LGE	3 (0.3-5)	0.8 (0-6.3)	0.193
GLS, %	-13.8 (-21.3- -9.3)	-13.5 (-18.6- -11.4)	1.000
GRS, %	30 (18.4-47.1)	27.5 (18.6-45.3)	0.937
GCS, %	-15 (-21.9- -10.6)	-13.2 (-20.3- -10.5)	0.677

Values are expressed as n (%) and median (IQR). LVIEDV, indexed left

ventricular end-diastolic volume; LVIESV, indexed left ventricular end-systolic

volumes; LVEF, left ventricular ejection fraction; RVIEDV, indexed right

ventricular end-diastolic volume; RVIESV, indexed left ventricular end-systolic

volume; RVEF, right ventricular ejection fraction; LGE, late gadolinium

enhancement; GLS, global longitudinal strain; GRS, global radial strain; GCS,

global circumferential strain.

Chapter 7. Discussion

The main findings of this study were that in VF cardiac arrest survivors 1) there is a high prevalence of LGE (71%), mainly with an ischemic pattern, 2) myocardial deformation is overall impaired, despite an only mildly impaired LVEF (54%), 3) there is no difference in LVEF between patients meeting the end-point and those event-free, 4) LGE extent, rather than its presence, is associated with a worse outcome, while 5) myocardial deformation is not a predictor of adverse recurrent events.

7.1 Late gadolinium enhancement

In a cohort of VF cardiac arrest survivors undergoing CMR, we found a high prevalence of LGE (71% of patients), mainly presenting with an ischemic distribution pattern (87% of all patients with LGE), confirming that the leading cause of cardiac arrest is ischemic (17). These findings are in keeping with previous data from Neilan et al. in a similar cohort of VF/VT cardiac arrest survivors, which showed on CMR a 71% prevalence of LGE with an ischemic pattern in 68% of patients (49). The presence and distribution pattern of LGE in our cohort led to the identification of a pathological substrate of the cardiac arrest in 79% of patients, which is very similar to the 76% reported by Neilan et al. (49). There is increasing evidence of the additional diagnostic role of CMR in cardiac arrest survivors, which comes from the superior ability of CMR to provide myocardial tissue characterisation. White et al. performed CMR in 82 cardiac arrest survivors which received routine non-CMR imaging and found that CMR was able to identify an underlying cause in 74% of patients as opposed to 51% provided by non-CMR imaging, and that nearly half of patients

where re-classified to a different diagnosis based on CMR (48). Similarly, in our previous study, we found that among cardiac arrest survivors with no evidence of an acute ischemic cause on angiogram (stable obstructive CAD with no culprit lesion or unobstructed coronaries), CMR was able to identify an underlying pathological substrate in 69% of the population, as compared to 54% as provided by trans-thoracic echocardiogram (TTE)(99); moreover, CMR was able to identify a pathological substrate in more than two thirds of patients with non-specific findings on TTE. We found that median LGE mass in our cohort of VF cardiac arrest survivors was 6.2% of LV myocardium (mean $10.7 \pm 13.4\%$), which was comparable to that reported by Neilan et al. ($9.9 \pm 5\%$ of LV myocardium). The association between myocardial scarring and ventricular arrhythmias has been extensively described, both in ischemic and non-ischemic cardiomyopathies (61)(109). In post-MI patients undergoing CMR prior to ICD implantation, scar extent was the strongest predictor of arrhythmic events (SCD, ICD discharge, ventricular arrhythmias) irrespective of LVEF (113)(114); Klem et al. have also shown that among patients undergoing evaluation of possible ICD implantation, those with LGE extent $>5\%$ and LVEF $>30\%$ had a higher risk of arrhythmic events than patients with LVEF $\leq 30\%$ but LGE extent $<5\%$ (115). On the other hand, among 300 patients with sustained and non-sustained VT undergoing CMR, those with LGE had higher risk of cardiac death/arrest, new VT episodes or appropriate ICD discharge; while LGE extent was the only predictor of recurrent events among patients with non-sustained VT, both LGE extent and reduced LVEF predicted recurrent events among patients with sustained VT (116). Most of studies assessing the role of LGE as predictor of adverse outcome were limited by small sample size and low number of events. A recent meta-analysis (117) on nearly 3000 patients, with both ischemic and

non-ischemic cardiomyopathies, confirmed the prognostic role of LGE, both in terms of presence/absence and extent (mass), which appears to be even superior in patients having a reduced LVEF (odds ratio doubles in patients with $LVEF \leq 30\%$ as compared to patients with $LVEF > 30\%$).

7.2 Myocardial strain

Myocardial deformation in our cohort was overall impaired, despite an only mildly impaired LVEF (median 54%), but it is well-recognised that myocardial strain is an early marker of disease and that it is often impaired before a reduction in LVEF is noted (89)(90). We found a significant difference in all myocardial strain components according to CMR findings (IHD, NIHD and structurally normal heart) ($p < 0.001$). Interestingly, while GCS and GRS were more impaired among IHD patients, GLS was more impaired in NIHD patients. Global longitudinal strain is believed to be more sensitive to acute injury, as compared to GCS and GRS; NIHD patients underwent CMR earlier compared to IHD patients (time to CMR 8 days vs 18 days in IHD patients), and the more severe impairment of GLS could be a consequence of earlier CMR imaging detecting more acute injury (118). The difference in myocardial deformation between patients with IHD, NIHD and SNH is likely a consequence of the presence of myocardial LGE: we've found a linear correlation between all strain components and both the presence and extent of LGE (both as number of myocardial segments with LGE and LGE mass as percentage of LV myocardium, $p < 0.001$ for both). A correlation between myocardial strain and myocardial LGE has been previously described, both in ischemic and non-ischemic cardiomyopathies. Myocardial deformation allows the differentiation of normal myocardial segments from segments with subendocardial and

transmural LGE, not only as absolute, global values, but also in the sub-analysis of endocardial and epicardial strain values, which both decrease with increasing degrees of MI extent (91). A significant difference in peak circumferential strain has been described between infarcted, remote and adjacent myocardial segments, and between remote and adjacent segments right after an acute MI, and at follow-up (95)(119). Similar findings have been described in NIHD: Mordi et al. found a correlation between the percentage of LGE and global circumferential strain, as assessed by CMR tagging, in a cohort of more than 500 patients referred for a clinically indicated CMR (most of patients were referred for stratification of suspected heart failure)(111). Similarly, a combined protocol, comprehensive of SpTE and LGE on CMR, studying DCM patients, found LGE in 56% and impairment of all myocardial strain components: there was a significant difference in myocardial deformation between patients with and without LGE (119). Interestingly, we found no difference in myocardial strain between VF cardiac arrest survivors with structurally normal heart on CMR and a control group of healthy volunteers, matched for age, gender and LVEF (known factors influencing myocardial strain). This finding differs from a recently reported reduction in 3D peak strain in patients with ventricular arrhythmias (premature ventricular beats, non-sustained VT or arrhythmias detected during catheter ablation/electrophysiologic study) and a structurally normal heart (120); the Authors, however, provided the segmental peak strain assessment and reported a correlation between regional variations in myocardial strain and underlying regional wall motion abnormalities.

7.3 Predictors of recurrent adverse events

Patients surviving cardiac arrest are at higher risk of recurrent adverse events, such as death and ICD discharge for recurrent ventricular arrhythmias. Among more than 2000 patients implanted with an ICD for primary (61%; mean LVEF 29%) or secondary prevention (39%; mean LVEF 37%), those treated for secondary prevention had a 74% increased risk of appropriate ICD therapy (51% 5-year incidence vs 37% in primary prevention)(121), although the long-term risk for all-cause mortality was comparable between the two groups. A study on post-MI cardiac arrest survivors (n=48), which were matched with cardiac arrest survivors without MI (n=48) and MI patients without cardiac arrest (n=96), showed a 67% 5-year end-point-free survival (end-point: death/recurrent ventricular arrhythmias) among post-MI cardiac arrest survivors, which was significantly lower compared to cardiac arrest survivors without MI (80%) and MI patients without cardiac arrest (92%)(122); it should be noted, however, that mean LVEF in the different groups was 34%. During a median follow-up of 24 months the composite end-point of death or appropriate ICD discharge/ATP in our cohort was 24%. The current practice in the centre where this study was conducted is in favour of programming the ICD in order to reduce shocks, so that arrhythmia detection interval is increased to allow self-termination of arrhythmias; this might explain the lower incidence of ICD discharge in our cohort as compared to the study by Neilan et al. (34% ICD discharge). Median LVEF in our cohort (54%) was higher than that reported in other studies assessing recurrent events after a first episode of cardiac arrest, so that the lower incidence of recurrent events in our cohort might in part be explained by a better functional class. There was however no difference in LVEF between patients experiencing adverse recurrent events and those with a more

favourable outcome (40% vs 45%, $p=0.128$). Left ventricular ejection fraction is increasingly recognised as an unsatisfactory prognostic marker (115) and in our cohort 7 patients meeting the end-point had $LVEF \leq 35\%$, while the remaining 17 patients meeting the end-point had $LVEF > 35\%$, which means they wouldn't have even fallen into the group of patients eligible to receive an ICD as primary prevention. In a multi-centre study on more than 1000 patients undergoing assessment of LVEF and scarring on CMR both a reduced LVEF (mean LVEF in the population was $45 \pm 18\%$) and the presence of myocardial segments with LGE were independent predictors of mortality; however, in patients with mildly impaired LVEF ($\geq 50\%$), those with >4 myocardial segments with LGE had worse outcome than those with less myocardial segments with LGE ($p=0.02$) (123). We found that the prevalence of LGE was higher in patients experiencing recurrent adverse events, although it did not reach statistical significance (LGE was found in 83% of patients meeting the end-point vs 64% of patients not meeting the end-point, $p=0.075$). However, LGE extent, both in terms of number of segments with LGE ($p=0.041$) and LGE mass as percentage of LV myocardium ($p=0.022$) were significantly higher in patients meeting the end-point. Interestingly we found that transmural LGE extension did not differ between patients with and without adverse outcome [0 (0-3) vs 0 (0), $p=0.126$]. This likely suggests that not only the absolute amount of LGE, but also the number of myocardial segments involved by LGE, are important prognostic factors, more than the presence of LGE or its locally transmural extent. When considering the ROC curve analysis for LGE extent, we found an AUC of 0.65 (SE 0.06, 95% CI 0.53-0.78), with a cut-off of 4.3% of LV myocardium maximising the best sensitivity and specificity for prediction of recurrent events ($p=0.0048$); this is lower than the 8.1% of LV myocardium reported by Neilan et

al. in a similar population of VT/VF cardiac arrest survivors (49), but similar to the 5% reported by Klem et al. in a population referred to CMR for evaluation of ICD implantation (115). Chimura et al. (119) combined SpTE for strain assessment and LGE CMR to assess patients with DCM for a composite end-point of cardiac death, re-hospitalisation for HF and cardiac transplantation (SCD and ventricular arrhythmias were included among the secondary end-points): despite a strong correlation between all myocardial strain components and LGE, only GLS (but not GRS or GCS) and LGE were independent predictors of worse outcome. Having a normal GLS was a predictor of better outcome, also irrespective of the presence of LGE. Similar to our findings, LVEF, which was overall severely impaired (mean LVEF of 33%) in their cohort, did not prove to be a predictor of adverse outcome. Another study assessing myocardial strain with CMR followed-up for 5 years 210 DCM patients with reduced LVEF (mean 36%); patients with worse outcome (SCD, ICD discharge) had a trend towards a higher prevalence of LGE (51% vs 34%, $p=0.07$) and significantly more impaired myocardial deformation in all three directions. All myocardial strain components were predictors of adverse outcome and GLS was an independent predictor of adverse outcome irrespective of both LVEF and the presence of LGE (110). Another study performed with CMR tagging on more than 500 patients referred for clinically indicated CMR found that LVEF, LGE and GCS were independent predictors of all-cause mortality, aborted SCD and hospitalisation for heart failure; interestingly, patients with LVEF $>35\%$ with LGE and impaired GCS had worse outcome than those with LVEF $<35\%$ (111). We found no difference in myocardial deformation between patients with and without adverse outcome, even when considering only patients implanted with an ICD. Many echocardiographic and CMR studies described a correlation

between impaired myocardial deformation and adverse outcome: there is however a wide heterogeneity in populations studied (ischemic and non-ischemic), none of whom resembles our population of cardiac arrest survivors, and an even wider heterogeneity in their methods (SpTE vs CMR derived strain, CMR-derived strain based on different vendors). Finally, in most of these studies mean LVEF was severely impaired, describing populations with advanced heart failure and functional class impairment; in our population LVEF was only mildly impaired (median 54%) and this might explain why myocardial deformation was not able to risk stratify patients. In order to identify predictors of adverse outcome, we tested biventricular volumes and function, LGE presence and extent and myocardial deformation on univariate analysis; only left ventricular volumes, right ventricular ejection fraction and LGE extent as % of LV myocardium showed a significant association on univariate analysis ($p < 0.05$) and were tested on multivariate analysis. Only LGE extent as % of LV myocardium showed an association with outcome, although the p-value was borderline significant ($p = 0.059$). In a similar cohort of VT/VF patients followed-up for all-cause mortality and appropriate ICD intervention, LGE extent proved to be the strongest predictor of events, among different demographic (age, gender) and clinical characteristics (diabetes, LVEF, LVEDV)(49).

7.4 Limitations

Our study has some limitations. First of all, we only have data on VF cardiac arrest survivors referred to CMR and not on those surviving a cardiac arrest that were not referred to CMR; VF cardiac arrest survivors were referred to CMR at the discretion of the clinical care team, and this might represent a selection bias, but at the same time it represents real world practice of a high volume, third level Cardiovascular centre. The range of normal strain values is quite wide, both as a consequence of age, gender and heart rate related variations (78)(80), but mainly secondary to the different studies that have assessed strain normality in different populations and using different vendors(124); intra and inter-observer variability also vary considerably in different studies (80). To reduce strain analysis variability in our study, only one experienced observer assessed myocardial deformation and repeated measurements on 29 randomly selected patients, six months after the first assessment; moreover, global strain assessment was preferred over segmental analysis, as this is known to be less robust and less reproducible (80)(78): this resulted in excellent intra-observer agreement for all three myocardial strain components (ICC=0.92 for GLS, ICC=0.94 for GRS and ICC=0.85 for GCS). Time to CMR differed significantly between groups, mainly based on clinician's discretion: it is recognised that the earlier performance of CMR increases the chances to detect myocardial oedema, thus increasing the diagnostic capability of the imaging technique. However, myocardial oedema sequences were not systematically performed in our patient's cohort, so that we cannot exclude the concomitant presence of myocardial oedema, which, according to recent evidence from echocardiographic studies in Tako-Tsubo cardiomyopathy (125)(126), might in part have contributed to myocardial strain impairment. We did not systematically

perform T1 mapping in our cohort; there is growing evidence that diffuse, rather than focal, myocardial fibrosis, as assessed by the novel T1 mapping technique, stratifies IHD and NIHD patients according to their arrhythmic risk (127), thus improving selection of primary prevention ICD implantation. Systematic inclusion of the T1 mapping technique might be useful in stratification of recurrences after VF cardiac arrest, and its role should be assessed with powered studies. Finally, outcome data were collected retrospectively and patients not currently followed-up at our Institution might have met the end-point after being lost to follow-up, which could not be accounted for.

Chapter 8. Conclusion

Cardiovascular magnetic resonance has proved to be an important diagnostic tool in patients surviving out of hospital cardiac arrest, identifying a pathological substrate of the VF cardiac arrest in 79% of cases. While CMR-derived LVEF and myocardial strain assessment was not able to detect patients at an increased risk of adverse events, an LGE extent $>4.3\%$ of LV myocardium identified a subgroup of patients at higher risk of adverse events.

8.1 Future directions

Cardiovascular magnetic resonance has emerged as an important diagnostic tool and prognostic predictor in different cardiomyopathy groups, but further studies, on larger populations, are warranted in order to confirm and expand the role of CMR as a risk stratification tool in patients surviving cardiac arrest. The latest mapping sequences (T1 and T2 mapping), which provide a detailed characterisation of how the myocardial tissue and the interstitial space interact with each other, may allow a better delineation of the complex pathological mechanism behind ventricular arrhythmias and better clarify the importance of triggers (i.e. transient myocardial ischemia), on a predisposing myocardial background (i.e. diffuse myocardial fibrosis), in arrhythmogenesis. Finally, a prospective registry, aiming at scanning cardiac arrest survivors more than once during their follow-up, may help distinguish early and late predictors of recurrent events and further help in the difficult stratification of arrhythmic risk in this cohort of patients.

References

1. De Vreede-Swagemakers J, Gorgels AP, Dubois-Arbouw WI, van Ree JW, Daemen MJ, Hiuben LG, et al. Out-of-hospital cardiac arrest in the 1990s: a population-based study in the Maastricht area on incidence, characteristics and survival. *J Am Coll Cardiol*. 1997;30(6):1500–5.
2. Benjamin EJ, Blaha MJ, Chiuve SE, Cushman M, Das SR, Deo R, et al. Heart Disease and Stroke Statistics—2017 Update: A Report From the American Heart Association. *Circulation*. 2017; 135: e146-603.
3. Polnitsky CA, Capone RJ, Gagnon DE, McGinnis K. Prehospital Coronary Care. Proposal for a uniform reporting system. *JAMA*. 1977;(237):134–7.
4. McNally B, Robb R, Mehta M, Vellano K, Valderrama AL, Yoon PW, et al. Out-of-hospital cardiac arrest surveillance --- Cardiac Arrest Registry to Enhance Survival (CARES), United States, October 1, 2005--December 31, 2010. *MMWR Surveill Summ* 2011; 60: 1-19.
5. Nishiyama C, Brown SP, May SJ, Iwami T, Koster RW, Beesems SG, et al. Apples to apples or apples to oranges ? International variation in reporting of process and outcome of care for out-of-hospital cardiac arrest. *Resuscitation* 2014; 85: 1599–609.
6. Perkins GD, Jacobs IG, Nadkarni VM, Berg RA, Bhanji F, Biarent D, et al. Cardiac arrest and cardiopulmonary resuscitation outcome reports: Update of the Utstein resuscitation registry templates for out-of-hospital cardiac arrest. *Circulation* 2015; 132: 1286-300.
7. Cummins RO, Chamberlain D a, Abramson NS, Allen M, Baskett PJ, Becker L, et al. Recommended guidelines for uniform reporting of data from out-of-hospital cardiac arrest: the Utstein Style. A statement for

- health professionals from a task force of the American Heart Association, the European Resuscitation Council, the Heart and Stroke Foundation of Canada, and the Australian Resuscitation Council. *Circulation*. 1991;84(2):960–75.
8. Wnent J, Masterson S, Gräsner JT, Böttiger BW, Herlitz J, Koster RW, et al. EuReCa ONE – 27 Nations, ONE Europe, ONE Registry: a prospective observational analysis over one month in 27 resuscitation registries in Europe – the EuReCa ONE study protocol. *Scand J Trauma Resusc Emerg Med* 2015; 23: 7.
 9. Gorgels APM, Gijsbers C, de Vreede-Swagemakers J, Lousberg A, Wellens HJJ. Out-of-hospital cardiac arrest--the relevance of heart failure. The Maastricht Circulatory Arrest Registry. *Eur Heart J*. 2003;24:1204–9.
 10. Myerburg RJ, Junttila MJ. Sudden cardiac death caused by coronary heart disease. *Circulation*. 2012;125(8):1043–52.
 11. Ilkhanoff L, Goldberger JJ. Out-of-hospital cardiac arrest: Getting beyond the tip of the iceberg. *Circulation*. 2012;126(7):793–6.
 12. Basso C, Aguilera B, Banner J, Cohle S, d'Amati G, de Gouveia RH, et al. Guidelines for autopsy investigation of sudden cardiac death: 2017 update from the Association for European Cardiovascular Pathology. *Virchows Arch [Internet]*. *Virchows Arch* (2017). <https://doi.org/10.1007/s00428-017-2221-0>.
 13. Berdowski J, Berg RA, Tijssen JG, Koster RW. Global incidences of out-of-hospital cardiac arrest and survival rates: Systematic review of 67 prospective studies. *Resuscitation* 2010; 81: 1479–87.
 14. Norris RM. Circumstances of out of hospital cardiac arrest in patients with ischaemic heart disease. *Heart*. 2005; 91: 1537–40.

15. Jabbour RJ, Sen S, Mikhail GW, Malik IS. Out of hospital cardiac arrest: Concise review of strategies to improve outcome. *Cardiovasc Revascularization Med* 2017; Available from: <http://dx.doi.org/10.1016/j.carrev.2017.03.011>
16. Engdahl J, Holmberg M, Karlson BW, Luepker R, Herlitz J. The epidemiology of out-of-hospital “sudden” cardiac arrest. *Resuscitation*. 2002; 52(3): 235–45.
17. Mehta D, Curwin J, Gomes J a, Fuster V. Sudden death in coronary artery disease: acute ischemia versus myocardial substrate. *Circulation* 1997;96(9):3215–23.
18. Chugh SS, Kelly KL, Titus JL. Sudden cardiac death with apparently normal heart. *Circulation* 2000; 102: 649-54.
19. Corrado D, Basso C, Thiene G. Sudden cardiac death in young people with apparently normal heart. *Cardiovasc Res*. 2001;50(2):399–408.
20. Evaluation SC. Survivors of Out-of-Hospital Cardiac Arrest With Apparently Normal Heart: Need for Definition and Standardized Clinical Evaluation. Consensus Statement of the Joint Steering Committees of the Unexplained Cardiac Arrest Registry of Europe and of the Idiopathic Ventricular Fibrillation Registry of the United States. *Circulation* 1997;95(1):265–72.
21. Arsenos P, Gatzoulis K, Dilaveris P, Manis G, Tsichris D, Archontakis S, et al. Arrhythmic Sudden Cardiac Death: substrate, mechanism and current risk stratification strategies for the post-myocardial infarction patient. *Hell J Cardiol*. 2013;(54):301–15.
22. Zaman S, Kovoov P. Sudden cardiac death early after myocardial infarction: pathogenesis, risk stratification, and primary prevention.

Circulation 2014;129(23): 2426–35.

23. Rubenstein JC, Lee DC, Wu E, Kadish AH, Passman R, Bello D, et al. A comparison of cardiac magnetic resonance imaging peri-infarct border zone quantification strategies for the prediction of ventricular tachyarrhythmia inducibility. *Cardiol J.* 2013; 20(1): 68–77.
24. Stojanovska, Fadranka, Garg, Anubhav, Patel, Smita, Melville, David, Kazerooni, Ella, Mueller G. Congenital and Hereditary Causes of Sudden Cardiac Death in Young Adults : Diagnosis , Differential Diagnosis, and Risk Stratification. *Radiographics.* 2013;(33):1977–2001.
25. Semsarian C, Ingles J, Wilde AA. Sudden cardiac death in the young: the molecular autopsy and a practical approach to surviving relatives. *Eur Heart J* 2015; 36: 1290-6.
26. Corrado D, Migliore F, Basso C, Thiene G. Exercise and the risk of sudden cardiac death. *Herz.* 2006;31(6):553–8.
27. Maron BJ, Doerer JJ, Haas TS, Tierney DM, Mueller FO. Sudden deaths in young competitive athletes: analysis of 1866 deaths in the United States, 1980-2006. *Circulation.* 2009;119(8):1085–92.
28. Sweeting J, Semsarian C. Sudden cardiac death in athletes: still much to learn. *Cardiology Clinics* 2016; 34: 531-41.
29. Kocovski L, Fernandes J. Sudden Cardiac Death: A Modern Pathology Approach to Hypertrophic Cardiomyopathy. *Arch Pathol Lab Med* 2015;139(3):413–6.
30. O’Mahony C, Elliott P, McKenna W. Sudden cardiac death in hypertrophic cardiomyopathy. *Circ Arrhythmia Electrophysiol.* 2013;6(2):443–51.
31. Koutalas E, Kanoupakis E, Vardas P. Sudden cardiac death in non-ischemic dilated cardiomyopathy: A critical appraisal of existing and

- potential risk stratification tools. *Int J Cardiol* 2013;167(2):335–41.
32. Lubitz SA, Goldbarg SH, Mehta D. Sudden Cardiac Death in Infiltrative Cardiomyopathies: Sarcoidosis, Scleroderma, Amyloidosis, Hemachromatosis. *Prog Cardiovasc Dis*. 2008;51(1):58–73.
 33. van der Bijl P, Delgado V, Bax JJ. Noninvasive imaging markers associated with sudden cardiac death. *Trends in Cardiovascular Medicine*. 2016; 26: 348-60.
 34. Mazeika P. Aborted sudden cardiac death: a clinical perspective. *Postgrad Med J*. 2001;77(908):363–70.
 35. Fernández-Falgueras A, Sarquella-Brugada G, Brugada J, Brugada R, Campuzano O. Cardiac Channelopathies and Sudden Death: Recent Clinical and Genetic Advances. *Biology (Basel)* 2017;6(1):7.
doi:10.3390/biology6010007
 36. Basso C, Perazzolo Marra M, Rizzo S, De Lazzari M, Giorgi B, Cipriani A, et al. Arrhythmic Mitral Valve Prolapse and Sudden Cardiac Death. *Circulation*. 2015;132(7):556–66.
 37. Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). *European Heart Journal* 2017, ehx393, <https://doi.org/10.1093/eurheartj/ehx393>.
 38. Noc M, Fajadet J, Lassen JF, Kala P, Mccarthy P, Olivecrona GK, et al. Invasive coronary treatment strategies for out-of-hospital cardiac arrest : a consensus statement from the European Association for Percutaneous

- Cardiovascular Interventions (EAPCI)/ Stent for Life (SFL) groups.
Eurointervention 2014; 10: 31-7.
39. Agewall S, Beltrame JF, Reynolds HR, Niessner A, Rosano G, Caforio ALP, et al. ESC working group position paper on myocardial infarction with non-obstructive coronary arteries. Eur Heart J. 2017;38(3):143–53.
 40. Monsieurs KG, Nolan JP, Bossaert LL, Greif R, Maconochie IK, Nikolaou NI, et al. European Resuscitation Council Guidelines for Resuscitation 2015. Resuscitation 2015;95:1–80.
 41. Price S, Uddin S, Quinn T. Echocardiography in cardiac arrest. Curr Opin Crit Care [Internet]. 2010;16(3):211–5.
 42. Labovitz AJ, Noble VE, Bierig M, Goldstein SA, Jones R, Kort S, et al. Focused Cardiac Ultrasound in the Emergent Setting : A Consensus Statement of the American Society of Echocardiography and American College of Emergency Physicians. J Am Soc Echocardiogr 2010;23(12):1225–30.
 43. Guidelines for the Use of Transesophageal Echocardiography (TEE) in the ED for Cardiac Arrest. Ann Emerg Med [Internet]. 2017;70(3):442–5.
 44. Blyth L, Atkinson P, Gadd K, Lang E. Bedside Focused Echocardiography as Predictor of Survival in Cardiac Arrest Patients : A Systematic Review. Academic Emergency Medicine 2012; 19: 1119–26.
 45. Tsou P, Kurbedin J, Chen Y, Chou EH, Lee MG, Lee MC, et al. Accuracy of point-of-care focused echocardiography in predicting outcome of resuscitation in cardiac arrest patients: A systematic review and meta-analysis. Resuscitation 2017;114:92–9.
 46. Wu KC. Sudden Cardiac Death Substrate Imaged by Magnetic Resonance Imaging: From Investigational Tool to Clinical Applications.

- Circ Cardiovasc Imaging. 2017;10(7). pii: e005461. doi: 10.1161/CIRCIMAGING.116.005461.
47. Mahrholdt H, Wagner A, Judd RM, Sechtem U, Kim RJ. Delayed enhancement cardiovascular magnetic resonance assessment of non-ischaemic cardiomyopathies. *Eur Heart J*. 2005;26(15):1461–74.
 48. White JA, Fine NM, Gula L, Yee R, Skanes A, Klein G, et al. Utility of cardiovascular magnetic resonance in identifying substrate for malignant ventricular arrhythmias. *Circ Cardiovasc Imaging*. 2012;5:12–20.
 49. Neilan TG, Farhad H, Mayrhofer T, Shah RV, Dodson JA, Abbasi SA, et al. Late Gadolinium Enhancement Among Survivors of Sudden Cardiac Arrest. *JACC Cardiovasc Imaging* 2015;8: 414-423.
 50. Dastidar AG, Rodrigues JCL, Johnson TW, De Garate E, Singhal P, Baritussio A, et al. Myocardial Infarction With Nonobstructed Coronary Arteries: impact of CMR early after presentation. *JACC Cardiovasc Imaging* 2017; 10: 1204-6.
 51. Nolan JP, Soar J, Cariou A, Cronberg T, Moulaert VRM, Deakin CD, et al. European Resuscitation Council and European Society of Intensive Care Medicine 2015 Guidelines for Post-resuscitation Care. *Intensive Care Med* 2015; 41: 2039-56.
 52. Nielsen N, Wetterslev J, Al-Subaie N, Andersson B, Bro-Jeppesen J, Bishop G, et al. Target temperature management after out-of-hospital cardiac arrest - A randomized, parallel-group, assessor-blinded clinical trial - Rationale and design. *Am Heart J* 2012;163(4):541–8.
 53. Borne RT, Katz D, Betz J, Peterson PN, Masoudi FA. Implantable cardioverter-defibrillators for secondary prevention of sudden cardiac death: A review. *J Am Heart Assoc*. 2017;6(3):1–11.

54. Priori SG, Blomström-Lundqvist C, Mazzanti A, Blom N, Borggrefe M, Camm J, et al. 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. *Eur Heart J* 2015;36(41):2793–867.
55. Champagne J, Geelen P, Philippon F, Brugada P. Recurrent cardiac events in patients with idiopathic ventricular fibrillation, excluding patients with the Brugada syndrome. *BMC Med* 2005;3(1):1.
56. Ridgway JP. Cardiovascular magnetic resonance physics for clinicians: part I. *J Cardiovasc Magn Reson* 2010;12(1):71.
57. Pennell DJ. Ventricular volume and mass by CMR. *J Cardiovasc Magn Reson*. 2002;4(4):507–13.
58. Pennell DJ. Cardiovascular magnetic resonance. *Circulation*. 2010;121(5):692–705.
59. Schulz-Menger J, Bluemke DA, Bremerich J, Flamm SD, Fogel MA, Friedrich MG, et al. Standardized image interpretation and post processing in cardiovascular magnetic resonance : Society for Cardiovascular Magnetic Resonance (SCMR) Board of Trustees Task Force on Standardized Post Processing. *J Cardiovasc Magn Reson* 2013;15(1):1.
60. Beltrami CA, Finato N, Rocco M, Feruglio GA, Puricelli C, Cigola E, et al. Structural Basis of End-Stage Failure in Ischemic Cardiomyopathy in Humans. *Circulation* 1994; 89: 151-63.
61. Baritussio A, Scatteia A, Bucciarelli-Ducci C. Role of cardiovascular magnetic resonance in acute and chronic ischemic heart disease. *Int J Cardiovasc Imaging* 2017; doi: 10.1007/s10554-017-1116-0. [Epub ahead of print].

62. Dastidar AG, Rodrigues JCL, Baritussio A, Bucciarelli-ducci C. MRI in the assessment of ischaemic heart disease. *Heart*. 2016;102:239–52.
63. Kim RJ, Fieno DS, Parrish TB, Harris K, Chen E, Simonetti O, et al. Relationship of MRI Delayed Contrast Enhancement to Irreversible Injury, Infarct Age, and Contractile Function. *Circulation*. 1999;(100):1992–2002.
64. Ibrahim T, Bülow HP, Hackl T, Hörnke M, Nekolla SG, Breuer M, et al. Diagnostic Value of Contrast-Enhanced Magnetic Resonance Imaging and Single-Photon Emission Computed Tomography for Detection of Myocardial Necrosis Early After Acute Myocardial Infarction. *J Am Coll Cardiol* 2007;49(2): 208-16.
65. Flett AS, Hasleton J, Cook C, Hausenloy D, Quarta G, Ariti C, et al. Evaluation of Techniques for the Quantification of Myocardial Scar of Differing Etiology Using Cardiac Magnetic Resonance. *JACC Cardiovasc Imaging* 2011;4(2):150–6.
66. Eitel I, Friedrich MG. T2-weighted cardiovascular magnetic resonance in acute cardiac disease. *J Cardiovasc Magn Reson [Internet]*. BioMed Central Ltd; 2011;13(1):13.
67. Kerensky RA, Wade M, Deedwania P, Boden WE, Pepine CJ. Revisiting the Culprit Lesion in Non – Q-Wave Myocardial Infarction : Results From the VANQWISH Trial Angiographic Core Laboratory. *J Am Coll Cardiol* 2002;39(9): 1456-63.
68. Raman SV, Simonetti OP, Winner MW, Dickerson JA, He X, Mazzaferri EL, et al. Cardiac Magnetic Resonance With Edema Imaging Identifies Myocardium at Risk and Predicts Worse Outcome in Patients With Non – ST-Segment Elevation Acute Coronary Syndrome. *J Am Coll Cardiol* 2010;55(22):2480–8.

69. Walls M, Verhaert D, Raman SV. Myocardial edema imaging in acute coronary syndromes. *J Magn Reson Imaging*. 2011;34(6):1243–50.
70. Francone M, Bucciarelli-Ducci C, Carbone I, Canali E, Scardala R, Calabrese FA, et al. Impact of Primary Coronary Angioplasty Delay on Myocardial Salvage, Infarct Size, and Microvascular Damage in Patients With ST-Segment Elevation Myocardial Infarction. *J Am Coll Cardiol* 2009;54(23):2145–53.
71. Aletras AH, Tilak GS, Natanzon A, Hsu L, Gonzalez FM, Hoyt RF, et al. Retrospective Determination of the Area at Risk for Reperfused Acute Myocardial Infarction With T2-Weighted Histopathological and Displacement Encoding With Stimulated Echoes (DENSE) Functional Validations. *Circulation* 2006; 113: 1856-70.
72. Dastidar AG, Rodrigues JCL, Ahmed N, Baritussio A, Bucciarelli-Ducci C. The Role of Cardiac MRI in Patients with Troponin-Positive Chest Pain and Unobstructed Coronary Arteries. *Curr Cardiovasc Imaging Rep* 2015; 8: 28.
73. Gallagher S, Jones DA, Anand V, Mohiddin S. Diagnosis and management of patients with acute cardiac symptoms , troponin elevation and culprit-free angiograms. *Heart* 2012;98: 974–81.
74. Monney PA, Sekhri N, Burchell T, Knight C, Davies C, Deaner A, et al. Acute myocarditis presenting as acute coronary syndrome : role of early cardiac magnetic resonance in its diagnosis. *Heart* 2011; 97: 1312–8.
75. Tornvall P, Gerbaud E, Behaghel A, Chopard R, Collste O, Laraudogoitia E. Myocarditis or “ true ” infarction by cardiac magnetic resonance in patients with a clinical diagnosis of myocardial infarction without obstructive coronary disease : A meta-analysis of individual patient data.

- Atherosclerosis 2015; 241: 87-91.
76. Caforio ALP, Pankuweit S, Arbustini E, Basso C, Heymans S, Gimeno-Blanes J, et al. Current state of knowledge on aetiology , diagnosis , management , and therapy of myocarditis : a position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. Eur Heart J 2013; 34: 2636–48.
 77. Laissy JP, Hyafil F, Feldman LJ, Juliard JM, Schouman-Claeys E, Ste PG, et al. Differentiating Acute Myocardial Infarction from Myocarditis : Diagnostic Value of Early- and Delayed-Perfusion Cardiac MR imaging. Radiology 2005; 237: 75–82.
 78. Claus P, Omar AMS, Pedrizzetti G, Sengupta PP, Nagel E. Tissue Tracking Technology for Assessing Cardiac Mechanics: Principles, Normal Values, and Clinical Applications. JACC Cardiovasc Imaging. 2015;8(12):1444–60.
 79. Simpson RM, Keegan J, Firmin DN. MR assessment of regional myocardial mechanics. J Magn Reson Imaging. 2013;37(3):576–99.
 80. Scatteia A, Baritussio A, Bucciarelli-Ducci C. Strain imaging using cardiac magnetic resonance. Heart Failure Reviews 2017;22(4):465–76.
 81. Zerhouni EA, Parish DM, Rogers WJ, Yang A, Shapiro EP. Human Heart: Tagging with MR Imaging -- a Method for Noninvasive Assessment of Myocardial Motion. Cardiac Radiology 1988; 169: 59-63.
 82. Aletras AH, Ding S, Balaban RS, Wen H. DENSE: Displacement Encoding with Stimulated Echoes in Cardiac Functional MRI. J Magn Reson 1999; 137: 247-52.
 83. Jung B, Zaitsev M, Hennig J, Markl M. Navigator gated high temporal resolution tissue phase mapping of myocardial motion. Magn Reson Med.

2006;55(4):937–42.

84. Pedrizzetti G, Claus P, Kilner PJ, Nagel E. Principles of cardiovascular magnetic resonance feature tracking and echocardiographic speckle tracking for informed clinical use. *J Cardiovasc Magn Reson* 2016;1–12.
85. Schuster A, Stahnke VC, Unterberg-Buchwald C, Kowallick JT, Lamata P, Steinmetz M, et al. Cardiovascular magnetic resonance feature- tracking assessment of myocardial mechanics: Intervendor agreement and considerations regarding reproducibility. *Clin Radiol*. 2015;70:989–98.
86. Onishi T, Saha SK, Delgado-Montero A, Ludwig DR, Onishi T, Schelbert EB, et al. Global longitudinal strain and global circumferential strain by speckle-tracking echocardiography and feature-tracking cardiac magnetic resonance imaging: comparison with left ventricular ejection fraction. *J Am Soc Echocardiogr* 2015; 28(5): 587–96.
87. Onishi T, Saha SK, Ludwig DR, Onishi T, Marek JJ, Cavalcante JL, et al. Feature tracking measurement of dyssynchrony from cardiovascular magnetic resonance cine acquisitions: comparison with echocardiographic speckle tracking. *J Cardiovasc Magn Reson* 2013; 15: 95.
88. Schuster A, Hor KN, Kowallick JT, Beerbaum P, Kutty S. Cardiovascular Magnetic Resonance Myocardial Feature Tracking: concepts and clinical application. *Circ Cardiovasc Imaging* 2016;9(4):e004077. doi: 10.1161/CIRCIMAGING.115.004077.
89. Smiseth OA, Torp H, Opdahl A, Haugaa KH, Urheim S. Myocardial strain imaging: How useful is it in clinical decision making? *Eur Heart J* 2016; 37: 1196-1207.
90. Kalam K, Otahal P, Marwick TH. Prognostic implications of global LV

- dysfunction: a systematic review and meta-analysis of global longitudinal strain and ejection fraction. *Heart* 2014;100(21):1673–80.
91. Altiok E, Neizel M, Tiemann S, Krass V, Becker M, Zwicker C, et al. Layer-specific analysis of myocardial deformation for assessment of infarct transmuralty: Comparison of strain-encoded cardiovascular magnetic resonance with 2D speckle tracking echocardiography. *Eur Heart J Cardiovasc Imaging*. 2013; 14: 570-8.
 92. Aly MFA, Kleijn SA, Menken-Negroiu RF, Robbers LF, Beek AM, Kamp O. Three-dimensional speckle tracking echocardiography and cardiac magnetic resonance for left ventricular chamber quantification and identification of myocardial transmural scar. *Neth Heart J* 2016; 24: 600-8.
 93. Shah AM, Solomon SD. Myocardial deformation imaging: Current status and future directions. *Circulation*. 2012; 125: e244-8.
 94. Gao P, Yee R, Gula L, Krahn AD, Skanes A, Leong-Sit P, et al. Prediction of arrhythmic events in ischemic and dilated cardiomyopathy patients referred for implantable cardiac defibrillator: evaluation of multiple scar quantification measures for late gadolinium enhancement magnetic resonance imaging. *Circ Cardiovasc Imaging*. 2012;5:448–56.
 95. McComb C, Carrick D, McClure JD, Woodward R, Radjenovic A, Foster JE, et al. Assessment of the relationships between myocardial contractility and infarct tissue revealed by serial magnetic resonance imaging in patients with acute myocardial infarction . *Int J Cardiovasc Imaging*. 2015;31(6):1201–9.
 96. Taylor RJ, Umar F, Lin ELS, Ahmed A, Moody WE, Mazur W, et al. Mechanical effects of left ventricular midwall fibrosis in non-ischemic cardiomyopathy. *J Cardiovasc Magn Reson* 2016; 18: 1.

97. Anthony AH, Tilak GS, Hsu LY, Arai AE. Heterogeneity of Intramural Function in Hypertrophic Cardiomyopathy: Mechanistic Insights from MRI Late Gadolinium Enhancement and High-resolution DENSE Strain Maps. *Circ Cardiovasc Imaging*. 2011;4(4):425–34.
98. Reiter T, Ritter O, Prince MR, Nordbeck P, Wanner C, Nagel E, et al. Minimizing Risk of Nephrogenic systemic fibrosis in Cardiovascular Magnetic Resonance. *J Cardiovasc Magn Reson*. 2012;14(1):31.
99. Baritussio A, Zorzi A, Ghosh Dastidar A, Susana A, Mattesi G, Rodrigues JCL, et al. Out of hospital cardiac arrest survivors with inconclusive coronary angiogram: Impact of cardiovascular magnetic resonance on clinical management and decision-making. *Resuscitation* 2017;116:91–7.
100. Anyfantakis ZA, Baron G, Aubry P, Himbert D, Feldman LJ, Juliard JM, et al. Acute coronary angiographic findings in survivors of out-of-hospital cardiac arrest. *Am Heart J*. 2009;157:312–8.
101. Preston LM, Calvin JE, Class S, Parrillo JE KL. Coronary angiographic morphology in unstable angina: comparative observations of culprit lesions in saphenous vein graft versus native coronary arteries. *J Invasive Cardiol*. 2002;14(2):81–6.
102. Abbasi S a, Ertel A, Shah R V, Dandekar V, Chung J, Bhat G, et al. Impact of cardiovascular magnetic resonance on management and clinical decision-making in heart failure patients. *J Cardiovasc Magn Reson* [Internet]. *Journal of Cardiovascular Magnetic Resonance*; 2013;15(1):89. Available from: <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3851265&tool=pmcentrez&rendertype=abstract>
103. White JA, Fine NM, Gula L, Yee R, Skanes A, Klein G, et al. Utility of

Cardiovascular Magnetic Resonance in Identifying Substrate for Malignant Ventricular Arrhythmias. 2016;12–21.

104. Almehmadi F, Joncas SX, Nevis I, Zahrani M, Bokhari M, Stirrat J, et al. Prevalence of myocardial fibrosis patterns in patients with systolic dysfunction: prognostic significance for the prediction of sudden cardiac arrest or appropriate implantable cardiac defibrillator therapy. *Circ Cardiovasc Imaging* [Internet]. 2014;7:593–600. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/24902587>
105. Perazzolo Marra M, De Lazzari M, Zorzi A, Migliore F, Zilio F, Calore C, et al. Impact of the presence and amount of myocardial fibrosis by cardiac magnetic resonance on arrhythmic outcome and sudden cardiac death in nonischemic dilated cardiomyopathy. *Heart Rhythm* [Internet]. Elsevier; 2014;11(5):856–63. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/24440822>
106. Klem I, Shah DJ, White RD, Pennell DJ, Van Rossum AC, Regenfus M, et al. Prognostic value of routine cardiac magnetic resonance assessment of left ventricular ejection fraction and myocardial damage: An international, multicenter study. *Circ Cardiovasc Imaging*. 2011;4(6):610–9.
107. Estner HL, Zviman MM, Herzka D, Miller F, Castro V, Nazarian S, et al. The critical isthmus sites of ischemic ventricular tachycardia are in zones of tissue heterogeneity , visualized by magnetic resonance imaging. *HRTM* [Internet]. Elsevier Inc.; 2011;8(12):1942–9. Available from: <http://dx.doi.org/10.1016/j.hrthm.2011.07.027>
108. Schmidt A, Azevedo CF, Cheng A, Gupta SN, Bluemke DA, Foo TK, et al. Infarct Tissue Heterogeneity by Magnetic Resonance Imaging Identifies Enhanced Cardiac Arrhythmia Susceptibility in Patients With Left

- Ventricular Dysfunction. 2007;2006–14.
109. Bucciarelli-Ducci C, Baritussi A, Auricchio A. Cardiac MRI Anatomy and Function as a Substrate for Arrhythmias. *Europace* [Internet]. 2016;18(suppl 4):iv130-iv135. Available from: http://fdslive.oup.com/www.oup.com/pdf/production_in_progress.pdf%5Cnhttp://www.ncbi.nlm.nih.gov/pubmed/27899565%5Cnhttp://www.ncbi.nlm.nih.gov/pubmed/28011840
 110. Arenja N, Riffel JH, Fritz T, André F, Aus dem Siepen F, Mueller-Hennessen M, et al. Diagnostic and Prognostic Value of Long-Axis Strain and Myocardial Contraction Fraction Using Standard Cardiovascular MR Imaging in Patients with Nonischemic Dilated. *Radiology* 2017;283(3):681–691.
 111. Mordi I, Bezerra H, Carrick D, Tzemos N. The combined incremental prognostic value of LVEF, late gadolinium enhancement, and global circumferential strain assessed by cmr. *JACC Cardiovasc Imaging*. 2015;8(5):540–9.
 112. Xu H, Chen J, Yang Z, Li R. Early Marker of Regional Left Ventricular Deformation in Patients With Hypertrophic Cardiomyopathy Evaluated by MRI Tissue Tracking : The Effects of Myocardial Hypertrophy and Fibrosis. 2017;1–9.
 113. Boyé P, Abdel-Aty H, Zacharzowsky U, Bohl S, Schwenke C, Van Der Geest RJ, et al. Prediction of life-threatening arrhythmic events in patients with chronic myocardial infarction by contrast-enhanced CMR. *JACC Cardiovasc Imaging* [Internet]. Elsevier Inc.; 2011;4(8):871–9. Available from: <http://dx.doi.org/10.1016/j.jcmg.2011.04.014>
 114. Rijnierse MT, Allaart CP, Haan S De, Harms HJ, Huisman MC, Beek AM,

- et al. Non-invasive imaging to identify susceptibility for ventricular arrhythmias in ischaemic left ventricular dysfunction. 2016;1–9.
115. Klem, Igor, Weinstaf, Jonathan, Bahnson, Tristram, Hegland, Don, Kim, Han, Hayes, Brenda, Parker, Michael, Judd, Robert, Kim R. Assessment of Myocardial Scarring Improves Risk Stratification in Patients Evaluated for Cardiac Defibrillator Implantation. *J Am Coll Cardiol*. 2012;(60):408–20.
 116. Dawson DK, Hawlisch K, Prescott G, Roussin I, Di Pietro E, Deac M, et al. Prognostic role of CMR in patients presenting with ventricular arrhythmias. *JACC Cardiovasc Imaging* [Internet]. Elsevier Inc.; 2013;6(3):335–44. Available from: <http://dx.doi.org/10.1016/j.jcmg.2012.09.012>
 117. Disertori M, Rigoni M, Pace N, Casolo G, Masè M, Gonzini L, et al. Myocardial Fibrosis Assessment by LGE Is a Powerful Predictor of Ventricular Tachyarrhythmias in Ischemic and Nonischemic LV Dysfunction: A Meta-Analysis. *JACC Cardiovasc Imaging*. 2016;9(9):1046–55.
 118. Nguyen BL, Capotosto L, Persi A, Placanica A, Rafique A, Piccirillo G, et al. Global and regional left ventricular strain indices in post-myocardial infarction patients with ventricular arrhythmias and moderately abnormal ejection fraction. *Ultrasound Med Biol*. 2015;41(2):407–17.
 119. Chimura M, Onishi T, Tsukishiro Y, Sawada T, Kiuchi K, Shimane A, et al. Longitudinal strain combined with delayed-enhancement magnetic resonance improves risk stratification in patients with dilated cardiomyopathy. *Heart* [Internet]. 2017;103(9):679–86. Available from: <http://heart.bmj.com/lookup/doi/10.1136/heartjnl-2016-309746>

120. Tang X, Yu S, Yu Y, Ren H, Li S, Zhou L, et al. Left ventricular myocardial strain in ventricular arrhythmia without structural heart disease using cardiac magnetic resonance. *Am J Transl Res* [Internet]. 2017;9(6):3006–16. Available from: www.ajtr.org
121. Van Welsenes GH, Van Rees JB, Borleffs CJW, Cannegieter SC, Bax JJ, Van Erven L, et al. Long-term follow-up of primary and secondary prevention implantable cardioverter defibrillator patients. *Europace*. 2011;13(3):389–94.
122. file:///Users/annabaritussio/Documents/Bristol Workshop/SD/Papers/Letti/Epidemiology/Long-term follow-up of primary and secondary prevention ICD patients Welsenes Europace 2011.pdfSingla I, Hreybe H, Saba S. Risk of death and recurrent ventricular arrhythmias in survivors of cardiac arrest concurrent with acute myocardial infarction. *Indian Pacing Electrophysiol J*. 2008;8(India RF-14 LG-English PT-Journal: Article DD-20080328):5–13.
123. Klem I, Shah DJ, White RD, Pennell DJ, Van Rossum AC, Regenfus M, et al. Prognostic value of routine cardiac magnetic resonance assessment of left ventricular ejection fraction and myocardial damage: An international, multicenter study. *Circ Cardiovasc Imaging*. 2011;4:610–9.
124. Vo HQ, Marwick TH, Negishi K. MRI-Derived Myocardial Strain Measures in Normal Subjects. *JACC Cardiovasc Imaging* 2017; pii: S1936-878X(17)30253-X. doi: 10.1016/j.jcmg.2016.12.025.
125. Cai L, Addetia K, Medvedofsky D, Spencer KT. Myocardial strain may be useful in differentiating Takotsubo cardiomyopathy from left anterior descending coronary artery ischemia. *Int J Cardiol* 2017;230:359–63.
126. Tibrewala A, Freed BH, Akhter N. Importance of temporal changes in

myocardial strain in Takotsubo cardiomyopathy. *BMJ Case Rep* 2017; pii: bcr-2017-220719. doi: 10.1136/bcr-2017-220719.

127. Chen Z, Sohal M, Voigt T, Sammut E, Tobon-gomez C, Child N, et al. Myocardial tissue characterization by cardiac magnetic resonance imaging using T1 mapping predicts ventricular arrhythmia in ischemic and non – ischemic cardiomyopathy patients with implantable cardioverter-defibrillators. *Hear Rhythm* 2015;12(4):792–801.

Aknowledgements

Most special thanks go to my parents, which have been an inexhaustible support over the years: most of what I have done, achieved and enjoyed during these three years of PhD training wouldn't have been possible without their love, help and support.

A deeply thankful thought goes to Dr Chiara Bucciarelli-Ducci, which has been a mentor and a guide, both of my professional and personal life; nobody has ever believed and invested in me as much as she did.

A very grateful thought goes to my PhD Supervisor, Dr Martina Perazzolo Marra, who's first introduced me to my greatest passion, Cardiovascular Magnetic Resonance, and who's made me walk my very first steps in this field.

A special thank goes to the entire staff of the Department of Cardiac, Thoracic and Vascular Sciences of the University of Padova, for being vital part of my training, since I was a junior Doctor.

And last, but not least, a grateful thought goes to the friends (and colleagues) coming from all over the world, that I had the pleasure and honour to meet during the time spent abroad: Alessandra Scatteia, Estefania De Garate Iparraguirre, Roberto Marsico, Amardeep Ghosh Dastidar, Iwan Harries, Sarah Moharem-Elgamal, Elena Milano, Kostantina Mitrousi, Fawaz Bardooli, Mark Hamilton, Nathan Manghat, Stephen Lyen, Christopher Benjamin Lawton and all the Radiographers at the Bristol Heart Institute, Philippa Hazlewood, Jack Flahavan. My journey wouldn't have been the same without them.