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Cardiovascular Magnetic Resonance Evaluation and Risk Stratification of Myocardial Diseases

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TO MY FAMILY

Johanna, Emma, Eetu, Akseli and Anna
ABSTRACT

Advanced cardiovascular magnetic resonance (CMR) may provide information of the myocardium beyond conventional imaging. The present thesis was designed to assess whether myocardial tissue characterization by CMR improves the diagnostic and prognostic evaluation of non-ischemic cardiomyopathies (NICMs) (studies I-III) and ischemic heart disease (IV).

The specific objectives were (I) to evaluate the prognostic value of late gadolinium enhancement (LGE) and wall motion abnormality index (WMAi) compared to traditional risk factors in suspected NICM; (II) to assess the clinical and imaging predictors of severe cardiac inflammation, i.e. cardiac sarcoidosis (CS) or giant cell myocarditis (GCM); (III) to define the imaging characteristics of PRKAG2, a unique glycogen storage cardiomyopathy, which have not been systematically reported by CMR; (IV) to evaluate the nature of left ventricular (LV) remodeling by repeated CMR after revascularized myocardial infarction (MI), with specific attention to non-transmural infarcts.

In studies (I-II), a retrospective cohort of 86 consecutive patients referred for CMR due to suspected NICM was identified between November 2008 and April 2010. Patients with ischemic heart disease were excluded. CMR images were analysed for LGE and WMAi. Patients were followed-up for (I) major adverse cardiac events (MACEs) and (II) final diagnoses. In study (III), CMR and genetic testing were performed in two families harboring PRKAG2 mutations. In study (IV), altogether 41 patients underwent prospectively repeated CMR during the recovery phase (7 – 30 days), and the chronic infarct phase (≥ 6 months), after the first revascularized MI. Transmural MI was defined as ≥75% enhancement in at least one myocardial segment.

We found that (I) in suspected NICM, LGE gives additional prognostic information compared to left ventricular ejection fraction (LVEF) and sustained ventricular tachycardia, while the absence of WMAi may give prognostic information beyond normal LVEF. The cumulative event ratio after three years was 4% in patients without LGE, 26% with LGE, and 43% with LGE ≥17% of LV muscle volume. Patients without WMAi did not experience MACEs. In study (II), LGE extent and sustained ventricular tachycardia predicted independently CS or GCM. Especially, multifocal LGE was useful in identifying severe cardiac inflammation, with 52-fold unadjusted odds ratio. In study (III), altogether six individuals had a PRKAG2 mutation: five with a known R302Q mutation (family 1), and one with a novel H344P mutation (family 2). We found that PRKAG2 cardiomyopathy may present with eccentric distribution of left ventricular hypertrophy, involving focal mid-infero-lateral pattern in the early disease stage, and more diffuse pattern but focusing on interventricular septum in advanced cases. We also found that in patients at earlier stages of disease, T1
values may be reduced, while in the advanced disease stage T1 mapping may result in higher values caused by fibrosis. In study (IV), we found that peak CK-MB has a strong association with chronic scar size and WMAi after revascularized non-transmural MI. Moreover, considerable infarct resorption happened after the first-month recovery phase, and LV mass resorption was related to age, being more common in younger patients.

In conclusion, extensive amount of LGE should be considered as a sign of poor prognosis in NICM, even though the final diagnosis is uncertain. LGE, especially multifocally distributed, is useful in identification of severe cardiac inflammation. CMR is a valuable tool in detecting diffuse and focal myocardial abnormalities in PRKAG2 cardiomyopathy. Peak CK-MB provides robust estimation of infarct size and predicts chronic LV function after revascularized MI.
TIIVISTELMÄ

Kehittyneet sydämen magneettikuvaus (MK) -menetelmät voivat paljastaa sydänlihaksen sisäisestä rakenteesta tietoa, jota perinteisellä kuvantamisella ei ole saatu. Tämän väärtöskirjan tarkoitus oli selvittää parantaako sydänlihaksen karakterisointi MK:lla ei-iskeemisten kardiomyopatioiden (tutkimukset I-III) ja iskeemisen sydäntaudin (IV) diagnostiikkaa ja ennusteellista arviota.

Spesifiset tavoitteet olivat (I) selvittää varjoainetehosteiseen sydänlihaksen jälkitehostuman ja seinämän liikehäiriöiden ennusteellista merkitystä epäillyssä ei-iskeemisessä kardiomyopatiassa verrattuna perinteisiin riskitekijöihin; (II) etsiä klusiinisiä tekijöitä ja MK-löydöksiä, jotka ennustavat vakavaa tulehdus- ja seinämän liikehäiriöiden läheistä sydänlihaksen suurta, ts. sydänsairkoidiosia (cardiac sarcoidosis, CS) tai jättisolumyokardiittia (giant cell myocarditis, GCM); (III) tutkia PRKAG2-kardiomyopatian, ainutlaatuisen perinnöllisen sydänlihaksen glykogeenikertymäsairauden, MK-löydöksiä, joita ei ole aiemmin romattanut sydäntaudintutkimuksessa, sydäntaudin väärin suunniteltuna ja (IV) selvittää toistetun MK:n avulla sydämen vasemman kammion muovaumista revaskularisoidun akuutin sydäninfarktiin jälkeen, kiinnittäen huomiota pienempään ei-transmuraalisiin infarkteihin.

Tutkimuksissa (I-II) identifioitiin 86 potilaan retrospektiivinen kohortti kaikista potilasta sen jälkeen kun tapahtui sydämen MK:seen epäillyn ei-iskeemisen kardiomyopatian takia marraskuun 2008 ja huhtikuun 2010 välillä. Iskeemistä sydäntaudia sairastavat suurin osa potilaista olivat iskeemisissä ja sydäntaudin diagnosointi on pyrittävä suorittamaan sydänlihaksen MK:lla. Potilaita seurattiin (I) merkittävien sydäntapahtumien ja (II) lopullisten diagnoosien selvitämiseksi. Tutkimuksessa (III) sydämen MK ja genetiikkaa tehtiin kohdassa suvussa, joissa tiedettiin olevan PRKAG2-mutaation kantajia. Tutkimuksessa (IV) 41 potilasta tutettiin prospektiivisesti toistuvalla sydämen MK:lla toipumisvaiheessa (7-30 päivää) ja krooniseen vaiheeseen (>6 kuukautta) ensimmäisen revaskularisoidun sydäninfarktiin jälkeen. Transmuraalisen sydäninfarktiin määritelmänä käytettiin ≥75% jalkitehostumaa vähintään yhdessä sydänlihaksen segmentissä.

Havaittimme että (I) epäillyssä ei-iskeemisessä kardiomyopatiassa jälkitehostuma tuo ennusteellista lisääntyvää tietoa vasemman kammion ejektiofraktioon tai pitkkyvyneeseen kammiovykykardiiaan; ja että paikallisten sydänlihaksen liikehäiriöiden yhteys sydänlihaksen myokardiovasen seinävyvyyn määrittää sydänlihaksen lain kohdalla hyvin. Potilailta, joilla ei ollut paikallisia liikehäiriöitä, ei ollut alsenkin tapahtumia.

Tutkimuksen johtopäätökseä voidaan todeta että laaja sydänlihaksen jälkitehostuma magneettikuvassa pitäisi tulkita huonon ennusteen merkkinä ei-iskeemisessa kardiomyopatiassa, vaikka lopullinen diagnoosi olisi avoin. Jälkitehostuma, etenkin läiskittäinen, on hyödyllinen vakavan sydäntulehdoksen tunnistamisessa. Magneettikuvauksen arvokas menetelmä sydänlihaksen diffuusien ja paikallisten poikkeavuuksien havaitsemisessa PRKAG2-kardiomiopatiassa. CK-MB:n huippuarvo on hyvä mittari infarktin koosta ja myöhemmästä vasemman kammnopaimon toiminnasta sydäninfarktin revaskularisaation jälkeen.
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Pauli Pöyhönen
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LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following publications:


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ABBREVIATIONS

BSA body surface area
CABG coronary artery bypass grafting
CAD coronary artery disease
CI confidence interval
CK-MB creatine kinase MB
CMR cardiovascular magnetic resonance
CS cardiac sarcoidosis
DCM dilated cardiomyopathy
ECV extra-cellular volume
ECG electrocardiography
EMB endomyocardial biopsy
FWHM full width at half maximum
GCM giant cell myocarditis
HCM hypertrophic cardiomyopathy
HR hazard ratio
IQR interquartile range
LGE late gadolinium enhancement
LV left ventricle
LVEF left ventricular ejection fraction
LVH left ventricular hypertrophy
MI myocardial infarction
MRI magnetic resonance imaging
NMR nuclear magnetic resonance
NYHA class New York Heart Association functional class
NICM non-ischemic cardiomyopathy
OR odds ratio
PCI percutaneous coronary intervention
PET positron emission tomography
ROC receiver operating characteristic
RV right ventricle
SD standard deviation
SPECT single photon emission computed tomography
WMA wall motion abnormality
WMAi wall motion abnormality index
WPW Wolff-Parkinson-White syndrome
18F-FDG 18F-fluoro-2-deoxyglucose
1 INTRODUCTION

Cardiovascular magnetic resonance (CMR) provides information of the myocardium beyond conventional imaging. Different modalities of CMR may visualize both extra- and intracellular myocardial pathology, noninvasively and without ionizing radiation. Due to rapid technological development, the clinical value of CMR in diagnostics and risk stratification of non-ischemic cardiomyopathies (NICMs) and ischemic heart disease still needs validation.

NICM is a diverse group of myocardial diseases with a wide range of symptoms, such as heart failure, conducting abnormalities, or ventricular arrhythmias [1-3]. Early diagnosis of rare and severe inflammatory forms, such as cardiac sarcoidosis (CS) or giant cell myocarditis (GCM), may enable disease-specific treatment [4-6]. Differentiation of metabolic diseases, such as dominantly inherited PRKAG2, a unique glycogen storage cardiomyopathy, is important due to a prognosis different from sarcomeric hypertrophic cardiomyopathy (HCM) [7-10]. Although endomyocardial biopsy (EMB) has been the gold standard in diagnosing myocardial diseases, it has limited sensitivity and certain procedural risks [11]. Early suspicion of a specific etiology and risk stratification of NICM, using CMR, would be valuable for justification of invasive examinations.

Coronary artery disease (CAD) is still the leading cause of death worldwide [12]. After large acute myocardial infarction (MI), left ventricular (LV) remodelling carries an important prognostic value [13,14]. However, due to improved revascularization therapy, chronic infarct sizes tend to be smaller. The course of LV remodeling after smaller non-transmural MIs is less well established and there has been a lack of prospective studies with repeated CMR imaging.

Standard CMR enables accurate evaluation of myocardial anatomy and function, including local wall motion abnormality (WMA). Late gadolinium enhancement (LGE) visualizes the expansion of extracellular space related to processes such as focal myocardial necrosis, fibrosis, inflammation or infiltration [15,16]. Parametric mapping methods, such as T1-, T2, and T2*-mapping, reflect both intra- and extracellular signal in the myocardium [17]. Elevated native T1 times have been reported in fibrosis [18], oedema [19], amyloidosis [20], and lower in iron overload [21] and focal fat infiltration [22]. Native T2-mapping enables quantification of myocardial oedema and inflammation on an absolute scale. Measuring T1-relaxation times before and after the administration of contrast agent provides an estimate of the myocardial extra-cellular volume (ECV), which may be increased in diffuse fibrosis [23-25].

The present thesis was designed to assess whether myocardial tissue characterization by CMR improves the diagnostic and prognostic evaluation of NICMs (studies I-III) and ischemic heart disease (IV). We aimed (I) to
evaluate the prognostic value of LGE and WMA index (WMAi) compared to traditional risk factors in suspected NICM; (II) to assess the clinical and imaging predictors of severe cardiac inflammation, i.e. CS or GCM; (III) to define the imaging characteristics of PRKAG2, a unique glycogen storage cardiomyopathy, which have not been systematically reported by CMR; (IV) to evaluate the nature of LV remodeling by repeated CMR after revascularized MI, with specific attention to non-transmural infarcts.
2 REVIEW OF THE LITERATURE

2.1 NON-ISCHEMIC CARDIOMYOPATHY

2.1.1 CLINICAL IMPORTANCE OF NICM

NICM is a common clinical challenge. NICMs are defined as diseases of the myocardium in which the heart muscle is structurally and functionally abnormal, in the absence of significant CAD, cardiac loading condition such as hypertension or valvular disease, or congenital heart disease [26]. As a diverse group of diseases, NICMs are classified as primary cardiomyopathies involving predominantly the heart or cardiomyopathies secondary to systemic disease (Figure 1). The etiology of NICM is frequently genetic, while some forms are acquired.

The clinical presentation and prognosis in NICM is highly variable and depends on the etiology of the disease [2,3]. In a typical setting, a patient has heart failure with ventricular arrhythmias or conduncion disorders. Early diagnosis of severe and specific forms of NICM, such as CS and GCM, may enable unique anti-inflammatory treatment and proper patient surveillance [4-6]. Patients with PRKAG2, a unique glycogen storage cardiomyomyopathy, may benefit from distinction of other forms of cardiac hypertrophy, due to high risk of complete heart block [10,27] and sudden cardiac death [28].
2.1.2 CARDIAC SARCOIDOSIS

Sarcoidosis is a systemic disease characterized by inflammatory noncaseating granulomas in multiple organs. Lungs are the most commonly involved organ in sarcoidosis, while other frequently involved organs are lymph nodes, skin, eyes, heart, nervous system, liver, spleen, musculoskeletal, renal, and endocrine systems[6,29]. The estimated annual incidence of sarcoidosis per 100,000 people in the United States is 11 – 36 cases [30] and in Northern European countries 5 – 40 cases [29]. In Finland, the annual incidence and prevalence of sarcoidosis has been 11.4 and 28.2 cases per 100,000 people [31]. Clinical CS is estimated to occur in approximately 5% of patients with sarcoidosis [32], but myocardial involvement in autopsy has occurred in at least 25% of the patients with sarcoidosis [33]. Moreover, sarcoidosis can be clinically isolated to the heart [34]. In Finland, the annual detection rate of CS was 0.31 cases per 100,000 adults between 2008-2012, while the prevalence was 2.2 cases per 100,000 adults in 2012 [35]. Sarcoidosis usually develops before the age of 50 years [29].

The exact etiology of sarcoidosis remains unknown. However, it is considered to be due to an exaggerated immune response, in which so far unknown antigens trigger T cells leading to the formation of granuloma lesions [6].

CS has a varying clinical picture depending on which regions of the myocardium are affected. The most common symptoms are complete heart
block, ventricular arrhythmias and congestive heart failure [36,37]. Complete heart block is the most common finding reported in 23-30% of patients [36] and the ventricular tachycardia (VT) in 23% of patients [37].

Histologically, the diagnosis of CS on EMB is based on the presence of non-caseating granuloma, with or without foci of lymphocytic myocarditis, necrosis or giant cells [38]. However, sarcoid infiltration in the myocardium is usually local or patchy, involving basal segments, and mid-ventricular EMB lacks sensitivity. The sensitivity of EMB in detecting CS is estimated to be approximately 20-32% [34,39,40] and the diagnostic yield can be improved by repeated imaging guided biopsies [34]. According to expert consensus criteria of Heart Rhythm Society, the diagnosis of CS requires either histological confirmation from myocardial tissue or clinical diagnosis from invasive and non-invasive studies [41]. Clinical diagnosis of CS requires histological verification of extra-cardiac sarcoidosis, along with typical cardiac symptoms/signs, LGE pattern on CMR, or 18F-fluoro-2-deoxyglucose (18F-FDG) uptake on positron emission tomography (PET), and the reasonable exclusion of other causes.

The early identification of CS is important since patients may benefit from immunosuppressive treatment. In a study of 42 patients with CS, the 5-year transplantation-free survival was 69.8% [38]. The prognosis in CS may be improved with corticosteroids [42,43], and with current medical and device (intra-cardiac defibrillator or pacemaker) treatment the transplantation free 5-year survival was as good as 90% [35].

2.1.3 GIANT CELL MYOCARDITIS

GCM is a rare and frequently fatal inflammatory disease of the myocardium [5,44]. It has histological and clinical similarities with CS, but is thought as a distinct disease entity [38,43,45]. Typical symptom of GCM is rapidly progressing congestive heart failure, often associated with ventricular arrhythmias or distal conducting block, and approximately 20% of patients with GCM have known autoimmune disorders [5,38,44,46]. The true incidence and prevalence of GCM are not known, but it is predominantly a disease of young and middle aged adults [5].

The diagnosis of GCM is obtained by endomyocardial or surgical biopsy, explanted heart or autopsy, and histologically based on the presence of myocyte necrosis and widespread inflammatory infiltrate, including multinucleated giant cells and lymphocytes, in the absence of non-caseating granulomas [5,38]. The sensitivity of the first EMB to diagnose GCM has been 68%, while repeated EMBs have increased the sensitivity up to 93% [46].

Similarly as in CS, early identification of GCM may enable proper immunosuppressive treatment. In a study of 73 patients with GCM, the 5-year transplantation-free survival was 21.9% [38]. The prognosis in GCM may be improved with combined immunosuppressive therapy [5,46]. The
transplant-free 5-year survival of 32 patients with GCM treated with combined immunosuppression was 52% [46]. GCM seems have worse prognosis than CS [38].

2.1.4 PRKAG2 CARDIOMYOPATHY
PRKAG2 cardiomyopathy is an autosomal dominantly inherited metabolic disease of the myocardium which is characterized by cardiac hypertrophy, progressive conducting abnormalities and ventricular pre-excitation (Wolff-Parkinson-White [WPW] syndrome) [7-10]. PRKAG2 mimics HCM, and the prevalence has been estimated to be 0.23 – 1% in patients with HCM [10,47]. Although PRKAG2 is rare, it is more frequent in children and adolescents [48]. PRKAG2 patients have a high risk of complete heart block [10,27] and a risk of sudden cardiac death caused by atrial fibrillation with rapid antegrade conduction through an accessory pathway [28]. Thus, patients may benefit from early identification, surveillance and cardiac device therapy.

PRKAG2 cardiomyopathy is diagnosed by genetic testing with appropriate clinical phenotype. There are relatively few histopathological reports on the hearts of patients with PRKAG2 cardiomyopathy. Typically, PRKAG2 gene defect causes a unique cardiac histopathology with excess intracellular vacuoles filled with glycogen, enlargement of myocytes, and no myocyte disarray which is typical for sarcomeric HCM [9]. However, in a case report, a patient with an end-stage PRKAG2 had severe fibrofatty myocardial replacement[49]. Also, in some cases abundant interstitial fibrosis and myocyte disarray in the absence of glycogen accumulation has been reported [10,50]. Previously, only two case reports of CMR findings in PRKAG2 cardiomyopathy had been reported [51,52], demonstrating left ventricular hypertrophy (LVH), and LGE in interventricular septum.

2.1.5 ENDOMYOCARDIAL BIOPSY
EMB has been the gold standard in diagnosing myocardial diseases [11]. Typically 5 - 10 biopsy samples are obtained from the right ventricular (RV) septum using right internal jugular venous access. The femoral artery access may be used for LV biopsy. EMB is performed under fluoroscopic guidance, 2D-echocardiography, or both. Biopsy samples are submitted for light microscopic examination with stainings to diagnose diseases such as myocarditis, amyloidosis or transplant rejection [11,53]. Basic stainings include haematoxylin and eosin for histomorphological characterization and elastic trichome to visualize collagenous tissue [54]. If needed, special stainings, such as iron or congo red for amyloidosis, are performed. Specimens may be further analysed with transmission electron microscopy to diagnose metabolic or infiltrative diseases, immunofluorescence or immunohistochemistry, or PCR analysis of viral genomes.
However, EMB has limited sensitivity and certain procedural risks. The estimated complication rate in RV EMB has been 6% or less [11,55] (Table 1) and serious acute complications are estimated to occur in less than 1% of procedures using current flexible bioptomes [53]. LV EMB carries also a risk of stroke, which occurred in 2 (0.2%) of 622 patients in a retrospective study of Yilmaz et al. [56]. In the same study, combined RV and LV biopsies increased the diagnostic yield of EMB [56].

The sensitivity of EMB in detection of viral myocarditis has been only 45% [57], and even lower in other inflammatory diseases with focal or patchy myocardial distribution, such as CS [39,58], although the diagnostic rate may increase by multiple EMB sessions [34].

Except from cardiac transplant patients, the need and justification of EMB is typically considered based on a clinical syndrome rather than confirmed disease [11]. Indications for EMB include unexplained cardiomyopathy, such as suspected inflammatory disease or infiltrative cardiomyopathy, suspected cardiac tumor, anthracycline toxicity, or research use [53]. According to ACC/AHA/ESC guidelines, EMB should be performed in a new-onset heart failure of <2 weeks duration and hemodynamic compromise (class I recommendation), or new-onset heart failure of <3 months duration with LV dilatation and new ventricular arrhythmias, heart block, or failure to respond to usual treatment (class I recommendation) [11]. EMB may be useful in heart failure of >3 months duration with LV dilatation and new ventricular arrhythmias, heart block, or failure to respond to treatment (class IIa recommendation), or in suspected eosinophilic myocarditis (class IIa recommendation), or in heart failure with unexplained restrictive cardiomyopathy (class II recommendation) [11].

Table 1. Prospectively recorded complications in 546 consecutive right ventricular endomyocardial biopsy procedures in patients with new-onset unexplained cardiomyopathy.

<table>
<thead>
<tr>
<th>All complications</th>
<th>n (%)</th>
</tr>
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<tbody>
<tr>
<td>During introduction</td>
<td>15 (2.7%)</td>
</tr>
<tr>
<td>Arterial puncture</td>
<td>12 (2.2%)</td>
</tr>
<tr>
<td>Vasovagal reaction</td>
<td>2 (0.4%)</td>
</tr>
<tr>
<td>Prolonged bleeding</td>
<td>1 (0.2%)</td>
</tr>
<tr>
<td>During biopsy</td>
<td>18 (3.3%)</td>
</tr>
<tr>
<td>Arrhythmias</td>
<td>6 (1.1%)</td>
</tr>
<tr>
<td>Conduction abnormalities</td>
<td>5 (1.0%)</td>
</tr>
<tr>
<td>Possible perforation (pain or blood pressure decrease)</td>
<td>4 (0.7%)</td>
</tr>
<tr>
<td>Definite perforation</td>
<td>3 (0.5)</td>
</tr>
<tr>
<td>Death from perforation</td>
<td>2 (0.4%)</td>
</tr>
</tbody>
</table>

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Review of the literature

2.1.6 POSITRON EMISSION TOMOGRAPHY

PET combined with computed tomography using 18F-FDG tracer has been used in metabolic imaging of the myocardium. This may enhance the diagnostic work-up of suspected inflammatory cardiomyopathies.

Active inflammatory cells in the myocardium have high metabolic activity due to large energy demand [59]. Intravenously administered nuclear tracer 18F-FDG is transported across cell membranes via glucose transporters, fosforylated and trapped within the inflammatory cells [60]. As 18F-FDG decays producing two gammaphotons, detection of gammaphotons by a rotating gamma camera enables quantitative measurement of 18F-FDG activity within the myocardium, with good spatial resolution and contrast.

In addition to inflammatory cells, also normal myocytes use mainly glucose as their energy supply. However, in the fasting state, myocytes use mainly free fatty acids [60]. To visualize FDG uptake in inflammatory cells, prolonged fasting is used to suppress physiological FDG uptake within the myocardium.

Focal FDG uptake has been shown to identify sarcoid lesions in the myocardium [61]. According to a meta-analysis, 18F-FDG-PET had 89% sensitivity and 78% specificity for detecting CS [62]. 18F-FDG-PET imaging is usually combined with myocardial perfusion imaging, either with PET tracers 13N-ammonia or 82Rb, or with single photon emission computed tomography (SPECT) with 99mTc-labeled tracers or 201Tl [63]. According to current expert consensus of imaging patterns of CS, focal FDG uptake without perfusion defect represents early inflammation, FDG uptake with perfusion defect active inflammation, and perfusion defect without FDG uptake fibrosis [63]. PET may be also used to monitor disease activity of CS during anti-inflammatory therapy [64].

There is very limited data on using PET in GCM. In a retrospective study of 32 patients with histologically verified GCM, 12 patients underwent 18F-FDG-PET combined with myocardial perfusion imaging[46]. Of these 12 patients, ten had FDG uptake which was associated with perfusion defect in 9 patients. Two patients had perfusion defect without FDG uptake.

2.1.7 ECHOCARDIOGRAPHY

Echocardiography, using ultrasound waves reflecting from boundaries between tissues with different acoustic impedance, is a non-invasive, non-radiation and real-time examination to assess cardiac anatomy, function and blood flow. Echocardiography is usually the first-line imaging test to assess the phenotype of cardiomyopathy, including chamber sizes, ejection fraction, wall thickness, and systolic and diastolic function [65]. 2-dimensional echocardiography can be used to visualize WMA based on wall thickening and endocardial motion, using a standardized myocardial segmentation [66] (Figure 2). Regional myocardial contractility can be further assessed with tissue doppler imaging or speckle-tracking technique [67]. However,
echocardiography has limited ability to characterize myocardial tissue, such as visualize extracellular space or detect intracellular pathology. Also, echocardiography is quite insensitive and non-specific in detection of focal myocardial diseases, such as CS, especially in the early disease stage [68].

Figure 2. Recommended left ventricular segmentation and nomenclature for tomographic imaging of the heart. Reproduced with permission from Wolters Kluwer [66].

2.2 LEFT VENTRICULAR REMODELING AFTER MYOCARDIAL INFARCTION

MI is defined as death of cardiomyocytes caused by prolonged ischemia[69]. LV remodeling, i.e. subsequent ventricular morphological and functional changes after acute MI, is an important predictor of heart failure [14,70] and mortality [71]. Remodeling process is affected by several factors, including infarct size, success of primary revascularization and subsequent medication reducing ventricular wall stresses [14,72]. However, LV remodeling has been shown to occur regardless of successful coronary artery reperfusion therapy [73]. The early remodeling phase during the first weeks after MI involves predominantly infarct expansion and scar formation, while the subsequent late remodeling phase involves more adaptive changes in the non-infarcted myocardium to balance increased loading conditions [74,75]. These adaptive changes include myocyte hypertrophy, chamber dilatation or interstitial fibrosis.

Infarct size has been shown to be the best predictor of LV dysfunction after MI [14,72]. However, previous studies have mostly focused on large MIs and the following global LV remodeling. Moreover, it has been presented that
remodeling rarely occurs if infarct size is less than 18.5% of the total LV muscle volume [76]. Nevertheless, currently infarct sizes tend to be smaller due to advances in revascularization therapy. The course of LV remodeling after smaller non-transmural MIs is less well known and there has been a lack of prospective studies using repeated CMR imaging, providing high accuracy and normalized information of the LV anatomy, global and local function, and tissue injury [77]. That is, CMR may enable also the detection of subtle changes after MI.

Infarct size can be estimated also with cardiac biomarkers. According to current guidelines, the preferred biomarkers to detect cardiac necrosis are troponins due to high sensitivity and myocardial tissue specificity, while creatine kinase MB (CK-MB), an isoenzyme of creatine kinase found predominantly in heart muscle, is the best alternative [69]. After large reperfused MI, both troponins and CK-MB have showed a good correlation with infarct size and left ventricular ejection fraction (LVEF), although the relation might be less robust in smaller infarcts [78].

2.3 CARDIOVASCULAR MAGNETIC RESONANCE

2.3.1 MAGNETIC RESONANCE IMAGING – PHYSICS BEHIND THE SIGNAL

In 1946, two independent groups leaded by Felix Bloch [79] and Edwin Purcell [80] found nuclear magnetic resonance (NMR). NMR is a physical phenomenon in which atomic nuclei located in an external static magnetic field absorb energy from another radiofrequency magnetic field. All nuclei which have a magnetic resonance property, called nuclear spin, are able to interact with magnetic field. The observed signal in NMR is based on the detection of electromagnetic radiation emitted by these nuclei returning to their equilibrium energy state.

In 1973, Paul Lauterbur [81] and Peter Mansfield [82] presented that NMR can be used to produce an image of the density of nuclear spins. This method has later been named magnetic resonance imaging (MRI). MRI is primarily based on the detection of signals from hydrogen nuclei (¹H, protons) which are abundant in free water and lipid molecules within the human body. After NMR induction by radiofrequency magnetic field, the return of the spin system to its original state, called relaxation, is detected and processed to an image.

A unique feature of MRI is to characterize soft tissue composition, because the signal is affected by local environment of hydrogen nuclei. The magnitude of the MRI signal is dependent on the density of hydrogen nuclei in tissue, the release of energy from the spin population to the surrounding molecular structure (spin-lattice interaction, T1-relaxation) and the exchange of energy between spins (spin-spin interaction, T2-relaxation) [83]. T2*-
relaxation time reflects T2-relaxation combined with the effect of local magnetic field inhomogeneities. That is, different tissues have different T1- and T2-relaxation times. By changing the acquisition parameters of the MRI signal, images can be weighted by T1- or T2-time. This is done by MRI pulse sequences containing different radiofrequency pulses and magnetic field gradients. T1 and T2 magnetic relaxation properties are used to generate image contrast and tissue characterization in MRI, which is the basis for multimodality.

MRI is a non-invasive technique, which does not use ionizing radiation, radioactive isotopes or iodinated contrast agent. Images can be obtained in any tomographic planes irrespectively of body habitus.

2.3.2 CMR

CMR assesses the function and structure of the cardiovascular system. CMR is optimized for heart movement by electrocardiography (ECG) -gating, breath-hold and rapid imaging sequences. Breath-hold is used to avoid respiratory motion of the heart, while ECG-gating to synchronize imaging to cardiac cycle [83].

During the 1980’s clinical imaging of cardiac morphology and function by CMR begun [84]. Also the characterization of tissue, such as oedema, using T1- and T2-relaxation times started. In the 1990’s and 2000’s, paramagnetic contrast agents, gadolinium chelates, enabled myocardial perfusion imaging and detection of extracellular space expansion, such as myocardial scar. During the 2010’s, the development of parametric mapping methods has enabled the visualization of intracellular pathology and diffuse myocardial fibrosis.

In the following, the most common clinical modalities of CMR are presented.

2.3.3 IMAGING OF VENTRICULAR MORPHOLOGY AND FUNCTION

Spin echo based techniques are used to obtain dark blood images of cardiac morphology[85], and gradient echo based techniques to obtain bright blood images, which are used for high temporal resolution cine movies, measurement of chamber dimensions, wall thickness and functional analysis [86] (Figure 3).

CMR is an accurate and highly reproducible technique in measuring ventricular dimensions and global function, and considered as a standard reference [87]. Furthermore, cine imaging has been shown to be accurate and reproducible method to assess also LV regional function [88]. For a measurement of myocardial volumes and ejection fraction, a stack of short-axis cine slices are obtained, epi- and endocardial borders are delineated, and summations of discs method applied. Myocardial mass can be calculated by multiplying the volume of myocardial wall by the specific gravity of the
myocardium (1.05 g/mm$^3$). Volumes are typically indexed to body surface area (BSA), age and gender. Also, visual scoring of WMA has been shown to be an accurate and reproducible method to estimate LVEF [89].

![Cardiovascular magnetic resonance cine images (bright blood) of a patient with cardiac sarcoidosis. Basal short-axis view (A) and longitudinal 4-chamber view (B) demonstrate left ventricular hypertrophy. Courtesy of Pauli Pöyhönen.](Image)

### 2.3.4 OEDEMA IMAGING

T2-weighted triple inversion recovery turbo spin echo (fat suppression) technique produces excellent visualization of free water content in the myocardium [90], which is due to a long T2 time of water-bound hydrogen nuclei. This method is useful in the detection of myocardial oedema, e.g. related to acute inflammation or infarction [91]. Evaluation of focal myocardial oedema is performed by drawing a region of interest within the myocardium and skeletal muscle in the same short-axis slice (Figure 4). The relative T2 signal intensity is then calculated by dividing the myocardial signal intensity by skeletal muscle signal intensity. The best cut-off value for identification of myocarditis from healthy controls was a relative T2 signal intensity of 1.9 with 84% sensitivity and 74% specificity [91]. However, the sensitivity of T2-weighted imaging to detect chronic inflammation is low - only 36% of patients with chronic active myocarditis in EMB were identified and none of the patients with borderline inflammation [92]. Thus, the sensitivity of regional oedema to detect less severe inflammation is reduced [93]. Moreover, images should be obtained either using a surface coil with an effective intensity correction algorithm or using a body coil [93]. For quantitative signal intensity measurements, a body coil is recommended due to a homogenous signal of the whole myocardium [94]. To solve the limitations of T2-weighted imaging, such as magnetic field inhomogeneity, parametric mapping of absolute T2 relaxation times has been developed [95], see below.
Figure 4. Left panel: T2-weighted short-axis image visualizing left ventricular myocardial oedema in a patient with giant cell myocarditis. The anteroseptal signal intensity is more than two-fold compared to skeletal muscle indicating acute myocardial oedema. Right upper panel: anteroseptal rest perfusion defect due to microvascular obstruction caused by severe inflammation (white arrow). Right lower panel: anteroseptal (white arrow) and inferior late gadolinium enhancement (LGE) due to expansion of extra-cellular space of the myocardium. Courtesy of Pauli Pöyhönen.

2.3.5 PERFUSION IMAGING
Myocardial perfusion imaging by CMR is performed with a fast T1-weighted imaging during the first pass of intravenously administrated contrast agent [87]. Used contrast agent is gadolinium chelate, which is a paramagnetic extracellular agent that shortens the T1 relaxation time of hydrogen nuclei [96]. Gadolinium enhances the blood and extracellular space, but does not enter the intracellular space of the myocardium. Normally, the whole myocardium enhances during the first passage of gadolinium. The peak enhancement is reached one minute after the intravenous injection of gadolinium. Regional perfusion defect means slowed perfusion of the myocardium and consequent hypoenhancement. Myocardial perfusion defects are due to flow-limiting coronary artery stenosis or microvascular dysfunction[96].
For detection of CAD, both rest and stress perfusion images are acquired, along with LGE images to indicate scar. Pharmacological stress is provoked by a vasodilator, such as adenosine or dipyridamole, to induce maximal myocardial hyperemia. CMR first-pass perfusion yields a high diagnostic accuracy for the detection of angiographically verified coronary artery disease [97,98].

Rest perfusion images are used to detect microvascular obstruction. The extent of microvascular obstruction predicts outcome and LV remodeling after acute MI [99,100]. Rest perfusion defects may also occur in NICMs, as in HCM due to microvascular abnormalities or in severe cardiac inflammation due to compression of the microvasculature [63] (Figure 4).

2.3.6 LATE GADOLINIUM ENHANCEMENT

LGE imaging is used to visualize the increased extracellular space in the myocardium, which may be related to necrosis, fibrosis, oedema or infiltration. In a healthy myocardium, the amount of extracellular space is limited. However, in the diseased myocardium, extracellular space typically expands. Intravenous gadolinium distributes rapidly to the extra-cellular space, but does not penetrate to intracellular space across healthy cell membranes [101]. The mechanism of contrast accumulation in acute infarct is thought to be due to myocardial cell membrane rupture that allows gadolinium to diffuse into intracellular space, while in chronic infarct due to increased space between collagen fibers. Also, the contrast kinetics has been shown to be slower in diseased myocardium [102]. Similarly, in myocardial inflammation, with oedema and cell necrosis, or infiltration such as amyloidosis, there is an increase in the extracellular space.

LGE imaging is performed 5-20 minutes after the injection of gadolinium to detect the delayed retention of contrast agent. The typical pulse sequence is segmented inversion recovery prepared T1 weighted fast gradient echo sequence [103].

LGE differentiates between reversible and irreversible myocardial ischemic injury[104] and predicts the reversibility of myocardial dysfunction after revascularization[105]. Inversion recovery based LGE methods have shown almost a perfect match between the enhanced zone and true infarct size[101] (Figure 5). However, acute and chronic MI cannot be distinguished based on the presence of LGE alone. T2-weighted imaging, showing oedema after acute MI, and cine imaging showing wall thinning in case of chronic MI, may help in differential diagnosis. In a multicentre study, the sensitivity of LGE in detecting acute and chronic MIs were 99% and 94%, respectively [106]. After acute MI, LGE, reflecting necrosis, predicts independently cardiac outcome and adverse LV remodeling compared to LVEF [76,107]. Also in stable CAD, LGE, reflecting fibrosis, has been shown to be a non-invasive independent marker of worse prognosis [108].
Figure 5. Acute anterior myocardial infarction. Short-axis slices (A) and longitudinal 2-chamber view (B) demonstrate nearly transmural infarct in the perfusion territory of left anterior descending artery. The bull’s eye plot of infarcted tissue (%) per segment (C). The total infarct volume was 9% (FWHM-method) of the left ventricle. Segmentation according to AHA guidelines [66]. Courtesy of Pauli Pöyhönen.
LGE is an unspecific finding and may be related to different diseases. Different myocardial diseases have been shown to present with typical distributions of LGE [16], see Figure 6. The Distribution of LGE may aid in differentiation of ischemic heart disease and NICMs [15,16].

LGE after MI is always subendocardial and to a varying extent transmural, consistent with a coronary artery perfusion territory. In the first 15 minutes after coronary occlusion, there is little or no myocyte necrosis in the ischemic zone [16]. After that period, there is a wavefront of necrosis expanding from the subendocardium to the epicardium toward transmural infarct.
In NICM, the typical distribution of LGE is intramyocardial, subepicardial, or multifocal, and not confined to coronary artery perfusion territories. In DCM, approximately 30% of patients have a midmyocardial LGE, typically located septally and reflecting fibrosis, which has been associated with worse prognosis independently of ventricular remodeling [110-112]. The presence of fibrosis in DCM has been associated with more than 3-fold risk of cardiac death or transplantation [113] and with a 7-fold hazard per 10% increase in LGE extent for cardiovascular death or implantable cardioverter-defibrillator therapy [112]. In HCM, LGE is typically patchy and intramyocardial, and located in hypertrophied areas of the myocardium and ventricular junctions [16]. According to a meta-analysis of 1063 patients, approximately 60% of patients with HCM have LGE, which is associated with a 2.9-fold risk of cardiac death during 3 years follow-up [114]. In cardiac amyloidosis, a typical circumferential LGE of the entire subendocardium had a sensitivity of 88% and specificity of 90% in detecting histologically verified disease, and it was the best non-invasive parameter to predict one-year mortality, compared to ECG or doppler echocardiography [115].

In myocarditis, LGE is typically less intense and affecting the epicardium of the LV, predominantly lateral free wall, and may decrease significantly during the healing process [116]. In biopsy-proven viral myocarditis, the presence of LGE was the best adjusted predictor of all-cause and cardiac mortality, with corresponding hazard ratios of 8.4 and 12.8, respectively [117]. The pooled sensitivity and specificity of LGE in detection of myocarditis according to 5 separate studies was 35% and 83%[93].

In CS, LGE has typically patchy distribution affecting several myocardial layers, with often both ventricle involvement, and most frequently located in the basal septal and lateral free wall of the LV [118-122]. In a recent study of patients with extra-cardiac sarcoidosis, the presence of LGE had a sensitivity of 96.9% and a specificity of 100% to predict CS diagnosed by Heart Rhythm Society consensus criteria [123]. The presence of LGE in systemic sarcoidosis has been associated with more than 30-fold risk of cardiac death and ventricular arrhythmias, while normal CMR finding seems to imply a good prognosis irrespectively of other symptoms [124].

LGE imaging is usually included in the CMR protocol when there is a suspicion of a disease of the myocardium. Gadolinium contrast agent may be contraindicated in patients with previous allergic reaction, in severe renal dysfunction due to a risk of nephrogenic systemic fibrosis[125], or in pregnancy.

### 2.3.6.1 Evaluation of LGE

There are several different methods to measure LGE. The presence and extent of LGE can be assessed visually and by manual tracing, or using semiautomated techniques based on the signal intensity and pre-defined
Review of the literature

tresholds. The used method has a significant effect on the extent of LGE [126-128] (Figure 7).

Semi-automated methods include full width at half maximum (FWHM) technique or thresholding by 2, 3, 4, 5 or 6 standard deviations (SDs) above the mean remote “normal” myocardial signal. Two regions of interests are manually delineated. The first represents the remote myocardium with no enhancement, and the second the hyperintense myocardium with maximal signal intensity used for the FWHM technique. The hypointense area inside enhanced myocardium is defined as microvascular obstruction and included to LGE. Enhancement is first calculated per slice and the volume of LGE by summing all LV slices.

Visual scoring method based on the standard 17-segment model of the LV can be used to estimate LGE extent [129]. This method has been shown to be rapid and accurate method to estimate LGE both in CAD and NICMs [130-132]. In each segment, the percentage of enhancement is visually estimated and scored as 0 (no enhancement), 1 (0 – 25% enhancement), 2 (26 – 50% enhancement), 3 (51 – 75% enhancement) or 4 (76 – 100% enhancement). The total LGE score is calculated summing all segmental scores. To estimate

![Figure 7. Late gadolinium enhancement (LGE) evaluated with full width at half maximum (FWHM), 2SD and 5SD methods in a patient with acute myocardial infarction (MI) and a patient with cardiac sarcoidosis (CS). Images are basal short-axis views of the left ventricle. Red area represents LGE, red and green contours the endocardium and epicardium, pink circle the area of maximal signal intensity, and brown-lined area the normal myocardium without enhancement. LGE volume is given as a percentage of the total left ventricular muscle volume (only one slice shown). LGE volumes calculated with different methods have greater variability in CS, in which there is less intense but diffuse LGE. Courtesy of Pauli Pöyhönen.](image-url)
LGE volume of the LV, LGE score is expressed as a percentage of the maximum score of the LV (4 × 17 = 68) using formula: 100 × (LGE score)/68.

There is no consensus of the optimal method for LGE assessment. In a study containing patients with either acute MI, chronic MI or HCM, FWHM technique was statistically the most reproducible semi-automated method in all disease groups [128]. However, reproducibility of all different semi-automated methods was worse in HCM, but FWHM technique still giving acceptable results [128]. According to a recent study of patients with two days old acute MI, manual tracing had the lowest overall variability for quantification of infarct size when analysed by experienced observers [133].

2.3.7 PARAMETRIC MAPPING

Parametric mapping with CMR means myocardial tissue characterization by detecting quantitative changes in T1-, T2-, T2*-relaxation times and extracellular volume (ECV). These changes reflect both intra- and extracellular pathology in the myocardium [17] (Figure 8). Parametric mapping permits the detection of diffuse and local myocardial changes, because quantitative measurements can be made on absolute scale and there is no need for a reference tissue such as remote myocardium or skeletal muscle [17]. However, parametric mapping requires stability of imaging conditions and results are dependent on magnetic field strength and to a lesser extent on age and gender [134].

2.3.7.1 T1 mapping

Quantification of myocardial T1-relaxation times requires a series of co-registered source images to derive the estimate of T1-time in each location[25]. These T1 estimates are then presented as a map, in which values are encoded as signal intensity. Maps can be generated in short-axis or long-axis views, depending on the purpose. Native (noncontrast) T1 map is generated without the use of gadolinium contrast. The modified Look-Locker inversion recovery (MOLLI) sequence is widely used for T1 mapping.

Elevated native T1-times have been reported in fibrosis [18], oedema [19] and amyloidosis [20]. Low T1-times have been reported in iron overload [21] and focal fat infiltration [22]. Native T1 mapping has shown potential in the detection of Anderson-Fabry, a genetic X-linked lysosomal storage disease characterized by multiorgan involvement and sphingolipid accumulation within myocytes [22,135].
2.3.7.2 Diffuse fibrosis

Myocardial diseases often exhibit diffuse fibrosis which impairs the diastolic relaxation and compliance of the LV. Conventional LGE imaging visualizes focal expansion of the extra-cellular space in relation to healthy myocardium. However, in diffuse fibrosis, there may not be normal reference myocardium available. Furthermore, the resolution of LGE imaging may not be sufficient enough to detect microscopic interstitial fibrosis.

T1 mapping can be used to estimate ECV of the myocardium by measuring T1-relaxation times before and after the administration of contrast agent and correcting results for hematocrite [23-25]. Decreases in ECV may be seen in athlete’s heart, while mild increases in ECV are seen in diffuse fibrosis, and moderate to severe increases in amyloidosis, necrosis or scar [17].

2.3.7.3 T2 and T2* mapping

T2 mapping quantifies myocardial oedema and inflammation. Pixel-wise T2-maps are generated from a series of T2-weighted images. Elevation in T2 times are seen in acute inflammation and acute myocardial ischemia [95]. T2* mapping is used to detect myocardial iron overload due to repeated blood transfusions in anemia or increased iron absorption in hemochromatosis [17].
Figure 8. Parametric mapping of normal myocardium and patients with myocardial disease. Arrows indicate a relative change to normal myocardium in parametric map values. Reproduced with permission from BioMed Central [17].
3 AIMS OF THE STUDY

This study was designed to assess whether myocardial tissue characterization by advanced CMR methods improves the diagnosis and risk stratification of cardiomyopathies. The specific objectives were as follows:

1. To evaluate the additional prognostic value of LGE and WMAi on CMR compared to traditional risk factors in suspected NICM (I).

2. To assess the clinical and imaging predictors of severe cardiac inflammation, i.e. CS or GCM, at the era of CMR with LGE imaging (II).

3. To define the distinct imaging characteristics of PRKAG2, a unique glycogen storage cardiomyopathy, which have not been systematically reported by CMR (III).

4. To evaluate the nature of LV remodeling by repeated CMR after revascularized MI with specific attention to smaller non-transmural infarcts (IV).
4 MATERIALS AND METHODS

Studies in this thesis were planned and initiated in the Heart and Lung Center at the Helsinki University Hospital, and conducted in collaboration with HUS Medical Imaging Center, HUS Children's Hospital, Molecular Neurology Research Program of Helsinki University, Department of Biomedical Engineering and Computational Science of Aalto University, and Blueprint Genetics.

Studies (I-II) were essentially retrospective in nature and approved by the institutional review board of Helsinki University Hospital. In studies (III-IV) all participants gave written informed consent and projects were approved by the local institutional ethics committee.

4.1 STUDY DESIGN AND PATIENT SELECTION

4.1.1 NON-ISCHEMIC CARDIOMYOPATHY COHORT (I-II)

A retrospective cohort of 86 consecutive patients referred for CMR due to suspected NICM was identified between November 2008 and April 2010. Baseline CMR images were re-analysed. Medical records were reviewed for patient demographics, cardiovascular risk factors, symptoms and cardiac examinations. Patients were followed-up for (I) major adverse cardiac events (MACEs) and (II) final diagnoses.

All included patients had suspected NICM, i.e. symptoms of heart failure, mechanical or electrical cardiac dysfunction, usually associated with ventricular dilatation or hypertrophy, or cardiac enzyme elevation, not related to atherosclerosis [26].

Patients with a history of MI or documented significant CAD, valvular heart disease, or congenital heart disease, were excluded. Significant CAD was defined as >50% stenosis in two or more epicardial vessels or > 50% stenosis in left main or proximal left anterior descending artery [136], presence of reversible perfusion defect in SPECT, or presence of CAD in explanted hearts.

Patients examined with neither angiography nor SPECT (n = 37, 43%) had only few risk factors for atherosclerosis and evident non-ischemic etiology for symptoms.

4.1.2 CMR FINDINGS IN PRKAG2 (III)

Seven subjects from two separate families harboring PRKAG2 mutations were recruited to this study. CMR and genetic testing were performed for all subjects. Clinical evaluation included review of hospital records, ECG and
Materials and methods

Echocardiography (index patients). Patients underwent electrophysiological study based on the decision of treating cardiologist.

The phenotypic triad of PRKAG2 cardiomyopathy was based on cardiac hypertrophy, pre-excitation and conduction system disease [137]. Ventricular pre-excitation was defined as a short PR interval (<120 ms), prolonged QRS interval (>110 ms), and an abnormal initial QRS vector (delta-wave), or finding of an antegradely conducting accessory pathway on electrophysiologic study. WPW was defined as evidence of supraventricular tachycardia with pre-excitation.

4.1.3 INFARCT SIZE AND LEFT VENTRICULAR REMODELING (IV)

The study (IV) was a CMR substudy of the prospectively conducted ISKE project (Imaging acute myocardial ischemia by body surface potential mapping). From June 2003 to June 2005, patients admitted to the Coronary Care Unit of Helsinki University Hospital for suspected acute coronary syndrome were screened during office hours. Inclusion criteria were prolonged chest pain ≥ 20 minutes within 48 hours of recruitment, associated with acute ischemia in the initial ECG (ST-segment elevation or depression, or T-wave inversion, in ≥ 2 contiguous leads), or elevated cardiac enzymes (CK-MB mass > 7 μg/L or troponin T > 0.03 μg/L), or both. Patients with contraindications for CMR, bundle branch block, atrial fibrillation, or need for ventilator support, were excluded.

All eligible patients were diagnosed with acute MI (elevated cardiac enzymes or scar at CMR) and underwent revascularization in the acute phase. Patients with prior MI, percutaneous coronary intervention (PCI), or coronary artery bypass grafting (CABG), were excluded. All patients were treated with successful PCI, CABG or thrombolysis in less than 3 days after the hospital admission, except one patient treated successfully with CABG after 9 days during the same hospital stay. Patients were also initiated on optimal secondary preventive medication for CAD.

To assess LV and scar remodeling, all patients were examined with two sequential CMR examinations after MI. The first CMR study was performed during the recovery phase (7 – 30 days) and the second during the chronic infarct phase (≥ 6 months) after MI. CK-MB was measured at hospital arrival, the following evening or morning, or both. The maximum value of these measurements, peak CK-MB, represented a measure of infarct size. In most patients, peak CK-MB was measured 12 – 24 hours after the onset of chest pain.

4.2 CMR PROTOCOL

CMR imaging was performed with a 1.5-T imager (Magnetom Avanto or Sonata; Siemens, Erlangen, Germany) using a body array coil (I,II,IV) or a
32-channel cardiac coil (III) as a receiver. In study (III), two patients with a pacemaker underwent imaging according to previously published magnetic resonance safety protocol for pacemaker patients [138].

4.2.1 CINE IMAGING
Breath-hold cine CMR was performed using retrospectively ECG-gated segmented true fast imaging with balanced steady-state free precession (bSSFP) TrueFISP sequence.

Cine CMR images were acquired in vertical, horizontal long-axis and short-axis planes covering the whole LV or both ventricles. Typical imaging parameters were TR/TE 3.0/1.6 ms, flip angle 52 degrees, 256 x 256 matrix and 240 x 340 mm field of view. Slice thickness was 6 mm. The temporal resolution was 42 – 49 ms.

4.2.2 LGE IMAGING
Five to fifteen minutes after intravenous injection of a contrast agent (gadoterate meglumine, Dotarem® 0.1-0.2 mmol/kg (I,II,III) or gadodiamide, Omniscan TM, GE Healthcare, 0.2 mmol/kg (IV)), LGE images were acquired in the same views as for cine images, using inversion-recovery turbo fast-low angle shot (FLASH) (I-II, IV) or inversion recovery spoiled gradient echo (IR-SPGR) sequence (III). Typical imaging parameters were TR/TE 2.58/ 2.3 ms (I-III) or TR/TE 8.6/4.3 ms (IV), flip angle 50 degrees, 256 x 256 matrix, and 240 x 340 mm field of view. Slice thickness was 8 mm. Inversion times were optimized to null the signal intensity of normal myocardium (240 – 360 ms).

4.2.3 PARAMETRIC MAPPING
In study III, non-contrast myocardial T1 mapping was performed in a mid-LV short-axis slice using a shortened Modified Look-Locker Inversion-recovery (ShMOLLI) sequence. Typical acquisition parameters were TR/TE 2.1/1.1 ms, flip angle 35°, 236 x 256 matrix, 331 x 360 mm FOV, 8 mm slice thickness, and inversion times ranging from 90 ms to circa 5000 ms.

Non-contrast myocardial T2 mapping was performed using a T2-prepared bSSFP sequence to produce three single-shot T2-weighted images, each of which with a different T2-preparation time (TE\textsubscript{T2P} = 0 ms, 25 ms and 55 ms). Other scanning parameters were TR = 4 x RR intervals, flip angle 35°, 192 x 154 matrix, 360 x 289 mm FOV, and 8 mm slice thickness.
4.3 CMR IMAGE ANALYSIS

Images were analysed in consensus with two experienced (>10 years of experience) cardiac radiologists and cardiologist. Analysis was done blinded to clinical outcome. Segments with any artifacts due to a pacemaker were excluded in analysis. Image analysis was performed visually and using either Leonardo (Siemens Medical Solutions, Erlangen, Germany) or QMass MR software® (version 7.6, Medis Medical Imaging Systems, Leiden, Netherlands).

4.3.1 VOLUMETRY

Ventricular volumes, masses and wall thicknesses were evaluated by tracing manually epicardial borders (excluding epicardial fat) and endocardial borders (excluding papillary muscles) at end-diastole and end-systole for short-axis slices [139]. Volumetric indices were obtained by dividing values by body surface area.

In study (III), normal ventricular volumes and masses for adults were obtained from the references [139,140] and for children (<18 years) from the reference [141], using similar 1.5 T MR scanner and bSSFP pulse sequence as ours. Normal LV wall thickness values for adults were obtained from the reference[142] (similar scanner, sequence and QMass software tool as ours). Hypertrophy was defined as increased LV wall thickness in one or more myocardial segments, or RV free wall thickness, of more than two SDs above the population mean (z-score > 2). There were no available reference values for LV wall thickness based on the 17-segment-model for children. Therefore, we used adult CMR references for the 17-year-old female (BSA 1.83 m²) and for the 16-year old male (BSA 1.33 m²). BSA-standardized echocardiographic reference values were used for all children for measurement of maximal wall thickness [143].

4.3.2 LATE GADOLINIUM ENHANCEMENT

Three different methods to estimate LGE were used. In studies (I-II), LGE was evaluated using the visual scoring method based on the standard 17-segment model of the LV, leaving out the apex [129].

In study (III), LGE percentage of the LV was calculated using QMass software. Hyperenhanced pixels were defined using FWHM method.

In study (IV), LGE area was manually delineated in each segment. The LGE percentage of the LV was then estimated by dividing the sum of segmental LGE areas by the total area of all segments. Infarct transmurality was evaluated as the percentage of enhanced area in each segment. We defined transmural MI as having ≥ 75% enhancement in at least one myocardial segment.

In studies (I-II), disease specific patterns were sought using standard
criteria [16]. Multifocal LGE, affecting several myocardial layers, not confined to coronary artery perfusion territories, was considered as suggestive for severe cardiac inflammation, i.e. suspected CS or GCM [122,144,145].

4.3.3 WALL MOTION ABNORMALITY (I, II, IV)
WMA was estimated using the visual scoring method [67]. The degree of WMA in each segment was scored as 0 (normokinesia), 1 (hypokinesia), 2 (akinesia) or 3 (dyskinesia). The WMA index (WMAi) of the LV was then calculated as the sum of all segmental scores.

4.3.4 PARAMETRIC MAPPING (III)
Motion corrected myocardial T1 relaxation time maps were generated using QMass software. T1 estimates were computed on a per-pixel basis by non-linear curve fitting using the three-parameter signal model. Mid-LV short-axis T1 analysis was performed by measuring the mean T1 values separately for the anterior, anteroseptal, inferoseptal, inferior, inferolateral and anterolateral segments (six segments). In addition, complete mid-ventricular mean T1 value was calculated. T1 values were compared with published normal values of the healthy myocardium 962 ± 25 ms obtained with similar scanner and sequence[134].

Motion corrected myocardial T2 relaxation time maps were acquired [95]. In-plane motion between images was corrected using a fast non-rigid registration algorithm. Pixel-wise T2 maps were generated using curve-fitting based on two parameter equation by assuming mono-exponential signal decay. Segmental analysis for T2 values was performed similarly as for T1 values.

4.4 GENETIC ANALYSIS (III)
The index patient in family 1 was examined with a novel next generation sequencing strategy, oligonucleotide-selective sequencing[146], targeting 69 known genes associated with cardiomyopathies (Core Cardiomyopathy Panel, Blueprint Genetics, Helsinki, Finland, http://blueprintgenetics.com/). Median sequence coverage per base pair was 137x, while 97.3 % of the target region was covered with >15x. A heterozygous missense variant in the PRKAG2 gene, c.905G > A (p.R302Q), was identified. In several earlier studies, this variant has been characterized as a disease mutation associated with familial WPW and severe LVH mimicking HCM [8,27,50] Direct Sanger sequencing was used to confirm the detected variant and to test other family members.

The index patient in family 2 was examined with a custom-designed panel
of 117 cardiomyopathy-related genes (HaloPlex kit of 500Kb, Agilent Technologies). A heterozygous missense mutation was identified in the PRKAG2 gene. The novel mutation p.H344P (c.1031A > C) segregated with the disease in the family and was not found in 3250 Finnish controls (Sequencing Initiative Suomi (SISu) database, http://www.sisuproject.fi/). The p.H344P mutation alters an evolutionarily conserved site in the protein. Using bioinformatics prediction tools SIFT and PolyPhen-2, the variant was rated as deleterious and possibly damaging, which strengthens the idea of pathogenicity.

4.5 ACQUISITION OF FOLLOW-UP DATA (I,II,IV)

In studies (I-II), the follow-up data was collected for MACEs (I) and for final diagnoses (II) until April 30th 2012. Information was based on medical records and mortality data from the national registry of Statistics Finland.

4.5.1 MAJOR ADVERSE CARDIAC EVENTS (I)

In study (I), a MACE was defined as cardiovascular death, aborted sudden death or cardiac transplantation, based on hospital records and mortality information from Statistics Finland. Event times were measured from CMR to the first event. Aborted sudden death was defined as documented resuscitation from cardiac arrest or appropriate implantable cardioverter-defibrillator therapy, i.e. antitachycardia pacing or shock, for ventricular tachycardia or fibrillation.

4.5.2 FINAL DIAGNOSES (II)

In study (II), final diagnoses were based on AHA guidelines [26]. In our clinical practice, EMB was performed when there was a clinical suspicion of severe inflammation or infiltrative cardiomyopathy [11,53]. Samples were taken under fluoroscopic and ultrasound imaging guidance, and analysed by an experienced cardiac pathologist.

The histological diagnosis of CS in EMB was based on the presence of non-caseating granuloma, with or without foci of lymphocytic myocarditis, necrosis or giant cells [38]. GCM was diagnosed by the presence of myocyte necrosis and widespread inflammatory infiltrate, including multinucleated giant cells and lymphocytes, in the absence of non-caseating granulomas [5,38].

In PET, a finding suggestive of cardiac inflammation was defined as focally increased FDG uptake with reduced myocardial perfusion [61,62,147]. In mediastinal lymph nodes inflammatory finding was defined as increased FDG uptake.
4.5.3 MAJOR ADVERSE CARDIAC EVENTS (IV)
In study (IV), MACEs were post-hoc collected until the end of year 2012 based on local and national registries, including university and local hospital records, general practitioners’ records and the mortality information from Statistics Finland, without direct contact to patients. The survival time was calculated from the first CMR. A MACE was defined as cardiovascular death, aborted sudden death, heart failure hospitalization, or recurrent MI.

4.6 STATISTICAL ANALYSES

4.6.1 PRESENTATION OF VARIABLES
Continuous variables are presented as median (interquartile range, IQR) or mean (± SD), as appropriate, and categorical variables as frequency (%). In study (III), LV indices are given as absolute values and standardized (z-scores) to age, gender, BSA and normal myocardial function. BSA was calculated with Mosteller’s method.

4.6.2 COMPARISON OF VARIABLES
Comparison between continuous normally distributed independent variables was performed with Student’s t-test, otherwise with Mann–Whitney U test. Comparison between categorical variables was performed with Pearson Chi-Square test with continuity correction, Fisher’s exact test or Mann–Whitney U test. In study (IV), variables between recovery and chronic phase CMR were compared with related samples Wilcoxon signed rank test. Presented correlation coefficients were calculated using Spearman’s method. A p-value of < 0.05 was considered statistically significant and all statistical tests were 2-sided.

4.6.3 STATISTICAL PACKAGES
Statistical analyses were performed using the SPSS 20 and 21 packages (SPSS, Chigaco, IL, USA). In study (III), R language and environment for statistical computing (Version 2.15.3, R Core Team 2013, R Foundation for Statistical Computing, Vienna, Austria) was used for graphical output of segmental LV wall thickness.

4.6.4 SURVIVAL PLOTS
Kaplan-Meier method was used to plot and compare (Log rank) survival curves (I). Receiver operating characteristic (ROC) curves were used to find the best cut-off values of LGE extent and WMAi (optimal combination of
sensitivity and specificity) for prediction of MACEs (I).

4.6.5 REGRESSION MODELS

In studies (I) and (IV), univariate Cox regression analysis was performed to identify the predictors of MACEs. Variables with statistical significance \( p < 0.05 \) (entry cut-off) were considered in the multivariate model (I). Forward stepwise multivariate Cox regression was performed to study the independency of variables. The number of variables in the model was limited to three (at least 5 events per each covariate [148]). All variables in the model were tested to satisfy Cox proportional hazard assumption by plotting hazard function and logarithm of hazard function. If needed, continuous variables were made to dichotomous using the cut-off values taken from literature or close to median. In study (II), logistic regression was performed to evaluate the predictive significance, and related odds ratio (OR), of each variable in identifying CS or GCM. Due to limited number of patients with CS or GCM, only two variables were included in a multivariate model [148], excluding significantly correlated variables. In study (IV), linear regression analysis was performed to identify predictors of chronic phase LVEF, reaching sufficient normality of residuals.
5 RESULTS

5.1 PROGNOSTIC VALUE OF LGE AND WMAI IN NICM (I)

5.1.1 PATIENT CHARACTERISTICS
The first study included a cohort of 86 patients suspected for NICM (median age 53 years; 45% female). The most frequent clinical manifestations at baseline were decline in functional capacity (67%), defined as New York Heart Association (NYHA) functional class II-IV, ventricular arrhythmias (40%) and heart failure (44%) (Table 2).

Patients underwent extensive diagnostic evaluation: CMR (n=86, 100%), echocardiography (n=86, 100%), coronary angiography (n=47, 55%), EMB (n=41, 48%), PET (n=21, 24%), electrophysiological study (n=14, 16%), mediastinoscopy (n=4, 5%), SPECT (n=4, 5%) and histopathology of explanted heart (n=2, 2%).

After cardiac examinations, 65 patients (76%) were finally diagnosed with NICM, 15 (17%) with LVH and 6 (7%) with idiopathic arrhythmia (Table 3). The most common disease categories were inflammatory heart disease (n=23, 27%) and DCM (n=22, 26%).

5.1.2 LGE AND WMAI
On CMR, 61 patients (71%) had LGE and 56 patients (65%) WMA of the LV. The median LGE volume was 7% (0 – 25%) of the total LV muscle volume in all patients, and 13% (6 – 32%) in LGE positive patients alone. The median WMAi was 4 (0 – 12) in all patients, and 7 (4 – 19) in WMA positive patients. There were a total of 1462 myocardial segments (17 segments/patient x 86 patients). The segmental extent of LGE and WMA were significantly associated (p<0.001); abnormal wall motion was found in 20% of segments without LGE and in 75% of segments enhancing more than 50%.

5.1.3 PREDICTORS OF MACES
After CMR, patients were followed-up for a MACE in a median of 835 (780 – 998) days. Altogether 15 of 86 patients (17%, annual event rate: 7.6%/year) reached an endpoint during follow-up with 5 cardiovascular deaths, 2 cardiac transplantations and 8 aborted sudden deaths.

In univariate Cox regression analysis, significant predictors of MACEs were NYHA class III-IV (hazard ratio [HR] 2.8, p = 0.049), sustained VT (HR
Results

3.8, p = 0.023), atrioventricular block of any degree (HR 3.8, p = 0.022), stroke volume (HR 0.968, p = 0.032), LVEF on CMR (HR 0.959 per 1% increase in LVEF, p = 0.009), LGE volume (HR 1.028 per 1% increase in LGE, p < 0.001) and WMAi (HR 1.067 per 1 point increase in WMAi, p = 0.012). In multivariate analysis, the best overall model to predict cardiac events included LGE volume (HR 1.027, p = 0.003), sustained VT (HR 4.8, p = 0.011) and LVEF (HR 0.962, p = 0.034).

Among patients with LGE, there was an event rate of 26% (14 of 61) compared with 4% (1 of 25) in LGE negative patients (p = 0.041, Log rank) (Figure 9A). Similarly, the presence of WMA was a significant predictor of worse outcome during follow-up, since there were no events in patients with normal wall motion (p = 0.002, Log rank) (Figure 9C). Based on a ROC curve (Figure 10), the highest event rate was observed in patients with LGE volume of ≥17% with 12 events in 28 patients and a cumulative event ratio of 43% after three years (Log rank, p < 0.001) (Figure 9B). Patients with LVEF < 50 % (p = 0.014, Log rank) were also at increased risk (Figure 9D). Moreover, in the subgroup of patients with preserved LVEF (≥50%, 47 patients), the absence of WMA (30 patients) resulted in no events during follow-up, but 17 patients with WMA were still at risk with 4 events (Log Rank, p = 0.005) (Figure 9E).
Table 2. Baseline characteristics of all patients suspected for non-ischemic cardiomyopathy (n=86).

<table>
<thead>
<tr>
<th>Demographics</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, year</td>
<td>53 (42-61)</td>
</tr>
<tr>
<td>Gender, female</td>
<td>39 (45)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cardiovascular risk factors</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyslipidemia</td>
<td>51 (59)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>34 (40)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>7 (8)</td>
</tr>
<tr>
<td>Smoking</td>
<td>19 (22)</td>
</tr>
<tr>
<td>Family risk for CAD</td>
<td>11 (13)</td>
</tr>
<tr>
<td>Sum of risk factors (1-5)</td>
<td>1 (1-2)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Symptoms</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Syncope or presyncope</td>
<td>21 (24)</td>
</tr>
<tr>
<td>Palpitation</td>
<td>34 (40)</td>
</tr>
<tr>
<td>Chest pain</td>
<td>31 (36)</td>
</tr>
<tr>
<td>NYHA-class</td>
<td>2 (1-3)</td>
</tr>
</tbody>
</table>

| Heart failure             | 38 (44) |

<table>
<thead>
<tr>
<th>Arrhythmias</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrial fibrillation</td>
<td>25 (29)</td>
</tr>
<tr>
<td>Ventricular fibrillation</td>
<td>9 (10)</td>
</tr>
<tr>
<td>Sustained VT</td>
<td>9 (10)</td>
</tr>
<tr>
<td>Nonsustained VT</td>
<td>16 (19)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Conducting abnormalities</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>AVB of any grade</td>
<td>39 (45)</td>
</tr>
<tr>
<td>Distal AVB</td>
<td>7 (8)</td>
</tr>
</tbody>
</table>

| Cardiac enzyme elevation*  | 32 (37) |

Values are median (IQR) or n (%).
* Troponin T, Troponin I or CK-MB.
Abbreviations: AVB = atrioventricular block, CAD = coronary artery disease, IQR = interquartile range, NYHA-class = New York Heart Association functional class, VT = ventricular tachycardia.
**Table 3.** Final diagnoses of all cohort patients suspected for non-ischemic cardiomyopathy (n=86).

<table>
<thead>
<tr>
<th>Non-ischemic cardiomyopathy*</th>
<th>65 (76)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inflammatory heart disease</td>
<td>23 (27)</td>
</tr>
<tr>
<td>Myocarditis nonspecific</td>
<td>9 (10)</td>
</tr>
<tr>
<td>Cardiac sarcoidosis</td>
<td>8 (9)</td>
</tr>
<tr>
<td>Giant cell myocarditis</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Pericarditis</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Eosinophilic myocarditis</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Dilated cardiomyopathy</td>
<td>22 (26)</td>
</tr>
<tr>
<td>Cardiomyopathy nonspecific</td>
<td>8 (9)</td>
</tr>
<tr>
<td>Infiltrative cardiomyopathy or storage disease</td>
<td>5 (6)</td>
</tr>
<tr>
<td>Non-compaction cardiomyopathy</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Hypertrophic cardiomyopathy</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Tako-Tsubo cardiomyopathy</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Ion channelopathy (Long-QT syndrome)</td>
<td>1 (1)</td>
</tr>
</tbody>
</table>

Other diagnoses 21 (24)

<table>
<thead>
<tr>
<th>Other diagnoses</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Left ventricular hypertrophy**</td>
<td>15 (17)</td>
</tr>
<tr>
<td>Idiopathic arrhythmia</td>
<td>6 (7)</td>
</tr>
</tbody>
</table>

Values are n (%).

* Classification of cardiomyopathies based on AHA 2006 guidelines[26]. Cardiomyopathy nonspecific had characters of several cardiomyopathies.

** Hypertensive heart disease (n=8) and left ventricular hypertrophy without hypertension (n=7).
Figure 9. Kaplan Meier analysis of event-free survival in patients discriminated with the presence of late gadolinium enhancement (LGE) on cardiovascular magnetic resonance (A), with LGE volume of $\geq 17\%$ (B), with the presence of segmental wall motion abnormality (SWMA) (C), and with left ventricular ejection fraction (LVEF) of $<50\%$ (D). In the patient cohort with preserved LVEF ($\geq 50\%$), the absence of SWMA (30 patients) resulted in no events during follow-up, while 17 patients with SWMA were still at risk with 4 events (E). Reproduced with permission from BioMed Central (I).
Results

Figure 10. Receiver operating characteristic curves of late gadolinium enhancement (LGE) volume, segmental wall motion abnormality (SWMA) score and left ventricular ejection fraction (LVEF) for prediction of events during follow-up, with corresponding area under curve 0.832 (95% confidence interval [CI]: 0.716 – 0.948), 0.769 (95% CI: 0.666 – 0.872) and 0.704 (95% CI: 0.565 – 0.844). The optimal cut-off values with the best combination of sensitivity and specificity were LGE volume of ≥ 17 %, SWMA score of ≥ 5 and LVEF < 46 %. Reproduced with permission from BioMed Central (I).

5.2 DETECTION OF CS OR GCM IN NICM (II)

The second study was based on the same cohort of 86 patients with suspected NICM as study (I). During a follow-up, altogether 11 patients (13%, 95% CI: 6 – 20%) were diagnosed with CS (n=8) or GCM (n=3) (Table 4). The delay from CMR to the final diagnosis of CS or GCM was in median 21 days (range: 0 – 219 days, IQR: 1 – 84 days).

5.2.1 REVIEW OF HISTOLOGICAL DATA

Altogether 41 of 86 patients (48%) underwent one or more EMBs, with a total number of biopsy procedures 55 and maximum number per patient 3. EMB was taken from LV/RV in 5/50 procedures, and performed in a median of 3 days after CMR (IQR: 3 days before – 32 days after). In 31 (76%) patients, when CMR was performed before EMB, LGE images were used to direct the biopsy towards the abnormal region of the myocardium.

The biopsy verification of CS was based on EMB (3 patients), mediastinal lymph node biopsy (4 patients) and extracardiac biopsy (1 patient), with
appropriate clinical and imaging findings (Table 4). The diagnosis of GCM was based on EMB (1 patient) with appropriate clinical and imaging findings. In addition, two patients with a suspicion of GCM in EMB were diagnosed with GCM; one with rapidly progressed new-onset heart failure, sustained VT, FDG uptake in PET and LGE finding suggestive of cardiac inflammation; and the other with rapidly progressed new-onset heart failure, LGE and T2-weighted imaging findings on CMR suggestive of cardiac inflammation.

5.2.2 REVIEW OF PET PERFORMANCE
Twenty-one (24%) of 86 patients underwent 18F-FDG-PET by clinical indication, in a median of 35 (16 - 136) days after CMR. Of these 21 patients, seven had a finding suggestive of cardiac or mediastinal lymph node inflammation and six eventually reached histological verification. Specifically, four patients with FDG uptake in lymph node were diagnosed with CS by mediastinal lymph node biopsy, one patient with a positive PET finding in heart was diagnosed with CS by cutaneous biopsy, and one patient having a positive PET finding in heart was diagnosed with GCM by EMB.

5.2.3 PREDICTORS OF CS OR GCM
Considering baseline clinical characteristics (Table 2), there were no differences in age, gender, background diseases or cardiovascular risk factors between patients diagnosed with CS or GCM and others. However, patients with CS or GCM had more palpitations (73% vs. 35%, p = 0.022), shorter course of cardiac symptoms (median 1 – 4 weeks vs. 1 – 3 months, p = 0.007), higher prevalence of VT (64% vs. 24%, p = 0.012), sustained VT (45% vs. 5%, p = 0.001) and atrioventricular block of any degree (82% vs. 40%, p = 0.020) compared to others.

Septal abnormalities in echocardiography (73% vs. 39%, p = 0.049) were associated with CS or GCM (Table 5). The median LVEF based on CMR was not different between patients with CS or GCM and others (43% vs. 55%, p = 0.089). However, reduced stroke volume (median 62 ml vs. 75 ml, p = 0.020), LGE volume (37% vs. 6%, p < 0.001), presence of LGE (100% vs. 67%, p = 0.029) and multifocal LGE (91% vs. 16%, p < 0.001) on CMR were associated with CS or GCM. LGE was distributed mainly in septal and basal segments of the LV in patients with CS or GCM, with corresponding LGE volumes 55% of septal and 54% of basal segments.

Logistic regression was performed to find predictors of CS or GCM (Table 6). Variables with strongest univariate association with CS or GCM were sustained VT (OR=14.8, 95% CI=3.1–70.2; p = 0.001), LGE volume (OR = 1.05 per 1% increase in LGE, 95% CI=1.02–1.08; p = 0.001) and multifocal LGE (OR=52.5, 95% CI=6.1–449.1; p<0.001). In a multivariate model, sustained VT (OR 20.8, 95% CI 3.5–123.8; p = 0.001) and LGE volume
(OR=1.06, 95% CI=1.02–1.09; p=0.001) were independent predictors of CS or GCM. The ability of multifocal LGE in detection of severe cardiac inflammation was studied separately. Altogether 10 (91%) of 11 patients with CS or GCM had multifocal LGE on CMR versus 12 (16%) of 75 patients with other diagnoses (p<0.001). Multifocal LGE had a sensitivity and specificity of 91% and 84% in identifying CS or GCM, while corresponding positive and negative predictive values in our cohort were 45% and 98%, respectively.
<table>
<thead>
<tr>
<th>Biopsy</th>
<th>Imaging</th>
<th>Clinical</th>
</tr>
</thead>
<tbody>
<tr>
<td>EMB</td>
<td>Media-stinal lymph node biopsy</td>
<td>CMR Multifocal LGE*</td>
</tr>
<tr>
<td>1 CS</td>
<td>+/-</td>
<td>-</td>
</tr>
<tr>
<td>2 CS</td>
<td>++/+</td>
<td>-</td>
</tr>
<tr>
<td>3 CS</td>
<td>+++/+</td>
<td>-</td>
</tr>
<tr>
<td>4 CS</td>
<td>+/-</td>
<td>+/-</td>
</tr>
<tr>
<td>5 CS</td>
<td>+/-</td>
<td>+/-</td>
</tr>
<tr>
<td>6 CS</td>
<td>+/-</td>
<td>+/-</td>
</tr>
<tr>
<td>7 CS</td>
<td>++/-</td>
<td>++/+</td>
</tr>
<tr>
<td>8 CS</td>
<td>++/-</td>
<td>-</td>
</tr>
<tr>
<td>9 GCM</td>
<td>+++/+</td>
<td>-</td>
</tr>
<tr>
<td>10 GCM</td>
<td>++/(+)</td>
<td>-</td>
</tr>
<tr>
<td>11 GCM</td>
<td>++/(+)</td>
<td>-</td>
</tr>
</tbody>
</table>

+/- means that examination was done once, ++/+ twice and +++/ three times. 
/+ means positive, /(+) suspected and /- negative finding. 
+ means the presence of symptom or sign, - the absence. 
* Multifocal LGE, affecting several myocardial layers and not confined to coronary artery perfusion territories, was considered as suggestive of severe inflammation (suspected CS or GCM finding). 
† Active inflammation in heart was defined as focal FDG uptake with perfusion defect and in mediastinal lymphatic node as FDG uptake. 
‡ Nonsustained ventricular tachycardia. 
§ Although not having multifocal LGE, this patient had LGE of 4% of left ventricular muscle volume located in basal and mid septum, along with septal wall motion abnormality. Also, PET showed septal and lateral nonhomogenous FDG uptake in heart, not clearly focal, without perfusion defect. 
|| Also finding suggestive of oedema in T2-weighted images. 
Abbreviations: AVB = atrioventricular block, CHF = congestive heart failure, CS = cardiac sarcoidosis, CMR = cardiovascular magnetic resonance, FDG = fluorodeoxyglucose, GCM = giant cell myocarditis, LGE = late gadolinium enhancement, PET = positron emission tomography, VF = ventricular fibrillation, VT = ventricular tachycardia. 
Reproduced with permission from Taylor & Francis (II).
## Results

Table 5. Imaging characteristics of cardiac sarcoidosis (CS) or giant cell myocarditis (GCM) versus others.

<table>
<thead>
<tr>
<th></th>
<th>All patients (n=86)</th>
<th>CS or GCM Yes (n=11)</th>
<th>CS or GCM No (n=75)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Echocardiography</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVEDD, mm</td>
<td>55 (48-61)</td>
<td>56 (51-61)</td>
<td>54 (47-62)</td>
<td>0.609</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>50 (31-62)</td>
<td>43 (26-54)</td>
<td>52 (34-63)</td>
<td>0.234</td>
</tr>
<tr>
<td>Regional wall motion abnormality</td>
<td>30 (35)</td>
<td>4 (36)</td>
<td>26 (35)</td>
<td>1.000</td>
</tr>
<tr>
<td>Septal abnormality*</td>
<td>37 (43)</td>
<td>8 (73)</td>
<td>29 (39)</td>
<td>0.049</td>
</tr>
<tr>
<td>Thinning of basal septum</td>
<td>2 (2)</td>
<td>1 (9)</td>
<td>1 (1)</td>
<td>0.241</td>
</tr>
<tr>
<td>Increased LV wall thickness†</td>
<td>32 (37)</td>
<td>5 (45)</td>
<td>27 (36)</td>
<td>0.740</td>
</tr>
<tr>
<td><strong>CMR</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVEDV, ml/m²</td>
<td>78 (64-110)</td>
<td>77 (65-92)</td>
<td>80 (63-111)</td>
<td>0.766</td>
</tr>
<tr>
<td>LVESV, ml/m²</td>
<td>36 (25-69)</td>
<td>45 (30-68)</td>
<td>35 (25-70)</td>
<td>0.477</td>
</tr>
<tr>
<td>Stroke volume, ml</td>
<td>73 (58-85)</td>
<td>62 (53-69)</td>
<td>75 (60-88)</td>
<td>0.020</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>52 (35-61)</td>
<td>43 (29-54)</td>
<td>55 (36-64)</td>
<td>0.089</td>
</tr>
<tr>
<td>LGE presence</td>
<td>61 (71)</td>
<td>11 (100)</td>
<td>50 (67)</td>
<td>0.029</td>
</tr>
<tr>
<td>LGE extent, score</td>
<td>5 (0-17)</td>
<td>25 (17-30)</td>
<td>4 (0-11)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LGE extent, % of LV muscle volume</td>
<td>7 (0-25)</td>
<td>37 (25-44)</td>
<td>6 (0-16)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LGE extent, % of septal LV</td>
<td>15 (0-35)</td>
<td>55 (35-65)</td>
<td>10 (0-25)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LGE extent, % of basal LV</td>
<td>8 (0-25)</td>
<td>54 (29-71)</td>
<td>8 (0-17)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Multifocal LGE‡</td>
<td>22 (26)</td>
<td>10 (91)</td>
<td>12 (16)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

| **18F-FDG-PET§**       |                     |                      |                     |         |
| Heart and lymph node   | 3 (14)              | 3 (38)               | 0 (0)               |         |
| Heart only             | 3 (14)              | 3 (38)               | 0 (0)               |         |
| Lymph node only        | 1 (5)               | 1 (13)               | 0 (0)               |         |
| None                   | 14 (67)             | 1 (13)               | 13 (100)            |         |

Values are median (interquartile range) or n (%).

* Diameter, motion or brightness.
† Unexplained increase, excluded symmetric hypertrophy related to hypertension.
‡ Multifocal LGE, affecting several myocardial layers and not confined to coronary artery perfusion territories, was considered as suggestive of severe cardiac inflammation (suspected CS or GCM finding).
§ Only 21 patients underwent 18F-FDG-PET. Active inflammation in heart was defined as focal FDG uptake with perfusion defect and in mediastinal lymph node as FDG uptake.

**Abbreviations:** CMR = cardiovascular magnetic resonance, CS = cardiac sarcoidosis, GCM = giant cell myocarditis, FDG = fluorodeoxyglucose, LGE = late gadolinium enhancement, LVEDD = left ventricle end-diastolic diameter, LVEDV = left ventricle end-diastolic volume, LVEF = left ventricular ejection fraction, LVESV = left ventricle end-systolic volume, PET = positron emission tomography.

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Table 6. Logistic regression analysis; significant predictors of cardiac sarcoidosis (CS) or giant cell myocarditis (GCM).

<table>
<thead>
<tr>
<th>Predictors</th>
<th>Univariate analysis OR (95% CI)</th>
<th>p-value</th>
<th>Multivariate analysis OR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical and ECG</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Palpitation</td>
<td>5.0 (1.2-20.6)</td>
<td>0.025</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptoms &lt; 3 months</td>
<td>9.7 (1.2-80.0)</td>
<td>0.034</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ventricular fibrillation or tachycardia</td>
<td>5.0 (1.2-20.6)</td>
<td>0.025</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ventricular tachycardia</td>
<td>5.5 (1.5-21.1)</td>
<td>0.012</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sustained VT</td>
<td>14.8 (3.1-70.2)</td>
<td>0.001</td>
<td>20.8 (3.5-123.8)</td>
<td>0.001</td>
</tr>
<tr>
<td>AVB of any degree</td>
<td>6.8 (1.4-33.4)</td>
<td>0.019</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Echocardiography</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Septal abnormality†</td>
<td>4.2 (1.0-17.3)</td>
<td>0.044</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CMR</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke volume, ml</td>
<td>0.957 (0.920-0.994)</td>
<td>0.025</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LGE presence‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LGE extent, % of LV</td>
<td>1.048 (1.019-1.078)</td>
<td>0.001</td>
<td>1.056 (1.022-1.091)</td>
<td>0.001</td>
</tr>
<tr>
<td>Multifocal LGE§</td>
<td>52.5 (6.1-449.1)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Including two of the most significant univariant variables which were not significantly correlated.
† Diameter, motion or brightness.
‡ OR could not be calculated, since all the patients with CS or GCM had LGE.
§ Multi-focal LGE, affecting several myocardial layers and not confined to coronary artery perfusion territories, was considered as suggestive of severe cardiac inflammation (suspected CS or GCM finding).

Abbreviations: AVB = atrioventricular block, CI = confidence interval, CMR = cardiovascular magnetic resonance, CS = cardiac sarcoidosis, ECG = electrocardiografía, GCM = giant cell myocarditis, LGE = late gadolinium enhancement, LV = left ventricular, OR = odds ratio, VT = ventricular tachycardia.

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5.3 CMR FINDINGS IN PRKAG2 (III)

Six individuals in two separate families were examined with CMR (Figure 11). Altogether six had a PRKAG2 mutation: five R302Q mutations in family 1 and one novel H344P mutation in family 2. One 19-year-old male did not have a PRKAG2 mutation. The median age of the six mutation carriers was 23 years (range 16 – 48 years) and the median BSA 1.76 m² (range 1.33 – 1.88 m²). Two of mutation carriers were females. All mutation carriers completed otherwise full CMR imaging protocol, but one patient lacked T1 and T2 mapping.

Clinical phenotypes of examined family members are presented in Figure 11. Based on hospital records, no other risk factors for LVH such as hypertension or chronic kidney disease were detected.

5.3.1 VENTRICULAR VOLUMES, FUNCTION AND HYPERTROPHY

All six PRKAG2 mutation carriers presented with normal age, gender and BSA standardized LV and RV end-diastolic volume (EDV), stroke volume and EF.

Nevertheless, three of six had LV mass above age and gender limits. In family 1, two R302Q mutation carriers (aged 23 and 48 years) had markedly elevated LV mass (203 g/m² [z-score 18.8] and 157 g/m² [9.6]) (Figure 12) and three (aged 16, 24 and 26 years) normal LV masses (Figure 13). In family 2, the 17-year-old female with an H344P mutation had also increased LV mass (68 g/m² [2.2]).

All mutation carriers had LVH, defined as wall thickness > 2 z-scores in one or more LV myocardial segments. The median maximal wall thickness was 13 mm (range 11 – 37 mm), with the corresponding z-score 3.2 (range 2.3 – 19.0). Segmental distribution of LVH had two different patterns (Figure 14). Two symptomatic R302Q mutation carriers (aged 48 and 23 years) with markedly elevated LV mass had hypertrophy throughout the myocardium, but predominantly in the interventricular septum (Figure 14A and 14D), with the maximal (based on z-scores) wall thickness of 31 mm (z-score 11.8) and 37 mm (19.0) in the mid-anteroseptal segment. Other mutation carriers with normal or only mildly increased LV mass (three R302Q carriers: aged 26, 24 and 16 years; one H344P carrier: aged 17 years) presented with LVH in a non-symmetric pattern with the maximal wall thickness located in mid-inferolateral or mid-inferior segments (Figure 14B, 14C, 14E and 14F).

The median RV free wall thickness of all mutation carriers was 5 mm (range 2 – 6 mm).
5.3.2 T1 AND T2 MAPPING
In family 1, the mutation negative male (19 years old) had a mean mid-LV T1 relaxation time of 963 ms. Three male siblings (aged 26, 24 and 16 years) with the R302Q mutation, asymmetric LVH and without LGE, had a mean T1 value of 918 ± 11 ms. The oldest male in the family (48 years) with the R302Q mutation, extensive LVH and LGE, had a mean T1 value of 973 ms (mid-anteroseptal, -anterior and -anterolateral segments excluded due to artifact caused by pacemaker), while corresponding segments had a mean LGE volume of 8%.

In family 2, the female H344P mutation carrier (17 years) with asymmetric LVH and without LGE, had a mean T1 value of 966 ms.

T2-relaxation times were within normal limits in all study individuals.

5.3.3 LGE
Only two of six mutation carriers had left ventricular LGE, with 11% and 22% enhancement of the LV (Figure 12). These patients also presented with severe LVH. The distribution of LGE was patchy and diffuse, but focusing on the most hypertrophic segments. None of the mutation carriers had LGE in the RV.

5.3.4 HISTOLOGY
None of the patients examined with CMR underwent EMB. However, the father in family 2 (H344P carrier) had diffuse cardiac hypertrophy, with maximal LV and RV wall thickness of 31 and 9 mm, intracellular vacuolization with positive periodic acid-Schiff staining indicative of glycogen, and focal fibrosis in the explanted heart. The amount of left and right atrial fat was also increased.
Figure 11. Pedigrees of two families with PRKAG2 cardiomyopathy and clinical phenotypes of patients. Individuals with a PRKAG2 mutation (+) were identified, with R302Q substitution in family 1 (A) and H344P substitution in family 2 (B). Squares indicate males and circles females. Filled symbols indicate disease phenotype in affected individuals, i.e. cardiac hypertrophy (left half filled), pre-excitation (right upper quadrant filled), or conduction system disease (right lower quadrant filled). Open symbols denote unaffected individuals and shading uncertain clinical status. Arrows indicate index patients. Reproduced with permission from BioMed Central (III).
Figure 12. A 48-year-old male patient with PRKAG2 cardiomyopathy and a pacemaker. In short-axis and four chamber cine images septum is severely hypertrophied (A-B) (black arrows). Maximal septal and lateral wall thickness was 31 mm and 25 mm, respectively. Papillary muscles were excluded in the measurements. Anteroseptal, hypertrophic areas exhibit patchy late gadolinium enhancement (C-D) (white arrows). White arrow heads indicate artefact from pacemaker lead. Reproduced with permission from BioMed Central (III).
Results

Figure 13. A 16-year-old male patient with a PRKAG2 mutation. In short-axis and four-chamber cine images (A-B) inferolateral left ventricular wall is mildly hypertrophied (10 – 11 mm, maximal z-score 2.3) (white arrow), no late gadolinium enhancement is present (C-D). Reproduced with permission from BioMed Central (III).

Figure 14. (see figure on next page) Distribution of left ventricular hypertrophy of six PRKAG2 mutation carriers. Upper and lower values represent absolute (mm) and standardized (z-score) maximal wall thickness in the segment using adult references. Gray scaling of each segment is based on z-score. Members of family 1 with an R302Q mutation: I:1 (A), II:1 (B), II:2 (C), II:3 (D) and II:4 (E). A member of family 2 with an H344P-mutation: II:1 (F). The 16-year-old male (E), with body-surface-area (BSA) of 1.33 m², had hypertrophy in mid-infero-lateral segment (posterior free wall) of 10 mm (z-score 2.3) using the BSA-standardized echocardiography based reference values for children. Reproduced with permission from BioMed Central (III).
5.4 INFARCT SIZE AND LEFT VENTRICULAR REMODELING (IV)

A total of 85 patients were enrolled in the ISKE project. Derivation of the patients (n=41) who participated in the CMR study cohort with the first revascularized MI and two sequential CMRs is presented in Figure 15. The median peak CK-MB was 86 μg/L (range 5 – 736 μg/L, IQR 40 – 216 μg/L) (Table 7). Altogether 59% of the patients presented with an anterior infarct and half (47%) had a multiple vessel disease in coronary angiography. Most of the patients (n=35, 85%) were treated with PCI, four (10%) with CABG and 2 (5%) with thrombolysis only.

5.4.1 RECOVERY PHASE

The first CMR imaging, i.e. recovery phase CMR study, was performed in a median of 22 (9 – 29) days after hospital admission. Median scar size was 13% (range 0 – 42%, IQR 3 – 23%) of the total LV muscle volume. Six (15%) patients with minor infarcts, peak CK-MB ranging from 19 to 39 μg/L, had no visible scar at CMR. On the contrary, two patients with only small scars (2% and 5%) had normal peak CK-MB (5 and 7 μg/L). Of 41 patients, 33 (81%) had a non-transmural MI with a median peak CK-MB of 66 (30 – 146) μg/L, while eight patients with a transmural MI had a median peak CK-MB of 261 (209 – 557) μg/L.

In the whole study cohort (n =41), peak CK-MB had a strong correlation with recovery phase scar size (r = 0.80, p < 0.001) (Figure 16A), moderate correlation with end-systolic volume (ESV), LVEF and WMAi, and weak correlation with end-diastolic volume (EDV) (Table 8). The association between peak CK-MB and LV mass showed only a trend (r = 0.285, p = 0.071). There were similar correlations in the subgroup of non-transmural MIs (Table 8).

5.4.2 CHRONIC PHASE

The second CMR imaging, i.e. chronic phase CMR study, was performed in a median of 10 (8 – 16) months after hospital admission.

Peak CK-MB had a strong correlation with chronic scar size (r = 0.83, p < 0.001) (Figure 16B) and chronic WMAi (r = 0.75, p < 0.001) (Table 8), moderate correlation with chronic ESV and LVEF, showed a trend toward association with EDV, but was not correlated with chronic LV mass (r = 0.22, p = 0.175). Again, similar correlations were found in the subgroup of non-transmural MIs, although weaker with ESV and LVEF (Table 8).

Along with peak CK-MB, both recovery and chronic phase scar size had a strong correlation with chronic WMAi (r ≥ 0.80, p < 0.001 for both) (Figure 17), and similar strong correlations were found in patients with non-transmural MI.
Peak CK-MB, recovery phase scar size, EDV, ESV, LVEF, LV mass and WMAi, were all univariate predictors of chronic phase LVEF. By multivariate regression (stepwise forward method), the significant adjusted predictors of chronic phase EF were recovery LVEF (Beta = 0.595, p < 0.001) and peak CK-MB (Beta = -0.312, p = 0.012).

5.4.3 LATE REMODELING

Late remodeling, i.e. the change in LV volumetry, scar size, WMA or global LVEF between CMRs, was evaluated. There were no changes in median LV volumes or LVEFs, but there was a significant reduction in median scar size (13 vs. 8 %, p = 0.001), LV mass (78 g/m² vs. 72 g/m², p = 0.001), and WMAi (6 vs. 5, p < 0.001) between CMRs (Table 9).

Neither peak CK-MB, nor recovery scar size, were associated with the change in LV mass or WMAi between CMRs. All continuous baseline and recovery phase CMR variables were tested for the association with late remodeling parameters. The only significant correlation was found between age and LV mass change (r = 0.47, p = 0.002), meaning that younger age was associated with greater LV mass resorption between recovery and chronic phase (Figure 16D). The median proportional LV mass resorption was 6% (from 2% increase to 14% reduction), while younger half of the patients (< 60 years) experienced median LV mass resorption of 9% (6 – 17%) compared to 1% (1% increase to 10% resorption) in older patients (p = 0.007).

Considering those 35 patients who had visible scar at CMR, the median absolute and proportional scar size resorption between CMRs was 3% (0 – 8%) and 26% (0 – 50%), respectively. Recovery phase scar size had a negative correlation with absolute scar size change (r = -0.59, p < 0.001) (Figure 16C), i.e. large MIs had greater absolute scar resorption. However, there was no association between scar size and proportional scar size resorption.

5.4.4 LONG-TERM SURVIVAL

During a median follow-up of 7.7 (4.1 – 8.5) years, altogether nine (21%) patients reached a MACE. These events consisted of one cardiovascular death, one aborted sudden death, two heart failure hospitalizations and five recurrent MIs. In univariate Cox regression analysis of all baseline variables, recovery and chronic phase CMR indices, and late remodeling variables, the only significant predictor of MACEs was chronic phase WMAi (hazard ratio [HR] 1.15, 95% confidence interval [CI] 1.01 – 1.31, p = 0.038). In addition, the presence of multiple vessel disease (HR 4.6, 95% CI 0.9 – 22.3, p = 0.060), increase in EDV (HR = 1.04, 95% CI 1.00 – 1.08, p = 0.051) and in WMAi (HR = 1.23, 95% CI 0.98 – 1.55, p = 0.068) between CMRs, showed a trend in predicting adverse outcome.
Results

Figure 15. Study flow chart (A). Abbreviations: CMR cardiovascular magnetic resonance, MI myocardial infarction, UAP unstable angina pectoris, MACE major adverse cardiac event. Reproduced with permission from BioMed Central (IV).
Table 7. Baseline characteristics (n=41).

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
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<td></td>
</tr>
<tr>
<td>Age, year</td>
<td></td>
<td>60 (50-67)</td>
</tr>
<tr>
<td>Gender, male</td>
<td></td>
<td>34 (83)</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td></td>
<td>27 (24-30)</td>
</tr>
<tr>
<td><strong>Cardiovascular risk factors</strong></td>
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<td></td>
</tr>
<tr>
<td>Dyslipidemia</td>
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<td>35 (85)</td>
</tr>
<tr>
<td>Hypertension</td>
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<td>14 (34)</td>
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<tr>
<td>Diabetes</td>
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<td>8 (20)</td>
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<td>Smoking</td>
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<td>16 (39)</td>
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<td>Family risk for coronary artery disease</td>
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<td>25 (61)</td>
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<tr>
<td><strong>ST-elevation myocardial infarction</strong></td>
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<td>33 (81)</td>
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<td><strong>Culprit coronary artery</strong></td>
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<tr>
<td>Left anterior descending (or left main)</td>
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<td>24 (59)</td>
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<tr>
<td>Circumflex artery</td>
<td></td>
<td>5 (12)</td>
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<tr>
<td>Right coronary</td>
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<td>12 (29)</td>
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<td><strong>Multiple vessel disease</strong></td>
<td></td>
<td>19 (46)</td>
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<tr>
<td><strong>Anterior infarct</strong></td>
<td></td>
<td>24 (59)</td>
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<tr>
<td><strong>Method of reperfusion</strong></td>
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<td></td>
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<tr>
<td>Thrombolysis</td>
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<td>2 (5)</td>
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<tr>
<td>Primary percutaneous coronary intervention</td>
<td></td>
<td>35 (85)</td>
</tr>
<tr>
<td>Coronary artery bypass grafting</td>
<td></td>
<td>4 (10)</td>
</tr>
<tr>
<td><strong>Peak CK-MB (μg/L)</strong></td>
<td></td>
<td>86 (40-216)</td>
</tr>
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<td><strong>Discharge medication</strong></td>
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<tr>
<td>Aspirin</td>
<td></td>
<td>38 (93)</td>
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<tr>
<td>Clopidogrel</td>
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<td>37 (90)</td>
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<tr>
<td>Beta blocker</td>
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<td>40 (98)</td>
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<tr>
<td>ACE-inhibitor/AT2-blocker</td>
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<td>26 (63)</td>
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<tr>
<td>Statin</td>
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<td>40 (98)</td>
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<td>Nitrate</td>
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<tr>
<td>Warfarin</td>
<td></td>
<td>2 (5)</td>
</tr>
</tbody>
</table>

Values are median (interquartile range) or n (%). 
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### Table 8. Correlation between peak CK-MB and scar size, left ventricular volumes, ejection fraction (EF) and wall motion abnormality index (WMAi) at recovery and chronic phase after myocardial infarction.

<table>
<thead>
<tr>
<th></th>
<th>Recovery phase CMR (correlation to peak CK-MB)</th>
<th>Chronic phase CMR (correlation to peak CK-MB)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All (n=41)</td>
<td>Non-transmural MI (n=33)</td>
</tr>
<tr>
<td>Scar size, %</td>
<td>0.80</td>
<td>0.74</td>
</tr>
<tr>
<td></td>
<td>(p &lt; 0.001)</td>
<td>(p &lt; 0.001)</td>
</tr>
<tr>
<td></td>
<td>0.49</td>
<td>0.47</td>
</tr>
<tr>
<td></td>
<td>(p = 0.001)</td>
<td>(p = 0.001)</td>
</tr>
<tr>
<td>EDV, ml/m²</td>
<td>0.66</td>
<td>0.56</td>
</tr>
<tr>
<td></td>
<td>(p &lt; 0.001)</td>
<td>(p &lt; 0.001)</td>
</tr>
<tr>
<td></td>
<td>-0.64</td>
<td>-0.52</td>
</tr>
<tr>
<td></td>
<td>(p &lt; 0.001)</td>
<td>(p &lt; 0.001)</td>
</tr>
<tr>
<td>EF, %</td>
<td>0.69</td>
<td>0.60</td>
</tr>
<tr>
<td></td>
<td>(p &lt; 0.001)</td>
<td>(p &lt; 0.001)</td>
</tr>
<tr>
<td>WMAi, score</td>
<td>6 (3 - 12)</td>
<td>5 (1 - 9)</td>
</tr>
<tr>
<td></td>
<td>(p &lt; 0.001)</td>
<td>(p &lt; 0.001)</td>
</tr>
</tbody>
</table>

Values are Spearman correlation coefficients (p-value)

**Abbreviations:** CMR cardiovascular magnetic resonance, EDV end-diastolic volume, EF ejection fraction, ESV end-systolic volume, WMAi wall motion abnormality index.

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### Table 9. Left ventricular remodeling: comparison of CMR indices (n = 41).

<table>
<thead>
<tr>
<th></th>
<th>Recovery phase</th>
<th>Chronic phase</th>
<th>p-value</th>
</tr>
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<tbody>
<tr>
<td>LV end-diastolic volume, ml/m²</td>
<td>79 (61 - 90)</td>
<td>70 (65 - 82)</td>
<td>0.115</td>
</tr>
<tr>
<td>LV end-systolic volume, ml/m²</td>
<td>39 (28 - 48)</td>
<td>36 (28 - 43)</td>
<td>0.197</td>
</tr>
<tr>
<td>Stroke volume, ml/m²</td>
<td>38 (33 - 44)</td>
<td>37 (31 - 42)</td>
<td>0.138</td>
</tr>
<tr>
<td>LV ejection fraction, %</td>
<td>52 (45 - 57)</td>
<td>51 (45 - 56)</td>
<td>0.791</td>
</tr>
<tr>
<td>LV mass, g/m²</td>
<td>78 (69- 84)</td>
<td>72 (61 - 82)</td>
<td>0.001</td>
</tr>
<tr>
<td>WMAi, score</td>
<td>6 (3 - 12)</td>
<td>5 (1 - 9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Scar size, % of LV</td>
<td>13 (3 - 23)</td>
<td>8 (2 - 19)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Values are median (interquartile range).

**Abbreviations:** CMR cardiovascular magnetic resonance, LV left ventricular, WMAi wall motion abnormality index. Reproduced with permission from BioMed Central (IV).
**Figure 16.** Correlation of peak CK-MB with recovery (A) and chronic (B) scar size at cardiovascular magnetic resonance (n = 41). Correlation of recovery scar size with scar size change between CMRs (C); only patients with visible scar (n = 35) included. Correlation of age with left ventricular (LV) mass change between CMRs (D) (n = 41). Reproduced with permission from BioMed Central (IV).

**Figure 17.** Correlation of peak CK-MB (A, B), recovery scar size (C, D) and chronic scar size (E, F) with chronic ejection fraction (EF) and wall motion abnormality index (WMAi) (n = 41). Reproduced with permission from BioMed Central (IV).
DISCUSSION

The aim of this thesis was to evaluate whether myocardial tissue characterization with CMR methods, such as late gadolinium enhancement imaging, parametric mapping, or local wall motion abnormality index, would improve the diagnosis and risk stratification of myocardial diseases. Studies I-III focused on NICMs and study IV on ischemic heart disease.

6.1 PROGNOSTIC VALUE OF LGE AND WMAI IN NICM (I)

The first study demonstrates that in suspected NICM, the extent of left ventricular LGE predicts adverse cardiac outcome independently of traditional risk factors. The risk of reaching a MACE during follow-up increased 2.7% for every 1% increase in LGE volume, independently of sustained VT and LVEF. In our patients, the highest event rate was observed with LGE volume of ≥ 17%, resulting in a cumulative event ratio of up to 43% after three years.

Earlier, LGE has been shown to carry prognostic value in several specific disease entities of NICM. In DCM, LGE, representing typically mid-wall replacement fibrosis, has provided independent and incremental prognostic information [110,111,113]. In HCM, the presence and extent of LGE has been associated with adverse outcome [114,149,150], and extensive LGE has provided additional prognostic information of sudden cardiac death, especially in those patients otherwise at low risk [151]. In biopsy-proven viral myocarditis, the presence of LGE has been shown to be the strongest independent predictor of mortality compared to traditional cardiac risk factors [117]. In suspected CS, the presence of LGE has been the best adjusted predictor of adverse cardiac outcome [124]. In histologically verified CS, the extent of LGE has independently predicted serious cardiac events [152]. According to ESC guidelines for the management of ventricular arrhythmias, demonstration of fibrosis by LGE after acute myocarditis may be considered as an additional risk factor of sudden cardiac death in inflammatory heart disease [153]. Also, in suspected cardiac amyloidosis, a characteristic circumferential endomyocardial LGE has been shown to be a stronger predictor of mortality than other noninvasive parameters [115]. In advanced cardiac amyloidosis, LGE may progress to transmural, having the worst prognosis [154].

Ideally, LGE should be interpreted in the context of the specific disease, since the etiology of NICM itself has prognostic value. However, reaching the specific diagnosis is often a time-consuming process and remains unclear even after CMR. There has been limited information on the prognostic value
of LGE in suspected or newly diagnosed NICM, and whether the quantification of LGE provides additional prognostic information. In an earlier study of newly diagnosed NICM, the presence of LGE was associated with worse prognosis, but only traditional risk markers, such as LV performance and cardiac biomarkers, were independently associated with adverse outcome [155].

Our study adds to previous studies, that even though the final diagnosis or etiology is uncertain in NICM, extensive amount of LGE, along with its presence, should be considered as a sign of poor prognosis and activate more intensive diagnostics and surveillance.

The histological basis for LGE was probably heterogenic in this study, including replacement fibrosis, necrosis, oedema or amyloid infiltration. Our study included 23 (27%) of patients with inflammatory cardiomyopathy. It has been shown that patients with inflammatory cardiomyopathy may have wide-spread amounts of less intense LGE compared to patients with MI [93]. In our patients, the optimal cut-off value for LGE extent for event prediction during follow-up was a volume of ≥ 17%. This is considerably higher compared to a cohort study of patients with DCM, where the optimal cut-off value of LGE volume was 6.1% for event prediction[112]. This demonstrates the importance of taking into account the reference patient population, while interpreting cut-off values. After the etiology of NICM is diagnosed, LGE should be interpreted in that context.

In this study, up to 65% of patients had WMA, and WMAi predicted MACEs during follow-up (1 point increase in WMAi was associated with 6.7% increase in risk). Nevertheless, this association was not independent of traditional prognostic factors such as LVEF. WMAi and LVEF have strong interrelation, since they both represent global LV function [89]. However, the absence WMA was a strong predictor of good prognosis with no cardiac events during follow-up. WMAi may also provide prognostic information beyond preserved LVEF (≥ 50%), since in this subgroup patients with WMA were still at risk for cardiac events, although data was small.

### 6.2 DETECTION OF CS OR GCM (II)

In the second study we found that both sustained VT and the volume of left ventricular LGE are associated with the diagnosis of CS or GCM in suspected NICM. The adjusted ORs to predict CS or GCM were 20.8 (p = 0.001) for sustained VT and 1.06 (p = 0.001) for each 1% increase in LGE volume, respectively. Particularly, multifocal distribution of LGE, affecting several myocardial layers and not confined to coronary artery perfusion territories, was useful in detection of CS or GCM. Multifocal LGE predicted CS or GCM with 52-fold unadjusted OR (p < 0.001), sensitivity of 91%, and specificity of 86%.
Prognosis in CS or GCM may significantly improve with proper immunosuppressive therapy, which emphasizes the importance of early diagnosis. In the past study, the median transplantation-free survival was only 5.5 months from symptom onset in GCM [5]. However, more recently, in 26 patients with GCM managed with combined immunosuppression including cyclosporine, the estimated 5-year transplantation-free survival was 52% [46]. In a study of 42 patients with CS and 73 patients with GCM, the 5-year transplantation-free survivals were 69.8% and 21.9%, respectively [38]. The prognosis in CS seems to be better than in GCM, and may be improved with corticosteroids in CS [42,43] and with combined immunosuppressive therapy in GCM [5,46].

In this study, patients with CS or GCM had extensive amounts of LGE compared to others. In CS, the histological basis of LGE is inflammation, granuloma formation, and consequent fibrosis, seen in autopsy [156]. In GCM, the histological basis of LGE is on acute myocyte necrosis, replacement fibrosis and oedema related to severe cardiac inflammation [45].

In accordance with our study, LGE has been shown to be sensitive in detecting CS [118], with more than two-fold sensitivity compared to traditional clinical criteria [58]. LGE may also visualize boundaries between granulomas and normal myocardium [144]. The distribution of LGE is typically patchy and multifocal in CS, affecting several myocardial layers, with often both ventricle involvement, and most commonly located in the basal septal and lateral free wall of the LV [118-122]. LGE frequently affects the subepicardial layer with band-shaped and wide-spread pattern [144]. Sometimes, CS may have only focal presentation in the myocardium [156], but the amount of LGE has been shown to correlate with the duration of extra-cardiac sarcoidosis [144].

Considering GCM, there is very limited data on visualizing myocardial changes by LGE, probably due to the rarity the disease or hemodynamic instability of patients [43]. However, in a small study of histologically proven GCM, all patients had widespread and multifocal LGE in all layers of the myocardium, not restricted to coronary artery perfusion territories [145].

Thus, our finding that the presence of multifocal LGE was a strong predictor of severe cardiac inflammation supports and builds on the recent studies of patients with CS [122,144] or GCM [145]. Furthermore, the septal and basal wall dominance in LGE distribution in our patients is similar with previous studies in CS [118,119].

Other unadjusted predictors of CS or GCM in our study were palpitation, septal abnormality in echocardiography, reduced stroke volume on CMR, atrioventricular block of any degree, and a disease course less than three months. These findings support earlier studies. According to a systematic review, CS typically presents with conducting disorders (26 – 60% of patients), VT (2 – 42%), heart failure (24 – 68%) and palpitations (17 – 32%), while the typical presentation of GCM includes heart failure (75%), VT (14 – 29%), conducting disorders (15%) and chest pain (19%) [43].
In this study, 18F-FDG-PET was useful in finding mediastinal lymph node biopsy targets to detect CS, in cases of negative or only suggestive EMB. Specifically, in four cases of CS, PET showed inflammation in mediastinal lymph nodes and targeted them for biopsy. In a meta-analysis, PET had high diagnostic accuracy with 89% sensitivity and 78% specificity in detection of CS [62]. There is very limited data on PET in diagnosing GCM.

The diagnostic yield of 13% patients with CS or GCM is surprisingly high in our cohort, considering the known rarity of CS and GCM [5,6,29,44]. In our clinical practice, CMR and PET findings, suggestive of severe cardiac inflammation, justified repeated invasive biopsies. Altogether, 48% of patients underwent at least one diagnostic EMB, 11 patients repeated diagnostic EMBs, and 4 patients mediastinal lymph node biopsies. Furthermore, in the majority of patients (76%), the location of LGE on CMR was used to direct the biopsy towards the abnormal myocardial region, which in some studies has been shown to possibly increase the sensitivity of EMB [116,157].

6.3 CMR FINDINGS IN PRKAG2 (III)

In the third study, we were the first to describe the comprehensive CMR findings of six individuals with PRKAG2 mutation, which is known to cause a unique defect of the cardiac cell metabolism and intracellular glycogen deposition. We found that PRKAG2 cardiomyopathy may present with eccentric distribution of LVH. Three of six mutation carriers had LV mass above age and gender limits and others normal LV masses. However, all mutation carriers had LVH in at least one myocardial segment. Two patients with markedly increased LV mass showed a diffuse pattern of hypertrophy but predominantly in the interventricular septum, while other mutation carriers with normal or only mildly increased LV mass exhibited a non-symmetric mid-infero-lateral pattern of hypertrophy. T1 relaxation times were lowest in patients with the R302Q mutation, LVH and no LGE. Two patients with the PRKAG2 mutation and advanced disease had intramyocardial, patchy LGE in hypertrophic segments.

Marked LVH in PRKAG2 cardiomyopathy has been previously demonstrated by echocardiography [27,158]. In the series of 45 PRKAG2 mutation carriers, altogether 78% had LVH on echocardiography, with a mean wall thickness of 21 mm (range 13 – 45 mm) and varying pattern of hypertrophy, 46% having concentric, 29% asymmetric, and one distal hypertrophy, with often eccentric distributions [10].

Our study demonstrates that CMR based analysis of wall thickness revealed abnormal hypertrophy in all PRKAG2 mutation carriers, even in those subjects with normal LV mass. The finding of both diffuse and non-symmetric distribution of LVH in the same family (R302Q) may be explained by the different age of disease onset and generally progressive nature of
hypertrophy in PRKAG2 cardiomyopathy \[10\]. That is, PRKAG2 cardiac syndrome may express in the early stage with focal and mild LVH, and may later change to diffuse disease. Another explanation could be, that there are different patterns of hypertrophy even in the same family with the same mutation.

Our study is the first one to describe the behaviour of T1 or T2 relaxation times in a glycogen storage cardiomyopathy. In family 1, three males with the R302Q mutation, LVH and no LGE, presented with a lower mean mid-LV T1 value (918 ± 11 ms) compared to mutation negative male (963 ms) of their age and the mutation positive male with marked LVH and LGE (973 ms). This is consistent with the hypothesized T1 reduction by intracellular glycogen in the absence of significant fibrosis. Theoretically, macromolecular intracellular glycogen with hydrophilic bonding with water could reduce T1-relaxation time, as shown \textit{in vitro} \[159,160\]. Possible lipid accumulation, as demonstrated in a case report of end-stage PRKAG2, might also potent the shortening of T1 value \[49\]. Furthermore, PRKAG2 is distinguished from other cardiomyopathies with LVH by a remarkable absence of myocardial fibrosis \[161\]. On the other hand, in the advanced disease stage T1 relaxation times may be slightly increased and pseudonormalized due to extracellular fibrosis, as seen in Anderson-Fabry disease \[22,135\]. In our patients, T2-relaxation times were within normal limits, which excludes possible iron accumulation in the myocardium and its effect on T1 values \[162,163\].

Our patients with marked LVH and increased LV mass had widespread LGE. This could be explained by sarcolemmal damage in an advanced storage disease stage and subsequent gadolinium retention within intracellular space, as seen in a case report of a patient with large cardiomyocyte vacuoles due to cytosolic accumulation of glycogen in Danon disease\[164\]. Similar mechanism has been suggested to explain LGE in Anderson-Fabry disease with intracellular lipid accumulation \[22\].

\section*{6.4 INFARCT SIZE AND LEFT VENTRICULAR REMODELING (IV)}

The main finding of the fourth study was that peak CK-MB has a strong association with chronic scar size and WMAi after revascularized MI, with similar correlations in patients with non-transmural MIs. Peak CK-MB was also associated with chronic LVEF, independently of recovery phase LVEF. Considerable infarct resorption of one quarter in median happens after the first weeks recovery phase, which is independent of infarct size, and milder reduction of LV mass. LV mass resorption was related to age, being more common in younger patients.

Before the era of acute coronary reperfusion, it was shown that the peak value of CK-MB after acute MI significantly correlates with scar size at autopsy \[165\]. Since that, peak CK-MB has been shown to correlate well with
infarct size also after reperfusion [78,166-168]. However, these studies included mainly patients with large MIs. Our finding of the strong association between peak CK-MB and both recovery and chronic phase scar size after revascularized MI supports previous studies, and adds to current knowledge that the association is valid also in smaller non-transmural infarcts. However, in our patients, CMR missed small infarcts with peak CK-MB ranging from 19 to 39 μg/L, which is in accordance with previous studies by Choi et al. [169] and Hedström et al. [166].

The finding of 26% infarct resorption after the recovery phase supports earlier studies by Pokorney et al. [170], demonstrating 32% decrease in infarct mass from 1 week to 4 months, and 12% decrease between 4 and 14 months, and by Lund et al. [171], showing 26% infarct resorption between 5 days and 8 months, after reperfusion. Similarly as Pokorney et al., we found that proportional infarct resorption is not related to infarct size.

We found that peak CK-MB is correlated with recovery and chronic phase ESV, LVEF and WMAi after revascularized MI, with similar correlations in non-transmural MIs. Earlier, infarct size has been established as a strong predictor of LV dysfunction [14,72]. In a recent study of large reperfused STEMI (median peak CK-MB 240 IU/L), CK-MB correlated with one-month-follow-up LVEF at CMR [168], while in another study of large reperfused MI, CK-MB, troponin T, and troponin I were all associated with LVEF at one month SPECT [78]. However, it has been presented that LV remodeling rarely occurs with infarct size less than 18.5% of the LV muscle volume [76]. Lund et al. suggested that infarct size of 24% or more would be an important predictor of remodeling between acute and chronic phase [171]. Patients in our study had mainly non-transmural MIs, with a median peak CK-MB of 86 μg/L and scar size of 13% at one month CMR. That is, we showed that also after smaller non-transmural MIs, peak CK-MB, as well as recovery and chronic scar size, correlate with chronic global and local LV dysfunction.

There is limited prospective data available on the association between infarct size and chronic local WMAs. Our finding that peak CK-MB, recovery scar size, and chronic scar size, all correlate strongly with chronic WMAi (r ≥ 0.75 for all MIs, r ≥ 0.73 for non-transmural MIs; p < 0.001) supports the results of a recent retrospective analysis in which infarct size correlated with chronic WMAi but the association was more significant in transmural compared to non-transmural MIs [172].

Earlier, large MI has been associated with progressive LV remodeling [72]. In our patients, neither peak CK-MB nor scar size were associated with late remodeling between recovery and chronic phases. This is probably explained by the fact that most had small to intermediate sized MIs and the infarct related remodeling occurred primarily during the first weeks recovery phase. Earlier, it has been suggested that late remodeling would be triggered by factors such as progressive ischemia instead of initial infarct size [73].

The only variable associated with late remodeling in our patients was age; younger half having greater LV mass resorption (median 9% vs. 1%, p =
LVH is a compensatory mechanism after MI, but prolonged progression of hypertrophy is harmful, leading to heart failure. It has been presented that infarct-related remodeling is more pronounced in elderly patients due to inability to cope with myocardial stress[173], which could explain the association between aging heart and milder late LV mass resorption seen in our study.

### 6.5 LIMITATIONS

This thesis is based on four separate studies and certain limitations must be acknowledged.

The first study (I) of the prognostic value of LGE and WMAi in NICM employed a retrospective follow-up study design. The number of patients who eventually reached a MACE during follow-up was limited. However, all endpoints were life-threatening events. The results of the study should not be interpreted in any specific NICM entity due to patient heterogeneity. Nevertheless, suspected NICM reflects the real-life setting in which the need of CMR is considered. Finally, the presented cut-off values for LGE extent represent only our patient sample.

The second study (II), considering the detection of CS or GCM, was based on the same cohort as the first study. The number of patients who eventually reached the diagnosis of CS or GCM was limited due to rarity of the diseases. Moreover, CS and GCM are thought as distinct disease entities [38,43,45], although the histological differentiation remains challenging[174]. However, we pooled CS and GCM together due to their known similarity in symptoms and imaging findings, inflammatory nature, and the possible benefit of early diagnosis and immunosuppressive therapy. Considering LGE, it must be remembered that it is a nonspecific finding representing only increased extracellular space without differentiating between etiologies. Oedema in T2-weighted images is more sensitive in the detection of inflammation [93]. T2-weighted images were included in our imaging protocol but the quality was not optimal and results were not systematically analysed.

In the third study (III), considering CMR findings in PRKAG2, the reference values for LV wall thickness were based on the largest available study (similar software tool, MR scanner and sequence) with a mean age of individuals of 66 ± 9 years, which is considerably higher than our patients (median age 23 years, range 16 - 48). Therefore, both absolute and standardized values of wall thickness were presented, when appropriate. Also, there was considerable probability to obtain abnormal z-scores in some myocardial segments only by chance. To overcome this, we plotted the distribution of z-scores in adjacent segments to study the consistency of values. This study also lacked histological validation of imaging findings, although the histology of the explanted heart of the father in family 2 was presented. Due to small number of patients, we could not study correlations
between age, symptom duration and disease severity, neither did we study the time-related changes in the myocardium. However, according to an earlier study, LVH has a generally progressive nature in PRKAG2 [10], and thus different patterns of hypertrophy in the same family may represent different stages of the disease.

In the fourth study (IV), considering infarct size and LV remodeling, coronary artery patency was not verified after baseline. It must be mentioned that patients were treated with different revascularization strategies, such as thrombolysis, PCI or CABG, and the results cannot be generalized to solely one of these groups. Furthermore, according to a study by Tamaki et al., coronary reperfusion alters the kinetics of CK-MB and results in greater and earlier CK-MB release in the serum with equivalent infarct volume [175]. In our patients, some peak CK-MB values were measured before and some after revascularization, which had influence on peak values and possibly attenuated correlations to remodeling parameters. Finally, follow-up data was collected post-hoc and the number of MACEs was small.

### 6.6 CLINICAL IMPLICATIONS AND FUTURE DIRECTIONS

The results of this thesis may have an impact on the clinical practice.

The findings of the first study (I) suggest that even though the final diagnosis is uncertain in NICM, extensive LGE should be considered as a sign of poor prognosis and activate more intensive diagnostics and surveillance. This may sometimes justify potentially harmful invasive examinations [11]. On contrary, the absence of local WMAs on CMR implies very good prognosis.

The second study (II) suggests that CMR with LGE imaging is useful in differentiation of severe cardiac inflammation, such as CS or GCM, from other forms of NICM. The superior sensitivity of LGE to detect CS versus consensus criteria has been already previously shown [58]. However, our cohort with at least two years follow-up after CMR included unselected consecutive patients with suspected NICM, reflecting the real-life clinical setting. Based on our results, we suggest a prompt CMR-guided cardiac evaluation in a rapidly developed ventricular arrhythmia or recent-onset heart failure.

In future, the results of study I and II should be tested in prospective clinical trials. Combined 18F-FDG-PET and CMR technique also hold major promises for diagnosis and assessment of disease activity of CS [176].

The findings of the third study (III) suggest that multimodal CMR is a valuable tool in detecting diffuse and focal abnormalities in PRKAG2 cardiomyopathy, and may sometimes aid to differentiate it from other causes of LVH, such as hypertension or sarcomeric HCM. In future, these findings should be verified in a larger patient sample.
The results of fourth study (IV) suggests that at the era of increasing imaging modalities, peak CK-MB still provides robust estimation of infarct size and predicts chronic LV function after revascularized MI. In future, these findings should be verified with troponins, which are preferred markers in detection of acute MI according to current guidelines [69].
7 CONCLUSIONS

The present thesis was designed to assess whether advanced CMR methods improve the diagnostic and prognostic evaluation of NICMs (I-III) and ischemic heart disease (IV).

We found that

1. In suspected NICM, presenting with ventricular arrhythmias or heart failure, LGE extent gives additional prognostic information compared to traditional risk factors, while the absence of WMA may give prognostic information beyond normal LVEF. (I)

2. In suspected NICM, LGE volume and sustained VT predict independently CS or GCM. Multifocal LGE is useful in identifying severe cardiac inflammation. (II)

3. PRKAG2 cardiomyopathy may present with eccentric distribution of LVH, involving focal mid-infero-lateral pattern in the early disease stage, and more diffuse pattern focusing on interventricular septum in advanced cases. In patients at earlier stages of disease, T1 values may be reduced, while in the advanced disease stage T1 mapping may result in higher values caused by fibrosis. (III)

4. Peak CK-MB has a strong association with chronic scar size and WMAi after revascularized non-transmural MI. Considerable infarct resorption happens after the first-month recovery phase. LV mass resorption is related to age, being more common in younger patients. (IV)
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Conclusions


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Conclusions


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