

UCL INSTITUTE OF CARDIOVASCULAR SCIENCE



Improving the Access of Cardiac Magnetic Resonance in Low-Middle Income Countries to Improve Cardiac Care: Rapid CMR

PhD Thesis

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Declaration:

I, Katia Devorha Menacho Medina, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this been indicated in the thesis

Name: Katia D. Menacho Medina

Date: 30/06/2021

Updated: 24/11/2021

Dedication:

I dedicate this thesis to my parents, Olga and Julio, for nursing me with love and affection, my sisters, Patricia and Eli, my lovely grandmother Ermelinda and my husband, Alexander, for their dedicated support and partnership for success in my life.

Abstract

Non-communicable diseases— cancer and cardiovascular disease - are the leading causes of death in high-income countries (HICs). Cardiovascular disease, however, is increasing in Low-Middle Income Countries (LMICs) and is the emergent primary cause of mortality. Part of the reason is suboptimal therapies— from primary prevention to more advanced tertiary care. Not only are advanced therapies scarce but advanced diagnostic tests which apply to them are not fully available, and so diagnoses could be inaccurate and treatments poorly targeted.

Within the portfolio and hierarchy of cardiovascular diagnostic testing, Cardiac Magnetic Resonance (CMR) is a crucial diagnostic imaging test that redefines diagnosis and enables targeted therapies, but is expensive with inadequate training and poor availability in LMICs countries. I demonstrated that CMR could be made fast, easy, and cheap – sufficient for delivery in five LMICs countries in three continents. To achieve this, I developed an abbreviated CMR protocol, focused on the core of CMR - volumes, function, and scar imaging (with selected additions like iron quantification), and by embedding the technical quality protocol within clinical care, training, and mentoring, so it proved to have diagnostic utility and change management, as well being a self-sustaining and essential service.

I also used CMR as a research method in LMICs specifically to complement research in areas of a specific need to those countries, exploiting opportunities that were previously unavailable, with one chapter dedicated to evaluating early cardiovascular involvement in treated and non-treated people living with HIV in Peru, and a second chapter of the potential utility of CMR for screening cardiotoxicity and its comparison in precision with other cardiac imaging modalities in the UK, potentially extending the role of rapid CMR in HICs.

Unlike traditional PhDs in medicine, my research involved technology adaptation, transfer, and collaboration. The project was multi-layered with political, social, educational, training, and partnership aspects, along with more traditional aspects such as clinical effectiveness and cost-effectiveness analysis. I showed the use of advanced cardiac imaging in LMICs by breaking down barriers, demonstrating that Rapid CMR can be possible in new clinical environments where much need exists.

Funding: This research was funded by The Peruvian Scientific, Technological Development and Technological Innovation (FONDECYT), to whom I am extremely grateful.

Impact Statement:

Low-Middle Income Countries (LMICs) have the highest cardiovascular mortality and morbidity rates, significantly impacting national healthcare costs. One of the main reasons for this is the inadequate patient access to accurate diagnostic tests and treatment. Other contributing factors include a lack of trained healthcare providers.

CMR plays a crucial role in the assessment of cardiomyopathies, redefining diagnosis and enabling targeted therapies. CMR improves cardiac care when applied correctly, with most data and research coming from High-Income Countries (HICs). However, the adoption of CMR is still limited within LMICs. CMR is often perceived as an expensive, complicated, and slow technique, which can only be delivered by a very limited number of trained professionals.

My PhD started initially in 2016, as I wanted to introduce CMR to my home country, Peru, where there was no public access to CMR in the whole country. Having the support of academic institutions, embassies, scientific councils, and international scientific societies, we created a partnership program, www.rapidcmr.com, aiming to introduce a faster, cheaper, and user-friendly CMR protocol, focusing on the core utility of CMR: cardiac structure, function, and tissue characterization (scar). The research was embedded into an education and training program for LMICs, especially for those who refer the patients and those who deliver CMR.

By the end of my PhD, I was fortunate enough to implement my project as a multicentre prospective study in five LMICs, seven cities, and 11 centres. By using a 22-minute

contrast scan for cardiomyopathies and 10 -12 minutes scan to assess cardiac iron cardiomyopathy, there was a potential reduction in CMR cost between 30% to 60%. On the education side, five international conferences were successfully delivered in the participant countries, with at least 150 participants in each conference.

My research shows that abbreviated CMR protocols, if they are utilized in potentially high yield cases, could reduce cost, and increase effectiveness. Now, two new centres in Peru and one public centre in Cuba have started CMR with the abbreviated CMR protocol constituting as part of their clinical exams.

Furthermore, I moved one step forward and used CMR as a research method in LMICs specifically to complement research in areas of a specific need to those countries, exploiting previously unavailable opportunities. The data gathered can also support the utility of CMR for the early diagnosis of cardiac involvement in treated and non-treated people living with HIV, cardiac iron overload in Beta-Thalassemic patients, and the highest precision of an abbreviated CMR protocol compared to other imaging modalities for cardiotoxicity screening in oncology patients.

The application of rapid CMR protocols appears to have a bright future if delivered effectively and could potentially increase access to CMR in LMICs, potentially improving cardiac care. However, it is crucial to mention that a correct diagnosis is only the first step towards improved patient outcomes. Whether access to crucial diagnostics such as CMR will result in better targeted or improved treatment and an ultimate reduction in morbidity and mortality, will need to be further assessed with more large studies.

Acknowledgments:

Firstly, I would like to thank the patients who took part in the studies that constitute my thesis. Without their generosity, cooperation, and help I would not have been able to successfully progress through the different stages of my project. Some of the patient had to travel long distances and took great effort to attend their cardiac magnetic resonance scan. Thank you to all of them for agreeing to participate in the trial. This effort is dedicated to them.

I would like to acknowledge and thank my supervisors, Professor James Moon and Professor J Malcom Walker, for their continuous guidance, support, constructive criticism, enthusiasm, and encouragement over the last four years. I had a unique opportunity to carry out my project in five countries, focusing on improving the access of imaging technology for more people. It was a unique opportunity for a PhD student. Thank you to Professor Malcolm Walker, for his input into the clinical cardiology aspects of my project, particularly in the cardiac iron assessment patients with Beta-Thalassaemia in India.

I would like to express my sincere gratitude and heartfelt thanks to the UK Foreign Commonwealth Office, the UK Ambassador to Peru, Kate Harrison, and the UK Ambassador to Cuba, Sir Antony Stokes, for putting their trust in my project and for their unwavering support towards the educational program.

Importantly, I would like to thank the doctors and radiographers in the five participant countries where I implemented my project for their kind support towards the project

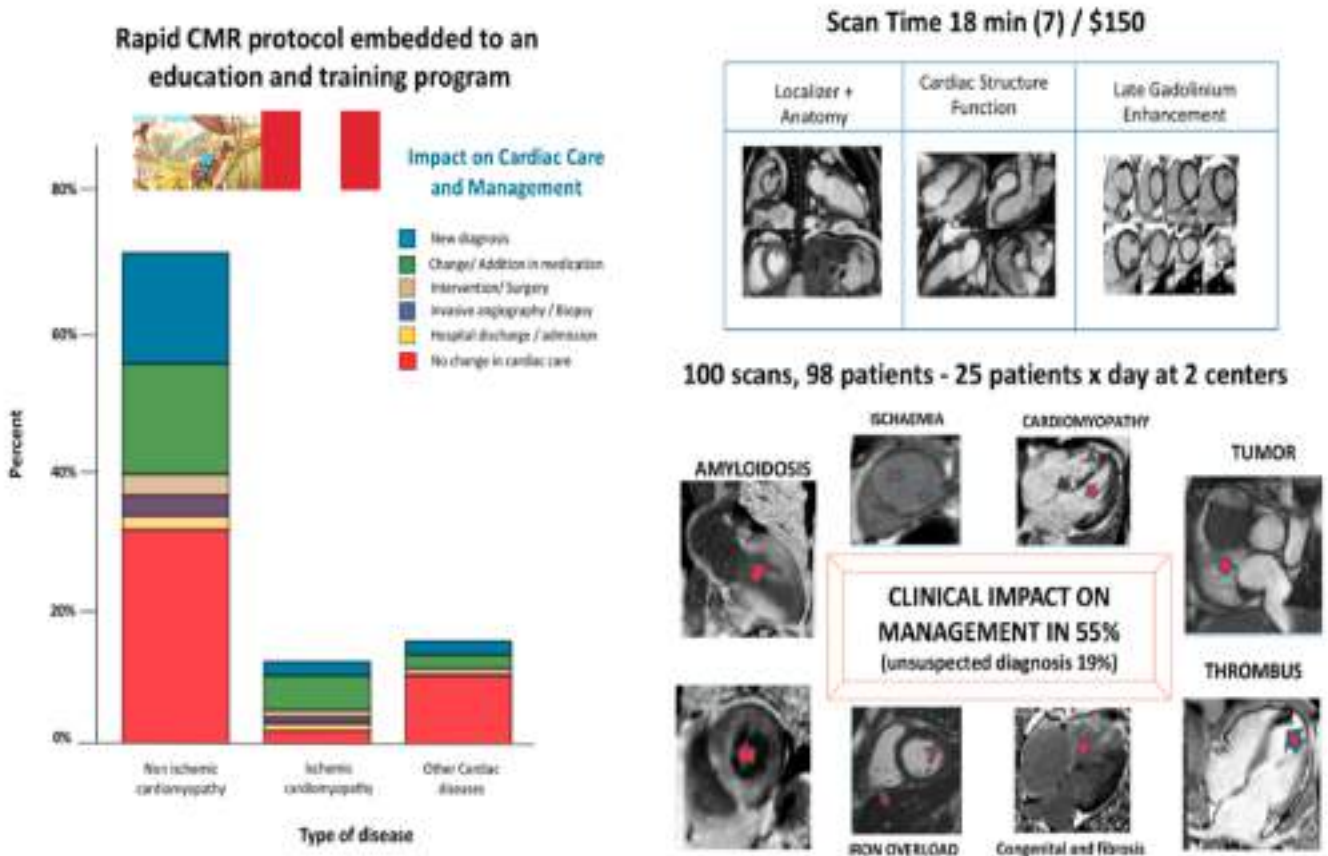
and the belief that theory can be made into practice throughout collaboration in research, education, and training.

I would like to thank the fellows at Saint Bartholomew's, colleagues, and dear friends – the teamwork and joint ideas they provided enabled our joint achievements: Anish Bhuva, Kris Knott, Paul Scully, Dr Andreas Seraphim, Amna Abdel-Gadir, Sabrina Nordin, Guilia Benedetti. I would also like to sincerely thank to Dr Anna Herrey, Dr Charlotte Manisty, Dr Thomas Treibel, Peter Kellman, Dr Mark Westwood, Dr Sam Mohiddin, Dr Neha Sekhri, Sandy Gardner, Jodee Cooper, Louise McGrath.

I would like to thank the Society of Cardiovascular Magnetic Resonance for the continuous support in the delivery of the education and training in the participant countries of my project, to the SCMR president, James Carr, Chief Executive Officer, Dr Chiara Bucciarelli-Ducci and the International Outreach Committee, and Dr Anna Herrey, Dr Yuchi Han, Dr Harold Litt, Dr Ron Jacob and Dr Juliano Fernandes.

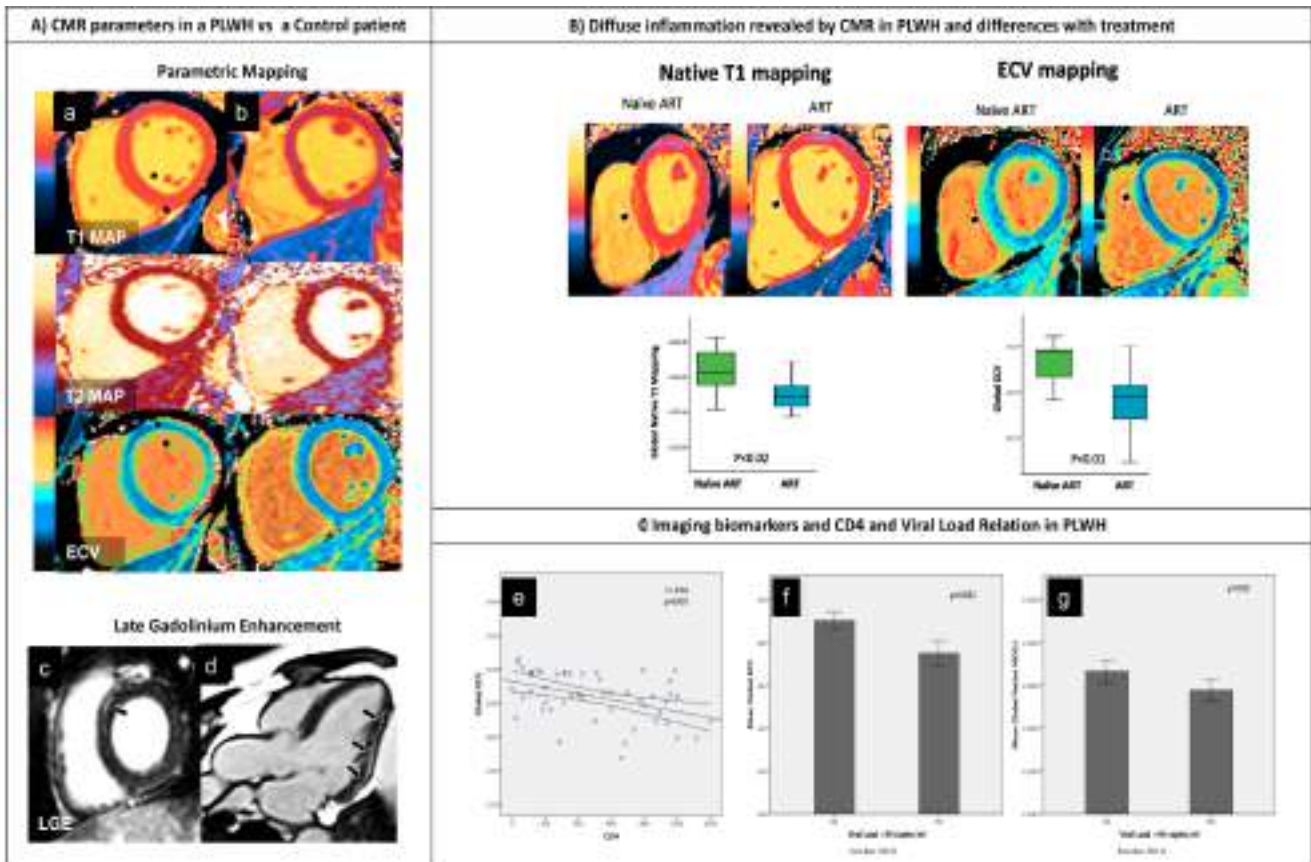
Lastly and most importantly, I would like to thank my husband Alexander for his support, patience, and tolerance during these last four years.

Visual abstract of Results:



Visual Abstract 1 (Chapter 4): Impact of Non-Invasive Cardiac Magnetic Resonance Assessment in Peru – INCA PERU study

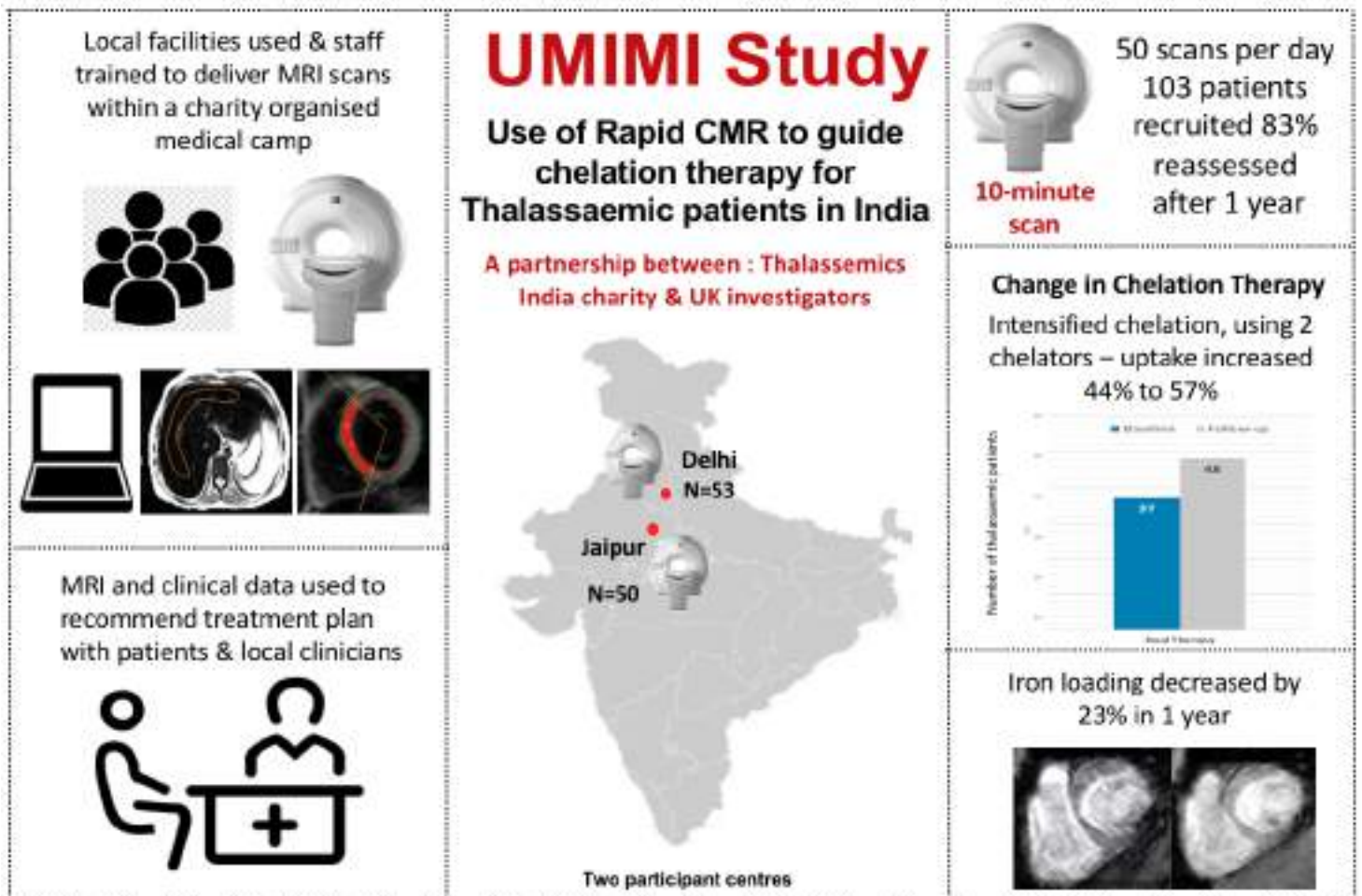
This project implemented a faster, cheaper, and easier CMR protocol embedded with a training and mentoring program in 2 centres in Lima - Peru, between 2016 and 2018. 98 participants were scanned, 25 patients per day. The abbreviated protocol had a cost of \$150, and the average time of scanning was 18-minute. Participants were followed for one year, and Rapid CMR impacted 55% of patients' care (new diagnosis and change in management).



Visual Abstract 2 (Chapter 5): *Early myocardial changes revealed by CMR in Asymptomatic People Living with Human Immunodeficiency Virus in Peru*

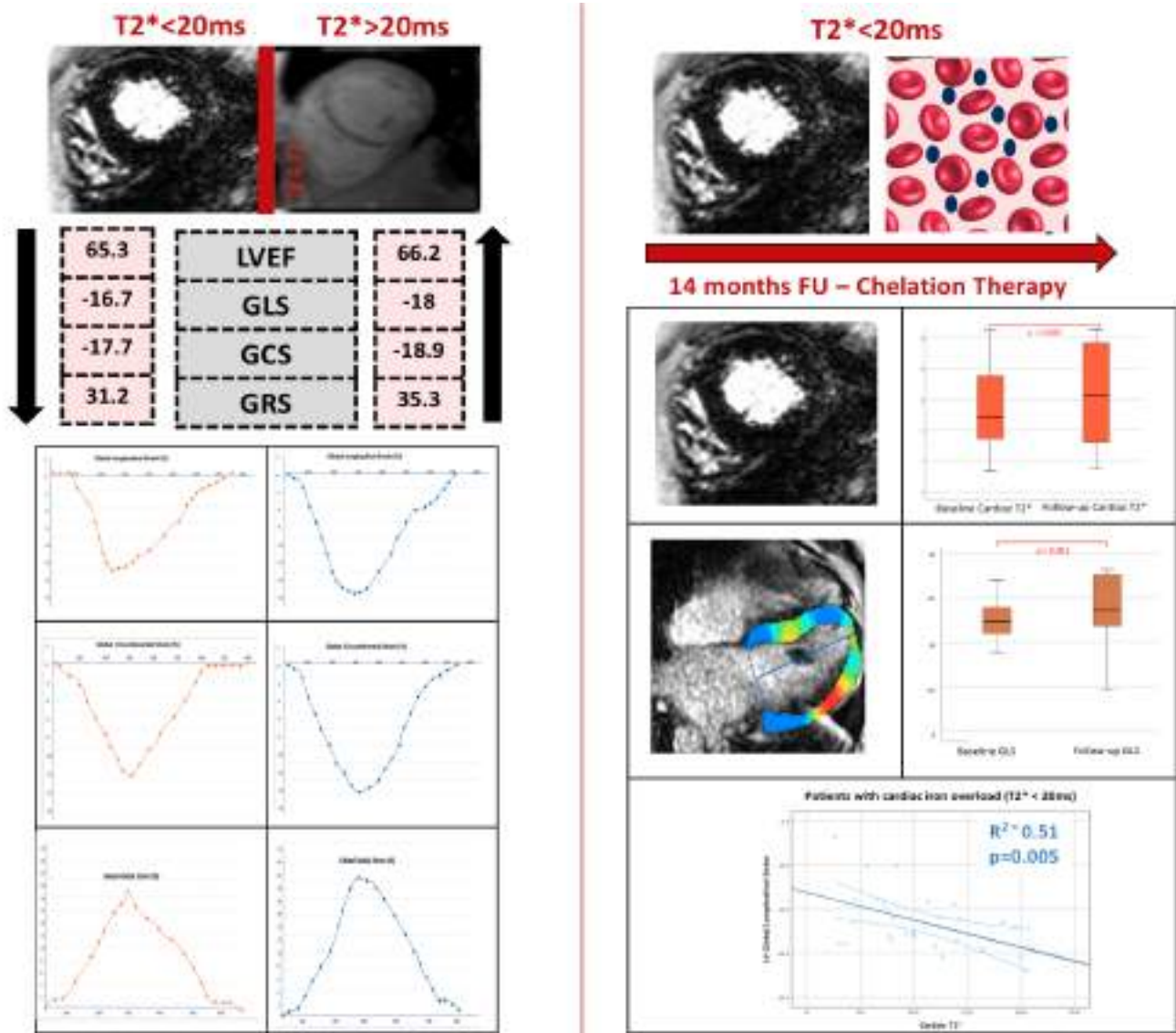
This study explored changes in myocardial function and structure in people living with HIV (PLWH) both on antiretroviral therapy (ART) and those who were ART-naïve, utilizing CMR in Peru, where untreated patients remain prevalent CMR in a PLWH. The data revealed a high prevalence of subclinical myocardial dysfunction with tissue characterization (oedema, inflammation, and fibrosis) changes in PLWH. Patients on ART have less pronounced changes. The markers of myocardial inflammation and fibrosis were associated with a detectable viral load and lower CD4 count, suggesting ART may be cardioprotective.

A - (a) PLWH participant and **(b)** control healthy volunteer showing an increase of cardiac native T1, T2 mapping, and ECV in PLWH **(c)** Basal antero-septum mid-wall **(d)** Infero-lateral sub-epicardial LGE in PLWH. **B -** Non-treated PLWH have elevated native T1 and ECV compared to those on ART. **C -** Inverse correlation between **(e)** ECV with CD4 total count and **(f, g)** Patients with a detectable viral load >40 copies/ml have higher global ECV and global native T1.



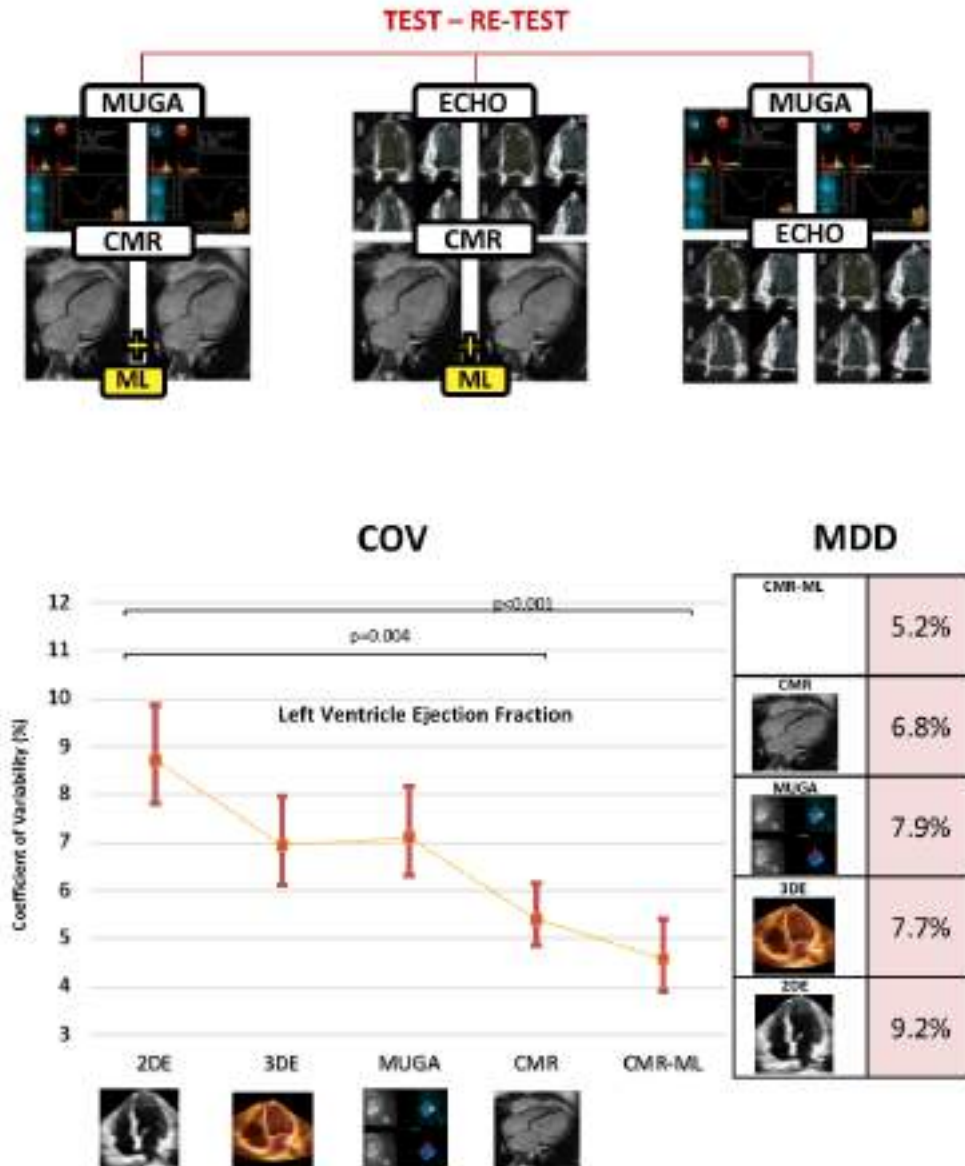
Visual Abstract 3 (Chapter 6): Improved cardiac iron using Rapid CMR to guide chelation therapy in Thalassaemic patients in India – UMIMI Study.

The UMIMI study explored the impact of incorporating a faster and easier Iron T2* CMR protocol in locally organized thalassaemia patient medical camps in two centres, two cities in India, and using this to guide chelation therapy. We scanned 103 patients, 50 participants x day, <10 minutes scan per patient. The study showed that the simplified CMR protocol linked to therapeutic recommendation via the patient camp model led to enhanced chelation therapy and a 23% reduction in cardiac iron in 1 year.



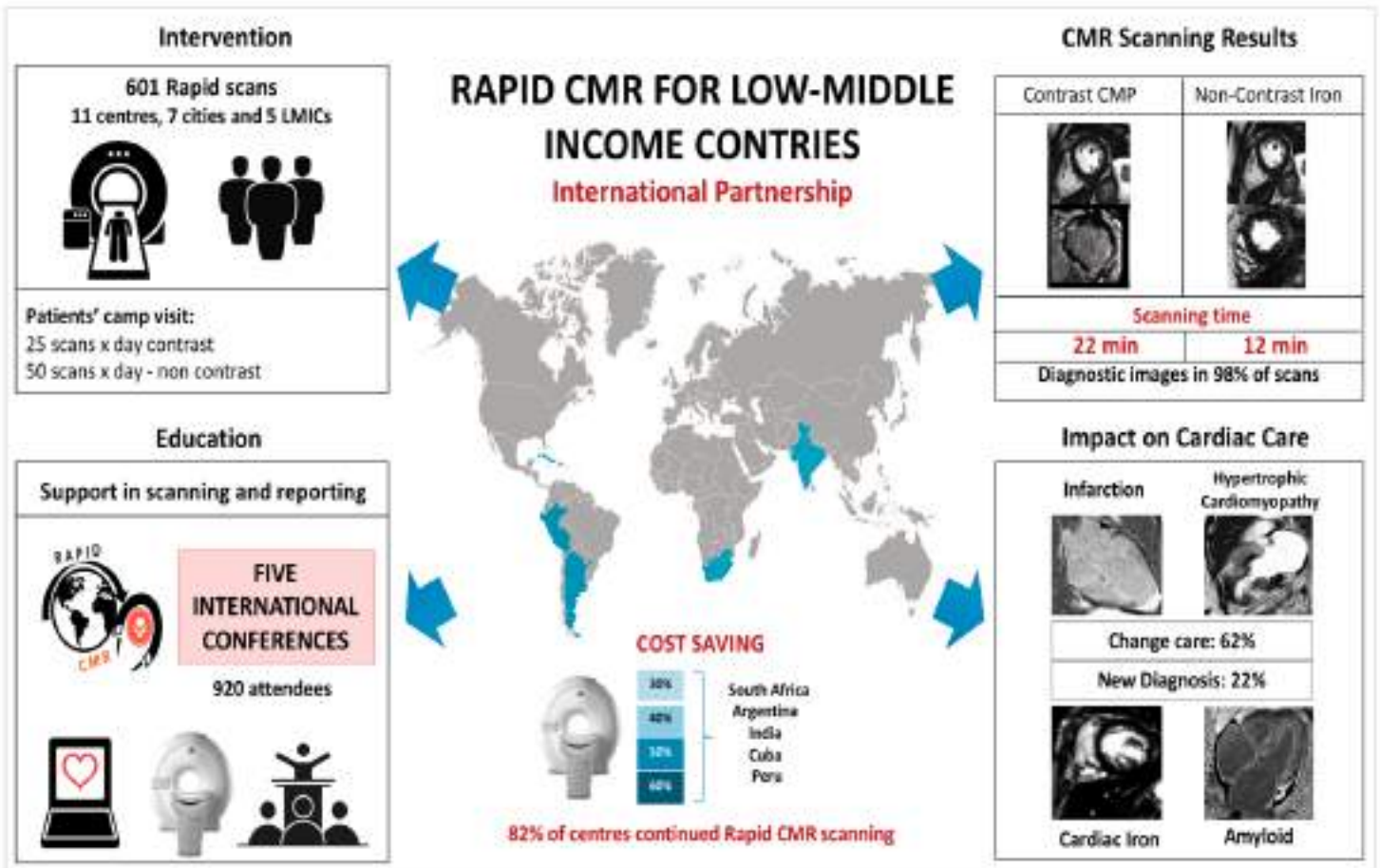
Visual Abstract 4 (Chapter 7): CMR Strain Feature-Tracking for early detection of LV systolic dysfunction in patients with Beta-Thalassaemia and myocardial iron overload

This study evaluated the diagnostic performance of CMR Strain Feature-Tracking to assess temporal changes in early systolic function due to myocardial iron overload (MIO) in transfusion-dependent thalassaemic patients treated with chelation therapy in India. Baseline GLS and GRS were significantly lower in MIO patients (T2* < 20ms) when compared to those without iron (T2* > 20ms). The data also detected a significant improvement in CMR-FT GLS strain, which correlated with a concurrent improvement in T2* CMR in patients with cardiac iron overload receiving chelation therapy. There was a good correlation between GLS and T2* CMR ($R^2 = 0.51$)



Visual Abstract 5 (Chapter 8): Comparison of the measurement precision of MUGA, CMR and echocardiography for serial cardiotoxicity screening in cancer patients

This study compared the precision of left ventricle ejection fraction (LVEF) and global longitudinal strain (GLS) measurement using repeat (test-retest) imaging across three modalities - 2D/ 3D echocardiography (2DE, 3DE), multi-uptake gated acquisition (MUGA) nuclear imaging, and cardiovascular magnetic resonance (CMR) with additional machine-learning (ML) analysis. The data revealed that 2DE had the highest CoV and minimal detectable difference (MDD) > 10% and it may not have sufficient precision to reliably detect the changes in LVEF deemed significantly by guidelines. These data also show the incremental value of analysis using machine learning for CMR LVEF (lowest CoV and MDD < 10%).



Visual Abstract 6 (Chapter 9): Improving the access of Cardiac Magnetic Resonance in Low-Middle Income Countries to Improve Cardiac Care – Rapid CMR

This multicentre prospective study followed up the initial pilot study in Lima – Peru (Chapter 4), aiming to evaluate the potential impact of a simplified and cheaper CMR protocol to assess cardiomyopathies in five low-middle income countries. The data showed that CMR could be done faster and cheaper (scanning time <22minutes, saving 30-60% of current CMR costs). When the abbreviated CMR protocol is linked to an educational and training program with supporting international networks and partnerships, it can be successfully implemented in LMICs, with high diagnostic quality and positive changes in patients' diagnosis, and management.

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Abbreviations:

CMR	= Cardiac Magnetic Resonance
DAC	= Development Assistance Committee
WHO	= World Health Organization
CVD	= Cardiovascular Disease
LMICs	= Low-Middle Income Countries
GNI	= Gross National Income
NCDs	= Non-communicable chronic diseases
PURE	= Prospective Urban Rural Epidemiology
HICs	= High-Income Countries
GDP	= Gross Domestic Product
PAF	= Population Attributable Fraction
CT	= Computed Tomography
CCTA	= Coronary Computed Tomography
PET	= Positron Emission Tomography
ECG	= Electrocardiogram
OECD	= Organization for Economic Cooperation and Development
LV	= Left Ventricle
LVEF	= Left Ventricle Ejection Fraction
2DE	= Two dimensional echocardiography
LGE	= Late Gadolinium Enhancement
MACE	= Major Adverse Cardiac Events
SPECT	= Single-photon emission tomography
TTE	= Transthoracic echocardiography
GRE	= Gradient Echo Imaging
TE	= Echo Time
MRI	= Magnetic Resonance Imaging
LIC	= Liver Iron Concentration
MIC	= Myocardial Iron Concentration
SSIR	= Highly accelerated real-time cine MRI sequence
CS	= Compressed Sensing
CTRCD	= Cancer therapeutics-related cardiac dysfunction
MOLLI	= Modified Look-Locker Imaging
BMI	= Body Mass Index
IHD	= Ischaemic Heart Disease
CAD	= Coronary artery disease
FFR	= Fractional flow reserve
MUGA	= Multigated Acquisition Scan
MINOCA	= Myocardial infarction with nonobstructive coronary arteries
HCM	= Hypertrophic cardiomyopathy
ARVC	= Arrhythmogenic right ventricle cardiomyopathy
LVNC	= Left Ventricle Non-compacted cardiomyopathy
DCM	= Dilated Cardiomyopathy
HIV	= Human Immune Deficiency
PLWH	= People Living with HIV
ART	= Antiretroviral therapy
FT-CMR	= Feature Tracking Cardiac Magnetic Resonance
GLS	= Global Longitudinal Strain
GCS	= Global Circumferential Strain
GRS	= Global Radial Strain
3DE	= 3D Echocardiography
ML	= Machine Learning
SSFP	= Steady-state free precession
TR	= Time of repetition
IR	= Single-shot inversion recovery
CNR	= Contrast-to-noise ratio
SNR	= Signal Noise Ration
RV	= Right Ventricle
RVEF	= Right ventricle ejection fraction
SAX	= Short Axis image
NRTI	= Nucleoside reverse transcriptase inhibitors
ECV	= Extracellular Volume
TM	= Thalassaemic Patients
TDT	= Transfusion Dependent Thalassaemia
DFX	= Deferasirox
DFP	= Deferiprone
DFO	= Deferoxamine
HV	= Healthy Volunteer
MIO	= Myocardial Iron Overload
BSA	= Body Surface Area

Poverty and Health in Low-Middle Income Countries

The poor suffer worse health and die younger

Strengthening the capacity of the public sector to carry out the core function of provider of health services is central to the development and implementation of pro-poor health systems



DAC Guidelines and Reference Series

Poverty and Health – World Health Organization, OECD, 2003

Chapter 1 Introduction

1.1 Cardiovascular disease in Low-Middle Income Countries:

Cardiovascular disease (CVD) is a major cause of morbidity and mortality globally, with a lifetime risk exceeding 60%. (1) 55 million deaths occurred globally in 2017, of which approximately 17.7 million were due to CVD. Therefore, prevention of CVD is a public health priority. Major advances in cardiovascular imaging, genomics, and epidemiology over the last five decades have substantially improved our understanding of the pathogenesis of CVD, with the identification and treatment of several major risk factors. (2) While coronary artery disease (CAD) and stroke remain important causes of death and disability in high-income countries (HICs), cancer is now responsible for twice as many deaths as CVD. In HICs, people have started living longer, and more people are dying now due to cancers (3) with lower CVD mortality rates. (4) However, incidence rates and age-standardized mortality rates continue to increase substantially in low and middle-income countries (LMICs), which now account for up to 85% of CVD prevalence and 30% of global CVD mortality. (5) (6). See Figure

1

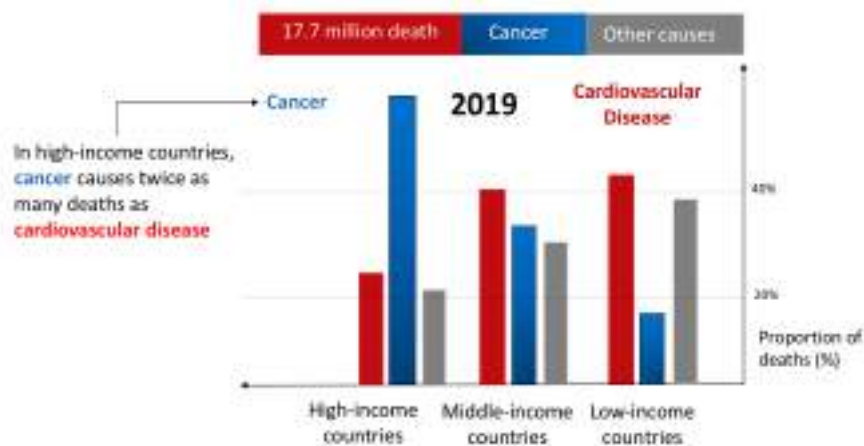


Figure 1: Cardiovascular Disease is still the leading cause of death worldwide. However, in HICs, cancer is the principal cause of mortality. Adapted from PURE study (*The Lancet*, Volume 395, Issue 10226, P785-794), March 2020. Figure reproduced with permission from Elsevier Lancet.

Definition of Low-Middle Income Countries (LMICs): The World Bank identifies six main geographic regions that are categorized as LMICs, a subgroup of middle-income countries: East Asia and the Pacific, Europe and Central Asia, Latin America and the Caribbean, the Middle East and North Africa, South Asia and Sub-Saharan Africa. (7) This distribution differs from the World Health Organization (WHO) regions and stratifies each region by income. Low-income countries are defined as reporting a gross national income (GNI) per capita of \leq \$1045, whereas middle-income countries report a GNI between \$1045 and \$12746. (8)

Transition in Population from Low-Middle Income Countries and High-Income Countries: Over the last 30 - 40 years, there have been marked improvements in the economy of low and middle-income countries. This economic development has contributed to the increase of worldwide life expectancy from 61.7 years in 1980 to 71.8 in 2015 (9). There has also been a shift from mainly nutritional deficiencies and infectious diseases to degenerative and non-communicable chronic diseases (NCDs). Developing countries have reached a rapid economic development and systemic industrialization leading to a higher prevalence of non-communicable chronic diseases. The increase of urbanization had brought a change in lifestyle behaviours, with an impact on health outcomes. Urbanization has influenced nutritional transition, with increasing availability of high calories food low in fibre, and an increase in the consumption of meats and refined carbohydrates, resulting in increases in obesity and other CVD risk factors. Also, a transition in mode of transportation had led to more motorized vehicles with less physical activity. (9, 10)

The Prospective Urban Rural Epidemiology (PURE) brings us new data of variation of common diseases between HICs and LMICs. CVD is still the major cause of mortality

globally. However, in the HICs included in the study, death from cancer was twice that from cardiovascular disease, whereas in the LMICs included in the study, death from cardiovascular disease was three times higher than from cancer, suggesting a transition in the main cause of death within the NCDs. See figure 2. Currently, in HICs, concomitant changes in lifestyle, dietary, and environmental exposure and increased access to health care are shifting the distribution of non-communicable diseases, such as the increase in lifestyle-related cancers (11). The authors state that if patterns of disease and related deaths in LMICs follow those in HICs, deaths from cancer will probably become the leading cause of death in these countries in the next few decades (12).

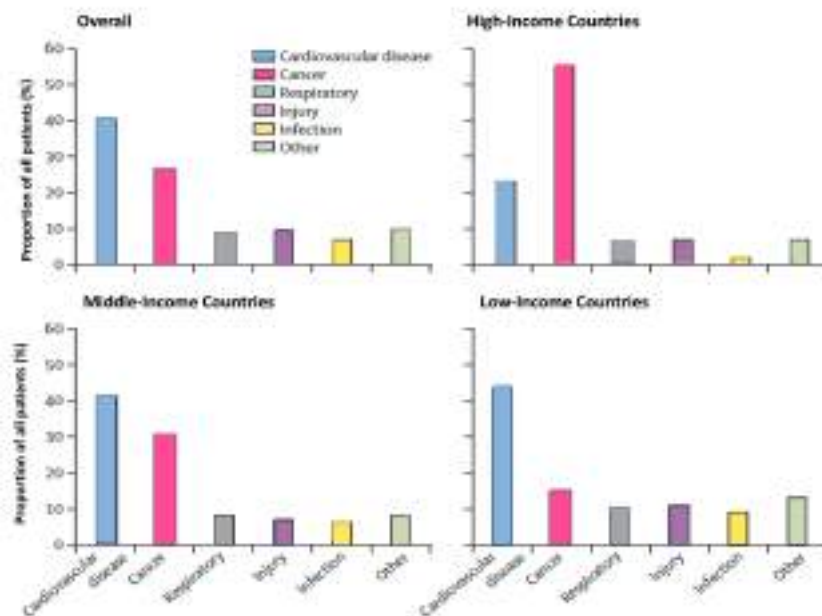


Figure 2: The most common causes of death as proportions of all deaths with a cause ascertained, overall, and stratified by country income level. Adapted from Dagenais et al. PURE study. *Lancet* 2020; 395: 785-94. Figure reproduced with permission from Elsevier *Lancet*.

Another important message from the PURE study is the strong inverse relationship between the gross domestic product (GDP) per capita in 2017, and the ratio of deaths from CVD to those from cancer is shown in Figure 3 – an increased GDP is associated with a lower incidence of deaths from cardiovascular disease compared with those from cancer.

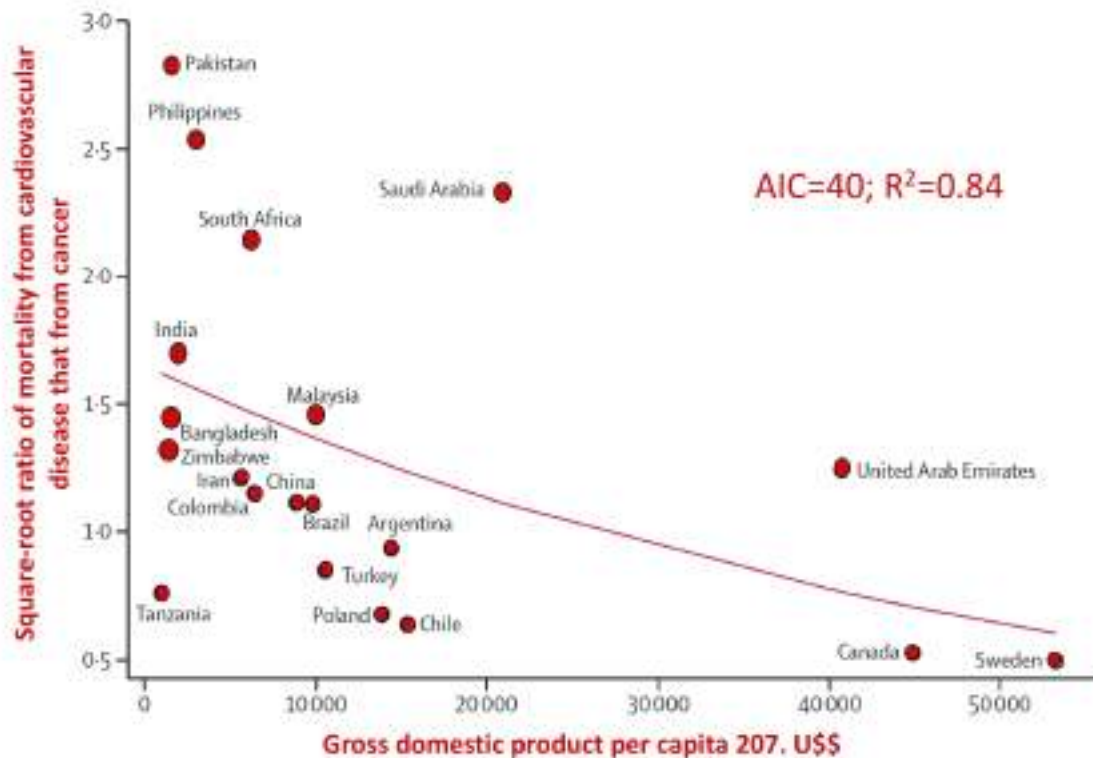


Figure 3: The relationship between gross domestic product per capita in 2017 and the square root of the ratio of deaths from cardiovascular disease to those from cancer, by country. AIC = Akaike's information criterion. Adapted from Dagenais et al. PURE study. *Lancet* 2020; 395: 785-94. Figure reproduced with permission from Elsevier *Lancet*.

Risk Factors in Low-Middle Income Countries: Most of the epidemiological studies assessing the risk factors for cardiovascular disease are restricted to individual countries, most of them coming from high-income countries (western Europe, North America) (13) (14) with fewer publications including a wider population (such as LMICs). It is still not completely clear whether the identified risk factors for IHD and stroke vary among different populations and regions. One important prospective study is The Global Burden of Disease Study (11), which collects different studies but combines different methods of data collection and analysis. There are two main international studies that have included these specific populations as case-control

cohorts. One, the INTERHEART study, focused on acute myocardial infarction (15), and the other on acute stroke (INTERSTROKE Study) (16), with a specific assessment of risk factors.

PURE study provides the most recent information which examined the association of potentially modifiable risk factors with mortality and cardiovascular disease in 162 534 participants without a prior history of CVD from 21 high-income, middle-income, and low-middle income countries. The participants enrolled in the PURE study had an average age between 35-70 years, and they were followed up for a median of 9.5 years (3). This study showed that most cardiovascular cases and deaths could be attributed to a small number of common modifiable risk factors. Some of the risk factors have a large global effect (hypertension, tobacco, education). However, household air pollution, poor diet, low education, and low grip strength had a stronger effect on death in low and middle-income countries than high-income countries (3). The study recommends that global health policies should be adapted to different groups of countries based on their risk factor assessment. See table 1

	Overall PAF (95% CI)	High-income country PAF (95% CI)	Middle-income country PAF (95% CI)	Low-income country PAF (95% CI)
1	Low education 12.5 (10.7 to 14.3)	Tobacco use 17.9 (1.2 to 34.6)	Hypertension 13.2 (11.2 to 15.1)	Poor diet 19.2 (9.0 to 29.4)
2	Tobacco use 11.3 (8.1 to 14.5)	Hypertension 13.1 (-7.4 to 33.6)	Tobacco use 12.6 (8.9 to 16.3)	Low education 13.7 (7.7 to 19.7)
3	Low grip strength 11.6 (7.3 to 16)	Abdominal obesity 11.4 (-6.1 to 28.9)	Low education 12.1 (5.2 to 18)	Low grip strength 10.9 (4.4 to 17.5)
4	Poor diet 11.1 (7.7 to 14.6)	Low education 7.2 (1.7 to 12.7)	Low grip strength 7.9 (5.0 to 10.7)	Household air pollution 9.0 (3.7 to 14.2)
5	Hypertension 8.8 (7.6 to 14.6)	Diabetes 5.9 (-0.4 to 12.2)	Poor diet 6.1 (-1.1 to 13.2)	Tobacco use 7.6 (0.7 to 14.5)
6	Household air pollution 6.6 (4.7 to 8.5)	Excess alcohol 5.5 (-0.5 to 11.5)	Abdominal obesity 4.7 (1.3 to 8.0)	Diabetes 6.7 (4.0 to 9.4)
7	Diabetes 5.5 (4.2 to 6.8)	Poor diet 2.7 (-3.8 to 9.1)	Diabetes 4.5 (4.1 to 4.8)	Hypertension 5.6 (0.5 to 10.7)
8	Abdominal obesity 2.8 (1.3 to 4.3)	Depression 2.3 (-3.0 to 7.6)	Low physical activity 3.0 (1.7 to 4.3)	Low physical activity 2.7 (0.4 to 5.0)
9	Depression 2.2 (1.4 to 3.0)	Low grip strength 1.6 (-8.1 to 11.4)	Depression 1.9 (0.6 to 3.2)	Depression 1.9 (0.4 to 3.4)
10	Low physical activity 2.2 (1.0 to 3.3)	Household air pollution 0 (-1.5 to 1.5)	Household air pollution 1.8 (-1.8 to 5.3)	Excess alcohol 1.8 (0.5 to 3.1)

Table 1: Rank order for the top ten risk factors for death in high-income, middle-income, and low-income countries along with their population-attributable factors. PAF: population-attributable fraction. Adapted from Yusuf et al. Modifiable risk factors, cardiovascular disease, and mortality in 155 722 individuals from 21 high-income, middle-income, and low-income countries (PURE): a prospective cohort study. *Lancet*. 2020;395(10226):795-808. Table reproduced with permission from Elsevier Lancet.

Just focusing on some risk factors, such as the case of education, low education was the factor most strongly associated with increased risk of major CVD and higher case fatality, despite lower proportions of CV risk factors in LMICs. Improving education and access to adequate health care could potentially mitigate some of the substantial excess burdens of CVD and mortality in LMICs and narrow the inequalities in global health (17).

Social Inequalities and their impact on Cardiovascular Disease: Despite significant efforts to identify, modify and treat individual-level risk factors, gross inequalities continue to be the main barrier, especially in poorly resourced economies. Imbalance in the social determinants of health has been attributed to the inequities in health observed between and within countries (18). A country, over time, can enter into an

epidemiological transition closely related to parallel changes in the economic, demographic, and nutritional sides. During this period, specific regions may be affected first. As the epidemic matures, the socioeconomically disadvantaged groups become increasingly more vulnerable, widening health inequality gap in a phenomenon known as the “the inverse social gradient.” (19)

Socioeconomically disadvantaged groups may have greater exposure to CV risk factors, poor working and living conditions, stress, lower rates of formal education, and reduced access to healthcare and health education. (19, 20)

Many effective interventions for CVD prevention and management can now be accessible but remain limited for poor developing countries. There are still significant treatment gaps in those countries because of poor prescribing practice, limited availability of key diagnostic tests and medicines, lack of enough number and appropriately trained healthcare providers, etc. (20, 21). Despite CVD in LMICs being a public health priority, limited attention has been paid as yet. However, there are potential strategies to prevent this epidemic from reaching its full potential magnitude. See Figure 4. This requires the rapid deployment of strategies already proven to be effective in HICs. Such strategies need to be tailored for LMICs to be affordable, effective, and accessible to the most in need. Ideally, the control of CVD in LMICs would involve a dual approach in which evidence-based clinical strategies for CVD prevention and treatment are complemented by evidence-based population-level strategies (20).

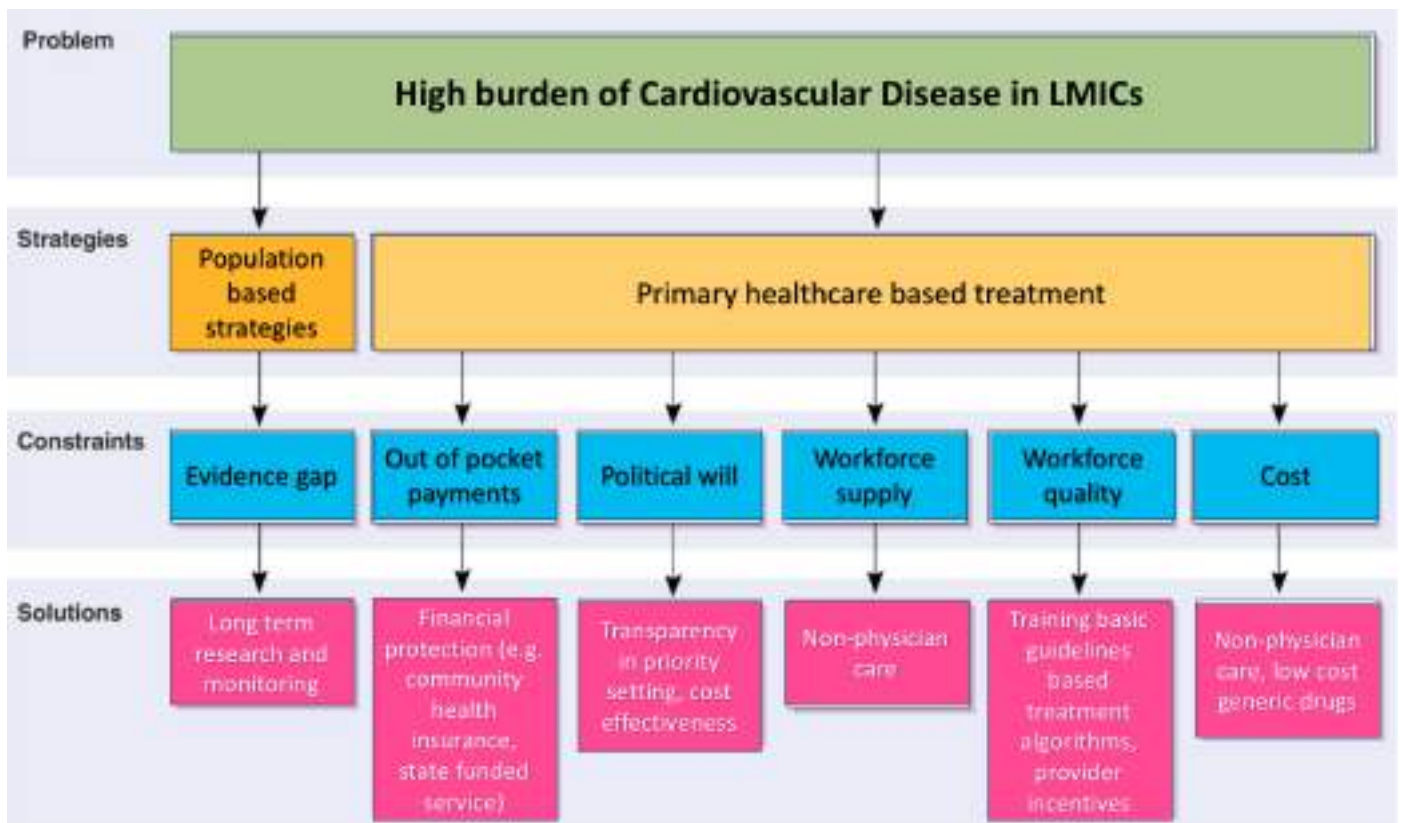


Figure 4: Solutions to Reduce Inequalities in Access to CVD Care. Adapted from Joshi et al. *Global Inequalities in Access to Cardiovascular Health Care: Our Greatest Challenge*. JACC, Volume 52, Issue 23, Pages 1817-1825, 2008. Figure reproduced with permission from Elsevier JACC Journal.

1.2 Diagnostic tests and their accessibility for Cardiovascular Care:

Without a precise diagnosis, clinical care is inefficient and generates unnecessary expenses. There are multiple diagnostic tests in cardiology ranging from simple non-invasive cardiac imaging modalities to invasive angiography. The optimal use of these exams is often controlled by diagnostic pathways, local availability, and cost constraints. An accurate diagnosis is necessary for targeted, often life-preserving therapy. There is a need to improve the access to cardiac diagnostic tests in the world. In the USA – Medicare analysis reveals a 78% increase between 1999-2008 in cardiovascular services and non-invasive testing compared to invasive procedures and evaluation and management. There is a rapid growth in advanced cardiac imaging

modalities (cardiac computed tomography CCTA/CMR/positron emission tomography PET). Still, these modalities are only responsible for a small percentage of the increased cost, relative to nuclear stress imaging and first-line trans-thoracic echocardiography (TTE), accounting for 48% of the total growth of services (22). Possible explanations for this are changes to the shift of imaging services from inpatient to outpatient settings.

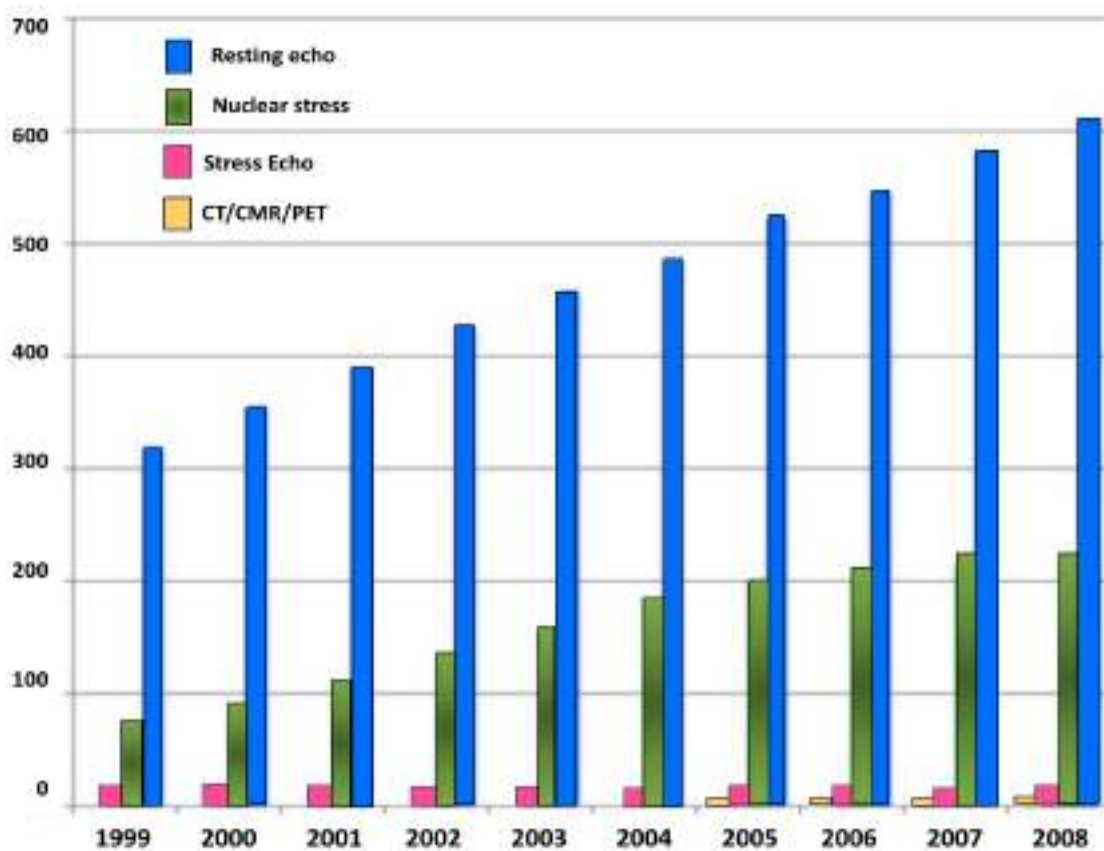


Figure 5: Non-invasive imaging services provided by cardiologists per 100 Medicare beneficiaries from 1999-2008. CMR accounts for a very small percentage of the total expenditures for cardiac imaging amongst Medicare Beneficiaries. Data adapted from Andrus et al. Medicare services provided by cardiologists in the United States:1999-2008 (23)

It is difficult to determine the accuracy of the single contribution of cardiac imaging diagnostic tests to improved cardiovascular outcomes. One example is cardiac stress imaging tests. A 3-fold increase of these techniques matched an increase in cardiac catheterization and revascularization rates and a decline of almost 50% in the age-

adjusted rate for coronary heart disease mortality between 1980 – 2000 (24). There is also the fact that cardiac imaging has become a target of various cost-saving measures to improve their access in developed countries, for example, Medicare and Medicaid Services in the USA between 2010-2013, with an overall reduction of 43% in reimbursement for nuclear imaging and echocardiography (25, 26) and Canada, with rapid growth in cardiac imaging ranging from 5-10% annually between 1992 and 2001 (27). Recent large population studies in the USA show around a 25% reduction in major adverse cardiovascular events that were independently associated with the use of non-invasive images, coronary computed tomography (CCTA), stress echocardiography, graded exercise stress test, and myocardial perfusion imaging) when compared to no testing in outpatients evaluated for stable angina (28).

-Access to Cardiac Diagnostic Tests in LMICs: Some therapies available in LMICs (bypass surgery, stenting) is expensive and effective, but only if targeted to the right patients. Appropriateness of any diagnostic test depends on disease pre-test probability and therapeutic options and diagnostic test performance, availability, and cost – particularly incremental cost and cost-benefits for each care pathway (29). In LMICs, the consequences of a lack of available diagnostic modalities may delay care and presentation at a more advanced stage of illness potentially resulting in increased hospitalization for heart failure or treatment for more extensive coronary artery disease; conditions with excessively high costs, consuming upwards of 80% of lifetime cost for healthcare. The projected economic burden of CVD in developing countries is expected to be dramatic, encompassing high costs on existing health care systems and budgets. Just a few registries reflect the availability of cardiac imaging diagnostic tests in LMICs. For example, in Brazil, between 2008-2014, a total of 4.653,884 cardiac

diagnostic procedures were performed in the country for the detection of acute coronary syndrome, with a total cost of USD \$271 million spent on these exams, with stress ECG most commonly used, followed by catheterization scintigraphy, and stress echocardiography, with most of the procedures taken in large urban centres in more economically developed Brazilian regions and with a geographic access gap in rural sectors and a significant mismatch between ACS mortality and test accessibility (30). Strategies to develop healthcare centres utilizing effective diagnostic approaches can dramatically influence the course of cardiovascular diseases within high-risk populations (31). It is crucial to understand the importance of strategies that foster the early detection and treatment in CVD. Therefore, it is reasonable to prioritize the improvement in the offer of diagnostic tests and, specifically, advanced cardiac imaging techniques in LMICs (32, 33).

1.3 Magnetic Resonance Imaging in the World:

The density of a diagnostic imaging unit could be one measurement to define the quality of a country's healthcare infrastructure. Regarding MRI units, their availability has rapidly increased over the past decade, especially in most countries from the Organization for Economic Cooperation and Development (OECD). Japan has the highest number of MRI scanners per capita where over 55 units are available per every million of its population, followed by the United States and Germany with rates of some 40 and 35 per one million inhabitants (34, 35) this compared to Israel and Hungary, where there are around five MRI units per every million.

Just in the United States, the absolute number of MRI exams has increased by more than twice between 2000 to 2013. However, in some countries such as Turkey, MRI is

being used systematically, resulting in overuse of these tests (by two-and-a-half times more between 2008 and 2013). See figure 6

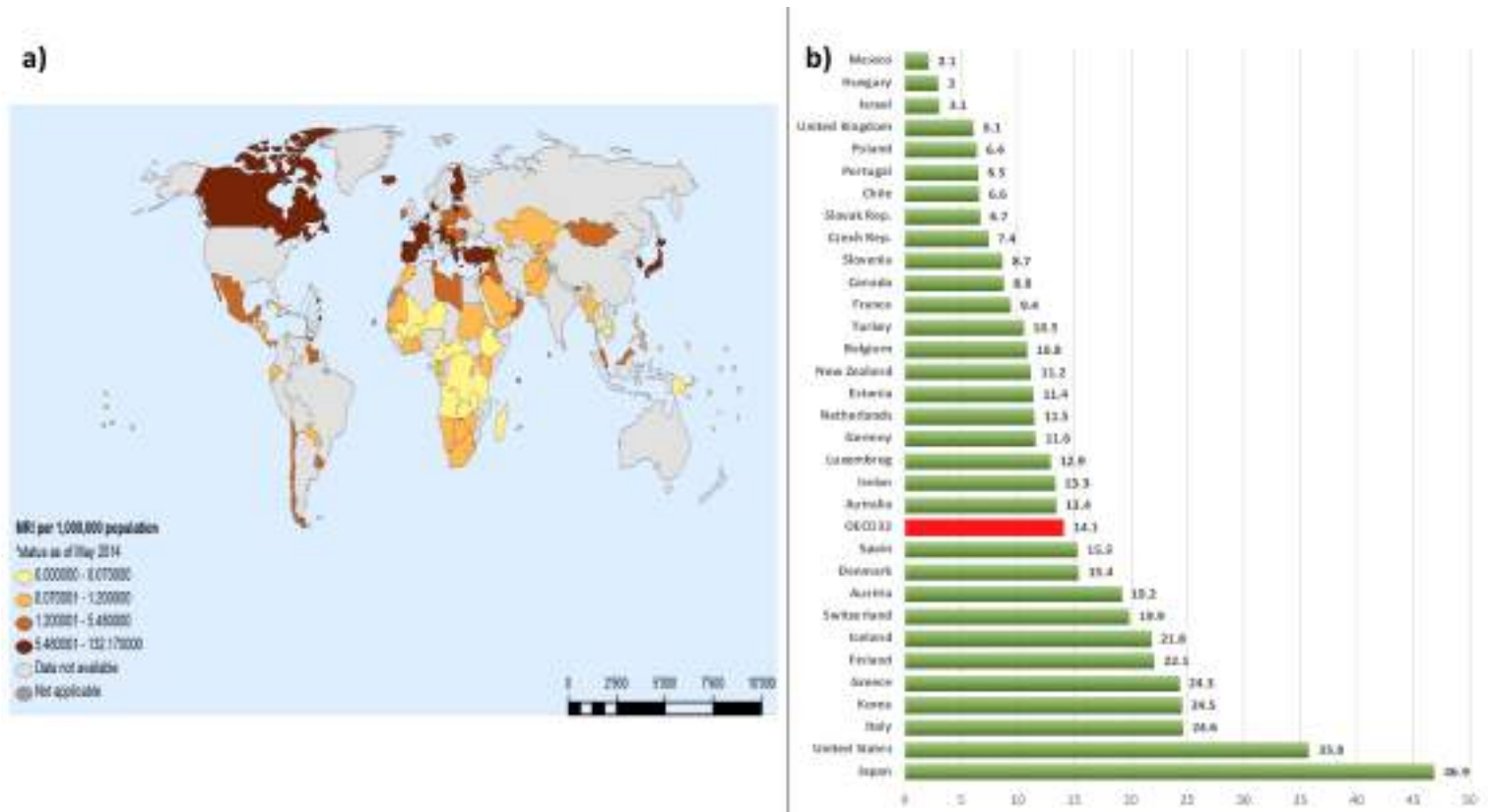


Figure 6: **Magnetic Resonance Imaging around the World:** a) Map of MRI units per million population Data source: Baseline country survey on medical devices. May 2014 update – WHO; b) MRI Units per country are shown in a bar graph. Source: OECD Health Statistics 2015. <http://dx.doi.org/10.1787/health-data-en>. ** For some countries, the number given here may substantially differ from those distributed by OECD and WHO (data do not contain freestanding imaging facilities nor military-owned facilities).

The biggest market for MRI is still the United States with some 45% of worldwide sales, followed by Europe, buying one-quarter of all units, and Japan, with 15%. Ten to fifteen machines per one million inhabitants may fully satisfy the population's medical needs to date.

1.4 Cardiac Magnetic Resonance:

Cardiac Magnetic Resonance (CMR) is a well-established advanced imaging modality for the functional and anatomical assessment of a wide range of CVD. CMR is a safe imaging technique. It does not use ionizing radiation as CT scans or X-rays and it

provides diagnostic, risk stratification, prognostic information and guiding management (36) (37). There is an extensive and growing evidence base for CMR as the reference standard imaging technique for a different spectrum of cardiac diseases, where CMR's unique contribution to tissue characterisation is the focus of most guidelines, consensus statements and publications, with additional applications constantly being added as the sciences progresses (38, 39). CMR is the most reliable test for measuring the structure and function of the heart, and two training guidelines in scanning and reporting have been recently updated by the Society for Cardiovascular Magnetic Resonance (40, 41). CMR adds real incremental value over other tests for imaging scarring in heart muscle and plays a key role in the differential diagnosis of ischaemic and non-ischaemic cardiomyopathies (42, 43).

1.4.1 Cardiovascular Magnetic Resonance for Volume and Function Assessment:

Echocardiography is a key diagnostic test for the diagnosis and management of cardiovascular pathologies. The assessment of left ventricle ejection fraction (LVEF) is one of the most common reasons for the indication of echocardiography. LVEF is a systolic function parameter that guides therapy in several clinical scenarios. The accuracy and reproducibility of LVEF is paramount for clinical decision-making (44). However, the reproducibility of LV volume measurements remains the main concern since manual tracing of the LV endocardial border using two-dimensional echocardiography (2DE) produces variability in measurement (45). CMR is considered the gold standard for assessment of LVEF due to superior inter-observer reproducibility (46), and recent data has confirmed lower mean temporal variability in LVEF with CMR compared with echocardiography in specific diseases such as for detection of cancer

therapy cardiotoxicity, see Figure 7 (47). CMR has the smaller interstudy variability, which is more likely related to the fact the measurements are derived directly from cine MRI images that encompass the entire heart rather than depending on measurements of only sample images, and the use of geometric models and dependence on acoustic windows such is the case of 2D echocardiography (48).

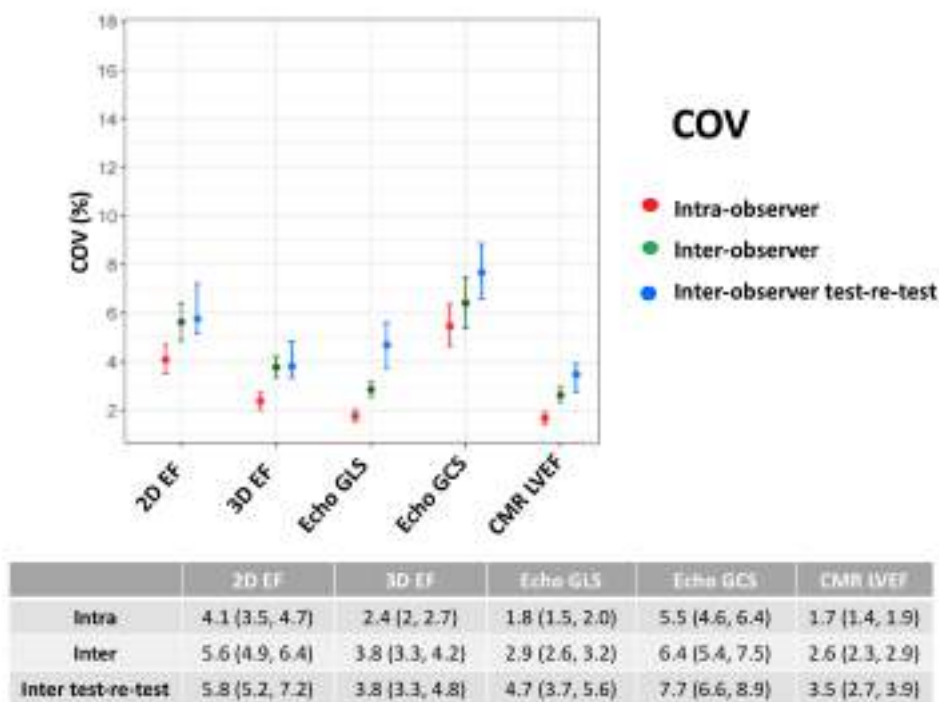


Figure 7: **Interobserver, intraobserver, and interobserver test-retest variability for LVEF with echocardiography and CMR represented as COV and 95% CI.** 2D, two-dimensional; 3D, three-dimensional; CMR, cardiovascular magnetic resonance; LVEF, left ventricle ejection fraction; COV, coefficient of Variability. Figure adapted from Lambert J, Lamacie M, Thampinathan B, et al. *Heart* 2020;106:817–8.

1.4.2 Cardiovascular Magnetic Resonance for Scar Imaging: Figure 8 and 9

Tissue characterisation and measurement of fibrosis is a mainstay of clinical care in Respiratory medicine, Nephrology, and Hepatology. Still, in Cardiology, this has been limited to the few patients who receive cardiac biopsies. The emergence of CMR is changing this. Myocardial fibrosis is inherently an important clinical parameter, as it represents one of the hallmarks of pathological remodeling of the myocardium (49-51).

The development of imaging parameters for the quantification of oedema, infarction, and scar has been followed by their adoption of the CMR community of non-invasive tissue characterisation.

Late Gadolinium enhancement (LGE) is one of the main indications for the increase in CMR usage. LGE allows a virtual histological assessment of the myocardium, with the pattern of scar suggesting cardiac disease aetiology (see figure 7) and the extent of LGE predicting risk ((36).

LGE plays a pivotal role in ischaemic cardiomyopathy. Kim et al. showed that the transmural extent of infarction predicted the recovery of contractile function after revascularization (52). These results were later confirmed by Selvanayagam et al., (53) providing that revascularisation did not induce infarction. LGE is the reference for non-invasive quantification of focal fibrosis, particularly infarct size, with the spatial resolution needed to determine transmural extent of infarction. The burden of LGE predicts function recovery after myocardial infarction (54) and revascularization (53), as well as mortality and MACE (55) (56, 57). Single-photon emission tomography (SPECT) and PET validation studies confirmed that CMR LGE had equal or better sensitivity for infarction (58), in particular in small subendocardial infarctions seen on histology (59, 60).

LGE method has proved to be reproducible (60) and performed with high sensitivity and a multicentre trial (61). LGE is established as a reference technique for the assessment of focal scar in both ischemic (52) and non-ischemic cardiomyopathies (62) such as hypertrophic cardiomyopathy (63, 64), infiltrative heart diseases (amyloid/Fabry disease/cardiac sarcoidosis/iron) (65-68), myocarditis (69) and other forms of inherited cardiomyopathies (70).

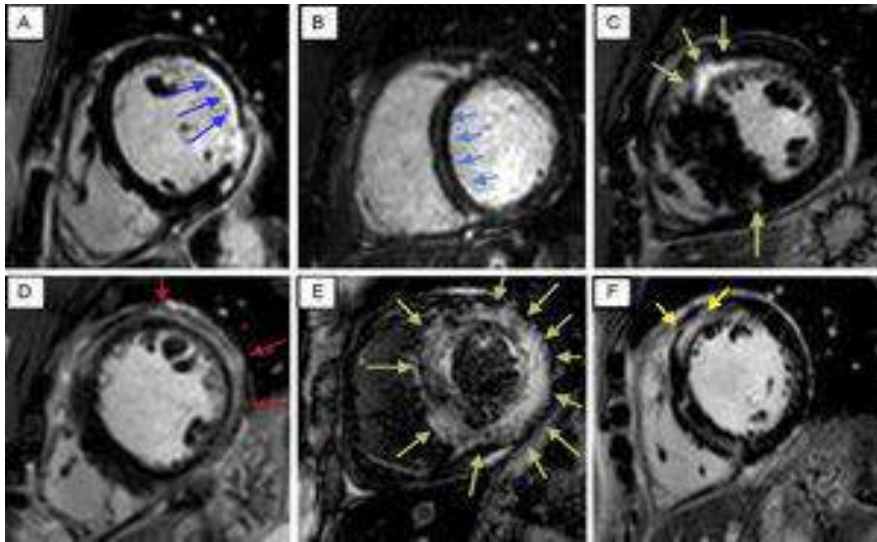


Figure 8: Typical patterns of late gadolinium enhancement supporting differentiation of various cardiomyopathies. A: Ischemic cardiomyopathy. B: Non-ischaemic cardiomyopathy. C: Hypertrophic cardiomyopathy. D: Myocarditis. E: Amyloidosis. F: Sarcoidosis. Adapted from Valbuena et al. *Cardiovascular Magnetic Resonance in Cardiology Practice: A Concise Guide to Image Acquisition and Clinical Interpretation*. *Rev Esp. Cardiol (English Edition)* 2016 Feb; 69 (2): 202-10

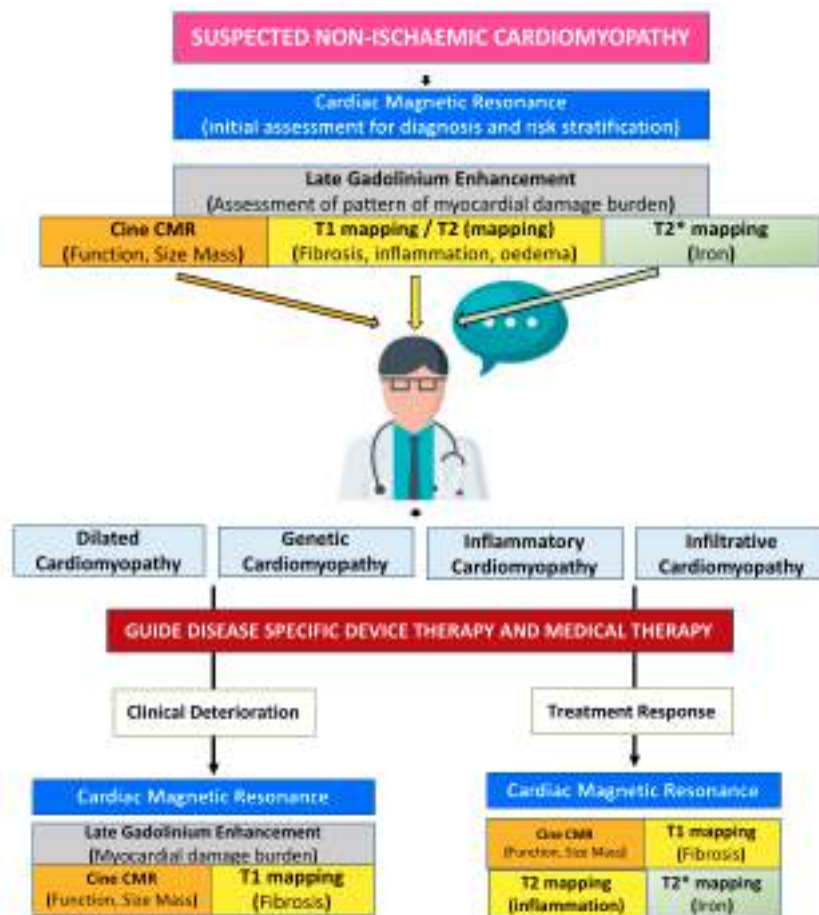


Figure 9: Evaluation of Non-Ischaemic Cardiomyopathies using CMR. Adapted from Patel, A. R et al. *J Am Coll Cardiol Imag.* 2017; 10 (10PA): 1180-93.

1.4.3 Cardiac Magnetic Resonance for Iron Quantification:

*This chapter is based on the following publication – review article: **Menacho Katia**, Menacho K, Abdel-Gadir A, Moon JC, Fernandes JL. T2* Mapping Techniques: Iron Overload Assessment and Other Potential Clinical Applications. *Magn Reson Imaging Clin N Am*. 2019 Aug;27(3):439-451. doi: 10.1016/j.mric.2019.04.008. PMID: 31279448. (71)*

T2* represents the decay of transverse magnetization due to a loss of coherence between spins and magnetic field inhomogeneity. (72) This relaxation is measured using gradient echo (GRE) imaging. This transverse relaxation is eliminated when a 180-degree pulse is applied using a spin-echo sequence (SE - true T2 relaxation) which removes the magnetic field inhomogeneity (73). The principle of T2* relaxation is involved in numerous MRI applications with GRE sequences such as perfusion techniques and functional imaging sequences.

-T2 imaging for assessing iron loading:* A fundamental principle to generate images for iron quantification is by applying a strong magnetic field and radiofrequency signals through GRE sequences, with time of decay controlled by the MRI scanner. The longer the echo time (TE), the darker the resultant image; iron-mediated darkening can be characterized by a half-time constant and is non-linearly proportional to the level of iron concentrations. Often, this darkening is described as a rate principle (R2*) rather than a time constant. The relaxation rate is just the reciprocal of time constant, $R2^* = 1000/T2^*$. The factor of 1000 is included because T2* is expressed in milliseconds (ms), and relation rates in expressed in Hertz (sec-1). (74, 75). To calculate T2*, an application of multiple radio frequency pulses leads to the generation of a series of images with different echo times (ET). (76)

-Traditional sequences to measure cardiac iron overload: Most updated international expert consensus suggests that for T2* cardiac iron loading assessment, a multi-echo

gradient echo with eight equally ranging from 2 to 18ms may be used on a 1.5T MRI scanner. (40) Fat saturation is needed for the liver but is not essential for heart images. Good shimming of the heart is a requirement for accurate measurements, and manual volume shimming may be required to reduce potential artifacts. Once adjusting these factors, both bright blood and dark blood techniques are validated and widely used clinically. (77) (78) Compared to bright blood technique, dark blood has shown to have superior reproducibility, less artifact susceptibility, and it is the preferred method to use clinically. (79)

-Clinical Application of Iron Overload assessment with T2:* Since its introduction in early 2001, the use of T2* imaging to guide therapy in patients with iron overload, coupled with improvement in chelator options and advances in other coadjutant management strategies, resulted in a significant reduction in cardiovascular death and disability in thalassemia major patients. (68, 80) T2* CMR is a recommended exam in practically all clinical guidelines relating to iron overload treatment (81-83), and its use has been summarized in specific recommendation statements as well.(84)

From a practical standpoint, transfusion-dependent patients should start monitoring myocardial T2* from the age of 10 years old if they are routinely followed and have a history of being well chelated. (85) However, patients in whom the treatment follow-up is unclear, have irregular chelation or very high liver iron concentrations (LIC), may perform their first MRI scan at ages as early as 7 years old as significant myocardial iron concentrations (MIC) have been described at this early age.(86). Once started, routine follow-up of myocardial iron concentrations should be performed yearly in most patients, with this interval varying from 6 months to 2 years depending on specific clinical conditions and service availability.(87) It is important to note that removal of

cardiac iron in the heart is a relatively slow process, and especially in acute settings (i.e. acute heart failure), the clinical condition will sometimes improve significantly. At the same time, T2* changes will not be proportional. (88) The main reason for this disparity is that T2* measures primarily chronically stored iron in lysosomes while the iron being mobilized by intensive chelation is in labile form, with little T2* effects. (84) Nevertheless, monitoring the effects of iron chelation or accumulation is a primary target of routine MRI scans in these patients. Any changes above the coefficient of variation of 4% for black blood images and 8% for bright blood images should be considered significant changes. (89) Another important clinical aspect of using T2* for iron overload assessment involves the correlation of T2* values and MIC. While for the liver, at a very early stage in the development of the technique, T2* values, and LIC correlations were established, for the heart, T2* was the main variable used for quantification until Carpenter et al. performed the comparison of this MRI value to MIC measured biopsied hearts. (90) As T2* and MIC are not linearly related, one must consider when assessing longitudinal changes in T2* values as significant changes in MIC occur when small variations are seen at low T2* values. The correlation of T2* and MIC can be seen in Figure 10 using the equation $MIC = 45 \times T2^{*-1.21}$. When reporting the iron concentrations obtained with various T2* techniques, the value of 20ms has been traditionally associated with the normal cut-off for non-iron overloaded myocardial tissue based on the initial data of Anderson et al. (91) that showed that almost all patients with T2* above these levels did not develop reductions in left ventricular ejection fraction. (91) However, despite the popularity of this number, other authors have shown that iron deposition is frequently found in patients with septal T2* above these levels. (92) Therefore, it would be more appropriate to consider the normal

myocardial T2* levels according to measurements performed in normal volunteers where normality was established at 36.1 ± 4.5 ms. (93) Nevertheless, traditional reporting tables for iron overload using T2* have used cut-offs based on clinical management strategies and prognostic data. Table 2 lists the values of myocardial T2*, MIC, and the reporting levels for iron overload in the heart. It is important to note that although a T2* levels <10ms is considered severe, risk elevates dramatically as T2* falls further from 10 to 8 to 6 and even 4ms.(94).

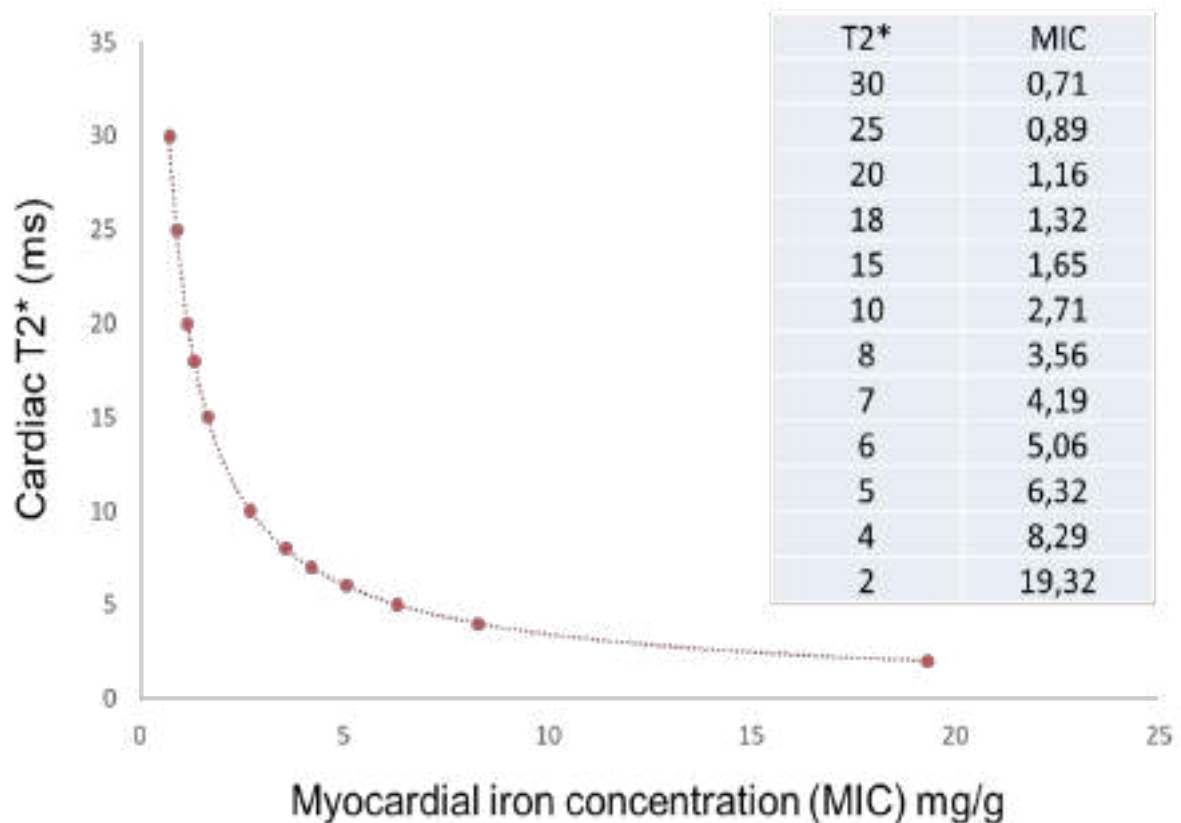


Figure 10: Correlation of myocardial T2* and myocardial iron concentration (MIC) with the corresponding curve and some calculated examples. From this graph, it is important to appreciate that changes in T2* above 30ms do not significantly change the final MIC values, whereas small changes in T2* (i.e., below 10ms) significantly increase MIC. Adapted from Menacho et al. T2* Mapping Techniques: Iron Overload Assessment and Other Potential Clinical Applications. *Magn Reson Imaging Clin N Am.* 2019 Aug; 27: 439-451.

T2* (ms) 1.5T	R2* (Hz) 1.5T	T2* (ms) 3.0T	R2* (Hz) 3.0T	MIC/LIC (mg/g dw)	Classification
Myocardium					
≥ 20	≤ 50	≥ 12.6	≤ 79	≤ 1.16	Normal
10 to 20	51 to 100	5.8 to 12.6	80 to 172	> 1.16 to 2.71	Mild to Moderate
< 10	> 100	< 5.8	> 172	> 2.71	Severe
Liver					
≥ 15.4	≤ 65	≥ 8.4	≤ 119	≤ 2.0	Normal
4.5 to 15.4	66 to 224	2.3 to 8.4	120 to 435	>2.0 to 7.0	Mild
2.1 to 4.5	225 to 475	1.05 to 2.3	436 to 952	> 7.0 to 15	Moderate
< 2.1	> 475	< 1.05	> 952	> 15	Severe

Table 2 – Reference Values for Liver and Myocardial Iron Concentrations for MRI (95, 96). LIC = liver iron concentration; MIC = myocardial iron concentration; We include T2* and R2* values at 3T but advise caution and recommend normality is defined locally, if 3T must be used. *Adapted from Menacho et al. T2* Mapping Techniques: Iron Overload Assessment and Other Potential Clinical Applications. Magn Reson Imaging Clin N Am. 2019 Aug; 27: 439-451.*

1.5 Cardiac Magnetic Resonance access around the world:

There is no unique registry that assessed the overall number of countries and centres that run a CMR as a standard service. There are just some specific registries for specific populations. For example, in the UK, 60 centres provided CMR services in 2011, performing ~1000 scans per million population per year (97). The number of CMR scans performed annually per centre has increased rapidly over the last years, about 44% more, but are concentrated in high volume centres. Centres without CMR on-site refer very few patients for CMR. CMR requirement is around 2200 scans per

million adult population and an upper limit of 44,000 scans per year. On the other hand, in the UK, it is recommended that every cardiac surgery centre should have CMR and that for quality, a minimum activity level is needed; around 500 scans per year is recommended. (97) Two worldwide surveys have been carried out to assess CMR practice and its impact on clinical care. The EuroCMR registry (98) and the Global CMR Registry (GCMR) (99). EuroCMR registry was a multicentre study, which enrolled more 27000 participants in 57 centres in 15 countries. The most important indications in the participant centres in Europe were risk stratification for suspected CAD/Ischaemia, myocarditis, and cardiomyopathies, and the assessment of viability where CMR results had a substantial impact on patient management (61.8%).

GCMR (100) is an initiative of the Society for Cardiovascular Magnetic Resonance (SCMR) started in 2013 to support developing of a global registry, with 10 centres contributing CMR data, with a total of 62,456 studies. The registry shows the overall predominance of CMR centres with more than ten years of experience and with most of them located in the USA (63%). The most common clinical indications for CMR are cardiomyopathy (21%), myocardial viability (16%), Stress CMR perfusion for chest pain syndromes (16%), and evaluation of arrhythmias (15%). Most CMR studies involved the use of gadolinium bases contrast media (95%). See Figure 11.

All these registries confirm an increase in CMR use in high-income economies such as North America, Europe, and some nations in Asia such as China (101). However, within these regions, the distribution in the access of this technology is very variable to patient care, as it has been recently reported by Mizia-Stec et al. (102) in the Euro-Observational Research Program (ESC-EORP) registry. This registry included 3208 patients with the diagnosis of cardiomyopathy in Europe. All the participant centres

were tertiary-level care. Less than one-third (29.7%) of patients underwent CMR, with a variable prevalence of CMR use (between 1% to 63.2%). The use of CMR varied greatly between cardiomyopathy subtypes, clinical profile of patients, and tertiary referral centre. The authors concluded that regardless of the potential value of CMR, the overall use of CMR in Europe is limited. See Figure 12.

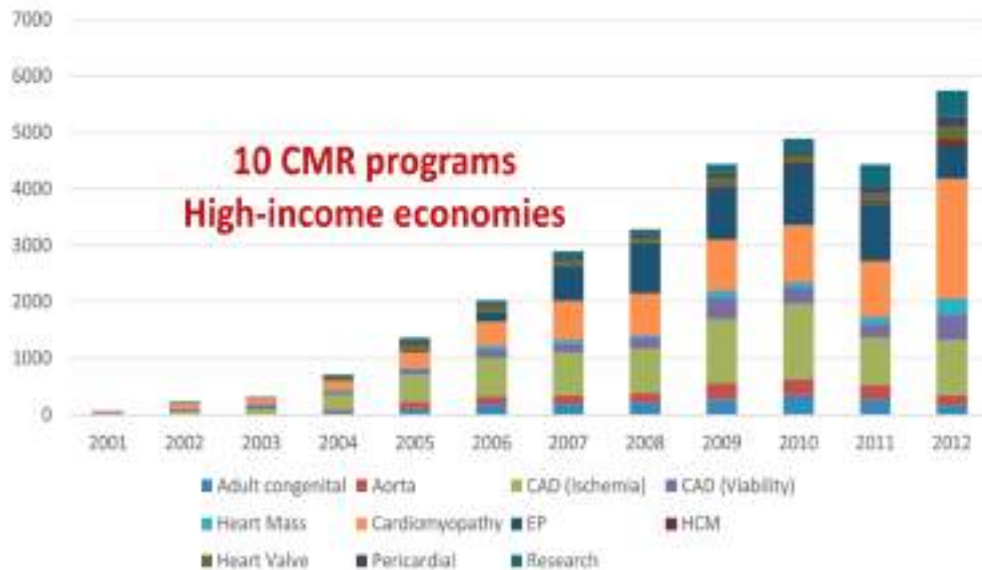


Figure 11: The Global CMR Registry (GCMR) – SCMR initiative. The use of CMR in clinical practice has grown in the last 20 years, but in high-experience centres in HICs. Adapted from Kwong R., et al. GCMR registry, JCMR 19, Article 23 (2017).

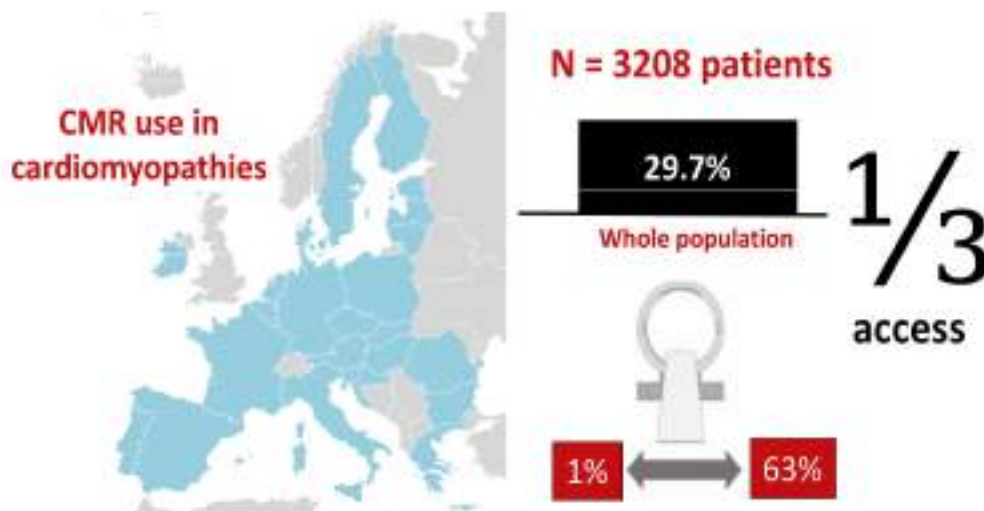


Figure 12: ESC- Euro-observational Research Program (ESC-EORP – Cardiomyopathy/ Myocarditis registry). 3208 participants with cardiomyopathies, only 29.7% of participants, had CMR with variable use (1%-63%). Adapted from Mizia-Stec et al. ESC-EORP registry. European Heart Journal – Cardiovascular Imaging, 2020 -00,1-9.

1.6 Cardiac Magnetic Resonance in Low-Middle Income Countries: See Figure 13

This chapter is based on the following publication – review article: Menacho Medina K, Seraphim A, Katekaru D, Abdel-Gadir A, Han Y, Westwood M, Walker JM, Moon JC, Herrey AS. Non-invasive rapid CMR for the assessment of cardiomyopathies in LMICs. Expert Rev Cardiovasc Ther. 2021 May;19(5):387-398. doi: 10.1080/14779072.2021.1915130. Epub 2021 May 24. PMID: 33836619.

Because of its cost, CMR to date is a modality frequently limited in its use HICs, which is reflected in the origin of published evidence, expert consensus, and standard protocols. In HICs, easy access to CMR and rapid progress within the technique can lead to four critical problems previously identified during the development of this research project (103). These problems can be applied to a wide range of advanced imaging modalities and should be avoided when trying to implement the use of these advanced imaging modalities in LMICs (103)

- (1) *Single modality overuse*: one service becoming locally dominant through internal resource competition exacerbating imbalance.
- (2) *Protocol bloat*: Because CMR can provide multiparametric imaging assessment (function, scar, perfusion, flow, mapping), scans start to get gradually longer with reducing yield from additional sequences and increasing costs
- (3) *Test layering*: Multiple scans are requested concurrently – this can occur through referrer uncertainty, differential confidence in local services, access barriers, or disconnections within diagnostic imaging provision or follow-up structures.
- (4) *Short interval repeat requests*: maximum yield from diagnostic testing is the initial assessment to secure the primary diagnosis. Subsequent interval scanning, particularly at a short time interval, becomes less cost-effective

Although there are MRI units available in LMICs in rapidly increasing numbers (104), there is little access to CMR (105). However, a lack of local expertise and access to training may result in inappropriate referrals, limited understanding of its usefulness and additional diagnostic value, and reluctance to use CMR. This pattern, together with lengthy and therefore costly scan times, is a significant barrier to the more widespread use of CMR in LMICs (106). Considering these surrounding obstacles in LMICs, the next step is to maximise cost benefits and access to CMR in those countries. The approach displayed here may be of value in HICs also, with new centers starting their CMR service or facing increasing demand on the number of scans:

- 1) *Focused CMR protocols – Rapid CMR*: Based on the principle that critical information cannot be obtained from any other imaging test:
 - a) Cardiac function (using cine images sequences), CMR is the gold standard exam for assessing cardiac volume, mass, and systolic function (40).
 - b) Scar imaging (using a standard late gadolinium enhancement technique - LGE). This type of sequence is available on most MRI scanners worldwide (107, 108).
 - c) Iron Quantification: CMR - T2* is the technique to assess cardiac iron levels. It is easy to standardize, highly reproducible, and guideline supported (109) (84)

Moreover, CMR can be made faster. One approach is to speed up image acquisition. Examples include the use of parallel imaging (110), compressed sensing (111) and CMR multitasking (112), Highly accelerated real-time CINE MR sequence (SSIR) (113), Score Sparsity Adaptive Composite Recovery (114). The main limitations of these techniques are the requirements of state-of-the-art

scanner models and software, access to which may be limited in LMICs. Thus, these solutions are mainly aimed at CMR units in high-resource centres, usually in HICs (115). See table 3.

- 2) *Wider adoption of a rapid CMR Protocol:* Where stakeholders should include healthcare providers, patients, policymakers and finance, and implementation partners (international and national education and research partners).
- 3) *Assessment of cost-effectiveness:* A faster, cheaper, and easier protocol will lead to cost-effective use of the modality.
- 4) *Explore new research fields in LMICs:* Aiming to generate new scientific hypotheses, research, evidence, and global impact (116). In addition, CMR can respond to specific research questions in LMICs, exploring opportunities that may not be available in HICs (117-119).

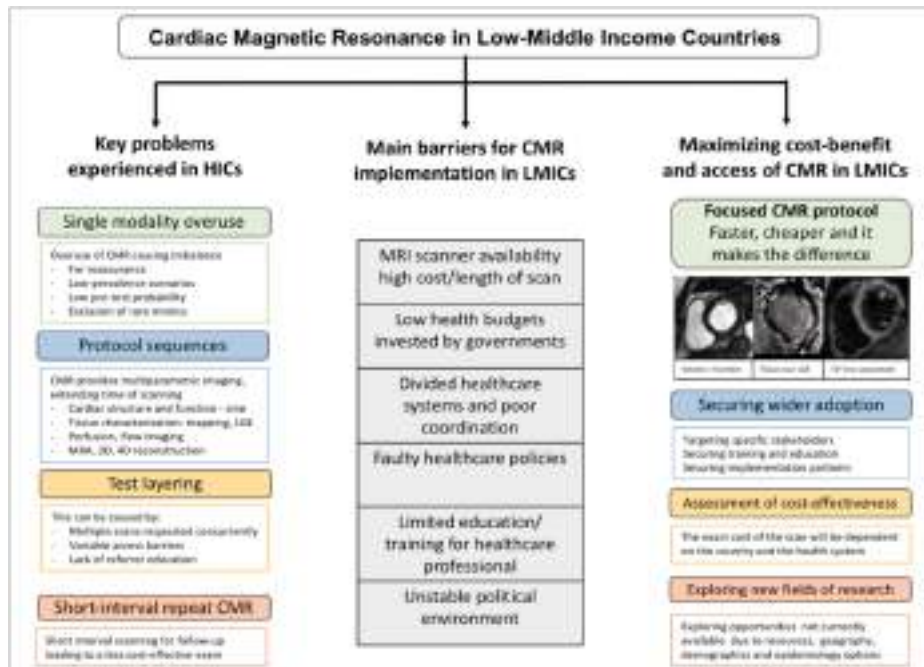


Figure 13: Barriers and Potential Strategies for Improving the Access of Advanced Cardiac Magnetic Resonance in Low-Middle Income Countries. HICs: High-income countries, CMR: Cardiac Magnetic Resonance, LGE: Late gadolinium enhancement, MRI: Magnetic Resonance Imaging, LMICs: Low-Middle Income Countries. Reprinted from Menacho Medina K, et al. Non-invasive rapid cardiac magnetic resonance for the assessment of cardiomyopathies in low-middle income countries. *Expert Rev Cardiovasc Ther.* 2021 May;19(5):387-398. doi: 10.1080/14779072.2021.1915130. Epub 2021 May 24. PMID: 33836619.

	Parallel Imaging (110)	Highly accelerated real-time CINE MR sequence (SSIR) (113)	Compressed Sensing (CS) (111)	Sparsity adaptive Composite Recovery SCoRe (114)	CMR Multitasking (112)
Characteristics	(a) image-based, sensitivity encoding (SENSE™) (b) k-space type (generalized autocalibrating partially parallel acquisitions (GRAPPA) method)	Use sparse data sampling and SSIR with k-t regularization	Enables reconstruction of images from significantly fewer lines (sparsity)	SCoRe is validated in a dynamic digital phantom as well as in retrospectively and prospectively undersampled cine CMR data.	Enables the acquisition of multiple types of data without electrocardiographic triggering or breath holds
Advantages	Improvements in imaging speed: -Shortening long examinations -Improving spatial resolution and/or anatomic coverage - Improving temporal resolution -Overcoming physiological constraints, detecting and correcting for physiologic motion, and streamlining workflow	Ultra-fast acquisition of a stack of short-axis views during a single breath-hold or even during free breathing. SSIR provides exact volumetric parameters when compared to a multi-breath-hold reference sequence for both LV and RV, and when acquired after contrast.	-Widely used for several applications: perfusion imaging, flow imaging, angiography, T1 mapping and real-time free-breathing cine imaging. -Recent availability of improved computer hardware is making CS practical	-SCoRe enables accelerated cine CMR from highly undersampled data -SCoRe adapts regularization weights based on noise power and level of sparsity in each transform, yielding superior performance without admitting any free parameters	CMR multitasking may provide a foundation for the development of setup-free CMR imaging for the quantitative evaluation of cardiovascular health in one 15-minute examination (T_1 mapping, T_1 - T_2 mapping and time-resolved T_1 mapping of myocardial perfusion).
Limitations	Limited to 2 to 3-fold acceleration factor (coil element) and reduction in signal to noise ratio (fewer data acquired) Prone to artifacts.	Remains in development and sequences are not yet used clinically. Not available in all scanner's models.	Remains in development and sequences are not yet used clinically It requires advances software.	CMR SCoRe requires the latest scanner models with updated and advanced software packages.	CMR multitasking requires the latest scanner models with updated and advanced software packages.

Table 3: Five accelerated techniques to improve scanning acquisition time with Cardiac Magnetic Resonance. Description of general characteristics, advantages, and limitations.

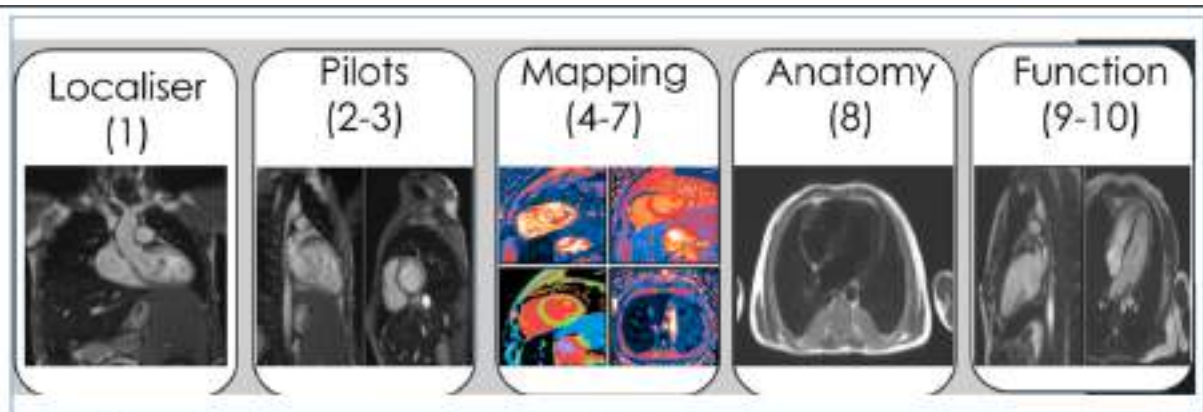
1.7 Abbreviated CMR Protocols: Experience in the Clinical Practice

-Cardiac Iron Overload Assessment: CMR has been repurposed to be faster, cheaper, and easier for focused deployment in LMICs. Abdel-Gadir et al. (120) implemented ultrafast CMR in Thailand in patients with thalassemia; non-contrast CMR (1.5T) was performed in ninety-seven participants and eleven healthy volunteers. CMR sequences are displayed in Figure 14. All the scans were performed in 2 days (12-hour working days). The mean scan duration was 8.3 ± 2.4 minutes, and analysis was completed within 1 minute of the last image acquisition. Fifteen participants had myocardial iron loading by T2*. The intervention could potentially reduce costs four-fold with a potential clinical and economic advantage of abbreviated CMR protocols. See table 4

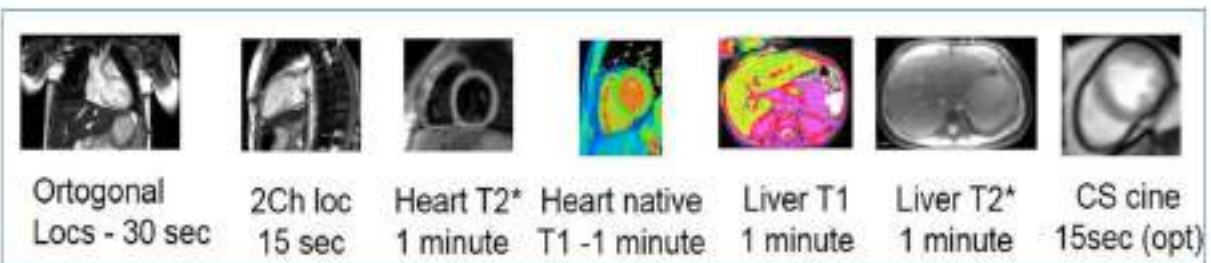
Fernandes et al. led a similar research project in India, in seven participants centres, enrolling 179 patients (each in a ten-minutes slot). They used an accelerated protocol that included short-axis prototype T1 MOLLI and T2* multiecho acquisition of the heart and liver (details of CMR sequences and protocol displayed in table 3). Automated maps for both sequences were generated by a post-processing prototype software and compared the results with a standard manual method of analysis. The median scan time was 5.2 minutes (IQR 4 to 7 minutes) with the completion of cardiac and liver iron analysis in most patients and similar results compared to manual analysis. See table 4 and Figure 14.

Rapid Cardiac MRI protocols to assess Cardiac and Liver Iron Overload		
Lead Researcher	Abdel-Gadir et al. (120)	Fernandes et al. (121)
Country	Thailand (one center)	India (7 centers)
Sequences included in the protocol (see figure 14)	Pilot localizers T1 mapping - mid short axis. T2* mapping – mid short axis. Transverse dark blood single-shot. fast spin echo stack for anatomic evaluation. Cine function: Longitudinal axis cine.	Orthogonal Localizer (30 seconds). 2CH Localizer (15 seconds). T2* mapping heart (1 minute). T1 mapping heart (1 minute). Liver T1 (1 minute). Liver T2* (1 minute). Compressed sensing cine (15 seconds – optional).
Length of Scan	8.3 ± 2.4minutes	5.2 minutes (4 – 7 min) 7.5±1.8min (with cine)
Number of participants	97	179
Comparison of automated vs. manual analysis	Automated Analyses only	-1.2ms (95% CI -1.7 to -0.8ms)
Cardiac iron by T2* <20ms (participant %)	15 (15.5)	Not available
Impact on management	Not available	Not available

Table 4: Two abbreviated CMR protocols (T2) for quantification of cardiac and liver iron, implemented in two low-middle income countries. The length of both scans was less than 10 minutes. Reprinted from Rapid Cardiac MRI protocols Feasibility and Potential Applications by Menacho K et al. Curr Radiol Rep (2020) 8:2*



Abdel-Gadir et al: UMIMI Study (16): and 8.3 ± 2.4 minutes protocol, 97 patients in Thailand. Cost of scan reduced by a factor of 4. Automated analysis of iron overload. 15% of patient with cardiac $T2^* < 20$ ms. Reprinted with permission of authors.



Fernandes Juliano et al (15): a 5.2 minutes (4 – 7 min)/ 7.5 ± 1.8 min (with cine). 7 centers in India. 179 patients. Comparison automated vs manual analysis: -1.2 ms (95% CI -1.7 to -0.8 ms). Reprinted with permission of authors.

Figure 14: Abbreviated CMR Protocols for $T2^*$ iron assessment proposed by Abel Gadir and Fernandes. Reprinted and modified from *Rapid Cardiac MRI protocols Feasibility and Potential Applications* by Menacho K et al. *Curr Radiol Rep* (2020) 8:2

- *Coronary Artery Disease*: Another major indication for CMR is the assessment of ischaemic heart disease (IHD), both from a diagnostic point-of-view as well as for risk stratification. Recent multicenter trials in patients with stable coronary artery disease (CAD) have shown that CMR is superior, and it is cost-effective when compared to SPECT (122), with comparable accuracy to fractional flow reserve - FFR (123). However, the main limitations of stress perfusion CMR are longer scan times (around 45-60 minutes), the requirement for advanced training for radiographers, and the need for specialized equipment. Foley et al., however, have demonstrated that perfusion

CMR can also be accelerated (124). The investigators scanned 18 patients with new chest pain and IHD. The average scan time was 17.2 ± 0.5 minutes. The authors reduced the scan time using the two following approaches: 1) speeding up the acquisition using novel CMR sequences such as 3D mDIXON LGE, and 2) by using only one IV cannula, acquiring only stress perfusion images, which is known to provide the highest diagnostic yield (40, 124, 125). See Figure 15.

This study's results are encouraging, suggesting that ischaemia assessment by CMR may take as little as 20 minutes. Such an abbreviated protocol not only increases efficiency but may also impact positively on the patient experience. However, the broader application of such protocols in LMICs is currently limited for several reasons. Firstly, access to the latest scanner models and software is required. Secondly, there is a need for specialised equipment and local expertise.

In contrast, many LMICs continue to rely on alternative methods of ischaemia evaluation, which may be more easily accessible or cheaper or more familiar, or all of the above. Examples include exercise treadmill tests, scintigraphy, cardiac CT, or proceed straight to angiography). These techniques reduce the likelihood of adoption of stress perfusion CMR into clinical practice in LMICs.

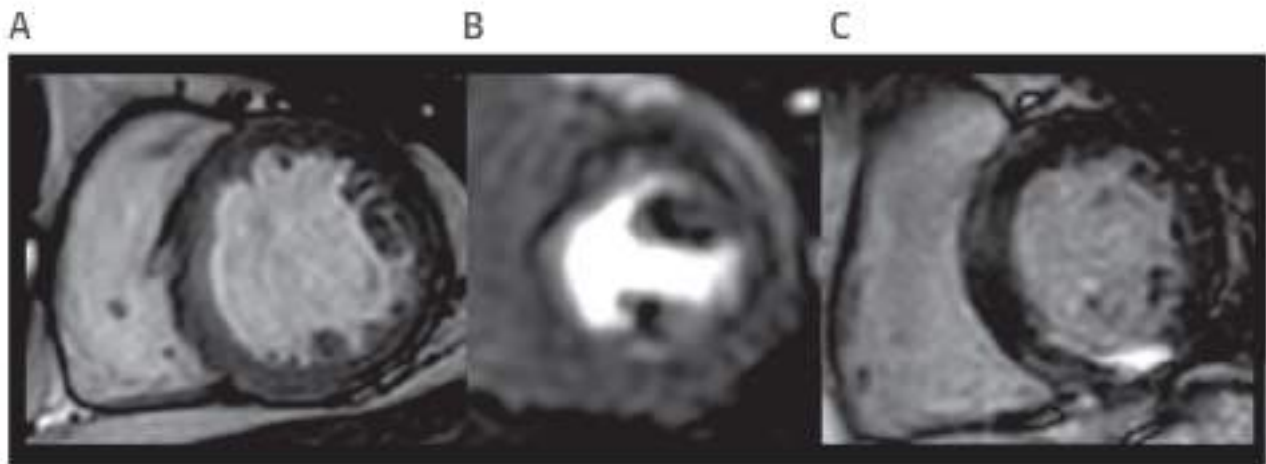


Figure 15: Representative Images from Rapid-IHD protocol – 15 participants had CMR for IHD investigation – Meantime for scanning $17.2 \pm 0.5\text{min}$ (A) Short-axis cine of the left ventricle. (B) Mid-ventricular slice of the left ventricle during stress perfusion showing an anterolateral perfusion defect. (C) Mid-ventricular slice showing late gadolinium enhancement imaging showing a subendocardial inferior scar. Adapted from Foley JRJ, et al. Rapid Cardiovascular Magnetic Resonance for Ischemic Heart Disease Investigation (RAPID-IHD). JACC Cardiovasc Imaging. 2020;13(7):1632-4.

-Other Indications: Additional sequences in CMR, such as parametric mapping (126), velocity encoded flow, and angiography, are more complex, not available in all scanner models, and higher need of training required. Therefore, these sequences may potentially reduce the incremental benefit of CMR if not selectively applied (103).

Cardio-oncology is another field, which could potentially benefit from rapid CMR protocols. There is an increasing awareness of the heart and circulation as potential targets for damage associated with cancer treatment, with cardio-toxicity often being the main determinant of treatment selection and patient outcome (127). In this context, early identification of cardiovascular involvement has primarily relied on cardiac blood biomarkers and LV function assessment by echocardiography or MUGA scintigraphy, and this continues to be reflected in international guidelines (128-130). In addition to a precise and reproducible assessment of LV function, the unique tissue characterisation properties of CMR have recently gained attention. This is of particular interest in novel

immunological therapies, where myocardial inflammation is a well-recognised phenomenon (131). In the future, CMR is therefore likely to play an increasing role in the early diagnosis of heart involvement, patient selection, and monitoring of cardio-protective strategies (132, 133). In the exceedingly busy schedule of current-day oncology patients, the use of abbreviated CMR protocols is an attractive proposition and currently under active investigation (134).

Chapter 2: Research Aims

2.1 Improving the access of Cardiac Magnetic Resonance in Low-Middle Income Countries – Rapid CMR

Improving the access of Cardiac Magnetic Resonance in Low-Middle Income Countries - Rapid CMR Study was the main project of my PhD and the focus of my funding application, which was granted by both the The Peruvian Scientific, Technological Development and Technological Innovation (FONDECYT), Global Engagement Office, University College London and The UK Foreign Commonwealth Office, Peru prosperity Fund 2016 – *Health project: Improving Cardiac diagnosis in Peru*. Most of my efforts were dedicated to this main research, and the data originating from this was the primary basis for the other papers I submitted/ am submitting.

2.1.1. Overview and Study Design:

Rapid CMR is a large multicentre study, 601 patients' observational study of cardiomyopathy patients in five countries, seven cities and eleven centres in Low-Middle Income Countries, and follow-ups between 12 months to 36 months. The impact of the abbreviated CMR protocol was determined by assessing the change in management and new diagnosis in patients.

2.1.2 Hypothesis: We hypothesized that an abbreviated CMR protocol, when embedded with a training and mentoring program, is feasible in LMICs, with an impact on clinical care. This abbreviated CMR protocol could be sustainable, and it could be adopted in more institutions for long-term legacy in LMICs.

These are the other hypothesis that are part of my thesis:

- The use of an efficient CMR protocol can affect treatment and outcome in LMICs. This hypothesis was assessed in chapter 6 of my thesis when studying Rapid CMR to guide chelation therapy in Thalassaemic patients in India – UMIMI study.

-The use of CMIR in LMICS can provide a greater insight into underlying pathophysiology. This hypothesis was assessed in chapter 5 when assessing early myocardial changes in asymptomatic people living with HIV and in chapter 7 when assessing CMR Strain feature tracking for early detection of LV systolic dysfunction in patients with Beta-thalassaemia and myocardial iron overload.

2.1.3 Aims:

The aims of the Rapid CMR project are three-fold:

- To implement an abbreviated CMR protocol for LMICs, and deliver it, embedding it within clinical care, training, and mentoring to promote sustainability
- To test whether the abbreviated CMR is of (in order) technical quality, diagnostic utility, changing management.
- To use CMR as a research method in LMICs, focusing on areas of a specific need to these countries, or exploiting opportunities not available (through geography, demographics, epidemiology or therapeutic options)

2.1.4 Study Design:

This was a multicentre, prospective observational cohort study of patients with the diagnosis of cardiomyopathies having an abbreviated CMR protocol, following the indication of the referral physician in 11 tertiary level referral centres in 7 cities, 5

LMICs. See figure 12. The research received ethical approval in *the United Kingdom*: REC reference: 14/LO/1948, amendment: 3.0, IRAS ID: 142036; University College London REC reference: 11255/002 (contrast CMR studies cardiomyopathies) and 11255/001 (non-contrast CMR studies – UMIMI study India), as well as the corresponding local ethical approval in the participant centres. The study followed the principles of the Helsinki Declaration, and all subjects gave written consent to participate. See Figure 16 for PhD Timeline and Figure 17 for Planned Study Flow Chart.

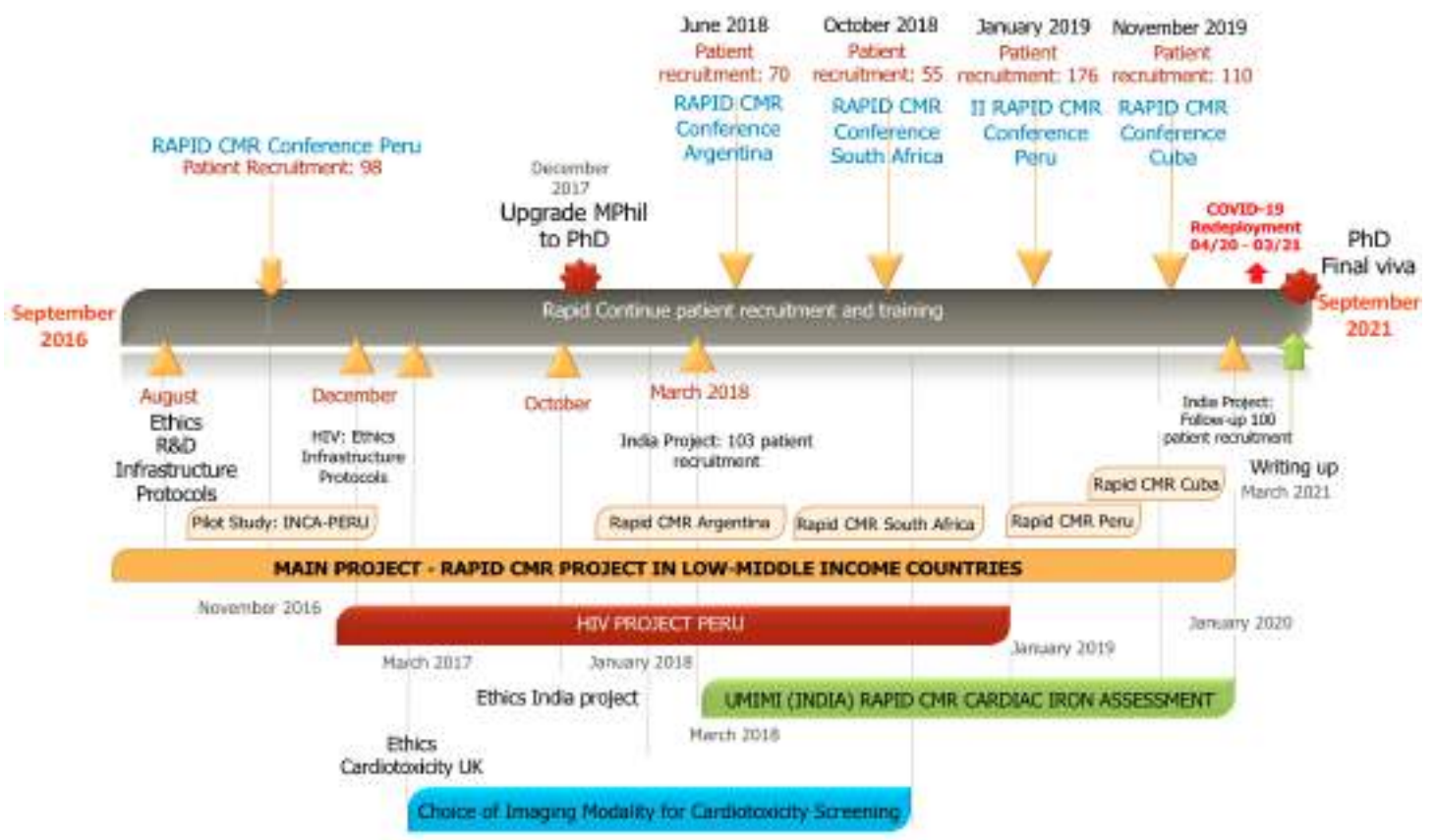


Figure 16: PhD Timeline – Improving the Access of Cardiac Magnetic Resonance in Low-Middle Income Countries to Improve Cardiac Care: Rapid CMR.

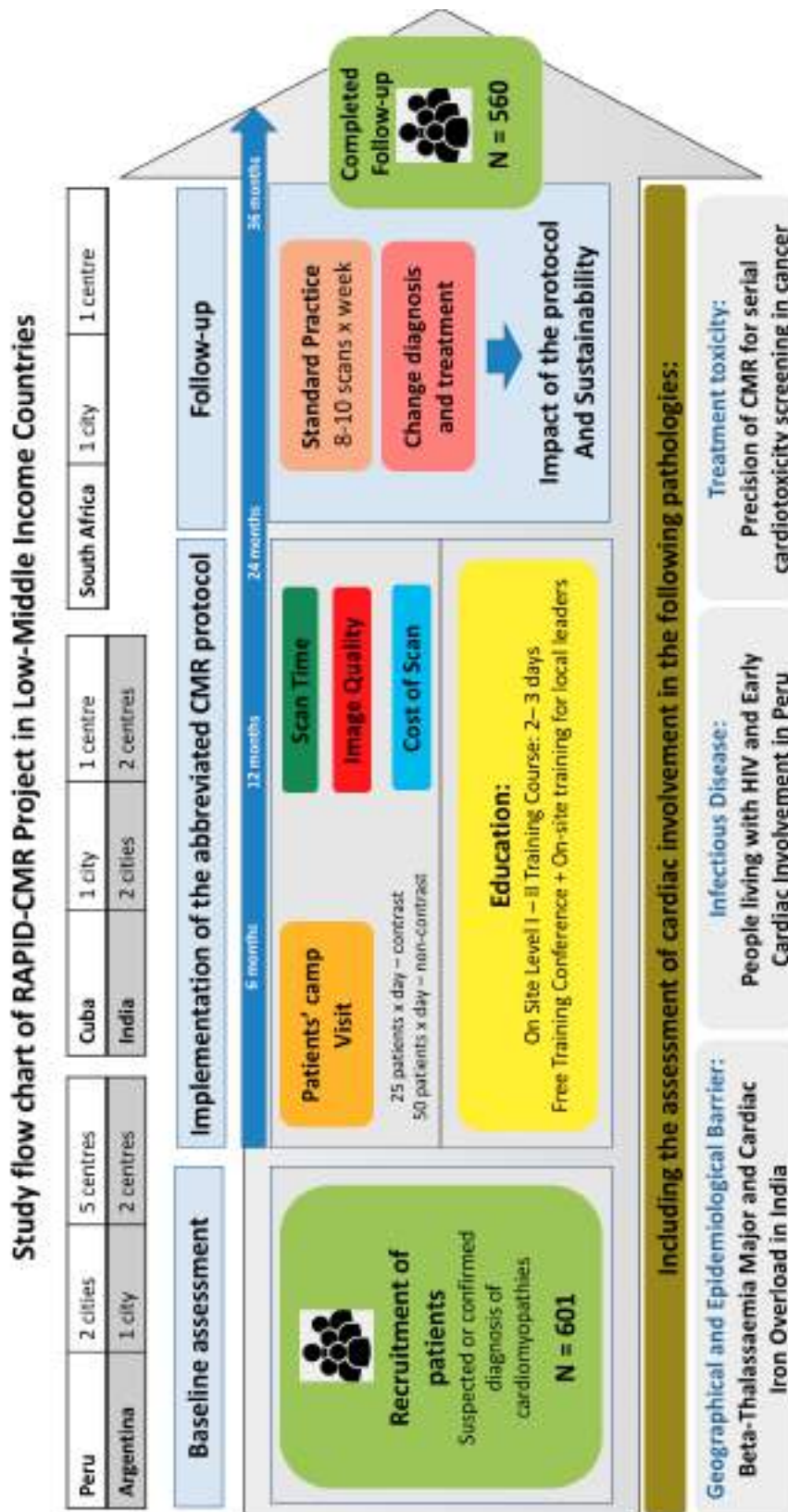


Figure 17: Planned Study Flow Chart for the Improving the Access of Cardiac Magnetic Resonance in Low-Middle Income Countries to Improve Cardiac Care: Rapid CMR Project

2.1.5 Patient Selection:

Inclusion criteria:

- Age \geq 18 years.
- a) Confirmed or suspected diagnosis of cardiomyopathies:
 - Myocardial infarction with nonobstructive coronary arteries (MINOCA).
 - Hypertrophic cardiomyopathy (HCM, including a first-degree family member of a patient with HCM).
 - Surviving patient post-cardiac arrest.
 - Ischaemic cardiomyopathy to assess viability.
 - Cardiotoxicity (including screening).
 - Arrhythmia induce cardiomyopathy.
 - Rare cardiomyopathies: cardiac Amyloidosis, cardiac iron overload cardiomyopathies (e.g. patients with Beta-Thalassemia, hemochromatosis), Fabry disease cardiomyopathy.
 - Cardiomyopathies in patients with autoimmune disease (e.g., Lupus, Systemic Sclerosis).
 - Myocarditis and pericardial diseases (e.g., constrictive pericarditis).
 - Idiopathic dilated cardiomyopathy - DCM (negative perfusion, normal angiogram).
 - Left Ventricle Non-compacted cardiomyopathy (LVNC).
 - Arrhythmogenic right ventricle cardiomyopathy (ARVC).

Exclusion criteria:

- Pregnancy.
- Breastfeeding.
- Creatinine clearance <30mcg / dl.
- Incompatible devices with CMR.
- Inability to complete the study protocol (e.g., claustrophobic patient).
- Morbid obesity (or inability to access the scanner).
- History of adverse allergic reaction to gadolinium.

2.1.6 Study Outcomes measures:

Impact on management: Patients were followed up between 6 to 36 months by their local care physician. Management changes related to the CMR results were reviewed in consultation with the local general care providers in each of the participant centres. A change of patient management will be reported if CMR resulted in:

- *New diagnosis (of a pathology not suspected before)*
- *Medication change*
- *Interventional treatment*
- *Hospital admission/discharge*

Cost evaluation: Reference of CMR cost in each participant centre was assessed individually, given the fact that health care structure and system is different in each country and cost charges are different. In general, we considered as reference the average cost from public and private hospitals that offer CMR at the time of the scan. The overall cost of the abbreviated CMR

protocol was assessed considering the following variables: hospital charges, contrast, cannula set and ECG sticker costs, and physician (reporting), nurse and radiographer payment per scan.

2.1.7 Recruitment

Patients were recruited by the local research team in each participant centre. Patients were referred by their local Cardiologist and Radiologists. Patients were approached in the in- or outpatient setting and given a patient information sheet (PIS) if interested. Participants provided their consent by signing a Consent Form. Then, they were referred for their CMR scans on the specific days of main intervention.

2.1.8 Justification of sample size/ Power calculations:

The sample size was pragmatic, having as a reference a previous cohort of our institution, Abdel Gadir et al (120) and availability of local MRI scanner time (1-2 working day per centre; 25 patients per 1 day session for abbreviated CMR contrast scans and, 50 patients per 1 day for abbreviated non-contrast CMR scan for cardiac iron assessment).

2.2 Sub-studies:

2.2.1 Impact of Non-Invasive Cardiac Magnetic Resonance Assessment in Peru – INCA PERU study

Background: Cardiac Magnetic Resonance improves the case of cardiac patients by improving diagnosis accuracy and better targeting therapy. However, it is not accessible in most LMICS.

Aims: To implement a faster, cheaper, and easier CMR protocol with a training and mentoring program, starting with a pilot intervention in Lima - Peru, and to assess the impact on patients with impact on clinical care.

2.2.2 Myocardial inflammation and oedema revealed in People Living with Human Immunodeficiency Virus.

Background: Human Immune Deficiency (HIV) related heart disease is an emerging major public health problem, despite effective, available therapy, and the pathophysiological mechanisms responsible for heart involvement remain elusive. Previous research focused only on antiretroviral treated (ART) individuals, thereby confounding interpretation.

Aims: To evaluate changes in myocardial function and structure in people living with Human Immunodeficiency Virus (PLWH) both on ART and those who were ART-naïve, utilizing advanced quantitative cardiovascular magnetic resonance (CMR) in a LMIC, Peru, where untreated patients remain prevalent.

2.2.3 Improved cardiac iron one year after using rapid Magnetic Resonance Imaging to guide chelation therapy: Ultrafast MRI for Iron Management in India – the UMIMI study

Background: Beta-thalassemia is an inherited hemoglobinopathy that requires lifelong transfusion and chelation to prevent iron overload complications. This condition poses a significant health burden, particularly in India, where there is a high prevalence of thalassemia. T2* CMR identifies myocardial siderosis and guides therapy. Traditional CMR methods employ long scan times contributing to cost and limiting access to many, particularly in lower-income nations.

Aims: We included rapid CMR assessment in a day-care thalassemic camp and used the results of cardiac and liver iron provided by CMR to provide recommendations for treatment. A second camp was organized 13 months later, where CMR and clinical assessments were repeated.

2.2.4 Cardiac Magnetic Resonance Strain Feature-Tracking for detection of LV systolic dysfunction in patients with Beta-Thalassemia and myocardial iron overload

Background: Cardiac iron deposition is one of the principal mechanisms causing cardiac complications and deaths in Beta Thalassaemic patients. LVEF detects iron-induced cardiomyopathy at the late stage of the disease.

Aims: To evaluate the diagnostic performance of Cardiac Magnetic Resonance feature tracking myocardial strain to assess temporal changes in early systolic dysfunction due to myocardial iron overload in Beta Thalassaemia patients.

2.2.5 Direct comparison of the measurement precision of MUGA, CMR, and echocardiography for serial cardiotoxicity screening in cancer patients

Background: Small changes in left ventricular ejection fraction (LVEF) gatekeeper major treatment decisions, particularly when screening for chemotherapy-related cardiotoxicity, meaning both measurement accuracy and precision must be high.

Aims: To compare the precision of LVEF and global longitudinal strain (GLS) measurement using repeat (test-retest) imaging across three modalities - 2D/ 3D echocardiography (2DE, 3DE), multi-uptake gated acquisition (MUGA) nuclear imaging, and cardiovascular magnetic resonance (CMR) with additional machine-learning (ML) analysis.

2.2.6 Improving the access of CMR in LMICs: Rapid CMR

Background: Cardiac Magnetic Resonance is an emerging imaging technique that provides reliable information for the diagnosis and guiding therapy to patients. We previously showed that a simplified CMR protocol could be implemented in a single centre in a capital city in one LMIC. However, access to CMR is still limited in most LMICs. To make this proof-of-principle study a reality in more LMICs, the rapid CMR program was implemented at a multicentre level.

Aims: This study aimed to evaluate the potential impact of a simplified and cheaper CMR protocol for the assessment of cardiomyopathies at a multicentre level in 5 LMICs, and implementing rapid CMR with an education and training program.

Chapter 3: Material and Methods

3.1 Ethical Approval:

The research received ethical approval in *the United Kingdom*: REC reference: 14/LO/1948, amendment: 3.0, IRAS ID: 142036; University College London REC reference: Ultrafast cardiac magnetic resonance in developing countries to improve cardiac care and 11255/001 (non-contrast CMR studies – Ultrafast Cardiac Magnetic Resonance for Iron Management in India – UMIMI study) and 11255/002 (Ultrafast cardiac magnetic resonance in developing countries to improve cardiac care) as well as the corresponding local ethical approval in each participant centres:

Peru - Lima: *Edgardo Rebagliati Martins Hospital*, Institutional Ethics Committee: IRB No 00003285/Arch 1047, NIT 832–2016–1066. *Hospital Central Fuerza Aerea del Peru*: Confirmation letter from Medical Director Dr Luis Luyo Vera on 26/01/2018. *Hospital Guillermo Almenara*: Confirmation Letter from Head of the Cardiology department Dr Gerald Levano Pachas on 19/01/18. *Hospital Militar*: Confirmation Letter (AA-11/5/d/1/15.00) from the General Director Erwin Solis Ochoa on 09/01/2019. **Arequipa:** Confirmation letter from Medical Director Dr Cesar A Flores, Sermedial Hospital, issued on 10/01/2019. *Chiclayo*: NIT – 1928-2019-4437.

- **Argentina – Buenos Aires:** *Instituto Medico de Alta Tecnologia (IMAT)* – Ethics Committee Approval Letter issued by the President of the Ethical Committee Dr Federico Lucas, on 14/05/2018. *Hospital Italiano* - Ethics Committee Approval Letter issued by President of the Ethics Committee (Ricardo Garcia Monaco) on 10/05/2018.

- **South Africa – Cape Town**, *Hospital Groote Schuur*. HREC REFR: 638/2018. Approval Letter raised by the Human Research Ethics Committee on 08/10/2018 (Professor M Blockman).
- **Cuba – La Havana**, *Instituto de Cardiologia y Cirugia Cardiovascular*: Ethic Committe Approval Letter issued by the President of the Ethical Committee Dr Antonio Castillo Guzman on 18/05/2019.
- **India**: - Institutional Ethics Committee – Clinical Studies, **New Delhi**: Reg. ECR/5/Inst/DL/2013/RR-16, Ref: IEC Application N: IAH/078/10/18, approved on 05/10/2018. **Jaipur**: N – IEC/2019/01 issued on 18/01/2019 (Dr Rohit Jain).

Sub-studies: Ethical Approval:

- *Myocardial inflammation and oedema revealed in People Living with Human Immunodeficiency Virus – Lima, Peru*. International Clinic in Lima, Peru (Research and Teaching Department, reference number: UDID 005 – 2017).
- *Direct comparison of the measurement precision of MUGA, CMR, and echocardiography for serial cardiotoxicity screening in cancer patients*: The study was approved by the UK National Research Ethics Service (16/LO/1815)
- *Ultrafast Cardiac Magnetic Resonance for Iron Management in India – UMIMI study*: Institutional Ethics Committee – Clinical Studies, New Delhi: Reg. ECR/5/Inst/DL/2013/RR-16, Ref: IEC Application N: IAH/078/10/18, approved on 05/10/2018. Jaipur: N – IEC/2019/01 issued on 18/01/2019 (Dr Rohit Jain).

3.2 Patients:

3.2.1 Patients referred for the Abbreviated CMR Protocol:

The local research team in each of the participant centres recruited patients (led by a Consultant Cardiologist or Radiologist with a Level II – III training in CMR and a Consultant Haematologist for the Thalassemic patient's cohort). Their case was previously discussed with the referral patient's physician, discussing the indication for the CMR scan and the specific question they want to be responded to after the imaging study. *The inclusion criteria* for the abbreviated CMR scan were: confirmed or suspected diagnosis of cardiomyopathies: myocardial infarction with nonobstructive coronary arteries (MINOCA), hypertrophic cardiomyopathy (HCM, including first-degree family member of a patient with HCM, surviving patient post-cardiac arrest), ischaemic cardiomyopathy to assess viability, cardiotoxicity (including cardiac function screening), dilated cardiomyopathy, arrhythmia induced cardiomyopathy, rare cardiomyopathies (cardiac amyloidosis, cardiac iron overload cardiomyopathies, Fabry disease with cardiac involvement, cardiomyopathies in patients with autoimmune disease (e.g., Lupus, Systemic Sclerosis), myocarditis, pericardial diseases (e.g., constrictive pericarditis), idiopathic dilated cardiomyopathy (negative perfusion, normal angiogram), non-compacted left ventricle cardiomyopathy, right ventricle arrhythmogenic cardiomyopathy. *The exclusion criteria* were: pregnancy, breastfeeding, creatinine clearance <30mcg / dl, incompatible devices with CMR, inability to complete the study protocol (e.g., claustrophobic patient), morbid obesity (or inability to access the scanner), history of adverse reaction to gadolinium.

3.2.2 People Living with HIV: For this sub-study, ART-treated and non-treated participants living with HIV, who were asymptomatic from a cardiac perspective, were recruited. Patients were referred from Cayetano Heredia Hospital, Infectious Disease Service, in Lima - Peru. All participants were older than 18-year-old. Treatment-naïve patients were defined as newly diagnosed patients with HIV infection, with CMR performed either before or within 14 days of the start of a first-line ART regimen (consisting of two nucleoside reverse transcriptase inhibitors and one non-nucleoside reverse transcriptase inhibitor).

3.2.3 Cardiotoxicity Screening in cancer patients: This sub-study included cancer patients referred for clinical cardiotoxicity surveillance using echocardiography, MUGA, or CMR at Barts Heart Centre, London, United Kingdom. Participants were aged 18 or above who were booked for a cardiac imaging investigation to assess their left ventricular systolic function as part of their routine screening for cardiac toxicity resulting from cancer therapies. Some patients were imaged before starting chemotherapy,

3.2.4 Beta-thalassaemic patients for Cardiac iron assessment: All patients were enrolled in Delhi and Jaipur in India. All participants had the diagnosis of Beta-Thalassemia intermedia and major, and they were over 16-year-old. The Thalassaemic Patient Society invited all participants to attend their routine Patient Camp in India, where this project was carried out.

3.3 Magnetic Resonance Imaging Scanners:

Participants underwent the abbreviated CMR protocol at different scanner models, following the accessibility of the machine in each participant centre:

- Lima, Peru: Hospital Nacional Edgardo Rebagliati Martins (1.5 Tesla, Magnetom Avanto, Syngo MR B15, Siemens Medical Solutions, Germany); Hospital Guillermo Almenara (1.5 Tesla, GE Healthcare Signa HDxt), Hospital Fuerza Aerea del Peru (Achieva 3.0T TX DR MR System); Hospital Militar (Ingenia 1.5T CX MR System).
- Arequipa, Peru: Hospital Sermedial (Ingenia 1.5T CX MR System).
- Buenos Aires, Argentina: Instituto Medico de Alta Tecnologia, IMAT (1.5T Aera, Siemens Medical Solutions, Germany) and Philips Ingenia 1.5T CX MR System. Hospital Italiano (1.5 Tesla, Magnetom Avanto, Syngo MR B17, Siemens Medical Solutions, Germany).
- Cape Town, South Africa: University of Cape Town and Groote Schuur Hospital, Cape Town, South Africa (1.5T Aera, Siemens Medical Solutions, Germany and 3T Magnetom Skyra Siemens Medical Solutions, Germany).
- New Delhi, India: Mahajan Imaging Centre (1.5T GE Healthcare Signa HDxt)
- Jaipur, India: Okay Diagnostic Centre (1.5T Siemens Avanto Syngo MR B17).

3.4 Abbreviated Cardiovascular Magnetic Resonance Protocol:

We originally developed the abbreviated CMR protocol (cardiac volumes, function, and tissue characterization with Late Gadolinium Enhancement) after scanning 12 Healthy Volunteer participants at the Heart Hospital, UCLH, using a 1.5T scanner, Avanto, Siemens, Healthineers, Erlangen Germany) in October 2016 (135). For the non-contrast CMR Protocol, 12 Healthy Volunteer participants were scanned at Mahajan Imaging Centre (1.5T GE Healthcare Signa HDxt), Delhi and Okay Diagnostic Centre (1.5T Siemens Avanto Syngo MR B17) in Jaipur, India in November 2018. All healthy volunteers had no history of cardiovascular disease or other comorbidity.

3.4.1. Abbreviated Non-Contrast CMR Cardiac Iron Protocol: (120, 121). See

Figure 18

- A. Localizers:** A pilot three-plane localizer, a transverse bright blood single shot-fast spin-echo stack for anatomic evaluation (optional ungated), with the following settings: repeat time (TR): 3.39ms, echo time (TE): 1/7ms, slice thickness 5mm, field of view (FOV): 360 x 360mm, red matrix 256 and flip angle 60.
 - B. Pilots:** Two chamber view and five slices short axis stack.
 - C. Volume and cardiac structure assessment - Longitudinal axis:** Steady-state free precession (SSFP) cine images were undertaken in four, two, three-chamber cine acquisitions) \pm aortic valve (optional). Retrospective ECG gating was used with 25 phases. Typical imaging parameters were: echo (TE) 1.1ms, time of repetition (TR) 2.7ms, flip angle 80°, Grappa factor 2, voxel size 1.8x1.8mmx6mm, x-y spatial resolution 1 to 2mm/pixel, slice thickness 8mm.
- (103)

D. Volume and cardiac structure assessment - SAX cine stack – echo time (TE) 1.1ms, time of repetition (TR) 2.7ms, flip angle 80°, Grappa factor 2, voxel size 1.8x1.8mmx8mm, x-y spatial resolution 1 to 2mm/pixel, slice thickness 8mm, inter-slice gap 2mm, 10 segments (true temporal resolution 27ms, reconstructed temporal resolution 22-33).

E. Iron Assessment: Cardiac (T2*) - 1 single mid short-axis slice, Liver (T2*) – a transversal single slice trying to cover the maximum liver parenchyma. T2* heart: Multiecho gradient echo with 6-9 echo times equally ranging from ~2ms to ~18ms – 1.5T (increment ~2ms). For liver: ~1ms, increment ~1ms, up to 12ms.

Optional: In patients with severe iron overload, a pulse sequence with shorter echo spacing could be helpful to accurately determine at ~1ms and extending to 1~2ms, with each echo iteratively spaced by ~1ms.

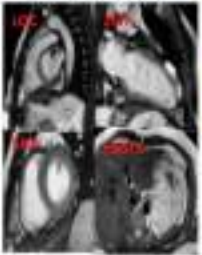
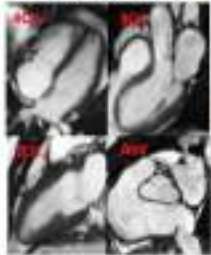
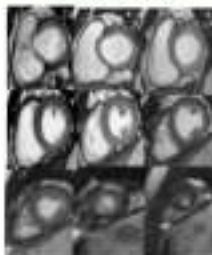

Localizer Scout	Longitudinal Cine	SAX CINE (SSFP)	T2*: HEART AND LIVER
<p style="text-align: center;">3 MINUTES</p> <p style="text-align: center;">LOCALIZER IMAGES</p> 	<p style="text-align: center;">3-4 MINUTES</p> <p style="text-align: center;">LONGITUDINAL CINE</p> 	<p style="text-align: center;">4-5 MINUTES</p> <p style="text-align: center;">SHORT AXIS CINE</p> 	<p style="text-align: center;">3 MINUTES</p> <p style="text-align: center;">T2* GRADIENT ECHO</p> 

Figure 18: Non-Contrast Rapid CMR Protocol for Cardiac and Liver Iron Assessment. ** For poor breath-holders and patients with arrhythmia, consider replacing cine and late gadolinium enhancement (LGE) with sequences in Table 5. Reprinted from Rapid Cardiac MRI protocols Feasibility and Potential Applications by Menacho K et al. I Curr Radiol Rep (2020) 8:2

3.4.2. Abbreviated Contrast CMR Cardiomyopathy Protocol: (135, 136). See

Figure 19

A. Localizers: A pilot three-plane localizer, a transverse bright blood single shot-fast spin-echo stack for anatomic evaluation (optional ungated), with the following settings: repeat time (TR): 3.39ms, echo time (TE): 1/7ms, slice thickness 5mm, field of view (FOV): 360 x 360mm, red matrix 256 and flip angle 60.

B. Pilots: Two chamber view, five slices short axis stack.

C. Volume and cardiac structure assessment - Longitudinal axis: Steady-state free precession (SSFP) cine images were undertaken in four, two, three-chamber cine acquisitions) \pm aortic valve (optional). Retrospective ECG gating was used with 25 phases. Typical imaging parameters were: echo (TE) 1.1ms, time of repetition (TR) 2.7ms, flip angle 80°, Grappa factor 2, voxel size 1.8x1.8mmx6mm, x-y spatial resolution 1 to 2mm/pixel, slice thickness 8mm. (103)

Contrast injection by hand (dose 0.1mmol/kg) gadoterate meglumine/gadobutrol. A low dose of contrast before cine imaging acquisition: The minimum dose of contrast suggested at 0.1mmol/kg: Endocardial definition is adequate after gadolinium contrast, performing accurate measurement of left ventricular mass and volumes. (136)

D. Volume and cardiac structure assessment - SAX cine stack - echo (TE) 1.1ms, time of repetition (TR) 2.7ms, flip angle 80°, Grappa factor 2, voxel size 1.8x1.8mmx8mm, x-y spatial resolution 1 to 2mm/pixel, slice thickness

8mm, inter-slice gap 2mm, 10 segments (true temporal resolution 27ms, reconstructed temporal resolution 22-33).

E. Late Gadolinium Enhancement Imaging: repeating cine views as needed, followed by an optional sequence to determine the optimal inversion time and segmented k-space late gadolinium enhancement acquisitions in multiple planes with Phase Sensitive Inversion Recovery sequence (PSIR) and magnitude reconstructions (MAGIR). Slice thickness 8mm TR: 9.8ms, TE: 4.6m, α : 21o, FOV 340 x 220 mm (transverse plane), sampled matrix size 256 x 115-135, 21 k-space lines acquired every other RR interval (21 segments with linear reordered phase encoding), spatial resolution 1.3 x 2.1 x 8 mm. (103)

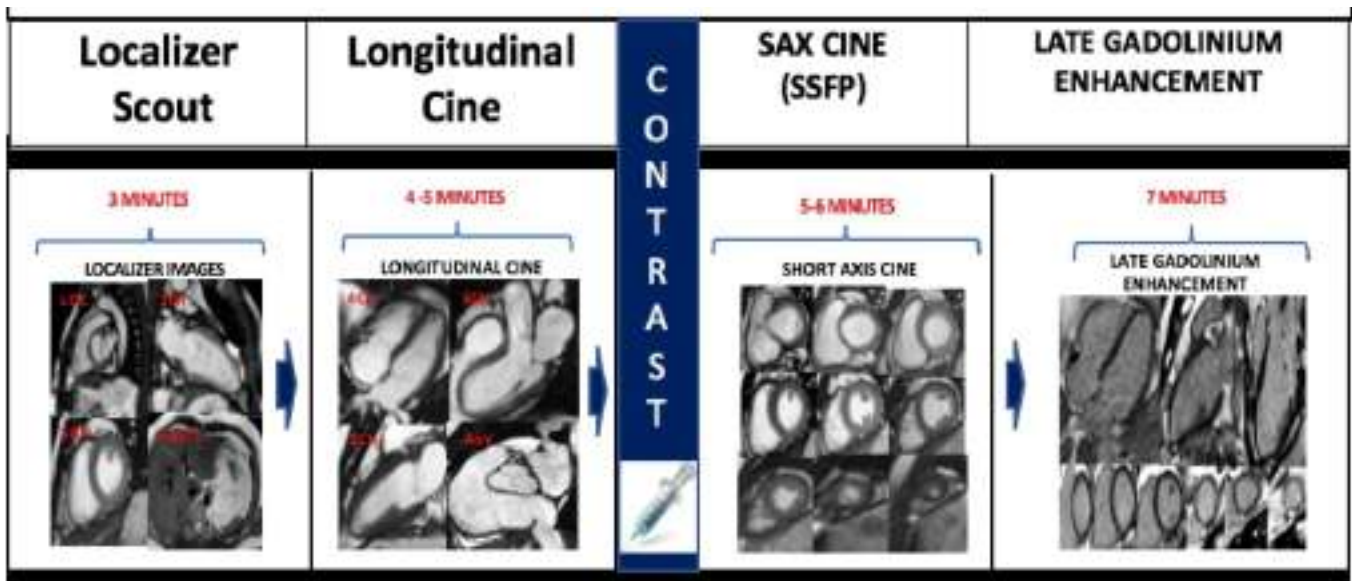


Figure 19: Contrast Rapid CMR Protocol ** For poor breath-holders and patients with arrhythmia, consider replacing cine and late gadolinium enhancement (LGE) with sequences included in Table 5. Reprinted from Rapid Cardiac MRI protocols Feasibility and Potential Applications by Menacho K et al. Curr Radiol Rep (2020) 8:2

Modifications of the abbreviated CMR protocol:

-For poor breath-holders and patients with arrhythmia, further modifications to the protocol were made. See Table 5. The use of one of the specific sequence was based on the availability of the sequences in the MRI scanner (103).

A) Imaging Poor Breath Holders - Cine Sequences (137)	
Acceleration Technique (113)	Comment
Reduce the number of phases for each breath-hold: <ul style="list-style-type: none"> - By reducing the acquisition matrix - By reducing the field of view (FOV) 	Reduces the Signal-noise ratio (SNR) Increases spatial resolution
Increase voxel size	Decrease spatial resolution
Use parallel imaging (110)	Prone to artifact
Acquire imaging in inspiration	Varying slice position with each breath-hold
B) Imaging Patients with arrhythmia – Cine Sequences	
Heart rate and rhythm control before scanning	Use beta-blockers or other antiarrhythmic medication
Use Prospective triggering (112)	Reduces SNR
Use Real-time imaging	Reduces temporal, spatial resolution, and SNR
C) Imaging Poor Breath-Holders and patients with arrhythmia – Late Gadolinium Enhancement	
Single-shot Inversion Recovery (IR) (138)	A single breath-hold. Moderately lower contrast-to-noise ratio (CNR), allowing fast and accurate determination of scar with a high spatial resolution

Table 5: Modification of Rapid CMR protocol for poor breath-holders, arrhythmia patients. Reprinted from Rapid Cardiac MRI protocols Feasibility and Potential Applications by Menacho K et al. I Curr Radiol Rep (2020) 8:2 (103)

- When available in the scanner, one single T1 mapping mid-SAX and 4CH view pre-contrast (native T1 mapping) and post-contrast (at 10 minutes post-contrast

administration)

- For Arrhythmogenic ventricular cardiomyopathy (ARVC):

1) Transaxial or oblique transaxial bSSFP cine images (slice thickness 5-6mm) covering the RV, including RV outflow tract (RVOT).

2) Selected black blood images (4CH, 3CH, 2CH, and 3 SAX slices: base, mid, and apex) + repeat same geometry with fat suppression.

- For Myocarditis:

1) Selected native T1 mapping, T2 mapping, or T2w STIR Sequences at 4CH, 3CH, 2CH, and 3 SAX slices: base, mid, and apex.

- For Pericardial Disease:

a) T1 or T2-weighted FSE images in one representative long-axis and one representative short-axis images to measure the pericardial thickness.

b) Real-time imaging during dynamic breathing manoeuvres for evaluation of ventricular interdependence (mid-ventricular short-axis).

3.5 Post-Processing Cardiac Magnetic Resonance Analysis

Imaging Reporting: Images were analysed using cvi42 (Circle Cardiovascular Imaging Inc, Version 5.11.4 – 1559, Calgary, Canada) with a provided typically a three-month ongoing license to participating centres. Scans were reported the same day by the local doctor, supported, and reviewed by the international visiting experts (final report signed-off by a doctor with a level 2 or 3 CMR EACVI – ESC certification or equivalent) (139). After the on-site intervention, the participant centres used other software (e.g. Osirix, ARGUS, and free online post-processing software for cardiac and iron T2* analysis - <http://www.isodense.com/mcdcm/mviewer.html>).

3.5.1 Post-Processing Analysis of Cardiac Iron T2*:

Cardiac T2*: Images were analyzed using CVI42 (Version 5.11.4 - 1559, Calgary, Canada). For cardiac iron assessment using the breath-hold GRE T2* Dark Blood – White Blood Sequence, the post-processing CMR analysis was restricted to the septum, drawing a full-thickness ROI by limiting the epicardial and endocardial border. A truncation method was applied to calculate cardiac iron values, discard the late “plateau” points and fit each ET to a monoexponentially equation (140). For liver T2* analysis, a full-thickness ROI was made to cover the maximum liver parenchyma and avoid blood vessels. See figure 20.

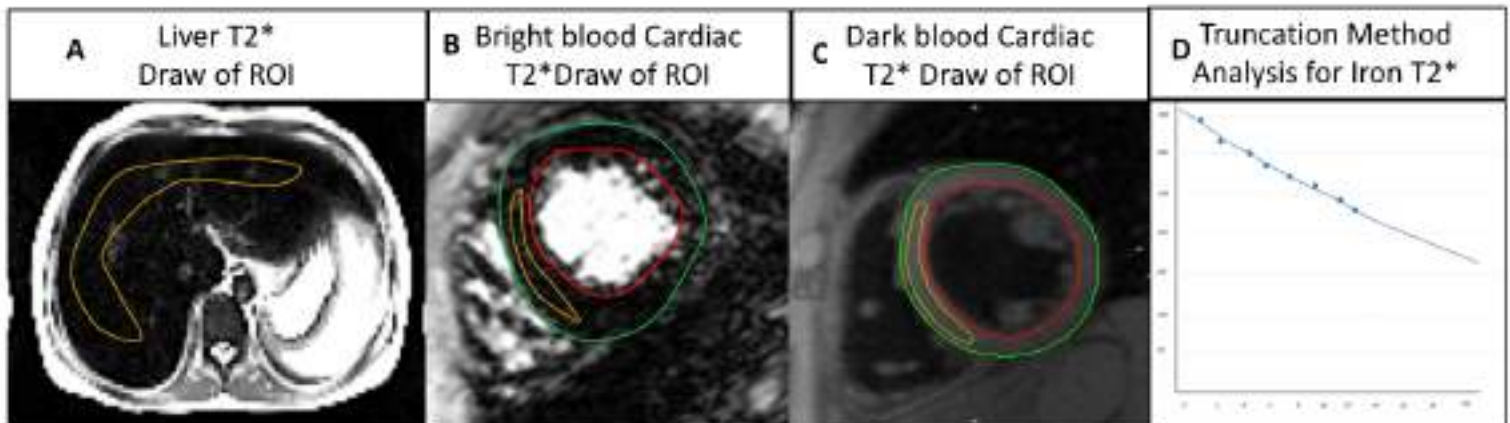


Figure 20: Analysis of Cardiac and Liver T2* Images: Example of (A) Liver T2*, (B) Bright Blood Cardiac T2*, (C) Dark Blood T2*; and (D) Truncation Method of analysis applied to obtain T2* CMR Results. For the regions of interest (ROI) in the liver, the borders were drawn, covering most of the liver parenchyma and avoiding blood vessels regions. For cardiac T2* ROI, endocardial (red) and epicardial (green) borders were manually drawn.

3.5.2 Post-Processing Analysis of Cardiac Function: CMR image analysis was performed using CVI42 software (Version 5.11.4 – 1559 - Circle Cardiovascular Imaging, Alberta, Canada) following international experts' consensus (41). Contiguous SAX slices were segmented using a semi-automated thresholding technique to derive left ventricle (LV) and right ventricle (RV) end-diastolic volume (EDV), end-systolic volume (ESV), stroke volume (SV), LVEF, RVEF, and LV mass, with allometric scaling using body surface area. To address basal slice variability, blood volume was included if there was over 50% of LV myocardium surrounding blood pool, and a longitudinal axis atrioventricular plane correction was used. The left ventricular outflow tract was included in the blood volume, and LV papillary muscles were included as part of LV mass and excluded from the LV volume. See Figure 21.

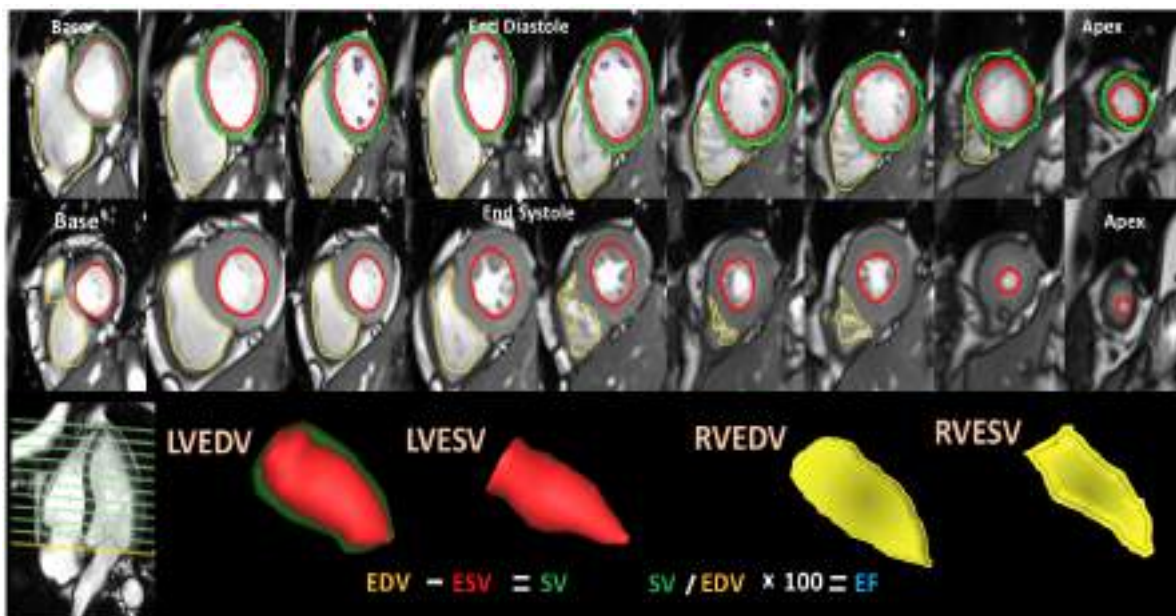


Figure 21: Post-Processing Analysis of Cardiac Systolic Function: Contiguous SAX slices were segmented using a semi-automated thresholding technique, defining the endocardial and epicardial contours, RV and LV end-diastolic volume (EDV), end-systolic volume (ESV), stroke volume (SV), EF and LV mass were derived by the software. LV papillary muscles were included as part of LV mass and excluded from the volume

- Post-processing of late gadolinium enhancement (LGE) of the left ventricle:

Most of the contrast scans indicated for assessing cardiomyopathy, a visual assessment of LGE were completed. Using the post-processing software CVI42 software (Version 5.11.4 – 1559 - Circle Cardiovascular Imaging, Alberta, Canada), the following steps were followed as advised by international experts consensus (41):

- *Modification of image window and level* if: 1) Detectable noise is present; 2) LGE regions are not saturated.
- *Criteria of LGE presence*: 1) High Signal Intensity (SI) areas that are brighter than the nulled myocardium; 2) Compare the positive results of LGE presence with one other orthogonal or matching the same plan but with a different readout direction.
- *Pattern of LGE*: 1) Coronary artery disease (CAD) pattern of distribution: The LGE distribution should involve the sub-endocardium and matches a coronary artery perfusion territory. 2) Non-CAD-type pattern of distribution: LGE usually spares the sub-endocardium, and it involves the mid-wall or the sub-epicardium. However, a global sub-endocardial distribution of LGE should still be considered in non-CAD type disease. (141)
- *For the interpretation of location and extension in CMR Viability Scans, using AHA 17-segment model*: Comparison of LGE images were made to cine images for a correct categorization of viability. The estimation of transmural extent of LGE was assessed in each segment as it follows: 0%, 1-25%, 26.50%, 51-75%, 76-100%. (142).

3.6 Recruitment of Participants

Patients were recruited by the local research team in each participant centre. Patients were referred by their local Cardiologist and Internal Medicine doctor. Patients were approached in the in- or outpatient setting and given a patient information sheet (PIS) if interested. Then, they were referred for their CMR scans on the specific days of the main intervention. Participants provided their consent by signing the Consent Form, provided and explained by the local and international team.

3.7 Cardiac Magnetic Resonance Image Quality:

Following image acquisition, datasets were assessed for image quality by a CMR expert on the field (Level II - III EACVI-ESC certified cardiologist)

- CMR images that did not answer the clinical question were considered as poor quality.
- Those with artifacts but still interpretable were graded as moderate quality.
- Images with optimal quality allowing definitive assessment of the clinical question were graded as good quality.

3.8 Study Outcomes measures:

Patients were followed up between 6 to 36 months by their local care physician. Management changes related to the CMR results were reviewed in consultation with the participant centres' local general care providers. A change of patient management would be reported if CMR resulted in:

- *New diagnosis (of a pathology not suspected before)*
- *Medication change*
- *Interventional treatment*

- *Hospital admission/discharge*

3.9 Cost evaluation:

Reference of CMR cost in each participant centre was assessed individually, given the fact that health care structure and the system is different in each country and costs charges are different. However, in general, we considered as reference the average cost from public and private hospitals that offer CMR at the time of the scan. To determine the overall cost of the abbreviated CMR protocol, the following variables were included: hospital charges, contrast and cannula costs, and physician (reporting), radiographer and nurse payment.

3.10 Statistical Analysis:

For the main project of my thesis, “Improving the access of Cardiac Magnetic Resonance in Low-Middle Income Countries – Rapid CMR”, statistical analysis was completed using SPSS (version 24.0, Statistical Package for the Social Sciences, International Business Machines, Inc., Armonk, New York, United States). Continuous data were expressed in mean with standard deviation, and categorical data were presented as absolute numbers and percentages. Normal distribution was formally tested using the Shapiro-Wilk test. Groups were compared using independent-samples t-test for normally distributed continuous variables, and the Mann-Whitney U test for non-normally distributed variables, and the Chi-squared test for binomial variables.

Continuous data were compared using two-sided Student's t-tests, and categorical variables compared using Chi-squared or Fisher's exact test. If demonstrated normality, Pearson correlation coefficient test was used, whereas Spearman

correlation coefficient was used for non-normality distributed variables. The unstandardized coefficient B and a 95% confident interval were requested. A two-sided p-value of <0.05 was considered significant.

For three sub-studies of my thesis: 1) Direct comparison of measurement precision of MUGA, CMR and echocardiography, 2) Myocardial inflammation and oedema revealed in People Living with Human Immunodeficiency Virus, and 3) Cardiac Magnetic Resonance Strain Feature-Tracking for detection of LV systolic dysfunction in patients with Beta-Thalassemia and myocardial iron overload, different methods of statistical analysis were used which will be described in the corresponding chapter (R analysis used for the research of direct comparison of measurement precision of MUGA, CMR, and echocardiography).

Chapter 4: Results 1: Impact of Non-Invasive Cardiac Magnetic Resonance Assessment in Peru – INCA PERU study

4.1.1 Preface

This chapter is based on the publication below

Menacho Katia, Ramirez Sara, Segura Pedro, Abdel-Gadir Amna, Illatopa Violeta, Bhuva Anish, Benedetti Giulia, Boubertakh Redha, Abad Pedro, MD; Rodriguez Bertha, Medina Felix, Treibel Thomas, Westwood Mark, Fernandes Juliano, Walker J Malcolm, Litt Harold, Moon James C. *INCA (Peru) study: impact of non-invasive cardiac magnetic resonance assessment in the developing world. J Am Heart Assoc. 2018;7:e008981. DOI: 10.1161/JAHA. 118.008981.*

My contribution to this sub-study was submitting the ethics in the UK (UCL) and Lima – Peru (Edgardo Rebagliati Hospital), recruiting, consenting, and performing the final clinical reports to the participants (post-processing analysis of cardiac function and visual assessment of LGE). I coordinated with the local research group to follow-up participants for assessing the impact of the abbreviated CMR protocol. Finally, I performed the statistical analysis and wrote the paper.

4.1.2 Introduction

Cardiac Magnetic Resonance is an emerging imaging technique with the capacity to transform cardiology analogously to the impact of brain MRI in neurology (143). Multiple new and different techniques are available using CMR (function, scar, perfusion, flow, mapping, and angiography), delivering valuable clinical insights with the potential of a high impact (144). However, these varied techniques may take it slow (typically 45 – 60 minutes), are expensive and complex, potentially out of reach for most inhabitants in LMICs. For example, in Peru, although MRI scanners are available for other indications, just two public hospitals undertook CMR in adults at the time of this intervention, performing a maximum of 6 – 8 scans per week each (around one

scan per million inhabitants per year), at the cost of \$400 (public) up to \$800 in private centres.

For clinicians, CMR's core incremental diagnostic utility over other methods is accurate estimation of LV function and the assessment of scan with late gadolinium enhancement (LGE). The utility of CMR is also measured in accordance with its impact on patient management and change on prognosis. The best example of this is the assessment of cardiac iron overload in patients with B-Thalassaemia major. A substantial 71% decrease in deaths has been observed in the UK thalassaemia cohort since introducing T2* CMR and improved of chelation. (68) An abbreviated non-contrast CMR scan was previously implemented in Thailand in patients with this condition. Non-contrast scanning was done in 8 minutes, reducing costs four-fold, and demonstrating rapid CMR protocols' clinical and economic advantage (120).

4.1.3 Aims:

The main purpose of the INCA Study was to deliver an abbreviated CMR protocol in patients with cardiomyopathies with an accurate diagnostic capacity linked to a training, education, and mentoring program that would permit a better adoption of this technology in Peru with an impact on patient's management and therapy.

4.1.4 Material and Methods

The research received ethical approval in the UK: REC reference 14/LO/1948, amendment: 3.0, IRAS: 142036 and Peru: Edgardo Rebagliati Martins Hospital, Institutional Ethics Committee: IRB N 00003285/Arch 1047, NIT 832-2016-1066. Participants gave written informed consent.

A cross-sectional study performed between November 2016 until November 2017 in two study centres in Lima, Peru. Observational outcome of patients with

cardiomyopathy who had a CMR scan for the evaluation of cardiac volumes, function and scar. Management and changes related to CMR were reviewed at 12 months.

- *CMR Protocol*: See Section 3.4.2, Figure 19 and Table 5 for more details of the CMR protocol.

- *Protocol implementation*: We embedded the abbreviated CMR scanning into clinical care and within education and mentoring program: 4 professionals from Peru visited the UK – London, Saint Bartholomew’s Hospital – Barts Heart Centre (two doctors, one technologist and one physicist) for one month. Preliminary scanning in Peru was mentored via live webcasting. A 2-day training course (190 attendees) was delivered in Peru for cardiologists, radiologists, and radiographers before scanning, followed by a 2-day reporting course (35 radiologists and cardiologists attending) after scanning. In total, 14 international faculties were involved from Europe, the USA, Brasil, and Colombia.

-*Patients*: On the 26th and 27th of November 2016, a total of 100 patients, referred by ten doctors from 6 public hospitals, underwent ultrafast CMR at two centres in Lima, Peru: Edgardo Rebagliati Martins National Hospital (1.5T Avanto, Siemens), and Delgado Private Hospital (1.5T Aera, Siemens).

- *CMR complications*: Major complications were predefined (death, resuscitation, complication requiring admission for at least one night). Minor complications were defined as any other clinically significant event, such as dyspnoea, chest pain, allergic reactions without shock)

- *CMR Post-Processing Analysis*: As described before. See section 3.5.2 and Figure 21.

- *Image quality*: As described before. See section 3.7.

- *Patient outcomes*: Presented after 12 months of follow up. As described before. See section 3.8.
- *Cost evaluation*: As described before. See section 3.9.
- *Statistical analysis*: As described before. See section 3.10.

4.1.5 Results:

4.1.5.1 Study Population: 100 patients were referred by cardiologists and haematologists (for cardiac iron overload assessment). Ninety-eight patients were scanned, mean age was 52 (36 – 65 years), 60% female. The main indications for the CMR scan were: Cardiomyopathy (hypertrophic cardiomyopathy in 26%; non-ischaemic dilated cardiomyopathy in 22% and ischaemic cardiomyopathy to assess viability in 15%). In addition, there were twelve other indications. See figure 22. The average time of scanning was 18 ± 7 minutes. See table 6. Before CMR scanning, 94% of patients had undergone prior transthoracic echocardiography, cardiac catheterization 14%, SPECT 7%, cardiac computed tomography 3%, and no previous CMR scan before the intervention.

All Patients (%)	98 (100%)
Age, mean (range), years	52 (36 - 65)
Male (%)	39 (40%)
Female (%)	59 (60%)
Height, mean (SD), m	1.62 (0.1)
Weight, mean (SD), kg	69 (11.7)
BMI, mean (SD), kg/m ²	24.8 (3.7)
Reader	
Cardiologist (%)	7 (70%)
Radiologist (%)	3 (30%)
Cardiology Referral (%)	94 (95%)
MRI Scanning duration, mean (SD), min	18 (7)
CMR exam	
Contrast enhanced (%)	(93) 95%
Non-contrast (%)	(6) 6%
Repeated scans (%)	(2) 2%

Table 6: Patient baseline and CMR Scan characteristics. BMI: indicates body mass index, CMR: Cardiac Magnetic Resonance, MRI: Magnetic Resonance Imaging

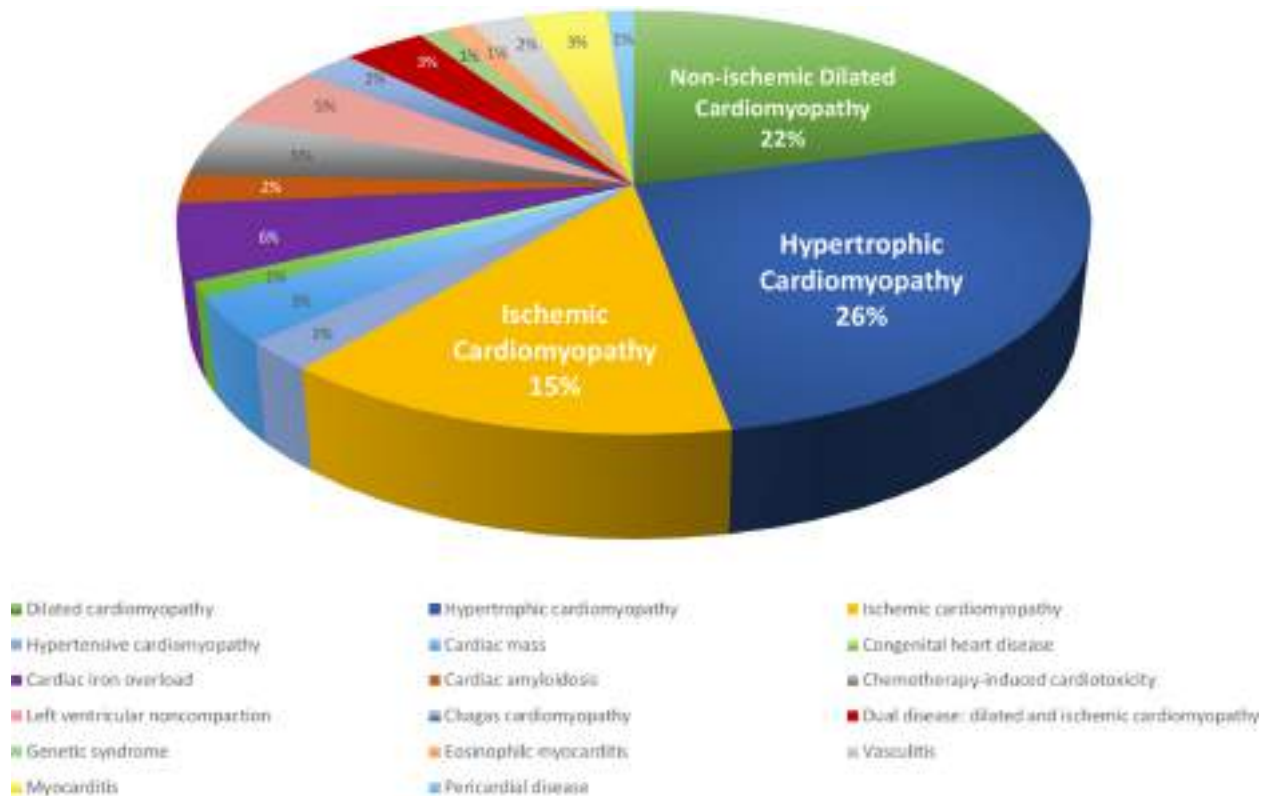


Figure 22: Different Cardiac Pathologies evaluated in the INCA Study

4.1.5.2 Scanning: The contrast dose used was 0.1mmol/kg (0.2ml/kg). All studies were performed without major complications. There was one minor complication (panic attack). Good image quality was reported in 91% of cases and moderate in 7%. Images were non-diagnostic in 2% of cases and therefore poor – although image quality was good, we required to repeat the scanning to confirm contrast administration and the unexpected finding of cardiac amyloidosis.

4.1.5.3 Extra-cardiac findings: Incidental extra-cardiac findings were found in 21% of cases but were judged to be of no clinical consequence. The most common were

dilated great vessels (13%) and lung parenchymal abnormalities (3%). One liver mass was found (subsequently confirmed malignant).

4.1.5.4 Cardiac Findings and Impact: CMR directly impacted clinical management at 12 months in 55% of the patients, either by revealing an unsuspected new diagnosis (19%) and leading to a change in management with therapeutic consequences (36%), see Table 7 and Figure 23, showing the impact of the rapid CMR protocol on patient management by the three main indications: non-ischaemic, ischaemic cardiomyopathy and other cardiac pathologies. In an additional 5%, a change in management was suggested but not delivered due to access barriers (e.g., for cardiac surgery or device therapy); including these patients, the abbreviated contrast CMR protocol would potentially impact care in 60% of patients. The abbreviated CMR protocol satisfied all imaging needs in 89% of the patients, without further non-invasive imaging. In the 7% where CMR was the first imaging technique performed, no other non-invasive imaging was needed. Figures 24 demonstrates a case of the application of the abbreviated CMR protocol and its impact on patient management.

Impact of the Abbreviated CMR protocol in Patient Care - INCA (PERU) Study	
All patients (%)	98 (100)
DIAGNOSIS	
Completely new diagnosis not suspected before (%)	19 (19)
THERAPEUTIC CONSEQUENCES	
Change/ Addition in medication (%)	22 (22)
Intervention/ Surgery (%)	6 (6)
Invasive angiography/ biopsy (%)	4 (4)
Hospital discharge/ admission (%)	3 (3)
OVERALL IMPACT	
Impact on patient management (%) (new diagnosis and therapeutic consequences)	55 (55)
NON-INVASIVE IMAGING ORDERED AFTER CMR	
Transthoracic – transoesophageal echocardiography (%)	6 (6)
Cardiac Computed Tomography (%)	3 (3)

Table 7: Impact of the Abbreviated CMR Protocol on Patient Management – INCA Study

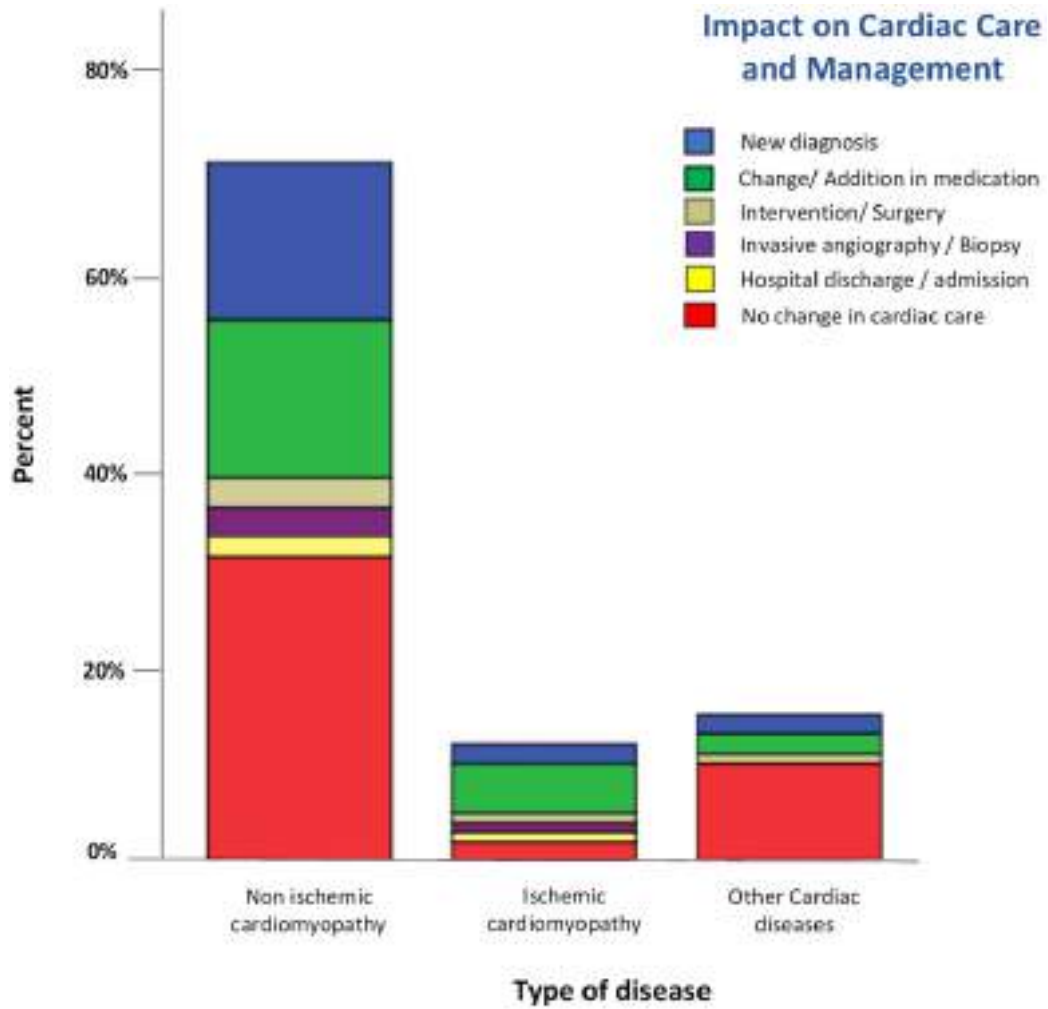


Figure 23: Impact of the Abbreviated CMR Protocol on Cardiac Care and Management by Indication. CMR: Cardiac Magnetic Resonance

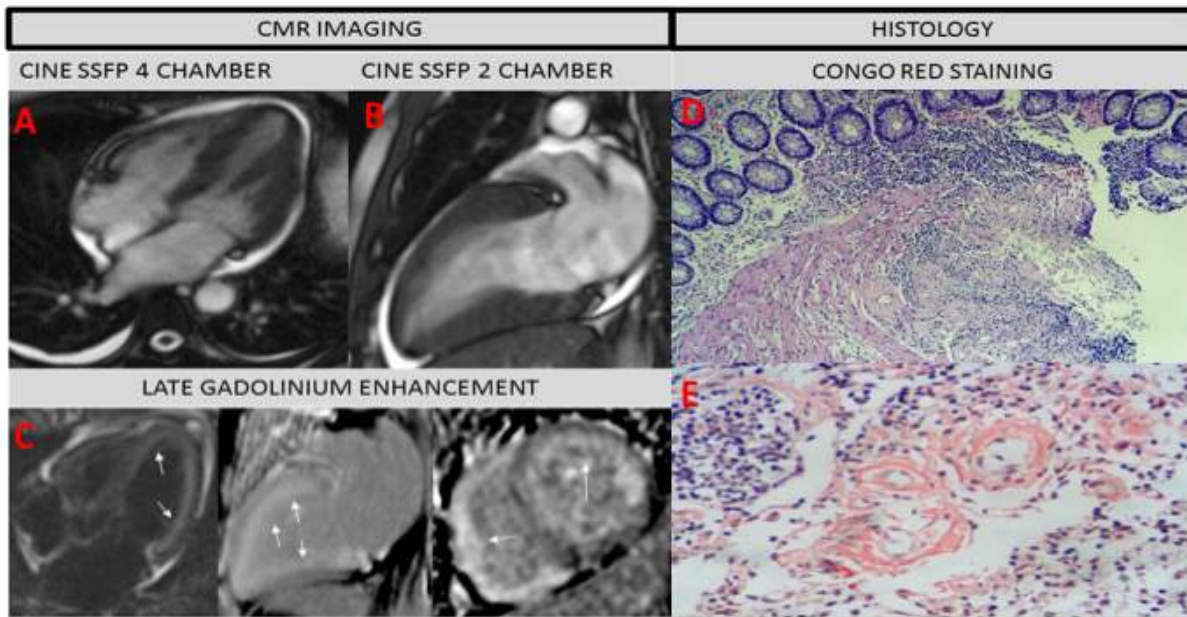


Figure 24: Completely new diagnosis by CMR: 52-year-old personal trainer who complained of SOB and tiredness. Previous echocardiogram showed hypertrophy. Cardiologist referral was suspicious of Fabry's Disease. CMR study: **A) 4 chamber, B) 2 chamber cine steady free precession** revealed pleural and pericardial effusion, LV hypertrophy and mild systolic dysfunction, and **C) Contrast CMR (LGE: 4, 2 and SAX chambers)** showed diffuse sub-endocardial enhancement in both ventricles (white arrows), suggestive of Cardiac Amyloidosis (most likely type AL). Labial salivary gland biopsy revealed **D) Hematoxylin-eosin stain, panoramic view:** amyloid tissue infiltrating the muscularis mucosae and blood vessels, **E) Congo red stain, original magnification x 8:** Type AL positive Congo red staining. The patient died 6 months after diagnoses. Biopsy images shared by courtesy of Dr Jose Luis Arenas Gamio, Pathology Service, Guillermo Almenara Irigoyen Hospital, Lima – Peru.

4.1.6 Discussion:

In LMICs, MRI scanners are available. However, there are some barriers that prevent the delivery of CMR. CMR is usually linked as a complex and expensive scan, taking at least 60 minutes to complete one scan, and it requires trained staff for scanning and reporting. All this may result in a poor suffering more from cardiac disease, with fewer diagnostic tools being available for them and, therefore, treatment is limited. We did three things to make CMR suitable for major centers in LMICs healthcare systems, using Peru as the pilot exemplar:

- 1) Creating national/international support structures for a service at the political and healthcare system levels
- 2) Creating an education/mentoring system for both those delivering the technology and referrers
- 3) By focusing on the core utility of CMR: volumes and scar imaging.

We made CMR faster, cheaper, and easier. We delivered high-quality CMR at two sites with patients referred from 10 clinicians at six sites; all patients attended in public hospitals. CMR scanning was 2-3 times faster, and 3-5 times cheaper than usual and changed the care in 55% of subjects scanned.

Cardiovascular diseases are a major concern in LMICS, as previously discussed. WHO indicates that three times as many deaths from cardiovascular causes are occurring in LMICs, affecting males and females equally, but occurring at younger ages (7). Healthcare systems need to cost appropriate, accessible to most of the population, and capable of making a diagnosis, implementing appropriate therapy, and monitoring that therapy. In cardiology, the key diagnostic tests are the ECG, echocardiography, angiography, cardiac CT, and cardiac MRI. This hierarchy is typically truncated with the absence of the more expensive, technically demanding tests such as CMR. Echocardiogram is still the first imaging technique option for cardiac patients as it is portable, inexpensive, and recommended by international guidelines. Modern MRI scanners can all do cardiac scanning with the addition of electrocardiogram (ECG) gating and appropriate sequences, the basic examples being supplied routinely with scanner purchase. CMR is perceived as slow, expensive, and complex, not only for imagers to analyse and interpret but also for clinicians who decide whom to refer. For the INCA study, an approach was taken focusing on technology delivery and

investment in education and mentoring. In Peru, a broader landscape was emphasized in a generalizable cohort of patients, where the evaluation of cardiac function, volumes, and scar were important diagnostic criteria. The average time of scanning was 18 minutes, mainly focusing on this core utility. We initially decided not to do complex imaging particularly cardiac tumours, but clinician demand meant that we had a number of such cases, increasing scan-length (but also adding to yield). We were not expecting the high clinical utility we encountered. The clinical utility found in Peru of 55% having changed care after CMR is somewhat less than demonstrated in international registries, as European/US registries have reported that CMR changed care in 61.8% of patients (98). However, we would have reached these levels in our study by including the 5% of patients. A change in management was appropriate but not possible due to access barriers, mainly in patients coming from poor economic resources.

This study was structured to result in a sustainable service, however, this requires multiple aspects: *Political support*: was obtained from the UK Overseas Development Office via the embassy to one Peruvian minister of health - ESSALUD, with scanning in both the public and private sectors. We also were careful to include software solutions so the analysis was not perceived as a barrier. *Education/training in-depth*: Four Peruvians came to the UK to receive training (a cardiologist, radiologist, technologist, and physicist). We implemented a 2-day training course for cardiologists and radiologists with a specific technologist track – including lectures delivered by technologists. *Partnership*: all scanning was conducted in partnership (day one mainly overseas technologists; day two mainly Peruvian); slots for attendance at scanning were available to clinicians, and all reporting was done by overseas level 3 reporters

(expertise is known to be important (145) but within a level 1 SCMR reporting course as a training exercise in partnership, and subsequent free 1-year membership sponsored by SCMR. *Quality:* The rapid CMR protocol was tested in advance using freely available video conferencing software. We used low-dose gadolinium (0.1mmol//Kg) for cost, and so the blood pool was not bright at the time of LGE imaging acquisition (146). Safety was demonstrably high, and the imaging answered the clinical question in 91% of cases – we used criteria for quality based not directly on artifact but on the ability of the scan to answer the clinical questions. *Follow-up:* the 12-month outcome adjudication was to ensure outcomes were not just technical but clinical (care changed in 55%), to ensure no major additional investigations being triggered (91% of patients), and to engender engagement.

4.1.7 Study limitations: We only included limited advanced sequences (no mapping, no perfusion, and flow only for selected cases).. The study was described as assessing CMR in the developing world, but we mainly described the impact of CMR in the capital city/leading centers in one LMICs (Lima-Peru), it did not unequivocally demonstrated sustainability.

4.1.8 Conclusion: Advanced cardiac diagnostic CMR, using an abbreviated and focused CMR protocol (cardiac volumes and scar), is possible using existing infrastructure in a capital city in Lima – Peru, in 18 minutes for \$150, resulting in a major impact on patients cardiac care if it is delivered with quality, education, and training.

Chapter 5: Results 2: Myocardial inflammation and oedema revealed in People Living with Human Immunodeficiency Virus.

5.1.1 Preface: This chapter is based on the publication below

Menacho Katia, Seraphim Andreas, Ramirez Sara, Liana Falcon, Jorge Alave MD, Claudia Banda MD, Fernando Mejia, Daniela Salazar, Astrid Putri, Flavio Mosto, Pedro Gonzales, Camila, Veronica Culotta, Julio Menacho, Anna S Herrey, Ntobeko A. B. Ntusi, J Malcolm Walker, James C Moon. *Myocardial Inflammation and Edema in People Living with Human Immunodeficiency Virus* January 2020. *JACC Cardiovascular Imaging*. Vol. 13, No 5, 2020, May 2020: 1276-95. 10.1016/j.jcmg.2019.12.005

My contribution to this sub-study was to prepare the project proposal and submitting the ethics in the local hospital in Lima – Peru (Clinica Internacional), recruiting and consenting participants, and performing the final clinical reports to the participants (post-processing analysis of cardiac function and tissue characterization). I performed the statistical analysis, analysed data, and wrote the paper.

5.1.2 Background

Human immunodeficiency virus (HIV) is a major public health problem, and an estimated 37 million people living with HIV (PLWH) in 2017 (147). Despite major advances in diagnostic methods and global coverage of antiretroviral therapy (ART), one million people died from HIV-related illnesses in 2017. (147)

ART has transformed HIV infection into a chronic disease, generating new diagnostic and treatment dilemmas. The burden of HIV-related cardiovascular disease has tripled over the last 20 years, with cardiovascular risk comparable to diabetes mellitus. (148) Presentations range from diastolic dysfunction and impaired elasticity to acute myocardial infarction, myocarditis, cardiomyopathy, heart failure, and stroke. (149) (150) Pathophysiological mechanisms remain elusive. (151) Multiple mechanisms

have been proposed, including cardiomyocyte viral infiltration, (152) myocarditis from opportunistic infections, (153) chronic inflammation through immune-mediated dysregulation, (154) reduced vascular function, (155) accelerated atherosclerosis, (156) and treatment-related toxicity. (157, 158)

Recent advances in CMR include strain imaging for detecting early functional changes and myocardial tissue characterization with mapping to quantify underlying pathophysiological processes. In other diseases, these parameters are used as early disease markers, to stage disease, predict prognosis and monitor therapy. (159, 160)

One of the challenges in understanding HIV-cardiomyopathy is that most data are either from the pre-ART era prior to advanced investigational techniques or conducted more recently - exclusively on treated patients. Any changes present in treated individuals may be either HIV or treatment-related, confounding mechanistic insights. There are still many untreated individuals in the world, but they are in economic areas where access to healthcare resources is limited, and research infrastructure may not be present. We previously showed that CMR can be faster, cheaper and easier for focused deployment in LMICs (135). The primary focus was to improve clinical care through superior diagnostics and the targeting of therapy. A parallel research agenda sought partnerships to address the specific needs of LMICs and to form part of global research collaborations by exploiting opportunities not available in traditional research environments (through geography, demographics, epidemiology, or therapeutic options).

5.1.3 Aims:

We sought insights into the underlying pathophysiology of myocardial disease in both treated and untreated PLWH. We did this by implementing advanced CMR in an upper middle-income country, Peru.

5.1.4 Material and Methods:

5.1.4.1 Study population:

A single-centre cross-sectional study, with recruitment performed over a 1 year (2017-2018). The study was approved by University College London (REC reference: 11255/002) and by the International Clinic in Lima, Peru (Research and Education Department, reference number: UDID 005 – 2017). Each participant provided witnessed, written informed consent. A total of 51 PLWH were recruited. All participants were asymptomatic from a cardiac perspective. Among this 51 PLWH, 26 were receiving ART, and 25 patients were treatment-naïve. Treatment-naïve patients were defined as newly diagnosed patients with HIV infection, with CMR performed either before or within 14 days of the start of a first-line ART regimen (consisting of 2 nucleoside reverse transcriptase inhibitors (NRTI) and one non-nucleoside reverse transcriptase inhibitor (NNRTI)). (161) 21 healthy controls, selected by frequency matching were included. Of the ART treated group: 22 (85%) received NNRTIs and NRTIs and 4 (15%) received protease inhibitors (PIs) and NRTIs, the average time since the initial diagnosis of HIV was 5 ± 4.4 years.

Inclusion criteria were: age ≥ 18 years, no history or symptoms of cardiovascular disease, no hepatitis C infection, and no contraindications to contrast CMR (e.g., renal clearance < 30 ml/min or previous adverse reaction to gadolinium contrast). Data

collected included CD4 count, viral load, hematocrit, anthropometric measurements, and cardiovascular risk factors.

5.1.4.2 CMR Imaging

CMR data comprised myocardial volumes and function, including left ventricular ejection fraction (LVEF), global circumferential strain (GCS), global longitudinal strain (GLS), and tissue characterization with native T1, T2, extracellular volume fraction (ECV) mapping, and late gadolinium enhancement (LGE). All scans were performed on a 3T magnetic resonance imaging (MRI) scanner (Magnetom; Prisma; Siemens Medical Solutions, Erlangen, Germany). The MRI protocol included: **Localizers**, pilot 2 chamber, 5 slice short axis stack, and a transverse dark blood single-shot fast spin echo stack for anatomic evaluation. **Volume and cardiac structure assessment:** 1) three long-axis cine views: four-, two-, three-chamber segmented k-space cine acquisitions, 2) Short axis (SA) cine stack. Cine images were acquired using a balanced, segmented steady-state free precession (bSSFP), covering the left ventricle (LV). Image parameters were time to echo (TE) of 1.1ms, time of repetition (TR) of 2.6ms, a flip angle of 80, IPAT factor 2, voxel size 1.8mm x 1.8mm x8mm (6mm for long axis), and for SA stack, a 2mm inter-slice gap. **Mapping:** T1 maps were acquired using MyoMaps, consisting of a single-shot SSFP-based Modified Look-Locker Inversion Recovery (MOLLI) using a 5s(3s)3s sampling protocol. (162) For T2 maps, 3 single-shot images were acquired at different T2-preparation times (0, 24, and 55 milliseconds), and imaging parameters were: TR 215.04ms; TE 1.34ms; flip angle 12°; repetition time 3×R-R interval; acquisition matrix 116×192; slice thickness 8mm; field of view adjusted as per subject size. **Post-contrast imaging:** gadolinium contrast [0.1 mmol/kg Gadoterate meglumine – Dotarem; Guerbet, S.A France] imaging was

performed from 5 to 15 minutes for LGE and at 15 minutes (T1 mapping) allowing calculation of the extracellular volume fraction (ECV).

5.1.4.3 CMR Analysis

CMR was performed using CVI42 (Version 5.11.4 - 1559, Calgary, Canada).

- **LV volumes and mass** analysis were performed by manual contouring of the endo- and epicardial borders at end-diastole and end-systole with papillary muscle and trabeculations included in the LV mass. For T1 and T2 mapping, 3-short axis (base, mid and, apex) were manually contoured for endo and epicardial border. Partial volume of blood was minimized by applying an automatic 20% offset from the endocardial and epicardial border. Global post-contrast T1 mapping allowed calculation of extracellular volume fraction using the calculation $= (1-Hct) \times [\Delta R1_{\text{myocardium}}]/[\Delta R1_{\text{blood}}]$.
- **CMR feature tracking/strain analysis:** Longitudinal strain was measured from longitudinal axis cine images (4ch, 2ch, 3ch). Short axis cine images were analysed at apical, mid-ventricular, and basal levels to assess radial and circumferential strain. Endocardial and epicardial borders were manually delineated with the initial contour set at end-diastole. In case of insufficient tracking, as defined by deviations of the contour from the endocardial and epicardial borders, contours were manually corrected and the algorithm reapplied. (163) Pericardial effusions were assessed using cine SSFP imaging. Pericardial effusion was defined as >5mm pericardial fluid measured in end-diastole.

5.1.4.4 Blood analysis:

CD4+ T-cell counts were assessed with flow cytometry, and HIV-1 RNA was determined with an ultrasensitive reverse-transcriptase polymerase chain reaction. Undetectable viral load was defined as <40copies/ml. (164) Amongst treatment-naive HIV patients, mean CD4+ cell count was 378 (313) vs. 614 (672) in ART-treated HIV patients ($p<0.001$). Amongst treatment-naive HIV patients, an undetectable viral load (<40copies/ml) was present in 0 vs 21 (81%) in ART-treated HIV patients ($p<0.001$).

5.1.4.5 Statistical Analysis

As described in section 3.10. The associations between ECV or native T1 with either CD4 count or detectable viral load were corrected for potential confounding factors (age, gender, LVEF) and presented as a partial correlation coefficient (r). All statistical tests were two-tailed, and statistical significance was defined as $p < 0.05$.

5.1.5 Results:

Seventy-two subjects (21 healthy controls and 51 PLWH, 25 treatment-naïve, 26 on ART) were evaluated. As shown in Table 8, there were no significant differences in baseline characteristics between patients and controls for age ($p=0.13$), sex ($p=0.41$), body mass index - BMI ($p=0.17$), systolic/diastolic blood pressure ($p=0.14/0.56$). Hematocrit was lower for PLWH participants (40.3 ± 3.9 vs $42.1 \pm 2.9\%$, $p=0.04$). The groups were well-matched for cardiac risk factors, including the presence of arterial hypertension, diabetes mellitus, smoking status, alcohol consumption, dyslipidaemia, and family history of coronary disease.

	PLWH N= 51	Controls N= 21	P value
General characteristics			
Age, years	36±11	39±11	0.13
Men %	41(80%)	15(71%)	0.41
Body mass index, mean (SD) kg/m ²	25.6±4.2	27.3±3.4	0.17
Weight, mean (SD) kg	69.8±14	75.6±12.3	0.141
Height, mean (SD) cm	168±8.9	169±10.7	0.56
Waist Circumference, mean (SD) cm	82.7±12	85.1±9.1	0.55
Hip circumference, mean (SD) cm	88.3±10.2	94.5±7.5	0.09
Waist-hip ratio	0.93±0.1	0.90±0.1	0.06
Systolic Blood Pressure, mean (SD) mmHg	107.9±10.2	107.5±13.2	0.9
Diastolic Blood Pressure, mean (SD) mmHg	67.9±8.2	68.6 ±7.1	0.82
Laboratory exams			
Haematocrit, mean (SD), mg/dl	40.3±3.9	42.1±2.9	0.04
Cardiac Risk Factors			
Arterial hypertension (%)	2(4%)	1(4%)	1
Smoking (%)	10(20%)	4(19%)	1
Alcohol (%)	16(31%)	5(24%)	0.58
Dyslipidaemia (%)	5(10%)	1(4%)	0.66
Family history of IHD (%)	12(23%)	2(10%)	0.21
PLWH: People living with HIV; Kg: Kilograms; g: grams; mm: millimetres; ms: milliseconds; ml: millilitres; SD: Standard deviation; cm: centimetres; dl: decilitres			

Table 8: Participants baseline characteristics

Compared with controls, LV cavity volume and mass were similar, but LV functional measures were reduced (Table 9): (LVEF 61.4 ± 4.1 vs $64.7 \pm 2.4\%$, $p=0.001$; GCS - 20.1 ± 4.2 vs $-23.9 \pm 4.8\%$; $p=0.001$; GLS -17.6 ± 3.3 vs $-21.0 \pm 3.8\%$, $p=0.002$). PLWH had increased native T1 (1294 ± 20 vs 1230 ± 9 ms, $p<0.001$), T2 (41.5 ± 2.4 vs 36.4 ± 1.4 ms, $p<0.001$) and global ECV (28.5 ± 1.5 vs $24.8 \pm 0.9\%$; $p<0.001$), Figure 25 A (a-b)

	PLWH N= 51	Controls N= 21	<i>P value</i>
Cardiovascular magnetic resonance			
LV end-diastolic volume, mean (SD) ml	148±30	149±25	0.909
LV end-systolic volume, mean (SD) ml	56.7±12	51.9±8.5	0.109
Stroke volume, mean (SD) ml	91±20.1	95±18.6	0.438
LV ejection fraction, mean (SD), %	61.4±4.1	64.7±2.4	0.001
Global circumferential strain, mean (SD), %	-20.1±4.2	-23.9±4.8	0.001
Global longitudinal strain, mean (SD), %	-17.6±3.3	-21±3.8	0.002
LV mass, mean (SD) g	107±31	114±21	0.318
LV papillary muscle, mean (SD) g	3.2±1.3	2.5±0.9	0.06
Global T1 native mapping MOLLI, mean (SD), ms	1294±20	1230±9	<0.001
Global T1 post contrast MOLLI, mean (SD) ms	658±38	709.1±16	<0.001
Global extracellular volume, mean (SD)%	28.5±1.5	24.8±0.9	<0.001
Global T2 mapping, mean (SD)%	41.5±2.4	36.4±1.4	<0.001
Pericardial effusion (>5mm) %	15 (29%)	0 (0%)	0.004
Presence of LGE, (%)	20 (39%)	0 (0%)	<0.001
PLWH: People living with HIV; Kg: Kilograms; g: grams; mm: millimetres; ms: milliseconds; ml: millilitres; SD: Standard deviation			

Table 9: Comparison of CMR parameters in HIV infected individuals and Healthy Volunteers

Controls

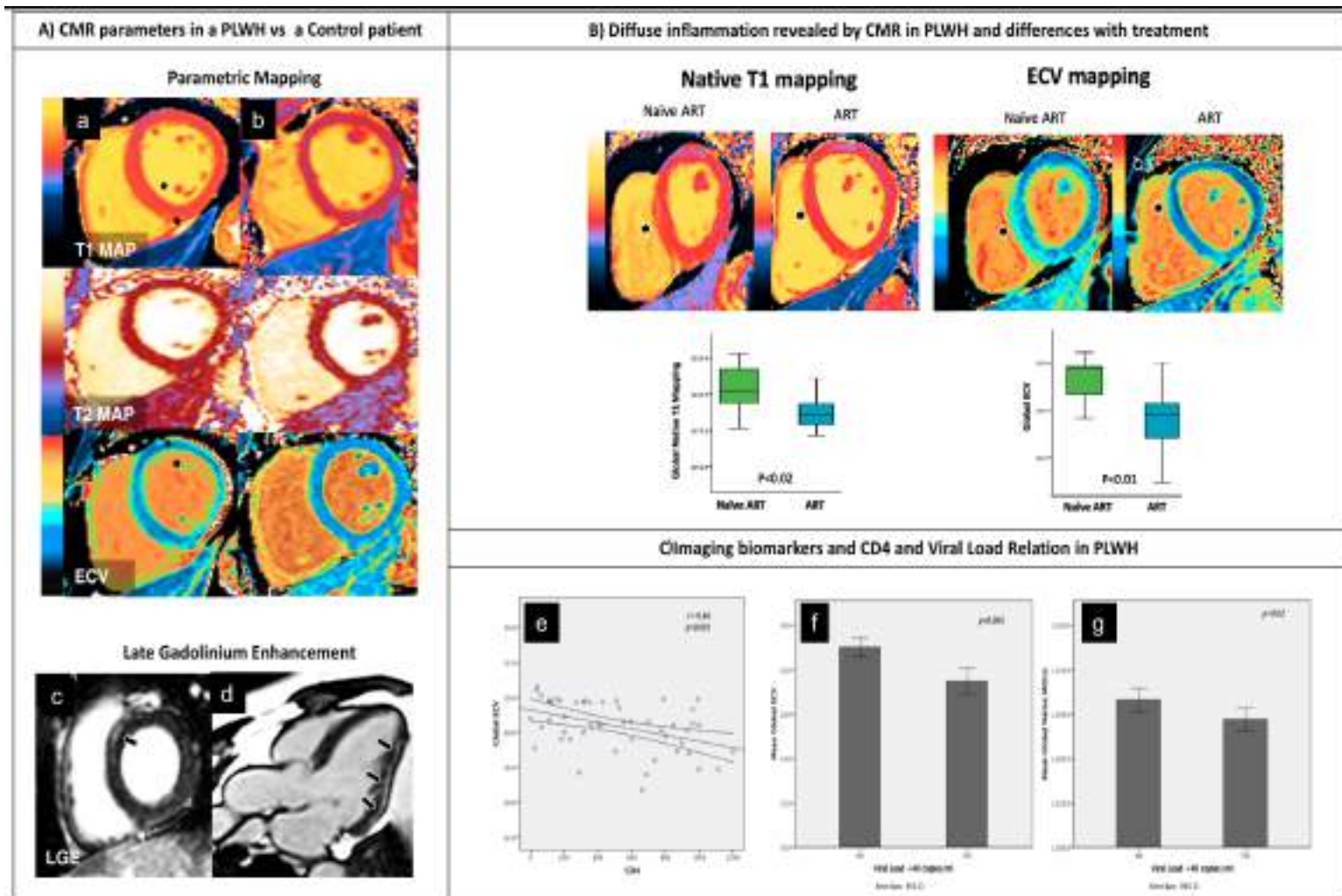


Figure 25A: CMR in a PLWH (a) and control healthy volunteer (b) showing an increase of cardiac native T1, T2 mapping, and ECV in PLWH (c) Basal antero-septum mid-wall (d) Infero-lateral sub-epicardial LGE in PLWH. **Figure 25B:** Non-treated PLWH have elevated native T1 and ECV compared to those on ART. **Figure 25C:** Inverse correlation between (e) ECV with CD4 total count and (f, g) Patients with a detectable viral load >40 copies/ml have higher global ECV and global native T1.

Amongst PLWH, 39% had LGE vs. none of the controls ($p<0.001$). LGE was mid or epicardial in the septal and inferolateral walls, Figure 25A (c-d). Non-trivial pericardial fluid/effusions ($\geq 5\text{mm}$) were more common among PLWH compared to controls (29 vs 5%, $p=0.004$). Comparisons between ART-treated and naïve patients are shown in Table 10. The two subgroups were similar in terms of age, sex, and hematocrit. There were no significant differences between treated and untreated HIV patients for LV

volumes or function: EF ($p=0.25$) GLS ($p=0.25$) GCS ($p=0.23$), presence of pericardial effusion ($p=0.31$), LGE ($p=0.91$) and T2 mapping ($p=0.99$). However, untreated PLWH had higher global native T1 (1304 ± 20 vs. 1285 ± 16 ms; $p<0.001$) and ECV (29.3 ± 0.7 vs. $27.7\pm 1.3\%$; $p<0.001$) compared to those on ART. Figure 25B.

For all PLWH, higher ECV was associated with a lower CD4 count when accounting for age, gender, and LVEF ($r=-0.46$, $p=0.001$) – see Figure 25 C (e) higher native T1 was not significantly associated with lower CD4 count after accounting for age, gender and LVEF ($r=0.21$, $p=0.16$).

Patients with a detectable viral load had higher ECV (29 ± 1.1 vs. 27.5 ± 1.3 , $p<0.001$) and higher native T1 (1300 ± 21.2 vs. 1286 ± 16.8 , $p=0.02$) than patients with an undetectable viral load - see Figure 25 C (f-g) a detectable viral load remained positively associated with higher ECV ($r=0.56$, $p<0.001$) and native T1 ($r=0.34$, $p=0.02$) after accounting for age, gender and LVEF.

	PLWH naïve to ART N=25	PLWH on ART N=26	P value
General characteristics			
Age, years	32.8±12.2	36.7±10.4	0.112
Men %	20(80%)	21(81%)	0.95
Total CD4 cells count, median (IQR)	378(313)	614(672)	0.01
Viral load <40 copies/ml	0(0%)	21(81%)	<0.001
Haematocrit	39.2±3.62	40.5± 3.86	0.22
Cardiovascular magnetic resonance			
LV end-diastolic volume, mean (SD) ml	141±32	154±27	0.112
LV end-systolic volume, mean (SD) ml	55±14	59±10	0.28
Stroke volume, mean (SD), mean (SD) ml	86.2±21	95.7±19	0.09
LV ejection fraction, mean (SD) %	60.7±4.7	62±3.1	0.25
Global circumferential strain, mean (SD) %	-19.7±4.9	-20.5±3.5	0.23
Global longitudinal strain, mean (SD) %	-17.4±3.3	-17.8±3.9	0.25
LV mass, mean (SD) g	101.6±4.3	111.8±30	0.24
LV papillary muscle, mean (SD) g	3.1±1.3	3.3±1.3	0.73
Global T1 native mapping MOLLI, mean (SD) ms	1304±20	1285±16	<0.001
Global T1 post contrast MOLLI, mean (SD) ms	652±44	664±31	0.28
Global extracellular volume, mean (SD) %	29.3±0.7	27.7±1.3	<0.001
Global T2 mapping, mean (SD) %	41.5±2.2	41.5±2.6	0.99
Pericardial effusion, %	9(36%)	6(23%)	0.36
LGE presence, %	10(40%)	10(38%)	0.91
PLWH: People living with HIV; Kg: Kilograms; g: grams; mm: millimetres; ms: milliseconds; ml: millilitres; SD: Standard deviation; IQR: Interquartile range			

Table 10: CMR parameters in treated and non-treated HIV infected individuals

5.1.6 Discussion:

We applied advanced CMR imaging techniques in ART-treated and ART-naïve PLWH and without cardiovascular symptoms to evaluate for presence of subclinical changes in myocardial structure and function. The main findings are: (1) PLWH have subclinical LV dysfunction, reflected by a reduced LVEF and reduced myocardial GLS and GCS compared to healthy volunteers; (2) PLWH demonstrated evidence of structural myocardial changes, reflected by the presence of LGE, an increase in native T1 and T2 values and an increase in global ECV; and (3) ART-naïve PLWH had elevated native T1 and ECV compared to those on treatment. Across all PLWH, higher ECV was associated with a lower CD4 count, and both higher ECV and native T1 were associated with a detectable viral load, independent of potential confounders.

Myocardial scar and inflammation in HIV infection

Consistent with previous studies (165-168), our data suggest the presence of myocardial structural changes amongst PLWH, identified with CMR imaging. In addition, similarly to these studies, we observed a non-ischemic pattern of LGE (165-168) predominantly involving the sub-epicardium or mid-wall, either in the basal inferolateral or septal walls. However, this is the first study that detected a significant expansion in ECV in patients with HIV, suggesting a higher degree of myocardial involvement than previously recognized (165). Identification of ECV expansion in asymptomatic and relatively young PLWH has significant implications. Raised ECV has been shown to have reasonable correlation with histological determined diffuse interstitial fibrosis in various disease models, and accumulating evidence suggests that raised ECV is associated with both mortality and adverse cardiovascular events, (169) with prognostic value likely to be superior to that of LGE (170).

Whether the increase in ECV detected in PLWH predominantly reflects diffuse myocardial fibrosis, inflammation, or the combination of the two pathologies is difficult to establish without correlation with histological data, particularly in the presence of elevated T2 values. Indeed, Lurz *et al.* (171) demonstrated the presence of significant inflammation weakens the correlation between ECV and histologically detected myocardial fibrosis in patients with clinical suspicion of inflammatory cardiomyopathy. Similar to previous studies, the distribution of LGE uptake and regional T1 elevation (i.e., inferolateral wall) noted in PLWH is similar to that seen in other forms of myocarditis (172). Also, the elevated T2 mapping values are seen in PLWH (irrespective of treatment status) suggests a degree of subclinical myocardial inflammation in these population. The higher prevalence of pericardial effusion amongst PLWH points towards an inflammatory process, which seems to be partially improved by ART. Positron emission tomography (PET) demonstrated arterial inflammation in patients who were adequately treated with ART, (173) and elevated levels of inflammatory biomarkers (IL-1, IFN-gamma), (174) troponin, NT-pro BNP, hsCRP, (157) can be detected even in ART-treated patients with HIV. There is a strong suspicion that myocardial inflammation is at least a key component of the pathophysiological mechanism of HIV cardiomyopathy, but whether this leads to the development of significant myocardial fibrosis remains unclear. Reasons for myocardial inflammation, despite the use of ART, remain a subject of debate, with evidence suggesting direct HIV virus infiltration of myocardial cells, infection with cardiotropic viruses (153, 175), and immune system dysregulation (153).

Possible adverse effects of ART on myocardial structure and function have also been previously reported, particularly with certain types of therapy (157, 158), with large

studies producing conflicting results. (176, 177) Dissecting the exact contribution of ART in the development of cardiovascular disease remains a challenge, given that most contemporary studies using advanced imaging modalities have been performed on patients with adequate viral load suppression. ART has been shown to be associated with the development of diabetes and other cardiovascular risk factors (178). Nevertheless, discontinuation of treatment was shown to be associated with increased risk of cardiovascular disease (179), and some studies in the pre-ART era confirmed the presence of myocardial inflammation in up to 50% of patients who died of AIDS on autopsy samples (180). Our data demonstrated that untreated patients had significantly higher native T1 and global ECV compared to patients on ART, although no differences in T2 values were detected. Despite the relatively small sample of this research, higher ECV was associated with a lower CD4 count, and PLWH with undetectable viral had lower ECV and T1 mapping when adjusted for age, sex, and LVEF. These findings support the notion that ART treatment is likely to be offering an overall protective effect on the cardiovascular system, mediated through modification of the extra-cellular matrix.

Myocardial function in HIV infection

In this study, PLWH had worse LV systolic function with reductions in LVEF, GLS, and GCS than controls, a finding consistent with a number of studies using echocardiography, (181) and CMR (165, 166). Notably, LVEF of PLWH remained within the normal range, and there was no significant difference among treated and ART-naïve patients in terms of systolic function indices. Reduction in myocardial strain indices, thought to represent a more sensitive marker of myocardial dysfunction compared to LVEF, have been used to identify subclinical LV dysfunction in a number

of cardiac disorders (182). However, the optimal approach for monitoring PLWH associated subclinical LV dysfunction remains unclear. Extrapolating from other models of cardiac disease, such as cardiotoxicity secondary to cancer-related treatment, it could be argued that HIV-infected patients may derive benefit from early treatment with cardioprotective agents (183). Nevertheless, a better understanding of the natural history and the evolution of HIV-related cardiomyopathy overtime is needed before making any recommendations.

Multiple mechanisms explaining cardiac dysfunction in the context of PLWH have been proposed (184). Myocardial fibrosis has been shown to affect myocardial velocities independent of LVEF (185) negatively. Similarly, low-level myocardial inflammation could also have an impact on myocardial mechanics (186). Of particular interest is the observation that our patient cohort consisted of a younger patient group in comparison to similar studies, (165) (166) (167, 168), suggesting that changes in myocardial structure and function are likely to be present early in the course of the disease.

5.1.7 Limitations

Despite being one of the largest studies of advanced cardiac imaging in PLWH, the study is limited by its small sample size. It is not powered to detect differences between different ART regimes and does not allow subgroup analysis. No biochemical data, including lipid profile and cardiac biomarkers were collected and no histological evaluation of myocardial tissue was performed. The absence of histological data complicates the differentiation of myocardial fibrosis and inflammation. Causality between HIV infection and findings cannot be confirmed. This finding raises several questions regarding the optimal management of these patients given the prognostic

capacity of myocardial indices such as LVEF, strain, LGE, and ECV, highlighting the need for prospective studies performing serial cardiac evaluation.

5.1.8 Conclusion

These data support a high prevalence of subclinical myocardial dysfunction with tissue characterization changes in patients living with HIV. Patients on ART have less pronounced changes, and markers of myocardial inflammation and fibrosis are associated with a detectable viral load and lower CD4 count, suggesting ART may be cardioprotective.

Chapter 6 – Results 3: Improved cardiac iron one year after using rapid Magnetic Resonance Imaging to guide chelation therapy: Ultrafast MRI for Iron Management in India – the UMIMI study

6.1.1 Preface: This chapter is based on the manuscript below was accepted for publication at EHJ Quality of Care and Clinical Outcomes (EHJ-QCCO-D-21-00322R1).

Katia Menacho MD, Amna Abdel-Gadir MBBS, Redha Boubertakh Physics, Kartik Ganga MD, Vineeta Ojha MD, Surya Pratap MD, Louise McGrath RD, Joao Augusto MD, Mr Alexander Rikowski, Ms Nabila Mughal R, Mrs Shoba Tuli, VK Khanna MD, Tulika Seth, Sanjiv Sharma, Amita Mahajan MD, Rajiv K Bansal MD, Prabhar Srivastava MD, Harsh Mahajan MD, Vidhur Mahajan MD, Beatrix Wonke MD, Mrs Judith Walker MSc RN, Ms Seldon Tenzin BSc, Emmanuel Ako MD, James C Moon MD, J. Malcolm Walker M.

My contribution to this sub-study was submitting the UK (UCL) ethics, recruiting participants, and performing the final clinical reports to the participants (post-processing analysis of cardiac function and cardiac and liver T2). I also completed the statistical analysis, analysed data, and wrote the paper.*

6.1.2 Background: Thalassemia is the most common monogenetic disorder worldwide, and it is most common in Asia, the Mediterranean Basin, and the Middle East (187), with 23,000 cases of B-thalassemia major in newborn infants and 56,000 cases in infants annually (187) (188). There are over 100,000 transfusion-dependent thalassemia (TM) patients and 17,000 births of homozygous patients each year in India. (189). Transfusion-dependent patients and thalassemia care have been designated national strategic importance in India, but there are still many areas of concern (190). Unless regularly transfused, most patients do not survive beyond seven years (191). Transfusion allows survival, but it leads to organ iron accumulation.

Unless chelation treatment is undertaken, there is a high probability of mortality in early adulthood, mainly through cardiac iron toxicity. (192) and all three chelators (deferoxamine, DFO; deferiprone, DFP, and deferasirox DFX) are available, although, with variable access (193), Transfusions in India have been available for patients in an organized fashion for the last 20 years (194). However, assiduous adherence to chelation therapy is needed. The drugs have significant toxicity, are costly, and effective clinical care requires targeting therapy to organs rather than total body iron levels (195, 196). Therefore, it is crucial not only to assess the amount of myocardial (and hepatic) but also to monitor treatment effectiveness. Serum ferritin evaluates total body iron stores and continues to be used as a relatively cheap surrogate parameter to guide chelation therapy. However, the correlation with myocardial iron concentration is limited. (94). CMR is the accepted world standard for non-invasive detection and management of tissue iron loading (40). CMR - T2* is easy to standardize, reproducible, and guideline supported (197). When therapy is applied, guided by tissue iron assessment using the CMR T2* parameter, a >70% reduction in mortality has been previously reported (68). This CMR-guided approach to therapy for TM is routinely available primarily in HICs (191). CMR has been underused in LMICs such as India, despite MRI scanners being fairly widely available (198). Several obstacles prevent the widespread use of CMR to assess iron overload: including a perceived lack of expertise, lengthy scan times (despite contrast agent not being required), high costs, and a lack of training in analysis and data acquisition (199) (200). Consequently, care is based on inadequate iron loading information. The rational use of expensive and scarce resources, including chelators and transfusion, depends on sub-optimal clinical and laboratory measurements, based mainly on serum Ferritin levels.

Thalassemia “camps”, where patients from local and distant centres gather over a number of days for a concentrated effort of clinical assessment, have been effectively employed in India for many years (190). These camps could offer an opportunity to establish CMR, using a shortened protocol allowing up to 50 patients to be scanned on one magnet in one day (120, 201). Previously, Abdel-Gadir et al., has demonstrated the feasibility of rapid CMR using existing equipment with immediate reporting in one LMICs achieving 8-minute scans, 50 CMR scans a day with one scanner manufacturer (120, 201) Here, we exploit this experience to create and assess a new care model. This multi-disciplinary study brought together local leadership supported by expertise from the UK at two sites with two scanner manufacturers. Hematology, cardiology, and radiology worked together with patients and their advocates, supported by the charity sector Thalasseemics India (TI; <https://www.thalasseemicsindia.org>).

6.1.3 Aims:

To explore the impact of an organized thalassemia patient medical camp in a LMIC - India, linked to a faster and easier CMR protocol to guide chelation therapy and improve iron overload in the heart.

6.1.4 Material and Methods:

The study received approval in the United Kingdom - University College London - UCL REC Project ID/Title: 11255/001 and in India - Institutional Ethics Committee – Clinical Studies, New Delhi: Reg. ECR/5/Inst/DL/2013/RR-16 and in Jaipur: N – IEC/2019/01. Detailed clinical data in six domains was recorded using a browser-based software

(REDCap – Research Electronic Data Capture) (202). All subjects had been referred for a clinical CMR exam by their haematologists to assess tissue iron levels. A team of six from the UK traveled to India for each visit to train/partner with local personnel, help undertake assessments and support Cardiac Magnetic Resonance scanning. Baseline visit in November 2018 and follow-up visit in January 2020.

-Patients: Thalassaemic patients aged over 16-year-old, were contacted by IT as part of their regular patients' camp program. The charity had invited patients, who had previously attended TM patient camps, to be recruited into the research study by providing a locally produced patient information leaflet, translated, when necessary, from an original approved by the ethical committees.

-Study Implementation: Consent was obtained with the help of the local clinicians, and the clinical, laboratory, and treatment information was collected using a previously agreed clinical questionnaire (202). All patients underwent an ECG (CardioSecur-Pro, Personal MedSystems GmbH, 60329 Frankfurt am Main, Germany) and an abbreviated CMR scan which was reported by a trained doctor, blind to the patient's clinical status. The cardiac and liver iron T2* as well as cardiac function (LVEF) were available for clinical review by the senior clinicians (JMW, EA) aided by local clinicians. All patients received a record of their CMR results and recommendations for treatment. Three options were offered to patients, following the corresponding internationally agreed standards of care (196): **Treatment option one** 1) *Ejection Fraction > 60%, cardiac T2* > 20ms (no cardiac iron): No change in treatment;* 2) **Treatment option two;** *Ejection Fraction > 60%, T2*: 10 - 20ms (moderate/ mild cardiac iron overload) increase doses of current drug or change chelator to improve adherence;* 3) **Treatment option three:** *LVEF < 60% or T2* <10ms (severe cardiac iron overload) or liver*

T2 < 2.0ms. Recommended combination therapy at appropriate doses. The precise combinations to be determined by the patient's Haematologist. See Figure 26.*

A second visit from the UK team was organized 13 months after the first intervention; all patients who attended the initial evaluation were invited to attend for review. The evaluation followed the same pattern as established for the first visit. Those who failed to attend were contacted by telephone and date recorded. Each attendee received an updated report with results and recommendations as the first visit model. See Figure 26.

-Abbreviated CMR protocol: See Section 3.4.1. and Figure 18.

-CMR post-processing analysis: See Section 3.5.1 and Figure 20.

-Image quality: As described before. See Section 3.6.

-Statistical analysis: As described before. See Section 3.10

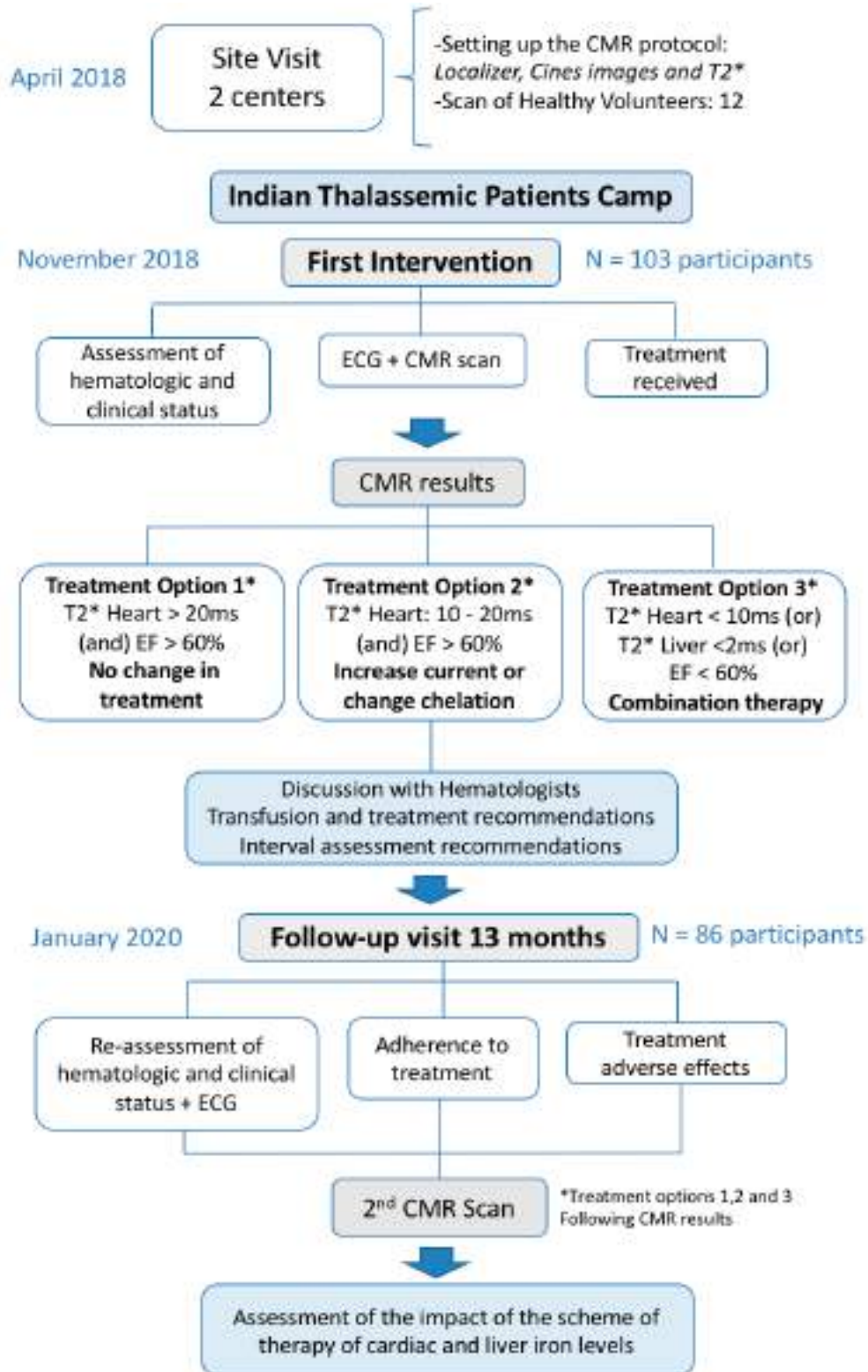


Figure 26: UMIMI Study – Design of the project

6.1.5. RESULTS:

6.1.5.1 *Characterization of the study population:*

One hundred three patients attended the baseline assessment, 53 from Centre 1 and 50 participants from Centre 2. The characteristics of the patients are shown in Table 11. The average age was 25 years (15 – 46 years), 52% being male; 28% of patients had had a splenectomy. The prevalence of reported diabetes was low at 8%; thyroid disease was reported in 13%. The average blood pressure was $116 \pm 11.7 / 79 \pm 9.5$ mmHg, heart rate 88 ± 12.7 bpm, with normal ECGs in 60%, borderline changes of uncertain clinical significance in 33%, and abnormalities in 7 patients (6.8%); these were QT interval >440 ms in 5, nodal rhythm in 1 and RBBB with QRSd > 120 ms in 1; no patients were in atrial fibrillation. There was a low reported history of heart failure (9.7%) or any other cardiac morbidity (6.7%), with no differences between the two centres. 48 (47%) of patients reported having had a previous MRI scan (87% centre 1 vs 60% centre 2; $p=0.002$), however, scan results were available for only seven participants (7%), despite 95% having their detailed medical records at the review.. The median baseline ferritin level was 1750 mcg/L (IQR 1859 mcg/l). All patients were receiving chelation therapy. The distribution of chelator treatment and average doses are shown in table 11. The proportion of patients taking DFX monotherapy was higher in the centre 1 cohort (45% vs. 12%, $p=0.001$). Combination therapy, using two chelators was similar in both centres (DFO + DFP: 6% vs 10%, $p=NS$; DFO + DFX: 19% vs. 18%, $p=0.004$; DFP + DFX: 19% vs 23% $p=NS$).

Clinical Data	Total	Centre 1	Centre 2	P value
Demographic				
Total (%)	103 (100%)	53 (52%)	50 (48%)	
Age (mean \pm SD)	25 \pm 7	26.7 \pm 6.7	23.2 \pm 7	0.013
Gender male (%)	54 (52%)	30 (57%)	24 (48%)	NS
BSA (m ²) (mean \pm SD)	1.49 \pm 0.2	1.55 \pm 0.21	1.42 \pm 0.2	0.0006
Thalassemic details				
Ferritin level (ng/dl) median \pm IQR	1750 \pm 1859	1846 \pm 2431	1700 \pm 2241	NS
Diabetes, n (%)	8 (8%)	7 (13%)	1 (2%)	0.034
Thyroid disease, n (%)	13 (13%)	11 (20%)	2 (4%)	0.01
Normal ECG (%)	62 (60%)	33 (62%)	29 (58%)	NS
Previous MRI (%)	78 (76%)	47 (87%)	31 (60%)	0.002
Iron loading Rate mg/kg/day (mean \pm SD) ⁺	0.38 \pm 0.1	0.43 \pm 0.1	0.34 \pm 0.1	0.0002
Chelation Therapy				
Desferrioxamine (DFO) n (%) Mean dose (32 \pm 13 mg/kg/day)	3 (3%)	1 (2%)	2 (4%)	NS
Deferipone (DFP) n (%) Mean dose (70 \pm 25mg/kg/day)	22 (21%)	6 (10%)	16 (33%)	0.001
Deferasirox (DFX) n (%) Mean dose (33 \pm 9.5mg/kg/day)	30 (29%)	24 (45%)	6 (12%)	0.001
Combined (DFO + DFP) n (%)	8 (8%)	3 (6%)	5 (10%)	NS
Combined (DFO+ DFX) n (%)	19 (19%)	10 (19%)	9 (18%)	NS
Combined (DFP+DFX) n (%)	21 (21%)	10 (19%)	11 (23%)	NS

Table 11: Demographic, clinical, and CMR data – UMIMI study Baseline first visit data. SD: Standard Deviation, ECG: Electrocardiogram, MRI: Magnetic Resonance Imaging. ⁺Iron Loading Rate Estimate: $(([\text{units of blood per year}] * 200) / [\text{weight}] / 365)^2$

6.1.5.2 Cardiac Magnetic Resonance Results:

- *Scanning time:* The overall average time of scanning was 11.3 minutes \pm 2.5 at the baseline intervention but significantly lower on the second visit: 9.8 minutes \pm 2.4 ($p < 0.001$).

- *Image Quality:* All CMR scans were performed without significant complications. Good image quality was reported in 90% of the baseline intervention cases, moderate in 8%; 1 patient had non-diagnostic images due to poor breath-holding secondary to overt heart failure (graded as poor quality).

- *Extra Cardiac Findings:* Extra-cardiac findings were found in 29% of studies. These findings did not add to clinical information available for these patients, and there were no changes in any clinical management. Small pericardial effusions were observed in 10% and 77% of patients had enlarged spleen. Extramedullary hematopoiesis was found in 13% of the patients. Other unusual findings reported: cirrhotic fibrotic liver in 1 patient, remnant spleen in 2 patients, kidney cysts in 2 patients.

6.1.5.3 Baseline Iron and Cardiac Function results:

The overall baseline cardiac T2* value was 29.2 ± 11.9 ms, with a mean LVEF of $64.5\% \pm 5.7$. At the first visit, 30 patients (29%) had a cardiac T2* < 20 ms, suggesting significant iron loading; 13 patients (6%) had severe cardiac iron levels (T2* < 10 ms), and 12 patients (12%) had an LVEF $< 60\%$. Seven patients (6%) had cardiac iron overload and an LVEF $< 60\%$. Between the two participant centers, the prevalence of T2* values < 20 ms was 21 (40%) in centre 1 vs. 9 (18%) in centre 2, $p < 0.02$. Data is summarized in Table 12.

The mean liver T2* was 4.8 ± 4.2 ms, suggesting at least moderate iron levels; 48% had severe liver iron overload ($T2^* < 2.2$ ms), and only three patients had no liver iron ($T2^* > 17$ ms).

Twelve healthy volunteers were scanned (six in each participant centre), the overall T2* value was 37.5 ± 3.5 (37.4 ± 3.2 for centre 1 vs 38 ± 4.6 for centre 2, $p=0.7$) and mean LVEF of 66.6 ± 5.9 (66.4 ± 4.5 for centre 1 vs 66.9 ± 5.8 for centre 2, $p = 0.1$)

CMR variable	All patients	Centre 1	Centre 2	P value
Total (%)	103 (100%)	53 (52%)	50 (48%)	
Time of scanning (min) (mean \pm SD)	11.3 ± 2.5	13.2 ± 4.2	10.6 ± 2.4	<0.052
Heart T2* (ms) (mean \pm SD)	29.2 ± 11.9	29.5 ± 12.1	30.8 ± 11.6	0.12
T2* <20ms, N (%)	30 (29%)	21 (40%)	9 (18%)	<0.02
T2* <10ms), N (%)	13 (6%)	8 (15%)	5 (10%)	<0.019
Liver T2* (ms) (mean \pm SD)	4.8 ± 4.2	4.9 ± 4.2	4.7 ± 5.5	0.84
LVEF (%) (mean \pm SD)	64.5 ± 5.7	65.9 ± 5	66.9 ± 4.9	0.23
RVEF (%) (mean \pm SD)	67.1 ± 6.1	66.7 ± 6.9	67.6 ± 5.8	0.051

Table 12: Baseline Cardiac Iron and Cardiac Structure and Function Results. SD: Standard deviation, HV: Healthy Volunteer, LVEF: Left Ventricle Ejection Fraction

6.1.5.4 Follow-up results:

-Change in Therapy: At the 13-month follow-up visit, the overall number of participants who attended the Thalassaemic camp was 86 (83%). Chelation data was missing for 2 of them. Six patients were lost to follow up, and one died in the follow-up period; this

individual had presented at the baseline exam in overt cardiac failure due to iron load. Of the remaining ten patients who were unable to attend the second visit, all were alive, and none reported cardiovascular morbidity.

The dominant change between the first and second visits was the reduction in the use of monotherapy [47(55%) vs. 39(45%), $p=0.032$] and increase in the use of combined oral chelators [37(43%) vs. 48(55%), $p=0.002$]. See Table 13 and Figure 27. The average doses used changed little: DFO (-11mg/kg/day \pm 14.9, $p=0.01$) DFP (+2.8 mg/kg/day \pm 23, $p=NS$) DFX (+2.5 mg/kg/day \pm 9.5, $p = 0.03$).

		Chelation						
		None n (%)	DFO n (%)	DFP n (%)	DFX n (%)	DFO + DFP n (%)	DFO + DFX n (%)	DFP + DFX n (%)
Baseline	103	0 (0%)	3 (3%)	22 (21%)	30 (29%)	8 (8%)	19 (19%)	21 (21%)
Participants who completed 13 months follow-up								
Baseline	86	0 (0%)	4 (5%)	16 (19%)	27 (31%)	7 (8%)	18 (21%)	14 (16%)
Follow-up	86	1 (1%)	2 (2%)	11 (13%)	24 (28%)	2 (2%)	15 (17%)	31 (36%)

Table 13: Baseline Medication and Change in Therapy after 13 months follow-up: Desferrioxamine (DFO), Deferiprone (DFP), Deferasirox (DFX), combined Desferrioxamine + Deferiprone (DFO + DFP), Combined Desferrioxamine + Deferasirox (DFO + DFX), Combined Deferiprone + Deferasirox (DFP + DFX). *Therapy information was missed for 2 participants.

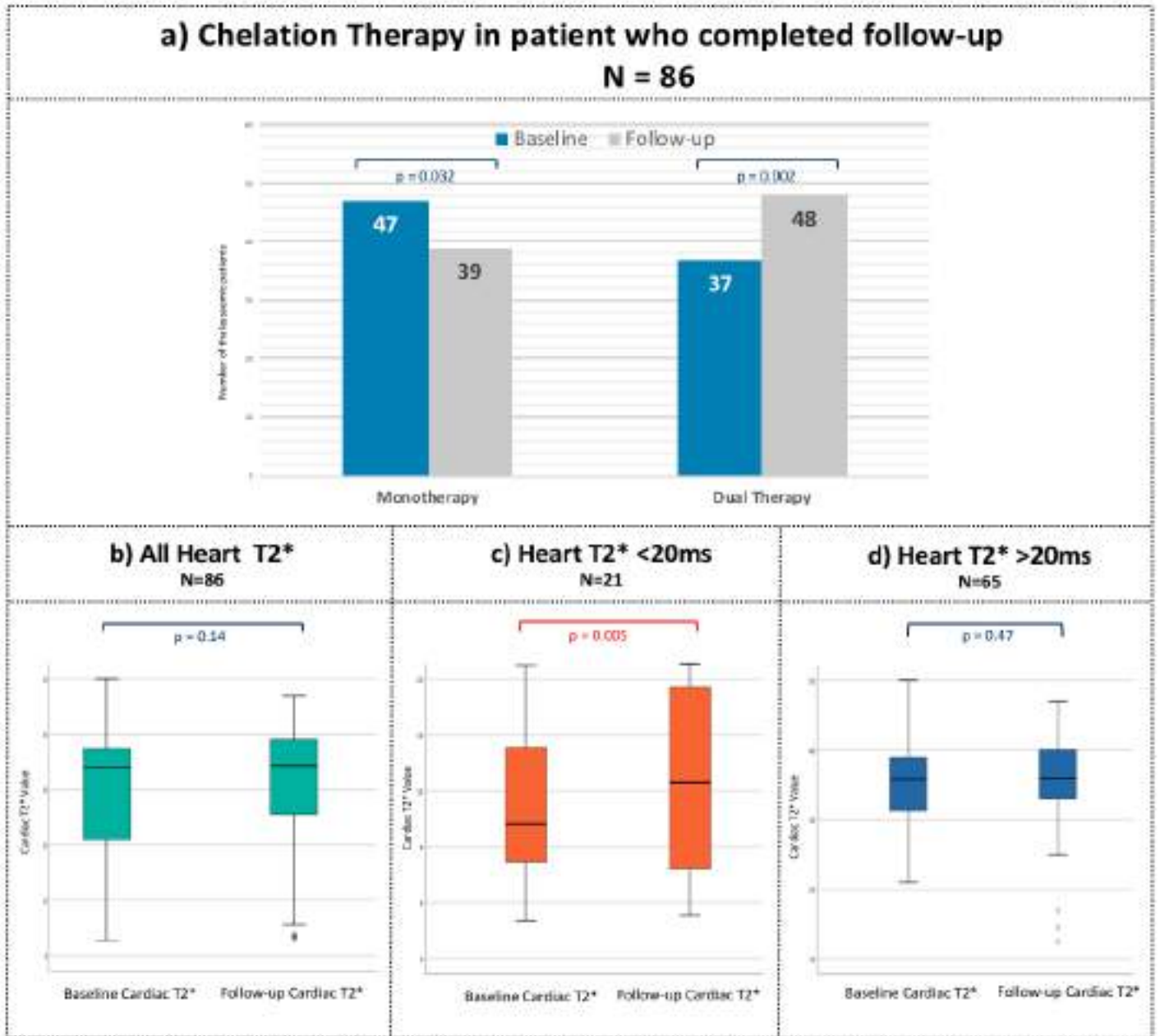


Figure 27: UMIMI Study: a) Change in Monotherapy and Dual Chelation Therapy between Baseline and Follow-up intervention (N= 86 patients) and overall changes in cardiac Iron T2* in b) All thalassaemic patients; c) Thalassaemic patients with Cardiac T2* <20ms; and d) Thalassaemic patients with Cardiac T2* >20ms.

Overall average cardiac iron measured by T2* was 29.1ms \pm 11.9 at baseline and 30.2ms \pm 11.7 at follow-up (p=0.12). LVEF did not change significantly (65.1% \pm 5.3 vs. 66% \pm 4.8, p=0.06). The liver T2* did not change (4.8ms \pm 4.2 vs. 4.9ms \pm 4.5, p=0.61). See Table 14.

	Baseline	13 months Follow-up	p value
All participants who completed follow-up N = 86			
Heart T2* (ms) (mean \pm SD)	29.2 \pm 11.8	30.2 \pm 11.7	0.14
T2* <20ms, N (%)	21 (24%)	14 (16%)	<0.001
Severe cardiac iron (<10ms), N (%)	10 (12%)	6 (7%)	<0.001
Liver T2* (ms) (mean \pm SD)	4.8 \pm 4.2	4.9 \pm 4.5	0.61
LVEF (%) (mean \pm SD)	65 \pm 5.3	66 \pm 4.8	0.06
Cardiac T2* <20ms N = 20			
Heart T2* <20ms (mean \pm SD)	10.9 \pm 5.9	13.5 \pm 8.7	0.005
LVEF (%) (mean \pm SD)	65 \pm 8.1	66 \pm 7.3	0.61
Cardiac T2* >20ms N = 66			
Heart T2* <20 (ms) (mean \pm SD)	34.7 \pm 6.4	35.4 \pm 6.9	0.47
LVEF (%) (mean \pm SD)	66 \pm 4.2	66 \pm 3.8	0.06

Table 14: CMR Iron Status and Left Ventricle systolic function data – comparison between basal and 13 months follow-up – UMIMI study. SD: Standard Deviation, LVEF: Left Ventricle Ejection Fraction.

Twenty-one participants with clinically significant iron loading (T2*<20ms) completed both visits. Cardiac T2* increased significantly from 10.9ms \pm 5.9 at baseline to 13.5ms \pm 8.7 at the follow-up visit (p=0.005). Given the linearity of R2* (1/T2*) to iron concentration, this represents a 23% reduction in cardiac iron. Of the entire cohort who completed the follow-up, in 7 (8%) patients, T2* became normal (T2* >20ms) and 3

participants (2%) with no cardiac iron overload by T2* at the first visit became abnormal (T2*<20ms) at the second. Cardiac function did not change in the group as a whole 64.9% ± 8.1 vs. 65.6% ± 7.3 (p=0.6). This was also true for the 8 participants with a baseline EF<60% who returned to the follow-up visit (LVEF: 56.2% ± 3.6 vs. 57.9% ± 4.6, p = 0.2). There was a poor correlation between T2* and LVEF in patients with cardiac siderosis (R²=-0.1, p = 0.5).

6.1.6 Discussion:

The current death rate in patients with thalassemia in India is roughly equivalent to that in the United Kingdom in the 1980s (191). Dhanya et al. (203) identified that ineffective transfusion, infections, and lack of appropriate chelation continue to be significant risk factors for mortality in India. Cardiac MRI T2* is a key test for diagnosis, guiding therapy, and is associated with improved outcomes where it is applied in patients with TM. The role of CMR takes more importance in countries where there is a high prevalence of inherited hematological conditions, such as India (189, 190, 204), impeding the delivery of optimal therapy. There are several barriers that block CMR delivery, including the perception by healthcare providers that it is a time-consuming, expensive, and intricate technique. We did four things to make CMR more accessible and relevant to the local conditions in India: **firstly**, *embedding our project to a in a locally organized Thalassemic medical camp*; **secondly**, we used an agreed, structured clinical evaluation, which included a CMR scan to guide therapy; **thirdly**, we implemented an abbreviated 10 minutes CMR protocol; **fourthly**, we trained the local care providers to enable them to undertake the CMR scans.

The UMIMI project was undertaken in two centers in India on regularly transfused TM patients, referred for cardiac iron and clinical assessment by their local hematologists. The selection of patients was controlled by the local advocate charity Thalasseemics India and was thus not a random selection within the region. It was not possible, nor was it felt ethical to include a non-intervention group denied the opportunity for an MRI scan. All the components for the patients' clinical, and imaging assessment were completed at the visit and recommendations for management could be based on the result of the rapid CMR and discussed with the patient, with a written record for their haematologist. See summary of the intervention in figure 28.

At the follow-up visit, only those patients with clinically significant cardiac iron loading ($T2^* < 20\text{ms}$ at baseline) had improved; the prevalence of $T2^* < 20\text{ms}$ falling from 24% to 16%. No changes in LVEF were seen in this young population, which was not unexpected; it would be unusual to see changes in cardiac function in this age group (205), despite cardiac iron overload. There was only one patient in clinical cardiac failure at the baseline visit and despite intensive therapy, this individual did not survive.

Our study focused on tackling healthcare delivery barriers by using the opportunity provided by a day-care thalassaemic medical camp visit. We found that a third of participants had cardiac iron overload, and 97% of patients had liver iron. Previous experience had shown that CMR could be performed in less than 10 minutes in Thailand (120) and India (121). However, such rapid CMR protocols on patients' therapy and tissue iron loading, have not previously been investigated. In this study, we embedded the CMR scanning in a familiar patient medical camp scenario, emphasizing the evaluation of cardiac function and iron status, ensuring the

involvement of local radiographers and doctors. The duration of scans shortened between visits, reflecting the local staff's increasing familiarity with the techniques. This intervention was associated with a change in chelator therapy with more patients receiving combination treatment with the two oral drugs, and it is highly likely that enhanced chelator treatment was associated with an improvement in cardiac T2* over a relatively short period time. The adoption of regular MRI scanning for T2* measurement and intensified chelation has previously been credited with improving mortality in thalassaemia via improved cardiac iron loading (68, 91, 206), so that it is not unreasonable to suggest that this result in India is consistent with previous experience. Demonstrating a practical method to incorporate an abbreviated CMR scanning into the routine care of thalassaemic patients in India has been achieved. The next steps require that this methodology is adopted more widely, establishing if the benefit can be sustained and clinical outcomes improved.

6.1.7 Limitations: This study is limited by its small sample size. It is not powered to detect differences between different chelation therapies and does not allow subgroup analysis. The follow-up period is only 13 months, which may not reflect a significant improvement in cardiac iron status. No regression analysis was performed to examine the relationship between the variables tested due to the limited sample size. No biochemical data were collected, and no histological evaluation of the myocardial iron deposit was performed.

6.1.8. Conclusion: These data demonstrate that a faster and simpler CMR protocol can be successfully embedded into a thalassaemic medical patients' camp model and that improvements in cardiac iron loading may follow. In those countries where cardiac iron has been improved, there has been a demonstrable improvement in survival for

TM patients, and it would be reasonable to predict similar outcomes could be achievable in India by wider adoption of these management techniques to improve iron loading.





Patients Camp workflow – UMIMI study			
Number	Time	Activity	Example
1	20 min	Clinical Data Collection + ECG Local haematologist + UK team Simultaneous translation and interpretation by local professionals.	
2	10 min	CMR scanning Supervision and support from UK CMR physicist and radiographer	
3	8 min	Post-Processing and Analysis By a Level III CMR expert in reporting. Use of Post-processing software for a rapid delivering of results	
4	15 min	Treatment plan discussed and agreed with patient and local team	
<p>Baseline Visit: 103 patients and Follow-up at 13 months: 86 patients, 2 centres Total Magnet time: 6-7 hours per day – 25 scans per days (2 days– 2 centres) Increase in the use of combined oral chelators (43%) to (55%). Cardiac iron loading decreased by 23% in one year</p>			

Figure 28: Summary of the UMIMI project – Patient Camp Workflow

Chapter 7 – Results 4: Cardiac Magnetic Resonance Strain Feature-Tracking for detection of LV systolic dysfunction in patients with Beta-Thalassemia and myocardial iron overload

7.1.1 Preface: This chapter is based on the manuscript below, which will be submitted to JACC Cardiovascular Imaging

Katia Menacho MD, *Andreas Seraphim* MD, *Amna Abdel-Gadir* MBBS, *Redha Boubertakh* Physics, *Kartik Ganga* MD, *Vineeta Ojha* MD, *Surya Pratap* MD, *Louise McGrath* RD, *Joao Augusto* MD, *Mr Alexander Rikowski*, *Ms Nabila Mughal* R, *Mrs Shoba Tuli*, *VK Kanna* MD, *Amita Mahajan* MD, *Rajiv K Bansal* MD, *Prabhar Srivastava* MD, *Harsh Mahajan* MD, *Vidhur Mahajan* MD, *Beatrix Wonke* MD, *Mrs Judith Walker* MSc RN, *Ms Seldon Tenzin* BSc, *Emmanuel Ako* MD, *James C Moon* MD, *J. Malcolm Walker*.

My contribution to this sub-study was submitting the UK (UCL) ethics, recruiting participants, and performing the final clinical reports to the participants (post-processing analysis of cardiac function and cardiac and liver T2). I also performed the statistical analysis, analysed CMR strain data, and wrote the manuscript.*

7.1.2 Background:

Heart disease is the main factor in mortality for patients with beta-thalassemia, including heart failure, arrhythmias, and myocardial infarction, with cardiac iron deposition as the principal mechanism causing these deaths and complications (207). Therefore, it is essential to precisely assess iron deposits in the heart and ideally deploy an early compromise with non-invasive technology. CMR T2* can detect and myocardial iron overload (MIO), with international guidelines validating CMR T2* as the most reliable technique for detection cardiac iron, allowing diagnosis and treatment before cardiomyopathy and heart failure develop (208). CMR T2* is easy to standardize, reproducible, and guideline supported (197). When therapy is applied

appropriately, guided by CMR, a >70% reduction in mortality can occur in Thalassaemic patients (191). There are other parameters measured by CMR, such as global LV systolic function. CMR is considered the gold standard imaging modality for the assessment of LVEF due to superior accuracy and high interobserver reproducibility (46, 209). However, LVEF detects iron-induced cardiomyopathy at the late stage of the disease (210), mainly when heart T2* iron overload is severe (T2* <10ms) (211). Myocardial deformation imaging can be a more sensitive marker of LV dysfunction, and it may detect early cardiac involvement, as proven in other clinical scenarios (212). In Thalassaemic patients with cardiac iron overload, strain echocardiography has shown to detect subclinical myocardial dysfunction, independent of CMR T2* values (213).

Myocardial strain deformation can now be calculated from standard CMR cine images using feature tracking software (214). Recent data in population with myocardial iron deposit are encouraging, suggesting that CMR feature-tracking (CMR-FT) can be a sensitive parameter for early detection of systolic dysfunction, even with normal CMR T2* suggesting no cardiac iron overload (215-217). However, most of these studies are designed as a single intervention, without prospective data to understand better the role of CMR-FT to detect early changes in cardiac function (84) and to assess subsequent myocardial iron overload. These gaps were evaluated in the present study using an abbreviated CMR protocol for cardiac function and cardiac and liver iron assessment in a Low-Middle Income Countries (LMICs) - India, the **UMIMI study**, which provides a reliable information about heart and liver iron content and linking these results to simple agreed prescribed chelation, transfusion, and one-year follow-up in Indian Thalassaemic patients from two centres in two cities in India.

7.1.3 Objectives: To evaluate the diagnostic performance of CMR feature tracking myocardial strain to assess temporal changes in early systolic dysfunction due to myocardial iron in Beta Thalassemic patients treated with chelation therapy.

7.1.4 Material and Methods: See section 6.1.4. for ethics and patient's information.

7.1.4.1 Abbreviated CMR protocol: See Section 3.4.1. and Figure 18.

7.1.4.2 CMR post-processing analysis: See Section 3.5.1 and Figure 20.

7.1.4.3 CMR feature-tracking analysis:

Semi-automated feature tracking analysis was performed using CVI42 software (Version 5.11.4 - 1559, Calgary, Canada). The three long-axis cine (4 chamber, 2 chamber, 3 chamber) and short-axis cine images at apical, mid-ventricular, and basal levels were analyzed. For global longitudinal strain (GLS), three long-axis cine CMR series using standard 2, 3, and 4-chamber views were analysed. For global circumferential strain (GCS) and radial strain (GRS), three short-axis cine SSFP series at the apical, middle, and basal LV sections were analyzed. Endocardial and epicardial borders were manually delineated with the initial contour set at end-diastole. In the case of suboptimal tracking, as defined by deviations of the contour from the endocardial and epicardial borders, contours were manually corrected, and the algorithm reapplied. Two operators independently analyzed all CMR data sets. CMR parameters were indexed to the calculated body surface area (BSA).

-Statistical analysis: As described before. See Section 3.10. Furthermore, receiver operating characteristic (ROC) analysis was performed to differentiate between patients and controls based on CMR parameters by calculating areas under the curve (AUC) and reliability. Mixed linear models were used to evaluate temporal changes for

systolic strain parameter, ejection fraction, and cardiac T2* for multiple pairwise comparisons of the one-time point (13 months follow-up) with baseline. The relationships between change in systolic strain with LVEF and T2* changes at 13 months were assessed by Pearson's correlation coefficients. The intra-class correlation coefficient was calculated to analyze the inter-operator analysis agreement. Statistical significance was defined as a two-sided p-value < 0.05.

7.1.5 Results:

7.1.5.1 General Clinical Data: See section 6.1.5.1 and Table number 11.

7.1.5.2 Baseline results

The overall baseline cardiac T2* value was 29.2ms ± 11.9, with a left ventricular mean ejection fraction (LVEF) of 64.5% ± 5.7. At the first visit, 30 patients (29%) had myocardial iron overload (cardiac T2* < 20ms); 13 patients (6%) had severe cardiac iron (T2*<10ms) and 12 patients (12%) had an LVEF< 60%. Seven patients (6%) had cardiac iron overload and LVEF <60%. LV systolic function (EF, GLS, GRS, and GCS) were decreased in patients with T2* <20ms) compared to patients with T2* (>20ms). All differences were significant except GCS and LVEF. In patients with T2* >20ms, GLS and GRS parameters were still significantly impaired compared to healthy volunteers. See Table 15.

	T2* < 20ms (N=30)	p-value	T2* > 20ms (N=73)	p-value	Healthy Volunteers (N=12)
Heart T2* (ms) (mean ± SD)	11.2±5.6	<0.001	34.9 ±6.3	0.17	37.5 ± 3.5
Liver T2* (ms) (mean ± SD)	3.4 ± 2.8	0.023	5.1 ± 4.7	<0.001	20.5 ± 7.6
LVEF (%) (mean ± SD)	65.4 ± 7.9	0.3	66.2 ± 4.5	0.63	66.7 ± 5.3
Global longitudinal strain (CMR - GLS)**	-16.7 ± 3.3	0.03	-18 ± 2.9	<0.001	-21.4 ± 3.1
Global circumferential strain (CMR - GCS)**	-17.7 ± 3.2	0.06	-18.9 ±2.7	0.19	-20.1 ± 2.4
Global radial strain (CMR-GRS)**	31.2 ± 9.6	0.03	35.4 ± 8.3	0.002	37.5 ± 3.4

**Unable to acquire interpretable CMR GLS, GRS and GCS% in 3 out of 103 patients

Table 15: Baseline comparison of Beta-Thalassemic patients with cardiac iron overload (T2* < 20 ms) and without myocardial iron deposition (T2* > 20 ms) and healthy volunteers. SD: Standard Deviation, LVEF: Left ventricle ejection fraction, CMR: Cardiac Magnetic Resonance, GLS: Global longitudinal strain, GCS: Global Circumferential Strain, GRS: Global Radial Strain

7.1.5.3 Follow-Up Results:

At the 13-month follow-up visit, 86 (83%) attended. The dominant change in therapy between the first and second visits was the reduction in the use of monotherapy and increase in the use of combinations of the two oral chelators (DFP+DFX) as it follows (*baseline: follow-up*): DFO 4(3%) : 2(1%), DFP 16(19%) :13(14%), DFX 27(33%) : 24(29%), DFO + DFP 7(8%) : 2(2%), DFO + DFX 17(20%) : 13(16%), DFP + DFX 14(17%) : 31 (37%).

Overall average cardiac iron measured by T2* was $29.1\text{ms} \pm 11.9$ at baseline and $30.2\text{ms} \pm 11.7$ at 13-month follow-up, without a significant change between both values ($p=0.12$). LVEF improved on the follow-up visit, but changes were not significant ($p=0.06$). The analysis of strain function showed that only global longitudinal strain function improved significantly at 13 months follow-up (-18 ± 3.1 vs. -19 ± 2.9 , $p < 0.001$). Twenty-one participants with MIO completed both visits. Cardiac T2* increased significantly from $10.9\text{ms} \pm 5.9$ at baseline to $13.5\text{ms} \pm 8.7$ at the follow-up visit ($p=0.005$). LVEF and strain function assessed by GLS, GCS and GRS also showed improvement. However, this improvement was only significant with GLS; LVEF: $64.9\% \pm 8.1$ vs $65.6\% \pm 7.3$ ($p=0.6$); GRS 32.1 ± 9.1 vs 33.3 ± 7 ($p=0.26$); GCS: -17.9 ± 3.2 vs -18.1 ± 3 ($p=0.2$) and GLS: -16.43 ± 3.2 vs -17.9 ± 3.6 ($p=0.006$). In patients with T2* $>20\text{ms}$, cardiac iron changes were not significant ($34.7\text{ms} \pm 6.3$ vs. 35.4 ± 6.9 , $p=0.47$). LVEF, GLS, GCS, GRS showed an improvement, but the improvement was only significant for GLS: -18.2 ± 2.9 vs. -19 ± 2.7 ($p < 0.001$). See Figure 29 and Table 16.

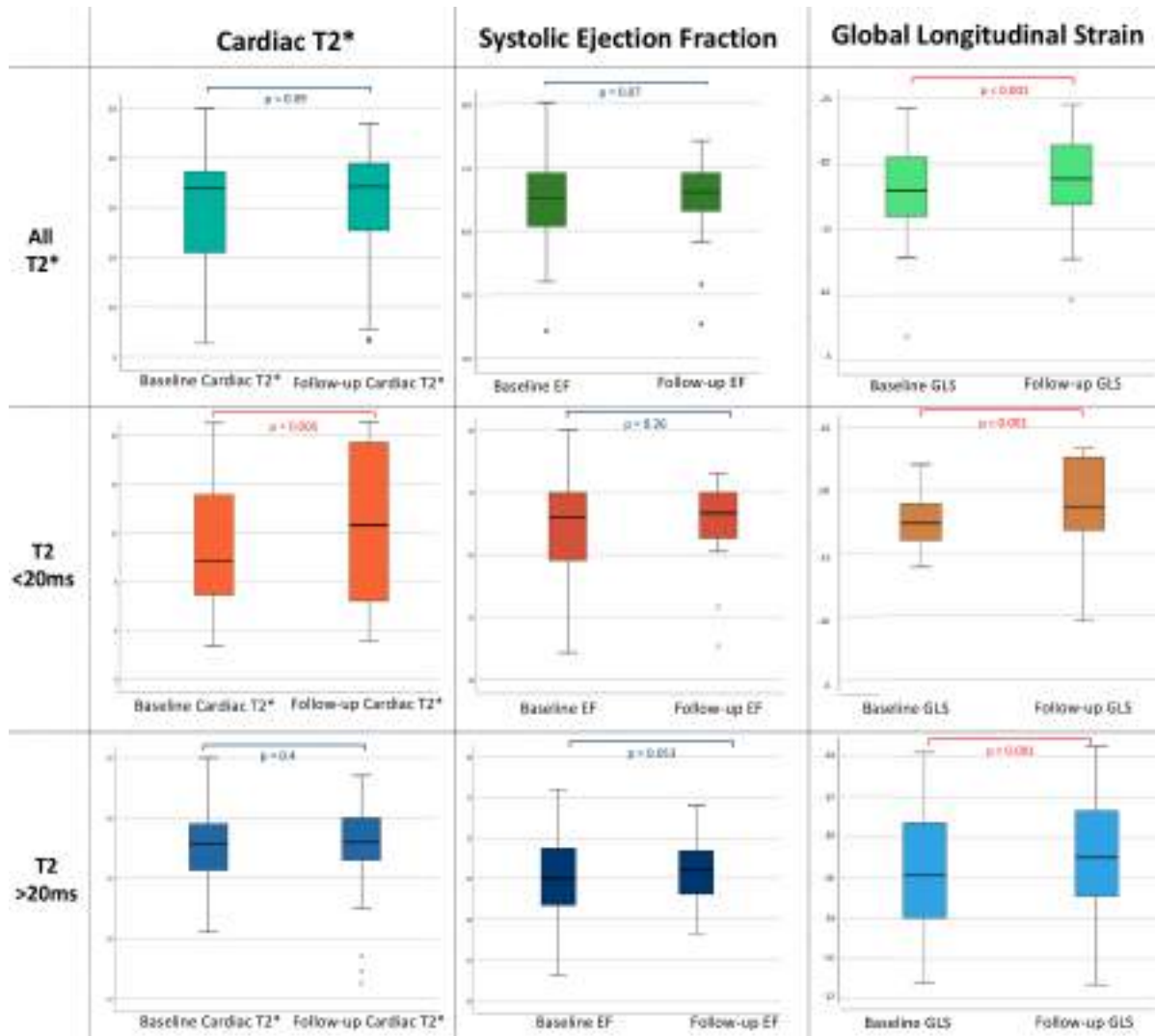


Figure 29: Cardiac Iron ($T2^*$) and systolic function (LVEF and GLS) change in Beta-thalassemia patients after 13 months follow-up – UMIMI study: Overall all the group had a significant improvement in GLS after instructions in the change of the therapy following CMR results. Patients with cardiac iron ($T2^* < 20\text{ms}$) showed improvement in iron levels and GLS. Even in participants with no cardiac iron ($T2^* > 20\text{ms}$), there was a significant improvement in GLS.

LVEF: Left ventricle ejection fraction, CMR: Cardiac Magnetic Resonance, GLS: Global longitudinal strain, GCS: Global Circumferential Strain, GRS: Global Radial Strain

CMR Variable	Baseline	13 months Follow-up	p value
All participants who completed follow-up N = 86			
Heart T2* (ms) (mean \pm SD)	29.2 \pm 11.8	30.2 \pm 11.7	0.14
T2* <20ms, N (%)	21 (24%)	14 (16%)	<0.001
Severe cardiac iron (<10ms), N (%)	10 (12%)	6 (7%)	<0.001
Liver T2* (ms) (mean \pm SD)	4.8 \pm 4.2	4.9 \pm 4.5	0.61
LVEF (%) (mean \pm SD)	65 \pm 5.3	66 \pm 4.8	0.06
Cardiac T2* <20ms N = 20			
Heart T2* <20ms (mean \pm SD)	10.9 \pm 5.9	13.5 \pm 8.7	0.005
LVEF (%) (mean \pm SD)	64.9% \pm 8.1	65.6% \pm 7.3	0.6
Global longitudinal strain (GLS)	-16.43 \pm 3.2	-17.9 \pm 3.6	0.006
Global circumferential strain (GCS)	-17.9 \pm 3.2	18.1 \pm 3	0.2
Global radial strain (GRS)	32.1 \pm 9.1	33.3 \pm 7	0.26
Cardiac T2* >20ms N = 66			
Heart T2* <20 (ms) (mean \pm SD)	34.7 \pm 6.4	35.4 \pm 6.9	0.47
LVEF (%) (mean \pm SD)	66 \pm 4.2	66 \pm 3.8	0.06
Global longitudinal strain (GLS)	-18.2 \pm 3 ⁺⁺	-19 \pm 2.9 ⁺⁺	<0.001
Global circumferential strain (GCS)	-18.9 \pm 2.9 ⁺⁺	-19.2 \pm 2.6 ⁺⁺	0.6
Global radial strain (GRS)	34.9 \pm 8.8 ⁺⁺	35.4 \pm 7.7 ⁺⁺	0.21

⁺⁺ Unable to acquire interpretable CMR GLS, GCS. GRS% in 3 out of 86 patients at follow-up intervention.

Table 16 - CMR Left Ventricle systolic function and cardiac iron data – comparison between basal and 14 months follow-up patients camp – UMIMI study.

SD: Standard Deviation, LVEF: Left ventricle ejection fraction, CMR: Cardiac Magnetic Resonance, GLS: Global longitudinal strain, GCS: Global Circumferential Strain, GRS: Global Radial Strain

7.1.5.4 Correlation between T2* and systolic function:

In the overall group with Beta-thalassemia, there was a low significant correlation between T2* and GLS ($R^2 = -0.3$, $p = 0.02$), T2* and LVEF ($R^2 = 0.22$, $p = 0.02$) and LVEF and GLS ($R^2 = -0.3$, $p < 0.001$). GLS correlation with T2* was also significant within the group with cardiac iron overload ($T2^* < 20\text{ms}$) $R^2 = -0.51$ ($p = 0.005$). See figure 30.

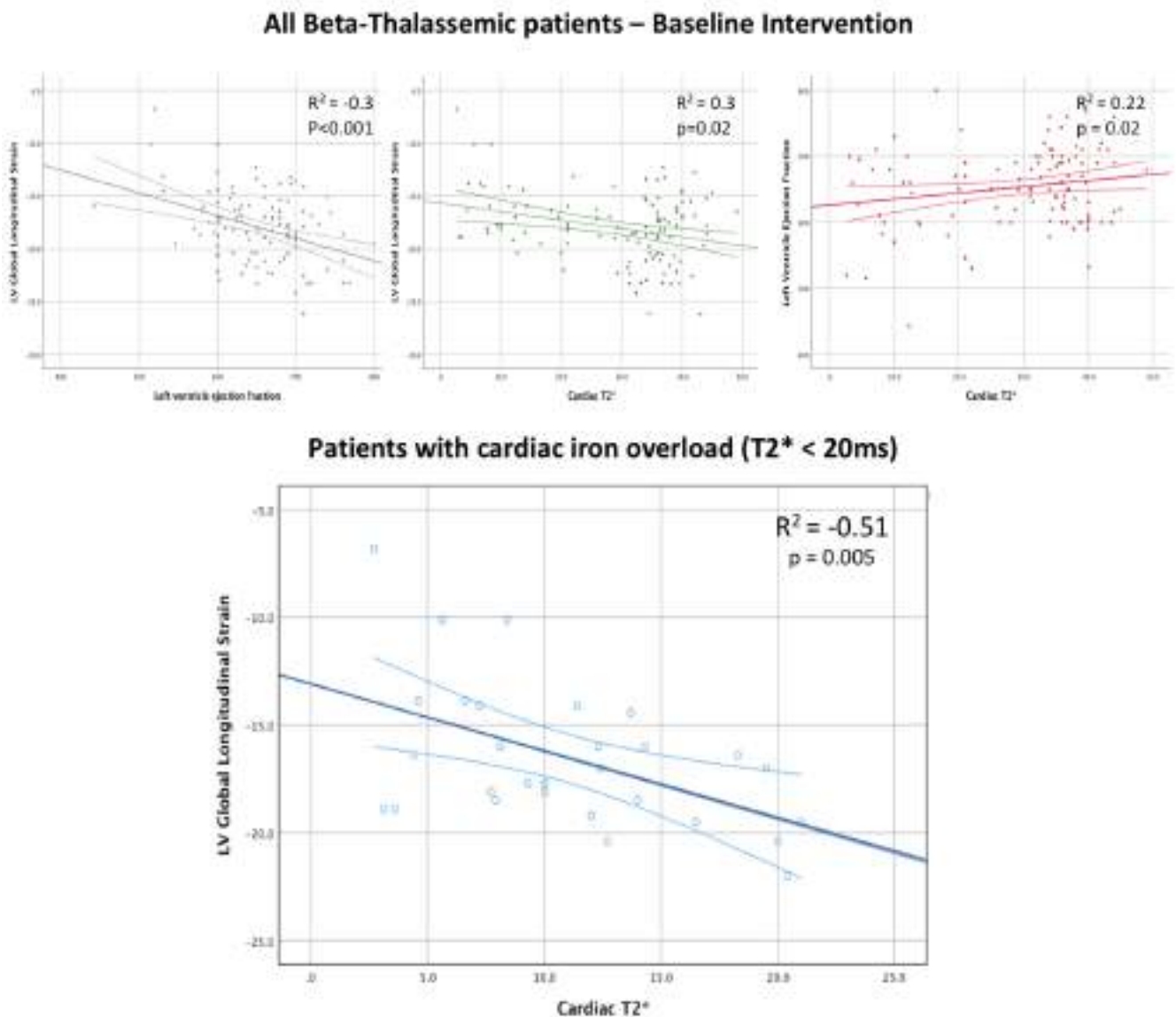


Figure 30: Correlation between cardiac systolic function parameters and cardiac iron level. There was an overall weak correlation between LV GLS with LVEF, LV GLS with cardiac T2, and LVEF with cardiac T2*. The correlation was stronger between LV GLS and Cardiac T2* in patients with cardiac iron overload ($T2^* < 20\text{ms}$).

There was a poor and no significant correlation between $T2^*$ and LVEF, GRS, and GCS in both groups, $T2^* < 20\text{ms}$ and $T2^* > 20\text{ms}$

Analysis of the ROC curve - baseline data showed an area under the curve of 0.7 (95% CI 0.6 - 0.82) with the best GLS cut-off of -18.5% to indicate LV systolic impairment in patients with myocardial iron overload ($T2^* < 20\text{ms}$) with a sensitivity of 88% and a specificity of 54%. The area under the curve was under 0.7 for LVEF, GCS, and GRS, suggesting that any of these variables are suitable for detecting significant MIO. See figure 31.

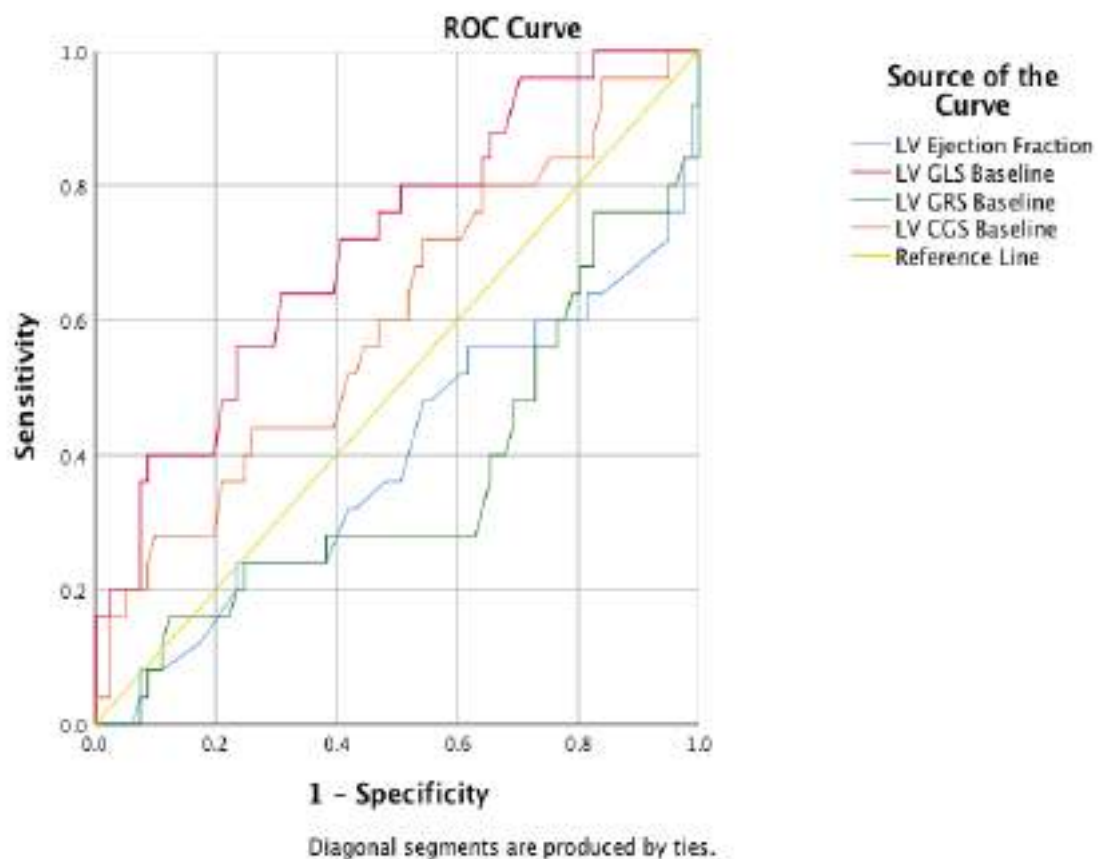


Figure 31: Distribution of global longitudinal (a), circumferential (b), and radial (c) strain values in patients with myocardial $T2^* < 20\text{ms}$.

LVEF: Left ventricle ejection fraction, CMR: Cardiac Magnetic Resonance, GLS: Global longitudinal strain, GCS: Global Circumferential Strain, GRS: Global Radial Strain

7.1.6 Discussion:

In this prospective study, we investigated whether temporal changes in myocardial strain measured by FT-CMR preceded or coincided with cardiac iron changes detected by T2* CMR in a cohort of patients with Beta-thalassemia treated with iron chelation guided by cardiac iron status. To the best of our knowledge, this is the first study to use FT-CMR to examine longitudinal changes in a cohort of patients with Beta-Thalassemia. There were significant changes in FT-GLS and CMR T2* in patients with MIO on the follow-up assessment. We did not find significant changes in LVEF, radial, and circumferential strain in the cohort of patients with and without cardiac siderosis. Furthermore, CMR FT-GLS showed a good correlation with septal T2*. Taking together these results, it is very likely that GLS is the most useful parameter to detect early myocardial injury in thalassemic patients.

It has been of particular interest to identify subclinical cardiac dysfunction before the development of LVEF impairment. It seems that the heart tolerates the oxidative stress from the iron deposit for an extended period before going to systolic heart failure (218). This is the reason why patients with myocardial iron deposits still have normal LVEF. Myocardial deformation imaging can be a more sensitive marker of LV dysfunction and detect early cardiac involvement before global ejection fraction changes occur. In Thalassemic patients with myocardial iron, a few echocardiography studies have shown that myocardial strain detects subclinical myocardial dysfunction, preceding the decline of LVEF (213, 219-221). There are several advantages with echocardiography and strain analysis as it is an accessible and cheaper exam. However, it has several limitations as it does not measure cardiac iron. Its efficiency depends on the adequacy of the acoustic window and image quality. CMR is the gold standard exam to assess

cardiac iron and left ventricle systolic function (40). FT- CMR for quantifying global left ventricular strain is a fast and robust technique, carrying crucial clinical information in different clinical scenarios, such as cardiotoxicity (212, 222). However, for most patients, CMR access is limited; it is an expensive exam, requiring specialized training and advanced software analysis.

Our main project (UMIMI study) tackled the limitation of CMR access in low resource centers. We implemented an abbreviated CMR protocol in India. This protocol included assessing routine and conventional volumes, systolic function, and cardiac/liver iron. The total length of the scan last 10 minutes, and we managed to scan 103 Thalassemic patients in 2 cities – 2 centers, 50 patients per day. The LV cine images acquired in the rapid protocol are standard sequences, and they were used for a more advanced post-processing analysis with CMR-FT, avoiding additional time-consuming image acquisitions.

In our study, CMR-FT was decreased in all (GLS, GRS, and GCS) in patients with myocardial iron overload ($T2^* < 20\text{ms}$), and these variables were reduced together with LVEF in the group of $T2^* > 20\text{ms}$ when compared to healthy volunteers, suggesting that even in the absence of myocardial iron overload, there is still subclinical impairment of cardiac function that can be detectable with CMR-FT. These results are very similar to what has been described by another study with CMR-FT (215). GLS has proven to be the most sensitive parameter of LV strain in the setting of cardiac disease (222-225). Current evidence confirms that iron deposits are higher in the subepicardial region (oblique fibers), with a progressive reduction through the layers and the endocardium (90, 226) with the longitudinal fibers run from the sub-endocardium. Based on this, one could expect the early involvement of GCS in these patients. However, this was not

shown in the present study. As previous studies (215, 216) we demonstrated that GLS remains the best predictor of early cardiac involvement; a possible explanation for these findings may be related to the endocardium being more vulnerable to stress and damage than other diseases (227). Our study provides longitudinal data following the changes of myocardial iron in transfusion-dependent thalassaemic patients receiving chelation therapy who have reduced longitudinal, radial and circumferential strain, showing a significant improvement in cardiac T2* and GLS after 13 months follow-up. This study is one of the few studies, including CMR-FT strain that reveals a good correlation between myocardial iron deposition by cardiac T2* and myocardial strain GLS in patients with myocardial iron overload, which is still evident in patients with T2* >20ms. This may raise additional questions about the cut-off point of 20ms to define cardiac iron overload by T2*. The internationally accepted cut-off points for iron load assessment by T2* of 20ms is known to be conservative, prioritizing specificity over sensitivity. Furthermore, previous studies have shown that iron deposition is still found in patients with normal T2* in the septum (>20ms); studies on T1 mapping and its correlation with T2* suggest that 26ms would be a more appropriate cut-point for T2 (228). Another possible hypothesis is a different pathophysiological mechanism to myocardial iron, which can cause GLS impairment, such as chronic tissue hypoxia from chronic anemia as an initiating factor for subsequent iron-induced cardiomyopathy.

Our research has some limitations. Firstly, our cohort is small, with only 103 participants, with a drop-off of 14% in the follow-up. Also, not all 103 participants completed the scan at baseline due to claustrophobia, and strain images were not available due to poor-image quality in 3 participants. However, this is the most

extensive prospective study to evaluate LV strain using CMR-FT in Thalassaemic patients treated with chelation therapy. CMR-FT post-processing software is not accessible in all centers, and costs may limit the routine adoption of this technique.

7.1.7 Conclusion: In this longitudinal study using CMR-FT, there was a significant improvement in GLS, which correlated with a concurrent improvement in T2* CMR in patients with MIO receiving chelation therapy. GLS may be a promising method to monitor subclinical myocardial dysfunction in Thalassaemic patients with MIO.

Chapter 8 – Results 5: Direct comparison of the measurement precision of MUGA, CMR and echocardiography for serial cardiotoxicity screening in cancer patients

8.1.1 Preface: This chapter is based on the manuscript below that will be submitted to the European Heart Journal.

**Veronica Culotta, *Katia Menacho, Anish Bhuvu, Rhodri Davies, Ana Ferreira, Patricia Carneiro, Arjun Ghosh, Mark Westwood, Leon Menezes, Guy Lloyd, James C. Moon and Charlotte Manisty*

*Drs Veronica Culotta and Katia Menacho are joint first authors.

My contribution to this sub-study was recruiting participants, post-processing analysis of CMR (including GLS) and MUGA. I also contributed creating to the database, performed part of the statistical analysis, analysed and wrote the manuscript.

8.1.2 Background:

Screening for cancer therapeutics-related cardiac dysfunction (CTRCD) is a guideline-recommended component of managing of patients receiving many potentially cardiotoxic treatments, such as anthracyclines and HER2 receptor monoclonal antibodies (44, 129, 229, 230). Results dictate important clinical decision-making, including cancer treatment withdrawal and initiation of heart failure therapy to minimise downstream clinical cardiovascular events (127). CTRCD is defined as a decrease in LVEF of $\geq 10\%$ from baseline to a value below the lower limits of normal (44, 129, 229, 230). In order to be confident that a fall in ejection fraction (EF) represents a true pathological decline in cardiac function rather than the result of measurement variability, quantification of LVEF needs to have sufficient inter-study reproducibility

(precision) to confidently detect differences that represent the biology of cardiotoxicity (defined as $\geq 10\%$ reduction).

Echocardiography is currently the first-line recommended imaging modality for the measurement of LVEF (44, 129, 229, 230). 2D echocardiographic (2DE) measures of LVEF are limited by geometric assumptions and dependence on acoustic windows, leading some authors to question the validity of the modality for LVEF measurement in the context of CTRCD (231). Previous studies have demonstrated both superior intra and inter-observer reproducibility with 3D echocardiography (3DE) compared with 2DE (232) and lower inter-study temporal variability (233). CMR is the gold standard for assessment of LVEF due to superior inter-observer reproducibility (209), and recent data has confirmed lower mean temporal variability in LVEF with CMR compared with echocardiography (47). However, there is no available data with repeat studies acquired with multiple imaging modalities on the same day to minimise variability due to physiological differences in loading conditions and enable optimal assessment of true measurement precision.

Myocardial deformation imaging by 2DE GLS provides a more sensitive and reproducible marker of LV dysfunction than LVEF (47) (212). Strain measurements can also be derived from standard CMR cine images using feature-tracking software, and CMR-derived strain has been shown to track early cardiotoxicity changes in breast cancer patients (234). As strain measurements are increasingly incorporated into clinical practice and guidelines (44) (129, 229, 230), a direct comparison between strain modalities in the context of cardiotoxicity screening is appropriate.

Scan precision may also be improved by reducing the impact of human operator variability. Semi-automated techniques have been incorporated into

echocardiographic analysis software, and fully-automated machine learning (ML) algorithms have been shown to have similar precision to humans for measuring LVEF by CMR (235) (236). The added value of automated analysis for serial cardiotoxicity screening has not been assessed.

8.1.3 Objectives: We sought to identify the best clinical test for serial surveillance and detection of CTRCD by comparing head-to-head measurement precision (test-retest reproducibility) of 5 methods for LVEF (CMR manual, CMR-ML, 2DE, 3DE, and MUGA); and 2 for strain (CMR and echocardiography) in cancer patients at risk of CTRCD.

8.1.4 Material and Methods:

8.1.4.1 Patients and study design:

Cancer patients referred for cardiotoxicity surveillance at Barts Heart Centre, London, United Kingdom, were prospectively recruited. The study was approved by the UK National Research Ethics Service (16/LO/1815), and all patients gave written informed consent.

Patients underwent repeat (test-retest) imaging with the clinically-requested modality, together with additional test-retest imaging using a second modality on a single day (Figure 32). It was not feasible or tolerable for patients to undertake three modalities (6 tests) in a single subject within one day. A stratified recruitment approach ensured adequate representation of participants across the three modalities. To avoid unnecessary radiation, only patients for whom a MUGA scan had been requested clinically by their referring physician underwent nuclear imaging, and the repeat MUGA scan was acquired immediately without re-administration of radioisotope. Patients with standard contraindications to MRI, atrial fibrillation, or frequent ectopy were excluded

from all arms of the study.

All studies were completed within 4 hours to avoid physiological changes in loading conditions and therefore ensure consistency. Between repeat tests of a single modality, mobilisation, repositioning of patients, ECG leads, and repeat CMR isocentre were done.

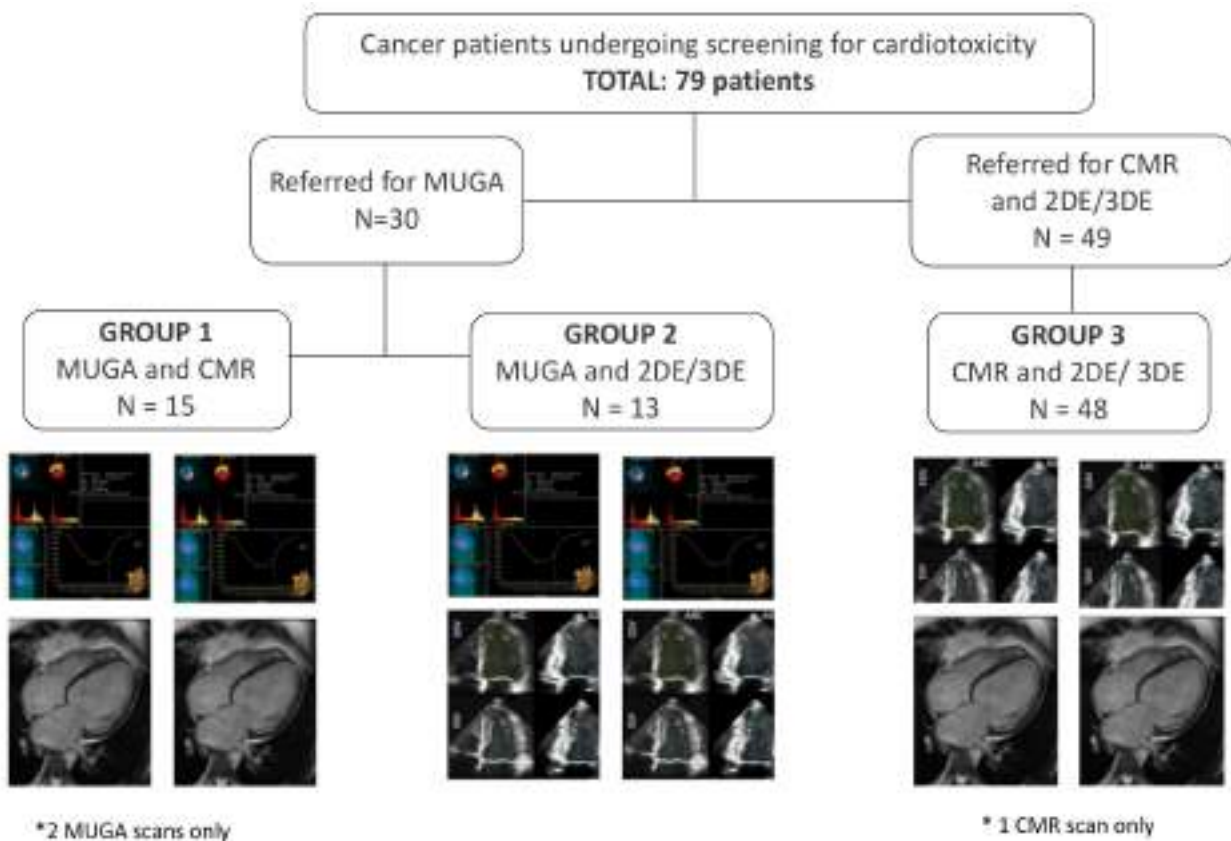


Figure 32: Study Design: Total number of participants enrolled in the study and distribution of the scans completed. 2DE: 2D Echocardiography, 3DE: 3D Echocardiography, MUGA: Multigated acquisition scan, CMR: Cardiac Magnetic Resonance, CMR-ML: Cardiac Magnetic Resonance Machine Learning.

8.4.1.2 Imaging Protocol and Analysis

Operators accredited in each of the three modalities acquired the scans, with the same operator acquiring the paired tests per modality. Each scan was then ascribed a separate randomly generated identification number. The study dataset was locked and batch analysed by a single independent, experienced operator for each modality

(blinded to study pairings) later to minimise bias.

- **Echocardiography:** 2DE and 3DE were performed and analysed (Vivid E9, GE, Horten, Norway) according to the American Society of Echocardiography protocols (237). Image settings were optimised with harmonics on and a frame rate of 80 frames per second for 2DE. A 3DE total volume dataset of the LV was obtained with gated (4 beats) acquisition with sector size, depth, and number of heartbeats optimised to obtain the highest possible volume rates (>40 frames per second). Images were saved digitally for subsequent offline analysis (software Echo PAC Version 113, GE). 2DE LV volumes and LVEF were calculated using Simpson's biplane method. 3DE volumetric analysis was performed with basal and apical guide points placed in the end-diastolic and end-systolic frames. Endocardial contours were then automatically generated, with manual adjustment if necessary. 2D speckle tracking was performed, end-diastole as the start of the QRS complex on the ECG and end-systole as the closure of the aortic valve. Repeat adjustments of the ROI were made if tracking quality was insufficient, and segments were excluded if adequate tracking was not achievable.
- **MUGA:** Scans were performed as per standard recommendations (238) with a single injection of radiotracer. Stannous medronate reducing agent was injected 20 minutes prior to the injection of 800 MBq of Tc-99m Pertechnetate. Images were acquired with a dual-head gamma camera (Philips Medical Systems) using a low-energy high-resolution collimator, with an energy window of 20% placed over a photopeak of 140 keV. ECG-gated data were acquired at 24 frames per cardiac cycle, with 128 × 128 matrix of 16-bit pixels. Acquisition

times were adjusted to achieve a minimum of 200,000 counts per frame. Patients were resting and supine, and the best septal view was individually adjusted from 45° left anterior oblique position with 10°–15° caudal tilt. For analysis, scintigrams were smoothed offline using standard algorithms, with background correction. The LV regions of interest, as well as a background activity, were selected automatically by the computer program Hermes (Functional Gated Analysis, FUGA version V4.7, Hermes Medical Solutions, Stockholm, Sweden) (239), using default settings (no zoom, application of a Butterworth filter with a cut-off of 5 and order 70, background ROI placed on the end-diastolic frame). LV time-activity curves were constructed, and LVEF was calculated as
$$\frac{([\text{background-corrected end-diastolic counts} - \text{background-corrected end-systolic counts}])}{(\text{background-corrected end-diastolic counts})} \times 100.$$

- **CMR:** *CMR protocol:* See Section 3.4.1; for *CMR post-processing analysis of cardiac function:* See Section 3.5.2 and Figure 20 and for *CMR Feature-Tracking analysis:* See Section 7.1.4.3.
- **ML automated analysis of CMR data:** Fully automated volumetric analysis was performed using deep convolutional neural networks (236). Models based on the U-net (240) were trained on a multi-institutional dataset of 1,923 patients, with a broad range of pathology, segmented by a single clinical expert (JCM). Segmentations from a SAX model were combined with a mitral annular plane model to define the basal extent of the ventricle.
- **Image quality assessment:** Before statistical analysis, datasets were scored as 'good' or 'inadequate' by the modality lead (Echocardiography GL, CMR JM,

Nuclear LM), all of whom have held National leadership roles in their respective modalities. Data were categorised as 'inadequate' if it met the following criteria:

- a) **CMR** - incomplete LV coverage, artifact obscuring any part of the LV (241).
- b) **Echocardiography** - 2DE: poor endocardial definition in more than two segments and apical descent >1 cm (fore-shortening). 3DE: more than two segments with poor endocardial tracking. GLS (2D): two or more segments with poor tracking in any of the three apical windows and 1cm of apical descent (237).
- c) **MUGA**: during acquisition - inadequate counts/frame and labelling with reduced target-to background ratio and during cardiac analysis – evidence of inadequate separation of the LV from other cardiac chambers, the inaccurate definition of the LV ROI (242).

8.1.4.3 Statistical Analysis:

Data were analyzed in R (R foundation, Vienna, Austria) using R Studio Server version 0.98 (Boston, Mass, USA). Continuous variables are expressed as mean \pm standard deviation (SD) or median and inter-quartile range (IQR) for data not normally distributed (formally tested using Shapiro-Wilk test).

Measurement of agreement between modalities was assessed using Pearson correlation coefficient and Bland-Altman limits of agreement (LoA). To quantify precision (test-retest reproducibility), several metrics were measured and compared using Levene's test. All tests were two-tailed and $p < 0.01$ was considered statistically significant following Bonferroni correction. Metrics calculated were:

- Absolute difference between scans
- Bland-Altman limits of agreement (LoA)

- Within-subject Coefficient of Variation (CV) - calculated as the ratio of the standard deviation of differences to the mean difference

Minimal detectable difference (MDD) – the level at which there is 95% confidence that a change exceeding this threshold represents a true difference and not just a measurement error. The standard error of measurement (SEM) was calculated as the square root of the mean squared error obtained from one-way analysis of variance, and the MDD was calculated as $1.96 \times \text{SEM}$ (243).

8.1.5 Results:

8.1.5.1 Patient Demographics: 79 patients (mean age 51.6 ± 11.7 years, 13% male) were recruited – 30 patients booked for echocardiography, 30 patients for MUGA, and 19 for CMR, all as part of their clinical cardiotoxicity screening pathway. This generated a dataset of 61-paired echocardiogram studies, 30-paired MUGA, and 64 paired CMR (three patients declined further imaging after just one imaging modality: CMR only for one participant, MUGA only in two participants but were still included). Adequate 3DE datasets could not be acquired in 12/61 (20%) of patients due to poor acoustic windows, including, prior mastectomy. The patient cohort was representative of the general population of cancer patients undergoing screening for cardiotoxicity (Table 17), and clinical characteristics were similar between modalities (Table 18).

Variables	Mean±SD or n (%)
Total participants	79
Age (mean ± SD)	51.7 ± 11.7
Female (%)	69 (87%)
Body mass index (BMI) (mean ± SD)	27.6 ± 5.6
BMI >25 -<30 (%)	22 (28%)
Obese (BMI ≥ 30) (%)	24 (30%)
Body surface area	1.82 ± 0.2
Primary Tumour	
<i>Breast Cancer</i>	56 (71%)
<i>Lymphoma</i>	8 (10%)
<i>Myeloma</i>	5 (6%)
<i>Other Haematological malignancy</i>	2 (3%)
<i>Gastro-intestinal malignancy</i>	4 (5%)
<i>Other cancer</i>	4 (5%)
Prior mastectomy (%)	21 (27%)
Prior radiotherapy (%)	25 (32%)
Anthracycline treatment (%)	53 (67%)
Anti- HER2 treatment (trastuzumab/ pertuzumab)	48 (61%)
Assessment stage	
<i>Baseline (pre-cancer treatment)</i>	10 (13%)
<i>Peri-treatment surveillance</i>	48 (61%)
<i>Post-Treatment surveillance/ late effects</i>	21 (26%)
Cardiovascular Comorbidities	
<i>Hypertension</i>	19 (24%)
<i>Diabetes Mellitus</i>	4 (5%)
<i>Smoker (current/ ex)</i>	14 (18%)
<i>Dyslipidaemia</i>	4 (5%)
<i>Pre-existing Cardiovascular disease</i>	2 (3%)

Table 17: Baseline patient demographics SD: Standard Deviation, BMI: Body Mass Index, CMR: Cardiac Magnetic Resonance, MUGA: Multigated Acquisition Scan

	2DE N = 61	3DE N = 49	CMR N = 64	MUGA N = 30
Age (mean ± SD)	52 ± 12	53 ± 11	52 ± 12	50 ± 10
Gender (% male)	17%	15%	15%	3%
BMI (mean ± SD)	26.9 ± 5.3	26.3 ± 5.2	27.7 ± 5.6	29.2 ± 6
BSA (mean ± SD)	1.79 ± 0.22	1.78 ± 0.22	1.81 ± 0.21	1.88 ± 0.21
Volume and Function Assessment				
LVEF (%) (mean ± SD)	57.7 ± 7.9	57.5 ± 8.1	64.5 ± 9.1*	60.1 ± 9
EDV (mean ± SD)	96.3 ± 27.9*	91.1 ± 25.3*	121.1 ± 32.1	123.7 ± 28.6
ESV (mean ± SD)	41.4 ± 17.6	39.1 ± 25.4	44.6 ± 21.7	57.1 ± 21.7*
SV (mean ± SD)	54.9 ± 15	52 ± 15.1	76.5 ± 17.7	70 ± 19.3
GLS (mean ± SD)	-18.1 ± 3.4		-19.4 ± 3.1	

Comparisons were non-significant between modalities except where indicated (* = p<0.05)

Table 18: Participant characteristics by imaging modality. SD: Standard Deviation, BSA: body surface area, BMI: body mass index, LVEDV: Left ventricle end diastolic volume, LVEF: Left ventricle ejection fraction, LVESV: Left ventricle end systolic volume, LVSV: Left ventricle stroke volume, 2DE: 2D Echocardiography; 3DE: 3D Echocardiography, MUGA: Multigated acquisition scan, CMR: Cardiac Magnetic Resonance, GLS: Global longitudinal strain

Across the whole cohort, LVEF of patients undergoing CMR measured higher than with other imaging modalities ($64.5 \pm 9.1\%$, $57.7 \pm 7.9\%$, $57.5 \pm 8.1\%$, $60.1 \pm 9.$, $p < 0.05$) for CMR, 2DE, 3DE, and MUGA respectively. However, the number of patients with LVEF <50% were not significantly different between modality groups.

8.1.5.2 Comparison of Precision between modalities

A test-retest difference of >5% occurred in 34% of patients using 2DE, versus 14%, 17%, 14% and 8% with 3DE, MUGA, CMR and CMR - ML respectively. Two patients had a LVEF difference of >10% with 2DE, but none had differences of this magnitude using other modalities. Using 2DE to assess the relative difference between repeat measurements of GLS, 23% of participants had significant inter-scan differences of > 15%, compared to 7% assessed by CMR. See Table 19.

Inter-scan (test-retest) difference	2DE		3DE		MUGA		CMR	
	All studies n=61	Good quality n=49	All studies n=49	Good quality n= 39	All studies n=30	Good quality n= 28	All studies n=64	Good Quality n=60
Absolute change in LVEF 5-10%	19	12	7	5	5	3	9	6
Absolute change in LVEF ≥10%	2	2	0	0	0	0	0	0
Relative change in GLS ≥15%	13 **	5					4 **	2

**Unable to acquire interpretable 2DE GLS in 11 out of 61 patients

**Unable to acquire interpretable CMR GLS% in 4 out of 64 patients

Table 19: Proportion of patients with clinically significant test-retest differences in left ventricular ejection fraction and GLS by imaging modality. LVEF: Left ventricle ejection fraction, 2DE: 2D Echocardiography, 3DE: 3D Echocardiography, MUGA: Multigated Acquisition Scan, CMR: Cardiac Magnetic Resonance, GLS: Global longitudinal strain.

For measurement of LVEF, the coefficient of variation (CoV) between repeat studies using the same modality was significantly lower with CMR than with 2DE (5.4%, (95% CI 4.9-6.2%) versus 8.7 % (95% CI 7.8-9.9%), $p < 0.004$), with no other differences

between modalities (6.9% [6.1-7.9%] and 7.1% [6.3-8.2%]) for 3DE and MUGA, respectively). When ML was used for CMR analysis, the CoV was further reduced (4.6% [3.9% - 5.4%]) and was also significantly lower than with 3DE and MUGA ($p=0.003$ and $p=0.02$ respectively). See Figure 33.

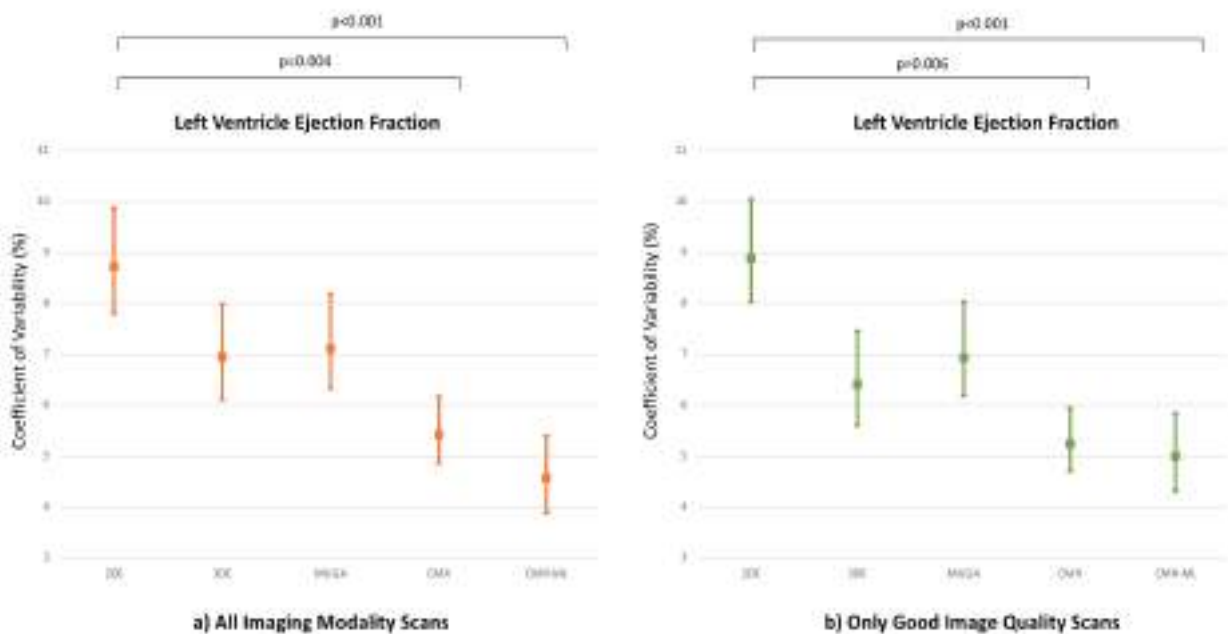


Figure 33: Comparison of test-retest reproducibility for Left Ventricle volumetric and functional assessment using 3DE, MUGA, CMR, and CMR Machine Learning compared with 2DE, represented as coefficient of variability and 95% CI, in a) All Imaging Modality Scans and b) Only good Image Quality Scan. 2DE: 2D Echocardiography, 3DE: 3D Echocardiography, MUGA: Multigated Acquisition Scan, CMR: Cardiac Magnetic Resonance, CMR-ML: Cardiac Magnetic Resonance Machine Learning, GLS: Global longitudinal strain.

There was no significant difference in the interstudy CoV for GLS when assessed using 2DE and CMR (10.5 vs. 9.3%, $p=0.49$). These differences in CoV meant that the calculated minimal detectable difference (MDD) in LVEF was close to 10% for 2DE, at 9.2%. Although lower with other techniques (7.7%, 7.9% and 6.8% for 3DE, MUGA and CMR respectively), ML for CMR analysis almost halved MDD (43% to 5.2%).

8.1.4.3 Impact of image quality on measurement precision:

Following grading of quality of imaging datasets by independent modality experts, 49/61 (80%) of 2DE, 39/49 (80%) of 3DE, 28/30 (93%) of MUGA, and 60/62 (94%) of CMR studies were graded as being of good quality. The test-retest CoV remained greater for 2DE than CMR 8.9 vs. 5.2%, $p < 0.006$), although there were no other differences between modalities, including for strain measures. See Table 20.

p Values	3DE		MUGA		CMR		CMR-ML		CMR-GLS	
	All studies	Good quality*	All studies	Good quality*	All studies	Good quality*	All studies	Good quality*	All studies	Good quality*
2DE	0.1336	0.1308	0.2038	0.2926	0.0035	0.0057	0.0001	0.0001		
3DE			0.9239	0.846	0.1336	0.2223	0.0026	0.0021		
MUGA					0.3303	0.2329	0.0189	0.0074		
CMR							0.0601	0.0417		
Echo-GLS									0.4922	0.5791

*Image quality was assessed by an independent blinded expert prior to analysis

Table 20: Statistical comparison of test-retest differences in LVEF and GLS between echocardiography (2DE, 3DE) MUGA, CMR, and CMR Machine Learning. LVEF: Left ventricle ejection Fraction, 2DE: 2D Echocardiography, 3DE: 3D Echocardiography, MUGA: Multigated Acquisition Scan, CMR: Cardiac Magnetic Resonance, CMR-ML: Cardiac Magnetic Resonance Machine Learning, GLS: Global longitudinal strain.

8.1.4.4 Inter-modality comparisons of LVEF measurement

For patients with paired repeat imaging datasets with two modalities available, correlation of LVEF measurements between modalities was moderate, with better

correlation with CMR using 3DE ($r=0.79$, $p<0.001$) than with 2DE ($r=0.71$, $p<0.001$) or MUGA ($r=0.54$, $p=0.06$). Correlation between CMR-derived GLS and echo-GLS was moderate ($r=0.50$, $p<0.001$). Using the average EF of both measurements within a modality, LVEF assessed by CMR was higher than that of 2DE, 3DE, or MUGA (Bland Altman limits of agreement, treating CMR as zero: 2DE, 3DE, and MUGA were $+5.8$ [$+3.9$ to $+7.8$]; $+5.3$ [$+3.5$ to $+7.2$] and $+4.6$ ($+9.2$ to $+0.1$), respectively, $p<0.01$. See Figure 34.

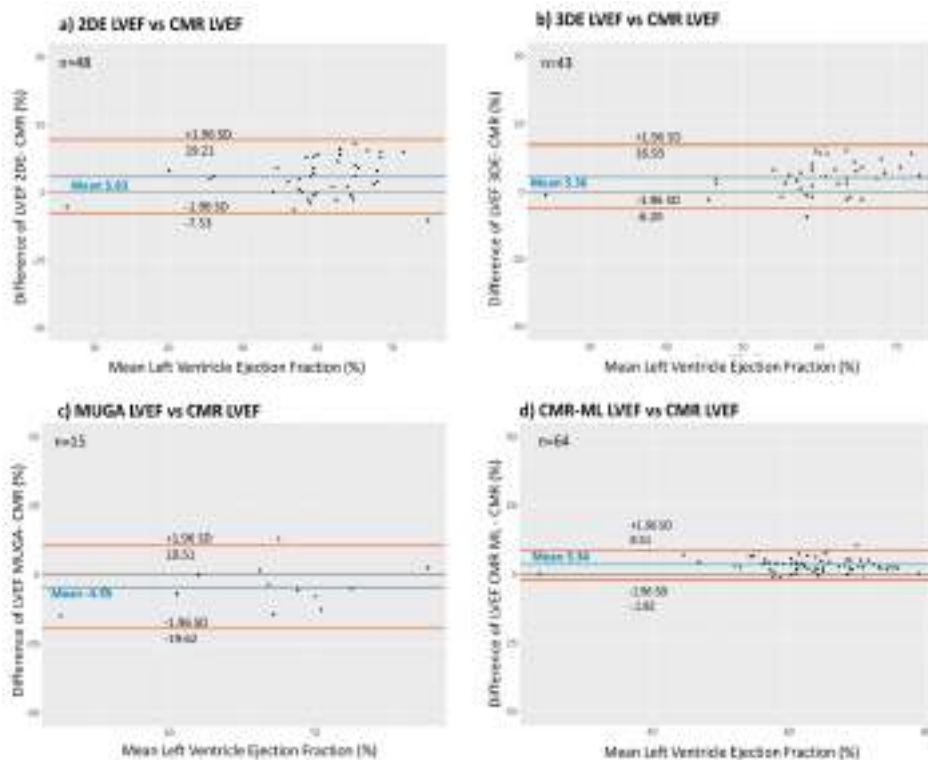


Figure 34: Bland-Altman Plots for Left Ventricular Ejection Fraction (LVEF) - Plots are compared for a) 2DE biplane Simpson method and CMR; b) 3DE method and CMR; c) MUGA method and CMR; and d) CMR-ML method and CMR. LVEF: Left ventricle ejection Fraction, 2DE: 2D Echocardiography, 3DE: 3D Echocardiography, MUGA: Multigated Acquisition Scan, CMR: Cardiac Magnetic Resonance, CMR-ML: Cardiac Magnetic Resonance Machine Learning.

There was no significant difference between GLS when assessed by CMR as compared to with echocardiography: $-19.4\% \pm 3.1$ versus $-18.1\% \pm 3.1$, $p=0.65$).

8.1.6 Discussion:

Echocardiography remains the first-line imaging modality for cardiotoxicity screening (44, 129, 229, 230). However, these data show that even in the best-case scenario (same day test-retest scans with constant clinical and physiological conditions), 2DE LVEF measurement has suboptimal precision. We show that the MDD for 2DE LVEF was close to the clinical change required to detect, with differences in LVEF between immediately consecutive repeat scans meeting the threshold for diagnosing cardiotoxicity in almost one in twenty-five patients. Using 3DE was better, with no significant difference in precision compared with gold standard CMR in patients with good quality image datasets, although there was a proportion of patients (20%) in whom acquisition of good quality 3DE images was not possible. CMR had the best inter-study reproducibility and the smallest MDD and measured GLS using feature tracking, with similar reproducibility and good correlation with 2DE-derived GLS.

8.1.6.1 Importance of precision in serial cardiotoxicity screening

Recent data showed that patients receiving HER2 targeted therapies whose treatment was interrupted due to cardiotoxicity had worse cancer outcomes, highlighting the importance of avoiding 'false positive' measurements of change in LVEF (244). Similarly, subclinical LV dysfunction following anthracycline chemotherapy has been found to occur early (within 12 months) and this can be at least partially reversed if heart failure treatment is instituted early (183). Serial cardiotoxicity screening therefore requires methods where small changes in function can be confidently detected to enable early diagnosis and treatment of cardiotoxicity and minimise the risk of inappropriate discontinuation of life prolonging cancer treatments.

8.1.6.2 Choice of imaging modality for cardiotoxicity screening

Current guidelines (44, 129, 229, 230) recommend echocardiography first-line for cancer cardiotoxicity screening, although MUGA still has widespread use due to its availability and its good published repeatability (245). CMR, although the gold standard of cardiac volumes and function, have been less favoured due to availability and cost constraints. LVEF values obtained by different techniques are not interchangeable, with higher LVEF values obtained using CMR, meaning that a single modality is used for screening throughout treatment. It is important to recognise that thresholds for diagnosing cardiotoxicity are based on evidence derived from echocardiographic studies. Therefore, further data on prognosis and outcome using CMR may be needed. 3DE is a more accurate marker of LV dysfunction than 2DE (231) (using CMR as the gold standard) hence the recent recommendation to use 3DE rather than 2DE where possible (44, 129, 229, 230). Unfortunately, acquisition of diagnostic 3DE images is not feasible in up to one-third of patients (246). CMR has repeatedly shown to have higher inter-observer reproducibility (209) and also permits evaluation of other cardiac structures and tissue characterization for detection of myocardial oedema, inflammation and fibrosis (247), offering the potential for exploring novel biomarkers of toxicity. There is wide geographical variation in access to CMR, however, abbreviated CMR protocols can deliver gold standard LV volumetric and functional assessment in shorter scans (average acquisition time 8 minutes) and without contrast, both reducing cost and increasing workflows (120). MUGA, despite consistently outperforming 2DE with respect to accuracy, reproducibility, intra and inter-observer variability for LVEF calculation (248), has been shown to be less accurate than CMR (249). This current data shows reasonable correlation and non-inferior reproducibility when compared to

CMR, however, MUGA requires exposure to ionising radiation – a major disadvantage for serial screening (242). MUGA also cannot assess for other cardiovascular pathology or detect early cardiac dysfunction.

8.1.6.3 Role of ML analysis on precision of LVEF quantification by CMR

The advent of ML algorithms for analysis of imaging data (250) means that the impact of human variation on measurement will be minimised. This is of particular importance for serial screening when different operators analyse sequential scans over time (often 5-10 years for patients receiving HER2 targeted therapies). CMR is well suited to the application of machine learning, with standardised DICOM formats and uniformity of myocardial and blood signal intensity. In line with previous work (235) CMR machine learning analysis has shown improving measurement precision over manual analysis, with a potential incremental value in the setting of cardiotoxicity screening.

8.1.6.4 Comparison of GLS assessment by CMR and echocardiography – correlation and precision

Mounting evidence supports the role of myocardial deformation imaging as a more sensitive biomarker of CTRCD than LVEF (251) (252). CMR feature-tracking derived GLS enables measurement of strain from standard 2D cine imaging and, therefore can be retrospectively measured from all CMR studies without additional sequences and time (253). This research showed that CMR-derived GLS both correlated well with measurements of GLS by speckle-tracking 2DE and had similar precision, although further prognostic data is needed. Although this study was designed to assess measurement precision in the cardiotoxicity setting, the findings have wider application to other clinical scenarios where serial measurement of LVEF and LV volumes is required – e.g., timing of intervention for valvular lesions or device implantation, etc.

8.1.7 Limitations: This study was designed to assess the precision of LVEF between modalities and therefore did not assess either the sensitivity, accuracy, or prognostic value of any of the modalities for detection and outcomes of cardiotoxicity. The study also did not determine which feature led to the differences in interstudy reproducibility (differences in image acquisition or piloting, versus differences in analysis). Echocardiography studies were performed without ultrasound contrast, with potential impact on 2DE outcomes. The study was a single-centre study, however, grading of image quality was performed by modality experts prior to image analysis and results were in keeping with standard clinical practice. Care was taken to minimise bias, including ascribing separate study numbers for each of the scans per patient and batching analysis performed posthoc by a single experienced operator per modality. The smaller MUGA dataset resulted from clinician preference for echocardiography or CMR for clinical cardiotoxicity screening as per guidelines. (230)

8.1.8 Conclusions: Serial screening for cardiotoxicity depends on biomarker precision. This study shows that 2D echocardiography lacks sufficient precision to reliably detect the changes in LVEF deemed significant by guidelines, even with good quality imaging. We propose that current guidelines take these results in conjunction with other data (47) into account and recommend consideration of alternative imaging modalities for screening – particularly where 3DE image quality is poor and for patients at the highest risk of cardiotoxicity. This study shows the incremental value of analysis using machine learning for CMR LVEF, with similar precision of CMR-derived GLS to speckle tracking GLS. Taken together, these data highlight the potential for more widespread application of CMR to cardiotoxicity screening, particularly using abbreviated imaging protocols to improve access.

Chapter 9 – Results 6: Improving the access of CMR in LMICs: Rapid CMR

9.1.1. Preface: This chapter is based on the manuscript below that has been submitted to European Heart Journal (under second revision). Manuscript Number: EURHEARTJ-D-21-03114R1.

K. Menacho, S. Ramirez, A. Perez, L. Dragonetti, D. Perez, D. Katekaru, V. Illatopa, S. Munive, B. Rodriguez, A.C Shimabukuro, K. Cupe, R. Bansal, I. Rodriguez, A Seraphim, Kris Knott, S. Guerrero, M. Lazo, D. Uscamaita, Marco Rivero, A. Peix, S. Mohiddin, Litt H, Y. Han, Fernandes J., R. Jacob, N. Ntusi, Manisty C, M. Westwood, A. Herrey, M. C Walker, J. C Moon

My contribution to this sub-study was designing the study, submitting the ethics in the UK (UCL), recruiting, consenting, and performing the final clinical reports to the participants (post-processing analysis of cardiac function and visual assessment of LGE). I coordinated with the local research group to follow-up participants to assess the impact of the Rapid CMR protocol. I performed the statistical analysis, interpretation and wrote the paper.

9.1.2. Background: Cardiac Magnetic Resonance is an emerging imaging technique with the capacity to provide reliable information for the diagnosis and guiding therapy to patients for better outcomes (254), providing prognostic information (255), and currently accepted by international guidelines (254). However, the access of CMR is still limited, with less access in LMICs and with most of the international registries reporting that CMR is a modality frequently used in HICs (100, 102, 107). Although MRI units are available in LMICs (104), several barriers prevent the use of CMR in those countries; for example, CMR is regarded as an expensive, long and complex technique, potentially out of reach for most patients in LMICs. There is also a lack of local expertise and access to training that results in inappropriate referrals, limited understanding of its usefulness, and preventing the worldwide spread of access to

CMR. Considering these obstacles in LMICs, the next step is to explore opportunities to maximize the cost-efficiency and access of CMR in those countries. This has been previously explored in my thesis with one pilot study where an abbreviated CMR protocol was implemented in a capital city, Lima – Peru (256).

9.1.4 Aims: To evaluate the potential impact of a simplified CMR protocol at a multicentre level in LMICs, implementing it with an education program for the assessment of cardiomyopathies

9.1.4 Material and Methods:

An international partnership was established between UK-UCL and Barts Heart Centre, London, UK, and each participating centre, with the support of the local cardiology and radiology societies (that supported advertising the Rapid CMR in their channels to local professionals), local scientific councils, and British embassies in Argentina, Peru, and Cuba (who co-financed the UK team visit), and the Society for Cardiovascular Magnetic Resonance (SCMR) (who sponsored one-two SCMR educators/trainers and provided no-fee SCMR certification for participants). A team of five doctors, experts in the field (UK, SCMR expert delegates) traveled for each visit to the participant countries to deliver an educational programme to local doctors and train/partner with local personnel to help perform assessments and support rapid CMR scanning. When possible, we additionally included experts from nearby countries with native language capabilities and encouraged the development of local networks for sustainability and mentorship.

9.1.4.1 Study Implementation: Patients were recruited by the local research teams. All participants provided written consent. The rapid CMR contrast demonstrator study

of 98 patients scanned in two centres in Peru were previously published (135) who remain included but with their 36-month follow-up and in multiple cases (iron overload, cardiotoxicity) interval scanning. Following this pilot project, ten additional participant centres contacted our research group as they wanted to initiate/improve their efficiency in CMR scans. There was one dedicated cardiac CMR scanner (Cuba, three days per week), five scanners with one-day-a-week CMR (Peru - one centre, South Africa - one Centre, Argentina – two centres, India – one centre), and five scanners performing no CMR before initiation of the project (Peru- four centres, and India-one centre). Scanner time was secured mainly during unused magnet time (weekends, national holidays), and the international delegation visit, educational program and “patients camp” visits were scheduled accordingly. Scans were at no cost to participants, and the costs were borne by the participant centre (scanner availability, staff support) and the research funding (providing contrast agent and ECG).

9.1.4.2 Education and Training program:

Education was a key component of our project, and it was delivered at two levels:

- 1) *CMR International Conferences*: These were two to three days on CMR scanning and reporting per country for local cardiologists, radiologists, and radiographers. All were free of charge. SCMR provided free Level One SCMR certification (139) for participants and a free one-year SCMR membership. CMR teaching included lectures by local/national/international speakers, direct CMR scanning observation, and a level 1 reporting course.
- 2) *Training for those delivering CMR*: Six CMR centres were already established pre the Rapid CMR intervention. Five were novice. For these, one to two international visiting doctors/radiographers delivered training in scanning and

reporting to the local team days before the main intervention. For both there was support during scanning days. Follow-up continuous support was given to local doctors remotely (technical/interpretation of difficult cases). We assessed the impact by measuring sustainability - the number of scans (and duration) delivered after the intervention period.

9.1.4.3 Abbreviated CMR Protocol:

- *CMR Protocol:* For this intervention, the project had access to 14 different models of scanners in the seven cities and five countries. See table 21. The core structure of the protocol was the assessment of cardiac volumes, function, and scar, using the available sequences in the scanner. See Section 3.4.2, Figure 19, and Table 5 for more details of the core CMR protocol. The project also ensured to follow some procedures to maximize the workflow surrounding CMR. See table 22. One to two weeks before the main intervention, the rapid CMR protocol was shared remotely and installed in the local MRI scanner (with the support of the local radiographers/ MRI engineering service). Preliminary scanning was done in healthy volunteers in each participant centre and mentored via live webcasting.

Scanner Information			Argentina	Cuba	Peru		South Africa	India	
MRI brand	Field	Model	Buenos Aires N = 69	La Havana N = 114	Lima N = 248	Arequipa N = 13	Cape Town N = 34	Delhi N = 53	Jaipur N = 70
Siemens	1.5T	Aera	15 (22%)	114 (100%)	63 (25%)	-	10 (29%)	-	-
	1.5T	Avanto	37 (54%)	-	83 (33%)	-	-	-	70 (100%)
	3T	Skyra	-	-	-	-	24 (71%)	-	-
Philips	1.5T	Ingenia	17 (25%)	-	33 (13%)	13 100 (%)	-	-	-
	3T	Achieva	-	-	56 (23%)	-	-	-	-
GE	1.5T	Signa HDxt	-	-	13 (5%)	-	-	53 (100%)	-

Table 21: : Model of the MRI scanners of the 11 participant centres of the Rapid CMR Project, Peru: Lima - Hospital Edgardo Rebagliati, Hospital Central Militar, Hospital Central de la Fuerza Aerea del Peru, Arequipa: Centro Salud Cerema, Argentina – Buenos Aires: Instituto IMAT and Hospital Italiano de Buenos Aires, Cuba – La Havana: Instituto de Cardiología y Cirugía Cardiovascular, South Africa – Cape Town: Groote Schuur Hospital in Cape Town, India: Delhi – Mahajan Imaging Centre, Jaipur: OK Diagnostic Imaging Centre.

See Figure 35 for the adding sequences to the protocol for the specific assessment of cardiomyopathies.

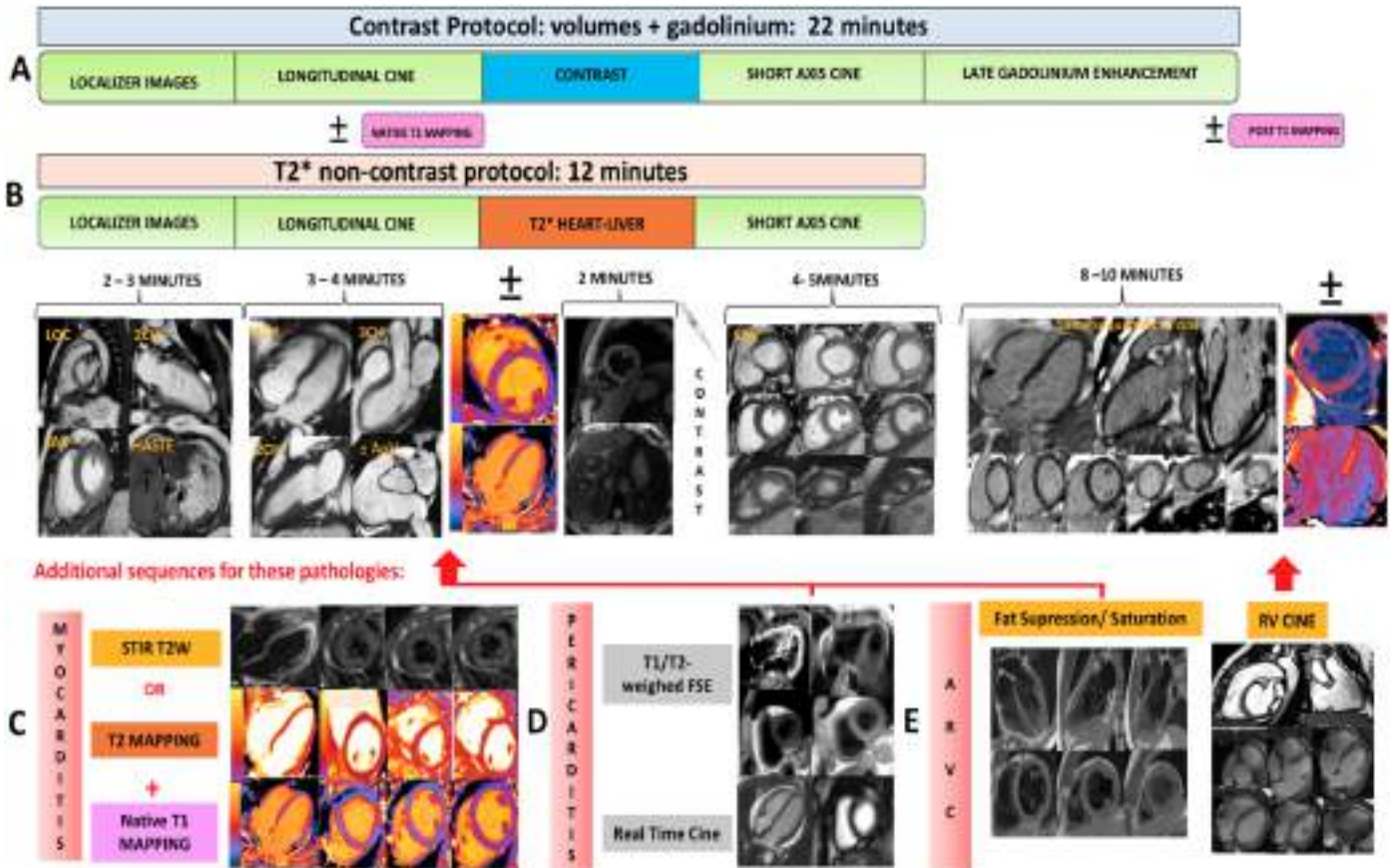


Figure 35: Abbreviated CMR Protocol: A) **22 minutes contrast-CMR protocol** for assessing **cardiomyopathies**, with the option to add T1 mapping sequence if available in the scanner and requested by the referral; B) **12 minutes T2* non-contrast protocol** to assess **MIO**. Additional sequences added for specific pathologies: C) STIR T2w or T2 mapping + T1 mapping for **myocarditis**, D) T1 or T2w FSE + real-time cine for **pericarditis (27 minutes scans)**, and E) Fat suppression and saturation + RV cine acquisition for **ARVC (30 minutes scan)**. ** If poor breath-holder patients, the protocol was modified using parallel imaging for cine images acquisition and in patients with arrhythmia, prospective triggering and real-time imaging sequences were acquired. CMR: Cardiac Magnetic Resonance, MIO: Myocardial Iron Overload, STIR: Short tau inversion recovery, FSE: Fast/Turbo Spin Echo, RV: Right Ventricle, ARVC: Arrhythmogenic right ventricular cardiomyopathy.

- *Protocol implementation:* See section 3.5

- *Patients:* Between November 2016 - 2019, a total of 601 patients, referred from 14 hospitals. See table 21 for more information about the participant hospitals.

- *CMR Post-Processing Analysis:* As described before. See section 3.5.2. and Figure 21.

- *Image quality:* As described before. See section 3.6.

- *Impact of the Rapid CMR Protocol on patients' care:* Patients were followed up between 6 to 36 months. See section 3.7.
- *Cost evaluation:* As described before. See section 3.8.
- *Statistical analysis:* As described before. See section 3.10.

	Tasks to perform to improve the workflow of scanning – Rapid CMR
Pre-Scanning Preparation	On arrival, patient changes into a hospital gown, open to the front, and hospital trousers as appropriate.
	Record patient height and weight on a form (e.g., safety questionnaire).
	Trained staff to check safety questionnaire and address any concerns.
	Trained staff to cannulate for gadolinium injection.
	Ensure ECG leads are placed in an 'L' or box position, achieving a minimum of 3/5 bars for a reliable ECG trace.
	Practice breath-holding commands with the patient (images usually acquired with few exceptions)
During the Scanning	Ensure the protocol is set it up on the scanner in advance, with patient details including height and weight.
	Have gadolinium contrast prepared for manual injection; suggested dose is 0.1mmol/kg ref (single dose of 0.1mL/kg for gadobutrol and 0.2mL/kg for gadoterate meglumine).
After the CMR Scan	Have at least two trained staff ready to aid the patient out of the scanner
	Verify ECG stickers and cannula have been removed from the patient in the preparation room.

Table 22: Optimisation of workflow surrounding the abbreviated CMR protocol – Rapid CMR

9.1.5 Results:

1) *Baseline characteristics:*

Six hundred one patients were referred from 14 hospitals, 7 cities in 5 countries: Peru, Lima and Arequipa, 7 centres, 261 (43%), Argentina, Buenos Aires, 3 centres, 69 (12%); Cuba, La Havana, 1 centre, 114 (19%); South Africa, Cape Town, one centre, 34 (6%) and India, Delhi and Jaipur, 2 centres, 123 (21%). Four hundred forty-nine patients (74%) were referred by Cardiologists, 131 (22%) by Haematologist (MIO indication), and 20 (3%) by others. The mean age of the patients was 46 ± 19 years, with a significantly younger population of patients for T2* CMR MIO assessment (28 ± 13 vs 53 ± 16 years, $p < 0.001$). 56% of participants were male. See Table 23.

Despite our request to perform CMR scans to assess cardiomyopathies, referrals requested CMR for other cardiac conditions as their patients were in urgent need of CMR and patients were from poor economic resources income. Indications for CMR were: cardiomyopathies in 433 (72%), assessment of viability in 98 (16%), myocarditis/pericarditis 35 (6%), valvular heart disease 9 (1%), cardiac tumours 6 (1%), aortic disease 5 (1%), and other indications (e.g. congenital) in 15 (2%). Within the group of cardiomyopathies, the indications were: DCM 259 (60%), HCM 126 (29%), ARVC 15 (6%), restrictive cardiomyopathy (RCM) 15 (3%) and unclassified 18 (4%). We assessed 18 different pathologies in total. See Figure 36.

Clinical Data	Total	Non-contrast scans	Contrast CMR scans	P value
Demographic				
Total (%)	601 (100%)	154 (26%)	446 (74%)	-
Age (mean \pm SD)	46 \pm 19	28 \pm 13	53 \pm 16	<0.001
Gender female (%)	267 (44%)	82 (53%)	185 (41%)	0.01
BMI (mean \pm SD)	25.2 \pm 5.4	21.4 \pm 3.7	26.1 \pm 5.2	0.02
BSA (mean \pm SD)	1.7 \pm 0.3	1.5 \pm 0.2	1.8 \pm 0.2	0.9
Imaging Modalities used before CMR				
Echocardiogram (%)	471 (78%)	51 (33%)	420 (94%)	<0.001
CTCA (%)	46 (8%)	0	46 (10%)	<0.001
SPECT/ DPD (%)	55 (9%)	0	55 (12%)	<0.001
CMR (%)	85 (14%)	48 (31%)	37 (8%)	<0.001
Referral				
Cardiologist	449	21	428	<0.001
Haematologists	131	131	0	<0.001
Others	20	0	20	<0.001

Table 23: Baseline characteristics of the patients enrolled in the Rapid CMR project. CMR: Cardiac Magnetic Resonance, BMI: Body Mass Index, BSA: Body surface Area, SD: Standard Deviation, CTCA: Cardiac Tomography Coronary Angiography, SPECT: Single Photon Emission Computed Tomography.

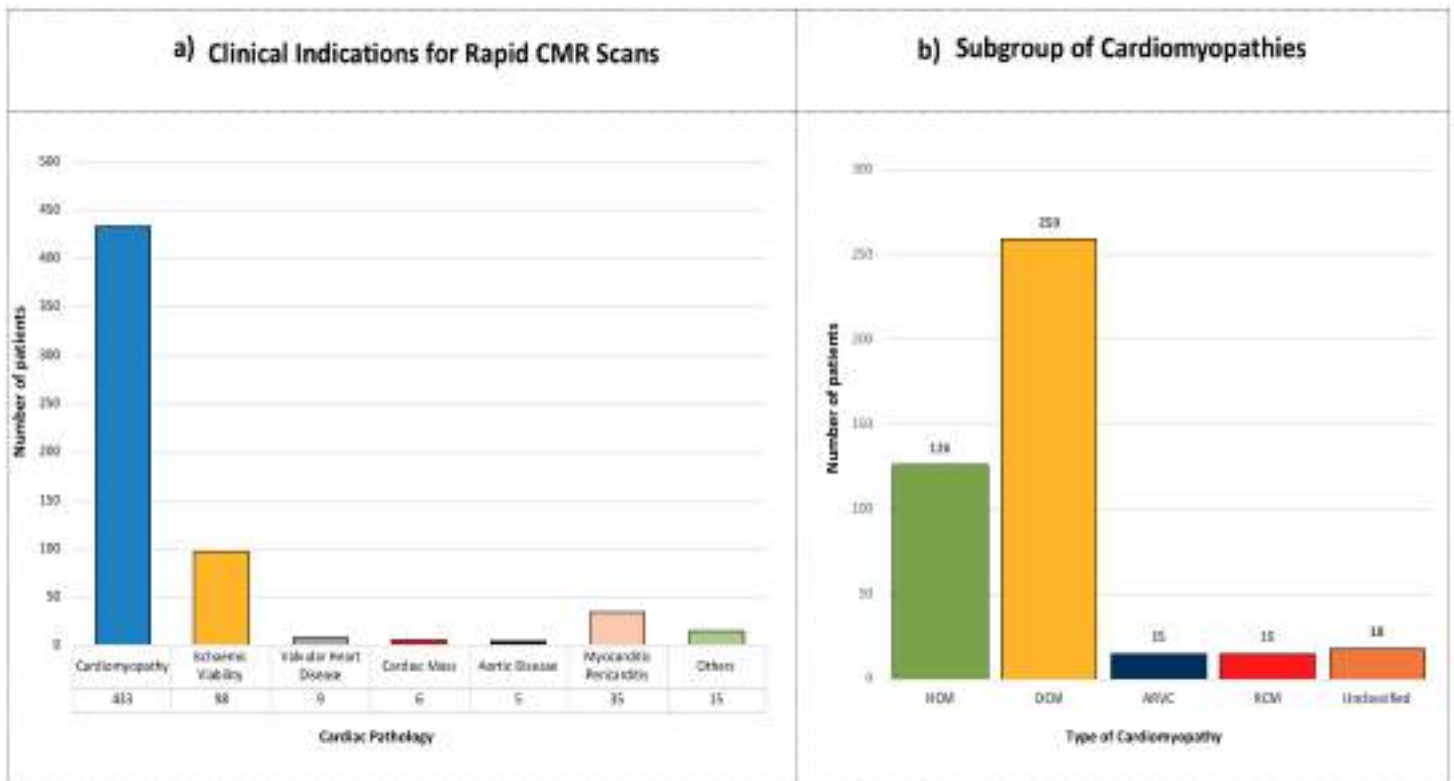


Figure 36: Clinical indications for using the abbreviated CMR protocol in all cardiac pathologies and within the group of cardiomyopathy sub-types. HCM: Hypertrophic Cardiomyopathy, ARVC: Arrhythmogenic Right Ventricle Cardiomyopathy, RCM: Restrictive Cardiomyopathy.

2) Cardiac Magnetic Resonance Results

Patients were scanned in eleven hospitals with MRI units, using fourteen different scanners (six models from three manufacturers at two field strengths, with scanner age at study time at 12 years \pm 3.4).

154 (26%) patients had a non-contrast scan, 149 (96%) for MIO, four other patients with chronic kidney disease and one patient denied receiving contrast). For the contrast CMR scanning (97% cardiomyopathy), 410 (94%) had undergone transthoracic echocardiogram (TTE) before CMR scan, 10% CTCA, 12% SPECT, and

8% had a previous CMR. Within the group of patients referred for a non-contrast T2* CMR scan to assess MIO, 31% had previously undergone CMR to assess cardiac iron. Among the 601 scans, 98% were of diagnostic quality. Good image quality was reported in 506 scans (84%), moderate in 85 (14%) with only 10 studies (2%) concluded as poor quality as they were non-diagnostic (5 patients were in fast atrial fibrillation, 3 patients were very poor breath holders and 2 patients had very frequent ventricular ectopic during the CMR scan). In total, arrhythmia was detected at the time of the scan in 58 (10%) of the total cohort, accounting for most of the 85 scans with moderate quality (the other 27 were graded as moderate due to poor breath-holding). Five hundred and thirteen (85%) of the scans were acquired in a 1.5T scanner. The average scanning time was 22 min \pm 6 minutes for the cardiomyopathy CMR protocol (volume + gadolinium) and 12 min \pm 4 minutes for the T2* CMR protocol for assessing MIO. 32 (5%) of the cardiomyopathy scans included pre and post T1 mapping sequences when available, with an average scan time of 25 min \pm 5 min. For other specific clinical indications, CMR scanning time was longer as additional sequences were added: myocarditis/pericarditis protocol (STIR and T2 FSE or T1/T2 mapping if available) in 27 min \pm 4, and ARVC protocol (with RV cine + fat suppression sequences) in 30 min \pm 10. See table 24.

	Type of Rapid CMR Protocol for the Detection of Cardiomyopathies				
	Iron CMR (cine + T2*) N = 149	CMP (cine + LGE) N = 350	CMP Mapping (cine + LGE + T1 mapping) N = 32	Myocarditis/Pericarditis (STIR/T1 FSE or mapping if available) N = 35	ARVC (RV cine + Fat Sat/Sup.) N = 15
Age	26 ±11	54 ±16	47 ±16	48 ±19	30 ±10
Time (mean ± SD)	12 ± 4	22 ± 6	25 ± 5	27 ± 4	30 ± 10
Image Quality					
Good (%)	129 (87%)	294 (84%)	28 (87%)	29 (82%)	12 (82%)
Moderate (%)	17 (11%)	49 (14%)	4 (13%)	6 (18%)	3 (18%)
Poor (%)	3 (2%)	7 (2%)	0 (0%)	0	0
Arrhythmia	2 (1%)	48 (14%)	4 (13%)	0 (0%)	4 (27%)

Table 24: Time of Scanning for the Rapid CMR protocol. Contrast CMR protocol for cardiomyopathies and non-contrast CMR scan to assess myocardial iron overload. Modification of the protocol and time of scanning for specific cardiac pathologies. CMR: Cardiac Magnetic Resonance, ARVC: Arrhythmogenic right ventricular cardiomyopathy, CMP: Cardiomyopathy, LGE: Late Gadolinium Enhancement, STIR: Short tau inversion recovery, FSE: Fast/Turbo Spin Echo, RV: Right Ventricle, SD: Standard Deviation, Sat/Sup.: Saturation and Suppression

In contrast CMR scans, 288 (64%) patients had positive LGE, and 36 (8%) of the scans were concluded as normal studies. Within the T2* CMR scans for MIO, 45 (30%) of patients had significant cardiac iron (cardiac T2* <20ms), detected for the first time in 36 (80%) of patients.

3) *CMR Impact on diagnosis and management*

560 (93%) patients completed their follow-up (median 24 months post-CMR). We could not contact 41 participants (no further visits registered in their medical records).

The abbreviated CMR protocol impacted clinical management in 62% of patients, either by revealing a new diagnosis (22%) – see figure 36 and table 25, or by leading to a change in their management (55%), with a higher impact on changing therapy when using the T2* CMR and detecting MIO vs. the contrast CMR scan (<0.001). After rapid CMR, 12% of patients with detected cardiomyopathies underwent further invasive interventions to complete their diagnosis (e.g., angiography, cardiac biopsy) and therapy (e. g. ICD).

The abbreviated CMR protocol satisfied all imaging needs in 87% of patients. Although non-blinded, rapid CMR did not miss any diagnosis initially found by echocardiography.

4) *Cost evaluation:*

Estimated cost savings for Rapid compared to conventional contrast CMR were between 30% to 60% (equivalent to 1/3 to 2/3 cheaper) with a range: 25-30% in Cape Town, 30% in Argentina, 40% in Cuba, and 50-60% in Peru. For non-contrast T2* CMR, the saving ranged between 40% in India to 50% in Peru. See Table 26.

5) *CMR Education Program:*

Five international conferences were delivered in Peru (November 2016 and January 2019), Argentina (June 2018), Cuba (November 2019), and South Africa (June 2018). Each conference had at least 180 attendees, with a total of 920 professionals. All

completing participants received no-fee level 1 SCMR certification and free SCMR membership. See www.rapidcmr.com for prior course details

A total of eighteen professionals were trained in CMR scanning and reporting (one to two professionals per centre - seven doctors and eleven radiographers in total. Thirteen out of eighteen professionals are still using their skills, with three doctors achieving a formal CMR training (equivalent to level 2 CMR Certification), but five professionals (three radiographers, one cardiologist, and one radiologist) did not continue CMR as the MRI units in two hospitals in Peru sustained permanent scanners breakdowns.

6) *Subsequent adoption of rapid CMR:*

Nine out of eleven of the participant centres continued using rapid CMR (two hospitals in Peru ceased due to scanner breakdowns), with services scanning one to two days per week. From the entire list of CMR indications, the participant centres continue using the rapid CMR protocol to assess cardiomyopathies in 2 to 8 patients per day (Table 26). We followed up sites and found that in the main, services were maintained, and even grew (Table 26) with a variety of different local funding solutions (public/private/charity).

Two new centres in two non-capital cities in Peru (Chiclayo and Huancayo) and one centre in La Havana, Cuba, initiated a CMR service (scanning 1/2 day per week) led by a CMR specialist physician with remote support from the international team of experts.

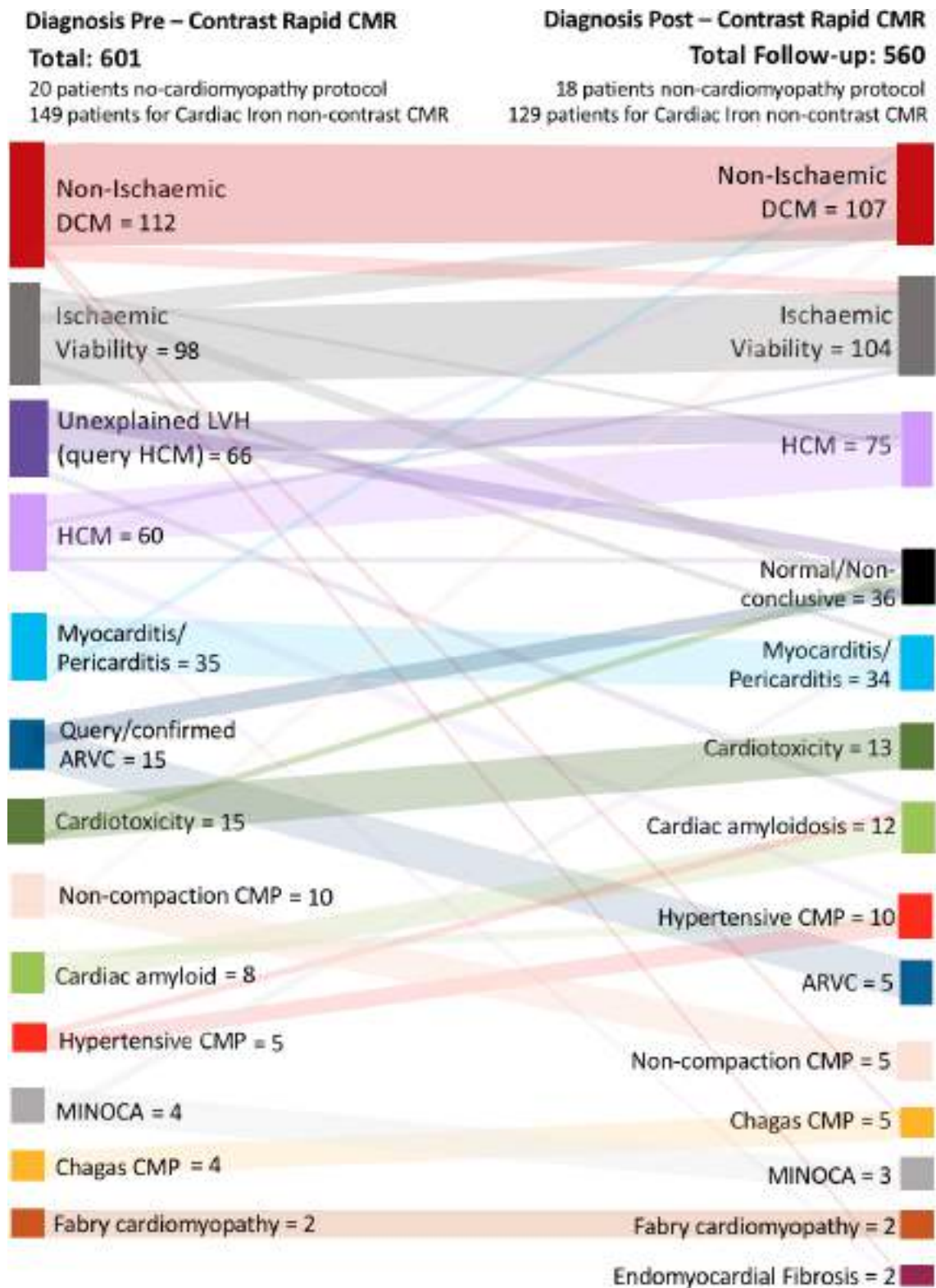


Figure 37: New diagnosis revealed by the abbreviated contrast CMR protocol in the cardiomyopathy patients' group. In total, 89 new diagnoses were found. CMR: Cardiac Magnetic Resonance. CMP: Cardiomyopathy, HCM: Hypertrophic Cardiomyopathy, LVH: Left ventricular hypertrophy, MINOCA: myocardial infarction with non-obstructive coronary arteries.

CMR Findings N (%)	Cohort	Cardiac T2* Iron scans	Contrast CMR scans	P-value
Abnormal Baseline CMR Results				
Number, N (%)	601 (100%)	149 (25%)	452 (75%)	-
Cardiac Iron Overload (T2* <20ms, N (%))	45 (8%)	45 (30%)	N/A	-
Presence of LGE, N (%)	288 (48%)	N/A	288 (64%)	-
Inconclusive CMR, N (%)	10 (2%)	0 (0%)	10 (2%)	P<0.001
Follow-up - Impact on patient Care				
Number, N (%)	560 (100%)	129 (23%)	431 (77%)	
New diagnosis, N (%)	125 (22%)	36 (28%)	89 (21%)	0.19
Change/Addition of new medication, N (%)	134 (24%)	36 (28%)	98 (23%)	<0.001
Intervention or surgery, N (%)	46 (8%)	0 (0%)	46 (8%)	<0.001
Coronary angiography or Biopsy, N (%)	21 (4%)	0 (0%)	21 (4%)	<0.001
Hospital discharge and admission, N (%)	25 (4%)	0 (0%)	25 (6%)	<0.001
Other Imaging modalities requested after CMR to support diagnosis and therapy				
Number, N (%)	560 (100%)	129 (23%)	431 (77%)	-
Echocardiography, N (%)	45 (8%)	3 (2%)	42 (9%)	<0.001
CTCA, N (%)	17 (3%)	0 (%)	17 (3%)	<0.001
SPECT, N (%)	12 (2%)	0 (%)	12 (2%)	<0.001

Table 25: Impact of the Rapid CMR protocol on patients' care. CMR findings during patients' camp scanning and assessing the impact of the abbreviated CMR protocol on patients' care and further additional cardiac imaging requested to support patients' care. CMR: Cardiac Magnetic Resonance, LGE: Late gadolinium enhancement, CTCA: Cardiac Tomography Coronary Angiography, SPECT: Single Photon Emission Computed Tomography.

Country	Argentina		Cuba	Peru					South Africa	India (Non-Contrast T2* CMR)	
City	Buenos Aires N = 69		La Havana N = 114	Lima N = 248				Arequipa N = 13	Cape Town N = 34	Delhi N = 53	Jaipur N = 70
Centre	Centre 1	Centre 2	Centre 3	Centre 4	Centre 5**	Centre 6	Centre 7**	Centre 8	Centre 9	Centre 10	Centre 11
Before Rapid CMR scan											
Number of days per week	1	2	3	0	1	0	0	0	2	1	0
Number of hours x day	5	5	5	0	5	0	0	0	5	2	0
CMR scans per day	4	5	3-4	0	4	0	0	0	5	2	0
Cost	\$400-500		\$600	\$400-\$600					\$350-\$500	\$70-\$100	
After Rapid CMR scan											
Number of days per week	1	2	3	1	1	1	1	1	2	1	1
Number of hours x day	5	5	5	4	5	4	4	4	5	2	2
CMR scans per day	5-7	6-7	7-9	6	6-8	6	6	6	6-7	4-6	4-6 ⁺
Rapid CMR Scans (30min x contrast scan) (20min x T2* scan)	5-6	3-4	6-8	4	4-6	4	4	4	5	4-6	4-6 ⁺
Cost Rapid CMR Scan	\$280-\$380		\$360	\$160-300					\$200-\$400	\$42-\$60	
% Saving	30%		40%	50%-60%					25-30%	40%	

Table 26: : CMR practice in the participant centres before and after the implementation of the Rapid CMR protocol.

Argentina – Buenos Aires:

Centre 1: Instituto IMAT.

Centre 2: Hospital Italiano de Buenos Aires.

Cuba – La Havana:

Centre 3: Instituto de Cardiologia y Cirugia Cardiovascular.

Peru – Lima:

Centro 4: Hospital ESSALUD Edgardo Rebagliati.

**Centre 5: Hospital Central Militar.

Centre 6: Hospital Central de la Fuerza Aerea del Peru.

**Centre 7: Hospital ESSALUD Guillermo Almenara.

Peru - Arequipa:

Centre 8: Centro Salud Cerema.

South Africa – Cape Town:

Centre 9: Groote Schuur Hospital in Cape Town.

India – Delhi:

Centre 10: Mahajan Imaging Centre.

India – Jaipur:

Centre 11: OK Diagnostic Imaging Centre.

** Faulty scanners, stopped CMR service (the number representing post-study to pre breakdown).

+ Ten scans done after Rapid CM camp visit. Starting that number of CMR scans this year.

9.1.6 Discussion

Our research group previously showed that a faster CMR protocol could be adopted in three single centres in the capital cities of Thailand and Peru (120, 135). We report now the ability to perform rapid CMR in multiple LMICs across three continents across different clinical environments utilising a variety of different scanners. These scans provided diagnostic image quality in the majority of cases at greatly reduced cost with an important impact on the care of the patient. This was achieved without having the most current scanner and software in many of the centres. To achieve this, four key strategies were employed: 1) a collaborative partnership between the investigators and local teams at multiple levels (a local healthcare champion, hospital team, political authorities, scientific societies, and embassies, 2) CMR training and education at two levels: first, referring physician and, second to those providing CMR services (cardiologists, radiologists, and technologists – acquisition and reporting) in the local language or English with translation, 3) a focused, rapid and less expensive CMR scan with sequences adapted to local scanners and software, 4) The integration of results into the care of the patient was with follow up to assess the impact. The rate of subsequent adoption in the participant centres was tracked.

This is the first study that tackles the education barrier of CMR in LMICs, where most professionals need to travel overseas and self-fund for expensive courses to receive certified training. We provided training at the local participant sites ensuring that the appropriate technology is available. It is important to emphasize that whilst we provided training for practioners (doctors and radiographers to deliver CMR), we made a large effort to train potential referrers by organising the five Level I CMR international conferences, aiming that they can be enthusiastic about CMR, to learn more

cardiology, and as a gateway for the (few) who want to take CMR further. Here we had a ratio of basic: advanced training of approximately 50:1. The level 1 training here is in no way wasted if they do not directly deliver CMR services but is perhaps the foundation of CMR incorporation into clinical practice.

94% of the patients were referred for the assessment of cardiomyopathies. Participants had at least one echocardiogram before CMR. These patients were still referred to CMR to complete their diagnosis or to support their therapy decision. In fact, for several pathologies, echocardiography is not sufficient to get critical information on causation, risk, therapy decision, and reversibility. In these scenarios advanced tissue characterization with late gadolinium enhancement adds important information on risk stratification (257) and prognosis (258). Our cohort represented several spectrums of cardiomyopathies, including iron cardiomyopathy in 130 Beta-thalassaemic patients, mainly from India, which is also part of a separate study of this thesis (UMIMI Study - Chapter 6 of the manuscript). The extension of LGE seen in some cardiomyopathies such as HCM patients was far more than is typically seen in a HIC with an established CMR service. We believe this is a marker of a lack of access to advanced imaging. In LMIC, patients with more advanced stages of HCM were typically seen, suggesting that cases that might have been picked up by CMR during the early stages of the disease may have been missed. The referral indications for rapid CMR were mainly to assess cardiomyopathies and differed compared to HICs where heart failure, cardiomyopathies, function and viability, and stress perfusion are commonly indicated (259).

The core structure of the abbreviated CMR protocol previously published in the INCA-PERU study (135) to assess specific cardiomyopathy pathologies. Adding these

sequences went out of the scope of our “keep it simple” approach and this happened due to different challenges: individual patients outside our planned remit (congenital, masses, valvular), where to turn them down would give them no CMR option; also referrers and local champions some of who had trained overseas who demanded guideline appropriate scans and in some cases of course ourselves. Even though we were delivering a research project, it proved difficult at times to not provide the same level of care we would in HIC parent institutions. Despite this, we showed that CMR can be acquired in 22 minutes on average for a core cardiomyopathy protocol. Even when adding other sequences for specific pathologies, we were able to scan patients in less than 30 minutes. Overall, this corresponds to a reduction in around 30-50% scanning time compared to an average CMR scan (40). The scanning time improved progressively once local radiographers gained experience (e.g., our second visit in Peru, the average scan time was 19 minutes vs. 24 minutes for the first visit in Cuba). and when we maximize the workflow surrounding CMR. (see table 12). Arrhythmias were detected in 10%, requiring protocol modification, but despite this, 98% of the scans were of diagnostic quality, similar to reports of conventional CMR scans from international surveys (107). In three centres (two in Peru and one in South Africa), we had access to T1 mapping sequences, and we were asked by the local research team to incorporate such sequences in the abbreviated CMR protocol. T1 mapping provides incremental value in specific pathologies such as Fabry disease (260) and cardiac amyloidosis (261), without the need of contrast. Here the (untargeted) yield was low, with none of these pathologies detected in 32 patients, although cardiac amyloidosis was found in some patients in the rapid core contrast CMR protocol.

The clinical utility of our abbreviated CMR protocol in patients' care was 62%, which is very similar to what international registries have found (100, 107), making a different diagnosis in 22% of the cohort. See two clinical cases in Figures 37 and 38. Still, six percent of the patients could not be contacted again. Many of those lost to follow-up lived in remote rural areas; we believe the impact of CMR in LMICs could be potentially higher than in HICs if these disadvantaged groups could be better tracked, although barriers to ongoing clinical management, including access to costly medications or devices, may limit this. Only 13% of our patients had additional cardiac imaging investigations triggered, mainly as part of the confirmation of a new diagnosis revealed by CMR, e.g., bone scintigraphy test to confirm cardiac amyloidosis.

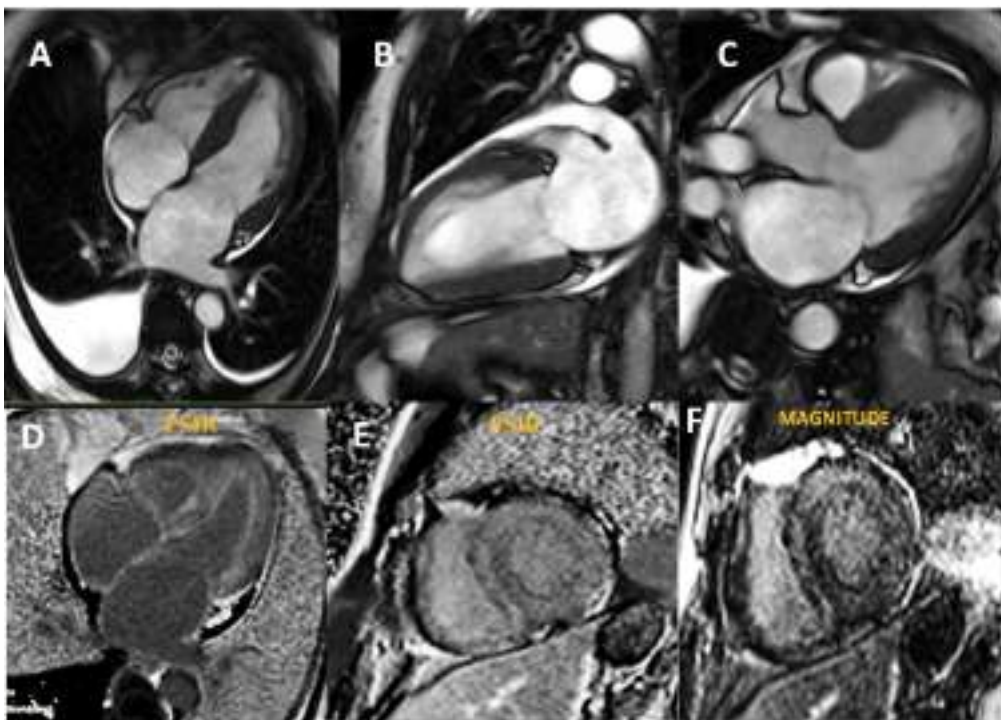


Figure 38: Lima, Peru – Length of scan 25 minutes: 73-year-old gentleman, who was referred for the diagnosis for septal HCM. Echocardiography findings were suggestive of Cardiac Amyloidosis. CMR study: (A) 4 chamber, (B) 2 chamber, (C) 3CH cine steady free precession revealed pleural and pericardial effusion, left ventricle hypertrophy and preserved systolic function, and (D-E) Contrast CMR (LGE: 4CH and basal short-axis views) and (F) SAX Magnitude view showing diffuse transmural enhancement in both ventricles (white arrows) and surrounding both atria and valve, suggestive of Cardiac Amyloidosis (most likely type AL). The diagnosis was confirmed later by labial salivary gland biopsy. Unfortunately, the patient died six months later.

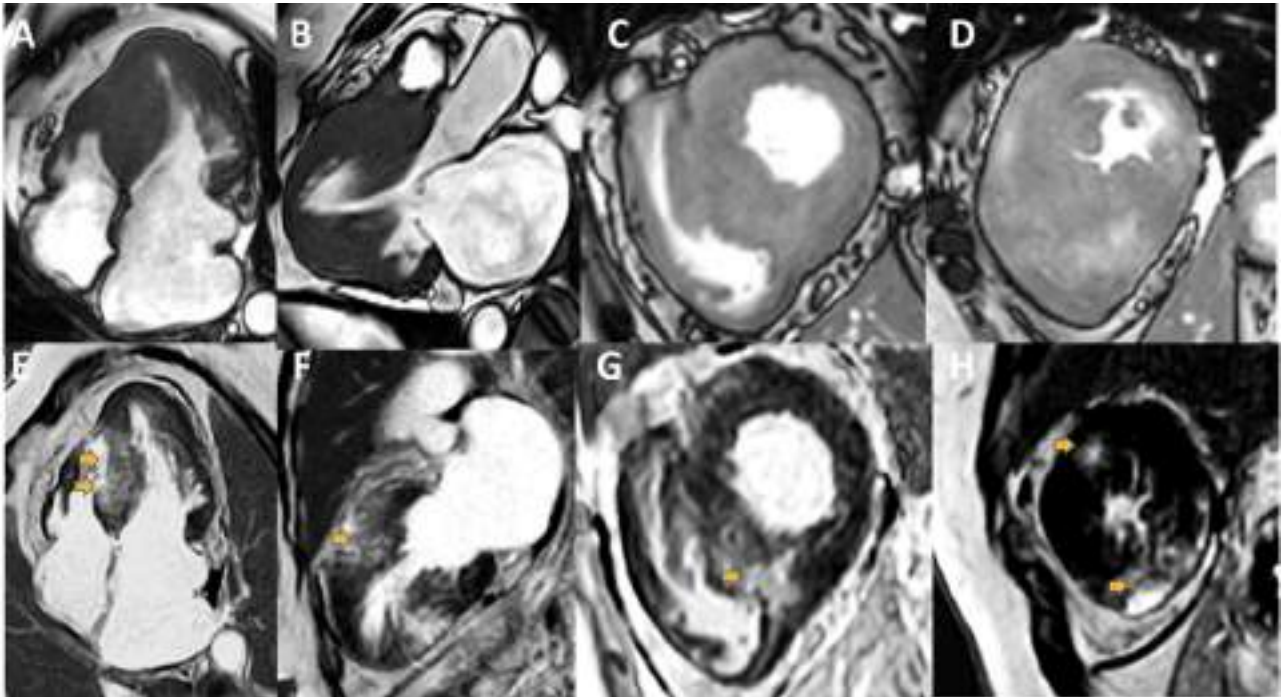


Figure 39: Buenos Aires, Argentina – Length of scan 20 minutes: 65-year-old lady, history of hypertrophic cardiomyopathy. CMR revealed: (A) 4 chamber and (B) 3 chamber cine images showing septal asymmetric hypertrophy, partial SAM, mitral regurgitation and two clefts in the lateral wall; (C) and (D) short-axis views show involvement of the right ventricle. (E-G) 4CH, 2CH, and SAX base and apex display patchy, non-ischaemic scar, matching segments with maximum hypertrophy. CMR concluded as asymmetrical septal HCM. The case was discussed in MDT and after considering the extension of fibrosis, the patient underwent to ICD implant (despite not fulfilling full criteria for SCD based on the ESC risk calculator).

Cost implications can only be broadly estimated due to different healthcare systems in the five countries. Our best estimate is that rapid CMR could reduce costs of contrast scans between 1/3 to 2/3 (equivalent to 30% to 60% of cost reduction). This does not include any cascading savings of better targeting of treatment. Further study would be needed to estimate this.

Further barriers remain: the lack of engineering and MRI maintenance service remains a barrier for service continuity - two of the eleven centres ceased MRI because of this.

The adoption of this protocol is not only for LMICs; it can also have an impact to improve CMR efficiency in HICs or for specific needs such as the current COVID-19 pandemic (262), where CMR needs to be adapted to allow safe practice and urgent studies.

9.1.7 Limitations: This was not a randomized study. No assessment was made of prior services when present. The study was of the willing and able – included centres all had had a local, supported champion. The study was in either capital cities or state capitals within LMICs: results are not expected to generalise beyond this. Scanners were those that were available. This study did not include specific sequences, such as perfusion CMR, a cost-efficient exam for inducible ischaemia (263), and with recent data supporting that perfusion CMR can be done faster (124, 264). However, the delivery of such technology is more complex in LMICs, and it is outside the scope of this project with the currently available infrastructure. Also, there are other forms to speed up CMR acquisition, e.g., compressed sensing (111). However, these types of solutions were not available in the MRI units of the participant centres we visited. No assessment on physician reimbursement, workloads, or whole care pathway costs were made. Our study does not fully address the barriers to a sustainable service, although “mission creep” and a gradual increase in scanning times once the initial implementation is over was observed. The team performed immediate CMR viewing, post-processing, and reporting in a way that would not necessarily be applicable to clinical services. There is a potential role of artificial intelligence for a more cost-effective and rapid CMR report (235), that we did not assess in this study.

9.1.8 Conclusions: CMR core clinical information can be provided more quickly, easily and less expensive. Our rapid CMR protocol can be delivered globally to major centres in LMICs (national/state capitals) and HICs alike. When incorporated into a clinical service and linked to an education/training program with a supporting international network and partnership, it can deliver high diagnostic quality and improve patient care. The initial data suggest these changes can be sustainable.

Chapter 10: Discussion and Conclusions:

10.1 Background:

My thesis explored the feasibility of implementing CMR in LMICs for the assessment of cardiomyopathies. Starting with a pilot study in 2016 – The INCA PERU study, where I promoted the adoption of Rapid CMR in my home country in the main public hospital in the capital city, where there was not CMR before. The next step was to extend this proof of principle to more LMICs, as a multicentre and prospective study. By the end of my PhD, the rapid CMR project was implemented in 11 centres in 7 cities and 5 countries.

For this PhD, I explored alternatives for the adoption of CMR and its promotion when technology was available by adopting a simplified CMR protocol, focusing on the core utility of CMR (cardiac structure, function, scar, and iron evaluation) where this technique contributes unique information, not assessed by other cardiac imaging modalities. Also, I evaluated the clinical effectiveness and cost-effectiveness of the abbreviated CMR protocol assessed on patients' care.

However, the scope of my project went further than the introduction of a simplified CMR scan in LMICs, as technology cannot be adopted without locally trained professionals who can deliver this cardiac imaging modality in their countries for sustainability. My research received support at a political and educational level, with health ministers, scientific councils, embassies, international and national scientific societies, and universities, creating a network and partnership of professionals, www.rapidcmr.com, who supervised and supported the project, providing a unique education opportunity to local professionals (technologists and physicians) and

organising scientific conferences in 4 of the 5 participant countries, where there was little or no CMR teaching before. Furthermore, I explored the utility of CMR as a research method in LMICs specifically to complement research in areas of a specific need in LMICs, exploiting opportunities not available, with three chapters of my thesis dedicated to evaluating these areas: HIV disease in Peru, Cardiac Iron in Thalassaemic patients in India and cardiotoxicity screening in cancer patients in the UK with a potential impact on improving access to CMR.

10.2 Technical Development:

As a by-product of the Rapid-CMR project, I developed the abbreviated CMR protocol. The abbreviated CMR protocol (cardiac volumes, function, and tissue characterization with Late Gadolinium Enhancement) was originally developed after scanning healthy volunteers. By focusing on the core utility of CMR, I showed that this protocol could be used throughout different scanner models in LMICs.

10.3 Key Findings

10.3.1 Impact of Rapid CMR in Peru – INCA PERU study

In this pilot study, a faster and cheaper protocol (18 minutes / \$150 contrast CMR protocol, focusing on just measuring cardiac volumes and scar) was possible for implementing in the capital city of one LMIC country, Lima-Peru), using existing infrastructure and showing good quality. This protocol resulted in an important impact on patient care.

10.3.2 Early myocardial changes revealed by CMR in Asymptomatic People Living with Human Immunodeficiency Virus in Peru

I explored the changes in myocardial function and structure in PLWH both on ART and those who were ART-naïve, utilizing CMR in a LMIC, Peru, where untreated patients remain prevalent. My data supported a high prevalence of subclinical myocardial dysfunction with tissue characterization (oedema, inflammation, and fibrosis) changes in PLWH. Patients on ART have less pronounced changes. I also showed that the markers of myocardial inflammation and fibrosis are associated with a detectable viral load and lower CD4 count, suggesting ART may be cardioprotective.

10.3.3 Improved cardiac iron using Rapid CMR to guide chelation therapy in Thalassemic patients in India

These data demonstrate that a faster and simpler CMR protocol could be successfully embedded into patients' care within the thalassemic medical camp model to guide chelation therapy and that improvements in cardiac iron loading followed in two centres – two cities in India.

10.3.4 CMR Strain Feature-Tracking for early detection of LV systolic dysfunction in patients with Beta-Thalassaemia and myocardial iron overload

This study evaluated the diagnostic performance of CMR Strain-FT to assess temporal changes in early systolic dysfunction in TDT treated with chelation therapy (using the cohort of patients from the UMIMI study). I found a significant improvement in CMR-

FT GLS strain, which correlated with a concurrent improvement in T2* CMR in patients with cardiac iron overload receiving chelation therapy.

10.3.5 Comparison of the measurement precision of MUGA, CMR and echocardiography for serial cardiotoxicity screening in cancer patients

This study carried out in the UK showed that 2DE does not have sufficient precision to reliably detect the changes in LVEF deemed significantly by guidelines, even with good 3DE quality imaging. These data also showed the incremental value of analysis using machine learning for CMR LVEF, with similar precision of CMR-derived GLS to 2DE speckle tracking GLS.

10.3.6 Improving the access of CMR in LMICs: Rapid CMR

In this multicentre prospective study, I showed that CMR could be done faster and cheaper (scanning time < 22minutes, saving 30-60% of current CMR costs) in 11 centres, 7 cities in 5 countries. When the abbreviated CMR protocol is linked to an educational and training program with supporting international networks and partnerships, it can be successfully implemented in LMICs, with high diagnostic quality and positive changes in patients' diagnosis, and management.

10.4 Implication of Findings: Clinical Insights and Potentials:

The findings presented in this thesis have important implications that I would like to address in the following statements:

1) *The following clinical implications and potentials are related in patients with cardiomyopathies in LMICs:*

- Although technology is available and rapidly increasing, access to CMR is still limited in LMICs. In Peru, the main barriers identified for CMR were the lack of local expertise and access to training, together with a long, complex, and costly CMR scan at the time of the intervention in 2016. The INCA PERU study demonstrated that a contrast CMR protocol could be delivered in 18 minutes at the cost of \$150, scanning 98 patients (25 patients x day – 2 centres). This protocol could be embedded into clinical care with education, and it had a major impact on patients' management, resulting in benefits for the patients and the healthcare system. This study provided the impression that resource scarcity is not a justification for the absence of key diagnostic tests in Peru. An abbreviated CMR protocol can potentially lead to the widespread use of this technology in more centres in LMICs. However, much work was still needed, in training imagers in centres with existing infrastructure and by delivering CMR with high quality and assessing its potential impact for sustainability.
- The next step of my research focused on further adopting the simplified CMR protocol in more LMICs for the assessment of cardiomyopathies, where technology was available. "*Rapid CMR*" was a multicentre prospective study, carried out in 11 centres, 7 cities and 5 countries. We highlighted the

incorporation of 4 key aspects for the widespread of CMR in LMICs: 1) Creating a national-international collaboration partnership, 2) Training and education to local care providers, 3) Delivering a focused and faster CMR protocol with sequences available for different scanners models and software, 4) Assessing the impact of rapid CMR protocol on patient's diagnosis and care. This research showed that CMR core protocol could be modified for specific scenarios (e.g. patients with arrhythmia) and pathologies (e.g., ARVC). These scenarios increased the length of CMR scanning, but still < 30 minutes of scanning, saving time and costs at around 30-60%, respectively.

Other advanced CMR key sequences (e.g., stress perfusion) were excluded from the focused CMR protocol. However, the delivery of such kind of technology is more complex in LMICs, and it is outside the scope of this project. Using novel techniques to speed up CMR scanning time was not possible as the MRI technology available in the participant countries did not permit us to use these solutions. Outcomes were changes in clinical cardiac management rather than major cardiac mortality and morbidity outcomes. This research has not demonstrated sustainability. The healthcare system organization and healthcare priorities in LMICs are different, and the complete adoption of an abbreviated CMR protocol could be more challenging.

- 2) *The following clinical implications and potentials are related to patients with Transfused Beta Thalassaemia Patients:*

- This is a research in transfusion-dependent thalassaemia patients at risk of cardiac siderosis, which has profound implications for management, potentially for survival, and for improved cost efficiency in India. CMR T2* is the gold standard for measuring heart iron loading and guiding therapy, but access is severely limited in India, despite technology being available. Treatment protocols linked to an objective assessment of risk through measurement of cardiac tissue iron levels by CMR have not previously been prospectively assessed. This is the first prospective study to undertake a rapid CMR protocol and use the results to base a treatment plan for these patients. We demonstrated that a rapid CMR scan could be incorporated into a thalassaemic patients' medical camp, completing 103 patients' assessments in 2 days, with a subsequent demonstrable impact on the optimization of their chelation therapy and reducing cardiac iron by 23%. Our data supports the contention that this approach can reduce elevated iron content in the heart, and, by dramatically reducing scan times (to 10min), the prospect is raised for many more patients in LMICs at risk of cardiac iron toxicity to benefit from risk stratification by CMR cardiac iron assessment. The next steps require that this methodology is adopted more widely in India and more LMICs with a higher prevalence of Beta-Thalassaemia and establishing if the benefit can be sustained and clinical outcomes improved.
- We also showed the potential role of CMR Strain Feature Tracking (GLS) to assess temporal changes of LV systolic function in Beta-Thalassaemic patients. After following-up on this cohort for 13 months and advising the optimization of chelation therapy based on CMR T2* cardiac iron results, GLS correlated with

a concurrent improvement in cardiac iron status. GLS proved to be the best discriminator between Thalassaemic patients with MIO. These findings suggest that in Thalassaemic patients, CMR-FT GLS could be an additional imaging biomarker to CMR-T2* for detecting cardiac involvement and early function changes in patients who are receiving chelation therapy and are indicated for routine CMR scans to guide iron levels and chelation therapy. This research suggests that further research should focus on the potential role of CMR-FT GLS, with-high quality control studies, larger populations, and the inclusion of contemporary control groups. The assessment of cardiac outcomes based on CMR-FT GLS should also be considered.

3) *The following clinical implications and potentials are related to People Living with HIV:*

By using advanced CMR imaging in ART-treated and ART- naïve PLWH and without cardiovascular symptoms in Peru, this data support the presence of early changes in myocardial structure and function, as previously published (165). PLWH had reduced cardiac function – LVEF, GLS, and GCS compared to healthy volunteers. PLWH also had cardiac structural changes, reflected by imaging biomarkers of oedema, inflammation, and fibrosis. For the first time, we showed that ART- naïve PLWH had elevated native T1 and ECV compared to those on treatment. Across all PLWH, higher ECV was associated with a lower CD4 count, and both higher ECV and native T1 were associated with a detectable viral load, which may support the notion that ART treatment is likely to be offering an overall

protective effect on the cardiovascular system. However, the sample size of the study limits the generalization of results. We did not collect biochemical data, and the absence of histological data complicated the differentiation between fibrosis and inflammation. This study raised further questions about the optimal management of these patients and whether earlier drug therapies could be used at this stage of cardiac involvement, highlighting the need for prospective studies performing a serial cardiac evaluation.

4) The following clinical implications and potentials are related to cancer patients for cardiotoxicity screening:

Serial screening for cardiotoxicity depends on biomarker precision. These data support a previous publication (47) highlighting that 2DE may not have sufficient precision to reliably detect the changes in LVEF deemed significant by guidelines, even with good quality imaging. It may be important to consider other alternative imaging modalities for screening – particularly when 3DE image quality is poor and for patients at the highest risk of cardiotoxicity. We also showed the incremental value of analysis using machine learning for CMR LVEF, with similar precision between CMR-derived GLS and 2DE speckle tracking GLS. These data highlight the potential for more widespread application of CMR for cardiotoxicity screening, particularly using abbreviated imaging protocols to improve access not only in LMICs but in HICs where there is a higher demand of cancer patients for cardiotoxicity screening. This study did not assess the sensitivity, specificity, or predictive value of any of the imaging modalities, and we did not determine the

specific feature of each imaging modality, which led to the differences in interstudy reproducibility. The limited number of patients (mainly in the MUGA group) may limit the extrapolation of our results. The access of each imaging modality is variable in each country which may only lead to a specific technique.

10.5 Upcoming Research

PERU: *Cardiac Adaptation in humans to high altitude: Evaluation of well-adapted and mal-adapted highlanders with chronic mountain sickness*

ANDES-PERU study

Research Group Peru:

- Dr José Luis Macarlupú B., Dr Francisco Villafuerte, Universidad Peruana Cayetano Heredia, Instituto de Investigación de Medicina de Altura, Lima, Perú
- Dr Marco Lazo, Dr Einar Maldonado Ms Yessica Quispe Orihuela, Hospital Nacional de Huancayo Ramiro Priale y Clinica Santo Domingo, Huancayo, Peru.
- Dr Julio Menacho López, Universidad Santiago Antunez de Mayolo, Huaraz – Ancash.

Research Group Italy – Highcare Laps, Auxologico Italian Institute:

-Gianfranco Parati, Grzegorz Bilo, Dr Camila Torlascco and member of the scientific committee.

Research Group United Kingdom:

-Dra. Katia Menacho, Dr Malcolm Walker, Profesor James Moon, University College London, Reino Unido

-Funding: Highcare Laps and UCL Global Engagement Office - £15000.

-Starting day: 01/01/2021 (Postponed due to COVID-19 Pandemic)

The study of human responses to hypoxia occurring as a consequence of low atmospheric pressure conditions is studied by high-altitude medicine (265). Previous studies have been performed to assess the effects of high-altitude exposure in people living at sea levels, demonstrating that this condition induces important changes in cardiovascular regulation, mainly due to hypoxia caused by decreased oxygen in the

ambient air. Despite the great number of individuals permanently living at high altitudes, much less evidence is available on the cardiovascular characteristics of highlanders, and even more, less research has been published about the cardiovascular system response to maladaptation in high altitudes called Chronic Mountain Sickness (CMS).

CMS is a poorly understood disease (266). Available studies are limited in number, with very small sample size, and usually not performed using state-of-the-art technology and equipment. Furthermore, CMS, whose estimated prevalence is approximately 6% in the Andean highlanders, is a condition not yet well understood. The challenging environment and the low resource availability of high-altitude locations can be held responsible for this knowledge gap (267).

Limited support has been done in Peru and, in general, in South American countries to this specific population. This is particularly concerning in Peru because it has 12 cities in the Andes foothills, representing 30% of the total population, and where is expected there will be an increase migration to altitude locations due to developing economic activities and population growth. Unfortunately, most of the Andean inhabitants have limited access to public healthcare services and they live in the rural areas, where poverty is higher, with 74.3% of people living in rural regions being poor (268). If a highlander has a maladaptive response to altitude and develops chronic mountain sickness, the best treatment option would be to relocate to lower-level cities or villages. However, many of them are unable to do this due to a scarcity of resources, poverty, and a co-dependence on family ties.

Objective: The proposed project aims to characterize two different populations of Peru: well-adapted healthy highlanders and mal-adapted highlanders suffering from Chronic Mountain Sickness in 1 main city: Cerro de Pasco (4330m a.s.l.).

Hypothesis: The hypothesis is that chronic hypoxemia and red cell response in highlanders with CMS, is associated with early phenotypic changes, with certain cardiac function changes compared to healthy highlanders, which can be identified and revealed with these non-invasive tests (advanced CMR) permitting early detection of the disease and may lead to early treatment intervention.

Design: This study will include 100 subjects, 50 well-adapted high-altitude residents and 50 high-altitude residents suffering from CMS. The well-adapted and CMS patients will be recruited in Cerro de Pasco and surrounding areas. Participants will be asked for their consent and provided a PIS. Then, they will be driven by bus to Huancayo Santo Domingo Private Hospital or Ramiro Priale Essalud National Hospital to have a CMR scan.

10.6 Future Directions:

There is research talent, capacity, and potential utility of CMR in LMICs, but yet, they are not reaching the levels needed to inject the unique insights of CMR (national adoption, assessment of specific diseases, geographies, or treatment pathways) into the global knowledge base. The next step of my project is to start a multicentre study with 15 participant centres in 9 countries in Latin America. A total of 2000 patients are expected to have the Rapid CMR protocol: Peru - Lima (6 public hospitals); Chile - Santiago de Chile (1 public hospital); Cuba - La Havana (2 public hospitals), Argentina - Buenos Aires (2 hospitals), El Salvador (2 hospital), South Africa (1 hospital),

Jamaica (1 hospital). For cardiac iron assessment in Thalassemic patients, we aim to start collaboration projects in Sri Lanka (1 centre) and India (6 centres, 5 cities). The next project was expected to occur in Chile in 2021, with ethical approval and an education program in place (Dr Jesus Urbina and Dr Sergio Uribe, Catholic University – Chile and Sotero del Rio Hospital). However, the project has been postponed due to the COVID-19 pandemic.

Assessment of specific areas of needs in the participant countries: The project aims to focus on areas of specific need to LMICs, contributing to a better diagnosis and treatment: Neglected Diseases (Chagas cardiomyopathy (Peru – Argentina)); tackling environmental barriers (Chronic mountain Sickness (Peru) at 3500m. a.s.l – discussed above), infectious diseases (HIV and early cardiac involvement (Peru, Cuba, Chile)) and treatment-related toxicity with cancer (Cuba). By using CMR, we will assess cardiac imaging biomarkers of inflammation/oedema/ fibrosis – for the earlier detection of diseases and the assessment of scar for correct diagnosis/risk stratification and prognosis.

10.7 Conclusions

This thesis evaluated the implementation of a simplified CMR protocol, focused on the core utility of CMR for the assessment of cardiomyopathies in LMICs. By embedding the technical quality CMR protocol within clinical care, training, and mentoring local professionals, Rapid CMR proved to have diagnostic utility, it changed management. Part of my research focused on using CMR as a research method in LMICs specifically to complement research in areas of a specific need to those countries, exploiting opportunities not previously available and showing the potential utility of CMR in those countries. My PhD involved technology adaptation, transfer, and collaboration. Rapid CMR can be possible in LMICs clinical environments where much need exists to improve cardiac care.

Chapter 11: Appendix

11.1 Prizes and Award related to research activity:

- **Young Ambassador - SCMR Outreach Committee – 22nd SCMR Annual Meeting on February 2019**, Bellevue City on Seattle’s Eastside.
- **Young Investigator Award. Runner-up. 22nd SCMR Annual Meeting on February 2019**, Bellevue City on Seattle’s Eastside.
- **Moderated Poster, Finalist**, Joint meeting EACVI and SCMR February 2018 in Barcelona, Spain.
- **Young Investigator Award. Winner. 2nd Place –EuroCMR Meeting on May 2017**, Prague – Czech Republic: Impact of Non-invasive CMR Assessment in the developing world
- **Best Clinical Case, Finalist**. EuroCMR 2016, Florence - Italy: Early diagnosis and treatment of Eosinophilic Myocarditis by CMR.

11.2 Publications during this studentship

** denotes first author publication in full manuscript

11.2 Published papers and letters:

11.2.1 Original Research

2021:

- 1. Use of quantitative cardiovascular magnetic resonance myocardial perfusion mapping for characterization of ischemia in patients with left internal mammary coronary artery bypass grafts.**

Seraphim, A., Knott, K. D., Beirne, A. M., Augusto, J. B., **Menacho, K.**, Artico, J., Joy, G., Hughes, R., Bhuvu, A. N., Torii, R., Xue, H., Treibel, T. A., Davies, R., Moon, J. C., Jones, D. A., Kellman, P., & Manisty, C. (2021).

Journal of cardiovascular magnetic resonance: official journal of the Society for Cardiovascular Magnetic Resonance, 23(1), 82.

<https://doi.org/10.1186/s12968-021-00763-y>

2. Prognostic Value of Pulmonary Transit Time and Pulmonary Blood Volume Estimation Using Myocardial Perfusion CMR.

Seraphim A, Knott KD, **Menacho K**, Augusto JB, Davies R, Pierce I, Joy G, Bhuva AN, Xue H, Treibel TA, Cooper JA, Petersen SE, Fontana M, Hughes AD, Moon JC, Manisty C, Kellman P.

JACC Cardiovasc Imaging. 2021 May 12: S1936-878X (21)00344-2. doi: 10.1016/j.jcmg.2021.03.029. Epub ahead of print. PMID: 34023269.

3. Prior SARS-CoV-2 infection rescues B and T cell responses to variants after first vaccine dose.

Reynolds CJ, Pade C, Gibbons JM, Butler DK, Otter AD, **Menacho K**, Fontana M, Smit A, Sackville-West JE, Cutino-Moguel T, Maini MK, Chain B, Noursadeghi M; UK COVIDsortium Immune Correlates Network, Brooks T, Semper A, Manisty C, Treibel TA, Moon JC; UK COVIDsortium Investigators, Valdes AM, McKnight Á, Altmann DM, Boyton R. *Science*. 2021 Apr 30: eabh1282. doi: 10.1126/science.abh1282. Epub ahead of print. PMID: 33931567; PMCID: PMC8168614.

4. Prospective Case-Control Study of Cardiovascular Abnormalities 6 Months Following Mild COVID-19 in Healthcare Workers.

COVIDsortium Investigators: Joy G, Artico J, Kurdi H, Seraphim A, Lau C, Thornton GD, Oliveira MF, Adam RD, Aziminia N, **Menacho K**, Chacko L, Brown JT, Patel RK, Shiwani H, Bhuva A, Augusto JB, Andiapen M, McKnight A, Noursadeghi M, Pierce I, Evain T, Captur G, Davies RH, Greenwood JP, Fontana M, Kellman P, Schelbert EB, Treibel TA, Manisty C, Moon JC;

JACC Cardiovasc Imaging. 2021 May 5: S1936-878X (21)00356-9. doi: 10.1016/j.jcmg.2021.04.011. Epub ahead of print. PMID: 33975819; PMCID: PMC8105493.

5. Hypertrophic cardiomyopathy: insights from extracellular volume mapping.

Castelletti S, **Menacho K**, Davies RH, Maestrini V, Treibel TA, Rosmini S, Manisty C, Kellman P, Moon JC.

Eur J Prev Cardiol. 2021 Mar 9:zwaa083. doi: 10.1093/eurjpc/zwaa083. Epub ahead of print. PMID: 33693514.

6. Measurement of T1 Mapping in Patients with Cardiac Devices: Off-Resonance Error Extends Beyond Visual Artifact but Can Be Quantified and Corrected.

Bhuva AN, Treibel TA, Seraphim A, Scully P, Knott KD, Augusto JB, Torlasco C, **Menacho K**, Lau C, Patel K, Moon JC, Kellman P, Manisty CH. *Front Cardiovasc Med.* 2021 Jan 29;8:631366. doi: 10.3389/fcvm.2021.631366. PMID: 33585589; PMCID: PMC7878555.

7. Healthcare Workers Bioresource: Study outline and baseline characteristics of a prospective healthcare worker cohort to study immune protection and pathogenesis in COVID-19.

Augusto JB, **Menacho K**, Andiapen M, Bowles R, Burton M, Welch S, Bhuva AN, Seraphim A, Pade C, Joy G, Jensen M, Davies RH, Captur G, Fontana M, Montgomery H, O'Brien B, Hingorani AD, Cutino-Moguel T, McKnight Á, Abbass H, Alfarih M, Alldis Z, Baca GL, Boulter A, Bracken OV, Bullock N, Champion N, Chan C, Couto-Parada X, Dieobi-Anene K, Feehan K, Figtree G, Figtree MC, Finlay M, Forooghi N, Gibbons JM, Griffiths P, Hamblin M, Howes L, Itua I, Jones M, Jardim V, Kapil V, Jason Lee WY, Mandadapu V, Mfuko C, Mitchelmore O, Palma S, Patel K, Petersen SE, Piniera B, Raine R, Rapala A, Richards A, Sambile G, Couto de Sousa J, Sugimoto M, Thornton GD, Artico J, Zahedi D, Parker R, Robathan M, Hickling LM, Ntusi N, Semper A, Brooks T, Jones J, Tucker A, Veerapen J, Vijayakumar M, Wodehouse T, Wynne L, Treibel TA, Noursadeghi M, Manisty C, Moon JC. *Wellcome Open Res.* 2020 Oct 12; 5:179. doi: 10.12688/wellcomeopenres.16051.2. PMID: 33537459; PMCID: PMC7836029.

2020

8. Cardiovascular Remodelling Experienced by Real-World, Unsupervised, Young Novice Marathon Runners.

D'Silva A, Bhuva AN, van Zalen J, Bastiaenen R, Abdel-Gadir A, Jones S, Nadarajan N, **Menacho Medina KD**, Ye Y, Augusto J, Treibel TA, Rosmini S, Ramlall M, Scully PR, Torlasco C, Willis J, Finocchiaro G, Papatheodorou E, Dhutia H, Cole D, Chis Ster I, Hughes AD, Sharma R, Manisty C, Lloyd G, Moon JC, Sharma S. *Front Physiol.* 2020 Mar 18; 11:232. doi: 10.3389/fphys.2020.00232. PMID: 32256389; PMCID: PMC7093496.

9. ** Myocardial Inflammation and Edema in People Living with Human Immunodeficiency Virus.

Menacho K, Seraphim A, Ramirez S, Falcon L, Bhuvu A, Alave J, Banda C, Mejia F, Salazar D, Putri A, Mosto F, Gonzales P, Culotta V, Menacho J, Herrey AS, Ntusi NAB, Walker JM, Moon JC.

JACC Cardiovasc Imaging. 2020 May;13(5):1278-1280. doi: 10.1016/j.jcmg.2019.12.005. Epub 2020 Jan 15. PMID: 31954657.

2018

10. INCA (Peru) Study: Impact of Non-Invasive Cardiac Magnetic Resonance Assessment in the Developing World.

** **Menacho K**, Ramirez S, Segura P, Nordin S, Abdel-Gadir A, Illatopa V, Bhuvu A, Benedetti G, Boubertakh R, Abad P, Rodriguez B, Medina F, Treibel T, Westwood M, Fernandes J, Walker JM, Litt H, Moon JC.

J Am Heart Assoc. 2018 Sep 4;7(17): e008981. doi: 10.1161/JAHA.118.008981. PMID: 30371164; PMCID: PMC6201420.

11. Proposed Stages of Myocardial Phenotype Development in Fabry Disease.

Nordin S, Kozor R, **Menacho-Medina K**, Abdel-Gadir A, Baig S, Sado DM, Lobascio I, Murphy E, Lachmann RH, Mehta A, Edwards NC, Ramaswami U, Steeds RP, Hughes D, Moon JC.

JACC Cardiovasc Imaging. 2019 Aug;12(8 Pt 2):1673-1683. doi: 10.1016/j.jcmg.2018.03.020. Epub 2018 May 16. PMID: 29778854.

12. Cardiac Phenotype of Prehypertrophic Fabry Disease.

Nordin S, Kozor R, Baig S, Abdel-Gadir A, **Menacho K**, Rosmini S, Captur G, Tchan M, Geberhiwot T, Murphy E, Lachmann R, Ramaswami U, Edwards NC, Hughes D, Steeds RP, Moon JC.

Circ Cardiovasc Imaging. 2018 Jun;11(6): e007168. doi: 10.1161/CIRCIMAGING.117.007168. PMID: 29853467; PMCID: PMC6023585.

13. Reappraising myocardial fibrosis in severe aortic stenosis: an invasive and non-invasive study in 133 patients.

Treibel TA, López B, González A, **Menacho K**, Schofield RS, Ravassa S, Fontana M, White SK, DiSalvo C, Roberts N, Ashworth MT, Díez J, Moon JC. *Eur Heart J*. 2018 Feb 21;39(8):699-709. doi: 10.1093/eurheartj/ehx353. PMID: 29020257; PMCID: PMC5888951.

2017

14. Left Ventricular Hypertrophy Revisited: Cell and Matrix Expansion Have Disease-Specific Relationships

Treibel TA, Kozor R, **Menacho K**, Castelletti S, Bulluck H, Rosmini S, Nordin S, Maestrini V, Fontana M, Moon JC.

Circulation. 2017 Dec 19;136(25):2519-2521. doi:

10.1161/CIRCULATIONAHA.117.029895. PMID: 29255128.

11.2.2 Submitted and recently accepted manuscript:**15.** Improved cardiac iron one year after using rapid Magnetic Resonance Imaging to guide chelation therapy: Ultrafast MRI for Iron Management in India – the UMIMI study**

Katia Menacho MD, Amna Abdel-Gadir MBBS, Redha Boubertakh Physics, Kartik Ganga MD, Vineeta Ojha MD, Surya Pratap MD, Louise McGrath RD, Joao Augusto MD, Mr Alexander Rikowski, Ms Nabila Mughal R, Mrs Shoba Tuli, VK Khanna MD, Tulika Seth, Sanjiv Sharma, Amita Mahajan MD, Rajiv K Bansal MD, Prabhar Srivastava MD, Harsh Mahajan MD, Vidhur Mahajan MD, Beatrix Wonke MD, Mrs Judith Walker MSc RN, Ms Seldon Tenzin BSc, Emmanuel Ako MD, James C Moon MD, J. Malcolm Walker M.

Accepted manuscript at European Heart Journal Quality of Care and Clinical Outcomes (EHJ-QCCO-D-21-00322R1).

16. Improving CMR access in Low-Middle Income Countries for Cardiomyopathy Assessment and Improved Cardiac Care: Rapid CMR

K. Menacho, S. Ramirez, A. Perez, L. Dragonetti, D. Perez, D. Katekaru, V. Illatopa, S. Munive, B. Rodriguez, A.C Shimabukuro, K. Cupe, R. Bansal, I. Rodriguez, A Seraphim, Kris Knott, S. Guerrero, M. Lazo, D. Uscamaita, Marco Rivero, A. Peix, S. Mohiddin, Litt H, Y. Han, Fernandes J., R. Jacob, N. Ntusi, Manisty C, M. Westwood, A. Herrey, M. C Walker, J. C Moon. has been submitted to European Heart Journal (under second revision). Manuscript Number: EURHEARTJ-D-21-03114R1.

11.2.3 Review articles, Journal Section and Newsletter:

2021

17. Non-invasive rapid cardiac magnetic resonance for the assessment of cardiomyopathies in low-middle income countries.**

Menacho Medina K, Seraphim A, Katekaru D, Abdel-Gadir A, Han Y, Westwood M, Walker JM, Moon JC, Herrey AS.

Expert Rev Cardiovasc Ther. 2021 May;19(5):387-398. doi:

10.1080/14779072.2021.1915130. Epub 2021 May 24. PMID: 33836619.

2020

18. **** Rapid Cardiac MRI Protocols: Feasibility and Potential Applications.**
Menacho Katia, Ntobeko Ntusi, James C Moon, Malcolm Walker, Jacob Ron.
Current Radiology Reports 8(2). February 2020.

2019

19. **** T2* Mapping Techniques: Iron Overload Assessment and Other Potential Clinical Applications.**
Menacho K, Abdel-Gadir A, Moon JC, Fernandes JL Magn Reson Imaging
Clin N Am. 2019 Aug;27(3):439-451. doi: 10.1016/j.mric.2019.04.008. PMID: 31279448.

2016

20. Cardiovascular magnetic resonance frontiers: Tissue characterisation with mapping

Rebecca Schofield, Anish Bhuvu, **Katia Menacho**, James C. Moon.
SA Journal of Radiology, 2016 20 (2), 1019.
<http://dx.doi.org/10.4102/sajr.v20i2.1019>

21. Cardiovascular magnetic resonance in hypertrophic cardiomyopathy and infiltrative cardiomyopathy

Rebecca Schofield, **Katia Menacho**, Silvia Castelleti, James C. Moon.
SA Journal of Radiology, 2016 20 (2), a 1020.

- **How We do Series– SCMR
Rapid CMR/ Establish CMR in developing countries**
Menacho K, Seraphim A, Bhuvu A, Herrey A, Moon J. Published June 2020

11.3 Presentations: Only first author presentations listed

- **Impact of non-invasive rapid cardiac magnetic resonance for the assessment of cardiomyopathies in developing countries**
Session: Improving the efficiency of advanced cardiac imaging.
ESC Congress Presentation Paris 2019.
- **Improving CMR Access in Developing Countries: Rapid CMR**
Best Oral Abstract Presentation Nomination, 22nd Meeting SCMR, Seattle, 2019:
- **Myocardial involvement in treated and untreated HIV patients: inflammation and edema revealed by CMR.**

Abstract Presentation, Quick Fire Session 22nd Meeting SCMR, Seattle, 2019:

- **Myocardial inflammation and Oedema Revealed by Cardiac Magnetic Resonance in Antiretroviral- Naïve and Antiretroviral- Exposed HIV Patients.**

E-poster moderated presentation: CMR 2018 – Barcelona, Spain. Selected to be presented at the Best Moderated ePoster Session on Saturday, February 3rd 2018.

- **Variability of left ventricular ejection fraction measurement by imaging modality for cardiotoxicity screening: Comparison between Radionuclide Ventriculography, 2D and 3D Echocardiography and CMR**

Moderated Poster Session. Sub-topic: Cross-Modality and Multi-modality Imaging Topics. May 2019. Lisbon, Portugal.

- **Poster presentation: Sinus of Valsalva, RCA aneurysm.**

at CMR 2018 Conference – Barcelona, Spain, February 3rd 2018.

- **Excellent case of RV cavernous haemangioma.**

Cardiac mass session. Oral Presentation: at CMR 2018 – Barcelona, Spain.

- **Impact of Non- invasive CMR Assessment in the developing world: INCA – PERU study.**

Oral Presentation: 2nd place best Oral abstract EuroCMR 2017, Prague Czech Republic

- **Early diagnosis and treatment of Eosinophilic Myocarditis by CMR.** Oral Presentation: Nomination for Best Clinical Case EuroCMR 2016 – Florence.

- **The RV and cardiac surgery more resilient than thought: multi-parametric quantification shows altered rather than reduced function**

Poster presentation 19th Meeting SCMR, Los Angeles 2016:

11.4 Invited speaker to international conferences during this studentship:

- **Iron Cardiomyopathy and T2* CMR**

XXVII Peruvian Cardiology Congress – Virtual Conference, 12th of May 2021.

- **Making CMR happening Everywhere.**

SCMR Virtual Conference. Scientific Sessions 2021, 18th to 20th of February

2021.

- **Efficient and effective CMR: Cardiomyopathy Protocol of 20 minutes.**
SCMR 23rd Annual Scientific Session 2020. SCMR/ISMRM Co-Provided Workshop. 12th – 13th of February 2020.
- **How to Establish CMR in Countries and Centres with Little or No Experience**
22th Meeting SCMR, Seattle, 2019.
- **Mapping techniques in CMR**
XXV Peruvian Cardiology Congress, Lima, Peru 12th of May 2019.
- **Value of CMR in Cardiotoxicity**
XXV Peruvian Cardiology Congress, Lima, Peru 12th of May 2019.
- **Value of CMR for the Assessment of Cardiomyopathy**
ECOSIAC Conference, Lima, Peru, 10th of May 2019
- **Anatomy and function of the heart's electrical system.**
Fundamentals of Cardiology Course, 22th Meeting SCMR, Seattle, 2019.
- **How to Stablish a CMR Service.**
CMR Congress of South Africa. 19-22nd of August 2021, Cape Town.
- **Improving the access of CMR in LMICs**
CMR Congress of South Africa. 19-22nd of August 2021, Cape Town.

11.5 Invited Speaker to National Conferences

- **Anatomy principles for CMR acquisition**
Radiographer Course, June 2018, Saint Bartholomew's Hospital
- **Rapid CMR in Peru – INCA-PERU Study**
Grand Round, St Bartholomew's Hospital 2017
- **3 minutes thesis presentation – Improving the access of CMR in LMICs**
Faculty Contest ICS, University College London

11.6 Teaching:

A) Chadburn Lecturer in Medical Education – Clinical Communication Skills Unit at Queen Mary University London. Started: April 2021.

B) Course director and organiser of the 4 conferences which were part of the teaching program of my PhD thesis in LMICs.

The following institutions sponsored the conferences or assigned world-recognised education faculty speakers:

- Society of Cardiovascular Magnetic Resonance (SCMR) – Outreach Committee: – supported by providing at least 2 international speakers.
- Interamerican Society of Cardiology (SIAC).
- University College London – Global Engagement Office
- Saint Bartholomew’s Hospital, Barts Heart Centre
- Peruvian Society of Cardiology and Radiology
- Argentinean Society of Cardiology and Radiology
- Cuban Society of Cardiology and Radiology
- University of Cape Town
- Buenos Aires National University
- La Havana National University
- Cayetano Heredia University
- Peruvian College of Physicians

1. **I International Conference in Rapid Cardiac Magnetic Resonance in La Havana -Cuba.**

1st to 3rd of November 2019. **183 participants.** Free Level I SCMR Certification and membership for participants.

I was a speaker in four talks: Chagas Cardiomyopathy and CMR, Cardiac iron Cardiomyopathy and CMR, Rapid CMR in LMICs, CMR Safety and Contrast.

2. **II International Course in Cardiac Magnetic Resonance in Lima – Peru** on the 26 and 27th of January 2019. **214 participants.** Free Level

I SCMR Certification and membership for participants.

I was a speaker in four talks: Chagas Cardiomyopathy and CMR, Cardiac iron Cardiomyopathy and CMR, Rapid CMR in LMICs, CMR Safety and Contrast.

3. **I International Rapid Cardiac Magnetic Resonance in Argentina**, 2-day Workshop in Buenos Aires, Argentina on the 2nd and 3rd of June 2018. **156 participants**. Free Level I SCMR Certification and membership for participants.

I was a speaker in two talks: Clinical cases in CMR and Rapid CMR in LMICs.

4. **I International Course in Cardiac Magnetic Resonance in Lima – Peru** on the 24 and 25th of November 2016. **176 participants**. Free Level I SCMR Certification and membership for participants.

I was a speaker in two talks. CMR safety and contrast, Principles of anatomy in CMR

C) Tutor to 2nd-year Medical Students, CMPP Module teaching 2018 - Clinical Skills Centre at UCL.

D) Hosted the Journal Club Sessions for BHF 4-year PhD students - Institute of Cardiovascular Science – UCL in 2019.

11.7 International Funding Awarded:

- **British Embassy in Cuba - International Trade Department. Title of the Grant: Rapid Cardiac Magnetic Resonance in Cuba.** Grant Awarded: £3760. November 2019.
- **UCL Global Engagement Office. Title of the Grant: Global Engagement Funds - Rapid Cardiac Magnetic Resonance Peru.** Total Grant Awarded: £7500. Starting date: November 2018, Ending Date: November 2020.

Postponed due to COVID-19.

- **UCL Catalyst Award Santander University: Global Engagement Office: £2500.** May 2018. This funding supported the Rapid CMR project in Argentina.
- **International PhD funding, awarded by the Peruvian Scientific and Technology Science Council.** (£130,000). The funding covered my PhD Studies between 2016 – 2019
- **Improving cardiac diagnosis in Peru, awarded by the Foreign Commonwealth Office – UK, British Embassy in Peru** (£79000). The funding covered my research project between August 2016 – December 2017.

11.8 Reviewer Invited for Scientific Journals:

1. JACC imaging: I accepted invitations to be a reviewer for 2 original research articles.
2. Frontiers in Cardiovascular Medicine: I am an editorial board member

11.9 Collaborators:

- **Ambassadors:**
 - o Kate Harrison, Ambassador of the UK in Peru
 - o Sir Antony Stokes, Ambassador of the UK in Cuba.
 - o UCL Global Engagement
- **International Faculty – Education Program Rapid CMR in LMICs:**
 - o Dr Juliano Fernandes, Jose Michel Kalaf Research Institute, Campinas, Brazil.
 - o Dr Redha Boubertakh, Barts Heart Centre, St Bartholomew’s Hospital London, UK.
 - o Professor James C Moon, Cardiac Imaging Department, , Barts Heart Centre, St Bartholomew’s Hospital London, UK.

- Professor Ntobeko Ntusi, Division of Cardiology, Department of Medicine, University of Cape Town and Groote Schuur Hospital, Cape Town, South Africa
- Dr Harold Litt, Perelman School of Medicine of the University of Pennsylvania, Philadelphia. Society for Cardiovascular Magnetic Resonance (SCMR), Mount Royal, USA.
- Dr Ron Jacob, the Heart and Vascular Institute, PENN Medicine/Lancaster General Health, Pennsylvania, United States of America.
- Dr Han Yuchi, Departments of Medicine (Cardiovascular Division) and Radiology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA
- Dr Mark Westwood, Barts Heart Centre, St Bartholomew's Hospital.
- Dr Diego Perez de Arenanza, Italian National Hospital, Buenos Aires, Argentina.
- Dr Juliano Fernandes, Jose Michel Kalaf Research Institute, Campinas, Brazil.
- Dr Anna Herrey, Barts Heart Centre, St Bartholomew's Hospital London, UK.
- Dr Sam Mohiddin, Barts Heart Centre, St Bartholomew's Hospital London, UK.
- Dr Andreas Seraphim, Barts Heart Centre, St Bartholomew's Hospital London, UK.
- Dr Kris Knott, Barts Heart Centre, St Bartholomew's Hospital London, UK.
- Dr Anish Bhuvu, Barts Heart Centre, St Bartholomew's Hospital London, UK.
- Dr Giulia Benedetti, Barts Heart Centre, St Bartholomew's Hospital London, UK.
- Dr Amna Abdel-Gadir, Barts Heart Centre, St Bartholomew's Hospital London, UK.
- RD Louise Mc-Grath, Barts Heart Centre, St Bartholomew's Hospital London, UK.
- RD Patricia Feuchter, Barts Heart Centre, St Bartholomew's Hospital London, UK.

- Rapid CMR Research Group - Peru:

- Dr Carlos Pinto, Cardiology Department, Peruvian Air Force Hospital, Lima.
- Dr Ivonne Rodriguez Fernandes, Cardiology Department, Sermedial, Arequipa.
- Dr Marco Medina Gonzales, Radiology Department, Sermedial, Arequipa.
- Rd Rafael Rodriguez, Radiology Department, Sermedial, Arequipa.
- Dr Juan Carlos Gonsales, Cardiology Department, Sermedial, Arequipa.
- Dr. Pavel Cruz Colca, Cardiology Department, Militar Hospital, Lima.
- Dra. Pamela Cutipa Torres, Radiology Department,, Militar Hospital, Lima
- RD Ruth Garay, Radiology Department, Militar Hospital, Lima
- Dr Diana Katekaru, Cardiology Department, Militar Hospital, Lima.
- Dr Sara Ramirez, Cardiology Department, Peruvian Air Force Hospital, Lima.
- Dr Omar Palacios, Cardiology Department, Peruvian Air Force Hospital, Lima.
- Dr Luis Luyo Vera, Cardiology Department, Peruvian Air Force Hospital, Lima.
- Rd Marco Antonio Rivero, Cardiology Department, Peruvian Air Force Hospital, Lima.
- Dr Violeta Illatopa, Cardiology and Cardiovascular Institute, Lima.
- Dr Sara Munive, Cardiology and Cardiovascular Institute, Lima.
- Dr Henry Anchante, Cardiology Department, Cayetano Heredia Hospital, Lima.
- Dr Felix Medina, Cardiology Department, Cayetano Heredia Hospital, Lima.
- Dr Percy Durand, Cardiology Department, Cayetano Heredia Hospital, Lima.
- Dr Martin Salazar, Cardiology Department, Cayetano Heredia Hospital, Lima.
- Dr Bertha Rodriguez, Radiology Department, Rebagliati Hospital, Lima.
- Rd Neil Amaya Rengifo, Radiology Department, Rebagliati Hospital, Lima.
- Rd David Uscamaita, Radiology Department, Rebagliati Hospital, Lima.
- Dr Victor Sanchez, Cardiology Department, Hipolito Unanue National Hospital, Lima
- Dr Alexandra Carpio, Heart Failure Unit. Arzobispo Loayza, National Hospital, Lima.
- Dr Kelly Cupe, Guillermo Almenara Hospital, Lima
- Dr Ana Shimabukuro, Guillermo Almenara Hospital, Lima
- Dr Salomon Guerrero, Almanzor Aguinaga National Hospital, Chiclayo, Peru.
- Dr Marco Lazo, Ramiro Priale Hospital National Hospital, Huancayo, Peru.

- RD Yesica Quispe, Ramiro Priale Hospital National Hospital, Huancayo, Peru.

- **Rapid CMR Research Group – Argentina:**

- Dr Laura Dragonetti, Radiology Department, IMAT Institute, Buenos Aires.
- Dr Roman Ricardo, Radiology Department, IMAT Institute, Buenos Aires.
- Dr De Lucas Federico, Radiology Department, IMAT Institute, Buenos Aires.
- Dr De Lucas Federico, Radiology Department, IMAT Institute, Buenos Aires.
- Dr Paz Ricapito, Radiology Department, IMAT Institute, Buenos Aires. .
- Rd Juan Bondarczuk, Radiology Department, IMAT Institute, Buenos Aires.
- Dr Oscar Montaña, Radiology Department, IMAT Institute, Buenos Aires. .
- Dr Diego Perez de Arenanza, Cardiology Department, Italian Hospital, Buenos Aires.
- Mariana Vasquez Durand, Cardiology Department, Cardiology Department, Italian Hospital, Buenos Aires.

- **Rapid CMR Research Group – Cuba:**

- Dr Aylen Perez, Cardiac Imaging Department, La Havana, Cardiac Imaging Department, La Havana.
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