University of Glasgow | College of Medical, Veterinary & Life Sciences

Head of College Scholars List Scheme

Summer Studentship

Report Form

This report should be completed by the student with his/her project supervisor. It should summarise the work undertaken during the project and, once completed, should be sent by email to: jill.morrison@glasgow.ac.uk within four weeks of the end of the studentship.

1. Student

   Surname: Henderson Forename: Matthew

   E-mail address: 2173037h@student.gla.ac.uk

2. Supervisor:

   Surname: Berry Forename: Colin

   E-mail address: Colin.Berry@glasgow.ac.uk

3. Research Project Report

   3.1 Project Title (maximum 20 words):

   Analysis of Sphericity Index and Transmurality Ratio in patients with Acute ST-Segment Elevation Myocardial Infarction

   3.2 Project Lay Summary (copied from application):

   Myocardial Infarctions (MI) are a major public health problem in the UK. Approximately half of all patients have 'failed myocardial reperfusion', manifesting as microvascular obstruction (MVO) on cardiac MRI. MVO is a risk factor for heart failure. For this project I will analyse left ventricular remodelling in the T-TIME trial participants. The primary objective in T-TIME is to assess the effects of low-dose, intra-coronary alteplase administered shortly after coronary reperfusion in patients with acute ST-segment elevation MI undergoing 'primary'

percutaneous coronary intervention (PPCI) (n=440). Efficacy assessments are undertaken using cardiac MRI 2-7 days and 3 months post-MI.

3.3 Start Date: 20/08/2018 Finish Date: 14/09/2018

3.4 Original project aims and objectives (100 words max):

Aim: To study left ventricular (LV) remodelling in patients following acute STEMI

Objective:
1) To analyse cardiac MRI scans of participants in the T-TIME clinical trial to assess left ventricular dimensions and their changes over time (2-7 days, 3 months).
2) To study novel measurements of LV remodelling, namely LV sphericity index and LV transmurality ratio to assess LV remodelling.

Hypothesis:
1) We hypothesise that measures of LV remodelling, LV Sphericity Index and the LV Transmurality Ratio, will associate with adverse health outcomes at 12 months;
2) LV remodelling indices will associate with a treatment effect as observed in the study population and in sub-groups.

3.5 Methodology: Summarise and include reference to training received in research methods etc. (250 words max):

The project took place at the imaging laboratory based at the BHF GCRC and Golden Jubilee. The study is coordinated by the Glasgow Clinical Trials Unit (CTU).

Background information was provided about the T-TIME trial including the protocol and background literature to read. Dr Peter McCartney and Prof Colin Berry provided training in imaging analysis methods using the relevant software, Medis® Suite MR (Medis, Leiden, NL). An initial training dataset of 20 patients was undertaken to develop experience in imaging and to quality assure the analyses. (intra- and inter-observer repeatability). Cardiac MRI's scans (2-7 days, 3 months) obtained in T-TIME participants (n=440) were then analysed.

To adjust for stature, the LV dimensions were indexed to body surface area. The Sphericity Index (at end-diastole and systole) were measured as the maximal longitudinal LV diameter (insertion point of mitral valve to LV apex) divided by the maximal short axis diameter. This was calculated in both the Vertical Long Axis (VLA)and Horizontal Long Axis (HLA) views. For transmurality ratio; the maximum infarct thickness and infarct zone wall thickness were measured on the short axis view. Transmurality ratio was calculated as the ratio of the infarct thickness to the infarct zone wall thickness. This data will be linked with the endpoints already archived in the Glasgow CTU database. Statistical analysis will be undertaken using summary statistics under supervision by a statistician in the Glasgow CTU. The analyses for LV remodelling are identified in the study protocol. The whole project will be compiled into a report.

3.6 Results: Summarise key findings (300 words max). Please include any relevant tables or images as an appendix to this report:

Background characteristics were included for the entire T-Time trial population. These will differ from the study population's baseline characteristics as only patients recruited from Glasgow (approximately half the study population) were included. The mean age of patients was 60.5 years (10.3). 85% of patients were male. The location of infarcts were: 47% inferior, 43.4% anterior, 7.5% posterior, 0.7% lateral and 1.4% other. For cardiovascular risk factors: 32% had hypertension, 23.2% had hypercholesterolaemia, 35.7% had a family history of IHD, 12.7% had diabetes, 47.5% were current smokers and 19.1% were former smokers.

90.9% of patients had an MRI performed at 2-7 days. For this the LVEDV was 168.3ml (144.8-199.5), LVESV was 93.7ml (77.5-113.3), LVEF was 44.6% (8.4) and the infarct size was 26.7% (13.2). 83.4% of patients received the 3-month scan. For this the LVEDV was 167.9ml (145.1-197.6), LVESV was 84.2ml (67.5-106.8), LVEF was 48.9% (8.5) and the infarct size was 18.9% (12.0).

393 cardiac MRI scans were analysed from the 208 Glasgow patients in the T-TIME trial. The mean value and standard deviation were calculated for Sphericity Index (VLA and HLA), Transmurality Ratio and Remodelling Index (Table 1). This was calculated at baseline and 3 months. Sphericity Index was calculated at both end-systole and end-diastole. The Sphericity Index from baseline to 3 months deceased by: 1.42% in VLA end-diastole, 1.72% in HLA end-systole and 2.6% in HLA end-diastole. Conversely, it increased by 1.85% in VLA end-systole. The mean Transmurality Ratio decreased by 14.8% from baseline to 3 months. The mean Remodelling Index decreased by 19.8% from baseline to 3 months.

Table 1: Means and Standard Deviations for Sphericity Index, Transmurality Ratio and Remodelling Index

Measurement	Baseline Mean	3 Month Mean	Baseline Standard Deviation	3 Month Standard Deviation
VLA End-Systole Sphericity Index	1.62	1.65	0.23	0.25
VLA End-Diastole Sphericity Index	1.41	1.39	0.17	0.18
HLA End-Systole Sphericity Index	1.74	1.71	0.28	0.26
HLA End-Diastole Sphericity Index	1.53	1.49	0.16	0.16
Transmurality Ratio	0.81	0.69	0.25	0.26
Remodelling Index	0.96	0.77	0.33	0.31

The Intra-observer variability (Table 2) was undertaken in 10% of study participants. The scans were re-analysed by the same observer 1 month after the original analysis. The Pearson Correlation Coefficient was calculated on SPSS to compare the correlation between the two sets of measurements.

Table 2: Intra-observer variability using the Pearson Correlation Coefficient

Measurement	Pearson correlation coefficient (r^2)
VLA End-Systole Sphericity Index	0.936
VLA End-Diastole Sphericity Index	0.966
HLA End-Systole Sphericity Index	0.919
HLA End-Diastole Sphericity Index	0.966
Transmurality ratio	0.990
Remodelling index	0.978

3.7 Discussion (500 words max):

The main results for T-TIME trial are currently under embargo pending presentation at the American Heart Association conference, Chicago on 12th November 2018. This prevented the analysis of LV remodelling measures in relation to adverse outcomes and treatments effects from being undertaken. These results will be available at a future date. Summary statistics were performed on the baseline and 3-month scans. There was generally no difference between mean sphericity index at baseline and 3 months in each of the 4 measurements. Sphericity index indicated little difference in the dimensions of the left ventricle at baseline and 3 months. A sphericity index of 1 suggests a globular heart, which is associated with adverse remodelling. The mean transmurality ratio decreased by 14.8% from baseline to 3 months. This is consistent with the 29% reduction in infarct size from baseline to 3 months. This highlights the reduction in infarct size that occurs with healing during remodelling.

Sphericity index is a novel measure of left ventricular remodelling post MI. Currently reported measures for left ventricular remodelling are left ventricular volumes: LVESV and LVEDV. Adverse remodelling is defined as an increase in volume of ≥12% compared to baseline[1]. LVESV and LVEDV are global measurements that may not detect changes in left ventricular dimensions especially when the LV volume doesn't increase above the 12% threshold. Sphericity index has the potential to detect changes in LV dimensions that may be missed by measuring changes in LV volumes alone[2]. Sphericity index was developed using transthoracic echocardiography (TTE), however, Cardiac MRI depicts cardiac morphology more accurately than TTE[3]. The NOMI trial measured sphericity index using cardiac MRI as a marker of LV remodelling[4].

Only the patients recruited in Glasgow (n=208) were included in the initial analysis due to the volume of analysis and associated time restrictions (4 weeks duration). Analysis of the first 50 scans was time consuming. There is a steep learning curve involved in learning complex cardiac MRI analysis with no previous experience. Progress was slow initially due to training and unfamiliarity with the specialised imaging software. The initial measurements had the greatest error. Accuracy and reproducibility of measurements improved as more scans were completed.

THE intra-observer variability for all the measurements was assessed using the Pearson Correlation Co-efficient, a Pearson co-efficient of 1 suggests there is no variability in the measurements. The r^2 >0.9 for all values suggesting a good correlation between measurements. For sphericity index the intra-observer variability was greater at end-systole than end-diastole. This may be because the endocardial border is less distinct at end-systole as well as variability in the identification of the end-systolic image.

One of the strengths of the T-TIME trial was the high uptake rate for MRI scans of 90.9%. This compares to the recent RELO-STEMI trial where the CMR uptake was 80.1% and in the INFUSE-AMI trial where it was 87.1%.[5,6] The higher uptake rate in T-TIME gives the trial greater power.

References

1- Bulluck H, Go Y, et al. (2017). Defining left ventricular remodeling following acute ST-segment elevation myocardial infarction using cardiovascular magnetic resonance. Journal of Cardiovascular Magnetic Resonance, 19(1).

2- Di Donato M. Dabic P, et al. (2006). Left ventricular geometry in normal and post-anterior myocardial infarction patients: sphericity index and 'new' conicity index comparisons. European Journal of Cardio-Thoracic Surgery, 29, pp.S225-S230.

3- Flachskampf F, Schmid M, et al. (2010). Cardiac imaging after myocardial infarction. European Heart Journal, 32(3), pp.272-283.

4- Janssens S, Bogaert J, et al. (2018). Nitric oxide for inhalation in ST-elevation myocardial infarction (NOMI): a multicentre, double-blind, randomized controlled trial. European Heart Journal, 39(29), pp.2717-2725.

5- Nazir S, Khan J, et al. (2016). The REFLO-STEMI (REperfusion Facilitated by LOcal adjunctive therapy in ST-Elevation Myocardial Infarction) trial: a randomised controlled trial comparing intracoronary administration of adenosine or sodium nitroprusside with control for attenuation of microvascular obstruction during primary percutaneous coronary intervention. Efficacy and Mechanism Evaluation, 3(9), pp.1-48.

6- Stone, G. (2012). Intracoronary Abciximab and Aspiration Thrombectomy in Patients With Large Anterior Myocardial Infarction. JAMA, 307(17), p.1817.

4 Reflection by the student on the experience and value of the studentship (300 words max):

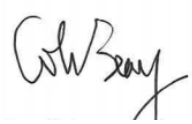
I feel very grateful to have been given the opportunity to spend 4 weeks of my summer in BHF cardiovascular research centre. I have been interested in cardiology since first learning about it in my first year of medical school. Thus, the studentship has been an invaluable experience which has furthered my interest in cardiology. I have thoroughly enjoyed undertaking my project and it has given me a great insight into the processes behind medical research. During the first few years of medical school there is little exposure to research. This studentship was thus a novel experience, which has been very enriching and taught me many important skills. During the 1st week I was provided with background reading. This furthered my knowledge on the research topic and made me familiar with the complex terminology. I was taught many useful skills in cardiac MRI analysis, using computer software such as Medis and Qmass. This has shown me the importance of IT in relation to clinical research.

It has been a pleasure working with the consultants and clinical fellows at the BHF, they have explained everything clearly and answered all my queries. This made it a very pleasant place to work. The studentship has allowed me to meet many experts in cardiovascular research. This has given me a great insight into the field and the opportunities that are available. Overall, the studentship has interested me in a future research career. I would recommend taking part in the scheme to all the students who get the opportunity.

5. Dissemination: (note any presentations/publications submitted/planned from the work):

A full report will be written with a view to presenting the work at conferences and submitting the work to a biomedical journal.

6. Signatures:

Supervisor  Date 5/10/2018 Student  Date: **04/10/2018**