Coronary Artery Motion Analysis for the Prediction of Clinical Coronary Artery Events

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Prediction is very difficult, especially about the future.

— Niels Bohr
Statement of Authentication

I Aiden James O’Loughlin declare that this thesis, submitted in fulfillment of the requirements for the award of Doctor of Philosophy at the University of Western Sydney, is my own work, unless otherwise referenced or acknowledged, and contains as its main content work which has not previously been submitted, in whole or in part, to any other tertiary educational institution.

...................................................

(Aiden O’Loughlin)
Abstract

This thesis examines the hypothesis that coronary artery motion analysis is predictive of the location of clinical coronary artery events. It includes a preamble that describes a clinical scenario highlighting this unmet clinical need and describes in detail the components of this thesis. The thesis includes an overarching statement and a series of published and unpublished manuscripts.

The published manuscripts describe in detail the findings that:

1. Qualitative coronary artery motion analysis predicts the location of culprit lesions responsible for ST segment elevation myocardial infarctions (published prior to commencement of this doctoral degree).
2. The pattern of qualitative coronary artery motion in patients with subsequent ST segment elevation myocardial infarction is not different to the pattern in angiographically normal coronary arteries.
3. Two-dimensional quantitative coronary artery motion analysis predicts the location of future non-ST segment elevation myocardial infarctions.
4. Quantitative coronary artery motion analysis using multislice computed tomography correlates with the location of coronary artery disease.

The unpublished manuscripts describe in detail (that):

5. Two-dimensional quantitative coronary artery motion analysis predicts the location of future ST segment elevation myocardial infarctions.
6. A four-dimensional quantitative method for coronary artery motion analysis and its relationship to both the location of
   a. stenotic disease, and
b. lesion location in ST segment elevation myocardial infarctions.

An important conclusion of this thesis is that coronary artery motion analysis has utility for the prediction of clinical coronary artery events, although further development and refinement of analysis methodology is required prior to its clinical application.
Preamble

Sitting in a hospital catheterization laboratory in the middle of the night waiting for a patient to complete their transfer from an affiliated hospital for primary angioplasty allows a little time to think. After satiating the desire for caffeine, thoughts usually turn to the patient and procedure about to be performed.

One such night, the information available was that the patient had inferior ST segment elevation (without the electrocardiogram being available for review) and had a diagnostic angiogram at the hospital three months previously. Review of the films showed focal non-obstructive plaques in both the left circumflex and right coronary arteries that were potential culprits.

After a successful procedure for a completely occluded right coronary artery, discussion with the patient further clarified a number of interesting questions. Where in the coronary arteries was the culprit located? What was at this location on the prior diagnostic angiogram? Why was the heart attack not predicted following the diagnostic angiogram just three months before? Why was this heart attack not preventable?

The short answer to these questions is that one of the limits of the current state of the art of interventional cardiology is that there is no current proven clinical strategy to predict and prevent a sequence of events such as that described above. Risk of this sequence of events can be reduced with lifestyle and medication interventions that this patient had been compliant with. No interventional devices have been shown to have favorable
efficacy and safety to prevent events such as these.

Within a few months of these nocturnal ponderings, I was attending the annual Cardiac Society of Australia and New Zealand meeting listening to Professor Harvey White describe the five most novel local research articles published in the preceding year. One of these was by Professor Nicholas Bett and Tsuyoshi Konta[1]. It described a qualitative method for the analysis of coronary artery motion and showed a strong correlation between the compression type of coronary artery motion and the location of stenotic coronary artery disease. Applying this method of coronary artery motion analysis to the research question of identifying the location of subsequent culprit lesions responsible for myocardial infarctions appeared feasible.

Using this qualitative method, I made the original finding (in work performed prior to enrolment for this degree) that this type of coronary artery movement is predictive of the location of the culprit lesion causing subsequent ST segment elevation myocardial infarction with a large odds ratio of 6.10 (p-value 0.005)[2]. This finding was independently reproduced in a much larger study by a group at a cardiology center of excellence elsewhere in Sydney[3].

This finding led to the research question of whether the compression type of coronary artery motion was present more often in patients who had subsequent myocardial infarctions. This question was addressed in this thesis in a case-control study where the coronary artery motion patterns in patients who would subsequently have STEMI were compared with patients without any coronary artery disease detectable by angiography.
No difference was found between the two groups in the frequency of the compression type of motion. Interestingly, the compression type of motion in both groups was more frequent in the proximal and mid portions of the coronary arteries, theoretically matching the previously described asymmetrical distribution of the location of culprits causing myocardial infarctions[4].

The qualitative method used to answer the two research questions described above had the limitations that it was both labor-intensive and open to potential observer bias. A quantitative method had the potential to address these limitations. A novel quantitative index of coronary artery motion derived from CT (computed tomography) coronary angiography that mirrored the compression type of coronary motion was described and shown to correlate with the location of coronary artery disease.

A novel quantitative index of coronary artery motion derived from invasive coronary angiography was described and shown to be predictive of the location of future culprit locations in both STEMI and non-STEMI populations. This novel quantitative method was performed by analysis of individual imaging frames from invasive coronary angiography. These two-dimensional coronary images introduce known measurement errors including the foreshortening[5] and out of plane magnification[6] artifacts that have been well described.

The next step to overcome these limitations was to use three-dimensional coronary reconstructions derived from coronary angiograms. This was performed with the two most widely available commercial software programs and preliminary results of this
research are included in the appendices. A strong sense of wanting to see “under the hood” of three-dimensional reconstruction software led to an ongoing collaboration with Dr Laurence Park and the development of prototype research software that has successfully reconstructed coronary arteries containing culprits for subsequent STEMI.

This body of work makes the following original contributions:

- using a previously described qualitative method to show that the patterns of coronary motion are the same in patients with subsequent STEMI and control patients with angiographically normal coronary arteries
- describing for the first time a quantitative method for coronary artery motion analysis and showing it is predictive of the culprit location for subsequent STEMI and non-STEMI
- describing and using a quantitative method for coronary artery motion applied to three-dimensional reconstructions of coronary arteries from both CT coronary angiography and conventional coronary angiography.

This body of work provided a journey into the unknown that was challenging. Although my conclusion to date is that the methods described remain unsuited to clinical application, I remain excited by the possibility that this work may contribute in some small way to the potential evolution of the management of patients with coronary artery disease.

**Keywords:** Coronary artery movement, Coronary artery disease, culprit lesion, Myocardial infarction, MSCT, Quantitative modeling
THESIS STRUCTURE

The work presented in this thesis includes an introduction, a series of four papers (three of which are published in peer-reviewed journals and one has been submitted to a peer-reviewed journal for publication), and appendices containing one previously published (prior to enrolment in this degree) and two unpublished draft manuscripts.

The three published papers are:


The paper submitted for publication is:

IV. Aiden O’Loughlin, Aaisha Ferkh, John K French, David AB Richards, A Robert Denniss, Annemarie Hennessy. Quantitative Coronary Artery Motion Analysis Predicts the Location of Future non ST Segment Elevation Myocardial Infarctions. Submitted to Physiological Measurement

The published research (performed prior to enrolment for this degree) showing that qualitative coronary artery movement analysis is predictive of the culprit location of subsequent ST segment elevation myocardial infarction is included in Appendix 1:


Further unpublished work undertaken as part of this thesis is included in Appendices 2 and 3:

Aiden O’Loughlin, Angelia Tjokrowidjaja, John K French, David AB Richards, A Robert Denniss, Annemarie Hennessy. A Novel Quantitative Index of Coronary Artery Motion from Four-Dimensional Coronary Angiography and the Location of Stenotic Coronary Artery Disease.

Aiden O’Loughlin, Aaisha Ferkh, John K French, David AB Richards, A Robert Denniss, Annemarie Hennessy. The Relationship between Coronary Artery Motion and Lesion Location in ST segment Elevation Myocardial Infarction-Analysis Using 4-dimensional Quantitative Coronary Artery Motion Measurement.
Authorship Attributions

Paper I: The compression type of coronary artery motion in patients with ST-segment elevation myocardial infarction and normal controls: a case-control study
-author attributions are listed in the published manuscript.

Paper II: A Novel Quantitative Index of Coronary Artery Motion from Multislice Computed Tomography and the Locations of Coronary Artery Disease
-The study was conceived by AO and DM. AO undertook the ethics application. Data collection was performed by LT and WT. Data analysis and manuscript preparation was performed by AO. AH, JF, DR and RD supervised AO and performed manuscript revision. All authors approved the final manuscript.

Paper III: Quantitative Coronary Artery Motion Analysis Predicts the Location of Future ST Segment Elevation Myocardial Infarctions.
-The study was conceived by AO. AO undertook the ethics application. Data collection was performed by AO and SK. Data analysis and manuscript preparation was performed by AO. AH, JF, DR and RD supervised AO and performed manuscript revision. All authors approved the final manuscript.

Paper IV: Quantitative Coronary Artery Motion Analysis Predicts the Location of Future Non-ST Segment Elevation Myocardial Infarctions
-The study was conceived by AO. AO undertook the ethics application. Data collection was performed by AO and AF. Data analysis and manuscript preparation was performed
by AO and AF. AH, JF, DR and RD supervised AO and performed manuscript revision.

All authors approved the final manuscript.
Acknowledgments

The work for this thesis would not have been possible without the support of my principal supervisor Professor Annemarie Hennessy. I would also like to acknowledge the other members of my supervisory panel: Professor A. Robert Denniss, Professor John French, and Associate Professor David Richards.

I would like to acknowledge students who I have the privilege of involving in data collection for a number of the research projects included in this thesis. Summer scholarship students Linda Tang for collecting data for Paper II, Samia Kazi who collected data for Paper III, and Angelia Tjokrowidjaja who collected data for the draft manuscript in Appendix 2, embedded honors student Aaisha Ferkh for data collection for Paper IV and Appendix 3.

I would like to acknowledge collaborators from the Australian National University (Professor Richard Hartley and his honors student Zaiga Thomann) and from the Department of Mathematics and Computer Science at the University of Western Sydney (Dr Laurence Park and Tanzila Chowdhury) for their efforts in developing prototype three-dimensional reconstruction software.

Lastly, but not least, I will like to acknowledge my wife, Ashleigh, for her support.
### Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>ACUITY</td>
<td>Acute Catheterization and Urgent Intervention Triage Strategy</td>
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<td>CAAS</td>
<td>Cardiovascular Angiography Analysis System</td>
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<td>CAM</td>
<td>Coronary artery motion</td>
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<td>CHA</td>
<td>Chicago Heart Association Detection Project in Industry</td>
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<td>CHD</td>
<td>Coronary heart disease</td>
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<td>CT</td>
<td>Computed tomography</td>
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<td>FA</td>
<td>Fibroatheroma</td>
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<tr>
<td>FIFA</td>
<td>Federation Internationale de Football</td>
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<td>HR</td>
<td>Hazard ratio</td>
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<tr>
<td>IVUS</td>
<td>Intravascular Ultrasound</td>
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<td>MACE</td>
<td>Major Adverse Cardiac Events</td>
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<td>MI</td>
<td>Myocardial Infarction</td>
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<td>MLA</td>
<td>Minimum lumen area</td>
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<td>MRFIT</td>
<td>Multiple Risk Factor Intervention Trial</td>
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<td>MSCT</td>
<td>Multislice computed tomography</td>
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<td>MULTISTRATEGY</td>
<td>Multicenter Evaluation of Single High-Dose Bolus Tirofiban Versus Abciximab With Sirolimus-Eluting Stent or Bare-Metal Stent in Acute Myocardial Infarction Study</td>
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<tr>
<td>NCEP</td>
<td>National Cholesterol Education Program</td>
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<tr>
<td>Non-STEMI</td>
<td>Non-ST segment elevation myocardial infarctions</td>
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<tr>
<td>PCI</td>
<td>Percutaneous Coronary Intervention</td>
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<td>PIT</td>
<td>Pathological Intimal Thickening</td>
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<tr>
<td>PROSPECT</td>
<td>Providing Regional Observations to Study Predictors of Events in the Coronary Tree</td>
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<td>QCA</td>
<td>Quantitative Coronary Angiography</td>
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<tr>
<td>QCAM</td>
<td>Quantitative measure of the compression type of coronary artery motion</td>
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<tr>
<td>QCAM4D</td>
<td>Quantitative measure of the compression type of coronary artery motion derived from four-dimensional coronary angiography</td>
</tr>
<tr>
<td>QRISK</td>
<td>Cardiovascular disease risk score for the United Kingdom</td>
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<tr>
<td>RESOLUTE</td>
<td>Randomised Comparison of a Zotarolimus-Eluting Stent with an Everolimus-Eluting Stent for PCI</td>
</tr>
<tr>
<td>SCORE</td>
<td>Systemic COronary Risk Evaluation</td>
</tr>
<tr>
<td>STEMI</td>
<td>ST segment elevation myocardial infarctions</td>
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<tr>
<td>STRATEGY</td>
<td>Single High-Dose Bolus Tirofiban and Sirolimus-Eluting Stent Versus Abciximab and Bare-Metal Stent in Acute Myocardial Infarction</td>
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<tr>
<td>SYNTAX</td>
<td>Synergy between PCI with Taxus and Cardiac Surgery</td>
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<td>SXscore</td>
<td>SYNTAX score</td>
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<tr>
<td>TCFA</td>
<td>Thin-cap fibroatheroma</td>
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<tr>
<td>ThCFA</td>
<td>Thick-cap fibroatheroma</td>
</tr>
<tr>
<td>TLR</td>
<td>Target lesion revascularization</td>
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<tr>
<td>US</td>
<td>United States</td>
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# Introduction

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1. Clinical Background

Reducing the mortality and morbidity due to new and recurrent events from coronary artery disease is one of the largest and most important clinical needs in medicine. Coronary artery disease is the leading cause of death worldwide. It is the cause of death for 3.8 million men and 3.4 million women each year[7]. Of all patients who die within 28 days of the onset of symptoms, two-thirds die before reaching hospital[7, 8].

Death and disability due to coronary artery disease has been described in the medical literature for several centuries[9]. The PROSPECT (Providing Regional Observations to Study Predictors of Events in the Coronary Tree) trial[10] studied the contemporary natural history of patients following their presentation with acute coronary syndromes. The 3-year cumulative rate of recurrent major adverse cardiovascular events was 20%.

In Australia, coronary heart disease death rates have been falling for several decades. From 1968 to 2006, the age-standardized death rate for coronary heart disease fell 76% (from 428.3 to 101.8 deaths per 100,000). Despite this dramatic reduction, coronary heart disease caused 17.1% of Australian deaths in 2006[11].

A similar reduction in coronary disease deaths has been seen in the United States. Between 1980 and 2000, the age-adjusted death rate for coronary heart disease fell from 542.9 to 266.8 deaths per 100,000 population among men and from 263.3 to 134.4 deaths per 100,000 population among women. The 47% decrease in the death rate was attributed to treatments, including secondary preventive therapies after myocardial infarction or revascularization (11%), initial treatments for acute myocardial infarction or unstable angina (10%), treatments for heart failure (9%), revascularization for chronic angina (5%), and other therapies (12%). Approximately 44% was attributed to changes in risk
factors, including reductions in total cholesterol (24%), systolic blood pressure (20%), smoking prevalence (12%), and physical inactivity (5%), although these reductions were partially offset by increases in the body-mass index and the prevalence of diabetes, which accounted for an increased number of deaths (8% and 10%, respectively)[12].

The attribution of these dramatic improvements in death rates to reduction of risk factors, and treatment of clinical events and their sequelae show the benefits that can be gained from innovations in our understanding and treatment of coronary artery disease.

1.1 Pathophysiology

Most coronary artery disease is due to atherosclerosis. Atherosclerotic lesions are asymmetrical focal thickenings of the intima[13]. The first visible lesions are fatty streaks, an accumulation of lipid-laden cells below the endothelium[14]. Fatty streaks can progress to atheromas, which are comprised of a center of foam cells and extracellular lipid droplets surrounded by a cap of smooth-muscle cells and collagen-rich matrix. Some lesions consist mainly of fibrous connective tissue, whilst others are mainly calcified[15]. Complicated lesions have a luminal surface defect which provides a nidus for the formation of thrombus[16].

Atherosclerosis develops as a response to endothelial injury. This model was first put forward by Virchow in 1856 and was revised by Ross and Glomset[17-19]. The shear stress of coronary blood flow has been proposed as the cause of endothelial injury[20]. Abnormal shear stress has been proposed as the explanation for the asymmetrical distribution of culprit lesions in patients with acute myocardial infarctions, occurring
most commonly in the proximal and mid segments of all three coronary arteries (the left anterior descending, left circumflex and the right coronary arteries). These locations have been termed spatial high risk segments[4, 21]. Local biomechanical injury due to coronary artery motion represents a possible alternative cause of injury. The absence of atherosclerosis from relatively immobile arteries such as the internal mammary arteries may reflect an absence of biomechanical injury[22].

In an examination of 400 cases of sudden coronary death published over a 15 year period[23], the frequency of coronary thrombus was 60%. The underlying etiology in 55 to 60% was plaque rupture, 30 to 35% plaque erosion and 2 to 7% calcified nodule. In the 40% of sudden coronary death patients where no acute thrombi were identified, healed infarctions and total occlusions are seen in the vast majority[23] and it is assumed that they die from arrhythmias[24]. To put this into context, in a study of the cause of sudden cardiac death over the age of 35 using national US mortality data from 1989 to 1998 [25], ischemic heart disease was the underlying cause in 62.2%, unspecified cardiovascular disease in 12.1% and cardiomyopathy/dysrhythmia in 9.3%. In turn, sudden cardiac death accounted for 63.9% of all cardiac deaths. Sudden cardiac death rates increase exponentially with age, rising from 34.1 per 100,000 men and 11.5 per 100,000 women aged 35 to 44 to 4073.3 per 100,000 men and 4171.8 per 100,000 women aged 85 years or over. Sudden cardiac death is the leading cause of death due to cardiovascular disease in the US, resulting in more than 300,000 deaths per year[26].

The physiological changes associated with unusual psychological stress, hypertension and a rise in catecholamine levels have been shown to be triggers for myocardial
In a study of US firefighters[29], as compared to the odds of death during nonemergency duties, the odds of death from coronary heart disease were 12.1 to 136 times as high during fire suppression, 2.8 to 14.1 times as high during alarm response, 2.2 to 10.5 times as high during alarm return, and 2.9 to 6.6 times as high during physical training. During the 2006 Federation Internationale de Football (FIFA) world cup in Germany, the incidence of cardiac emergencies in the greater Munich area on days of matches involving the German team was 2.66 times that during the control period (p<0.001)[30]. This was due to an increase in STEMI of 2.49 (95% CI, 1.47-4.23), non-STEMI of 2.61 (95% CI, 2.22-3.08), and cardiac arrhythmia of 3.07 (95% CI, 2.32-4.06). The earthquake that struck Los Angeles on January 17, 1994 at 4:31 a.m. was associated with an increase in sudden cardiac death related to atherosclerotic cardiovascular disease from a daily average of 4.6(+-2.1) in the preceding week to 24 on the day of the earthquake (p<0.001). Of the 24 deaths, 16 either died or had premonitory symptoms within the first hour after the initial tremor. Interestingly, during the six days after the earthquake, the number of sudden deaths declined to below the base-line value, to an average of 2.7(+-1.2) per day[26].

The chronobiology of sudden cardiac death has been described in a number of studies[31-33]. The data show a circadian variation in the rate of sudden cardiac death, with a low incidence in the night and a peak incidence from 7 to 9 a.m. Risk of sudden cardiac death was at least 70% higher during the peak period than was the average risk during the other times of the day[33]. Perhaps not surprisingly, there is a very similar pattern in the circadian variation of nonfatal myocardial infarction and episodes of myocardial ischemia[32, 34].
Pathophysiologica processes hypothesized to explain these observations include platelet activation[32], a prothrombotic state[32, 34], elevations in heart rate and blood pressure, reduced electrical stability, and endothelial dysfunction—that, in the presence of a vulnerable atherosclerotic plaque, cause plaque disruption and thrombosis[35].

In animal studies, administration of vasopressors significantly increase coronary artery motion parameters such as distance moved, maximum velocity, acceleration and deceleration[36]. Whether the biomechanical stress of increased coronary artery motion triggers plaque rupture causing myocardial infarction remains an interesting but untested hypothesis.

It is interesting to speculate on the mechanism by which coronary artery motion might contribute to the development and rupture of atherosclerotic plaques. The arterial wall has three layers. There may be differential compliance of the three layers to the mechanical stress of the stretch-compression type of coronary motion that may cause injury in those sections. In susceptible patients, the response to injury may lead to the development of atherosclerosis. This type of coronary artery motion might also lead to intimal tears and erosions at the time of plaque rupture and plaque erosion events. Intimal tears and erosions play a key role in the pathophysiological cascade leading to clinical coronary events. The amplitude of coronary artery motion may be increased in situations such as episodes of anger which have been shown to increase the risk of heart attack by over eight times in the subsequent two hours.[37]. Higher amplitude coronary artery motion may be a key mechanism for plaque rupture and erosion. Cardiac position and
rotation due to the respiratory cycle could also be speculated to play a role in these mechanisms.

From a clinical perspective, better understanding of the pathophysiology of triggering of these events may provide means of prevention, particularly given the recent proof-of-concept of the feasibility of provision of ad hoc therapy (in the form of aspirin or propranolol) at times of increased risk of triggering[38].

2. Predicting clinical coronary artery events in individuals

Assessing individual patient risk of coronary artery disease events identifies the following patient groups as very high risk: established cardiovascular disease, diabetes mellitus[39], smoking, family history of premature coronary disease, hypertension, chronic kidney disease, and dyslipidemias.

Some persons without established coronary heart disease (CHD) will have an absolute, 10-year risk for developing major coronary events (myocardial infarction and coronary death) equal to that of persons with CHD, i.e. >20 percent. They can be said to have a CHD risk equivalent. The Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III)[40] identified three such groups: patients with clinical atherosclerotic disease at other sites, patients with diabetes mellitus, and asymptomatic patients with multiple other risk factors who have an absolute, 10-year risk as high as that of persons with established CHD.
At the other end of the risk spectrum, patients without major risk factors for coronary artery disease have significantly lower relative risks of coronary heart disease mortality than those with risk factors (see Table 1).

Table 1. Mortality from Coronary Heart Disease and All Cardiovascular Diseases for Low-Risk Subcohorts and Others (Reproduced from Stamler et al.[41])

This translated into significantly greater life expectancy[41]. However, less than 10% of the cohorts enrolled in the Multiple Risk Factor Intervention (MRFIT)[42] and Chicago Heart Association Detection Project in Industry (CHA)[43] trials were in this low risk category.
Multivariate risk profiling has been used extensively for estimated coronary artery disease and cardiovascular disease in asymptomatic individuals. A number of tools have been developed, including the Framingham risk scores[40, 44, 45], the SCORE (Systemic CORonary Risk Evaluation)[46], the QRISK2[47] and the Reynolds risk score[48]. These tools allow estimation of predictive risk of coronary and/or cardiovascular events on the basis of baseline risk factors.

2.1 Intravascular Ultrasound and Angiography

The largest contemporary trial to assess currently available technologies in the catheterization laboratory for the prediction of the location of future coronary events is the PROSPECT trial[10]. The PROSPECT trial was a multicenter trial conducted at 37 sites in the United States and Europe. Six hundred and ninety seven patients with acute coronary syndromes were enrolled after successful percutaneous coronary intervention for their culprit lesion. Coronary angiography and gray-scale and radiofrequency intravascular ultrasound of the left main coronary artery and the proximal 6 to 8 centimeters of each of the major epicardial coronary arteries were performed.

Radiofrequency intravascular ultrasonography provides information about tissue composition that has been correlated with data from histological samples. 11 patients had complications during image acquisition. There were 10 dissections and 1 perforation resulting in 3 nonfatal myocardial infarctions.

During a median follow-up of 3.4 years, there were 149 major adverse cardiovascular events in 135 patients (See Table 2)[10]. This represents an event rate of over 20%,
almost equally divided between events related to culprit lesions (118 lesions in 83 patients) and events related to non-culprit lesions (104 lesions in 74 patients). Culprit lesion events were due to stent thrombosis (13), restenosis (107) and new stent-related side-branch lesions (5).

<table>
<thead>
<tr>
<th>Event</th>
<th>Events Related to Culprit Lesions</th>
<th>Events Related to Nonculprit Lesions</th>
<th>Indeterminate Events</th>
<th>All Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite cardiac events†</td>
<td>12.9 (83)‡</td>
<td>11.6 (74)</td>
<td>2.7 (17)</td>
<td>20.4 (13)</td>
</tr>
<tr>
<td>Death from cardiac causes, cardiac arrest, or myocardial infarction</td>
<td>2.2 (14)</td>
<td>1.0 (6)</td>
<td>1.9 (12)</td>
<td>4.9 (31)</td>
</tr>
<tr>
<td>Death from cardiac causes</td>
<td>0.2 (1)</td>
<td>0</td>
<td>1.8 (11)</td>
<td>1.9 (12)</td>
</tr>
<tr>
<td>Cardiac arrest</td>
<td>0.3 (2)</td>
<td>0</td>
<td>0.2 (1)</td>
<td>0.5 (3)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>2.0 (13)</td>
<td>1.0 (6)†</td>
<td>0.3 (2)</td>
<td>3.3 (21)</td>
</tr>
<tr>
<td>Rehospitalization for unstable or progressive angina</td>
<td>11.5 (74)</td>
<td>10.8 (69)</td>
<td>0.8 (5)</td>
<td>17.5 (113)</td>
</tr>
<tr>
<td>Other events</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Revascularization</td>
<td>10.9 (70)</td>
<td>10.5 (67)</td>
<td>0</td>
<td>17.1 (110)</td>
</tr>
<tr>
<td>Stent thrombosis‡</td>
<td>2.0 (13)</td>
<td>0</td>
<td>1.3 (8)</td>
<td>3.3 (21)</td>
</tr>
</tbody>
</table>

* Rates shown are Kaplan–Meier estimates at 3 years. Events occurred in 3 patients after the 3-year data presented here had been collected.
† Composite cardiac events were death from cardiac causes, cardiac arrest, myocardial infarction, or rehospitalization for unstable or progressive angina.
‡ Events related to culprit lesions were due to stent thrombosis (in 13 patients), restenosis (in 107 patients), and new stent-related side-branch lesions (in 5 patients).
§ All six myocardial infarctions were spontaneous infarctions; none were related to revascularization procedures.
¶ This category includes definite and probable stent thrombosis according to the Academic Research Consortium criteria.

Table 2. Kaplan–Meier Estimates for Cumulative Rates of Major Adverse Cardiovascular Events at 3 Years (reproduced from Stone et al.[10])

Angiographic data was not predictive of the location of non-culprit events. The mean angiographic diameter stenosis of the 106 non-culprit lesions was 32.3+/−20.6% at baseline. Thirty percent of lesions had a less than 30% stenosis, 37% had a 30-50% stenosis, 28% had a 50 to 70% stenosis and 5% had a greater than 70% stenosis. The most powerful baseline patient level independent predictors of non-culprit lesion events were insulin-requiring diabetes (HR (hazard ratio) 3.32, p=0.005), and previous percutaneous coronary intervention (HR 2.03, p=0.02).
A lesion on intravascular ultrasound (IVUS) was defined as at least three consecutive frames with a plaque burden of at least 40%[10]. No events arose from untreated segments with a plaque burden resulting in less than 40% loss of cross-sectional luminal area.

Grayscale IVUS measurements were performed in 55 of the 106 non-culprit lesions. The minimum lumen area (MLA) was <5.9mm$^2$ in 48 (87%) of the lesions and <=4.0mm$^2$ in 30 (55%) of the lesions. 48 (87%) of the lesions had a plaque burden of >=56%. Twenty five (45%) of the lesions had a plaque burden of >=70%. Forty five (82%) of the lesions had a length of >=11.2mm.

Radiofrequency IVUS measurements were performed in 51 of the 106 non-culprit lesions. The dense calcium area was >=0.2mm$^2$ in 34 (67%) of the lesions. The necrotic core area was >= 0.4mm$^2$ in 34 (67%) of the lesions. The fibrous tissue area was <75% in 33 (65%) of the lesions. The fibrofatty area was <22% in 33 (67%) of the lesions. Lesions were classified (see Figure 1) as thin-cap fibroatheroma, thick-cap fibroatheroma, fibrotic, fibrocalcific and pathologic intimal thickening. In lesions with multiple patterns, the most severe pattern (in the order of the classification given above) was selected. Twenty six (51%) of the 51 lesions were thin-cap fibroatheromas. Eighteen (33%) of the lesions were thick-cap fibroatheromas. Six (12%) of the lesions were pathological intimal thickening and 1 was a fibrocalcific plaque. There were no lesions classified as fibrotic plaques.
1. Fibrotic plaque
2. Fibrocalcific plaque
3. Pathological intimal thickening (PIT)
4. Thick-cap fibroatheroma (ThCFA)
5. Thin-cap fibroatheroma (TCFA)

Figure 1. Lesion classification according to radiofrequency IVUS (reproduced from Stone et al.[10])

Fibroatheromas (FA) were defined by the presence of >10% confluent necrotic core (NC; red color). If more than 30 degrees of the NC abutted the lumen in 3 or more consecutive frames, the fibroatheroma was classified as a thin-cap fibroatheroma (TCFA); otherwise it was categorized as a thick-cap fibroatheroma (ThCFA). Fibrotic plaque was defined as consisting mainly of fibrous tissue (FT; dark green color) with <10% confluent NC, <10% confluent dense calcium (DC; white color), and <15% of fibrofatty (FF; light green color). Fibrocalcific plaque was defined as mainly FT with >10% of confluent DC, with <10% of confluent NC. Pathological intimal thickening (PIT) was defined as ≥15% FF, with <10% confluent NC and <10% confluent DC. In addition, fibroatheromas were sub-classified as having single or multiple confluent NCs and containing or not containing
DC. The entire lesion was evaluated for lesion level radiofrequency-IVUS classification. Multiple lesion subtypes were considered as separate lesions if they were separated by $\geq 3$ consecutive image slices of different morphology; for example, multiple TCFAs were considered separate if they were separated by $\geq 3$ consecutive non-TCFA containing image slices.

The most powerful baseline lesion level predictors of non-culprit lesion events were the following three variables: a plaque burden of 70% or more (HR 5.03, $p<0.001$), thin-cap fibroatheroma (HR 3.35, $p<0.001$), and MLA of 4.0mm$^2$ or less (HR 3.21, $p=0.001$). Events occurred from lesions that included 0, 1, 2, or all 3 of these variables in 0.3%, 4.8%, 10.5% and 18.2% of lesions, respectively (see Figure 2).
Figure 2. Event Rates for Lesions That Were and Those That Were Not Thin-Cap Fibroatheromas, at a Median Follow-up of 3.4 Years. Event rates associated with 595 nonculprit lesions that were characterized as thin-cap fibroatheromas (TCFA) and 2114 that were not by means of radiofrequency intravascular ultrasonographic imaging are shown according to minimal luminal area (MLA) and plaque burden (PB) as detected on gray-scale intravascular ultrasonography. The inset shows an example of a thin-cap fibroatheroma imaged as radiofrequency ultrasonography. Data on prevalence are for one or more such lesions per patient. Lesions in patients with indeterminate events were excluded (reproduced from Stone et al.[10]).

Two thousand seven hundred and nine lesions overall were given a lesion classification based on radiofrequency IVUS. Five hundred and ninety five were classified as thin-cap fibroatheromas.
The authors of the PROSPECT trial concluded that the methods that they used for the detection of vulnerable plaque are not currently suitable for clinical application. All of the measures used had low specificity. As shown in figure 2, the event rate was only 18.2% when the three most predictive IVUS measures were combined. The C-statistic for 3 multivariate models using these three measures was in the range from 0.82-0.84. The IVUS catheters used cannot be used to evaluate the distal portions of the coronary arteries. Thus, only 51 of the 106 non-culprit lesions were seen on radiofrequency intravascular ultrasonography. There were adverse events during IVUS imaging.

The dynamic nature of coronary artery lesion morphology needs to be considered when interpreting the results of the PROSPECT trial. In a study[49] utilizing the same radiofrequency IVUS measurements as had been used in the PROSPECT trial, 99 patients underwent serial radiofrequency IVUS evaluation at a median of 12 months. The changes in lesion characteristics are shown in Figure 3.
Figure 3. Changes in Plaque Characteristics Assessed by VH-IVUS Between Baseline and Follow-Up (reproduced from Kubo et al.[49])

At baseline, 20 thin-cap fibroatheromas were identified. On repeat study, 15 (75%) had healed and evolved into a different lesion type. 13 became thick-cap fibroatheromas, and 2 became fibrotic. 12 new thin-cap fibroatheromas developed. At baseline, 6 were pathological intimal thickening and 6 were thick-cap fibroatheroma.

The Synergy between PCI (Percutaneous Coronary Intervention) with Taxus and Cardiac Surgery (SYNTAX) score (SXscore) is an angiographic grading tool used to determine pre-PCI complexity of coronary artery disease[50]. The SXscore was calculated
prospectively in 2033 of the 2,292 patients enrolled in the RESOLUTE All Comers study (RESOLUTE III All Comers Trial: A Randomized Comparison of a Zotarolimus-Eluting Stent With an Everolimus-Eluting Stent for Percutaneous Coronary Intervention). At 12 months, rates of myocardial infarction were significantly higher in patients with the highest SXscore tertile[51]. The SXscore was calculated retrospectively in 807 patients enrolled in the randomized STRATEGY (Single High-Dose Bolus Tirofiban and Sirolimus-Eluting Stent Versus Abciximab and Bare-Metal Stent in Acute Myocardial Infarction) and MULTISTRATEGY (Multicenter Evaluation of Single High-Dose Bolus Tirofiban Versus Abciximab With Sirolimus-Eluting Stent or Bare-Metal Stent in Acute Myocardial Infarction Study) clinical trials. At 12 months, re-infarction was significantly higher in patients with the highest SXscore tertile[52]. Similar results were found in 2,627 patients undergoing percutaneous coronary intervention in the ACUITY (Acute Catheterization and Urgent Intervention Triage Strategy) trial[53].

2.2 Stenosis

The summary of the results of six studies that evaluated the relationship between angiographic lesion stenosis severity and subsequent myocardial infarction[54-59] have previously been published[59]. This summary is shown in Table 3:
Table 3. Previous Angiographic Stenosis Studies

The most commonly proposed explanation for the finding that most myocardial infarctions occur at locations where there was previously non-obstructive coronary artery disease is that myocardial infarctions occur most commonly after plaque rupture events, and the clinical sequelae reflects thin-capped fibroatheroma, rupture area, lipid content, and platelet and clotting mechanism which result in vessel occlusion irrespective of preceding degree of stenosis.
2.3 Restenosis

Restenosis following percutaneous coronary intervention occurs due to neointimal tissue proliferation. A cascade mechanism involving platelets, polymorphonuclear leukocytes, and macrophage aggregation lead to medial smooth muscle cell migration and proliferation[60] with the development of neointima. Histopathological examples following balloon angioplasty are shown in Figure 4[61].

![Figure 4. Histopathology of Restenosis. (l=lumen, m=media, ni=neointima; arrowheads show medial rupture zone)](image)

In a histological study of 55 stents from 32 patients[62], increased numbers of inflammatory cells were seen with stent struts in contact with damaged media (medial laceration or rupture) or lipid core (see Figure 5).
Figure 5. Inflammatory cell infiltrates associated with stent struts were assessed in coronary arteries containing stents of three or less days’ duration. There were increased numbers of inflammatory cells associated with struts in contact with lipid core and damaged media compared with fibrous plaque (P<0.001).

Late neointimal growth was significantly greater (p<0.001) for stent struts in contact with damaged media than with plaque or intact media (see Figure 6).
Figure 6. In stents implanted for more than 30 days, neointimal thickness was increased at stent strut sites when medial laceration or rupture was present compared with struts in contact with plaque or with an intact media.

A number of risk factors have been identified for stent restenosis. In a combined analysis of six bare metal stent trials[8], smaller pre-treatment minimum lumen diameter (MLD) and reference diameter, smaller final MLD, longer lesion length and stent length, diabetes mellitus, unstable angina, and hypertension were independent predictors of target lesion revascularisation (TLR) (see Table 4). TLR was defined as any repeat percutaneous revascularization or surgical bypass of the original target lesion site that occurred 30 or more days after the index procedure and was driven by clinical findings (presence of ischemic symptoms and/or a positive functional ischemia study), in the presence of a diameter stenosis greater than 50% as determined by the angiographic core laboratory.
Table 4. Independent Correlates of Target Lesion Revascularization

<table>
<thead>
<tr>
<th>Variables</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Final MLD (per mm)*</td>
<td>0.39</td>
<td>0.29–0.51</td>
</tr>
<tr>
<td>Reference diameter (per mm)*</td>
<td>0.48</td>
<td>0.40–0.59</td>
</tr>
<tr>
<td>Stent length (per 5 mm, per lesion)*</td>
<td>1.06</td>
<td>1.03–1.10</td>
</tr>
<tr>
<td>Lesion length (per 5 mm)*</td>
<td>1.11</td>
<td>1.04–1.17</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.49</td>
<td>1.16–1.92</td>
</tr>
<tr>
<td>Pretreatment MLD</td>
<td>0.66</td>
<td>0.49–0.88</td>
</tr>
<tr>
<td>Cigarette smoking (in past yr)</td>
<td>0.64</td>
<td>0.47–0.88</td>
</tr>
<tr>
<td>History of prior MI</td>
<td>0.70</td>
<td>0.54–0.90</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>1.34</td>
<td>1.06–1.69</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.27</td>
<td>1.01–1.61</td>
</tr>
</tbody>
</table>

Variables listed in descending order of significance. *Colinear variable pairs (reference diameter/final MLD and stent length/lesion length) were tested in separate multivariable models. Other independent variables were not different between the two models.

CI = confidence interval; MI = myocardial infarction; MLD = minimal lumen diameter; OR = odds ratio.

Table 4. Independent Correlates of Target Lesion Revascularization

Other risk factors that have been identified include ostial location of stenosis[63], in-stent restenosis[63], stent strut thickness with similar[64] or different[65] stent design, coil stent design[66], biomechanical problems and stent under-deployment[67].

The longitudinal straightening effect of stents has been identified as a powerful predictor of restenosis. In a study of 404 patients[68], vessel angulation of greater than or equal to 33.5 degrees, a change in vessel angulation of greater than or equal to 9.1 degrees, and minimal lumen diameter (MLD) were all powerful independent predictors of major adverse cardiac events (see Table 5), which was comprised predominantly of restenosis.
Table 5. Odds Ratio and 95% Confidence Intervals of Parameters Included in a Multivariate Nominal Regression Analysis for Predicting Major Adverse Cardiac Events

3. Coronary Artery Motion Analysis

Qualitative patterns of coronary artery motion (CAM) (see Figure 7) and a method to classify individual segments has previously been described[1].

Figure 7. Patterns of Coronary Artery Motion (reproduced by Konta et al.[1]).

MLD = minimal lumen diameter; %DS = percent diameter stenosis.
The Compression type of coronary artery motion incorporates the Compression and Ostial Compression patterns and correlates with the degree of stenosis within coronary artery segments[1]. The Compression type of coronary motion has been shown to be a powerful independent predictor of the location of culprit lesions in patients having future STEMI[2]. This finding was independent of the severity of stenosis and the location being in a spatial high-risk segment. This finding was confirmed in a larger sample with qualitative coronary artery motion analysis performed following fibrinolysis for STEMI[3].

One key weakness of a qualitative method for assessing CAM is observer bias. Spatial high risk segments[4] and the association between stenosis and qualitative patterns of CAM[1] means there may have been a ready visual cue as to the possible location of the future culprit segment. Quantitative measures of CAM (such as that described for CT coronary angiography and illustrated in Figure 8) include change in vessel centerline length during the cardiac cycle may address this limitation.
Figure 8. Vessel reconstructions at two time points in the cardiac cycle. Landmarks for the left anterior descending and left circumflex coronary arteries are shown with matching colors in the reconstructions. Vessel centerline lengths for sections defined by these landmarks are used to calculate a quantitative measure of coronary artery motion.

Other quantitative measures of coronary artery biomechanics previously described include centerline and point trajectory lengths, displacement amplitude, displacement direction, torsion, twist, spectrum and curvature[69-72].
4. CT coronary angiography

Computed tomography (CT) coronary angiography technology has evolved rapidly in recent years and represents an alternative technology to invasive coronary angiography from which to derive measures of coronary artery motion. With the evolution of this CT coronary angiography have come improvements in the diagnostic accuracy for detection of coronary artery stenosis. In a 2008 meta-analysis of published data for 64-slice CT, the average patient-based detection of greater than or equal to 50% stenosis had a sensitivity of 98%, specificity of 88%, positive predictive value of 93% and a negative predictive value of 96%[73]. Similarly favorable diagnostic accuracy has been shown in single and multivendor multicenter trials[74-76]. This evolution has also resulted in the development of algorithms to optimize the image quality whilst minimizing the ionizing radiation dose administered to the patient. This has resulted in a change from predominantly retrospective studies where image data is acquired throughout the entire cardiac cycle to dose-modulated or prospective ‘step-and-shoot’ studies where image data is acquired predominantly from a pre-determined period within the cardiac cycle.

Cardiac motion causes blurring and is the major reason for non-diagnostic coronary artery image quality[77]. Capturing image data during a phase of the cardiac cycle when the heart is relatively immobile minimizes blurring. At relatively low heart rates, the mid-diastolic phase is well suited. At higher heart rates, the end-systolic phase may provide better image quality[78].
Whereas invasive coronary angiography provides imaging of contrast flow through the lumen of coronary arteries, CT coronary angiography also images the vessel wall. This allows measurement of plaque characteristics. In a study of 1,059 patients who underwent 64-slice CT coronary angiography, 15 had subsequent acute coronary syndromes during a follow-up of up to 50 months. Positive remodeling was defined as the diameter at the plaque site being at least 10% larger than the diameter in a more proximal normal-appearing reference segment. Plaque consistency was defined as a low attenuation plaque if the Hounsfield units were less than 30. As show in Figure 9, acute coronary syndromes occurred in 10 of 45 (22.2% of) patients with plaque with both these features, 1 of 27 (3.7%) patients with one of these features, and 4 of 820 (0.5%) of patients with neither of these features[79].

In a retrospective study of 458 patients who presented with low or intermediate risk acute chest pain who underwent first or second-generation dual source CT system, no patient without plaque had a major adverse cardiac event (MACE), such as myocardial infarction, revascularisation, cardiac death, or angina requiring hospitalization at a mean follow-up of 13 months[80]. By contrast, patients with four or more segments containing plaque had a hazard ratio of 151.77 compared to those with no plaque (p<0.001).
Figure 9. Acute Coronary Events in Patients on the Basis of Plaque Characteristics. Of the 45 patients showing 2-feature positive plaques, 10 (22.2%) developed acute coronary syndrome (ACS), whereas 1 of the 27 patients with 1-feature positive plaques had ACS (3.7%). Only 4 (0.5%) of the 820 patients with 2-feature negative lesions had an acute event, and none of the 167 patients with normal arteries developed ACS. LAP = low-attenuation plaque; PR = positive vessel remodeling (reproduced from Motoyama et al.[80]).

A published comparison of the properties of invasive coronary angiography, CT coronary angiography, and intravascular ultrasound typical of those most commonly used in clinical practice in Australia are shown in Table 6[81].
<table>
<thead>
<tr>
<th>Parameter</th>
<th>CCA</th>
<th>IVUS</th>
<th>CCTA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spatial resolution</td>
<td>200 µm</td>
<td>100–150 µm</td>
<td>350 µm</td>
</tr>
<tr>
<td>Temporal resolution</td>
<td>5–10 ms</td>
<td>NA</td>
<td>40–100 ms</td>
</tr>
<tr>
<td>Imaging</td>
<td>Projection/2DLumen</td>
<td>Cross-sectional Wall and lumen</td>
<td>Cross-sectional Wall and lumen</td>
</tr>
<tr>
<td>Parameter</td>
<td>% Diameter stenosis</td>
<td>Minimum luminal area</td>
<td>Minimum luminal area</td>
</tr>
<tr>
<td>Plaque character</td>
<td>Not applicable</td>
<td>Readily available</td>
<td>Readily available</td>
</tr>
<tr>
<td>Imaging area</td>
<td>All segments</td>
<td>Limited segments</td>
<td>All segments</td>
</tr>
<tr>
<td>Acquisition</td>
<td>Invasive</td>
<td>Highly invasive</td>
<td>Noninvasive</td>
</tr>
<tr>
<td>Radiation</td>
<td>5 mSv</td>
<td>&gt;5 mSv (part of PCI)</td>
<td>2–20 mSv</td>
</tr>
</tbody>
</table>

Table 6. Comparison of catheter coronary angiography, intravascular ultrasound, and coronary CT angiography

5. Innovation

Improved prediction of clinical events from coronary artery disease is a compelling clinical need. This introduction highlights the strengths and weaknesses of some key current technologies in meeting this need. The opportunity exists for innovation to improve prediction of events. This has the potential to lead to better utilization of current treatments and to provide inspiration for the development of novel treatments in the future.
6. Précis of the four publications

6.1 Paper I

The compression type of coronary artery motion in patients with ST segment elevation myocardial infarction and normal controls: a case-control study.

This paper makes the original contribution of exploring whether coronary artery motion patterns are different in patients who have subsequent ST segment elevation myocardial infarction and controls with angiographically normal coronary arteries. No statistically significant difference was found for the frequency of CAM types between the two groups. Coronary artery motion reflects the motion of the underlying myocardium and the results of this study were interpreted that the motion of the underlying myocardium is not different between these two populations. This does not, however, lead to the conclusion that coronary artery motion is not useful for predicting the location of the culprit lesion responsible for future events in at risk patients. It does suggest that more than just these patterns of coronary artery motion are required. It also suggests that the specificity of coronary artery motion for the prediction of the location of culprit lesions may be imperfect.

A specific focus in this paper was the Compression type of coronary artery motion. In work I performed and published prior to the period of PhD candidature (and included in Appendix 1), I have shown that this type of motion is a statistically significant independent predictor (odds ratio, 6.10, p-value 0.005) of the location of culprit lesions responsible for ST segment elevation myocardial infarction[2]. This odds ratio was
obtained by using a generalized linear mixed model with grouping by patient. The explanatory variables assessed were the type of CAM (with a binary classification as compression or non-compression types), stenosis, and high-risk segment. High-risk segments were defined as segments 1,2,9,10,17, and 19. These segments were selected to represent the known high-risk locations[4, 82] that make up the asymmetrical distribution of culprit lesions that have previously been shown to be responsible for ST segment elevation myocardial infarction.

Using the qualitative classification of coronary artery motion (shown in both Figure 7 of the Introduction (p.33) and Figure 1 of Paper I) described by Konta and Bett[1], the frequency of the different patterns of coronary artery motion were assessed. Table 2 of Paper I shows the results of this analysis. Given the results of the study described in the last paragraph, the hypothesis being tested was whether there was a higher frequency of the compression type of coronary artery motion in patients having subsequent ST segment elevation myocardial infarction than in patients with angiographically normal coronary arteries. The compression type of coronary artery motion was present in 32.9% of segments of patients having STEMI and in 33.1% of segments of control patients. The proportion of the compression type of CAM for individual artery segments for both patient groups is shown in Figure 3 of Paper I. A Chi-squared test did not show a difference between the patient groups for the individual coronary artery segments (p=0.59).

In an exploratory analysis included in Paper I, the distribution in coronary segments of the compression type of CAM was compared to the location of the culprit lesion
responsible for STEMI in 280 patients in a previously published report[4]. The results of this analysis are shown in Figure 4 of Paper I. The percent compression type of CAM and the percent of culprit lesions per centimeter of artery were highest for the proximal and mid parts of the right coronary artery (segments 1 and 2) and the proximal and mid parts of the left anterior descending coronary artery (segments 9 and 10).

Paper I reported research showing no difference in the proportion of the compression type of coronary artery motion between the patients having STEMI and normal controls. A possible explanation for these findings is that systemic factors determine whether a patient develops coronary atherosclerosis and local biomechanical and/or haemodynamic shear stress determines its location within the coronary arteries. This explanation is in keeping with the response to injury hypothesis of Ross[18].

The qualitative methodology used in Paper I relied on a visual assessment of coronary artery motion from angiographic data. The previously well described high-risk segments and the presence of coronary plaque and stenosis provided ready visual clues to the researcher making the visual assessment. This limitation led to the research question of whether a quantitative method could be used to describe and explore the relationship between current and future coronary artery disease and clinical events. A novel contribution of this thesis is the description and use of a quantitative method for the evaluation of coronary artery motion as described in Paper II with CT coronary angiography data and in Papers III and IV with invasive coronary angiograms.
6.2 Paper II

A novel quantitative index of coronary artery motion from multislice computed tomography and the location of coronary artery disease.

Paper II reports the original contribution of a quantitative measure of compression type of coronary artery motion (QCAM) using CT coronary angiograms. This paper reports the finding that QCAM correlates with the location of coronary artery disease and stenosis. Coronary arteries were divided into sections using landmarks that could be identified at two time-points in the cardiac cycle representative of both end-diastole and end-systole (illustrated in both Figure 8 of the Introduction (p.34) and Figure 1 of Paper II). The quantitative index of coronary artery motion QCAM was defined as the percent shortening of centerline lengths between the time points (QCAM=100x(centerline length for section X at end-systole)/(centerline length for section X at end-diastole)%).

QCAM was described for the first time in this paper and was found to be significantly less in coronary sections with plaque (94.3%+/-8.1%) than those without (99.0%+/-10.2%) (p=0.023). There was a significant correlation between QCAM and plaque stenosis (Spearman’s rank correlation coefficient, \( \rho = -0.192 \), p=0.018). The correlation between QCAM and plaque type was not statistically significant (Spearman’s rank correlation coefficient, \( \rho = -0.156 \), p=0.057), but may be of clinical significance.

This research was performed using CT coronary angiography studies that had been performed using a retrospectively gated protocol with acquisition of coronary images throughout the entire cardiac cycle. This type of acquisition protocol has become less frequently used with the evolution of coronary CT technology. Prospectively gated protocols are now much more commonly used. This often does not involve the
acquisition of data in the end-systolic phase of the cardiac cycle, precluding calculation of QCAM. Collection of CT data superfluous to that required for coronary image reconstruction causes an increased radiation dose to be administered. Therefore, it would currently not be ethical to undertake this approach for purely research purposes.

CT coronary angiography and invasive coronary angiography are fundamentally different imaging modalities with specific strengths and weaknesses that greatly influence any comparison of respective coronary assessment. CT coronary angiography scan conditions are more important for the resolution of the images obtained. Higher heart rates (>65 beats/min) and larger patients (body mass index >40) frequently lead to decreased image quality[83]. In phantom studies under ideal conditions, CT has the potential to quantify coronary stenoses at least as accurately as fluoroscopic angiography—with an advantage for lesions with noncircular geometry. This is not necessarily transferrable to the clinical setting due to reduced image resolution related to scan conditions[84]. Problems encountered clinically include more rapid heart rates, atrial fibrillation, and patient and coronary artery motion artifacts. Probably the greatest limitation for CT currently is its difficulty in visualizing the arterial lumen in the presence of severe coronary calcification due to the ‘blooming’ artifact. Analysis of the CorE-64 study showed that increasing coronary arterial segment calcification was associated with reduced diagnostic accuracy for detection of fifty percent or greater luminal stenoses[85].

An understanding of these potential limitations led to the concomitant development of a novel quantitative method using invasive coronary angiograms that is described in Papers III and IV.
6.3 Papers III (published) and IV (submitted for publication)

Quantitative coronary artery motion predicts the location of future ST segment elevation myocardial infarctions.

and

Quantitative coronary artery motion predicts the location of future non-ST segment elevation myocardial infarctions (submitted for publication).

Paper III provides the original contribution of a quantitative measure of the compression type of coronary artery motion obtained from analysis of invasive coronary angiograms and shows that it can predict the location of culprit lesions in patients who have subsequent ST segment elevation myocardial infarction. Coronary angiography frames were selected at end-diastole and end-systole in two views for each culprit artery for each patient. The coronary arteries were divided into sections and the ratio of the section lengths from end-systole to end-diastole was used to calculated QCAM. This method is illustrated in Figure 1 of Paper III.

In Paper III, QCAM was shown to be a statistically significant predictor of the location of culprit lesions responsible for future STEMI (p=0.0004 with t-test and p=0.026 with a generalized linear mixed model). This finding is reflected in the lower mean QCAM value for culprit sections (93.43) compared to non-culprit sections (103.51).

Figure 2 of Paper III shows QCAM for each section for each of the two views for each patient. The data is consistent with the main finding of this paper. However, it shows a
large overlap between QCAM for culprit sections and a subgroup of the non-culprit sections.

Paper IV (submitted for publication) makes the original contribution of extending the methodology of Paper III to a sample of invasive coronary angiograms of patients who have future non-STEMI. A statistically significant result was again shown for the relationship between QCAM and culprit sections, although the magnitude of the difference in the mean QCAM value for culprit sections (95.68) and non-culprit sections (98.16) was not as large as found in the sample of patients having STEMI. Figure 2 and 3 of Paper IV again showed the overlap between QCAM for culprit sections and a subgroup of the non-culprit sections.

This overlap represents the major limitation of this research’s potential clinical application. Possible explanations for this overlap are that these non-culprit sections are under the same biomechanical stress due to coronary artery motion as the culprit sections and could be potential culprit sections in the future. Alternatively, the overlap may be caused by measurement error introduced by the foreshortening artefact and out of plane magnification errors introduced by measuring a moving three-dimensional artery from a two dimensional image.

To further evaluate this limitation, use was made of three-dimensional coronary artery reconstruction software to minimise these potential measurement errors.
7. Précis of Unpublished Research

7.1 Appendix 2

In unpublished data included in a draft manuscript Appendix 2, the quantitative method of coronary artery motion analysis was extended to four-dimensional coronary analysis in a pilot study. For a sample of patients undergoing elective PCI for unstable angina, commercially available three-dimensional artery reconstruction software was used to create three-dimensional artery section reconstructions at two time points (end-diastole and end-systole) in the cardiac cycle. A quantitative measure of the compression type of coronary artery motion derived from four-dimensional coronary angiography, QCAM4D, was defined and used to see if there was an association between this measurement and sections containing stenosis being treated by PCI. The mean QCAM4D was not statistically significantly different between coronary sections being treated for percutaneous coronary intervention (7.57%+/−5.96%) than those that were not (8.70%+/8.73%) (p=0.67).

The result of this study was unexpected. The study was undertaken using a Leonardo workstation (IC3D, Siemens), which is derived from the Cardio-op B system (Paieon Medical, Rosh Ha'ayin, Israel). The system would not load historical angiograms (such as those used in Study design for Papers 1, 3 and 4) and a new population (patients with unstable angina undergoing elective coronary intervention) was sampled in this pilot study. It was originally considered that this might be the explanation for the unexpected finding, and the research direction shifted to the use of Cardiovascular Angiography.
Analysis System (CAAS) Quantitative Coronary Angiography (QCA) 3-dimensional (3D) software (Pie Medical Imaging BV, The Netherlands).

7.2 Appendix 3

In unpublished data included in a draft manuscript Appendix 3, QCAM4D was evaluated as a predictor of the location of culprit lesion for a subsequent STEMI. In a trial design similar to both the published manuscript in Appendix 1 and Paper III, angiograms of patients who subsequently re-presented with STEMI were evaluated. CAAS QCA 3D software was used to create three-dimensional artery section reconstructions at two timepoints (end-diastole and end-systole) in the cardiac cycle. QCAM4D was used to see if there was an association between this measurement and sections containing subsequent culprit lesions causing STEMI. A generalized linear mixed model did not find QCAM4D to be a statistically significant predictor of the locations of culprit lesions causing subsequent STEMI (p=0.32).

This result was again unexpected. The CAAS QCA 3D software program loaded historical angiography data, and the study design replicated that previously used in Appendix 1 and Paper III. Although the findings of this study were negative, the distribution plot of culprit and non-culprit segments across QCAM4D (Figure 5 of the draft manuscript) did suggest the possibility of a similar signal to that found in the qualitative and earlier quantitative studies.
8 Ongoing Research and Future Directions

To better understand the discrepancy between the qualitative/earlier quantitative and four dimensional study results, prototype four-dimensional reconstruction software was developed. This work was undertaken as collaborations initially with Professor Richard Hartley from the Australian National University and subsequently with Dr Laurence Park in the School of Mathematics and Computer Science, University of Western Sydney. Laurence and I jointly supervised Tanzila Chowdury, who undertook this work for an honours project.

The algorithms for the current iteration of this software are as follows:

1. Selection of end-diastolic and end-systolic frames from two coronary angiography views.
2. Semi-automated edge detection of the coronary arteries
3. Semi-automated centreline detection
4. Sectional point correspondence detection across all 4 centrelines
5. Centreline point correspondences
6. 3 dimensional centreline reconstructions at end-diastole and end-systole using epipolar geometry and camera properties
7. Calculation of centreline sectional lengths
8. Calculation of QCAM4D for centreline sections
An example of a right coronary artery centreline reconstruction using the current iteration of the software is shown below:

Future directions of research could involve developing this software further with specific tailoring to obtain quantitative measures of coronary artery motion and other quantitative measures of coronary physiology. Further software refinements could help clarify some of the discrepancies identified in the results of this thesis and potentially answer the question of whether quantitative coronary artery motion is useful in addressing the clinical need of predicting the location of future culprit events in patients with coronary artery disease. This hypothesis could be tested on large datasets - such as the dataset for the PROSPECT trial or its ongoing sequel, the PROSPECT II trial[86]. The PROSPECT II trial is enrolling 900 patients to examine two questions: whether coronary plaque
causing future clinical coronary events (vulnerable plaque) can be identified with intravascular ultrasound and near-infrared spectroscopy; and whether pre-emptive bioresorbable stenting of vulnerable plaque prevents myocardial infarctions.

A collaborative research effort with Pie Medical Imaging, the Netherlands, is also underway, and will again address the discrepancy in the results to date. A Research Cooperation Agreement prevents disclosure of the details of this research at this time.
References

7. Deaths from coronary heart disease [http://www.who.int/cardiovascular_diseases]


PAPER I

The compression type of coronary artery motion in patients with ST-segment elevation acute myocardial infarction and normal controls: a case-control study
The compression type of coronary artery motion in patients with ST-segment elevation acute myocardial infarction and normal controls: a case-control study

Aiden JC O’Loughlin1*, Karen Byth2, John K French4, David AB Richards4, Annemarie Hennessy1, A Robert Denniss1,3,5, Pramesh Kovoor3

Abstract

Background: Prediction of the location of culprit lesions responsible for ST-segment elevation myocardial infarctions may allow for prevention of these events. A retrospective analysis of coronary artery motion (CAM) was performed on coronary angiograms of 20 patients who subsequently had ST-segment elevation myocardial infarction treated by primary or rescue angioplasty and an equal number of age and sex matched controls with normal angiograms.

Findings: There was no statistically significant difference between the frequency of CAM types of the ST-segment elevation acute myocardial infarction and control patients (p = 0.97). The compression type of CAM is more frequent in the proximal and mid segments of all three coronary arteries. No statistically significant difference was found when the frequency of the compression type of CAM was compared between the ST-segment elevation acute myocardial infarction and control patients for the individual coronary artery segments (p = 0.59).

Conclusion: The proportion of the compression type of coronary artery motion for individual artery segments is not different between patients who have subsequent ST-segment elevation myocardial infarctions and normal controls.

Introduction

The three-dimensional motion of the heart is characterized by rotation (around the centre of gravity), radial displacement (towards or away from the center of gravity), and translational motion (displacement parallel to its long axis) [1]. The total translational motion of the left ventricle is on average 2.2 cm and is such that motion occurs most at the base and least at the apex of the heart [2].

Motion of individual segments of coronary arteries reflects the motion of the underlying myocardium. The classification system for different patterns of coronary artery motion (CAM) used in this study is derived from a system where CAM was classified into 10 patterns, which were grouped into 3 types: (1) compression type: the length of the arterial segment is shortened without vertical deviation of the artery; (2) displacement type: the location of the coronary artery shifts without change of the length or shape of the arterial segment; and (3) bend type: the coronary artery flexes into a curve [3].

The compression type of CAM for individual artery segments is associated with stenosis [3] and is a predictor of segments containing the culprit lesion responsible for ST-segment elevation myocardial infarctions (STEMIs) [4]. The compression type of CAM has recently been shown to be strongly associated with segments containing the culprit lesion in STEMI patients after successful fibrinolysis [5].

The hypothesis to be tested in this study is that the compression type of CAM is more likely to be present in patients who have subsequent STEMI than in age...
Methods
Twenty patients were identified who had coronary angiography after March 1998 and subsequently represented with a STEMI. STEMI was defined as ischemic chest pain with ST segment elevation of 1 mm in 2 contiguous limb leads or 2 mm in 2 contiguous chest leads. Patients were excluded if they had previous coronary artery bypass surgery or had stent thrombosis as the cause of STEMI. Twenty age and sex matched control patients were identified with normal coronary angiograms.

The CAM patterns of coronary segments were assessed retrospectively in both the STEMI and control patients. For the STEMI patients, the coronary angiography performed before the STEMI was used. The assessment was made blinded to the location of the future culprit segment. The CAM classification of Konta and Bett [3] was used. A schematic of this classification is shown in Figure 1. All three coronary arteries were assessed using all available views. In a single view, a visual comparison was made between the coronary segment at the start and end of systole. A single pattern of motion was assigned in each view. Each segment was then assigned a CAM pattern by synthesizing the assignment for all available views. The patterns of CAM were grouped into the compression type and non-compression type (the bend and displacement types).

Assessment of CAM was made in up to fourteen segments of the coronary arterial tree. The segments were given a numerical label as shown in Figure 2.

Clinical risk factors (hypertension, diabetes, smoking, family history and hypercholesterolemia) of all patients were obtained from the medical records.

Chi-squared tests were used for comparison of frequencies between groups. All statistical analyses were performed using Stata (version 10.0, StataCorp, College Station, TX).

The Royal Prince Alfred Hospital Ethics Review Committee approved the research protocol (reference X10-0159). The research protocol did not include obtaining patient consent.

Results
The demographics for the STEMI and control patients are shown in Table 1. The frequency of each pattern and type of CAM for all the segments of both the STEMI and control patients are shown in Table 2. 67% of segments in both the STEMI and control patients had a non-compression type of CAM. The bend type was present in 44% of segments in the STEMI patients and in 47% of segments in the control patients.
The displacement type was present in 23% of segments in the STEMI patients and in 20% of segments in control patients. 33% of segments in both the STEMI and control patients had the compression type of CAM. There was no statistically significant difference between the frequency of CAM types of the STEMI and control patients (p = 0.97).

**Table 1 Patient Demographics**

<table>
<thead>
<tr>
<th></th>
<th>STEMI patients</th>
<th>Control patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (+/-stdev)</td>
<td>61 (+/-11)</td>
<td>61 (+/-12)</td>
</tr>
<tr>
<td>Men (%)</td>
<td>80</td>
<td>80</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>25</td>
<td>25</td>
</tr>
<tr>
<td>Current smoker (%)</td>
<td>45</td>
<td>45</td>
</tr>
<tr>
<td>Hypercholesterolemia (%)</td>
<td>75</td>
<td>55</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>55</td>
<td>50</td>
</tr>
<tr>
<td>Family history of coronary artery disease (%)</td>
<td>25</td>
<td>35</td>
</tr>
</tbody>
</table>

**Table 2 Frequency of each pattern and type of CAM**

<table>
<thead>
<tr>
<th>Pattern of CAM</th>
<th>STEMI patients</th>
<th>Control patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-compression</td>
<td>161 (67.1)</td>
<td>164 (66.9)</td>
</tr>
<tr>
<td>Bend</td>
<td>106 (44.2)</td>
<td>114 (46.5)</td>
</tr>
<tr>
<td>Bend</td>
<td>12 (5.0)</td>
<td>14 (5.7)</td>
</tr>
<tr>
<td>Multiple bend</td>
<td>77 (32.1)</td>
<td>89 (36.3)</td>
</tr>
<tr>
<td>Hinge</td>
<td>8 (3.3)</td>
<td>8 (3.3)</td>
</tr>
<tr>
<td>Crease</td>
<td>9 (3.8)</td>
<td>3 (1.2)</td>
</tr>
<tr>
<td>Wave flex</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Displacement</td>
<td>55 (22.9)</td>
<td>50 (20.4)</td>
</tr>
<tr>
<td>Lever</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Linear displacement</td>
<td>31 (12.9)</td>
<td>13 (5.3)</td>
</tr>
<tr>
<td>Parallel displacement</td>
<td>24 (10.0)</td>
<td>37 (15.1)</td>
</tr>
<tr>
<td>Compression</td>
<td>79 (32.9)</td>
<td>81 (33.1)</td>
</tr>
<tr>
<td>Compression</td>
<td>71 (29.6)</td>
<td>65 (26.5)</td>
</tr>
<tr>
<td>Ostial compression</td>
<td>8 (3.3)</td>
<td>16 (6.5)</td>
</tr>
<tr>
<td>Total</td>
<td>240</td>
<td>245</td>
</tr>
</tbody>
</table>

**Figure 2 Coronary artery map.** The figure shows the numerical labeling of segments of the coronary tree.
The proportion of the compression type of CAM for individual artery segments for both patient groups is shown in Figure 3. The compression type of CAM was more frequent in the proximal and mid segments of the right (#1 and 2), the left anterior descending (#9 and 10) and to a lesser extent the left circumflex (#17 and 19) coronary arteries. The compression type was less frequent in the distal segments of the right (#3, 4, and 5), left main (#8), distal left anterior descending (#11), diagonal (#13), and the obtuse marginal branches (#18 and 20) of the left circumflex coronary arteries. No statistically significant difference was found when the frequency of the compression type of CAM was compared between the ST-segment elevation acute myocardial infarction and control patients for the individual coronary artery segments (p = 0.59).

Discussion
This study shows that the proportion of the compression type of coronary artery motion for individual artery segments is not statistically significantly different between patients who have subsequent STEMIs and age and sex matched controls.

The main limitations of this study are its small sample size and the potential observer bias in the qualitative assessment of CAM. The technique relies on a visual assessment. Knowledge of the asymmetrical frequency distribution of culprit lesions in patients with STEMIs [6] and the presence of stenosis within a segment may bias the qualitative visual assessor.

Although the exact pattern of CAM varies amongst individual patients, there are consistent themes of motion differences between the different coronary arteries [7,8] and along individual arteries [9]. The coronary segments that had high proportions of the compression type of CAM have previously been shown to include the site of most STEMIs [6,10]. The distribution in coronary segments of the compression type of CAM for the 40 patients in this study and the location of the culprit lesion responsible for STEMI in 280 patients in a previously published report [6] are shown in Figure 4. The percent compression type of CAM and the percent of culprit lesions per cm of artery was highest for the proximal and mid parts of the right coronary artery (segments 1 and 2) and the proximal and mid parts of the left anterior descending coronary artery (segments 9 and 10).

Previously published work has shown that the compression type of CAM is a predictor of the location of stenosis [3] and the culprit segment responsible for STEMI [5,11]. This study builds on this work by finding no difference in the proportion of the compression type
of coronary artery motion between the STEMI population and normal controls. A possible explanation for these findings is that systemic factors determine whether a patient develops coronary atherosclerosis and local biomechanical and/or haemodynamic shear stress determines its location within the coronary arteries.

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Authors’ contributions
AO and PK conceived the study. AO undertook the ethics application, data collection, data analysis, and manuscript preparation. KB recommended the statistical methods and supervised data analysis. JF, DR, AH and RD prepared statistical methods and supervised data analysis. All authors except KB read and approved the final manuscript.

Competing interests
The authors declare that they have no competing interests.

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References

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PAPER II

A Novel Quantitative Index of Coronary Artery Motion from Multislice Computed Tomography and the Location of Coronary Artery Disease
A Novel Quantitative Index of Coronary Artery Motion from Multislice Computed Tomography and the Location of Coronary Artery Disease

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Abstract  Background: We describe a novel quantitative index of coronary artery motion (QCAM) from multislice computed tomography (MSCT) and test its association with the location of coronary artery disease. Methods: 25 patients with known or suspected coronary artery disease underwent ECG-gated MSCT. The coronary artery images were divided into 150 sections using landmarks that could be identified at time points at end-diastole and end-systole. QCAM was derived from the change in centerline length of the coronary sections between these time points. Plaques were identified and classified by type and severity of stenosis. Results: The mean QCAM was significantly less in the coronary sections with plaque (94.3% +/-8.1%) than those without (99.0% +/-10.2%) (p=0.023). There was a significant correlation between QCAM and plaque stenosis (Spearman’s rank correlation coefficient, ρ=-0.192, p=0.018). The correlation between QCAM and plaque type approached statistical significance (Spearman’s rank correlation coefficient, ρ=-0.156, p=0.057). Sensitivity, specificity, positive and negative predictive values for the identification of coronary plaque within a section for QCAM <100% were 80%, 46%, 27% and 90% respectively. Conclusions: QCAM is a novel quantitative measurement of coronary artery motion that correlates with the location of coronary artery disease. Quantitative evaluation of coronary artery motion provides a new approach to understanding the biomechanics of coronary artery disease.

Keywords  MSCT, Coronary Artery Disease, Coronary Motion, Quantitative Modeling

1. Introduction

The response to endothelial injury model of atherosclerosis was first proposed by Virchow in 1856 [1] and revised by Ross and Glomset in 1973 [2-4]. The shear stress of coronary blood flow is the mechanism of injury most commonly implicated [5-10]. Local biomechanical injury due to the axial strain of cyclical coronary artery motion has also been shown to be an alternative mechanism of injury [11]. Coronary artery motion has been proposed to have an effect on the location of coronary artery disease by causing both low shear wall stress and increased wall strain [12]. We and other authors have previously shown that the compression pattern of coronary artery motion correlates with the location of coronary artery disease [13] and is predictive of the locations of culprit lesions in STEMI [14-16].

Multislice computerized tomography (MSCT) is one of the most exciting recent developments in cardiology. Rapid advances in technology have resulted in MSCT entering ‘prime-time’ in recent years [17, 18]. Meta-analyses as early as 2007 support the potential use of 64 slice computed tomography coronary angiography in place of conventional coronary angiography (CCA) in carefully selected populations [19]. MSCT is superior to CCA alone in the analysis of plaque characteristics. Plaque characteristics have been shown to be different in patients with acute myocardial infarction or symptomatic stable angina pectoris [20] and to be predictive of future acute coronary syndromes [21]. MSCT readily allows quantitative evaluations to be performed. Coronary artery calcification is an example of a quantitative measurement that currently contributes significantly to risk stratification especially in persons with intermediate risk assessed by conventional risk analysis [22].

2. Aim

We describe a novel quantitative index of coronary artery motion (QCAM) obtained from MSCT. We test whether
there is an association between QCAM and the location of coronary artery disease.

3. Methods

3.1. Ethical Approval of the Study Protocol

This study complied with the Declaration of Helsinki. The study was approved by the human research ethics committee of Royal Prince Alfred Hospital.

3.2. Patients

25 patients with known or suspected coronary artery disease who had undergone electrocardiographically-gated MSCT at Liverpool Hospital between April 2007 and January 2011 were evaluated. MSCT was performed using a retrospectively gated protocol on a 64 slice dual source cardiac CT scanner (SOMATON Definition, Siemens Healthcare). Patients were examined in a supine position, images extended from base of neck to the diaphragm during a single breath hold. Imaging parameters were as follows: detector collimation of 32×0.6 mm, slice acquisition 64×0.6 mm by means of a z-flying focal spot, gantry rotation time 330 ms, pitch of 0.2–0.43 adapted to the heart rate, tube current 400 mAs per rotation, and tube potential 120 kV. The patients were randomly retrospectively identified from a database of MSCT studies performed during this period. Clinical data of the patients and MSCT results was obtained from MSCT reports and medical records.

3.3. Calculation of QCAM

The images were reconstructed and manipulated on a dedicated cardiac work station. Raw data was reconstructed in 5% intervals throughout the cardiac cycle (which was defined as starting at the R wave). Vessel reconstructions that were representative of end-systole and end-diastole of the left ventricle were used for further analysis. The percent of the cardiac cycle for these two time points was recorded. The coronary arteries were divided into sections using landmarks that could be identified at both time points. Most landmarks were bifurcations. Figure 1 shows the concepts of vessel reconstructions at end-systole and end-diastole and landmarks. Centerline lengths from the ostium of the vessel to the identified landmarks were measured on curved multiplanar reconstructions. The centerline lengths for each section were derived (Section X = (Ostium to Landmark X) - (Ostium to Landmark (X-1)). QCAM was defined as the percent shortening of centerline lengths between the time points (QCAM=100x(centerline length for section X at end-systole)/(centerline length for section X at end-diastole)%).

3.4. Plaque Stenosis and Plaque Type Evaluation

Plaques within coronary sections were identified. Plaque stenoses were classified by the maximal luminal diameter stenosis seen on any plane and the severity of stenosis was graded as none, non-obstructive (<=50%) and significant (>50%). Plaque types were classified as calcified arterial plaques (CAP) when calcified tissue occupied >50% of the plaque area, plaques with <50% calcium as mixed calcified plaques (MCAP), and plaques without any calcium as non-calcified plaques (NCAP), as previously described [18].

3.5. Statistical Analyses

Statistical analyses were performed using Stata version 8.0 (College Station, TX). Numerical values are expressed as mean and standard deviation unless otherwise stated. p-values <0.05 were considered statistically significant. The distributions of QCAM for sections with and without plaque were tested with an unpaired t test. Spearman’s rank correlation coefficients were calculated for QCAM and both plaque stenoses and plaque types. Receiver operating characteristics (ROC) analysis was used to test the relationship between sensitivity and specificity at different cutoff values of QCAM.

4. Results

4.1. Clinical and MSCT Characteristics of the Patients

Baseline clinical characteristics of the patients are shown in Table 1. The age of the patients was 53.3(+/-15.6) years. 16 (64%) of the patients were male. MSCT details are shown in Table 2. Chest pain was the indication for the majority of examinations. The elevated heart rate and high radiation doses reflect the selective use of retrospectively gated examinations in this study. 30 coronary plaques were identified in 11 patients. 4 patients underwent subsequent conventional coronary angiography (CCA). 2 of the patients had CCA within one week of their MSCT examinations. 1 of these patients was then referred for coronary artery bypass surgery. 1 was managed medically. 1 patient had CCA 6
months later with percutaneous treatment of a left anterior descending stenosis (in a section reported as non-diagnostic on the MSCT examination due to heavy calcification). 1 patient had CCA 12 months later with only minor coronary disease identified.

Table 1. Baseline clinical characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Number (%)</th>
</tr>
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<tbody>
<tr>
<td>Age in years (+/-standard deviation)</td>
<td>53.3 (+/-15.6)</td>
</tr>
<tr>
<td>Male sex, number (%)</td>
<td>16 (64%)</td>
</tr>
<tr>
<td>Clinical information, Number (%)</td>
<td></td>
</tr>
<tr>
<td>Family history of premature coronary disease</td>
<td>5 (20%)</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>16 (64%)</td>
</tr>
<tr>
<td>History of Smoking</td>
<td>7 (28%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>8 (32%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>14 (56%)</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>138 (24%)</td>
</tr>
<tr>
<td>Obesity</td>
<td>10 (40%)</td>
</tr>
</tbody>
</table>

Table 2. MSCT details

<table>
<thead>
<tr>
<th>Detail</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indication,</td>
<td></td>
</tr>
<tr>
<td>Chest pain</td>
<td>19</td>
</tr>
<tr>
<td>Cardiomyopathy</td>
<td>3</td>
</tr>
<tr>
<td>Cardiac arrest</td>
<td>1</td>
</tr>
<tr>
<td>Congenital heart disease</td>
<td>1</td>
</tr>
<tr>
<td>Anomalous coronary artery</td>
<td>1</td>
</tr>
<tr>
<td>Heart Rate in beats per minute (standard deviation)</td>
<td>74.9 (+/-13)</td>
</tr>
<tr>
<td>Dose length product (standard deviation)</td>
<td>734 (+/-300)</td>
</tr>
<tr>
<td>Calcium scores Value (standard deviation)</td>
<td></td>
</tr>
<tr>
<td>Agatston score</td>
<td>89.9 (+/-279)</td>
</tr>
<tr>
<td>Volume score</td>
<td>71.4 (+/-225)</td>
</tr>
<tr>
<td>Mass in mgCaHA</td>
<td>17.8 (+/-56)</td>
</tr>
</tbody>
</table>

4.2. QCAM and Coronary Plaque

Vessel reconstructions that were most representative of end-systole occurred at 37.1 (+/- standard deviation of 5.1) % of the cardiac cycle. Vessel reconstructions that were most representative of end-diastole occurred at 73.2 (+/1 standard deviation of 7.3) % of the cardiac cycle. Frequency distributions of QCAM for coronary sections without and with plaque are shown in Figure 2 with further categorization by plaque stenosis and plaque type in Table 3. QCAM was significantly less for coronary sections with plaque (94.3% ±/−8.1%) than for those without plaque (98.9% ±/−8.1%) (p=0.023). There was a significant correlation between QCAM and plaque stenosis (Spearman’s rank correlation coefficient, ρ=−0.192, p=0.018). The correlation between QCAM and plaque type approached statistical significance (Spearman’s rank correlation coefficient, ρ=−0.156, p=0.057). Sensitivity, specificity, positive and negative predictive values for the identification of coronary plaque within a section for QCAM <100% were 80%, 46%, 27% and 90% respectively.

Table 3. QCAM categorized by plaque stenosis and plaque type

<table>
<thead>
<tr>
<th>Categorization</th>
<th>Sections</th>
<th>QCAM (+/-standard deviation)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plaque</td>
<td>Number</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>122</td>
<td>99.0 (+/-10.2)</td>
<td>0.023†</td>
</tr>
<tr>
<td>Present</td>
<td>30</td>
<td>94.3 (+/-8.1)</td>
<td></td>
</tr>
<tr>
<td>Plaque Stenosis</td>
<td></td>
<td></td>
<td>0.018†</td>
</tr>
<tr>
<td>None</td>
<td>122</td>
<td>99.0 (+/-10.2)</td>
<td></td>
</tr>
<tr>
<td>NonObstructive</td>
<td>25</td>
<td>94.1 (+/-7.4)</td>
<td></td>
</tr>
<tr>
<td>Significant</td>
<td>5</td>
<td>95.2 (+/-11.9)</td>
<td></td>
</tr>
<tr>
<td>Plaque Type</td>
<td></td>
<td></td>
<td>0.057†</td>
</tr>
<tr>
<td>None</td>
<td>122</td>
<td>99.0 (+/-10.2)</td>
<td></td>
</tr>
<tr>
<td>Non-calcified</td>
<td>10</td>
<td>95.1 (+/-9.1)</td>
<td></td>
</tr>
<tr>
<td>Mixed calcified</td>
<td>5</td>
<td>89.3 (+/-9.6)</td>
<td></td>
</tr>
<tr>
<td>Calcified</td>
<td>15</td>
<td>96.8 (+/-7.9)</td>
<td></td>
</tr>
</tbody>
</table>

†Unpaired t test †spearman’s rank correlation

Figure 2. Frequency distribution of QCAM for coronary sections without and with plaque

5. Discussion

In this study, QCAM, a quantitative index of coronary motion from MSCT, is described for the first time. The mean
QCAM was 4.7% less in coronary sections with coronary plaque than in those without plaque. This difference was statistically significant. Interestingly, the point estimates for QCAM were similar for both non-obstructive plaque and for plaque that caused significant stenosis. In terms of plaque type, the point estimate for QCAM was smallest for mixed calcific plaque and similar for non-calcified and calcified plaque. The small number of sections with mixed calcific plaque and the wide confidence interval for the point estimates preclude any further interpretation of this observation.

The frequency distribution of QCAM for coronary sections without and with coronary plaque (Figure 2) show considerable overlap of QCAM. In particular, a number of sections without plaque had QCAM values in the same range seen for sections with plaque. This is also reflected in the receiver operation characteristics of QCAM. Although the sensitivity (80%) and negative predictive value (90%) of a QCAM value of <100% for detection of coronary plaque within a section were excellent, the specificity (40%) and positive predictive value (27%) were disappointing.

QCAM measures change in centerline length of a section of the coronary artery during the cardiac cycle. The decision to use this as a quantitative measure of coronary artery motion was based on the results of previous qualitative evaluations of coronary artery motion. In particular, change in centerline length was thought to best mirror the compression type of qualitative motion, which has previously been shown to correlate with the location of coronary artery disease [13]. The results in this study extend this finding to a quantitative method using MSCT. The compression pattern of coronary artery motion has also been shown to be predictive of the location of culprit lesions in ST-segment elevation myocardial infarctions [14-16]. Whether QCAM is predictive of the location of culprit lesions in STEMIs is a clinically interesting hypothesis that remains to be tested.

This study has a number of limitations. Firstly, the use of landmarks to calculate QCAM results in averaging of the index over the artery section. This averaged index was then correlated with the coronary plaque. Plaque location was often focal and landmarks to calculate QCAM results in averaging of the index over the artery section. This averaged index was then correlated with the location of coronary artery disease. Quantitative evaluation of coronary artery motion using MSCT provides an opportunity to better understand the biomechanics of coronary artery disease.

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Ms Linda Tang was supported by a Summer Research Scholarship from the University of Western Sydney.

**Competing Interests**

The authors declare that they have no competing interests.

**REFERENCES**


PAPER III

Quantitative Coronary Artery Motion Analysis Predicts the Location of Future ST Segment Elevation Myocardial Infarctions
Quantitative Coronary Artery Motion Analysis Predicts the Location of Future ST Segment Elevation Myocardial Infarctions

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Abstract  Background: Coronary artery motion may contribute to the development of plaques that rupture and cause acute myocardial infarctions. This study evaluates whether a quantitative measure of the compression type of coronary artery motion obtained from analysis of coronary angiograms can predict the location of culprit lesions in patients who have subsequent myocardial infarction. Method: 28 patients were identified with coronary angiography performed on at least two occasions: related to primary or rescue percutaneous coronary intervention for a STEMI and coronary angiography before this that was available for review. These angiograms were used to determine a quantitative index of coronary artery motion (QCAM) (the ratio of the section lengths i.e. systolic length/diastolic length). The culprit section was subsequently identified and QCAM of this section was compared to non-culprit sections. Results: The two sample t-test comparing QCAM for the non-culprit and culprit sections was highly statistically significant with a p-value of 0.0004. The generalized linear mixed model with culprit section as the dependent variable and QCAM as the independent variable also showed a statistically significant result with a p-value of 0.026. Conclusion: QCAM is a predictor of the location of culprit lesions causing future ST segment elevation myocardial infarctions. Predicting the location of future culprit lesions using coronary angiography may allow targeted therapy to prevent myocardial infarctions.

Keywords  Coronary Artery Motion, Coronary Artery Disease, Myocardial Infarction

1. Introduction

Acute myocardial infarctions are usually caused by rupture of atherosclerotic plaques. Plaques form in the coronary arteries as a response to injury [1]. The location of plaques within the coronary arteries is asymmetrical [2], and their distribution is likely attributable to local biomechanical factors relating to fluid dynamics and wall mechanics. Coronary artery motion contributes to these biomechanical factors [3] and has been suggested to have an important role in the mechanisms of local injury [4].

Qualitative evaluation of coronary artery motion for artery segments has previously shown that the compression type of motion correlates with the location of disease and the degree of stenosis within coronary artery segments [5] and is independently predictive of the location of future culprit lesions responsible for ST segment elevation myocardial infarctions [6,7]. The compression type of coronary motion is defined as occurring when the length of the arterial segment is shortened without vertical deviation of the artery [5].

These findings have been extended to a quantitative method using multislice computed tomography coronary angiography [8]. A significant correlation was found between a quantitative measure of vessel centerline shortening and the location of coronary plaque and the degree of stenosis.

2. Objective

This study aims to see if a quantitative measure of the compression type of coronary artery motion (QCAM) predicts the location of culprit lesions in patients who have subsequent ST segment elevation myocardial infarction.

3. Methods
3.1. Patients

Patients were identified using the angiography databases at Westmead and Liverpool hospitals in Sydney with coronary angiography performed on at least two occasions:
1. related to primary or rescue percutaneous coronary intervention for an STEMI; and
2. coronary angiography before this that was available for review.

STEMI was defined as chest pain characteristic of ischaemia with ST segment elevation of ≥1mm in two contiguous limb leads or ≥2mm in two contiguous chest leads. Patients were excluded if they had previous coronary artery bypass surgery or acute stent thrombosis. The patients identified had coronary angiography at the hospitals between March 1998 and June 2010.

3.2. Calculation of QCAM

On the angiography performed prior to subsequent representation with acute myocardial infarction (2 above), all three of the main coronary arteries were examined in two angiographic views using ezDICOM, a digital imaging and communications in medicine software program [9]. Single frames were selected that best represented the coronary arteries at end-diastole and end-systole. End-diastole was defined as the largest cardiac silhouette within the cardiac cycle close to the peak of the R-wave in the ECG (when available), and end-systole was defined as the smallest silhouette close to the end of the T-wave. Each artery was divided into sections based on unique identifying points and corresponding points were identified in both angiographic views.

The length of each section was measured from the single frames selected at end-diastole and end-systole using the software program Image J [10] as demonstrated in Figure 1. The quantitative measure of coronary artery motion (QCAM) was defined as the ratio of the section lengths i.e. systolic length/diastolic length.

These analyses were performed blinded to the location of the culprit lesion responsible for the subsequent presentation.
with ST segment elevation myocardial infarction (1 above). An experienced interventional cardiologist subsequently identified the location of the culprit plaque and vessel.

3.3. Statistical Analysis

A two sample t-test was performed to compare QCAM for the non-culprit and culprit sections within the coronary arteries that contained a culprit lesion. A generalized linear mixed model was then used with culprit section as the dependent variable and QCAM as the independent variable. Grouping was by angiographic view and by patient.

3.4. Ethics Approval of the Study Protocol

This study complied with the Declaration of Helsinki. The human research ethics committee of Royal Prince Alfred Hospital approved the study.

4. Results

Twenty-eight patients were identified. Two hundred and eighty seven sections in the coronary arteries containing the culprit sections were identified and analyzed as shown in Table 1. The mean QCAM (ratio of end systolic length: end diastolic length) of the non-culprit sections was 103.51 compared to 93.43 for the culprit sections.

Table 1. Summary statistics for QCAM by non-culprit and culprit section types

<table>
<thead>
<tr>
<th>Section Type</th>
<th>Frequency</th>
<th>Mean</th>
<th>Standard Error of the Mean</th>
<th>Standard Deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-culprit</td>
<td>233</td>
<td>103.51</td>
<td>2.14</td>
<td>32.70</td>
</tr>
<tr>
<td>Culprit</td>
<td>54</td>
<td>93.43</td>
<td>1.83</td>
<td>13.41</td>
</tr>
</tbody>
</table>

Figure 2. QCAM for each section for each of the two views for each patient. Non-culprit sections are blue (circles) and culprit sections are red (squares).

The two sample t-test comparing QCAM for the non-culprit and culprit sections was highly statistically significant with a p-value of 0.0004. The generalized linear mixed model with culprit section as the dependent variable and QCAM as the independent variable also showed a statistically significant result with a p-value of 0.026.

5. Discussion

These results demonstrate a significant association between QCAM and the location of a subsequent culprit lesion. Hypotheses regarding the mechanism of this link include the compression type of CAM being a mechanical stress on vascular tissue causing injury to the endothelium. This could not only allow atherogenesis but repetitive stress during the cardiac cycle could weaken plaques already formed and increase the risk of rupture [5].

Despite the results showing a link with differing mean values of QCAM for culprit and non-culprit sections, Figure 2 demonstrates that the QCAM of a number of non-culprit sections lie within the distribution seen for culprit sections. This may suggest that these non-culprit sections are under the same biomechanical stress due to coronary artery motion as the culprit sections and could be potential culprit sections in the future. One alternative explanation is the measurement error introduced by the foreshortening artifact and out of plane magnification error inherent in measuring a moving three-dimensional artery from a two dimensional image. Three-dimensional reconstructions of coronary arteries may overcome this limitation.

There is no current direct clinical application for this research. Further development of this line of research does, however, lead to a number of conceivable future clinical applications. Better understanding of the biomechanical effects of current generation stent technologies may lead to stent strategies that result in lower rates of major adverse cardiac events. Previous reports have shown that longitudinal straightening effect of stents to be a statistically significant predictor of major adverse cardiac events [11]. Modeling of a double stent versus a single stent strategy for a curved artery has suggested higher flexibility, more conformity and lower recoil [12]. Whether the effect of different stent strategies on QCAM in the vessel sections around the stented segments will result in different clinical outcomes is an untested hypothesis.

Bioresorbable vascular scaffolds, which have been termed the ‘fourth revolution’ in interventional cardiology [13], have been shown to result in less coronary artery straightening when compared to metallic platform stents in a retrospective analysis of 102 patients [14]. The progressive disappearance of the polymeric scaffold will likely result in a different effect on QCAM compared to that of current generation stent technologies. If this generation of coronary devices is to be used for current stent indications and also for potential new indications such as the treatment of vulnerable plaques, as has already been reported in the literature [15], then their effect of treatment on coronary biomechanics, including QCAM, may have clinical significance.
6. Conclusion

This study identifies that QCAM is a predictor of the location of culprit lesions responsible for subsequent ST segment elevation myocardial infarctions. Predicting the location of future culprit lesions using coronary angiography may allow targeted therapy to prevent future myocardial infarctions.

Acknowledgements

Samia Kazi was supported by a Summer Research Scholarship from the University of Western Sydney.

Competing Interests

The authors declare they have no competing interests.

REFERENCES


PAPER IV

Quantitative Coronary Artery Motion Analysis Predicts the Location of Future Non-ST Segment Elevation Myocardial Infarctions
Quantitative Coronary Artery Motion Analysis Predicts the Location of Future Non-ST Segment Elevation Myocardial Infarctions

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Abstract

Background

Predicting the locations of coronary plaque rupture causing myocardial infarctions remains an elusive clinical need. Coronary artery motion analysis provides a clinically accessible method that has shown promise in addressing this need.

Methods

20 patients were retrospectively identified with coronary angiography performed on at least two occasions: related to percutaneous coronary intervention for a non-ST segment elevation myocardial infarction and coronary angiography on an occasion prior to this. A quantitative index of coronary artery motion (defined as the ratio of the section lengths i.e. systolic section length/diastolic section length) was measured for coronary sections on the earliest angiogram. The culprit sections were subsequently identified at the time of non-STEMI and the quantitative index of coronary artery motion of these sections was compared to non-culprit sections.

Results

A one-sample t-test comparing the quantitative index of coronary artery motion for the non-culprit and culprit sections was statistically significant with a p-value of 0.04.

Conclusions

The quantitative index of coronary artery motion predicts the location of culprit lesions causing future non-ST segment elevation myocardial infarctions. Predicting the location of future culprit lesions using coronary angiography may allow targeted therapy to prevent myocardial infarctions.
Introduction

Acute myocardial infarctions are usually caused by rupture of atherosclerotic plaques. Plaques form in the coronary arteries as a response to injury (1). The location of plaques within the coronary arteries is asymmetrical (2), and their distribution is likely attributable to local biomechanical factors relating to fluid dynamics and wall mechanics. Coronary artery motion contributes to these biomechanical factors (3) and has been suggested to have an important role in the mechanisms of local injury (4).

Qualitative evaluation of coronary artery motion for artery segments has previously shown that the compression type of motion correlates with the location of disease and the degree of stenosis within coronary artery segments (5) and is independently predictive of the location of future culprit lesions responsible for ST segment elevation myocardial infarctions (6, 7).

These findings have been extended to a quantitative method using both multislice computed tomography (CT) coronary angiography and invasive coronary angiography. A significant correlation was found between a quantitative index of vessel centreline shortening and the location of coronary plaque and the degree of stenosis in patients having CT coronary angiography (8). The quantitative index of the compression type of coronary artery motion obtained from analysis of invasive coronary angiograms used in this study has previously been shown to be predictive of the location of future culprit lesions responsible for ST segment elevation myocardial infarctions (9).

This study aims to see if a quantitative index of the compression type of coronary artery motion (QCAM) predicts the location of culprit lesions in patients who have subsequent non-ST segment elevation myocardial infarctions (non-STEMIs).

Methods

Patients

Patients were identified using the angiography database at Liverpool hospital in Sydney with coronary angiography performed on at least two occasions:
1. Related to coronary angiography and percutaneous coronary intervention (PCI) for a non-STEMI; and
2. Coronary angiography at least 6 months before this that was available for review.
Experienced interventional cardiologists performing the procedure on occasion 1 above made the diagnosis of non-STEMI. The diagnosis was made after evaluation of the patient’s clinical information, cardiac enzymes, and electrocardiograms. The diagnosis was recorded in the angiography database. Patients were excluded if they had previous coronary artery bypass surgery, stent thrombosis or in-stent or in-segment restenosis.

Calculation of QCAM

On the angiography performed on occasion 2 (above), the coronary arteries containing the subsequent culprit lesions were examined in two angiographic views using ezDICOM, a digital imaging and communications in medicine software program (10). Single frames were selected at end-diastole and end-systole. End-diastole was defined as the largest cardiac silhouette within the cardiac cycle close to the peak of the R-wave in the ECG (when available), and end-systole was defined as the smallest silhouette close to the end of the T-wave. Each artery was divided into sections based on unique identifying points and corresponding points were identified in both angiographic views.

The length of each section was measured from the single frames selected at end-diastole and end-systole using the software program Image J version 1.47t (11), as previously described(9). The quantitative index of coronary artery motion (QCAM) is the ratio of the section lengths represented as a percentage i.e. 100*(systolic length/diastolic length). A QCAM value of 100 represented no change in length of the section from end-diastole (ED) to end-systole (ES), with greater and lesser values corresponding to lengthening and shortening respectively.

These analyses were performed blinded to the location of the culprit lesion responsible for the subsequent re-presentation with non-ST segment elevation myocardial infarction. An experienced interventional cardiologist subsequently identified the location of the culprit plaque and culprit section.

Statistical Analysis

A one-sample t-test was performed to compare QCAM for the non-culprit and culprit sections. Data analysis was performed using STATA version 10 (StataCorp LP. College Station, TX, USA). A p value <0.05 was considered significant.

Ethics Approval of the Study Protocol
The human research ethics committee of Royal Prince Alfred Hospital approved the study (Protocol No X10-0159 & HREC/10/RPAH/291).

**Results**

Twenty patients were identified and analysed. The patients identified had their procedures at the hospital between December 1997 and October 2009. Table 1 shows patient demographics and culprit artery distribution. The culprit lesions causing non-STEMI were present in 9 left anterior descending coronary, 10 right coronary and 1 left circumflex coronary arteries. Patients represented with non-STEMI and had repeat angiography and PCI 198 days (6 months, 14 days) to 4195 days (11 years, 5 months, 26 days) after their prior angiograms.

<table>
<thead>
<tr>
<th>Culprit artery</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left anterior descending</td>
<td>9</td>
</tr>
<tr>
<td>Right</td>
<td>10</td>
</tr>
<tr>
<td>Left circumflex</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 1. Demographics of patient population and culprit artery distribution

<table>
<thead>
<tr>
<th>Age (years) +/- standard deviation</th>
<th>56 +/- 9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender (%)</td>
<td>80</td>
</tr>
</tbody>
</table>

One hundred and eighty nine sections in the coronary arteries containing the culprit sections were identified and analysed as shown in Table 2. The mean QCAM across all non-culprit sections was 98.16 (+/- 0.74 (standard error of the mean (SEM))). The mean QCAM across all culprit sections was 95.68 (+/-1.42 (SEM)). The one sample t-test comparing QCAM for the non-culprit and culprit sections was statistically significant with a p-value of 0.044.

Table 2. Summary statistics for QCAM by non-culprit and culprit section types

<table>
<thead>
<tr>
<th>Section Type</th>
<th>Frequency</th>
<th>Mean</th>
<th>Standard Error of the Mean</th>
<th>Standard Deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non- culprit</td>
<td>149</td>
<td>98.16</td>
<td>0.74</td>
<td>9.04</td>
</tr>
<tr>
<td>Culprit</td>
<td>40</td>
<td>95.68</td>
<td>1.42</td>
<td>8.96</td>
</tr>
</tbody>
</table>

Figure 2 shows QCAM for the twenty patients grouped by non-culprit and culprit sections and angiographic view. Non-culprits were scattered around the mean of 98.16 while culprit lesions were mostly distributed under 98, demonstrating an association between culprit lesions and
sections that shortened during the cardiac cycle.

Figure 2. Distribution of QCAM by non-culprit (NC) and culprit (C) sections and angiographic view.

Figure 3 shows the distribution of QCAM across artery sections in the two angiographic views for each individual patient. Although most sections had similar QCAM values in both views, some of the measurements varied considerably. For example, for patient 10-section 1 measured very different QCAM values of 80 and 106 in the first and second angiographic views respectively.
Figure 3. QCAM for non-culprit (blue) and culprit (red) sections for both angiographic views for each individual patient.

Discussion

These results demonstrate a significant association between QCAM and the location of a subsequent culprit lesion responsible for non-STEMI. This association may be due to the compression type of CAM being a mechanical stress on vascular tissue causing injury to the endothelium. This may play a role in both atherogenesis and plaque rupture (5). It may also play a role in the mechanism by which unusual psychological stress, hypertension and a rise in catecholamine levels have been shown to be triggers for myocardial infarctions (12-16). In animal studies, administration of vasopressors significantly increase coronary artery motion parameters such as distance moved, maximum velocity, acceleration and deceleration (17).

Despite the results showing a link with differing mean values of QCAM for culprit and non-culprit sections, Figure 2 demonstrates that the distribution of QCAM for non-culprit and culprit sections have considerable overlap. This suggests that non-culprit sections are under the same biomechanical stress due to coronary artery motion as the culprit sections and could be potential culprit sections in the future. An alternative explanation is that this overlap is due to measurement error introduced by the foreshortening artefact and out of plane magnification error inherent in
measuring a moving three-dimensional artery from a two dimensional image. A method of measuring a quantitative index of coronary artery motion with three-dimensional reconstructions of coronary arteries may overcome this limitation.

There is no current direct clinical application for this research. Further development of this line of research does, however, lead to a number of conceivable future clinical applications. Better understanding of the biomechanical effects of current generation stent technologies may lead to stent strategies that result in lower rates of major adverse cardiac events. Previous reports have shown that longitudinal straightening effect of stents to be a statistically significant predictor of major adverse cardiac events (18). Modelling of a double stent versus a single stent strategy for a curved artery has suggested higher flexibility, more conformity and lower recoil (19). Whether the effect of different stent strategies on QCAM in the vessel sections around the stented segments will result in different clinical outcomes is an untested hypothesis.

Bioresorbable vascular scaffolds, which have been termed the ‘fourth revolution’ in interventional cardiology (20), have been shown to result in less coronary artery straightening when compared to metallic platform stents in a retrospective analysis of 102 patients (21). The progressive disappearance of the polymeric scaffold will likely result in a different effect on QCAM compared to that of current generation stent technologies. If this generation of coronary devices is to be used for current stent indications and also for potential new indications such as the treatment of vulnerable plaques, as has already been reported in the literature (22), then their effect on coronary biomechanics, including QCAM, may have clinical significance.

**Conclusions**

This study identifies that QCAM correlates with the location of culprit lesions responsible for subsequent non-ST segment elevation myocardial infarctions. Predicting the location of future culprit lesions using coronary angiography may allow targeted therapy to prevent future myocardial infarctions.

**Acknowledgements**

The authors have no conflicts of interest to declare. There are no sources of financial support for the project to disclose.
References

10. Edzicom website.
Appendix 1

The Stretch-Compression Type of Coronary Artery Movement Predicts the Location of Culprit Lesions Responsible for ST-Segment Elevation Myocardial Infarctions

[Work completed prior to PhD enrolment]
The Stretch–Compression Type of Coronary Artery Movement Predicts the Location of Culprit Lesions Responsible for ST-Segment Elevation Myocardial Infarctions

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Background: Prediction of the location of culprit lesions responsible for ST-segment elevation myocardial infarctions may allow for prevention of these events by safe and easily deliverable local therapies.

Methods: A retrospective analysis of coronary movement was performed on coronary angiograms of patients who subsequently represented with ST-segment elevation myocardial infarction treated by primary or rescue angioplasty at a single institution.

Results: Twenty patients were identified. The stretch–compression type of coronary artery movement (CAM) was a statistically significant independent predictor of the segment containing the culprit lesion (odds ratio 6.10, p-value 0.005).

Conclusions: The stretch–compression type of coronary artery movement is an independent predictor of the location of culprit lesions responsible for ST-segment elevation myocardial infarctions.

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Keywords: Coronary artery movement; ST-segment elevation myocardial infarction; Coronary artery disease; Culprit lesion

Introduction

Patterns of coronary artery movement (CAM) are associated with the degree of stenosis within coronary artery segments. Coronary artery segments with the stretch–compression (SC) type of movement have more severe stenoses. The SC type of CAM may cause local biomechanical injury. Atherosclerosis at these sites may be a response to this injury.

Some coronary segments are at higher risk of being the site of plaque rupture leading to cardiac events. The majority of acute myocardial infarctions occur in the proximal and mid segments of all three coronary arteries. CAM is due to myocardial movement. The amplitude of CAM is related to the ejection fraction at the time of study. The ejection fraction may be reduced due to myocardial dysfunction during ST-segment elevation myocardial infarction (STEMI). The pattern of CAM observed at this time may not be representative of the CAM preceding the event. CAM patterns observed on angiography performed before the STEMI will likely provide a better assessment of CAM preceding plaque rupture.

The hypothesis of this study is that the stretch–compression type of CAM predicts the location of culprit lesions responsible for ST-segment elevation myocardial infarctions.

Patients and Methods

Patients were identified using the angiography database at Westmead public hospital with: (1) primary or rescue percutaneous coronary intervention for an STEMI; and (2) coronary angiography before this that was available for review. STEMI was defined as chest pain characteristic of ischaemia with ST segment elevation of ≥3 mm in two contiguous limb leads or ≥2 mm in two contiguous chest leads. Patients were excluded if they had previous coronary artery bypass surgery or acute stent thrombosis. The patients identified had coronary angiography at the hospital between March 1998 and June 2005.
The CAM patterns of coronary segments were assessed retrospectively on the coronary angiography performed before the STEMI and blinded to the location of the culprit lesion responsible for the subsequent STEMI. The classification of coronary segments and assessment of stenosis employed at Westmead public hospital was used.

The CAM classification of Konta and Bett was used. This classification system has 10 patterns of movement grouped into three types (compression, bend, and displacement). The patterns of CAM were then further grouped into the SC type (the compression type in Konta and Bett’s classification) and non-SC type (the bend and displacement types). All three coronary arteries were assessed using all available views. In a single view, a visual comparison was made between the coronary segment at the start and end of systole. A single pattern of movement was assigned in each view. Each segment was then assigned a CAM pattern by synthesising the assignment for all available views.

Assessment of CAM was made in up to five segments of the right coronary artery (RCA) (#1 proximal RCA, #2 mid RCA, #3 distal RCA, #4 poster descending branch, #5 first posterolateral branch), up to six segments of the left main and left anterior descending coronary artery (LAD) (#8 left main, #9 proximal LAD (defined as ending at the first septal branch), #10 mid LAD, #11 distal LAD, #13 first diagonal branch) and up to four segments of the left circumflex coronary artery (LCX) (#17 proximal LCX, #18 first obtuse marginal branch, #19 mid LCX, #20 second obtuse marginal branch). The presence and severity of stenosis on the previous angiogram had been assessed by an experienced cardiologist at the time of the angiogram. The degree of stenosis was estimated by visual inspection using an ordinal scale (1: no stenosis, 2: minor irregularities, 3: stenosis <50%, 4: 50–75%, 5: >75%, 6: complete occlusion).

High risk segments were defined as segments 1, 2, 9, 10, 17, and 19.

Statistical Analysis
Fisher’s exact test was used to test for an association between the pattern of CAM on the previous angiogram and the location of the culprit lesion identified at the time of the STEMI. Mann–Whitney tests were used for associations between the location of the culprit lesions and the category of stenosis; and the pattern of CAM and the location of the culprit lesion. A generalised linear mixed model was used to calculate odds ratios of a segment assessed on the previous angiogram being the subsequent culprit segment.

### Table 1. Patient Demographics

<table>
<thead>
<tr>
<th>Age (years) ± standard deviation</th>
<th>61 ± 11</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes (%)</td>
<td>25</td>
</tr>
<tr>
<td>Current smoker (%)</td>
<td>45</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>75</td>
</tr>
<tr>
<td>Family history of coronary artery disease (%)</td>
<td>25</td>
</tr>
</tbody>
</table>

### Table 2. Distribution of Stenosis by CAM Type

<table>
<thead>
<tr>
<th>Stenosis Category (%)</th>
<th>Non-SC Type of CAM (%)</th>
<th>SC Type of CAM (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1: Nil</td>
<td>65 (41)</td>
<td>16 (20)</td>
</tr>
<tr>
<td>2: Minor irregularities</td>
<td>63 (39)</td>
<td>33 (42)</td>
</tr>
<tr>
<td>3: Less than 50%</td>
<td>15 (9)</td>
<td>15 (9)</td>
</tr>
<tr>
<td>4: 50–75%</td>
<td>8 (5)</td>
<td>5 (6)</td>
</tr>
<tr>
<td>5: &gt;75%</td>
<td>6 (4)</td>
<td>10 (13)</td>
</tr>
<tr>
<td>6: Complete occlusion</td>
<td>3 (2)</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>160</td>
<td>79</td>
</tr>
</tbody>
</table>

### Table 3. Counts (and Percentages) of Non-Culprit and Culprit Segments by CAM Pattern and Stenosis Category

<table>
<thead>
<tr>
<th>CAM Type</th>
<th>Non-Culprit Segment (%)</th>
<th>Culprit Segment (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-stretch–compression</td>
<td>156 (71)</td>
<td>42 (20)</td>
</tr>
<tr>
<td>Stretch–compression</td>
<td>63 (29)</td>
<td>16 (80)</td>
</tr>
<tr>
<td>p = 0.003 (Fisher’s exact test)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stenosis category</th>
<th>Non-Culprit Segment (%)</th>
<th>Culprit Segment (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1: Nil</td>
<td>77 (35)</td>
<td>42 (20)</td>
</tr>
<tr>
<td>2: Minor irregularities</td>
<td>89 (41)</td>
<td>7 (35)</td>
</tr>
<tr>
<td>3: Less than 50%</td>
<td>27 (12)</td>
<td>3 (15)</td>
</tr>
<tr>
<td>4: 50–75%</td>
<td>12 (11)</td>
<td>1 (5)</td>
</tr>
<tr>
<td>5: &gt;75%</td>
<td>11 (5)</td>
<td>5 (25)</td>
</tr>
<tr>
<td>6: Complete occlusion</td>
<td>3 (1)</td>
<td>0</td>
</tr>
<tr>
<td>p = 0.004 (Mann–Whitney test)</td>
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### Table 4. Adjusted Odds Ratios of a Segment Containing the Subsequent Culprit Lesion

<table>
<thead>
<tr>
<th>Explanatory Variable</th>
<th>Odds Ratio (95% Confidence Interval)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SC type of CAM</td>
<td>6.10 (1.75–21.43)</td>
<td>0.005</td>
</tr>
<tr>
<td>Stenosis category (compared to category 1: no stenosis)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2: Minor irregularities</td>
<td>1.06 (0.28–3.99)</td>
<td>0.933</td>
</tr>
<tr>
<td>3: Less than 50%</td>
<td>1.13 (0.22–5.78)</td>
<td>0.880</td>
</tr>
<tr>
<td>4: 50–75%</td>
<td>1.02 (0.10–10.8)</td>
<td>0.990</td>
</tr>
<tr>
<td>5: &gt;75%</td>
<td>4.57 (0.95–21.89)</td>
<td>0.057</td>
</tr>
<tr>
<td>High risk segment</td>
<td>2.09 (0.58–7.52)</td>
<td>0.264</td>
</tr>
</tbody>
</table>
The association between the SC type of CAM and stenosis was reconfirmed using data from the prior angiograms in 20 STEMI patients (p = 0.0004). Table 2 shows the distribution of stenosis by CAM type.

We examined CAM in 239 coronary segments in the 20 patients. There was an association between the SC type of CAM and the location of a subsequent culprit lesion (p = 0.003). This is shown in Table 3 as well as the association of stenosis and culprit segment.

The adjusted odds ratio of a segment being the culprit segment for explanatory variables are shown in Table 4 and Fig. 1. The SC type of CAM was an independent predictor of the culprit artery segment (p = 0.005). The odds ratio of a segment being a culprit segment trended towards statistical significance for stenoses >75% (p = 0.057).

Discussion

These results show, for the first time, that the stretch-compression type of CAM is an independent predictor of the location of the culprit lesion in patients having an STEMI. This finding was independent of the severity of stenosis and the segment being a high risk segment defined by location.

The response to endothelial injury model of atherosclerosis was first put forward by Virchow in 1856 and revised by Ross and Glomset in 1973. The shear stress of coronary blood flow has been proposed as the cause of endothelial injury. Local biomechanical injury due to the SC type of CAM represents an alternative mechanism. The absence of atherosclerosis from relatively immobile arteries such as the internal mammary arteries could also possibly be explained by the relative absence of arterial motion.

The physiological changes associated with unusual psychological stress, hypertension and a rise in catecholamine levels have been shown to be triggers for STEMI. It is possible that they acutely increase the amplitude of coronary artery motion leading to acute plaque rupture.

The lack of a clear predictive value for degree of angiographic stenosis is consistent with previous studies. Whether the SC type of CAM is a cause or correlate of large histological plaques remains to be elucidated.

Some of the weaknesses of this study are its small sample size and the potential observer bias in the qualitative assessment of CAM. The small sample size resulted in wide confidence intervals for the estimated odds ratios of the explanatory variables. The technique relies on an eyeball assessment. The previously well described high risk segments and the association between stenosis and the SC type of CAM means there may have been a ready visual cue as to the possible location of the culprit segment. Assessment of CAM with quantitative techniques may address some of these problems. A number of promising methods that may be applicable to the quantitation of CAM include quantitative analysis of coronary motion using coronary angiography data and intravascular ultrasound.

This study shows that the SC type of CAM is an independent predictor of the location of culprit lesions responsible for STEMI. This may assist in the prevention of these events in the future by prophylactic treatment of these sites in high risk patients with safe and easily deliverable local therapies.

References


Appendix 2

A Novel Quantitative Index of Coronary Artery Motion from Four-Dimensional Coronary Angiography and the Location of Stenotic Coronary Artery Disease

(Draft manuscript under consideration by authors)
Title Page

Title

A Novel Quantitative Index of Coronary Artery Motion from Four-Dimensional Coronary Angiography and the Location of Stenotic Coronary Artery Disease

Running Head

QCAM4D and stenosis

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Abstract

Background
We describe a novel quantitative index of coronary artery motion (QCAM4D) from four-dimensional reconstructions of invasive coronary angiography and test its association with the location of stenotic coronary artery disease requiring elective percutaneous coronary intervention for unstable angina pectoris.

Methods
Eleven patients were identified who were undergoing elective percutaneous coronary intervention for unstable angina pectoris. The coronary arteries were divided into sections using readily available landmarks. Three-dimensional coronary reconstructions of the coronary arteries were made at end-systole and end-diastole. Sectional length and maximal percent stenosis for each section were calculated using IC3D software. QCAM4D was derived from the centerline lengths of the sections at end-systole and end-diastole. The section containing the stenosis being treated with percutaneous coronary intervention was recorded.

Results
The mean QCAM4D was not significantly different between coronary sections being treated for percutaneous coronary intervention (7.57% +/- 5.96%) than those that were not (8.70% +/- 8.73%) (p=0.67).

Conclusions
QCAM4D is a novel quantitative measurement of coronary artery motion. It was not found to correlate with coronary artery sections being treated for percutaneous coronary intervention.

Keywords: coronary artery disease. coronary motion . quantitative modeling
Introduction

Acute myocardial infarctions are most commonly caused by rupture of atherosclerotic plaques. Plaques form in the coronary arteries as a response to injury [1]. The location of plaques within the coronary arteries is asymmetrical [2], and their distribution is likely attributable to local biomechanical factors relating to fluid dynamics and wall mechanics. Coronary artery motion contributes to these biomechanical factors [3] and has been suggested to have an important role in the mechanisms of local injury [4]. Qualitative evaluation of coronary artery motion for artery segments has previously shown that the compression type of motion correlates with the location of disease and the degree of stenosis within coronary artery segments [5] and is independently predictive of the location of future culprit lesions responsible for ST segment elevation myocardial infarctions [6, 7].

These findings have been extended to a quantitative method using both multislice computed tomography (CT) coronary angiography and invasive coronary angiography. A significant correlation has been reported for a quantitative index of vessel centreline shortening and the location of coronary plaque and the degree of stenosis in patients having CT coronary angiography[8]. A quantitative index of the compression type of coronary artery motion obtained from analysis of invasive coronary angiograms has previously been shown to be predictive of the location of future culprit lesions responsible for both ST segment [9] and non-ST segment elevation myocardial infarctions (unpublished manuscript)[10].

This study describes a novel quantitative index of coronary artery motion (QCAM) from four-dimensional reconstructions of invasive coronary angiography and tests its association with the location of stenotic coronary artery disease in a sample of patients undergoing elective percutaneous coronary intervention for unstable angina.

Methods

Ethical approval of the study protocol

The study was approved by the human research ethics committee of Royal Prince Alfred Hospital.

Patients
Eleven patients undergoing percutaneous coronary intervention for unstable angina pectoris at Westmead Hospital between December 2007 and June 2010 were evaluated. Coronary angiography was performed at 15 frames per second on two Siemens angiography machines (Siemens Healthcare, Forchheim, Germany).

**Calculation of QCAM**

Three-dimensional (3D) quantitative coronary angiography was performed offline using 3D reconstruction software on the Leonardo workstation (IC3D, Siemens), which is derived from the Cardio-op B system (Paieon Medical, Rosh Ha'ayin, Israel). The contrast-filled non-tapered part of the guiding catheter was used to calibrate pixel size. Two orthogonal angiographic views of the target lesion in the ECG-gated end-diastolic and end-systolic frames were used for 3D-Quantitative Coronary Angiography (QCA) reconstructions. The site of minimum luminal diameter, and the proximal and distal coronary artery segments were manually identified on the first angiographic plane, and repeated in a second image. Proximal and distal planes were derived automatically, and the software automatically generated a 3D representation of the arterial lumen (Figure 1).
Figure 1
Representative three-dimensional reconstruction of vessel geometry using two orthogonal angiographic planes. (Top left) Coronary angiogram of right coronary artery in RAO 31 Cranial 25 view. (Top Right) Coronary angiogram of right coronary artery in RAO 38 Cranial 0 view. (Bottom middle) Three-dimensional reconstruction of vessel lumen in the LAO 46 Caudal 35 projection showing three-dimensional quantitative coronary artery measurements including diameter stenosis (%) and lesion length (L). Yellow cross defines the most severe stenosis in the artery section, ‘P’ defines proximal site.

A quantitative index of coronary artery motion derived from four-dimensional coronary angiography (QCAM4D) was defined as the percent shortening of centerline lengths between the time points

\[
QCAM4D = 100 \times \left( \frac{\text{centerline length at end-diastole} - \text{centerline length at end-systole}}{\text{centerline length at end-diastole}} \right) \%
\]

Statistical Analyses
Statistical analyses were performed using Microsoft Excel. Numerical values are expressed as mean and standard deviation unless otherwise stated. p-Values <0.05 were considered statistically significant. The distributions of QCAM4D for sections with and without a stenosis being targeted for elective PCI were tested with a Student’s t-test.

Results
Clinical characteristics of the patients
Baseline clinical characteristics of the patients are shown in Table 1.

Table 1 Baseline Clinical Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>(n=11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>56.9 (+/-10.3)</td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td>9 (82)</td>
</tr>
</tbody>
</table>

The mean QCAM4D was not significantly different between coronary sections being treated for percutaneous coronary intervention (7.57%+/−5.96%) and those that were not (8.70%+/−8.73%) (p=0.67).
Figure 2 shows a scatterplot of the % stenosis versus QCAM4D for artery sections being subject to elective PCI and those sections that were not undergoing PCI.

![Figure 2]

**Figure 2**
Scatterplot showing % stenosis versus QCAM4D for artery sections being treated with elective percutaneous coronary intervention (pink squares) and those not treated (blue diamonds)

**Discussion**

This study describes a novel quantitative index of coronary artery motion (QCAM) from four-dimensional reconstructions of invasive coronary angiography. An association with the location of stenotic coronary artery disease was not found. All of the artery sections containing the sections being targeted for PCI demonstrated shortening by QCAM4D. This was an expected finding. The vast majority of the sections not being targeted for PCI showed a similar distribution of QCAM4D. This finding was unexpected.

Possible explanations for the results of this study compared to the studies outlined in the introduction of this paper are the different population that was sampled. This study sample patients with unstable angina who were undergoing PCI. In contrast, the majority of previous studies showing an association between coronary artery motion were performed in patients with acute coronary syndromes who were undergoing PCI either concomitantly[6] or at some point in the future after a plaque rupture event[7, 9, 10]. The exceptions to this are the populations sampled in the original qualitative paper of Konta and Bett[5] and the previous CT coronary angiography study[8].
References

Appendix 3

The Relationship between Coronary Artery Motion and Lesion Location in ST-segment Elevation Myocardial Infarction (STEMI) – Analysis Using 4-dimensional Quantitative Coronary Artery Motion Measurement

(Draft manuscript under consideration by authors)
The Relationship between Coronary Artery Motion and Lesion Location in ST-segment Elevation Myocardial Infarction– Analysis Using 4-dimensional Quantitative Coronary Artery Motion Measurement

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Abstract

Background

Coronary artery motion may contribute to the development of plaques that rupture and cause acute myocardial infarctions. This study evaluates the relationship between coronary artery motion and lesion location in patients with subsequent ST segment elevation myocardial infarction (STEMI). The hypothesis tested in this study is that segments of the arteries that shorten during the cardiac cycle (i.e. from end-diastole to end-systole) predict the location of lesions responsible for STEMI. Three-dimensional quantitative coronary analysis software (CAAS QCA 3D) was used to measure four-dimensional quantitative coronary artery motion (QCAM4D) in different segments of the three main coronary arteries. QCAM4D is evaluated as a predictor of the location of culprit lesions causing subsequent STEMIs.

Methods

20 patients were identified who had angiography and subsequently re-presented at a later date and underwent further angiography for STEMI. The coronary arteries were divided into sections using readily available landmarks. Three-dimensional coronary reconstructions of the coronary arteries were made at end-diastole and end-systole. Sectional length and maximal percent stenosis for each section were calculated using CAAS QCA 3D software (Pie Medical Imaging BV, The Netherlands). QCAM4D was derived from the centerline lengths of the sections at diastole and systole.

Results

A generalized linear mixed model did not find QCAM4D to be a statistically significant predictor of the locations of subsequent STEMI (p=0.32).

Conclusions

QCAM4D was not predictive of the location of culprit lesions causing subsequent STEMI.
Introduction
Acute myocardial infarctions are usually caused by rupture of atherosclerotic plaques. Plaques form in the coronary arteries as a response to injury [1]. The location of plaques within the coronary arteries is asymmetrical [2], and their distribution is likely attributable to local biomechanical factors relating to fluid dynamics and wall mechanics. Coronary artery motion contributes to these biomechanical factors [3] and has been suggested to have an important role in the mechanisms of local injury [4].

Qualitative evaluation of coronary artery motion for artery segments has previously shown that the compression type of motion correlates with the location of disease and the degree of stenosis within coronary artery segments [5] and is independently predictive of the location of future culprit lesions responsible for ST segment elevation myocardial infarctions [6, 7].

These findings have been extended to a quantitative method using both multislice computed tomography (CT) coronary angiography and invasive coronary angiography. A significant correlation was found between a quantitative index of vessel centreline shortening and the location of coronary plaque and the degree of stenosis in patients having CT coronary angiography [8]. A quantitative index of the compression type of coronary artery motion obtained from analysis of invasive coronary angiograms has previously been shown to be predictive of the location of future culprit lesions responsible for both ST segment elevation myocardial infarctions [9] and non-ST segment elevation myocardial infarctions [10].

This study tests the hypothesis that four-dimensional quantitative coronary artery motion (QCAM4D) predicts the location of culprit lesions in patients who have subsequent non-ST segment elevation myocardial infarctions (non-STEMIs).

Methods

Patients
Patients were identified using the angiography database at Liverpool public hospital. The
patients had: 1. coronary intervention for a STEMI; and 2. coronary angiography before this that was available for review (initial coronary angiography). Classification as STEMI in the database was undertaken at the time of the angiogram under the guidance of the attending interventional cardiologist. Patients were excluded if they had previous coronary artery bypass surgery, stent thrombosis or in-stent or in-segment restenosis. The patients identified had coronary angiography at the hospital between December 1997 and November 2007. They re-presented with their culprit requiring PCI 372 days to 4195 days (11 years 5 months) later.

**Calculation of QCAM4D**

Figure 1 shows an example of a patient’s angiogram before and after STEMI. In this case, the culprit lesion was in the proximal segment of the right coronary artery (RCA). The patient’s angiograms before STEMI were analysed using the CAAS QCA 3D software (Pie Medical Imaging BV, The Netherlands). The three main arteries (the left anterior descending (LAD), left circumflex (LCX) and right coronary arteries (RCA)) were available for analysis in all the patients. Only the artery that further developed the infarct lesion was assessed, with the researcher blinded to the lesion location within the artery. The arteries were divided into sections according to distance from the origin. Up to 6 sections were identified in each of the 3 main arteries. 3D reconstructions of each section were made using CAAS QCA 3D by combining two different angiographic projections. The program was used to physically mark the boundaries of the section to be measured in both angiographic planes. The software then reconstructed a 3D image of the section and provided length and diameter measurements. Figure 2 demonstrates the use of CAAS QCA 3D to reconstruct a coronary artery section in 3D by using 2 angiographic views. Wang et al.’s “Standardized projections used for the coronary artery segments” (69) (Figure 3) guided the angiographic planes used in the formation of the 3D reconstructions. Sections were labelled by their location along the coronary artery, for example, proximal, mid and distal LAD.
Figure 1 Initial coronary angiogram (left) and subsequent STEMI angiogram (right) for one patient. The culprit is evident in the proximal section of the RCA in the STEMI angiogram (right).

Figure 2 Demonstration of 3D reconstruction (right) of a coronary artery section from 2 angiographic views (only 1 view is shown here on the left) using CAAS QCA 3D.
Figure 3 Standardized projections used for coronary artery segments. Reproduced from Wang et al. (69).

The length of each section was measured in end-diastole and end-systole and the percentage change in length was calculated. This was termed “percent stretch-compression” (%SC). The largest percent stenosis (%stenosis) in each section was calculated from diameter measurements. The section that contained the culprit lesion was then identified through the follow-up angiogram and correlated with %SC and %stenosis. The culprit lesion and section was identified by an experienced interventional cardiologist on the angiogram performed following subsequent presentation with ST segment elevation myocardial infarction.

Statistical Analysis
A generalized linear mixed model was used to test for an association between the %SC
measured for the section of the artery on the initial coronary angiogram and the location of the culprit section identified at the time of the STEMI. Grouping was by patient. The explanatory variables for each artery section were the percent stretch-compression (%SC) and the percent stenosis (%stenosis). Data analysis was performed using STATA version 10 (StataCorp LP. College Station, TX, USA). A p value <0.05 was considered significant.

**Ethics Approval of the Study Protocol**

The human research ethics committee of Royal Prince Alfred Hospital approved the study (Protocol No X10-0159 & HREC/10/RPAH/291). The ethics committee approved performance of the study without direct patient consent. The ethics committee agreed that it was impractical to obtain consent from patients after considering that procedures occurred up to 17 years previously, that patients may be deceased or difficult to locate, the absence of direct patient contact in the protocol, and the security measures used to protect the privacy of the patients.

**Results**

Twenty patients were identified and analysed. Table 1 shows patient demographics and culprit artery distribution. The culprit lesions were present in 11 LAD, 8 RCA and 1 LCx arteries. 102 sections were analyzed across all arteries.

**Table 1** Patient demographics and culprit artery distribution for STEMI group

<table>
<thead>
<tr>
<th>Age (years) +/- standard deviation</th>
<th>57 +/- 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender (%)</td>
<td>75</td>
</tr>
<tr>
<td>Culprit artery</td>
<td></td>
</tr>
<tr>
<td>Left anterior descending</td>
<td>11</td>
</tr>
<tr>
<td>Right coronary artery</td>
<td>8</td>
</tr>
<tr>
<td>Left circumflex</td>
<td>1</td>
</tr>
</tbody>
</table>
Table 2 shows the association between %SC, %stenosis and culprit section for STEMI. No significant relationship was identified between %SC and culprit section (P=0.32). The relationship between %stenosis and culprit lesion location was not statistical significant (P=0.09).

**Table 2** Generalized linear mixed statistical analysis showing relationship between %SC and %stenosis and culprit lesion location

<table>
<thead>
<tr>
<th>Culprit</th>
<th>Coef</th>
<th>StdErr</th>
<th>z</th>
<th>P-value</th>
<th>[95% Conf. Interval]</th>
</tr>
</thead>
<tbody>
<tr>
<td>% SC</td>
<td>0.03</td>
<td>0.03</td>
<td>-1.00</td>
<td>0.32</td>
<td>-0.08 0.03</td>
</tr>
<tr>
<td>% Stenosis</td>
<td>0.05</td>
<td>0.03</td>
<td>1.68</td>
<td>0.09</td>
<td>-0.01 0.11</td>
</tr>
<tr>
<td>Constant</td>
<td>0.22</td>
<td>2.74</td>
<td>0.08</td>
<td>0.94</td>
<td>-5.15 5.59</td>
</tr>
</tbody>
</table>
Figure 4 plots %SC for each section of the culprit arteries. A %SC value of 100 represented no change in length of the section from end-diastole (ED) to end-systole (ES), with variations above and below this value corresponding to lengthening and shortening respectively.

**Figure 4** Scatter plot arranged by patient number, demonstrating %SC for each coronary artery section. NC, non-culprit sections; C, culprit sections

%SC varied greatly throughout culprit and non-culprit lesions. The majority of culprit lesions had %SC values near 100 (e.g. patients 1-5) and below 100 (e.g. patient 12 & 16), while a small number had %SC above 100 (e.g. patient 14 & 19).
Figure 5 compares the distribution of non-culprit and culprit lesions across %SC. Non-culprit lesions were mainly scattered around the 100%SC value while culprit lesions were mostly distributed under 100%SC. However, this relationship did not reach statistical significance in our analysis (P=0.32).

**Figure 5** Distribution of %SC for culprit (C) and non-culprit (NC) sections.
Figure 6 groups the culprit and non-culprit sections by section number. Culprit lesions tended to cluster in the proximal and mid sections of the LAD and RCA. Only one LCx was analyzed, and the culprit lesion was in the mid section.

Figure 6 Distribution of non-culprit (NC) and culprit (C) sections across %SC. Grouping is by section number: 1, proximal RCA; 2, mid RCA; 3, distal RCA; 4, posterior descending artery; 9, proximal LAD; 10, mid LAD; 11, distal LAD; 16, proximal LCx; 17, mid LCx; 18, distal LCx.
Discussion

This study describes a novel quantitative index of coronary artery motion (QCAM4D) from four-dimensional reconstructions of invasive coronary angiography. QCAM4D did not predict the location of subsequent STEMI (p=0.32).

The result of this study was unexpected. Previous published studies performed in patients with acute coronary syndromes who were undergoing PCI either concomitantly[6] or at some point in the future after a plaque rupture event[7, 9, 10] have shown an association between the type of coronary artery motion underpinning QCAM4D and the location of culprit plaque rupture. Use of QCAM4D in this research was performed to reduce the measurement error of the methods used in these previous reports that were performed using 2-dimensional images from coronary angiography. The foreshortening artefact and out of plane magnification error inherent in measuring a moving three-dimensional artery from a two-dimensional image was hoped to be reduced by the three-dimensional reconstructions of coronary arteries used in the calculation of QCAM4D. The accuracy of the measurements of QCAM4D using the software and method described in this paper remains untested and requires validation before firm conclusions are made about the results presented in this paper.

Improved prediction of clinical events from coronary artery disease remains a compelling clinical need. Whether analysis of coronary artery motion has a role to play in meeting this clinical need requires further evaluation.
References