Contemporary Echocardiography

In

Non-ST Elevation

Myocardial Infarction

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Declaration of Work

Declaration

Name of candidate: *Nicola Jayne Smith*

This Thesis~~/Dissertation/Research~~ Project entitled *Contemporary Echocardiography in Non-ST Elevation Myocardial Infarction* is submitted in partial fulfilment for the requirements for the Unitec degree of *Master of Health Science.*

CANDIDATE'S DECLARATION

I confirm that:

- This Thesis~~/Dissertation/Research~~ Project represents my own work;
- Research for this work has been conducted in accordance with the Unitec Research Ethics Committee Policy and Procedures, and has fulfilled any requirements set for this project by the Unitec Research Ethics Committee.
  Research Ethics Committee Approval Number: *URB/11/EXP/002*

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Abstract

Background: Non-ST elevation myocardial infarction (NSTEMI) has only recently been included in the definition of acute myocardial infarction and literature is limited regarding the usefulness of echocardiography as a diagnostic tool in this setting. Since analysis of regional wall motion abnormalities (RWMAs) by standard echocardiography is highly reliant on observer experience, advanced modalities are suggested as possible complementary methods to perform quantitative RWMA assessment and observe underlying coronary artery disease (CAD); however, their utility has not been widely tested in a clinical setting.

Aim: The aim of this thesis was to explore the usefulness of echocardiography for determining systolic and diastolic dysfunction post NSTEMI and compare the results to coronary angiography. The viability and accuracy of utilising the advanced echocardiography modalities of tissue velocity imaging and speckle tracking derived velocity, strain and strain rate as novel indices for quantifying regional dysfunction and determining underlying CAD was also explored.

Method: A randomly selected data set of 55 patients admitted with NSTEMI to Christchurch Hospital, New Zealand, underwent standard echocardiography, advanced echocardiography analysis and angiography.

Results: Of 55 patients, 76% were male while 20% had diabetes and 56% were current or previous smokers. Patients with diabetes and/or smoking history were more likely to have multiple coronary lesions and nine fold more likely to require coronary artery bypass grafting. 36% of patients had a left ventricular ejection fraction (LVEF) < 60% while 18% had an LVEF < 50%. A left anterior descending (LAD) coronary artery regional infarction resulted in the lowest LVEF (50+/- 6%). Mild diastolic dysfunction was present in 80% of patients, while moderate to severe diastolic dysfunction was present in 13%. For the advanced modalities, strain and strain rate derived by tissue velocity imaging were statistically significant for all regions, except for detecting underlying CAD in the RCA territory with strain rate and for RWMA identification in the RCA territory with strain – although there was a trend towards statistical significance. Velocity did not correlate well with the territories for identifying RWMAs and underlying CAD. Good correlation was noted in the LAD and Cx regions with speckle tracking derived strain and strain rate for identifying both RWMAs. Good correlation was noted in the LAD region with strain and strain rate for identifying underlying CAD. Although there was statistical significance within these results, there was also variation and overlap.

Conclusions: The role of echocardiography in NSTEMI provides important information concerning systolic and diastolic dysfunction. We found excellent correlation between coronary angiography, clinical parameters and echocardiographic parameters. In general, the advanced imaging modalities correlated with both the presence of regional dysfunction and underlying CAD, however, there was overlap and variation within the data sets. With further technical and clinical refinement, these modalities may be useful supplementary tests to quantitatively evaluate RWMAs and to determine underlying CAD.

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Abbreviations

ACS	Acute Coronary Syndrome
AMI	Acute Myocardial Infarction
BSA	Body Surface Area
CABG	Coronary Artery Bypass Grafting
CAD	Coronary Artery Disease
CENSTEMI	Contemporary Echocardiography in Non-ST Elevation Myocardial Infarction
Cx	Circumflex Coronary Artery
DVD	Double Vessel Disease
ECG	Electrocardiogram
EF	Ejection Fraction
LAD	Left Anterior Descending coronary artery
LVEF	Left Ventricular Ejection Fraction
MRI	Magnetic Resonance Imaging
NSTEMI	Non-ST (segment) Elevation Myocardial Infarction
p	Probability (p-value)
RCA	Right Coronary Artery
RWMA	Regional Wall Motion Abnormality
RVSP	Right Ventricular Systolic Pressure
ST	Speckle Tracking
STEMI	ST Elevation Myocardial Infarction
SVD	Single Vessel Disease
TnI	Troponin I
TVD	Triple Vessel Disease
TVI	Tissue Velocity Imaging

Introduction

Non-ST elevation myocardial infarction (NSTEMI) is an acute coronary syndrome (ACS) involving acute coronary obstructions, which result in reduced oxygen to the myocardium. In 2007, the American College of Cardiology and the European Society of Cardiology altered the definition of an acute myocardial infarction (AMI), traditionally incorporating only ST elevation myocardial infarction (STEMI), to include unstable angina and NSTEMI [1]. Echocardiography is a cost effective, bedside, adjunct diagnostic tool, which involves using ultrasound to assess the structure and function of a heart after such an event; however, it was only recently included in The New Zealand Medical Journal Guidelines as a recommended test with NSTEMI presentations. Literature regarding the use of echocardiography with NSTEMI presentations is limited. Most studies have been conducted in STEMI patient cohorts. Moreover, a New Zealand audit in this field has shown surprisingly low application rates of this easily accessible test.

This study aims to describe the characteristics of NSTEMI presentation with echocardiography, specifically systolic and diastolic function. As echocardiography is highly subjective and requires an experienced operator, advanced imaging modalities such as tissue velocity imaging (TVI) and speckle tracking (ST) are suggested as modalities which provide quantitative assessment with reduced inter and intra-operator variation. These modalities, although well validated, have generally not been adapted by the clinical community (nationally nor internationally). Instead they are used mainly in the research environment. This study also aims to assess the validity and accuracy of performing these advanced modality techniques in a clinical setting.

To achieve these aims, Chapter One provides an overview of the relevant background material and identifies areas that have yet to be explored. Based on Chapter One, Chapter Two outlines the methods used to study NSTEMI echocardiography characteristics and advanced imaging modalities. Chapter Three provides the results of echocardiography and NSTEMI presentation characteristics, while Chapter Four discusses the results of Chapter Three in light of the background material presented in Chapter One. Chapter Five provides the results of the advanced imaging modalities, while Chapter Six discusses the results of Chapter Five in light of the background material presented in Chapter One. In Chapter Seven limitations of the study are discussed, while in Chapter Eight, a summary of the thesis is presented and conclusions are drawn and related back to the aims in the introduction.

Chapter One:

Literature Review

Contemporary Echocardiography

In

Non-ST Elevation

Myocardial Infarction

1 Chapter One: Literature Review

1.1 Non-ST Elevation Myocardial Infarction – An Overview

Non-ST elevation myocardial infarction (NSTEMI) has only recently been accepted as a form of acute coronary syndrome (ACS). In 2007, the American College of Cardiology and the European Society of Cardiology altered the definition of an acute myocardial infarction (AMI), traditionally incorporating only ST elevation myocardial infarction (STEMI), to include unstable angina and NSTEMI [1]. ACS is, therefore, an overarching term used to describe STEMI, NSTEMI and unstable angina. ACSs involve acute obstructions of coronary arteries, usually when an acute thrombus forms in an atherosclerotic artery. The aetiology of NSTEMI involves atheromatous plaque in coronary arteries becoming inflamed then rupturing exposing thrombogenic material [2]. This is mediated by a conformational change in membrane platelet glycoprotein receptors (IIb/IIIa), allowing aggregation of platelets, resulting in a thrombus, which interrupts blood flow (therefore oxygen) to the myocardium [3]. An AMI is myocardial necrosis from reduced blood flow to parts of the myocardium. Symptoms of NSTEMI include chest discomfort, dyspnoea, nausea and diaphoresis [4].

Diagnosis of an AMI is with biomarker elevation and electrocardiogram (ECG) changes (the latter distinguishes NSTEMI from STEMI). A STEMI is myocardial necrosis with acute ST-segment elevation and possible Q wave development, while a NSTEMI is myocardial necrosis without ST-segment elevation, with possible ST-segment depression and/or T wave inversion. Of note, as many as 20% of patients admitted with NSTEMI may show no ECG changes; therefore, a lack of ECG changes in a patient presenting with chest pain is not enough to rule out ACS and further tests should be carried out [5]. The management and outcome of AMI patients depends on the degree and location of the obstruction. With a STEMI, the coronary artery is usually totally occluded and requires urgent pharmacological or interventional revascularisation (coronary angioplasty). With a NSTEMI, the coronary artery is usually partially blocked and patients require antithrombotic therapy and/or revascularisation reducing the coronary artery stenosis [6].

This literature review focuses on the current state of knowledge regarding the benefits of utilising echocardiography as a front-line diagnostic tool with NSTEMI presentations and the usefulness of echocardiography as a predictor of prognostic outcome. Gaps in the literature will be presented as possible paths for future investigation.

1.1.1 NSTEMI versus STEMI Prognosis

Various studies, such as Allen et al. [7] and Montalescot et al. [8], have found prognostic outcomes of NSTEMI patients similar to STEMI patients. Published in 2006, Allen et al. [7] studied 760 patients: 26% presented with NSTEMI, 17% with STEMI. Unadjusted mortality over 10 years was highest in patients with NSTEMI. NSTEMI patients were associated with higher co-morbidity rates and reduced utilisation of medical therapies when compared with STEMI patients. After statistically controlling for baseline differences, they found STEMI patients had the highest mortality. This study may indicate that prior to controlling for baseline differences, NSTEMI patients are at risk of adverse prognosis resulting in-part from individual patient co-morbidities and risk factors. Furthermore, this suggests that patients presenting with NSTEMI are more likely to have higher rates of co-morbidities than their STEMI counterparts. This study was based on retrospective research and although published in 2006, utilised patients hospitalised between 1991 and 1992. Thus, the data predates modern therapies. Modern medications and protocol changes may affect the results of this study if repeated today.

In a more recent case series published in 2007, Montalescot et al. [8] compared STEMI with NSTEMI patient admissions on a large patient cohort of 2151, from multiple hospitals in France. They found STEMI patients were quicker to present to hospital (4 hours STEMI vs. 7 hours NSTEMI), were more likely to undergo percutaneous coronary intervention (71% STEMI vs. 52% NSTEMI) and on discharge were more likely to receive secondary prevention therapies. This management was not supported with the differences found in disease severity. The study found rates of re-hospitalisation were equivocal (36.7% STEMI

vs. 41.5% NSTEMI), in-hospital mortality rates were equivocal (4.6% STEMI vs. 4.3% NSTEMI) and one year mortality rates were equivocal (9% STEMI vs. 11.6% NSTEMI). The study suggested heart failure and age were the highest one-year mortality predictors. This study is pivotal to understanding the similarities between STEMI and NSTEMI presentations. Although prognostic outcome between NSTEMI and STEMI is comparable, patients presenting with NSTEMI are often treated less effectively than their STEMI counterparts [9].

1.1.2 Troponin I (TnI)

NSTEMI diagnosis requires acute presentation of patients with ischemic symptoms (such as chest, upper extremity, jaw and/or epigastric pain, possibly accompanied by dyspnoea, nausea or syncope), ECG changes (T wave inversion or ST depression) and enzyme biomarker elevation. The biomarker troponin I (TnI), measured in μg/L, is primarily utilised at Christchurch Hospital, New Zealand as a marker of acute myocyte necrosis. It uses the 99th percentile as a reference limit of elevation [10]. TnI is regarded as the most sensitive and specific biomarker for myocardial damage with levels beginning to rise around 3-4 hours post event [11]. An increased TnI value suggests elevated acute risk and reduced long term prognostic outcome [12]; however, it does not reflect the mechanism for elevation, so further pathology such as aortic dissection or pulmonary embolism should be excluded [1]. Echocardiography allows for quick differentiation of these diagnoses in most patients, so should be considered as a diagnostic tool upon NSTEMI admission for this reason alone.

1.1.3 NSTEMI Patient Characteristics

Risk stratification is an important part of the decision making process when a patient presents with NSTEMI [13]. Risk stratification involves analysing patient presentation symptoms, ECG tracings, biomarker elevations, patient characteristics, co-morbidities and risk factors. This process ensures adequate therapy is utilised on an individual patient basis, which reduces hospital stay, re-admission and, therefore, the cost to the public health system. Echocardiography is a quick and affordable diagnostic tool that assists in the risk stratification process, highlighting important individual characteristics of patients which may be useful for management.

The average age of patients presenting with NSTEMI has been well documented as the 7th decade of life [7, 14, 15]. The New Zealand ACS audit, performed by Ellis et al. [15], studied all ACS patients admitted to New Zealand hospitals in 2007 over a 14-day period. They found the interquartile range was of aged between 56 and 78 years. It is well documented that a higher proportion of males (than females) present with NSTEMI [7, 8, 15, 16]. Gehrie et al. [16] found females were more likely to have non-obstructive coronary artery disease on angiography than men (15.1% vs. 6.8%), with better prognostic outcomes, although the underlying pathophysiology for this was not studied. Atypical NSTEMI presentations and complaints are more common in women, the elderly and patients with diabetes [17], often making diagnosis particularly challenging.

Patient co-morbidities and risk factors such as diabetes and smoking, contribute to the prognostic outcome of individual NSTEMI presentations. Diabetes is a topical global disease due to its heavy demands on the health system [18]. Type II diabetes is due to high blood glucose levels - either the body does not make enough insulin or the body's cells do not respond properly to insulin [19]. Diabetes affects the heart in numerous ways. This includes metabolic disturbances and increased vascular permeability, which result in myocyte apoptosis, left ventricular hypertrophy, decreased myocardial perfusion and systolic and diastolic dysfunction [20], [21]. The New Zealand ACS audit [15] performed in 2007 found

19% of patients had diabetes mellitus. The 2004 Global Registry of Acute Coronary Events [22] performed a prospective study on 5403 patients admitted with ACS from 94 hospitals. They found one quarter of the patients had diabetes. These patients were more likely to be older, female, have co-morbidities and were less likely to be treated with effective medical therapies. They also had an increased risk of heart and renal failure and all-cause mortality. Danahoe at al [23] performed an audit on patients with ACS from 11 independent clinical trials, published in 2007. Of a total 62,036 patients (46,577 were diagnosed with STEMI and 15,459 were diagnosed with unstable angina/NSTEMI), 10,613 (17.1%) had diabetes. Mortality at 30 days for NSTEMI patients with diabetes was 2.1%, compared to 1.1% for non-diabetics, while the one-year mortality rate for NSTEMI patients with diabetes was significantly higher than that for non-diabetics (7.2 vs. 3.1%). They concluded that diabetes resulted in significant adverse prognosis, highlighting the need for aggressive strategies to manage this disease.

Smoking has also been linked to an elevated risk of AMI [17], however, regardless of public awareness, it is still a common community burden. The New Zealand ACS audit [15] found 17% of patients admitted with NSTEMI were current smokers, while 39% had smoked in the past. Published in 2012, George et al. [24] reported a link between smoking and coronary artery disease (CAD) using a prospective cohort study of more than 91,5000 patients. They found smokers were at higher risk of significant CAD than non-smokers when presenting with ACS. A limitation of this study was the failure to determine alternative risk factors such as diabetes, congestive heart failure or family history. It was also unclear whether ex-smokers qualified as non-smokers and what a significant smoking history would involve (i.e. cigarettes per day/packs per year).

Patient in-hospital mortality rates after an AMI vary depending on the degree of heart failure present. This was demonstrated by a landmark study published in 1967 by Killip et al. [25], who studied 250 patients in a coronary care unit over a two year period. From the data retrieved the Killip classification was created, which grades the severity of heart failure symptoms post AMI. Killip et al. [25] found the in-hospital mortality rate was approximately 10% and primarily determined by the severity of heart failure in NSTEMI and STEMI

presentations. Guidelines and clinical management have changed significantly since this study was published (1967), however, the trends between STEMI and NSTEMI admissions are still relevant. A global study [26], found the 30 day mortality rate overall was 6.2% for ACS patients and individually, was 7.4% for NSTEMI patients and 11.1% for STEMI patients, further supporting prognostic outcome similarities between the two syndromes. This study, however, was published in 2006. A repeat of the global study in 2009 by the same researchers found ACS 30 day mortality rates had decreased from 6.2% to 5.1%. This was thought to be the result of increased guideline adherence (as patient characteristics were similar in both studies), increased use of evidence based therapies/interventions and the availability of state-of-the-art cardiology departments [27].

1.2 Echocardiography and NSTEMI

In current clinical practice, echocardiography is recommended when a patient presents with STEMI and NSTEMI. The New Zealand STEMI Guidelines suggest '…acute echocardiography demonstrating regional wall motion abnormalities (RWMAs) may be a useful adjunct for diagnosis and assessment of complications' [28]. Similarly, the New Zealand NSTEMI guidelines recommend echocardiography "…in all patients with elevated troponin and those with ECG abnormalities to assess global and regional left ventricular function, assess the valves for defining differential diagnoses" [29]. The national audit [15] found 62% of patients admitted with STEMI received an echocardiogram, while only 22% of patients admitted with NSTEMI received an echocardiogram. This is surprising, as shown in previous studies, with current clinical management, STEMI and NSTEMI prognostic outcome is similar. This audit was performed in 2007, when the guidelines for NSTEMI did not include recommendations for echocardiography and modern clinical management of NSTEMI was still evolving.

Echocardiography is an excellent real time diagnostic procedure with moderate temporal and spatial resolution [1], useful for assessing mechanical complications or cardiac abnormalities and variants. With NSTEMI presentations, echocardiography is highly useful when assessing myocardial contraction - differentiating areas of endocardium which are contracting normally from areas which are hypokinetic (reduced motion), akinetic (no motion) or diskinetic (dyssynchronous motion).

Assessment of cardiac function by echocardiography may be split into two areas – systolic function and diastolic function. Echocardiographic indices helpful in the assessment of systolic dysfunction include left ventricular systolic volume, left ventricular ejection fraction (LVEF) - which represents the percentage of blood ejected from the left ventricle with each cardiac contraction, infarct size and location, mitral regurgitant jet severity and the presence of left ventricular hypertrophy [30]. Echocardiographic indices helpful in the assessment of diastolic dysfunction include grades of diastolic dysfunction, E/Em filling

pressures (early mitral inflow velocity to peak mitral annular velocity which is an estimate of left ventricular filling pressure), E:A ratio (mitral inflow Doppler ratio between early filling velocity and late filling velocity) and left atrial volume [31]. When compared with the vast pool of STEMI literature, there is a marked absence of studies assessing diastolic dysfunction in NSTEMI presentations. The available literature is limited to a small number of significant studies. This study hopes to add to the small pool of NSTEMI literature by assessing the degree of diastolic dysfunction present in a sample of NSTEMI patients.

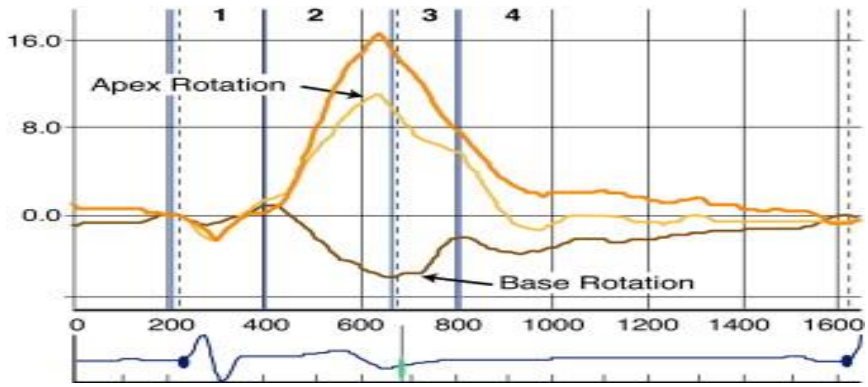
1.2.1 Echocardiography and Systolic Function

RWMAs often occur after an AMI and often result in global LVEF impairment, which is the most common form of systolic dysfunction in NSTEMI patients. RWMAs result in reduced myocardial contraction at the site of or downstream from the occlusion and are identified by visualising areas of reduced systolic endocardial thickening at the blood/tissue interface within the left ventricle. LVEF is generated from the difference in left ventricular end-diastolic and end-systolic volumes from two orthogonal planes of the left ventricle in the apical four chamber and apical two chamber views, using the Simpson's Biplane method [32]. These views are generated from the apical window which is located in the fifth to sixth intercostal space in the median axillary line. With the cursor marker pointing to approximately one o'clock the apical four chamber view is visualised. A 60º-90 º anti-clockwise rotation creates the apical two chamber view while a further 60 º anti-clockwise rotation creates the apical long axis view. RWMAs and global LVEF identified with echocardiography have been well-validated [33-36] and provide important information on the relationship between the location and extent of RWMAs present, ECG location and size, the status of the patient, complications and survival [37].

Infarct locations may be defined regionally: anterior, inferior or lateral or by afflicted coronary artery territory: left anterior descending (LAD), right coronary artery (RCA) or circumflex (Cx). Anterior infarcts and LAD occlusions are usually larger, associated with

lower LVEF and worse prognosis. A study published in 1987 by Hands et al. [38] assessed 42 patients (19 with anterior infarction, 23 with inferior infarction) presenting with their first STEMI. They found for similar sized inferior and anterior infarcts, anterior infarcts were associated with a lower resting LVEF, increased extent and size of resting RWMAs and increased exercise induced ST-segment elevation which contributed to a poorer prognostic outcome. Future studies may determine whether ST depression and T wave inversion is more marked in anterior NSTEMI infarctions than inferior infarctions. A study published in 2000 by McClements et al. [39] assessed 69 patients one week after AMI who received no thrombolytic therapy or revascularisation. They found a strong correlation between LVEF and the extent and size or RWMAs present. The LVEF was reduced most with an anterior infarction, suggesting that infarct size, location, severity and the extent of apical involvement were the most important predictors for LVEF. A study published in 1982 by Thanavaro et al. [40] assessed 1105 patients presenting with their first transmural AMI – 611 anterior and 494 inferior. They found patients with inferior infarctions had lower in-hospital mortality (9.1% vs. 15.6%; p 0.0014), and congestive heart failure rates (39.4% vs. 47.6%; p 0.006) than patients with anterior infarctions. Many different mechanisms have been investigated as explanations for greater LVEF impairment in anterior infarcts. The internal mechanics of cardiac function are complex and not completely understood. There are several layers of muscle in the myocardium which travel in different directions. Rotation occurs in the left ventricle with the apex and base rotating in opposite directions. The image below shows ST B-mode interpretation of torsion angles of the myocardium (Figure 1).

Figure 1: Torsion of the Myocardium with Speckle Tracking



In the ejection phase (indicated by the number 2 at the top of the graph) the apex moves in a counter-clockwise rotation, while the base moves in a clockwise rotation, with torsion recoil apparent in the isovolumic relaxation phase (indicated by the number 3 at the top of the graph) and early diastolic filling phase (indicated by the number 4 at the top of the graph). Note that the LV base moves with a lower magnitude than that of the LV apex.

Reproduced from Sengupta et al. [41]

Studies performed on dogs by LeWinter et al. [42] found regional differences within the myocardium. Fibres shortened more at the apex than the mid-ventricular or basal wall. Although the canine heart is similar in terms of physical mechanics to a human's, it is not a perfect model, so results must be approached with a degree of caution [43]. It is also reported that as the apex is supplied blood by a single vessel (the LAD), if occluded, it will affect the entire apical region circumferentially resulting in the significant reduction of long axis shortening. Also, left ventricular minor axis shortening, the main contributor to left ventricular stroke volume, is also mainly dependent on blood supply from the LAD to the anteroseptal wall [39, 44]. A study published in 1986 by Tamaki et al. [45] utilised isotope ventriculography to determine variations in regional contractility in the first ten days post AMI. They found contractile improvements were greater in patients with single vessel disease in the Cx or RCA regions than LAD region. Furthermore, contractility improved more with single vessel disease than with multiple vessel disease.

There is an absence of data regarding RWMAs associated with NSTEMI presentations and their relation to angiographic findings. One study published in 1998 by Weisman [37] determined the aetiology of chest pain presentations in an emergency department. He scanned 175 patients, 88 (51%) had no RWMAs while 87 (49%) had RWMAs present. Of the 87 patients with regional dysfunction, only 27 (31%) were diagnosed with an AMI. This study provides interesting information regarding the prevalence of RWMAs however does not differentiate between STEMI and NSTEMI nor does it state whether the RWMAs detected correspond to a specific occluded coronary artery. A retrospective audit was performed at Christchurch Hospital, New Zealand in 2007 utilising patients presenting with NSTEMI undergoing both echocardiography and angiography [46]. The study revealed 60% of NSTEMI patients had RWMAs on echocardiography, with 89% of the RWMAs correctly predicting the culprit artery identified with angiography.

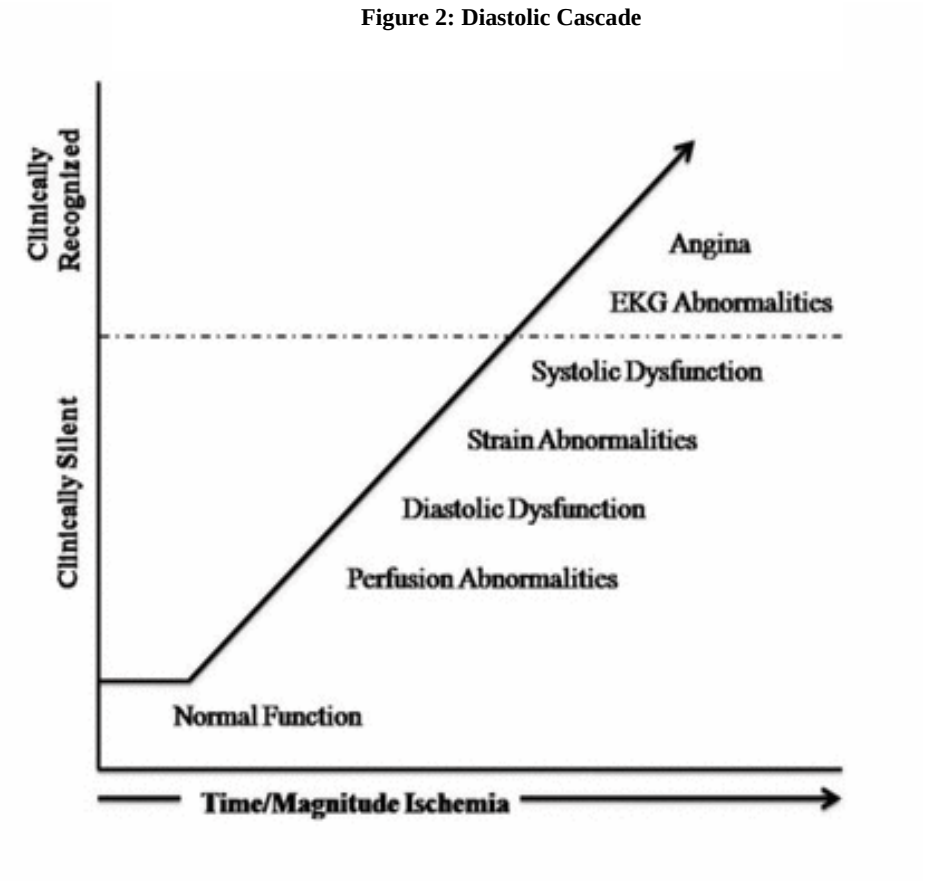
Further studies have described how left ventricular remodelling (adverse structural and functional changes in myocardium remote to the infarct zone) in response to myocardial infarction may be site specific and an important prognostic indicator of cardiovascular events in the future [47].

There are gaps in existing NSTEMI literature with regards to identification of regional dysfunction and determining if the dysfunction visualised corresponds to a culprit coronary artery determined with coronary angiography. This research project hopes to bridge the gaps in literature concerning NSTEMI admission and systolic function as addressed above, in a limited sample population of 55 patients.

1.2.2 Echocardiography and Diastolic Function

The diastolic phase of the cardiac cycle has historically been somewhat overlooked as a non-invasive, quick technique to further determine prognostic outcome. Diastolic dysfunction is the result of increased myocardial stiffness from a variety of factors including interstitial oedema, fibro-cellular infiltration and scar formation after an AMI [48]. A process termed the diastolic cascade (Figure 2), when diastolic dysfunction precedes systolic dysfunction [49-51], has been validated as an early indicator of congestive heart failure after an AMI [52-54]. The diastolic cascade begins with an oxygen supply and demand imbalance, followed by metabolic alterations within the myocardium. The physiology is rather complex, however, remodelling of the left ventricle post infarction (such as reparative interstitial fibrosis and the development of scar tissue) leads to impaired left ventricular relaxation, hypertrophy and asynchrony. Pre-existing diabetes may also predispose to diastolic dysfunction. Left ventricular hypertrophy, the primary cause of chamber stiffness, leads to diastolic dysfunction [55].

Figure 2: Diastolic Cascade



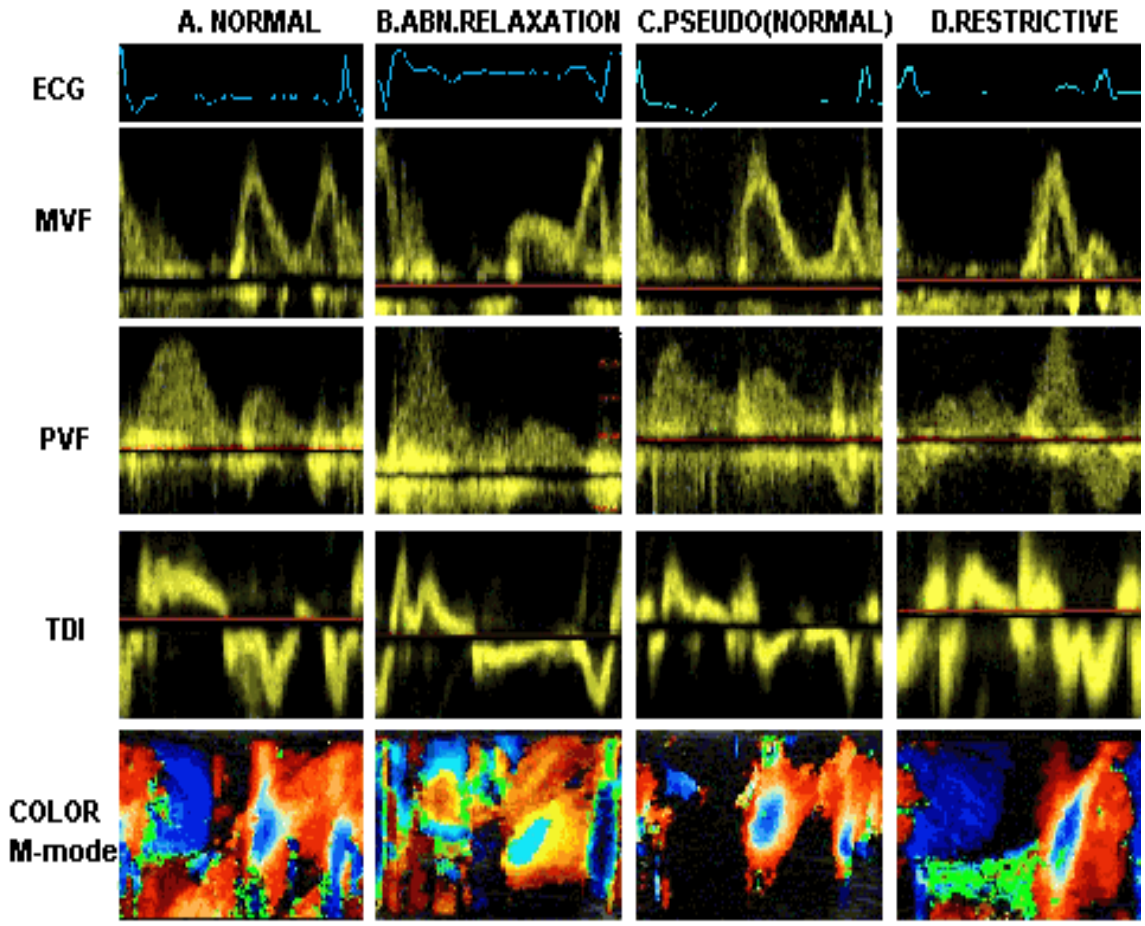
The diastolic cascade begins with perfusion abnormalities, which result in diastolic dysfunction, which then leads to systolic dysfunction (a reduction in left ventricular systolic function).

Where: EKG = electrocardiogram

Reproduced from Herzog et al. [56]

The determination of diastology by echocardiography is based mainly upon transmitral and septal tissue Doppler interrogation; however pulmonary vein inflow and colour m-mode flow propagation may also be used. Diastolic dysfunction can be broken down into four main patterns/grades (Figure 3). Grade one is mildly impaired diastolic dysfunction, with an abnormal relaxation pattern. Grade two is moderately impaired diastolic dysfunction, with a pseudonormal relaxation pattern. Grades three and four are severely impaired diastolic dysfunction, with restrictive relaxation patterns, defined by an increased E wave and a short E deceleration time (<140ms). Grade three is reversible, while grade four is not [30].

Figure 3: Diastolic Dysfunction Patterns



Diastolic dysfunction patterns identified with echocardiography. In this diagram, Grade one is abnormal relaxation, grade two is pseudonormal relaxation and grade three is restrictive relation (grade four is not shown). The MVF (mitral inflow) and TDI (tissue velocity imaging) profiles were used for this study.

Where: ECG = electrocardiogram; MVF = mitral inflow; PVF = pulmonary vein flow; TDI = tissue velocity imaging; colour m-mode = colour motion mode

Reproduced from Roelandt et al. [57]

A number of studies have examined whether restrictive diastolic dysfunction is useful in ACS presentations, to predict prognostic outcome, with have varied results. Occasionally studies have failed to demonstrate the value of these indices [58, 59]; however, the majority of studies find restrictive diastology to be an excellent predictor of clinical outcome, associated with higher left atrial filling pressures and increased rates of mortality post AMI [48, 58, 60-63]. A study published in 2010 by Hee et al. [64] validated restrictive diastolic

dysfunction as a predictor of clinical outcome post STEMI in a long term (five year) study of 100 patients. Restrictive diastolic dysfunction was defined as an E:A >2 and/or a mitral E deceleration time of <140ms. They found patients with restrictive diastolic dysfunction had higher myocardial enzyme levels ($p<0.001$), a high E:A ratio, lower tissue Doppler imaging septal Em, increased left atrial volume, decreased LVEF and a higher incidence of all-cause mortality. As this study was retrospective, echocardiography timings were variable (within a 6 week range) and pre-existing diastolic dysfunction and co-morbidities (such as diabetes or heart failure) were not determined. Published in 2008, a large meta-analysis involving 3396 patients from 12 prospective post infarction clinical trials found ~20% incidence of restrictive diastolic dysfunction. These patients were more likely to have diabetes, hyperlipidaemia, anterior myocardial infarction, increased left ventricular volume, decreased LVEF and a higher Killip Class [65]. Two interesting findings from this study were: that restrictive diastolic dysfunction predicted outcome even with preserved LVEF, and restrictive filling was associated with a three-fold increase in all-cause mortality. The large patient cohort of this study suggests it is reliable as an indicator of a true patient population.

In the past, diastolic impairment with a preserved LVEF (defined as >50% [30]) was thought to be relatively benign in the setting of AMI, but this is now known not to be the case [65]. Although restrictive diastolic dysfunction has been fairly well studied and validated in ACS presentations, less is true for mildly impaired and pseudonormal diastolic dysfunction. A prospective study on 125 patients post AMI found patients with pseudonormal diastolic dysfunction (defined when mitral E deceleration time was normal: 140-240ms, while propagation velocity was decreased) had a high occurrence of in-hospital heart failure and a poor prognostic outcome [60]. These patients were older with greater heart failure complications than those with normal or mildly impaired diastolic dysfunction. Studies which have assessed mildly impaired diastolic dysfunction have yet found no significant correlation with mortality rates when adjustments are made for age, Killip Class and LVEF [66, 67]. The fact that pseudonormal diastolic function is associated with raised filling pressures, while mildly impaired diastolic dysfunction is not, may indicate a link between filling pressures and prognostic outcome.

A filling pressure (E/Em) of >15 has been associated with a worse prognostic outcome. A review in 2004 performed by Khouri et al. [68] stated E/Em >10 was abnormal, while E/Em was highly specific for raised left atrial filling pressures. This has been confirmed by other studies [69, 70]. A retrospective study in 2004 of 250 patients with AMI found filling pressure to be a predictor of all-cause mortality [71]. Filling pressure is, however, affected by a number of factors including loading conditions (i.e. heart rate, beta-blockers and cardiac remodelling), which must be taken into account before relying heavily upon an E/Em value [72].

Left atrial dilatation is reported as a predictor of filling pressures and prognostic outcome. When a left atrium empties into a stiff left ventricle, left atrial pressures increase (as the walls of a left atrium are thin due to a normally low pressure environment) and dilatation occurs [73]. Left atrial dilatation has been associated with an increase in all-cause mortality [74, 75]. A prospective study was published in 2011 by Kuhl et al. [76] involving 384 patients presenting with NSTEMI. These patients underwent gated 64-slice coronary angiography to measure left atrial size and function and were then monitored over two subsequent years. Over two years, 9% of patients died. The left atrial minimal volume and fraction change were likely independent predictors of mortality, while left atrial maximal volume were likely not associated with increased mortality. Research published in 2004 by Beinart et al. [74] studied 55 patients admitted with AMI. They found patients with a left atrial volume >32mL/m^2 had higher rates of congestive heart failure, mitral regurgitation, larger left ventricular volumes and lower LVEF. These patients also had higher five year mortality rates than patients with a left atrial volume <32mL/m^2 (35% versus 14%). These studies confirm important prognostic information may be extrapolated from the size/volume of the left atrium.

The E:A ratio value is also recommended as an indicator of prognostic outcome. A meta-analysis (as yet unpublished) performed by Whalley et al. [77] utilising 2344 patients found E:A <1 had a mortality rate of 12.3%, E:A 1-2 had a mortality rate of 21.3% while E:A >2 had a mortality rate of 30.9%. The results showed that higher E:A ratios were related to increased rates of all-cause mortality.

1.3 Limitations of Current Clinical Echocardiography

Echocardiography is an effective, affordable, bedside diagnostic tool, but it relies on accurate individual assessment and interpretation of indices by an experienced reader, specifically for assessment of RWMAs post AMI. Also, often there are minute changes in systolic function which are too small or too quick for the human eye to process. For this reason, ultrasound manufacturers have created different methodologies for semi-quantifying or quantifying RWMAs, enabling less reliance upon individual interpretation, thereby reducing bias. Two methods to be evaluated in our research are tissue velocity imaging (TVI) and speckle tracking (ST) from which velocity (v), strain (%) and strain rate (/s) data may be derived.

1.4 Conclusion: Literature Review - Echocardiography Characteristics of NSTEMI Presentations

In summary, previous literature has shown that the presence of diastolic dysfunction with echocardiography plays a vital role in determining the prognostic outcome of patients post AMI and may also indicate significant underlying CAD [78]. As diastolic dysfunction has been observed to precede systolic dysfunction, it may characterise disease earlier than visualisation of RWMAs or LVEF decline. Most studies showing echocardiography as a predictor of outcome post AMI have been conducted in patients with STEMI. Data concerning the NSTEMI population is fairly limited in comparison and certainly warrants further investigation. It is likely that the more severe grades of diastolic dysfunction will occur in lower prevalence in this population, compared to the STEMI population. However, it has been shown in multiple clinical scenarios that once severe diastolic dysfunction is present, it carries poor prognosis, despite the underlying cause. Therefore, identification of diastolic dysfunction is an important adjunct to clinical information and may assist with management.

1.5 Advanced Imaging Modalities: Tissue Velocity Imaging and Speckle Tracking Derived Velocity, Strain and Strain Rate

To overcome the limitations posed by conventional two-dimensional echocardiography, new advanced echocardiographic modalities now enable semi-quantitative and quantitative assessment of regional dysfunction as well as the ability to detect underlying CAD. The two modalities to be evaluated in this research are tissue velocity imaging (TVI) and speckle tracking (ST). From these modalities, values for velocity (v), strain (%) and strain rate (/s) may be derived.

For TVI and ST derived velocity, normal segments (those with no RWMAs or CAD) will be positive in systole. Hypokinetic segments will be also positive in systole but of lower velocity. For TVI and ST derived strain and strain rate, normal segments (those with no RWMAs or CAD) will be high/increased negative waveforms in systole (further from the baseline). Hypokinetic segments will be negative; with lower/decreased strain values (will appear closer to the baseline). In the case of diskinesis, the waveforms of strain may be inverted (positive in systole when they should be negative). Studies determining normal values are discussed below, while normal TVI derived velocity, strain and strain rate values are shown in Table 21 in the appendix.

1.5.1 Tissue Velocity Imaging Derived Velocity, Strain and Strain Rate

TVI is a velocity based measurement which enables analysis (from time-interval calculations and myocardial contraction/relaxation velocities throughout the cardiac cycle) of signals from tissue which have high amplitude and low frequency [79]. TVI uses myocardial Doppler frequency shifts to quantify tissue motion [80], is relatively load independent and considered an accurate indicator of systolic and diastolic function [81]. TVI images were obtained from a GE Vivid 7 machine (software version 2.2.1., GE Vingmed Ultrasound

System, Horten, Norway) with data analysis performed on EchoPac (GE Vingmed Ultrasound System, Horten, Norway). The peak systolic myocardial velocity, strain and strain rate of all segments of the left ventricle is measured then trends are analysed and compared within the data set. A study published in 2010 by Dalen et al. [82] provided normal values for regional segmental assessment by measuring the peak systolic myocardial velocities in a large normal patient cohort (without prior cardiac history). TVI velocity traces are considered raw data as they are less processed than strain or strain rate traces and, therefore, the most reproducible [83].

TVI is based on the principle of Doppler, which was originally used for blood flow and obeys the basic laws of physics concerning fluid motion. Tissue Doppler contends with the motion of the myocardium, which is complex - the segments within the myocardium are affected by tethering of adjacent segments and by the overall translational motion of the heart [84]. To overcome this problem, myocardial strain and strain rate can be derived from TVI velocity traces on the prospectively on the GE Vivid 7 machine (software version 2.2.1., GE, Horten, Norway) or retrospectively with EchoPac (GE Vingmed Ultrasound System, Horten, Norway), if prompted. Strain is a dimensionless value. It is deformation (stretching) of an object, relative to its length, which may be positive (fibre lengthening) or negative (fibre shortening) [85]. Strain and strain rate provide regional and global information on myocardial contraction [80]. Strain rate provides information which is too fast for the human eye to process in real time. Post-processing of the waveforms allows comparisons between different areas of the myocardium [80]. The equations for strain (Figure 4) and strain rate (Figure 5) are described by the equations below:

Figure 5: Strain Rate

$$SR = \frac{v_a - v_b}{d}$$

Figure 4: Strain

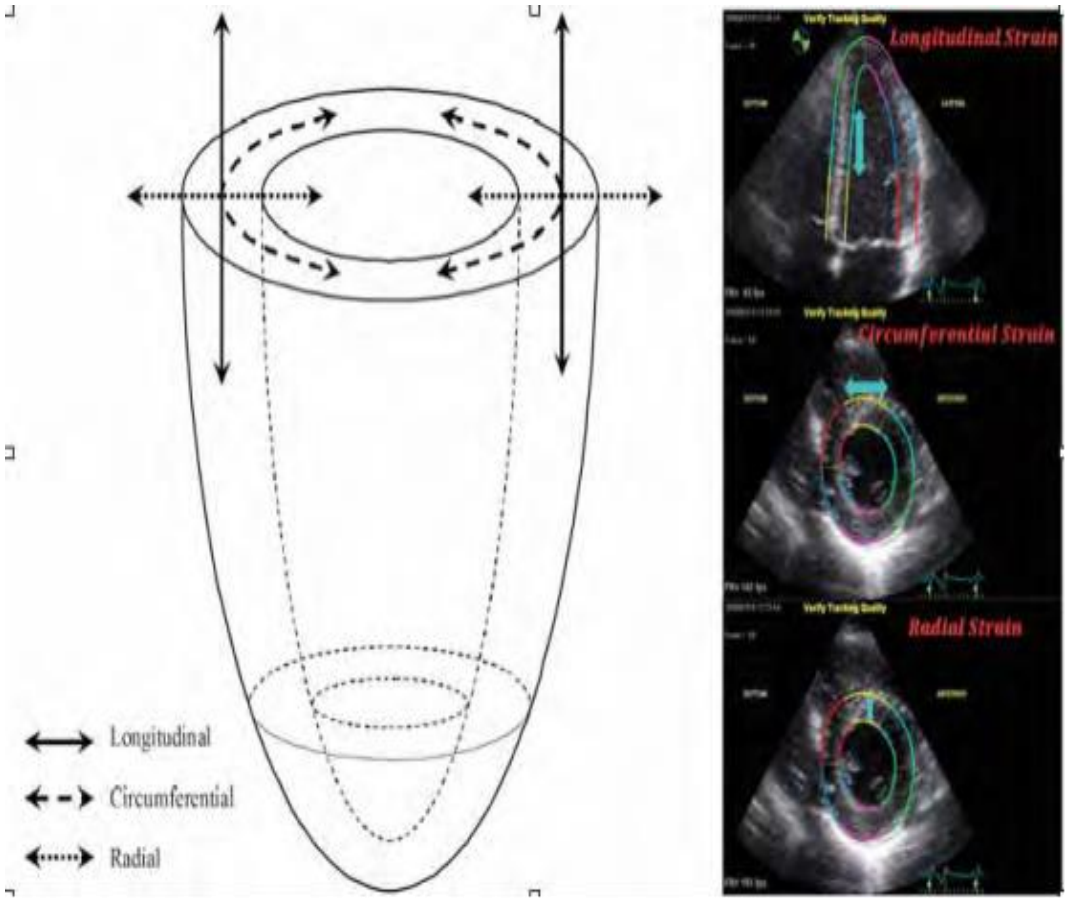
$$S = \frac{l - l_0}{l_0} = \frac{\Delta l}{l_0}$$

Where: S = strain; l = instantaneous length; l_0 = original length; Δl = change in length; SR = strain rate; v = velocity; v_a-v_b = difference in instantaneous myocardium at points $_a$ and $_b$; d = distance in instantaneous myocardium at a specific time

Reproduced from GE Healthcare [80]

TVI derived strain and strain rate imaging may be used to analyse longitudinal shortening - which is negative strain (apical views), transmural function - which is positive strain (apical and parasternal short axis views), or circumferential function - which is negative strain (parasternal short axis views) [86] (Figure 6). This research will focus on longitudinal (negative) strain and strain rate values obtained from the apical views, which studies suggest, are the most reproducible and the most accurate when assessing regional contraction and underlying CAD when compared with gold standard tests such as tagged magnetic resonance imaging (MRI) [86]. Transmural and circumferential strain indices are best proven for anterior and posterior segmental assessment and that is where their predominant clinical use lies.

Figure 6: Diagram of Longitudinal, Circumferential and Radial Strain



Reproduced from Leung et al. [87]

The figure shows cardiac motion in the longitudinal (which is shortening and negative), circumferential aka transmural (which is shortening and negative) and radial (which is thickening and positive) directions.

Regional assessment is performed by analysing the peak systolic strain and peak systolic strain rate in 15 segments of the left ventricle. The values from each segment may be compared with normal values by myocardial level (basal, mid, distal) or between walls (anteroseptal, anterior, anterolateral, inferolateral, inferior, inferoseptal) as suggested by Dandel et al. [82]. TVI derived strain rate is the most processed method of TVI imaging, so is the least reproducible, however, it is the least affected by tethering and torsion of the heart [85].

Various studies, including those of Urheim et al. [88] published in 2000 and Edvardsen et al. [89] published in 2002, have validated the feasibility of myocardial strain by Doppler echocardiography. Urheim et al. [88] induced apical ischemia in 13 anesthetised dogs. While the apical myocardium became diskinetic (indicated by strain and Doppler velocities), the basal segment values for strain by Doppler and strain by sonomicrometry and velocity of shortening by sonomicrometry were unchanged. Doppler velocities at the base showed decreased values (4.2+/-0.7 to 2.7+/-0.4cm/s) suggesting that strain is less influenced by cardiac tethering and cardiac motion. The major limitations of this study were that it was performed on anesthetised dogs and the sample population (13) was small. The study did, however, indicate the general trends and benefits of utilising TVI derived strain.

Edvardsen et al. [89] performed longitudinal and radial TVI strain and strain rate on 33 normal patients and 17 patients with AMI. In the 33 normal patients, the longitudinal myocardial Doppler velocities decreased from the base to the apex, while the myocardial strain and strain rate indices remained uniform. In the 17 patients with AMI, the infarcted segments showed only 1.5+/-4.3% longitudinal strain compared with -15.0+/-3.9% in remote myocardial segments. A further comparison between myocardial strain and strain rate indices and tagged MRI revealed excellent correlation with longitudinal values (r=0.89). Their study utilises a small patient population which is not indicative of a true population, therefore only trends should be analysed from this data. The frame rates used for TVI in their study ranged from 56-134 frames per second with a mean of 92. TVI involves the rapid analysis of increased velocity motion with very short duration, which means a high sampling rate is required. A study published in 2002 performed by Lind et al. [90] concluded frame rates with

a cut-off of 70 frames per second for E velocity analysis and 100 frames per second for all other systolic and diastolic analysis allowed an acceptable <10% deviation of results, with the optimal being between 141-203 frames per second (fps). This indicates that the frame rates used by Edvardsen et al. [89] were often lower than required (however, may conform to guidelines not stated in their research).

A study published in 2003 by Hasegawa et al. [79] investigated the ability of myocardial strain to quantify regional myocardial contraction in patients with normal wall motion and patients with RWMA. The study found that peak systolic strain values of segments with differing contraction were significantly different to one-another – normokinetic -20.1 ± 5.5%; hypokinetic -11.9 ± 5.0%; akinetic -6.3 ± 3.4%. There was no significant overlap, suggesting myocardial strain agrees well with visually assessed wall motion. This study is limited by its small sample population of 13 patients with normal wall motion, and 18 patients with RWMA resulting in possible sampling/bias issues.

Studies have also shown the ability of TVI to detect significant underlying CAD (>70% stenosis), with no visual RWMAs. A study published in 2008 by Choi et al. [91] showed mid and basal peak longitudinal strain cut off values of -17.9% to be indicative of detecting severe 3 vessel disease or left main CAD (sensitivity 78.9%, specificity 79.3%), when there was an absence of RWMA with standard echocardiography. The sample population enrolled in this study was limited (189 patients with suspected angina and 110 patients with suspected CAD); however, important information regarding the diagnosis of underlying CAD was identified with this study. Future studies should employ a larger patient cohort to confirm these results.

For TVI derived velocity, increased myocardial contraction results in higher systolic values. TVI derived strain and strain rate in systole result in negative values, therefore, better myocardial contraction results in values further away from the baseline (more negative), while abnormal or reduced motion is indicated by values closer to the baseline (less negative). In a heart with no diskinetic cardiac motion, strain and strain rate systolic values are always negative in systole. Although these methods appear to provide supplementary

quantifiable assessment of RWMA, TVI remains a Doppler based measurement. This means it is angle dependent and suffers from significant noise problems (especially at the apex), as well as difficulty in tracking the region of interest throughout the cardiac cycle and tethering from neighbouring segments [92].

1.5.2 Speckle Tracking Derived Velocity, Strain and Strain Rate

ST overcomes the limitations of TVI by tracking speckles (which result from constructive and destructive interference of ultrasound backscatter from structures within the myocardium, smaller than the wavelength of the ultrasound beam) from frame to frame with the geographic shift corresponding to local tissue movement [93]. The resulting information is then post-processed into traces showing the velocity, displacement, strain (a measurement of deformation) and strain rate (speed at which deformation occurs) of a specific myocardial segment [94]. ST is able to track the myocardium independently of cardiac translation and interrogation angle [95], with no significant base to apex gradient [85]. ST images were obtained from a GE Vivid 7 machine (software version 2.2.1., GE Vingmed Ultrasound System, Horten, Norway) with data analysis performed on EchoPac (GE Vingmed Ultrasound System, Horten, Norway). The peak systolic myocardial velocity, strain and strain rate of all segments of the left ventricle is measured then trends are analysed and compared within the data set.

Studies have determined the validity of ST [92, 96-98]. A study published in 2009 by Amundsen et al. [92] compared TVI derived strain rate with ST derived strain rate using tagged MRI as a reference. They found ST may be used alone or combined with TVI, providing acceptable regional myocardial values. Also, that ST strain values were more reproducible than tagged MRI values. A study published in 2005 by Cho et al. [96] compared ST derived strain and TDI derived strain with tagged MRI. They found values for tagged MRI comparable with TDI and ST derived strain when assessing segments with dysfunction.

Global strain, the average of the individual segmental strain within an imaging plane (apical four chamber, two chamber of apical long axis view) has been associated with LVEF. A study published in 2004 by Reisner et al. [97] found global longitudinal strain and strain rate values were good indicators of global left ventricular function with high sensitivity and specificity. The study had a small sample population of 27 patients post AMI. The study attempted to reduce bias by using a non-echocardiographer to interpret the results but this calls into question the ability/competence of the non-echocardiographer. A study published in 2006 by Becker et al. [98] suggested ST strain and strain rate assessment of regional LVEF, resulted in highly reproducible values with low intra-observer and inter-observer variation. The patient cohort was small (64). Frame rates were between 56-92 fps which is excellent as frame rates for speckle tracking should be around 40-80fps to maximise spatial resolution for frame-by-frame tracking of acoustic markers [99]. These studies confirm the feasibility of performing ST derived indices as accurate indicators of both regional and global systolic function.

Various studies have validated the use of ST strain and strain rate when identifying RWMA. Decreased ST derived longitudinal segmental strain values imply a regional myocardial infarction with greater sensitivity and specificity than TVI. A study published in 2007 by Gjesdal et al. [100] found peak systolic longitudinal strain values of -15% could identify an infarction (sensitivity 83%, specificity 93%) at the segmental level. The patient population sample was small (38) and the study only used the apical long axis window. A study published in 2010 by Eek et al. [101] found good correlation between infarct size, wall motion score index ($r=0.74$, $p=<0.001$) and global longitudinal strain ($r=0.68$, $p<0.001$) in patients with recent NSTEMI. The patient cohort was small (68), however, the study used tagged MRI, regarded as a gold standard test, as a reference. A study published in 2009 by Roes et al. [102] compared the ability of ST strain with contrast enhanced MRI to accurately assess the extent of endocardial scar tissue. Good correlation was found with cut-off values showing segments both without scar tissue (-10.4% +/- 5.2%) and with scar tissue (0.6% +/- 4.9%). They also found that a regional longitudinal strain cut off of -4.5% distinguished a non-transmural infarct from a transmural infarct (sensitivity 81.2%, specificity 81.6%).

1.5.3 Advanced Imaging Modalities: Current Lack of Clinical Utility

Neither TVI nor ST derived velocity, strain nor strain rate have been adapted as routine tests post AMI at the Christchurch Hospital, New Zealand Echocardiography Department. From discussions with others in the field, it is noted that few hospitals have adapted these modalities into routine (non-research) clinical practice. They are, however, often utilised in echocardiography research laboratories. The author has noted a greater number of research protocols from national and international studies performed at Christchurch Hospital, New Zealand are requesting the images required for analysis with these modalities. However, discussions with people in the field of echocardiography yield negative comments towards the use of strain in a clinical (non-research) setting and literature regarding the use of these modalities in a clinical (non-research) setting is limited.

Various literature reviews and studies, including those published in 2011 by Hoit et al. [103], in 2010 by Antoni et al. [104] and in 2005 by Ingul et al. [105], confirm the need for further research in this field. In their research conclusions, they state that, although their advanced imaging modality of choice was promising, more studies are required in the field to enable use of the modalities in a clinical (non-research) setting. Antoni et al. [104] found strain imaging a time consuming process, which means to use these modalities in a clinical setting, more time should be allocated for analysis, than that of a normal routine study. Choi et al. [91] studied the association between underlying CAD with no visible RWMA and strain imaging with the conclusion that the modalities 'might' be associated with CAD, indicating lack of surety. A literature review written by Marwick et al. [99] in 2009 suggested that the modalities were susceptible to artefact, with the user requiring a significant understanding of both complex cardiac mechanics and the methodology behind the imaging techniques. They also mention that there are significant technical challenges with image acquisition, and interpretation of waveforms which result in high inter and intra observer variability with a need for further research.

A literature review written by Thomas, G. [106] in 2004 stated TVI imaging was a 'retrograde development' based on 'debatable research and publication' with no clinical benefits. Furthermore, he stated that data obtained from any TVI method is flawed as it is an incorrect application of the Doppler technology. He argued that the four main flaws of TVI were as follows:

- To make meaningful measurements, the line of motion must be known - this is possible in blood motion (i.e. blood flow within the left ventricle), however, not with the complex mechanics of the left ventricle.
- Doppler was designed for fluid motion (i.e. the flow of blood within the left ventricular chamber), not tissue motion (i.e. the movement of the ventricle wall), which is slower than fluid motion. This may result in signals being eliminated on the basis of amplitude.
- The Doppler method uses mathematical approaches to indirectly assess motion which cannot really be measured.
- Also, the technique is ultra-sensitive, therefore, results in high rates of false positive waveforms. Furthermore, waveforms may be created when placing the sample volume outside of the cardiac region entirely.

This review is a compelling argument against the clinical utilisation of specifically TVI derived analysis.

These study conclusions and literature reviews offer insights into the current lack of clinical utilisation behind these advanced modalities. Limitations are often related to timing, technology, training constraints and the limited accuracy and reproducibility of clinical laboratory based strain.

1.6 Conclusion: Literature Review – Advanced Echocardiography Techniques

TVI and ST derived velocity, strain and strain rate have been well validated as modalities to assess regional myocardial motion and to determine underlying CAD. Despite positive validation studies, some literature reviews have debated the accuracy and importance of advanced modality imaging. It has been suggested that these are time consuming and possibly inaccurate techniques, best employed in the research lab. A very limited number of studies were found regarding the feasibility of utilising these new modalities in a clinical laboratory setting, on a randomly selected set of patients.

This study attempts to determine whether strain imaging is useful in a clinical (non-research) cardiac laboratory setting, and which modality is most accurate when identifying both regional dysfunction and underlying CAD.

Chapter Two:

Methodology

2 Chapter Two: Experimental Design and Methodology

The purpose of this chapter is to outline the overall aims of this thesis and describe the methods.

2.1 Aims

This study aimed to assess contemporary echocardiography in non-ST elevation myocardial infarction, and will be referred to as the CENSTEMI (Contemporary Echocardiography in Non-ST Elevation Myocardial Infarction) study/research throughout this thesis.

This study aimed to determine the usefulness and characteristics of echocardiography with NSTEMI presentations. This study also aimed to determine whether TVI and ST derived velocity, strain and strain rate modalities are effective, appropriate and beneficial to a clinical routine examination. Specifically:

- To describe the characteristics of patients presenting with NSTEMI at Christchurch Hospital, New Zealand
- To determine the usefulness and effectiveness of echocardiography when evaluating patients who present with NSTEMI
- To examine the correlation of abnormalities detected with new imaging modalities (TVI derived velocity, strain and strain rate, and ST derived velocity, strain and strain rate) with echocardiography and angiographic results in NSTEMI patients
- To determine the validity of performing these advanced modalities (TVI and ST derived velocity, strain and strain rate) in a clinical setting.

2.2 Hypothesis

- Echocardiography will be a useful adjunct imaging technique for assessing patients admitted with NSTEMI.
- While the advanced imaging modalities may indicate trends towards regional dysfunction or underlying CAD, the limited reproducibility and accuracy of these modalities on a randomly selected set of patients in a clinical setting may preclude them from being useful for prognosis.

2.3 Study Subjects

This prospective study was conducted at Christchurch Hospital, New Zealand using patients presenting with NSTEMI between June 2011 and April 2012. The subject population consisted of patients admitted to Christchurch Hospital, New Zealand with a first diagnosis of NSTEMI. To be eligible for this study, patients were only included when referred on the days that the sonographer (the author) was working with in-patients, which was one to two slots (a morning or an afternoon slot) per week, because there was only one sonographer to perform the scans (the author) and there is only one GE Vivid 7 ultrasound machine (software version 2.2.1., GE Vingmed Ultrasound System, Horten, Norway) at Christchurch Hospital, New Zealand, which was solely used for this study to ensure consistency. Thus, 55 patients were recruited between June 2011 and April 2012 and included in this study. NSTEMI was defined as a chest pain presentation with an elevation in TnI over 0.03µg/L [29]. ECG changes did not necessarily have to be present for a diagnosis of NSTEMI. If ST-segment elevation was present, the diagnosis was STEMI and, therefore, the patient was ineligible for the study. To be eligible for the study patients had to be referred for an inpatient echocardiogram and also have in-patient coronary angiography planned. Approval for the study was obtained from the Upper South B Regional Ethics Committee of the Ministry of Healthy (ethics register number: URB/11/EXP/002).

2.3.1 Inclusion Criteria

Patients were included in the study if they met the following criteria:

- Presented to the hospital with a first diagnosis of NSTEMI
- NSTEMI was defined as chest pain and TnI elevation over 0.03µg/L
- Listed for both echocardiogram and angiogram during admission

2.3.2 Exclusion Criteria

Patients were excluded from the study for the following reasons:

- evidence of STEMI (ST segment elevation on ECG);
- any rhythm other than sinus (i.e. atrial fibrillation/flutter)
- presence of significant (moderate or greater) valve disease
- previous cardiac surgery/procedures

Patients were not excluded for poor window quality as one of the goals of this study was to assess the utility of echocardiography and the advanced imaging modalities in a routine NSTEMI patient population.

2.4 Study Protocol

A full echocardiogram according to the American Society of Echocardiography [107] standards was performed by the author on each patient to assess cardiac structure and function. Three to five minutes was added at the end of each scan to capture the images required for off-line advanced imaging analysis.

Patient demographics (clinical details such as age and gender, smoker) were recorded prospectively at the time of the echocardiogram in an EXCEL spread-sheet. All patients were asked at the time of echocardiography if they had a history of diabetes mellitus and if they answered yes, details were recorded relating to duration and treatment. All self-reported clinical information was corroborated by the review of the patient's clinical records.

None of the patients required urgent revascularisation, and no patients required a coronary angiogram or echocardiography for the sole purpose of this study. All investigations were indicated as part of routine care.

2.5 Echocardiography

This section will cover the methodology used for acquisition, analysis, measurements and calculations performed for echocardiography and coronary angiography. Statistical analysis of the data obtained will also be covered.

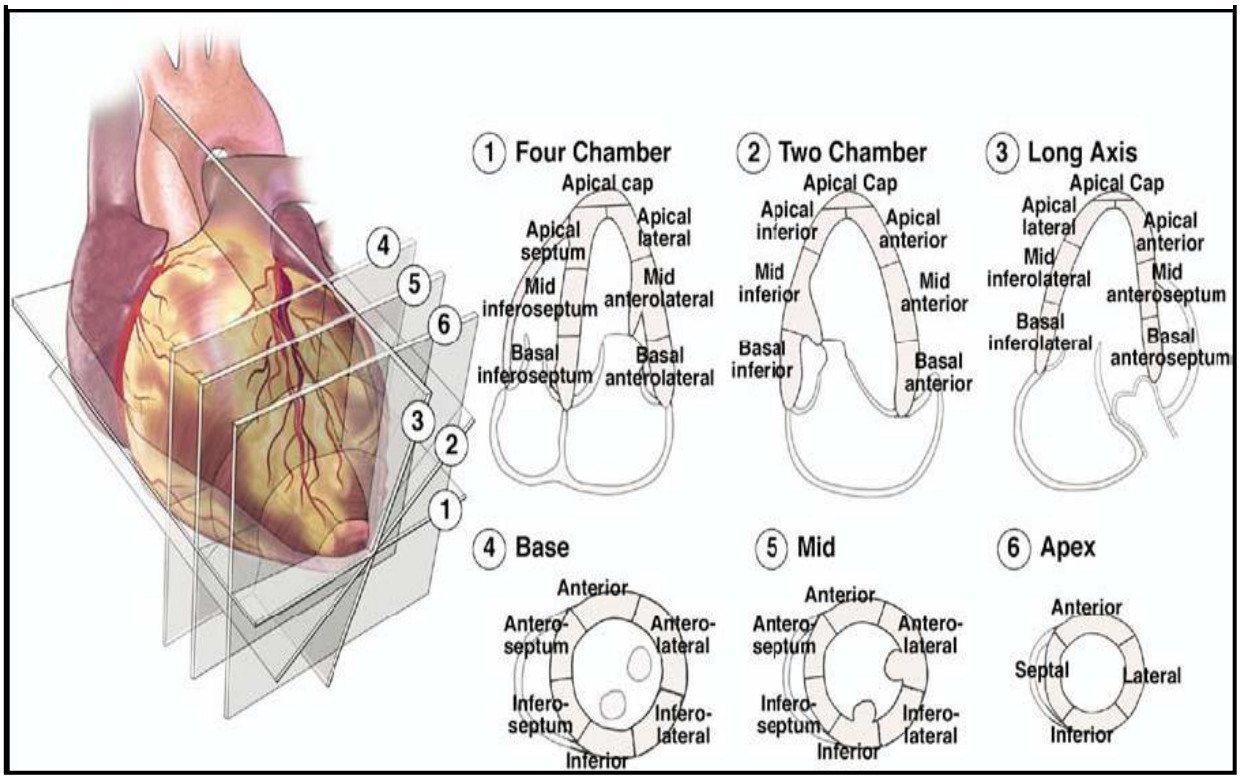
2.5.1 Echocardiography Acquisition

All echocardiographic images were acquired by the author, on a GE Vivid 7 ultrasound machine (software version 2.2.1., GE Vingmed Ultrasound System, Horten, Norway), with a matrix phased array M4S 1.5-4.0 MHz frequency transducer, using second harmonic imaging mode. All studies were performed in the echocardiography laboratory using a purpose built echocardiography bed with a mattress cut out to enable apical imaging in the left decubitus position. The author performed all of the echocardiography imaging.

A standard echocardiography study was performed inclusive of standard echocardiographic imaging, m-mode, conventional and tissue Doppler imaging. Parasternal and apical images were performed with the patient in left lateral decubitus position with their left arm extended above their head, and their right arm along their side. Subcostal and suprasternal images were performed with the patient lying supine. The images were optimised ensuring clear delineation of the blood/endocardial interface by adjusting gains and compensation where required and ensuring on-axis orientation.

From the apical window, the apical four chamber, apical two chamber and apical long axis views were obtained by rotating the transducer. These views show the segments of the heart - inferoseptum, anterolateral, inferior, anterior and inferolateral (Figure 7).

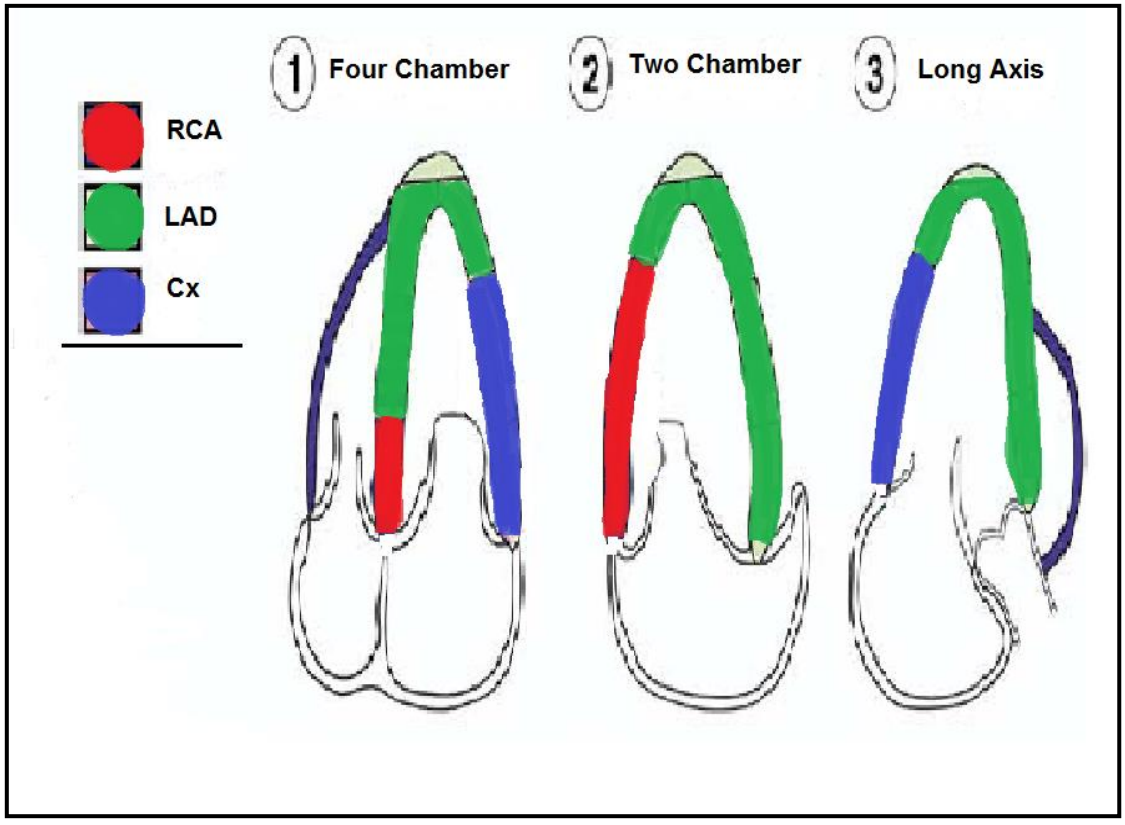
Figure 7: Segment Analysis of Walls of the Left Ventricle in the Apical (1,2,3) and Parasternal Short Axis (4,5,6) Window



Reproduced from Lang et al. [32]

The segments of the left ventricle correspond to coronary artery territories – left anterior descending (LAD), circumflex (Cx) and right coronary artery (RCA) (Figure 8). Note: Definitive amendments to coronary artery territories were made for the purpose of this research from original image; mid inferoseptal and distal anterolateral (apical lateral) segments – LAD; Basal to mid anterolateral segments – Cx; Basal to mid inferolateral – RCA.

Figure 8: Coronary Distributions of the Left Ventricle in the Apical (1,2,3) and Parasternal Short Axis (4,5,6) Windows



Reproduced and altered (from the original image by the author) from Lang et al. [32]

For TVI and ST derived modalities, gain was optimised and the sector was aligned to ensure the left ventricle filled the entire sector (inclusive of the mitral annulus/valve) - a narrow sector size, limiting the angle of insonation by ensuring the transducer was parallel with the cardiac walls, frame rates were optimised as much as possible (ST required 40-80 frames per second) [99], TVI required 105-211 frames per second [90] and images were

captured during patient breath hold to minimise translation. A three beat loop of the apical four chamber view with one focal zone was captured for later off-line ST analysis. Then, three to four beat loops of each wall were captured with TVI overlay for later off-line analysis. The cine loops were stored digitally on the hospital's ProSolv (ProSolv CardioVascular Client 4.0.2) archive system.

2.5.2 Echocardiography and Angiography Analysis, Measurements and Calculations

All echocardiography imaging and analysis was performed independently and without knowledge of the coronary artery angiography images or report. Analysis of RWMAs was performed by a single cardiologist, offline at a time separate to the image collection. All measurements were performed by the author, as recommended by the American Society of Echocardiography [107].

2.5.2.1 Regional Wall Motion Analysis

Regional wall motion was assessed from the standard echocardiographic images obtained from the apical four chamber, apical two chamber, and apical long axis on Prosolv (ProSolv CardioVascular Client 4.0.2), by a single experienced echocardiologist. The echocardiologist determined the presence of RWMAs by assessing the degree of endocardial thickening of each of the cardiac walls. The independence of this analysis from the remaining echocardiography analysis was a critical component as this formed a comparative group.

2.5.2.2 All Other Echocardiography Analysis

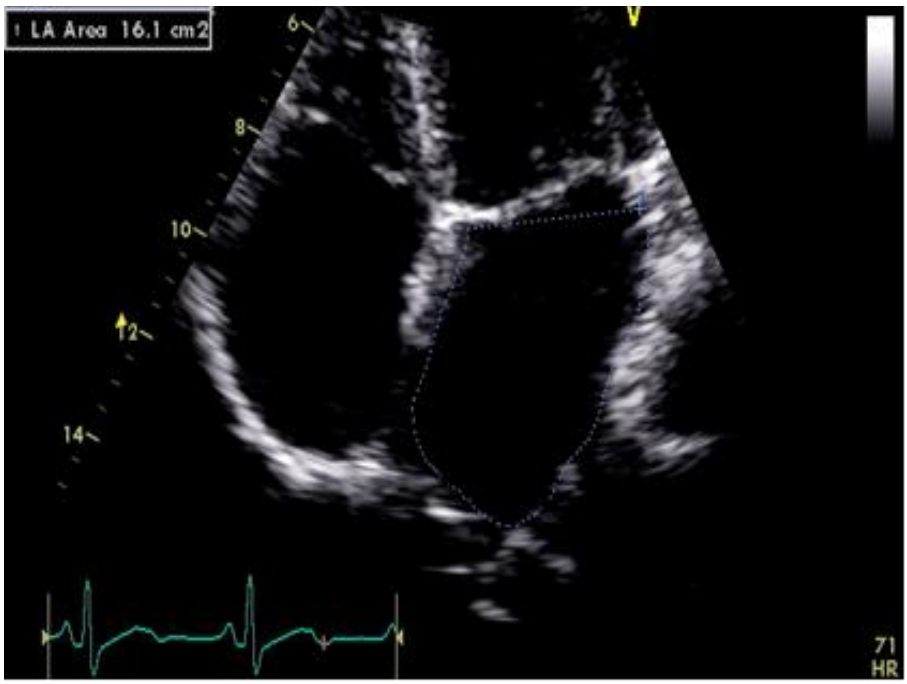
All other echocardiographic advanced imaging analysis was performed by the author, offline on EchoPac (GE Vingmed Ultrasound, Horten, Norway). TVI and ST derived velocity, strain, strain rate were performed and analysed by the author. This analysis was performed blind to the report from the echocardiologist and blind to the coronary angiography results.

2.5.2.3 Two Dimension Measurements and Calculations

2.5.2.3.1 Left Atria Area

The left atrial area was obtained from the apical four chamber view (Figure 9). The left atrium was zoomed and frozen in end-systole (just prior to mitral valve opening). The blood-tissue interface was traced from annulus to annulus.

Figure 9: Left Atria Area



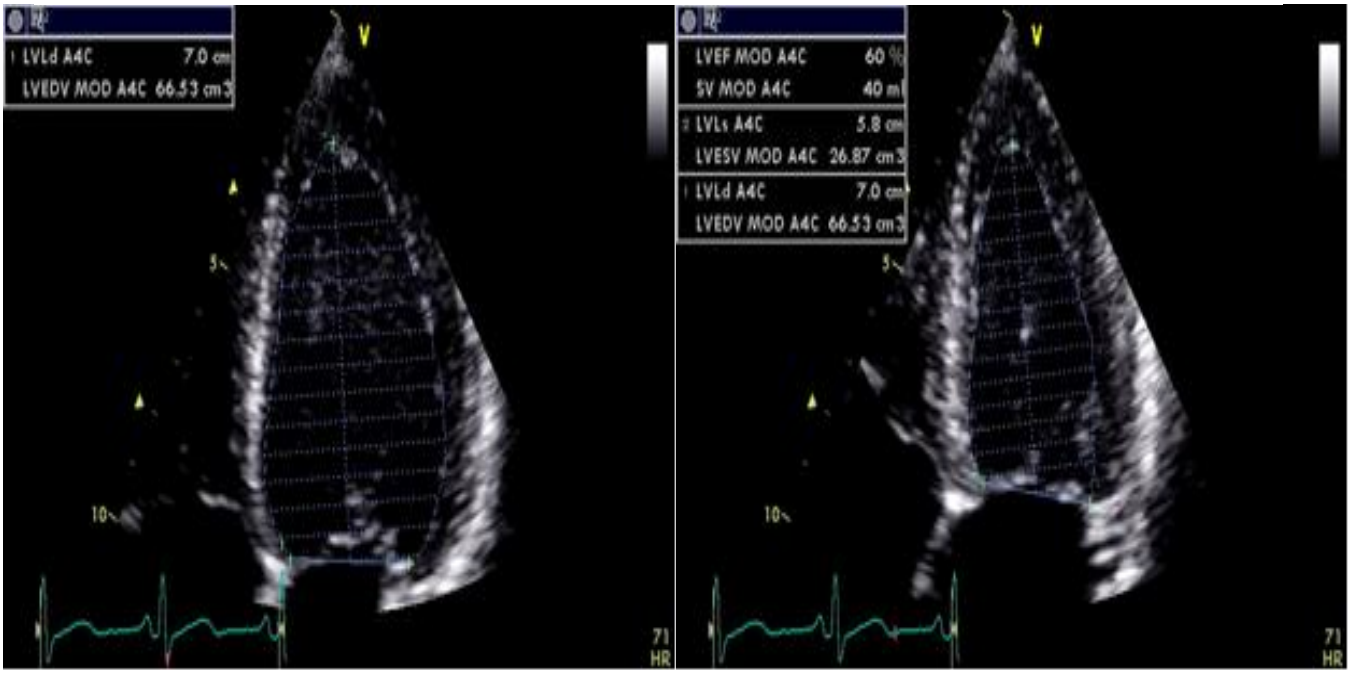
2.5.2.3.2 Left Ventricular Volumes and Ejection Fraction

The left ventricular volumes and LVEF were obtained from the apical four chamber and apical two chamber views at breath hold using the Simpson's Biplane method. The LVEF was calculated according to the following formula:

$$\textbf{EF (\%) = (EDV-ESV/EDV) x 100}$$

The left ventricular endocardial border was traced manually at end-diastole and end-systole (Figure 10) following the blood/tissue interface from annulus to annulus excluding the papillary muscles. The length was measured from the centre of the mitral annulus to the left ventricular apex. Left ventricular ejection fractions were calculated using the modified Simpson's Biplane rule. A preserved LVEF was determined as higher than 50% (50-59% = low-normal systolic function), while a normal LVEF was determined as higher than 60%.

Figure 10: Simpson's Biplane Ejection Fraction: End Diastole (left) and End Systole (right)

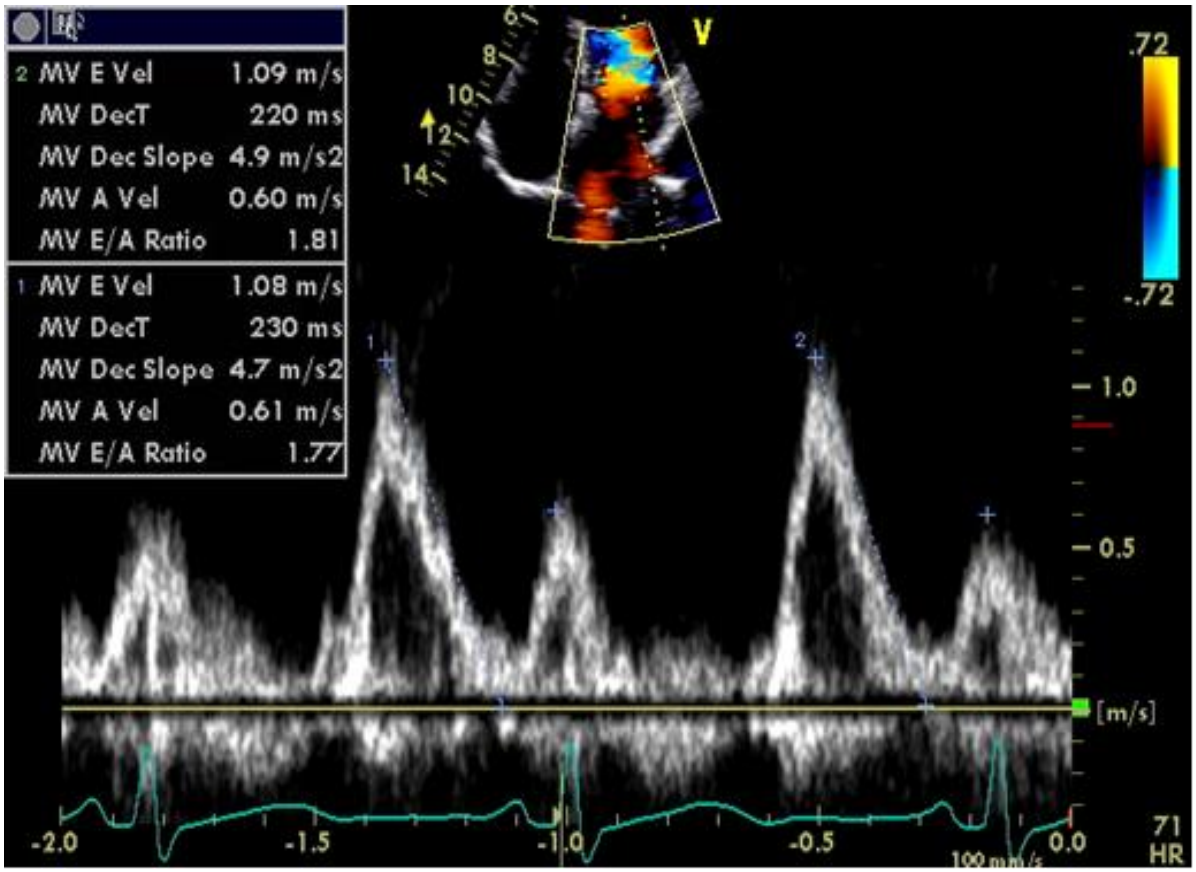


2.5.2.4 Doppler Measurements and Calculations

2.5.2.4.1 Transmitral Flow

The transmitral flow trace was obtained from the apical four chamber view (Figure 11). Using pulsed wave Doppler, the sample volume (set at 1-2mm) was placed at the mitral valve leaflet tips, acquiring two to three beats. Early diastolic flow velocity (E), late diastolic flow velocity (A) and mitral E deceleration time were measured.

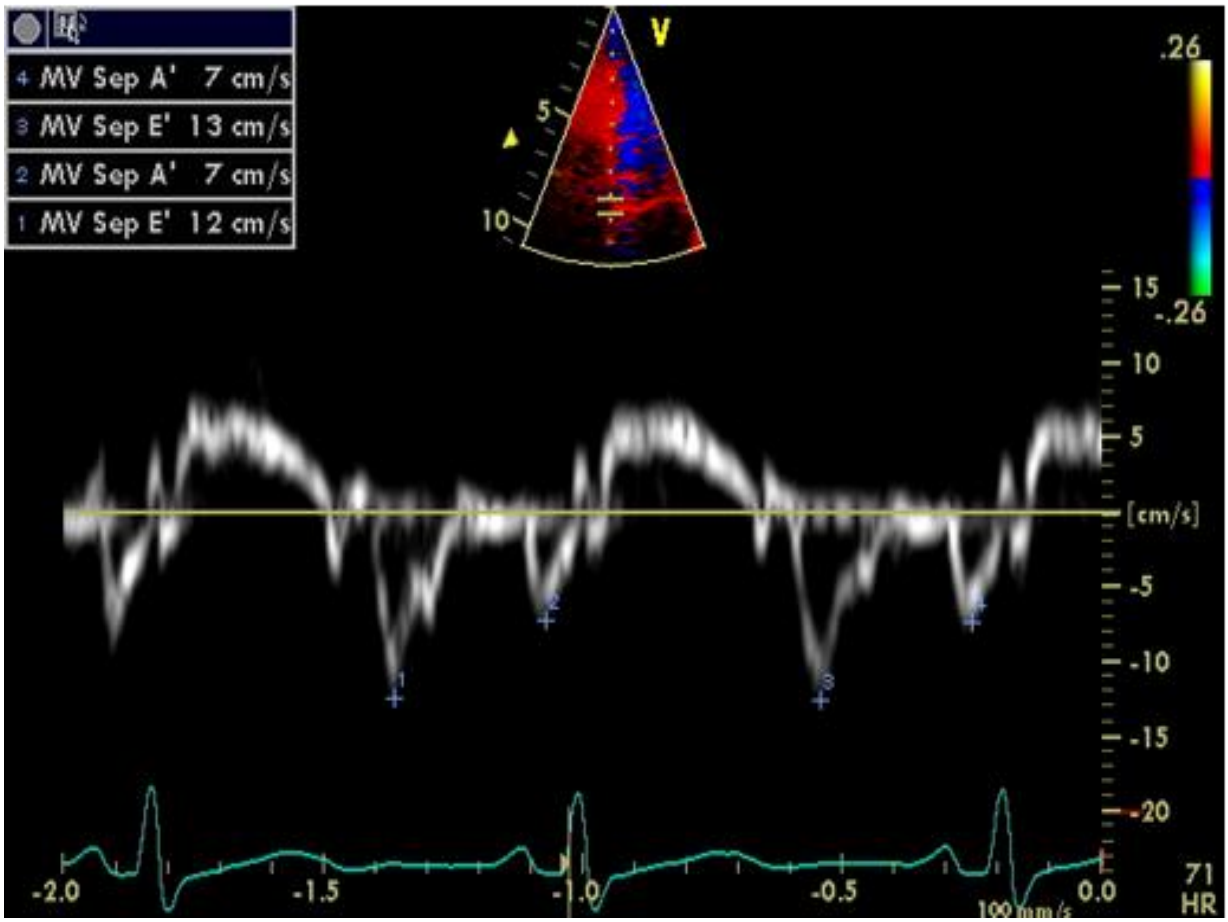
Figure 11: Transmitral Inflow



2.5.2.4.1.1 Tissue Velocity Imaging at the Mitral Annulus

TVI was obtained from the apical four chamber view of the left ventricle at breath hold. Tissue velocity was overlaid on the image. Using pulsed wave Doppler the sample volume (set at 3-5mm) was placed at the corner of the medial/mitral annulus, acquiring two to three beats. Early diastolic velocity (Em) and late diastolic velocity (Am) were measured (Figure 12).

Figure 12: Tissue Doppler Imaging Septal Annulus



2.5.2.5 Advanced Echocardiography Measurements

2.5.2.5.1 Event Timing – Defining Systole

Event timing enabled the identification of TVI and ST derived velocity, strain and strain rate waveforms and their relation to the cardiac cycle. To determine the length of systole using aortic valve opening and aortic valve closure, a left ventricular outflow tract trace was obtained.

Pulsed wave Doppler was performed in the apical five chamber view, with a sample volume (set at 3-5mm) placed just proximal to the aortic valve in the left ventricular outflow tract, acquiring two to three beats. The time was measured between the R wave (on the ECG) and aortic valve opening, then between the R wave (on the ECG) and aortic valve closing (Figure 13).

To determine the length of diastole using mitral valve opening and mitral valve closure a transmitral flow trace was obtained as described above. The time was measured between the R wave (on the ECG) and mitral valve opening, then between the R wave (on the ECG) and mitral valve closing (Figure 14).

Figure 13: Event timing of Aortic Valve Opening and Closure - Systole

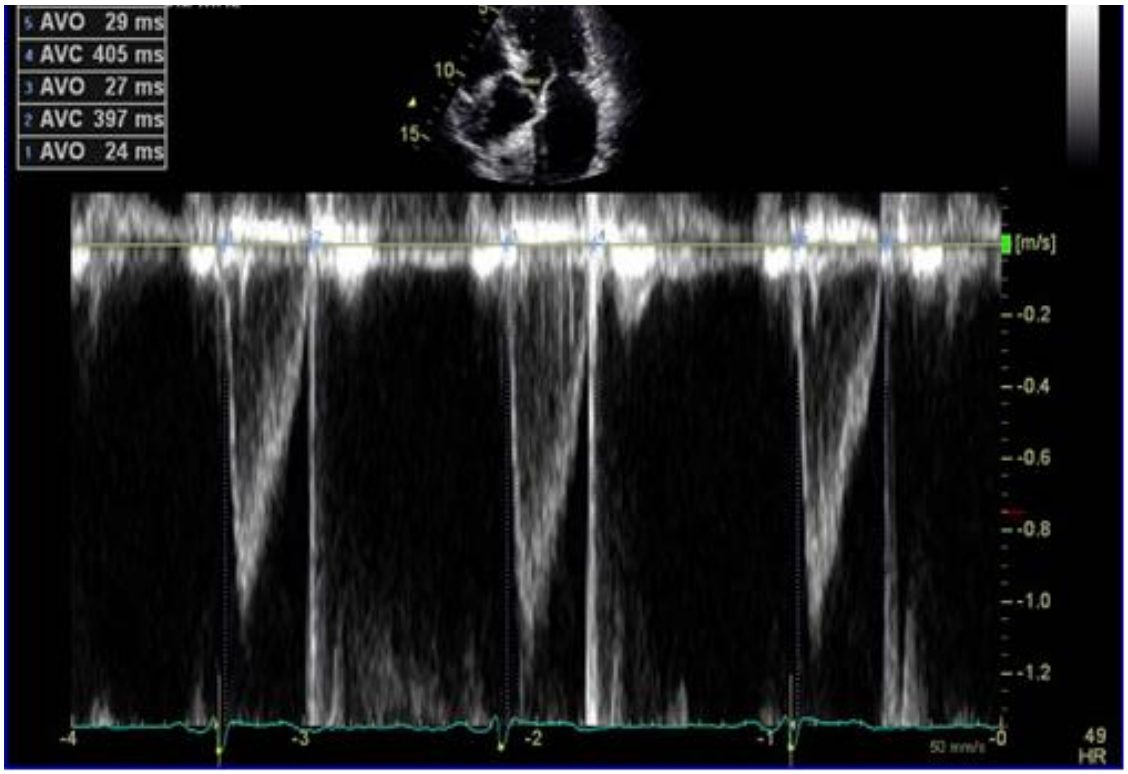
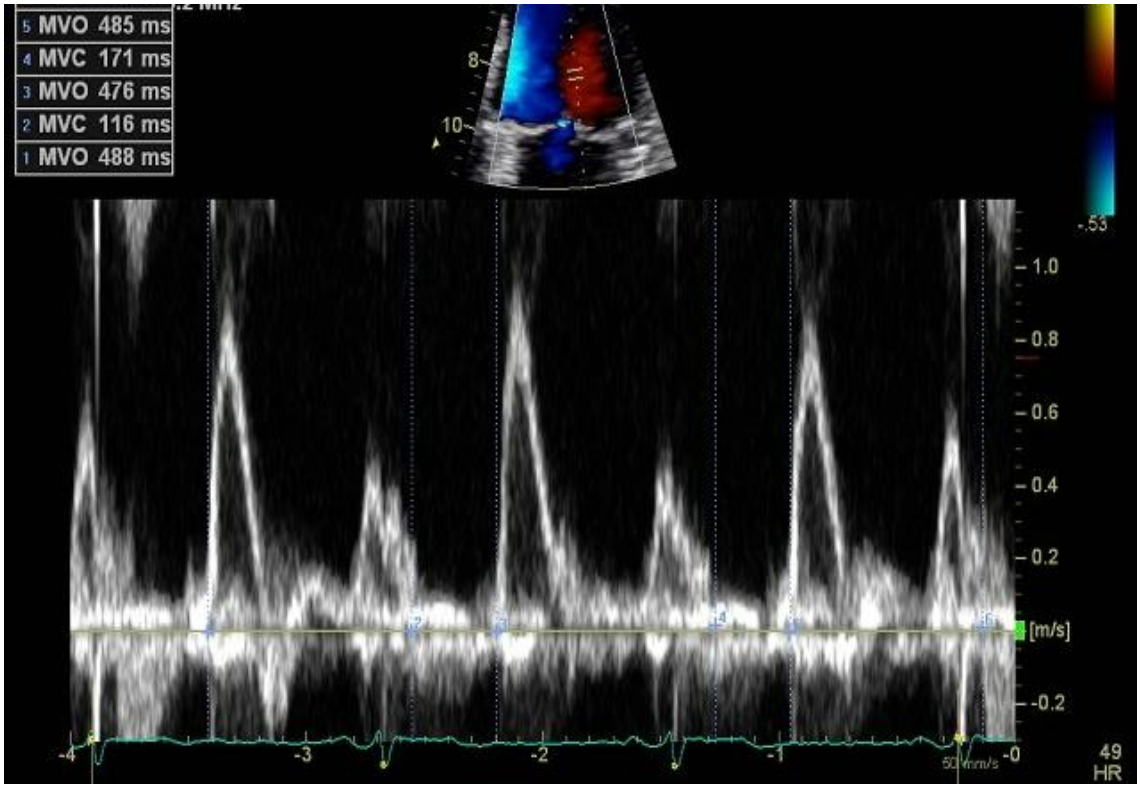


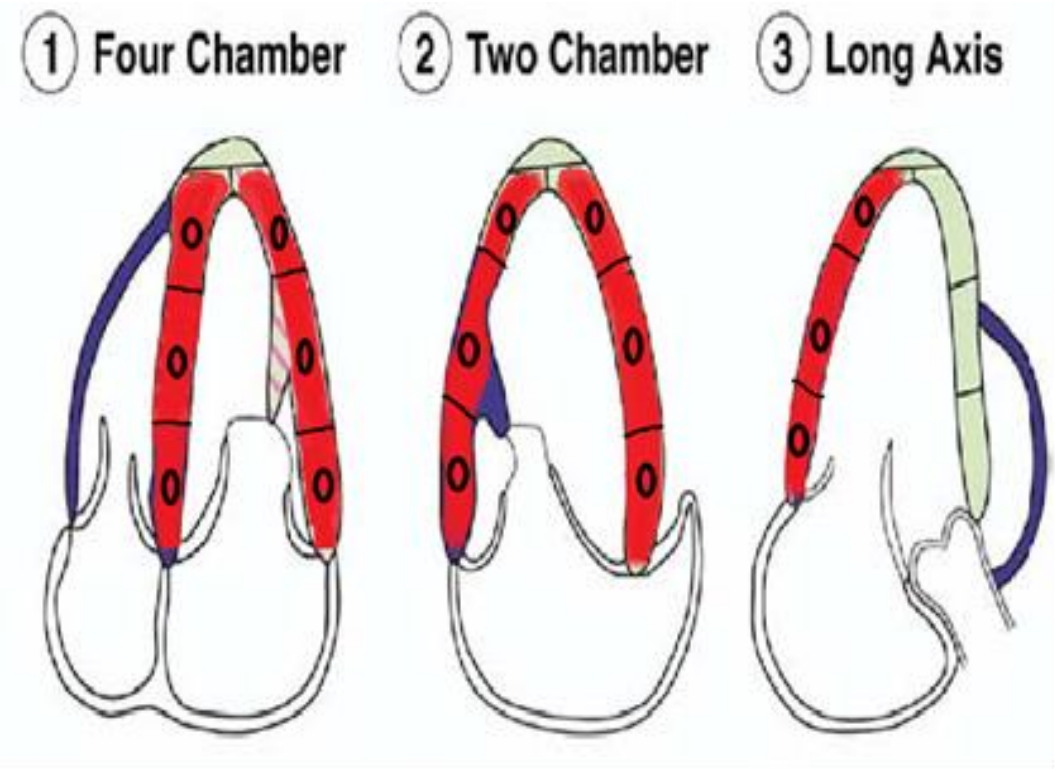
Figure 14: Event Timing of Mitral Valve Inflow Opening and Closure - Diastole



2.5.3 TVI Derived Velocity, Strain and Strain Rate

The tissue velocity overlay images of the left ventricle optimised for the five walls (as described above) were selected individually. A pulsed wave Doppler sample volume (5-8mm) was placed at the basal (defined as the area between the mitral valve annulus and the tips of the papillary muscles), mid (defined as the area between the tips of the papillary muscles to the base of the papillary muscles) and distal (defined as the area between the base of the papillary muscles to the apex) segments, enabling analysis of 15 segments (Figure 15). The apex was excluded. The sample volume position was finely manipulated within the segment to avoid artefact, drop-out or nonsensical signals (Figure 15). Waveforms were acquired for TVI derived velocity, strain and strain rate. Traces were not performed or excluded if there was artefact (i.e. reverberation artefact from rib, etc.) or interference (i.e. from lung, etc.).

Figure 15: Segmental Analysis and Approximate Sample Volume Placement

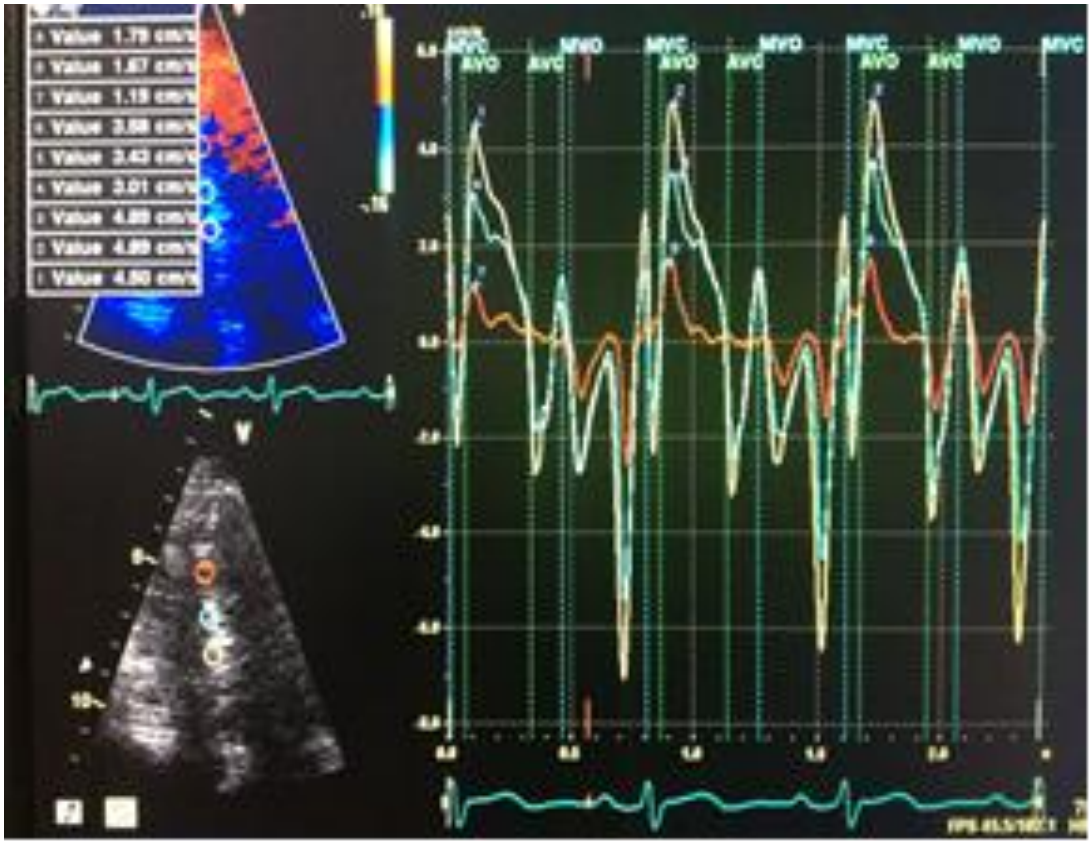


Areas in red indicate 15 segments analysed, while black circles indicating approximate sample volume positioning when performing TVI analysis.

Reproduced and altered (from the original image by the author) from [32]

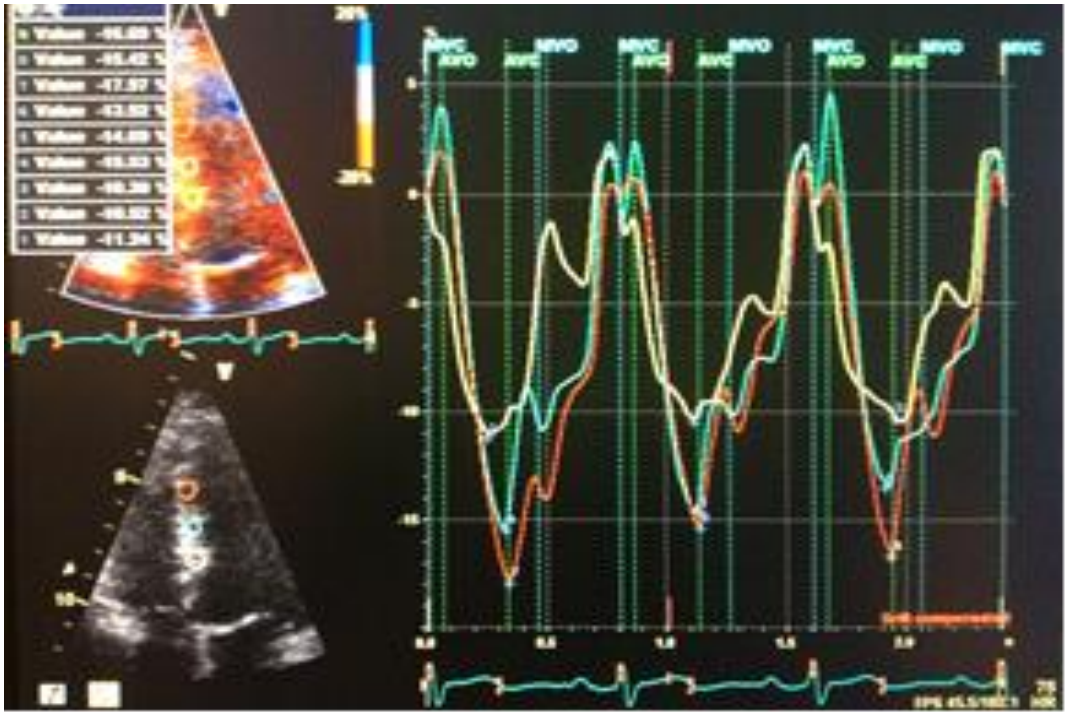
From the resulting waveforms, the following measurements were performed: Systolic (S') velocity – from the baseline up to the peak systolic waveform (Figure 16); peak negative strain – from the baseline down to the peak systolic waveform (Figure 17); and peak negative strain rate – from the baseline down to the peak systolic waveform (Figure 18). The data for each segment, for each modality, was averaged by the number of beats captured (three to four beats) then transferred to an EXCEL spread-sheet. In the EXCEL spread-sheet, the data of each modality (TVI and ST derived velocity, strain and strain rate) for each vessel territory (LAD, Cx and RCA) was averaged resulting in territorial velocity, strain and strain rate.

Figure 16: TVI Derived Velocity



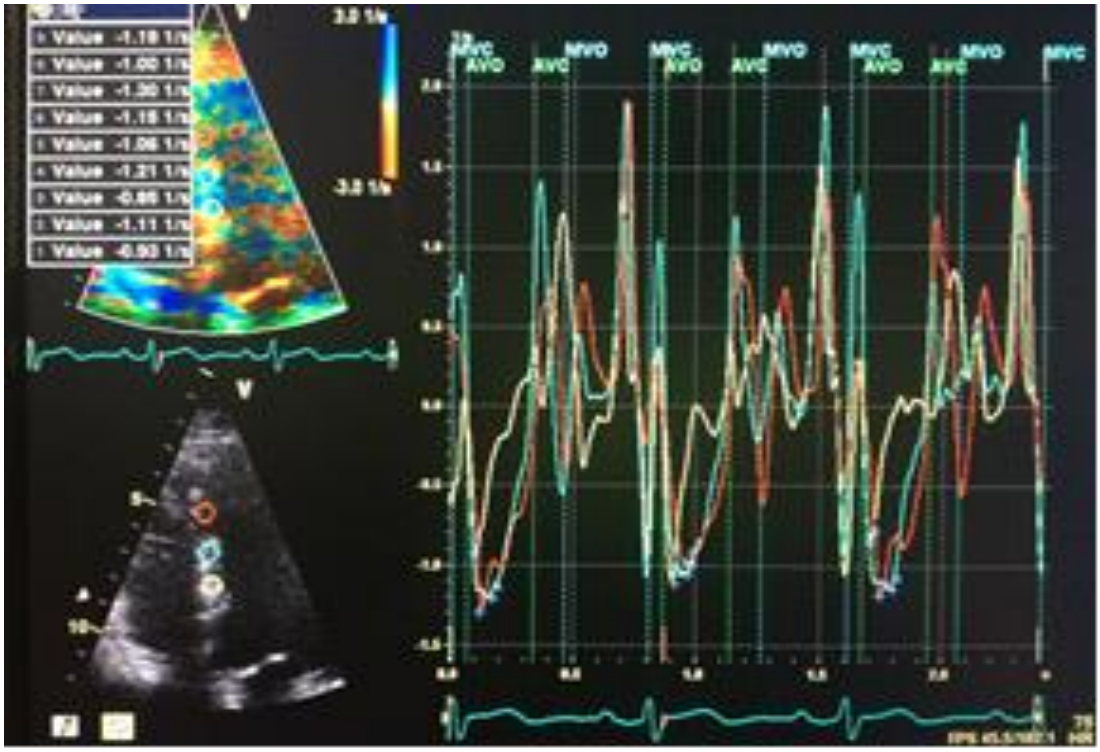
Peak systolic velocities of the basal, mid and distal wall are positive and measured three times to ensure reproducibility

Figure 17: TVI Derived Strain



Peak systolic strain values of the basal, mid and distal walls are negative and measured three times to ensure reproducibility

Figure 18: TVI Derived Strain Rate

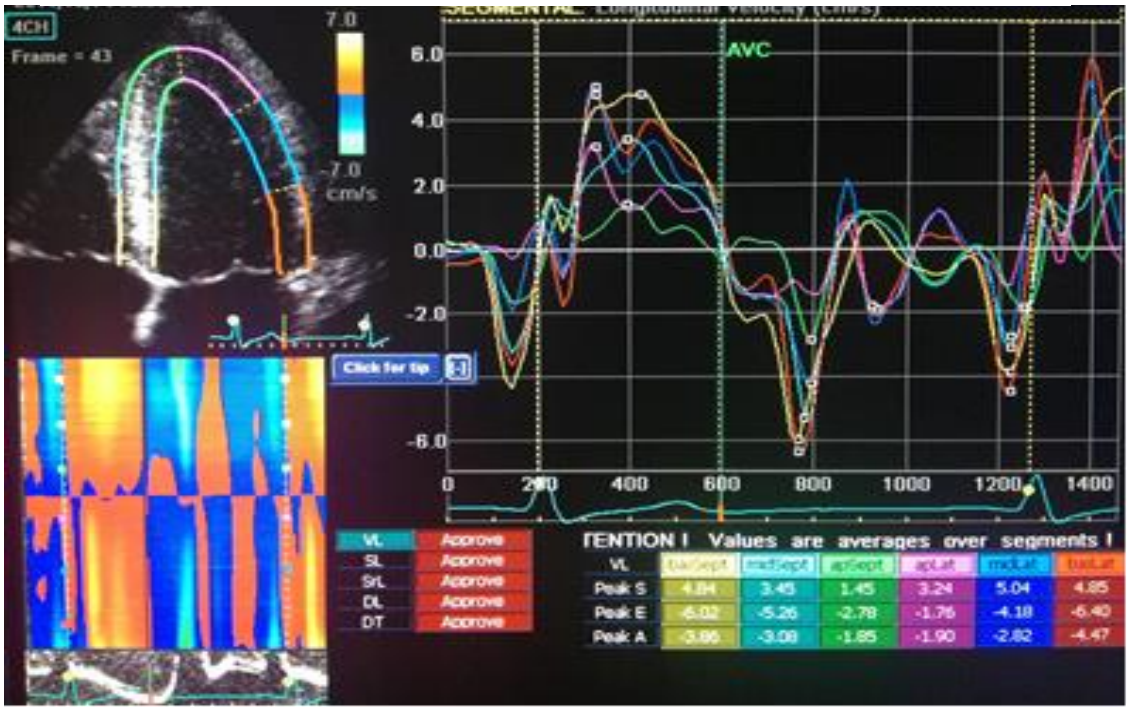


Peak systolic strain rate of the basal, mid and distal wall are negative and measured three times to ensure reproducibility

2.5.4 ST Derived Velocity, Strain and Strain Rate

The images with no TVI overlay, optimised for the left ventricle in the apical four chamber view were used for ST. The ST modality (also called 2D strain) was selected on EchoPac (GE Vingmed Ultrasound System, Horten, Norway) and the blood/tissue interface was manually traced around from the inferoseptal mitral annulus following the endocardium around to the anterolateral mitral annulus. The trace was analysed by EchoPac (GE Vingmed Ultrasound System, Horten, Norway) automatically showing the segments which were tracked well or tracked insufficiently, then approved manually by the author. The resulting waveforms were automatically displayed with calculated data on peak systolic velocity, peak systolic strain and peak systolic strain rate by the machine (Figure 19). Global strain was also calculated. The data was transferred to an EXCEL spread-sheet. In the EXCEL spread-sheet, the data of each modality for each vessel territory was averaged resulting in territorial velocity, strain and strain rate.

Figure 19: Speckle Tracking Derived Velocity, Strain and Strain Rate



The machine generates waveforms of the segments of the myocardium and provides measurements of velocity, strain and strain rate

2.6 Coronary Angiography

The patients' height (cm), weight (kg) and body surface area (m^2) were calculated prior to the angiography procedure. Coronary angiography was performed using standard clinical techniques by the cardiologist assigned to angiography on the specific day. Images were stored in the hospital's ProSolv (ProSolv CardioVascular Client 4.0.2) archive system. Standard diagnostic coronary artery angiography was undertaken according to clinical requirement, including contrast injections to all major vessels.

2.6.1 Angiography Analysis

The angiography images were analysed on Prosolv (ProSolv CardioVascular Client 4.0.2) by an experienced cardiologist. A single cardiologist determined the presence and severity of coronary artery stenosis in each of the major coronary artery territories (LAD, Cx and RCA). Significant coronary artery stenosis was defined as 70% or greater diameter stenosis. The cardiologist was blind to the echocardiography results including ST and TVI.

2.7 Statistical Analysis

Statistical analysis was performed using SAS JMP version 10 by a biostatistician at Christchurch Hospital, New Zealand. Linear regression fit was used to test for correlation between LVEF and the advanced echocardiography indices. A non-parametric Wilcoxon test was used for comparison of these indices between patient groups. Patients were grouped on the presence and absence of RWMAs in each territory and on the presence and absence of CAD in each territory. Statistical significance was taken as $p<0.05$.

2.8 Summary: Methodology

Echocardiography is a quick, cost effective, bedside diagnostic tool which is useful in the assessment of both systolic and diastolic dysfunction when patients present with NSTEMI. From the background explored in Chapter One, it was noted there were gaps and shortages in the literature concerning the analysis of systolic and diastolic dysfunction with NSTEMI presentations. Particular areas which require further investigation include determining the prevalence of regional dysfunction visualised on NSTEMI admission and to determine whether the regional dysfunction correctly identified culprit coronary arteries (as identified by coronary angiography).

Also, although well validated in literature, TVI and ST derived velocity, strain and strain rate are not utilised clinically at many national and international centres. This CENSTEMI methodology has been specifically formulated to show trends within the data set of TVI and ST derived velocity, strain and strain rate when compared to the three major coronary artery territories with RWMAs and underlying CAD. Also, it was important to determine the validity of performing these tests in a routine clinical (non-research) setting.

Methodology has been specifically selected to investigate the aims (as above), as determined by gaps and shortages in literature (as outlined in the literature review).

Chapter Three:

Results - Part I

NSTEMI Characteristics

And

Standard Echocardiography Features

3 Chapter Three: Part I Results - NSTEMI Characteristics and Standard Echocardiography Features

3.1 Introduction

This chapter presents the results of an audit of the 55 randomly selected patients enrolled in this study who were admitted to Christchurch Hospital, New Zealand between the dates of June 2011 and April 2012 with NSTEMI who fulfilled the inclusion criteria.

3.2 Patient Characteristics

Fifty-five patients with NSTEMI were included in this study. 76% were male with an average age of 66 years. 13% of the patients were smokers while 18% of the patients were ex-smokers (time since smoking ceased was not available). 20% of the patients had type II diabetes, with a mix of diet or medically controlled disease (Table 1).

Table 1: NSTEMI Patient Characteristics of 55 Patients Admitted to Christchurch Hospital, New Zealand (June 2011 and April 2012)

Patient Characteristics of NSTEMI presentations (n=55)	
Variable	**Mean ± SD or n (%)**
Age (years)	65.9 ± 10.8
Gender (male)	42 (76%)
Height (cm)	171.7 ± 8.7
Weight (kg)	85.6 ± 16.9
BSA (m^2)	2.0 ± 0.3
Smoker	7 (13%)
Ex-Smoker	10 (18%)
Type 2 diabetes	11 (20%)

Where BSA = body surface area

3.3 Admission Characteristics

All patients (100%) presented with chest pain; one patient had associated dyspnoea and one other associated vertigo. On admission, ECG in the Emergency Department showed 47% of the patients had no significant waveform changes, while the remaining patients had either T wave inversion, ST- segment (ECG) depression or a combination of the two. The peak TnI level ranged from 0.03µg/L to 31µg/L (Table 2).

Table 2: NSTEMI Patient Admission Characteristics of 55 Patients Admitted to Christchurch Hospital, New Zealand

Admission Characteristics of NSTEMI Presentations (n=55)

Variable	Mean ± SD or n (%)
Main presenting symptoms	55 (100%) Chest pain 1 (2%) Dyspnoea 1 (2%) Vertigo
Main ECG changes (none or either 1 or both)	26 (47%) none 17 T wave inversion/14 ST segment depression (53%)
Heart rate (beats per minute)	63 ± 10
Peak TnI (µg/L)	2.53 ± 5.38 (range = 0.03-31)

Where ECG = electrocardiogram and TnI - Troponin I

3.4 Event Timing: Admission, Echocardiography, Angiography and Discharge

The timing of events was recorded for each patient from admission to echocardiography, angiography, and (if required) in-hospital coronary artery bypass grafting (CABG) to discharge. From admission, patients waited an average of 1.4 ± 1.1 days for an echocardiogram and 3.1 ± 1.4 days for angiography. Patients who were not referred for CABG were discharged an average of 4.1 ± 1.6 days after admission. The patients who were referred for in-hospital CABG were discharged an average of 19 ± 3.2 days after admission (Table 3).

Table 3: Timing of Admission, Echocardiography, Angiography, Coronary Artery Bypass Grafting and Discharge

Timing of Patient Events

Variable	Mean ± SD (days)
Admission to Echocardiography (days)	1.4 ± 1.1
Admission to Angiography (days)	3.1 ± 1.4
Admission to Discharge – patients not requiring in-hospital CABG (days)	4.1 ± 1.6
Admission to Discharge – patient requiring in-hospital CABG (days)	19 ± 3.2

Where: CABG - coronary artery bypass grafting

3.5 Echocardiography Results

3.5.1 Echocardiography Systolic Results

The mean LVEF for the sample population was 60 ± 9%. 35 had an LVEF greater than 60%, 10 had an LVEF between 50-59%, 10 had an LVEF between 40-49% and 0 patients had an LVEF <40% (Table 4).

Table 4: Systolic Function Characteristics of NSTEMI Presentations

Systolic Function Characteristics of NSTEMI Presentations (n=55)

	Mean ± SD or n (%)
Ejection Fraction (%)	60 ± 9
Ejection Fraction ≥ 60%	35 (64%)
Ejection Fraction 50-59%	10 (18%)
Ejection Fraction 40-49%	10 (18%)
Ejection Fraction <40%	0

Where: SD = standard deviation and NSTEMI = non-ST elevation myocardial infarction

LVEF was compared with the presence and absence, of CAD as identified with angiography. Of the 55 patients, all of those with an LVEF 50-59% and 90% of those with an LVEF 40-49% had RWMAs present. 11% of patients with RWMAs had a normal systolic function (LVEF ≥60%); of these 75% had RWMAs in the RCA region. 60% of patients with an LVEF between 50-59% had an LAD RWMA and 40% had an RCA RWMA. CAD was present in 100% of the patients with an LVEF between 50-59%, and in 90% of patients with an LVEF between 40-49% (Table 5).

Table 5: Left Ventricular Ejection Fraction Groups compared with Regional Wall Motion Abnormalities

Left Ventricular Ejection Fraction Compared with Coronary Artery Disease

	LVEF ≥ 60% (n=35)	**LVEF 50-59% (n=10)**	**LVEF 40-49% (n=10)**
RWMA Present	4 (11%)	10 (100%)	9 (90%)
LAD RWMA	0	6 (60%)	5 (50%)
RCA RWMA	3 (75%)	4 (40%)	0
LAD + RCA RWMA	1 (25%)	0	0
LAD + Cx RWMA	0	0	1 (10%)
RCA + Cx RWMA	0	0	1 (10%)
TVD RWMA	0	0	2 (22%)
CAD Present	22 (63%)	10 (100%)	8 (80%)

Where LVEF = left ventricular ejection fraction; RWMA = regional wall motion abnormalities; LAD = left anterior descending coronary artery; RCA = right coronary artery; Cx = circumflex coronary artery; TVD = triple vessel disease and CAD = coronary artery disease

3.5.2 Echocardiography Diastolic Results

3.5.2.1 Diastolic Dysfunction Grading

Of the 55 patients, 80% had mildly impaired diastolic function, 7% of patients had normal diastolic function, 11% had pseudonormal diastolic function and 2% had restrictive diastolic function. 7% of patients had an E:A ratio greater than 1.5, while 20% of patients had E/Em greater than 15 (Table 6).

Table 6: Echocardiography Derived Diastolic Function Indices

Diastolic Indices of NSTEMI Patients

Variable	Mean ± SD or n (%)
E velocity	69.8 ± 22.2
A velocity	80.6 ± 20.1
E:A ratio	1.03 ± 1.04
E:A ratio < 1	36 (65%)
E:A ratio 1.0-1.5	13 (24%)
E:A ratio > 1.5	4 (7%)
E:A ratio N/A	2 (4%)
E DT	265.8 ± 81.5
TVI Em Velocity	6.59 ± 1.9
TVI Am Velocity	10.4 ± 2.08
E/Em	11.6 ± 5.2
E/Em < 8	11 (20%)
E/Em 8-14	32 (58%)
E/Em >14	11 (20%)
Undefined E/Em	1 (2%)
Normal diastolic function (Grade 0)	4 (7%)
Mildly impaired diastolic function (Grade 1)	44 (80%)
Pseudonormal diastolic function (Grade 2)	6 (11%)
Restrictive diastolic function (Grade 3)	1 (2%)

Where: E = early filling velocity; A = late (atria) filling velocity; E DT = early filling velocity deceleration time; E:A ratio = mitral inflow Doppler ratio between early filling velocity and late filling velocity; E/Em = filling pressure; N/A = not available and TVI = tissue velocity imaging

Diastolic dysfunction grades were compared with patient age, TnI, LVEF, RWMA, CAD, CABG, E:A ratio and E/Em to determine trends within the data (Table 7).

Table 7: Characteristics of Diastolic Function Grades in NSTEMI Patients

Characteristics of Diastolic Function Grades in NSTEMI Patients

Diastolic Function Classification	**Mean Age (years)**	**TnI (µg/L)**	**LVEF (%)**	**RWMA Present**	**CAD Present**	**CABG**	**E:A ratio**	**E/Em**
Normal (n=4)	50 ± 5.3	0.8 ± 1.1	65 ± 3	0	0	0	1.3 ± 0.3	9.3 ± 2.5
Mildly Impaired <65 years old (n=17)	56 ± 5	1.2 ± 2.3	59 ± 9	7 (41%)	13 (76%) SVD 4 DVD 4 TVD 5	4 (24%)	0.9 ± 0.4	9 ± 3.2
Mildly Impaired >65years old (n=27)	73.9 ± 6.3	3.6 ± 7.3	61 ± 9	11 (41%)	21 (75%) SVD 14 DVD 5 TVD 2	2 (7%)	0.8 ± 0.2	12 ± 4.3
Pseudonormal (n=6)	68 ± 8	3.3 ± 4.7	54 ± 10	4 (67%)	5 (83%) SVD 2 DVD 2 TVD 1	2 (33%)	1.4 ± .2	22 ± 4.5
Restrictive (n=1)	66	4	41	1(100%)	1 SVD 0 DVD 0 TVD 1	0	1.2	9

Where: TnI = Troponin I; LVEF = left ventricular ejection fraction; RWMA = regional wall motion abnormalities; CABG = coronary artery bypass grafting; SVD = Single vessel disease; DVD = Two vessel disease; TVD =Triple vessel disease; E:A ratio = mitral inflow Doppler ratio between early filling velocity and late filling velocity and E/Em = filling pressure;

3.5.2.2 Diastolic Dysfunction with Preserved Ejection Fraction

The characteristics of patients with diastolic dysfunction were assessed. Diastolic dysfunction was defined as grade 1 (mildly impaired) or higher. A preserved LVEF was defined as >50% (Table 8).Of 55 patients, 40 had grade 1 or higher diastolic dysfunction with a preserved LVEF. 15 patients had mildly impaired diastolic dysfunction <65 years old, 22 patients had mildly impaired diastolic dysfunction >65 years old and 3 patients had pseudonormal diastolic dysfunction.

Table 8: Characteristics of Patients with Diastolic Dysfunction and Preserved Ejection Fraction (>50%)

Diastolic Dysfunction with Preserved Ejection Fraction (>50%)

	Mean Age (years)	TnI (µg/L)	LVEF (%)	RWMA	CAD	RVSP (>30mmHg)	E:A ratio	E/Em
Mildly Impaired <65 years old (n=15)	57.5 ± 5.3	1.12 ± 2.4	62 ± 6.6	4	11	34 ± 5	0.9 ± 0.4	9.9 ± 3.3
Mildly Impaired >65years old (n=22)	74 ± 5.2	3.9 ± 8	63 ± 5.8	8	18	32 ± 5	0.74 ± 0.2	11.3 ± 3.8
Pseudonormal (n=3)	65 ± 5.7	2 ± 2.3	63 ± 8.5	1	2	34	1.2 ± 0.2	22 ± 6.2

Where: TnI = Troponin I; RWMA = regional wall motion abnormalities; CAD = coronary artery disease; RVSP = right ventricular systolic pressure; E:A ratio = mitral inflow Doppler ratio between early filling velocity and late filling velocity and E/Em = filling pressures

3.5.2.3 Diastolic E:A ratio > 1.0 in Patients with Pseudo-normal and Restrictive Diastolic Dysfunction

E:A ratio > 1.0 was assessed in patients with pseudonormal and restrictive diastolic dysfunction. The mean age was 68 ± 9 years old, the mean LVEF was 52 ± 12% and the mean E/Em was 20 ± 6 (Table 9).

Table 9: Characteristics of Patients with E:A ratio >1.0 in Patients with Pseudo-normal and Restrictive Diastolic Dysfunction

Patients with E:A ratio >1.0 and Pseudonormal or Restrictive Diastolic Dysfunction (n=7)	
Variable	**Mean ± SD or n (%)**
E:A ratio distribution	1.4 ± .4
Age (years)	68 ± 9
Ejection Fraction (%)	52 ± 12
Coronary Artery Disease Present	6 (86%)
E/Em	20 ± 6
Pseudonormal Diastolic Dysfunction	6 (86%)
Restrictive Diastolic Dysfunction	1 (14%)

Where: E:A ratio = mitral inflow Doppler ratio between early filling velocity and late filling velocity and E/Em = filling pressures

3.5.3 *Assessment of Regional Wall Motion Abnormalities with Echocardiography*

Out of the 55 patients admitted with NSTEMI, 23 were noted to have RWMAs on echocardiography. 48% of RWMAs were in the LAD region and 30% in the RCA region. Multiple RWMAs were noted in 22% of patients. No RWMAs were solely in the Cx region. Of the 4 groups, RCA infarcts had an LVEF 58 +/- 6%, LAD 50 +/- 6%. Patients with multiple RWMAs had an LVEF 46 +/- 4% (Table 10).

Table 10: Regional Wall Motion Abnormalities Assessment

Regional Wall Motion Abnormalities Present

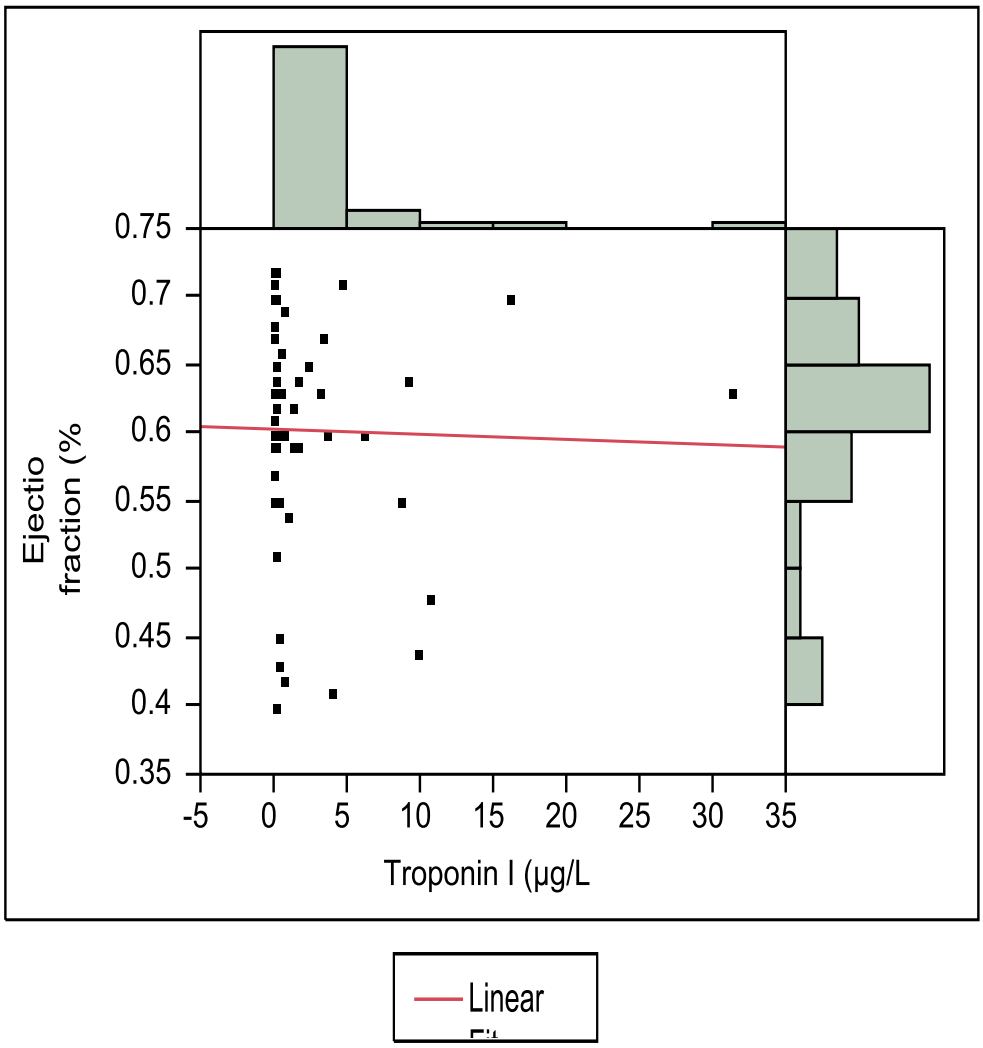
RWMA (n=23)	**RWMA Present**	**Ejection fraction (%)**
LAD	11(48%)	50 ± 6
Cx	0	N/A
RCA	7 (30%)	58 ± 6
Multiple	5 (22%)	46 ±4

Where: RWMA = Regional wall motion abnormalities; LAD = Left anterior descending coronary artery; Cx = Circumflex coronary artery; RCA = Right coronary artery and Multiple = Two or three region regional wall motion abnormalities noted

3.5.4 Correlation of Troponin I with Ejection Fraction

Troponin I (TnI) and LVEF were assessed to determine whether peak TnI correlated with RWMAs (i.e. myocardial necrosis) or systolic dysfunction, which would result in a reduced LVEF. Graph 1 shows there was no correlation between TnI and LVEF (p value was 0.8698). Of note, whilst the LVEF showed a slightly left skewed normal distribution, TnI was clearly not normally distributed and heavily skewed to the left.

Graph 1: Bivariate Fit of Ejection Fraction (%) by Troponin I (µg/L)



3.5.5 Further Echocardiography Pathologies

The routine echocardiography examination was reviewed to detect further significant pathologies.

All (100%) patients had tricuspid regurgitation, while mitral regurgitation was also found in 46 patients (83%). Aortic regurgitation was noted in 15 patients (27%).

A minority of patients had right ventricular or right atrial dilatation (4% and 5% respectively). While, a raised right ventricular systolic pressure (>30mmHg) was noted in 45% of the patients.

A degree of left ventricular hypertrophy (wall thickness greater than 12mm) was detected in 40% of patients while 22% of patients had proximal descending aorta dilatation (diameter greater the 37mm).

These results are displayed below, in Table 11.

Table 11: Pathologies Noted With Echocardiography

Other Pathologies Noted with Echocardiography

Pathology	Number of Patients with pathology (n=55)
Aortic regurgitation (n=15 (27%))	13 (23%) mild 2 (4%) moderate
Mitral regurgitation (n=46 (83%))	43 (78%) mild 3 (5%) moderate
Tricuspid regurgitation (n=55 (100%))	52 (95%) mild 3 (5%) moderate
RVSP above 30mmHg	25 (45%)
RV dilatation	2 (4%)
LA dilatation	8 (15%)
RA dilatation	3 (5%)
Left ventricular hypertrophy (n=22 (40%))	20 mild (36%) 2 moderate (4%)
Descending aorta dilatation	12 (22%)

Where: RVSP = Right ventricular systolic pressure (mmHg); RV=– Right ventricle; LA = Left atrium; RA = Right atrium; LVH = Left ventricular hypertrophy

Patients presenting with NSTEMI were divided into five groups: those discharged following angiography, those requiring CABG, those with a re-admission, those requiring CABG and who re-admitted and those who had CABG then died. These variables were compared to patient echocardiography characteristics and TnI **(**Table 12**).**

Table 12: Patient Events Post NSTEMI Compared with Echocardiography Characteristics

Patient Events Post NSTEMI

	No event after angiography / angioplasty (n=39)	**CABG (n=6)**	**Re-Admission (n=8)**	**CABG + Re-Admission (n=1)**	**CABG + Deceased (n=1)**
Ejection Fraction (%)	61 ± 8	57 ± 9	61 ± 8	71	48
TnI	3 ± 6	2.6 ± 4.2	0.6 ± 1.1	0.4	10.7
Left atria dilatation	6 (15%)	2 (33%)	1 (14%)	0	0
Aortic dilatation	9 (23%)	2 (33%)	1 (14%)	0	1
Diastolic function	Grade 0: 4 Grade 1: 31 Grade 2: 3 Grade 3: 1	Grade 1: 4 Grade 2: 1	Grade 1: 8	Grade 1: 1	Grade 2: 1
E:A ratio	1.1 ± 1.2	1.1 ± 0.6	0.82 ± 0.4	0.8	1.19
E/Em	11 ± 4.9	14 ± 6.2	13 ± 5.5	-	22

Where: CABG =Coronary artery bypass grafting and TnI = Troponin I; E:A ratio = mitral inflow Doppler ratio between early filling velocity and late filling velocity and E/Em = filling pressures

3.6 Angiography Results

This section will look at the results of angiography to determine the presence and absence of CAD in patients presenting with NSTEMI. Of the 55 patients, 40 had significant disease present. For 37% of patients the LAD was the culprit coronary artery and for 13% of patients the RCA was the culprit coronary artery. The Cx was not deemed a significant single culprit artery in any of the 40 patients with significant CAD. Prevalence of two vessel disease (where two of the three main coronary artery vessels were deemed culprit arteries) and triple vessel disease (where all three of the main coronary arteries were deemed culprit arteries) was 27% and 23% respectively (Table 13).

Table 13: Angiography Results – Culprit Coronary Arteries

Culprit Coronary Arteries

Coronary Artery	Patients with significant disease present (n=40)
LAD	15 (37%)
Cx	0
RCA	5 (13%)
Two vessel disease	11 (27%)
Triple vessel disease	9 (23%)

Where: LAD = Left anterior descending coronary artery; Cx = Circumflex coronary artery; RCA = Right coronary artery

3.6.1 Agreement between RWMA with Echocardiography and the Presence and Absence, of CAD with Angiography

The correlation between RWMA assessment with echocardiography and CAD with angiography was assessed. There were 63 possible regions in 21 patients with both RWMA present on echocardiography and CAD present on angiography. Two of the 55 patients with RWMA but no CAD, were excluded from this comparison. Of the patients with RWMA, 74% of the regions were correctly identified by echocardiography as having either normal or abnormal (hypokinetic/akinetic) function associated with CAD, while 21% of the segments were not identified/missing (deemed normal when in fact they were abnormal) and 5% of the segments were incorrectly identified (deemed abnormal when in fact they were normal - RWMAs were noted when there was no associated CAD). The 13 regions with no identified RWMAs, where CAD was present, were from patients with multiple vessel disease, with at least one of the culprit arteries in each case correctly identified with echocardiography (Table 14).

Table 14: Regional Wall Motion Abnormalities Identified with Echocardiography: Comparison with Angiography Results

Regional Wall Motion Abnormalities Identified with Echocardiography: Comparison with Angiography Results

Correlation of wall motion assessment with angiography	**Regions identified (regions n=63)**
Identified a correct CA (correct)	47 (74%)
No RWMA identified but CAD present (missing)	13 (21%)
RWMA identified does not match culprit coronary artery (wrong)	3 (5%)

Where: CA = coronary artery; CAD = coronary artery disease and RWMA = regional wall motion abnormality

RWMAs present on echocardiography were compared with CAD detected with angiography to determine the prevalence of a false negative or false positive diagnosis. Of the 55 patients, 40 had CAD and 23 patients had RWMAs. Of the 55 patients, 2 showed RWMAs on echocardiography with no evidence of CAD on coronary angiography suggestive of false positive results. Of the two patients, one had type II diabetes and an LVEF of 43% (Table 15).

Table 15: Specificity versus Sensitivity of Regional Wall Motion Abnormality Analysis with Echocardiography

Specificity versus Sensitivity of RWMA Analysis with Echocardiography

		Coronary Artery Disease Present		
		Yes	No	Total
RWMA Present on Echo	Yes	21	2	23
	No	19	13	32
	Total	40	15	55

Where: RWMA = regional wall motion abnormalities

The distribution of CAD in patients with no evidence of RWMAs with echocardiography and the number of patients from each category requiring CABG was assessed. Angiography showed 19 (48%) of patients with CAD had no identifiable RWMAs. CAD with no reciprocal RWMA was noted in the LAD territory (37%) and the RCA territory (16%). As noted earlier, the Cx was not identified as a single culprit coronary artery in any of the 55 patients (Table 16).

Table 16: Coronary Artery Disease with no Corresponding Regional Wall Motion Abnormalities

Coronary Artery Disease with No Visual Regional Wall Motion Abnormalities

Coronary Artery	Patients (n=19)	Require CABG (n=4)
TVD	4 (21%)	3 (75%)
DVD	5 (26%)	1 (25%)
LAD	7 (37%)	0
RCA	3 (16%)	0
Cx	0	0

Where: CABG = coronary artery bypass grafting; TVD = triple vessel disease; DVD = double vessel disease; LAD = left anterior descending coronary artery; RCA = right coronary artery and Cx = circumflex coronary artery

3.7 Re-admission and Mortality

Re-admission was assessed up to, and including August 13th 2012. Of the 55 patients, nine patients represented to hospital (Table 17). Re-admission times varied greatly (49 +/- 60 days). Eight of the nine patients readmitted with chest pain, while one was re-admitted with syncope after taking glyceryl trinitrate spray for angina. Four of the patients had diabetes and only one of the patients had undergone CABG. Tests and treatments for these patients were not assessed. As of 13th August 2012, one of the 55 patients has died. No further survival analyses have been conducted as the event rate is so low.

Table 17: Re-admission Characteristics

Re-admission Characteristics

Re-admission timings (days)	49 ± 60
Sex	78% male
Troponin I	0.6 ± 1.1
Reason	8 Chest Pain 1 Syncope post GTN
Smoker	1 Current 2 Ex-smokers
Diabetes	4
Ejection Fraction (%)	62 ± 8
Coronary artery disease	7
Coronary artery bypass grafting	1

Chapter Four:

Discussion - Part I

NSTEMI Characteristics

And

Standard Echocardiography Features

4 Chapter Four: Part I Discussion - NSTEMI Characteristics and Standard Echocardiography Features

4.1 Introduction

In 2007 the American College of Cardiology and the European Society of Cardiology altered the definition of a myocardial infarction, traditionally incorporating only STEMI, to include unstable angina and NSTEMI presentations [108], which have since been updated [1]. The New Zealand 2012 NSTEMI management guidelines [29] state "an echocardiogram is recommended in all patients with elevated TnI and those with electrocardiogram abnormalities to assess global and regional left ventricular function, to assess the valves, defining all differential diagnosis". It is therefore surprising that the New Zealand ACS audit [15] found echocardiography was only performed in 22% of patients who presented with NSTEMI. This chapter explores the benefits of utilising echocardiography as a diagnostic tool in NSTEMI presentations, detailing characteristics of admission, echocardiography and angiography for a randomly selected set of 55 patients admitted to Christchurch Hospital, New Zealand between June 2011 and April 2012.

4.2 Patient Characteristics

The 'average NSTEMI' patient from this research data set was aged 66 years old (±10.8) and male (76%). Current literature in this field varies in thought regarding the prevalence of male and female NSTEMI presentations. The Global Registry of Acute Coronary Events 2004 [22] included 11,543 patients from 14 countries. They found 53% of the patients were ≥ 65 years of age and around two thirds of the patients were male (inclusive of all acute coronary events). A study published in 2010 by Ellis et al. [15] found the mean age of patients presenting with NSTEMI was 67 years, while 58% of patients were male. This CENSTEMI study revealed a similar average age to the two studies mentioned above, but the

higher prevalence of male patients agreed more with the Global Registry of Acute Coronary Events study [22]. A higher percentage of male patients could be due to chance alone, owing to the small sample size or it could be the result of entry criteria that required coronary angiography to be planned. It is possible that males are more likely to be referred for angiography than females. Also, females often present with atypical symptoms and a less-severe past medical history. Literature suggests that females, are therefore, often treated less aggressively due to misdiagnosis resulting in poorer prognostic outcomes [109].

One fifth of the patients presenting with NSTEMI in this study had type II diabetes (20%), while over half the patients (56%) were current or former smokers. Similar numbers were found in New Zealand ACS audit [15] with 19% and 59% respectively. In this CENSTEMI study, overall, those who were current or former smokers, and/or those who had diabetes, had a higher incidence of significant coronary artery lesions than patients who had neither diabetes nor ever smoked (79% versus 67% respectively). Interestingly, patients who smoked and/or were diabetic (n=24) were associated with a nine-fold requirement for CABG than patients who had neither diabetes nor smoked (n=31) (29% versus 3% respectively). The decision to proceed to CABG was clinical and was required if cardiologists were unable to successfully unblock culprit lesions with angioplasty or if the coronary disease was significantly diffuse. These figures are consistent with our understanding that diabetes and smoking predispose a patient to a significantly increased burden of cardiovascular disease [110-115].

4.3 Admission Characteristics

NSTEMI diagnosis requires acute presentation of patients with ischemic symptoms (such as chest, upper extremity, jaw or epigastric pain, possibly accompanied by dyspnoea, nausea or syncope [1], biomarker elevation (Troponin I (TnI)), measured in µg/L, is primarily utilised at Christchurch Hospital, New Zealand as a marker of acute myocyte necrosis, using

the 99th percentile as a reference limit of elevation) and ECG changes (T wave inversion or ST depression).

All patients presented with chest pain, 53% of patients had ECG changes (T wave inversion and/or ST depression), and all patients had an elevated peak TnI. Patients with myocardial necrosis, which results in visual endocardial damage, will have RWMAs. This is where regions of endocardium fail to contract normally (defined as hypokinetic, akinetic or diskinetic), and, therefore, will have reduced LVEF (as measured by the Simpson's Biplane method).

Peak TnI values were compared to LVEF. We did not find any correlation between TnI elevation and LVEF impairment. Although peak TnI is an effective indicator of acute myocyte necrosis [1], this CENSTEMI study shows that TnI elevation does not correlate with the extent of endocardial damage identified with echocardiography. A study published in 2009 by Piotrowska-Kownacka et al. [116] assessed 34 patients presenting with STEMI. TnI was measured on admission and cardiac MRI was used to determine regional dysfunction and LVEF. They found TnI on admission could not predict infarct size or early LVEF. The outcomes of the Piotrowska-Kownacka study [116] and this CENSTEMI research suggest that TnI will only indicate the event of an acute coronary process, not the extent of LVEF impairment whether considering TnI on admission or at peak respectively. Therefore, this CENSTEMI study argues against using peak TnI to select patients for echocardiography.

The average time from admission to echocardiography was 1.4 days (±1.1) and from admission to angiography was 3.1 days (±1.4). A study published in 2012, performed by Theile et al. [117] assessed the outcome of NSTEMI patients following early (<2 hours), intermediate (10-48hours) or selective (67.2 hours) angiography using both peak creatine kinase myocardial banding activity during hospitalisation with death, non-fatal infarction, refractory ischemia and re-hospitalisation within six months as endpoints. The study found that intermediate or selective angiography did not significantly alter patient prognosis. In this CENSTEMI study, the average time from admission to angiography was calculated at 74.4 ± 33.6 hours suggesting that the selective strategy of angiography is utilised most commonly at Christchurch Hospital, New Zealand. The Theile et al. [117] study provides reassuring data

about the time from admission to angiography at Christchurch Hospital, New Zealand, suggesting that while in hospital, the selective strategy of angiography does not affect the prognostic outcome of patients. However, the Theile et al. [117] study did not test any echocardiographic parameters. Echocardiographic parameters may have assisted in diagnosing the severity of the event (e.g. RWMA size/severity and LVEF both short and long term). It would be interesting to repeat the study, including echocardiography, to determine whether early, intermediate or selective revascularisation affects the severity of regional dysfunction or results in further LVEF impairment. A study published in 2012 by DeWinter et al. [118] suggested early intervention for high risk ACS patients was a safe and practical approach resulting in reduced mortality. A study published in 2010 by Sami et al. [119] found high rates of adverse cardiovascular events result from unstable angina and NSTEMI admissions, furthermore, an early-invasive strategy would benefit high risk patients, while an early-conservative strategy would benefit low risk patients.

In this study, the average time from admission to discharge was 4.1 days (±1.6). It was not possible to compare this data to the New Zealand ACS Audit as they did not assess hospital length of stay following NSTEMI. This is surprising as important information is gained regarding the cost and utilisation of public hospital resources. The New Zealand NSTEMI guidelines do, however, suggest that an invasive approach is cost effective as it reduces hospital stay [29]. This approach is limited by time and staffing constraints and the need to prioritise acute cardiac presentations.

In the study the average time from admission to in-hospital CABG was 19 days (±3.2). Again, it was not possible to compare this data to the New Zealand ACS Audit [120], as they did not assess hospital length of stay following NSTEMI.

4.4 Echocardiography

4.4.1 Systolic Function

Systolic function is the function of the heart in systole, or the contraction and ejection phase of the cardiac cycle. Systolic function may be determined by echocardiography, both regionally (visual assessment of the degree of contraction of regions in the heart), or globally (by estimation of left ventricular volumes using the Simpson's Biplane method).

LVEF was assessed in the 55 patients using the Simpson's Biplane method. LVEF was most preserved in patients with regional dysfunction in the RCA territory (58±6%); LAD regional dysfunction resulted in the lowest single region LVEF (50±6%), while patients with multiple regions of dysfunction had the lowest overall LVEF (46±5%). As covered in the literature review, multiple studies have reported anterior infarcts result in greater LVEF impairment with a worse prognostic outcome than other regional infarcts [121-125]. In patients with an anterior infarction and LVEF impairment, peak circumferential strain at the apex is decreased. This results in reduced magnitude of apical rotation in the ejection phase and delays torsion recoil in the early diastolic phase. Inferior infarcts do not affect the apex of the heart (as blood supply is via the RCA coronary artery) so, presumably, have a lesser effect on the severity of systolic dysfunction present after an AMI. Further explanations of pathophysiology regarding the effect of regional dysfunction on LVEF were covered in the literature review.

For this study, LVEF was separated into ≥60%, 50-59%, 40-49% and <40%. 90% of patients with an LVEF between 40-49% had CAD. The two patients with no CAD and a LVEF between 40-49% was reassessed to determine the cause of systolic dysfunction. On review, the patient had global systolic impairment and a dilated right ventricle with raised right sided pressures (57mmHg before right atrial pressure), so NSTEMI may have been a secondary diagnosis for this patient, a co-incidental diagnosis or an incorrect diagnosis. All of the patients with an LVEF between 50-59% had CAD.

Apart from the two patients with LVEF impairment and no CAD, the results suggest regional dysfunction and reduced LVEF result from significant CAD due to myocardial necrosis as explained earlier. 67% of the patients with an LVEF ≥60% had CAD, suggesting that these patients had minor (mild hypokinesis, or hypokinesis in a region such as the RCA which affect LVEF less than that of a LAD regional infarction) or no regional dysfunction. Of all 55 patients, 36% had a LVEF <60%, while 18% had a LVEF <50%. These results show the advantages of utilising echocardiography as a tool to determine the degree of systolic dysfunction, which would alter post medical/clinical management of the patient.

Medical therapies such as beta-blockers and angiotensin-converting-enzyme inhibitors are often under-prescribed in New Zealand [9, 120], so the knowledge of cardiac dysfunction may reinforce the requirement for prescribing these readily available, often subsidised medications. Patients with regional dysfunction or LVEF impairment are often routinely re-examined with echocardiography after discharge from hospital to determine improvement. The results of the echocardiogram often effect the management of the patient (alterations in medication and follow up consultations with cardiologists as required). If echocardiography is not performed after an AMI, then left ventricular dysfunction may not be identified and subsequently not followed-up. Furthermore, the New Zealand Transport Authority [126] requires a LVEF of ≥ 40% to deem someone fit to drive. This has repercussions for the wider community, both in terms of safety and the loss of income for families for whom driving is a profession. In this CENSTEMI research, no patients had a LVEF below 40%; however, a significant infarct (such as in the LAD region) may impair the ventricular function below 40% (which has been seen in cases at Christchurch Hospital, New Zealand). Alternatively, a significant infarct may also result in an ischaemic cardiomyopathy. Without the aid of echocardiography, a small number of patients with an LVEF <40% may be un-diagnosed. This has far-reaching repercussions. The data from this CENSTEMI study would suggest there are enough diagnostic benefits to warrant performing echocardiography as part of most ACS admissions.

4.4.2 Diastolic Function

Diastolic dysfunction is the abnormal function of the heart during the diastolic filling or relaxation phase of the cardiac cycle [127]. Very few (4%) of this cohort had normal diastolic function (grade 0); 80% had mildly impaired diastolic dysfunction (grade 1), 11% had pseudonormal diastolic function (grade 2), and 2% had restrictive diastolic dysfunction (grade 3). This is perhaps not surprising given the average age of this patient cohort (66 years) and the natural decline in diastolic function (seen as E:A <1) is demonstrated in people over 65 years [78, 128, 129].

4.4.2.1 The Diastolic Dysfunction Cascade

The process of the diastolic cascade, which has been well validated, describes how diastolic dysfunction precedes systolic dysfunction. This provides an early warning sign of congestive heart failure [30, 130]. Diastolic dysfunction may also indicate the presence of underlying CAD (even when no visual RWMAs are present on standard echocardiography) and provides valuable information on prognostic outcome regarding mortality, re-infarction and congestive heart failure [51, 131]. Diastolic dysfunction with a preserved LVEF may be the only indication of underlying damage to the myocardium from a NSTEMI event and may present within a very short time frame [132]. Diastolic dysfunction has been associated with cardiac remodelling, which results in progressive left ventricular dilatation, the development of heart failure and death following an AMI event, irrespective of the presence of systolic dysfunction [133]. Diastolic heart failure describes a clinical syndrome defined by the European Society of Cardiology [134] as the presence of signs or symptoms of heart failure with a preserved LVEF (>50%) and evidence of abnormal relaxation. It has been suggested that up to 40-50% of patients display this phenomena [135]. Heart failure symptoms were not evaluated in this CENSTEMI patient cohort so the presence of diastolic heart failure cannot be assessed in this study.

In this study, 40 patients presented with at least mild diastolic dysfunction and a preserved LVEF. 37 (84%) patients had mildly impaired diastolic dysfunction (out of the original 44 patients with mildly impaired diastolic dysfunction) with preserved LVEF, and 3 (5%) patients had pseudonormal diastolic dysfunction (out of the original 6 patients with pseudonormal diastolic dysfunction) with preserved LVEF. A higher proportion of patients with preserved LVEF had mild diastolic dysfunction (84%) than with pseudonormal diastolic dysfunction (50%). The results of this CENSTEMI study agree with literature in this field as pseudonormal dysfunction is essentially a progressively worse form of mildly impaired diastolic dysfunction. This means patients with pseudonormal diastolic dysfunction are more likely to have systolic dysfunction (LVEF impairment) than patients with mildly impaired diastolic dysfunction.

In this study, two of the three patients with pseudonormal diastolic dysfunction and a preserved LVEF, had CAD identified by coronary angiography. This confirms that diastolic dysfunction may be the result of a remodelling process [132].

Of the 51 patients with diastolic dysfunction (44 mildly impaired; 6 pseudo-normal; 1 restrictive diastolic dysfunction), 11 (28%) had no CAD. In these cases, the NSTEMI event may not be the cause of diastolic dysfunction; however, even in the patients with CAD, the NSTEMI event cannot be concluded as the cause of diastolic dysfunction. Diastolic dysfunction may be a pre-existing condition, which can be caused by a number of conditions including hypertension, age, obesity, aortic stenosis, myocardial disorder/disease and diabetes [136], all of which may result in CAD. Understanding the pathological process that leads to diastolic dysfunction, and subsequently systolic dysfunction is complex and beyond the scope of this thesis. But this research highlights the multi-faceted echocardiography abnormalities that co-exist in patients with ACSs and especially in this group who present with NSTEMI. Previously, these were an almost ignored group of patients and there is little research about the implications of such findings.

4.4.2.2 Normal Diastolic Function

Very few patients displayed true normal diastolic function (n=4). These patients were the youngest in age, had an average LVEF within normal limits, the lowest peak TnI, neither RWMA nor CAD present, an acceptable average E:A ratio and an E/Em within normal limits. Normal diastolic dysfunction post AMI is associated with lower rates of cardiac death [48], suggesting a better prognostic outcome than patients with a degree of diastolic dysfunction. The average values obtained in this study agree with reference limits of normal diastolic function [78]. This was a very small group of patients in the study and, it is therefore, difficult to draw inferences from. It is interesting in itself, however, that a very small number of NSTEMI presentations have normal diastolic function, and also, all of the patients with normal diastolic function in this study had no CAD. This would suggest that patients presenting with NSTEMI who have normal diastolic function, are often likely to have no CAD. Further testing is required on a larger patient cohort to confirm this.

One patient with normal diastolic function had a peak TnI elevation of 2.4 with lateral ischemia (ST depression in leads I/aVL) on ECG. However echocardiography and coronary angiography results were normal. Reasons other than ischemia for TnI elevations are discussed below – *Angiography Results*. There are a number of possible explanations for the misinterpretation of lateral ischemia with ECG. These include: the patient may have another unknown pathology causing ST segment depression (such as left ventricular hypertrophy, digitalis effect, metabolic or a non-ACS injury i.e. contusion [137]), a degree of ST depression may be normal for this particular patient or the ECG may have been misread in the Emergency Department. Further testing would be required to determine the cause.

4.4.2.3 Mildly Impaired Diastolic Dysfunction

Abnormal filling is best determined by Doppler and is identified by a decreased early filling velocity (E), longer E deceleration time (DT), increased late filling (A) and a prolonged isovolumic relaxation time [78]. The patients with mild diastolic impairment were split into two groups (<65years of age and ≥65 years of age). This is because diastolic dysfunction has been associated with an age dependent decline affecting the left ventricular filling in a normal patient population due to the age related process of fibrosis of cardiac tissue [78, 128].

Mildly Impaired Diastolic Dysfunction <65 years of age

The patients with mildly impaired diastolic dysfunction and aged <65years (n=17) were older, and had higher TnI and E/Em than those with normal diastolic function. The LVEF and E:A ratio were lower, 41% had RWMA and 76% had significant CAD. These results fit well with the expected parameters of mildly impaired diastolic dysfunction [78], and are indicative of the milder end of diastolic dysfunction.

Mildly Impaired Diastolic Dysfunction ≥65 years of age

The patients with mildly impaired diastolic dysfunction and aged ≥65 (n=28) had higher TnI and E/Em than those with normal or mildly impaired diastolic function <65 years of age, and a similar LVEF. The E:A ratio was lower in this patient group. 39% of these patients had RWMA, while 75% had CAD. Published in 2011, Kane et al. [138] performed a study on 2042 patients aged >45 years to determine the age related changes in diastolic dysfunction and the relationship between these changes and the risk of developing heart failure. One examination was performed between 1997 and 2000, with surviving patients returning for a second examination between 2001 and 2004. They found diastolic dysfunction of any grade increased from 24% prevalence on first examination to 39% on second examination. They also found age was predictive of the development of diastolic dysfunction (especially in patients >65years) and was the greatest predictor of heart failure [129, 138]. This

CENSTEMI study shows that echocardiography parameters between the two age groups (<65 and ≥65 years of age), are similar. Perhaps it did not have a population size large enough to show significant differences between the groups. However, differences are minimal between the age groups and more evident between the degrees of diastolic dysfunction, which is what this CENSTEMI research found.

4.4.2.4 Psuedonormal Diastolic Dysfunction

The six patients with pseudonormal diastolic dysfunction were older, had the highest E:A ratio and E/Em, 67% with RWMA and 83% had CAD. Diagnosing pseudonormal diastolic dysfunction is important as it has a prognosis similar to that of restrictive diastolic dysfunction: a meta-analysis published in 2009 by Somartne et al [139] included 887 patients from seven studies. They found a 4-fold increase in the rate of mortality in patients with pseudonormal diastolic dysfunction, compared with mildly impaired diastolic dysfunction. This further confirms that patients with pseudonormal and restrictive diastolic dysfunction have similar risks of death. An E/Em >15 has been associated with elevated left atrial and left ventricular diastolic pressures, which are predictors of cardiac mortality [41, 69, 140, 141]. An Em <3cm/s is associated with 'significant excess mortality' [141]. Two of the patients had both E/Em >20 and Em ≤3cm/s, which would suggest a very poor long-term prognostic outcome. One of these two patients required in-hospital CABG and subsequently died, which correlates with the literature described. It is interesting that a small number of NSTEMI presentations had pseudonormal diastolic dysfunction, with LVEF impairment and high filling pressures. It would be interesting to follow these patients with serial echocardiograms to assess whether the diastolic dysfunction declines further and to determine the prognostic outcome of these patients. However, for a reliable study, a larger patient cohort would be required.

4.4.2.5 Restrictive Diastolic Dysfunction

The one patient with restrictive diastolic dysfunction in this study had a short E velocity deceleration time, a high peak TnI and the lowest LVEF. These indices agree with literature in this field, which suggest patients with restrictive diastolic dysfunction have significantly abnormal cardiac filling profiles which result in poor prognostic outcomes [64, 142].

A study performed by Hee et al. [64] published in 2010, assessed the prognostic outcome in patients with restrictive filling patterns (defined as an E:A ratio of >2 and E DT of <140ms). They found that a restrictive filling pattern was a good predicator of all-cause mortality, regardless of left ventricular systolic function. The patient in our research had both restrictive diastolic dysfunction and LVEF impairment. A study published in 2011 by Prasad et al. [142] assessed 20 patients with restrictive diastolic dysfunction post STEMI and found association with the duration of AMI, the infarct size and the prognostic outcome. The patient in this CENSTEMI research with restrictive diastolic dysfunction did indeed have a very large LAD RWMA with an LVEF of 41%; these results agree with findings in the Prasad et al. study [142]. The E/Em (9) in this patient was lower than expected.

A higher E/Em (E/Em >15) is associated with restrictive filling profiles as it relates to the left ventricular filling pressures, therefore, stiffness of the left ventricle resulting in restrictive diastolic dysfunction [69]. As the echocardiogram was performed a matter of hours after the event, perhaps the remodelling process of the left ventricle, which ultimately results in stiffness and therefore raised filling pressures, has yet to take place. Filling pressures are, however, reliant upon a number of factors including heart rate, loading conditions and the use of certain medications, while Doppler interrogation of the septal mitral annulus is affected by cardiac translation and motion affecting the accuracy of the measurement [66]. These may be the reasons for the low E/Em in this patient.

4.4.2.6 E:A Ratio

The average E:A ratio for patients with pseudonormal and restrictive filling profiles was elevated 1.4±0.5 and 1.2 respectively. Patients with pseudonormal or restrictive diastolic dysfunction and an E:A ratio >1 were assessed. All seven patients who met this criteria had TnI elevation, systolic impairment and CAD.

A study (unpublished data) performed by Whalley et al. [77] found E:A ratio was a powerful predictor of all-cause mortality and prognostic outcome. In an analysis of 3128 patients, E:A ratio <1 was associated with 127 deaths, E:A ratio 1-2 was associated with 143 deaths and E:A ratio >2 was associated with 197 deaths. One of the patients in this CENSTEMI study required in-hospital CABG and subsequently died. This correlates with the prognostic outcomes identified in the study performed by Whalley et al. [77].

4.4.3 Other Pathologies

Along with RWMA assessment, echocardiography is used clinically to assess many aspects of cardiac structure and function. Coexistent pathologies from the patients admitted with NSTEMI were assessed.

4.4.3.1 Valve Regurgitation

The prevalence of valvular regurgitation was determined with echocardiography using colour pulsed wave Doppler. All patients had a tricuspid regurgitation, the majority (83%) had mitral regurgitation and a minority (27%) had aortic regurgitation. Studies published in 1987 by Akasaka et al. [143], and in 1990 by Klein et al. [144], assessed the age-related prevalence of valvular regurgitation in normal, healthy volunteers. Prevalence of aortic regurgitation for a normal population aged between 60 and 69 years was 24%, which correlates well with the findings in this CENSTEMI study. The data obtained with this CENSTEMI study found a slightly higher prevalence of both mitral and tricuspid regurgitation (83 vs. 67% and 100 vs. 81% respectively) than those found by Akasaka et al. [143] and Klein et al. [144]. There are at least two plausible explanations for the increased prevalence of mitral and tricuspid regurgitation. The first, there may be a degree of valvular dysfunction post infarction (functional regurgitation - regurgitation secondary to the infarction which may be timing related) and, secondly, as these studies were performed in 1988 (Akasaka et al. [143]) and 1990 (Klein et al. [144]), colour Doppler technology may have improved somewhat since then resulting in better visualisation of smaller or eccentric regurgitant lesions.

4.4.3.2 Right Ventricular Systolic Pressures

Nearly half of the patients in this study had at least mildly raised pulmonary pressures. A study published in 2008 and performed by Weeks et al. [145] showed right ventricular systolic pressure was an indicator of left ventricular end diastolic pressure and, therefore, a predictor of heart failure. Left ventricular end diastolic pressure was determined in 25 heart failure patients with preserved LVEF (56% of whom had CAD) following administration of Nesiritide. Right ventricular systolic pressure was found to correlate most with left ventricular filling pressures, pulmonary capillary wedge pressures, pre-A wave and left ventricular end diastolic pressure.

This prevalence of elevated right ventricular systolic pressure in this CENSTEMI study may allude to the presence of heart failure in these patients; however, further testing is required.

4.4.3.3 Left Atrial Dilatation

The prevalence of left atrial dilatation was not common in this study (15%). Other studies have assessed left atrial size and its contribution to mortality in NSTEMI patients [146] [76].

A study published in 2010 by Boyd et al. [146] found when compared with age-matched normal controls, left atrial volumes were larger within 48 hours of presentation for NSTEMI, and continued to enlarge up to 12 months post NSTEMI (27.6±7.4 vs. 30.2±8.9mL/m^2 respectively). It may be that the CENSTEMI study echocardiography was performed too early in the time course of AMI to detect significant left atrial enlargement; perhaps the patient cohort was too small to show these changes; also in this CENSTEMI study, left atrial

area (which may underestimate the size of the left atrium) was measured instead of left atrial volume.

A study published in 2011 by Kuhl et al. [76] studied a cohort of 385 patients admitted with NSTEMI and found that reduced left atrial fractional change and left atrial ejection fraction predicted a poor prognosis in low-risk NSTEMI patients. Longer term follow-up would be required to confirm these findings.

However, this CENSTEMI study did find a small group of patients with left atrial dilatation, and for this group, this may be an important finding. Left atrial dilatation has been consistently linked to long-term diastolic dysfunction and poor prognosis. Although the prevalence of left atrial dilatation may be low, its prognostic significance in patients with NSTEMI warrants further investigation.

4.5 Angiography Results

Of the 55 patients admitted with NSTEMI, 40 (73%) patients had significant CAD. A study published in 2002 by Koyma et al. [147] found CAD present in 90% of 125 patients admitted with NSTEMI. Lower prevalence of culprit coronary lesions in this CENSTEMI study may be due to small sample size, which may not be indicative of a true population. Or, NSTEMI diagnosis criteria may have affected the results. The Koyma et al. [147] study did not require TnI elevation as a determinant of NSTEMI, whereas this CENSTEMI study did. This suggests that patient selection criteria may be a reason for the different results.

The LAD was the most common single vessel culprit artery (37%), followed by the RCA (13%). The remaining 50% comprised of double vessel and triple vessel lesions. The Cx was not the sole culprit artery in any of the 55 patients.

The patients with significant CAD were older, had higher peak TnI and lower LVEF. A study published in 2010 by Hong et al. [148] determined the differences in culprit lesions between STEMI and NSTEMI patients. Of 185 patients admitted with NSTEMI, culprit coronary lesion prevalence was as follows: LAD 52%, RCA 28% and Cx 18%. A similar trend was noted in this CENSTEMI study: the LAD was the most common culprit lesion, followed by RCA and lastly Cx. Hong et al. [148] used only single vessel CAD in their study to determine the culprit coronary distribution, hence the values for each vessel are higher than those found in this CENSTEMI study. An audit published in 2008,- by Dixon et al. [149] included 30,386 NSTEMI patients to determine the distribution of culprit lesions with related prognostic clinical outcome. Culprit coronary lesion prevalence was as follows: LAD 38%, RCA 34% and Cx 28%. The LAD values are similar between the Dixon et al. [149] research and this CENSTEMI study with familiar trends of culprit coronary artery prevalence noted – LAD prevalence > RCA prevalence > Cx prevalence. In the Dixon et al. [149] study, the culprit artery was determined by the first attempted coronary artery re-vascularised during coronary angiography. This is in comparison to this CENSTEMI research, where culprit lesions were identified as >70% stenosis, and any region with significant stenosis (>70%) was included as a culprit coronary artery (enabling inclusion of double and triple vessel culprit coronary arteries). Dixon et al. [149] concluded that the Cx coronary artery was the

least likely culprit lesion, due in part to its geometry (resulting in different shear wall stress) and/or due to probability. These studies support the trends noted in this CENSTEMI research.

Of the 55 patients, 13 (24%) patients had no significant CAD noted with angiography. Previous studies have assessed the prevalence of false-positive AMI diagnosis, determined by coronary angiography in the STEMI population [150-152] , however, little research has been performed in the NSTEMI population. Perugini et al. [152] suggested the main causes for a false-positive STEMI diagnosis prior to coronary angiography were 'absent or minimal coronary lesions, Tako-Tsubo, or chronic ischaemic heart disease without culprit lesion, repolarisation, left bundle branch block, pericarditis, left ventricular hypertrophy and myocarditis'. These syndromes may explain the 24% of patients in this study diagnosed with NSTEMI who had no significant coronary lesions identified with coronary angiography. Similarly, a study published in 2010 by Larson et al. [150] found of 1335 patients with suspected STEMI who underwent coronary angiography, 14% had no culprit coronary lesion while 9.5% had no significant CAD. Differential biomarker elevation provides another explanation for 'false-positive' NSTEMI diagnosis. Guidelines suggest the use of the 99th percentile as a reference limit of an elevated TnI level [1], however, TnI is not exclusive for ACS. Possible cardiac causes include acute heart failure, aortic dissection, pericarditis/myocarditis or tachycardia.

Of the 24% of patients with no CAD, 11 had mitral regurgitation (all cases were mild), while six patients had raised RVSP. No other obvious cardiac causes for TnI elevation level were identified with echocardiography, which provides a quick, non-invasive, diagnostic tool to rule out many those alternate diagnoses. Causes for non-cardiac TnI elevation include pulmonary embolism, stroke, sepsis or renal failure [153]. It is rare that a TnI elevation cannot be explained; further testing is required to elucidate the condition behind a significant biomarker elevation.

4.5.1 RWMA Assessment and CAD

Regional wall motion assessment was possible in all 55 patients. 23 (42%) patients had regional dysfunction noted on echo. A retrospective study published in 2007 by Bridgman et al. [46] utilising NSTEMI patients at Christchurch Hospital, New Zealand found 60% of patients had RWMA identified with echocardiography. Of these patients, 89% correctly identified the culprit coronary lesion. This CENSTEMI research had a marginally lower number of patients with regional dysfunction visualised with echocardiography, and a marginally lower number of correctly identified culprit lesions (74%) which may be due to the small patient cohort, patient window quality or chance.

Of the 23 patients with regional dysfunction, two had no associated CAD. Of the remaining 21 patients, the cardiologist correctly identified 47 of 63 regions with abnormal function corresponding to CAD. Three regions from three patients were identified as abnormal (RCA in all cases) when there was no corresponding CAD - while another region in the heart was affected by a culprit coronary artery (LAD in all cases) with no corresponding regional dysfunction. Coronary artery anatomy variations between patients, difficulty in interpreting the cardiac myocardial thickening (due to artefacts, motion etc.) and patient window quality may explain these misinterpretations.

Of the 55 patients, 19 had CAD, but no corresponding regional dysfunction. This means that there was no visual necrosis of cardiac tissue around or downstream of the culprit coronary lesion. Regional wall motion assessment is a subjective measure that requires significant expertise and experience. It is often complicated by difficult echocardiography windows and a lack of "baseline" for comparison. The presence of RWMAs is, however, in itself an interesting finding in an echocardiography examination as it is likely indicative of a degree of cardiac necrosis from the NSTEMI event itself.

4.5.2 Sensitivity versus Specificity

Of the 55 patients, RWMAs were identified in two male patients, both of whom had no significant CAD identified with angiography. In patient A, a RWMA was identified in the RCA region with no corresponding CAD: LVEF was 68% and there was a minor TnI rise, with no other significant echocardiography abnormalities. On re-review of the echocardiogram, mild hypokinesis in the RCA territory is confirmed, suggesting there may be an underlying, undiagnosed disease process present, or perhaps this is a normal variant for this patient.

Patient B had an LVEF of 43% and a small peak TnI rise. On review of the echocardiogram, the left ventricle was dilated, with mild-moderate mitral regurgitation, and raised filling pressures. Appearances suggest overall heart failure. The sensitivity and specificity of using echocardiography to determine RWMA association to CAD using coronary angiography was assessed by Medina et al. in 1985 [154]. They found that the predictive accuracy of detecting RWMA in patients with a dilated left ventricle had a sensitivity of 83% and a specificity of 57%, while the accuracy of RWMA detecting significant CAD had a sensitivity of 95%, a specificity of 100% and a predictive accuracy of 95%. This suggests that echocardiography is highly suited for detecting RWMA.

The risk of a false positive RWMA identified by echocardiography is a diagnostic angiogram to investigate the cause. Angiography is regarded as a semi-invasive procedure and carries increased patient risk. The risk of a false-positive diagnosis is out-weighed by the benefit of performing coronary angiography. The risk of performing a coronary angiogram in a non-compromised patient and finding nothing outweighs the risk of not performing the test at all, with the risk of missing something important. This mantra is echoed in previous literature [150-152], all of which determined the prevalence of false-positive STEMI diagnosis with coronary angiography. Perugini et al. [152] found a false-positive diagnosis was an ‘acceptable and unavoidable price to pay to guarantee the lowest possible frequency of false negatives’. These studies are reassuring when faced with the possibility of false-positive RWMA diagnoses with echocardiography.

4.6 Re-admission Rates

Of the 55 patients, only nine (16%) were re-admitted. There were no outstanding characteristics noted within this group. Seven of the patients underwent coronary angioplasty for culprit coronary stenosis. Research published in 2012 by Khawaja et al. [155] studied 30 re-admission rates in 15,498 patients who underwent percutaneous coronary intervention. 9.4% re-admitted within 30 days. The researchers found that the patients who re-admitted were more likely to be female and have less high school education, unstable angina, cerebrovascular disease, transient ischaemic attack, renal dysfunction and/or chronic obstructive pulmonary disease.

In this CENSTEMI study, as only nine patients were re-admitted, the patient cohort was too small to make assumptions from. Furthermore, social and alternative reasons for re-admission were not determined. However, a review written in 2012 by Hernandez et al. [156] suggested that future prediction, regarding re-admission was difficult and that a certain degree of vulnerability presents itself after an acute cardiac hospitalisation.

It is possible that there are no obvious explanations, patient characteristics or features which would predict nor explain re-admission rates in this CENSTEMI study and that it is due to chance alone.

4.7 Advanced Imaging Modalities

Of the patients with CAD, the culprit coronary artery was correctly identified by associated RWMAs in 74% of patients. 21% of patients had no RWMA identified but CAD present while in 5% of patients RWMAs did not match the culprit coronary artery. This, as discussed above, could be due to a number of reasons, such as image quality; perhaps there

were no RWMA to be visualised; or perhaps the changes in the myocardium are so subtle that they are undetectable to the human eye.

Recent studies suggest TVI and ST derived velocity, strain and strain rate imaging may provide valid, quantitative global and regional assessment. Furthermore, these tests are suggested to possess the ability to identify early and subtle changes in systolic function, as well as the presence of underlying CAD, all while reducing the subjective nature of echocardiography. Although well validated, advanced modality imaging has failed to be integrated into a standard routine examination in a clinical (non-research) laboratory.

4.8 Conclusion: NSTEMI Characteristics and Echocardiographic Features

In conclusion, the role of echocardiography in patients presenting with NSTEMI remains under-utilised. Yet, it is recommended in the 2012 ACS guidelines and this CENSTEMI study found it an invaluable tool for detecting structural and functional abnormalities.

The patients studied in this thesis represent a fairly typical NSTEMI group, presenting to a public hospital in New Zealand. The data obtained in this study has shown the usefulness of echocardiography when identifying systolic and diastolic dysfunction. The usefulness of using echocardiography as a diagnostic tool for assessing co-cardiac pathologies was also assessed. Echocardiography was efficiently used to determine cardiac pressures (right ventricular systolic pressure), dilatation of chambers (left atrial chamber) and regurgitant lesions.

This study has also shown that the degree of TnI elevation cannot be used to select a subset of patients for echocardiography.

There were patients with CAD and an absence of visual RWMAs. There were also a very small number of patients who were possibly misdiagnosed (misdiagnosed as a NSTEMI or incorrect RWMA identification). Utilisation of advanced imaging modalities such as TVI and ST may provide additional information to determine underlying CAD. Literature suggests using advanced modalities (TVI and ST derived velocity, strain and strain rate) to determine or confirm regional dysfunction and/or underlying CAD. Therefore, these advanced echocardiography modalities were tested (TVI and ST derived velocity, strain and strain rate) in a standard, clinical (non-research) environment on the same randomly selected set of 55 NSTEMI patients.

Chapter Five:

Results - Part II

Advanced Echocardiography Techniques

5 Chapter Five: Results Part II – Advanced Echocardiography Techniques

5.1 Introduction

This chapter explores the ability of advanced echocardiography imaging modalities to detect RWMAs and CAD with NSTEMI presentations. The values for TVI and ST derived velocity (υ), strain (ϵ) and strain rate (s^{-1}) were grouped and averaged into the three major vessel territories – LAD, Cx, RCA resulting in territorial velocity, strain and strain rate. Comparisons were made between velocity, strain and strain rate and the presence, and absence, of RWMAs and underlying CAD. Statistical significance was taken as $p<0.05$.

5.2 Patient Characteristics

This is an extension of the study previously described in Results I/Discussions I and includes the same 55 randomly selected patients. TVI was possible in all patients; ST was possible in 53 patients. As discussed in methods, there were 15 possible segments (basal, mid and distal segments of the inferoseptal, anterolateral, inferior, anterior and inferolateral walls) available for interrogation by TVI from the three imaging views (apical four chamber, two chamber and long axis). There were 6 possible segments (basal, mid and distal segments of the inferoseptal and anterolateral walls) available for interrogation by ST from the apical four chamber view. Out of 825 segments available for interrogation with TVI, assessment was possible in 754 (91%). Out of 330 segments available for interrogation with ST, assessment was possible in 305 (92%) (Table 18).

Table 18: Segmental Assessment with TVI and ST in 55 Patients

Segmental Assessment with TVI and ST in 55 Patients

	Basal S	**Mid S**	**Distal S**	**Basal AL**	**Mid AL**	**Distal AL**	**Basal I**	**Mid I**	**Distal I**	**Basal A**	**Mid A**	**Distal A**	**Basal IL**	**Mid IL**	**Distal IL**
TVI Indices	55	55	55	53	43	50	55	54	55	51	43	36	53	49	47
Total TVI (n/825)	Total segments deemed suitable for interrogation n = 165			Total segments deemed suitable for interrogation n = 146			Total segments deemed suitable for interrogation n = 164			Total segments deemed suitable for interrogation Total n = 130			Total segments deemed suitable for interrogation Total n = 149		
ST Indices	51	53	53	48	51	49	*N/A*	*N/A*	*N/A*	*N/A*	*N/A*	*N/A*	*N/A*	*N/A*	*N/A*
Total ST indices (n/330)	Total segments deemed suitable for interrogation Total n = 157			Total segments deemed suitable for interrogation Total n =148			*N/A*			*N/A*			*N/A*		

The total number of TVI segments for available for interrogation was 825 (15 segments x 55 patients); the total number of ST segments available for interrogation was 330 (6 segments x 55 patients); 3 segments of each cardiac wall x 55 patients = 165 segments available for interrogation on each cardiac wall and where: S = septal; AL = anterolateral; I = inferior; A = anterior; IL= inferolateral; Indices – velocity, strain and strain rate, TVI = tissue velocity imaging

5.3 RWMA Assessment

Univariate correlations between territorial strain from the advanced echo imaging modalities - TVI and ST derived velocity (cm/s), strain (%) and strain rate (/s) - and the presence and absence, of RWMAs in the three major vessel territories - LAD, Cx and RCA - were assessed. The p-values are grouped in Table 19 (after the graphs: p. 140) for quick comparison, while statistical significance is shown in Table 21 (after the graphs: p 141).

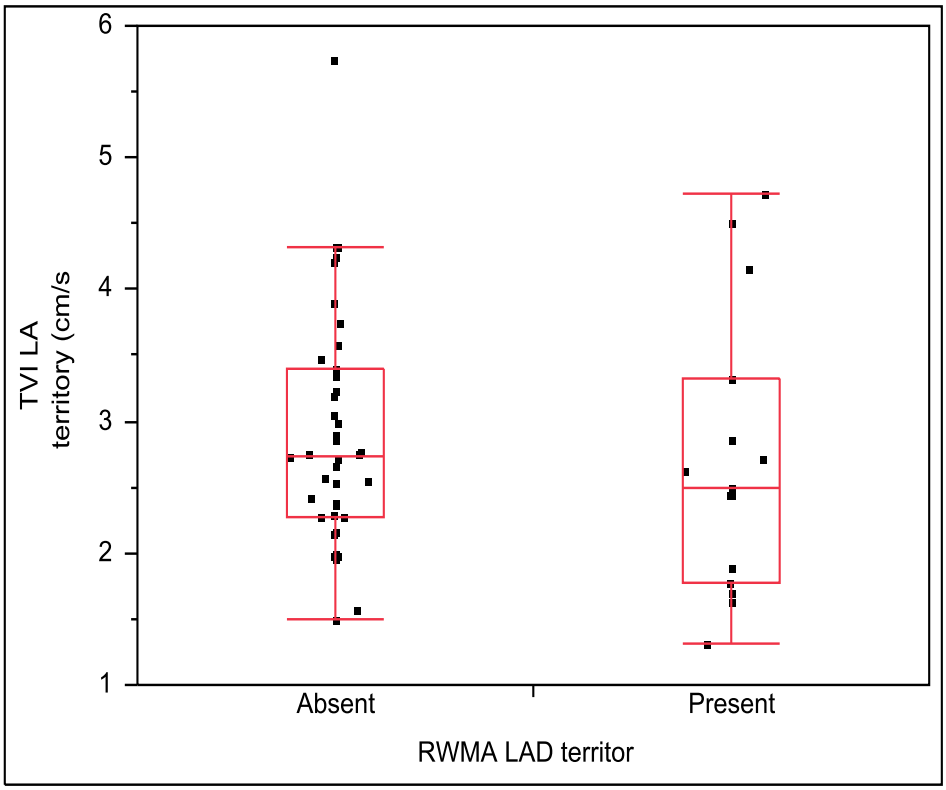
5.3.1 Tissue Velocity Imaging

Below are the results from analysis between RWMAs and TVI derived velocity, strain and strain rate. For each modality a comparison was made between the group of patients with and without RWMAs present on standard echocardiography. In general, there was overlap between the groups, although significant group mean differences were observed.

5.3.1.1 TVI Derived Velocity for RWMA assessment

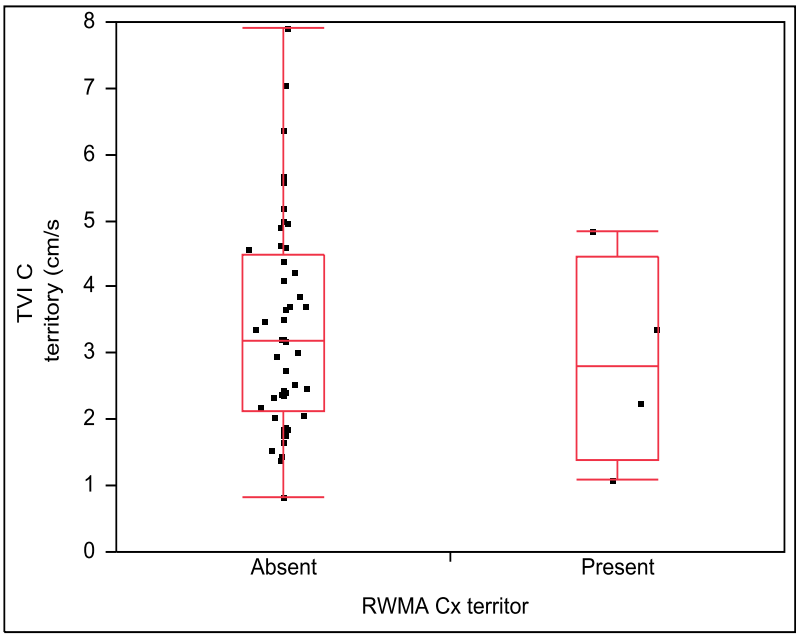
TVI derived velocity (cm/s) was not different with the presence and absence of visual RWMAs on standard echocardiography imaging, in any of the three major vascular territories: p= 0.36 for LAD territory (Graph 2), p=0.58 for Cx territory (Graph 3) and p=0.50 for RCA territory (Graph 4). No regions were statistically significant.

Graph 2: One-way Analysis of TVI LAD territory (cm/s) By RWMA LAD territory



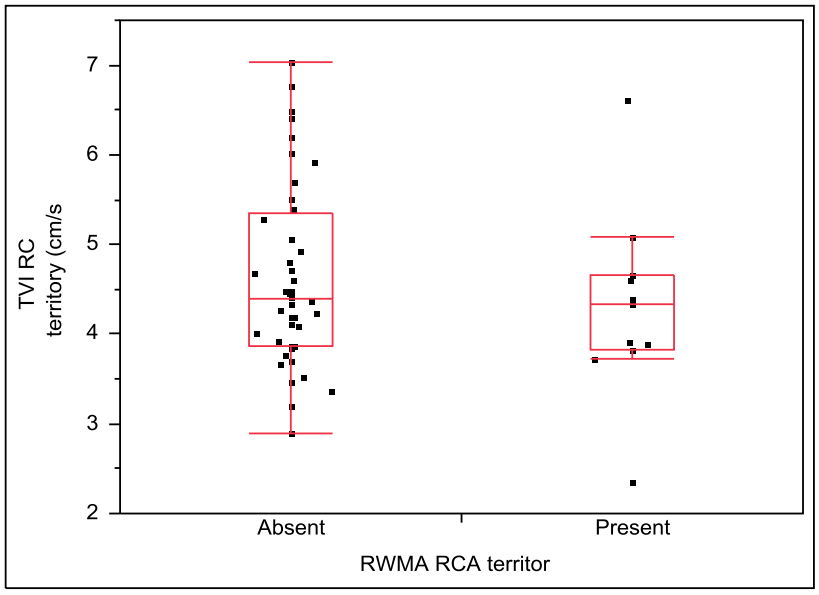
Where: TVI = tissue velocity imaging; LAD = left anterior descending coronary artery; RWMA = regional wall motion abnormality

Graph 3: One-way Analysis of TVI Cx territory (cm/s) By RWMA Cx territory



Where: TVI = tissue velocity imaging; Cx = circumflex coronary artery territory and RWMA = regional wall motion abnormality

Graph 4: One-way Analysis of TVI RCA territory (cm/s) By RWMA RCA territory

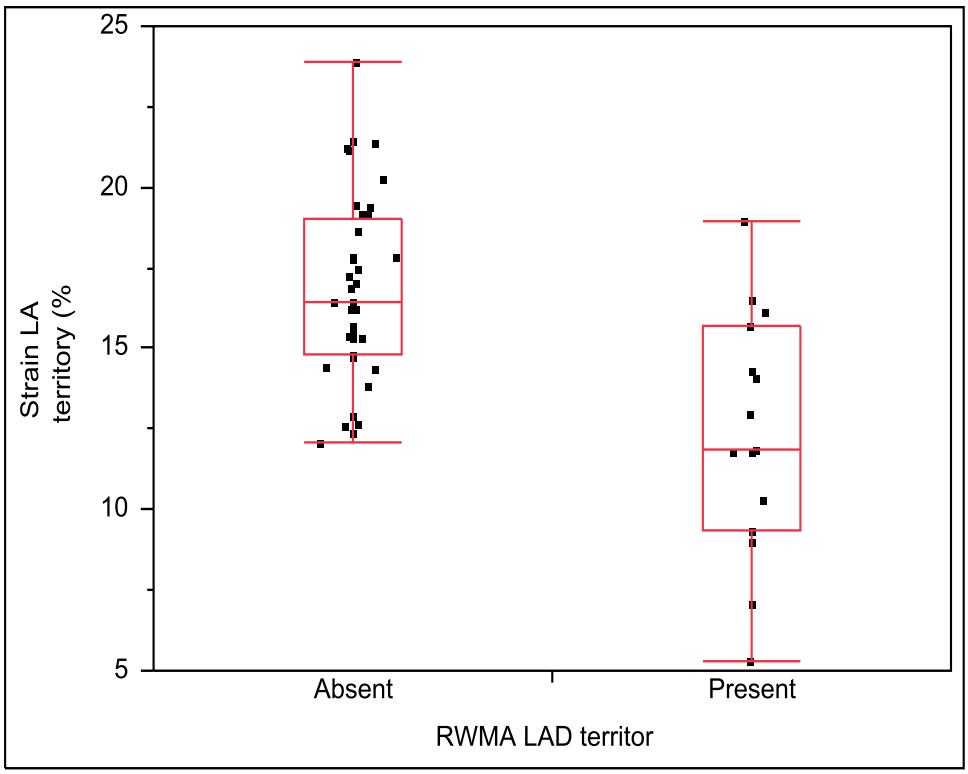


Where: TVI = tissue velocity imaging; RCA = right coronary artery territory; RWMA = regional wall motion abnormality

5.3.1.2 TVI Derived Strain for RWMA assessment

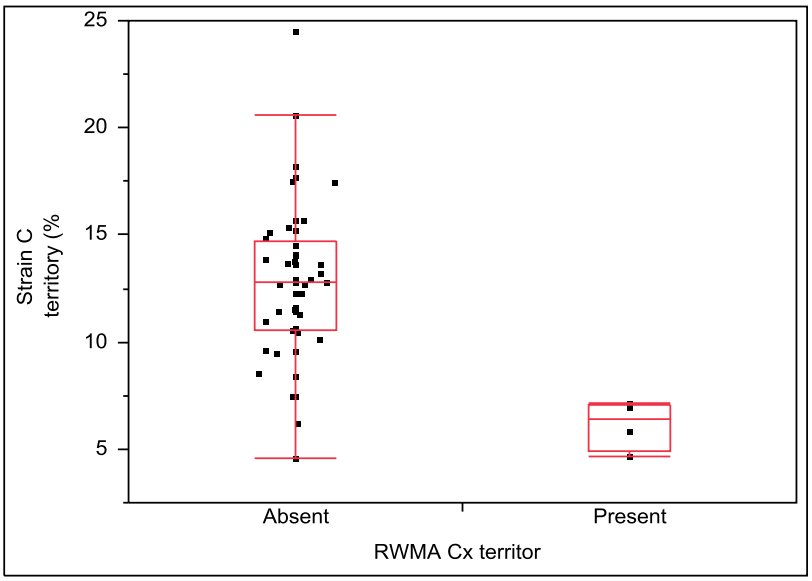
TVI derived strain (%) correlated with the presence and absence, of RWMAs on standard echocardiography in the LAD and Cx regions. Values were decreased (closer to the baseline), in territories where a RWMA was present: p=0.0002 for LAD territory (Graph 5), p=0.002 for the Cx territory (Graph 6), p=0.06 for the RCA territory (Graph 7). The RCA region showed a trend towards statistical significance. The LAD and Cx regions were statistically significant.

Graph 5: One-way Analysis of Strain LAD territory (%) By RWMA LAD territory



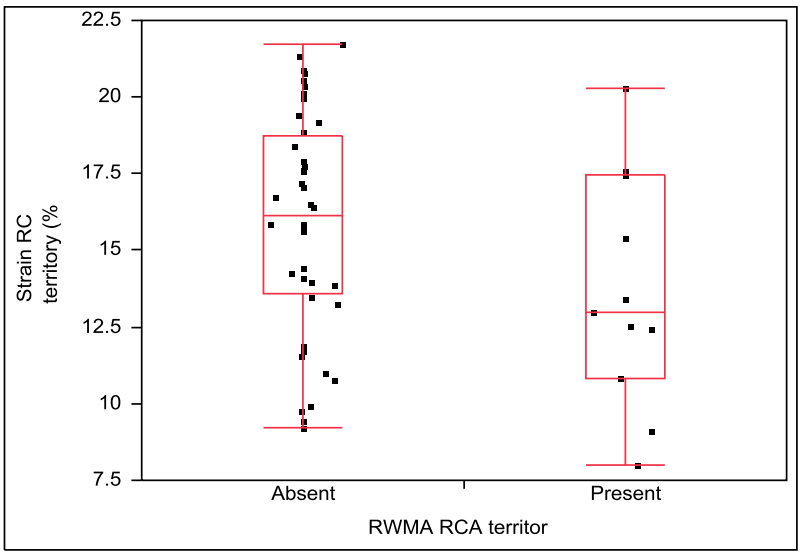
Where: LAD = left anterior descending coronary artery territory; RWMA = regional wall motion abnormality

Graph 6: One-way Analysis of Strain Cx territory (%) By RWMA Cx territory



Where: Cx = circumflex coronary artery territory; RWMA = regional wall motion abnormality

Graph 7: One-way Analysis of Strain RCA territory (%) By RWMA RCA territory

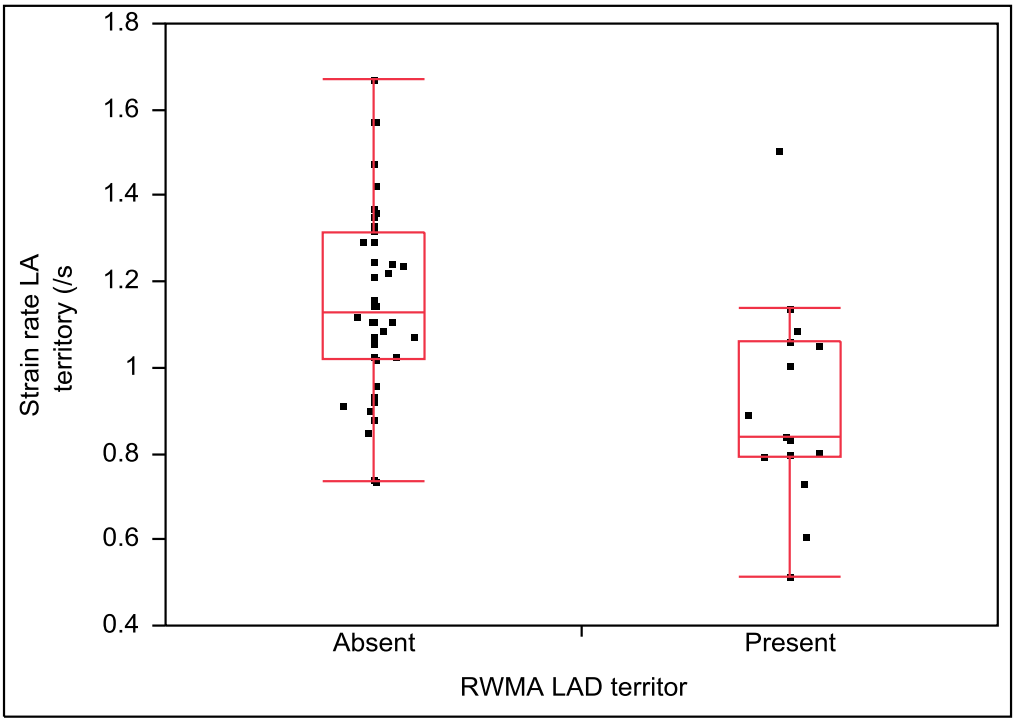


Where: RCA = right coronary artery territory; RWMA = regional wall motion abnormality

5.3.1.3 TVI Derived Strain Rate for RWMA Assessment

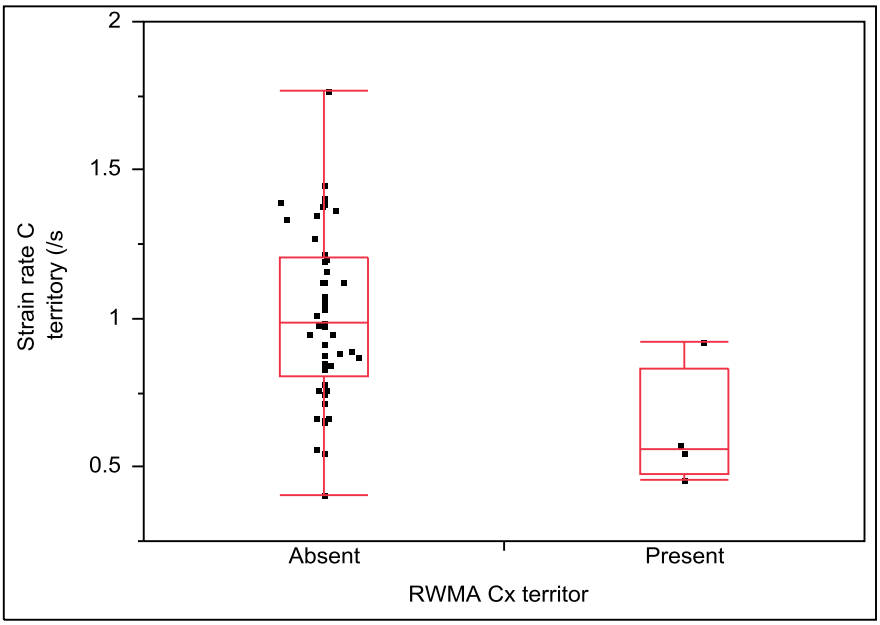
TVI derived strain rate (/s) correlated with the presence and absence, of RWMAs on standard echocardiography. Values were decreased (closer to the baseline), in territories where a RWMA was present: p=0.0007 for LAD territory (Graph 8), p=0.01 for Cx territory (Graph 9), and p=0.01 for RCA territory (Graph 10). All the regions were statistically significant.

Graph 8: One-way Analysis of Strain rate LAD territory (/s) By RWMA LAD territory



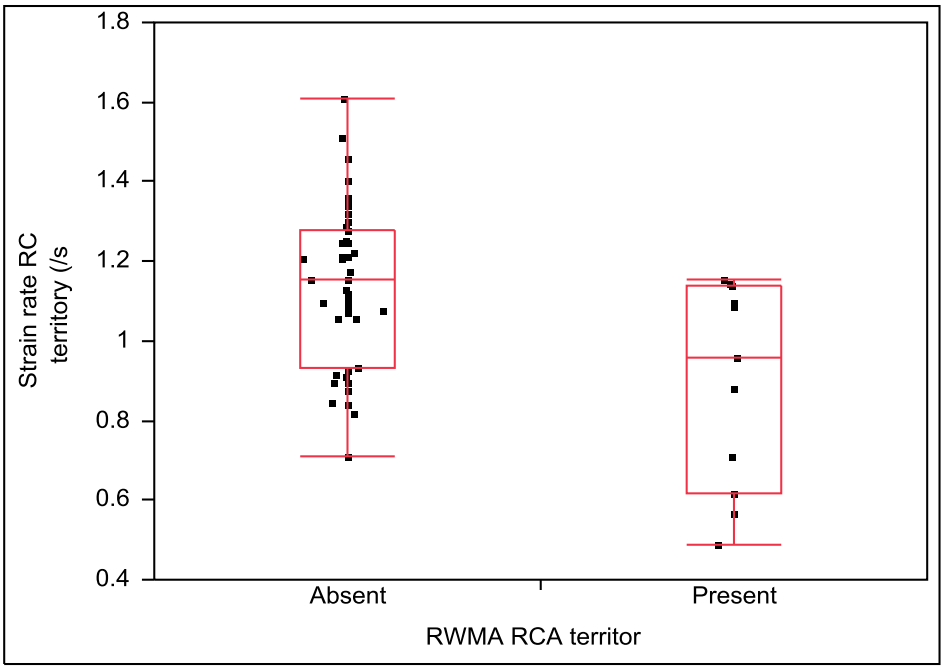
Where: LAD =left anterior descending coronary artery territory; RWMA = regional wall motion abnormality

Graph 9: One-way Analysis of Strain rate Cx territory (/s) By RWMA Cx territory



Where: Cx = circumflex coronary artery territory; RWMA = regional wall motion abnormality

Graph 10: One-way Analysis of Strain rate RCA territory (/s) By RWMA RCA territory



Where: RCA =right coronary artery territory; RWMA = regional wall motion abnormality

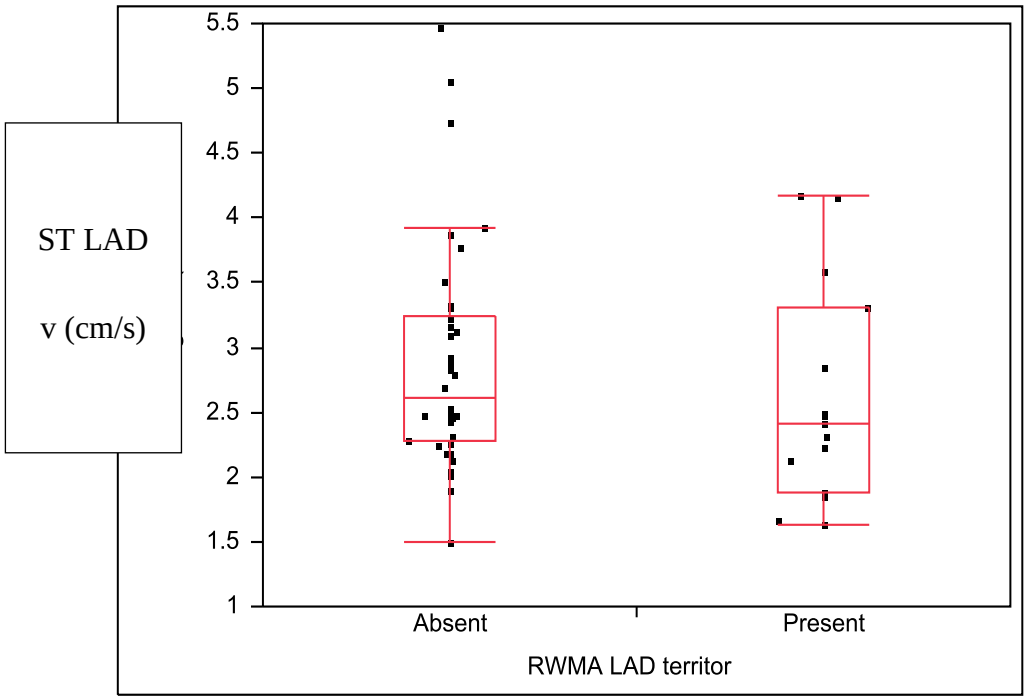
5.3.2 Speckle Tracking

Below are the results from analysis between RWMAs and TVI derived velocity, strain and strain rate. For each modality a comparison was made between the group of patients with and without RWMAs present on standard echocardiography. In general, there was overlap between the groups, although significant group mean differences were observed.

5.3.2.1 ST Imaging Derived Velocity for RWMA Assessment

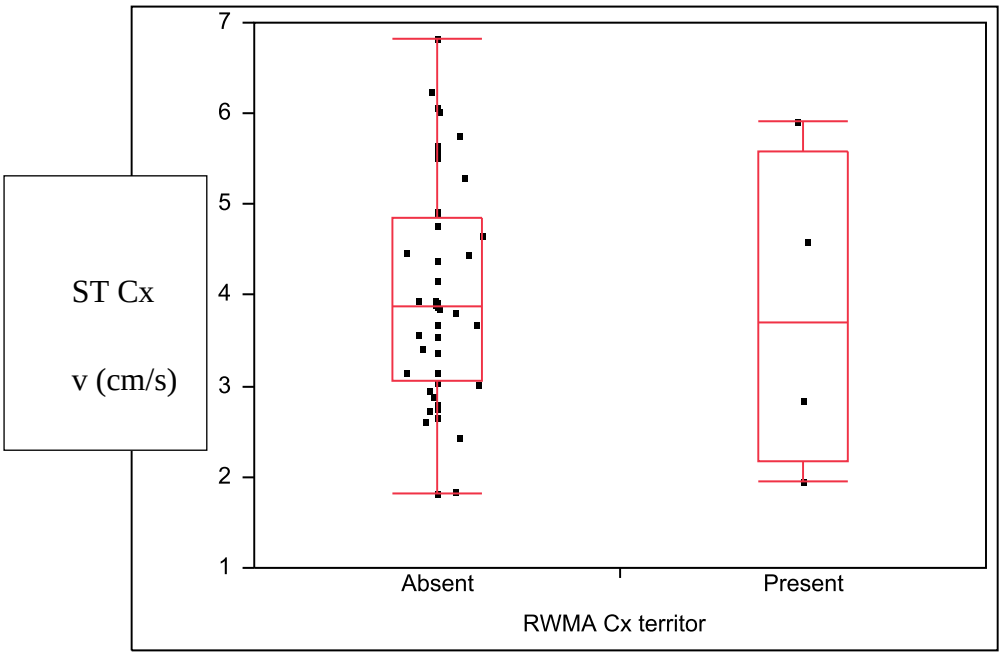
ST derived velocity (cm/s) was not different with the presence and absence of visual RWMAs on standard echocardiography imaging, in any of the three major vascular territories: p=0.23 for LAD territory (Graph 11), p=0.78 for Cx territory (Graph 12), and p=0.46 for the RCA territory (Graph 13). No regions were statistically significant.

Graph 11: One-way Analysis of LAD Speckle tracking Velocity (cm/s) By RWMA LAD territory



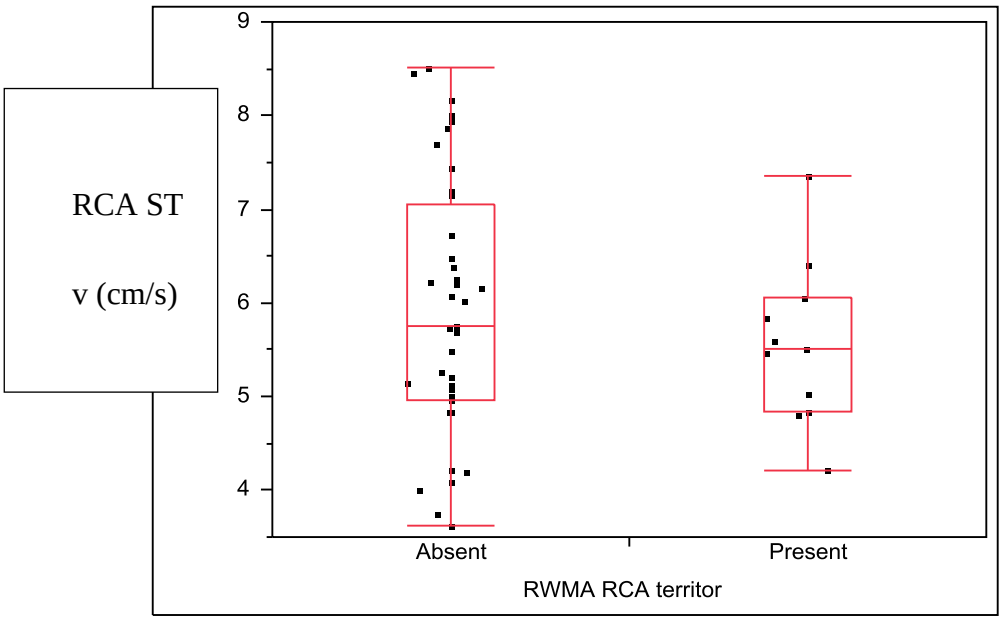
Where: v = velocity; ST = speckle tracking; LAD = left anterior descending coronary artery territory; RWMA = regional wall motion abnormality

Graph 12: One-way Analysis of Cx Speckle tracking velocity (cm/s) By RWMA Cx territory



Where: v = velocity; ST = speckle tracking; Cx = circumflex coronary artery territory; RWMA = regional wall motion abnormality

Graph 13: One-way Analysis of RCA Speckle tracking velocity (cm/s) By RWMA RCA territory

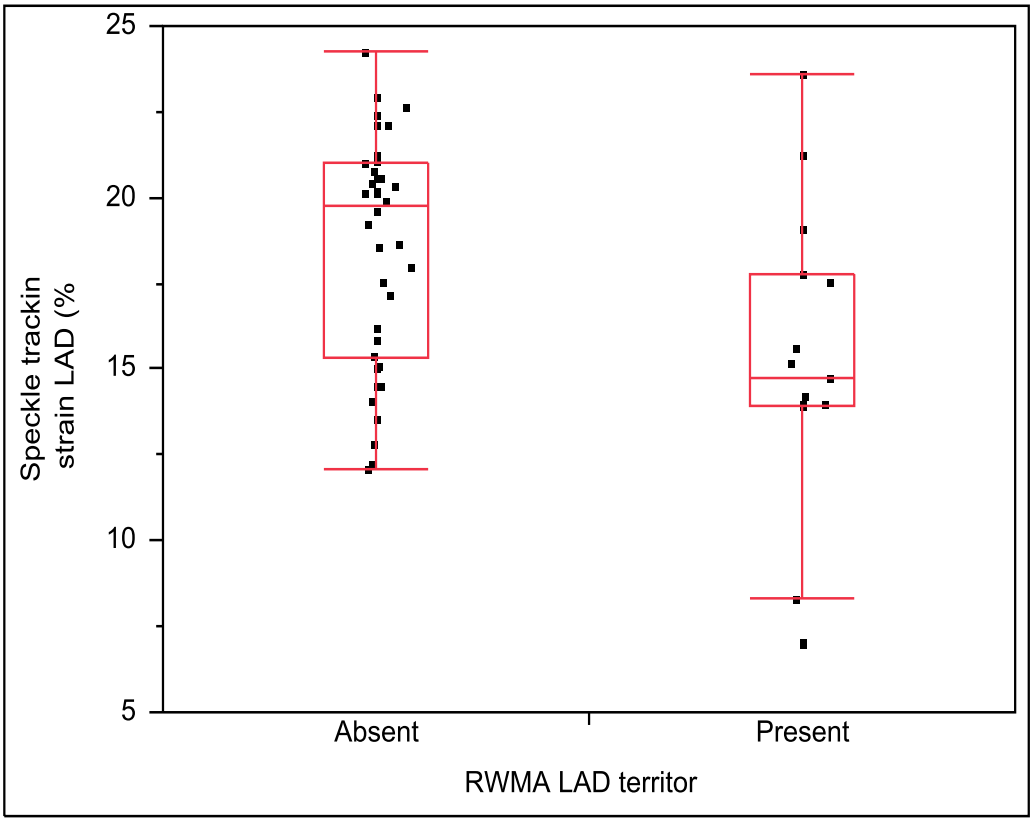


Where: v = velocity; ST = speckle tracking; RCA = right coronary artery territory; RWMA = regional wall motion abnormality

5.3.2.2 ST Imaging Derived Strain for RWMA Assessment

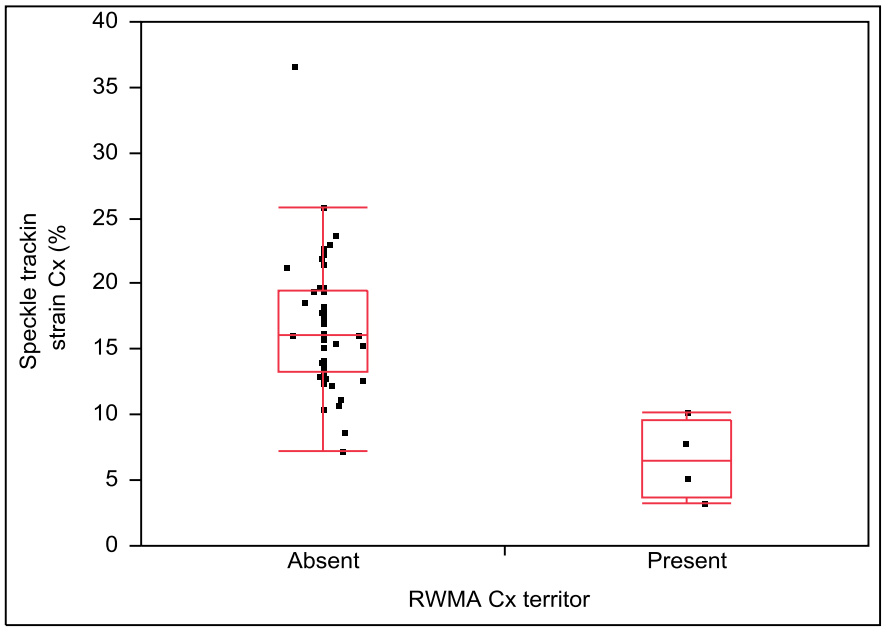
ST strain correlated less well than TVI strain (%) in territories where RWMAs were evident on standard echocardiography imaging in the RCA and Cx territories. Values were decreased (closer to the baseline) when RWMAs were visualised with standard echocardiography: p=0.01 for LAD territory (Graph 14), p=0.001 for Cx territory (Graph 15), and p=0.25 for RCA territory (Graph 16). The LAD and Cx regions were statistically significant.

Graph 14: One-way Analysis of Speckle tracking strain LAD (%) By RWMA LAD territory



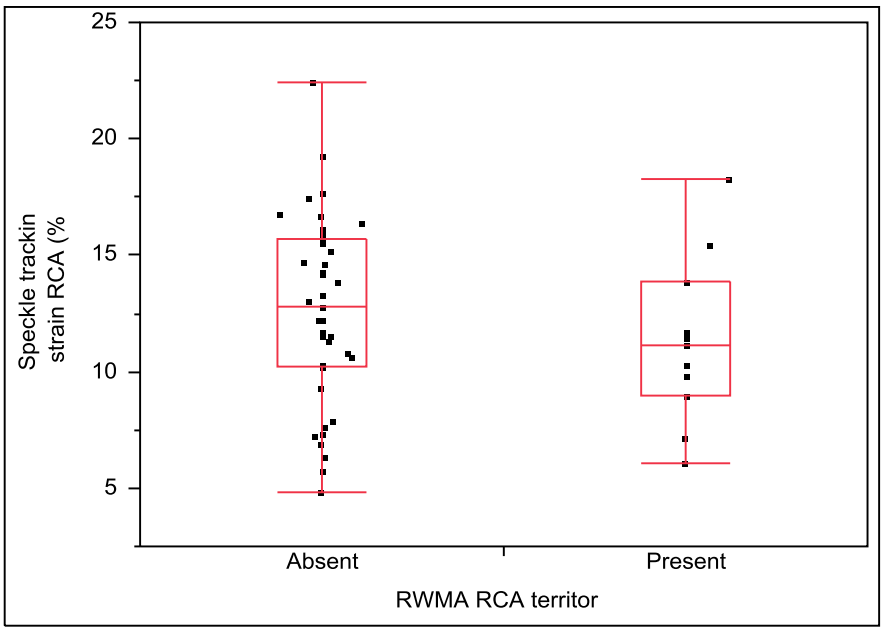
Where: LAD =left anterior descending coronary artery territory; RWMA = regional wall motion abnormality

Graph 15: One-way Analysis of Speckle tracking strain Cx (%) By RWMA Cx territory



Where: Cx = circumflex coronary artery territory; RWMA = regional wall motion abnormality

Graph 16: One-way Analysis of Speckle Tracking Strain RCA territory (%) By RWMA RCA territory

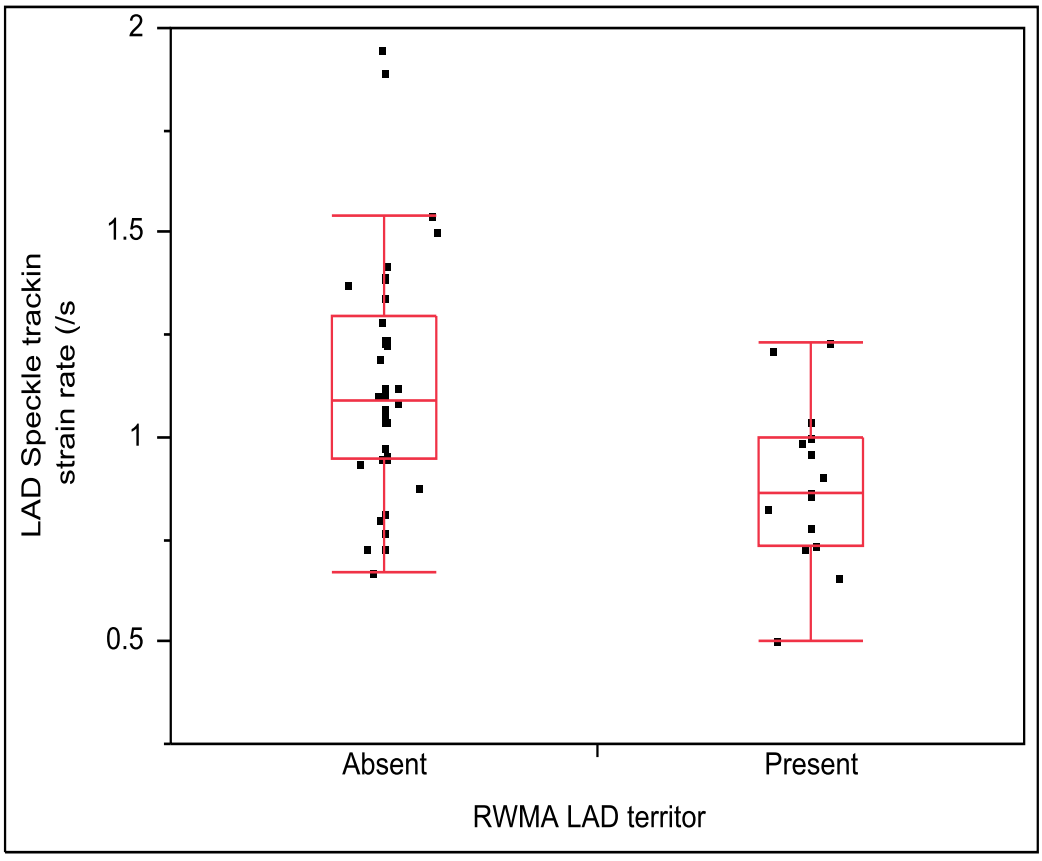


Where: RCA = right coronary artery territory; RWMA = regional wall motion abnormality

5.3.2.3 ST Imaging Derived Strain Rate for RWMA Assessment

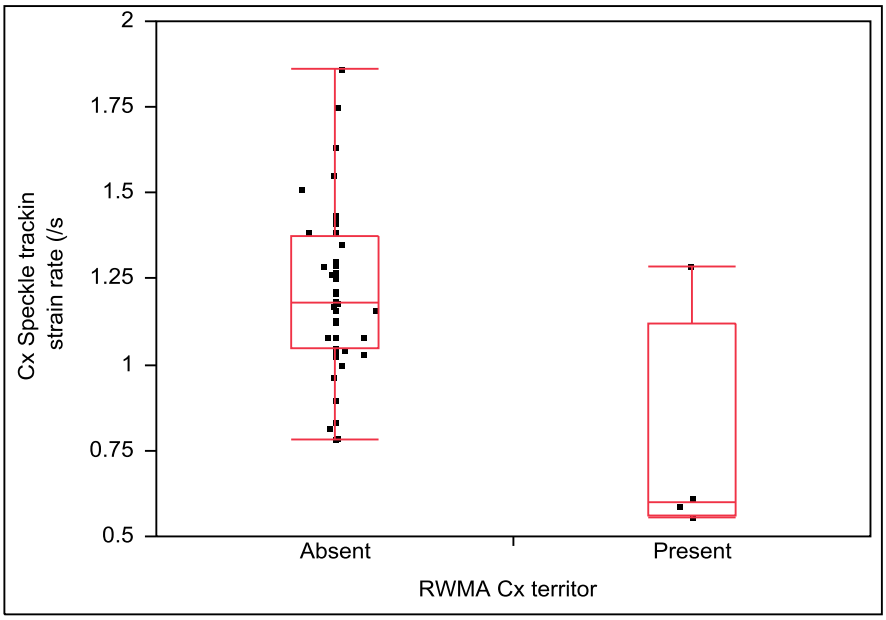
ST strain rate correlated less well than TVI strain rate (/s) in territories where RWMAs were evident on standard echocardiography imaging. Values were decreased (closer to the baseline) where a RWMA was visualised with standard echocardiography: p=0.002 for LAD territory (Graph 17), p=0.03 for Cx territory (Graph 18), and p=0.97 for RCA territory (Graph 19). The LAD and Cx regions were statistically significant.

Graph 17: One-way Analysis of LAD Speckle tracking strain rate (/s) By RWMA LAD territory



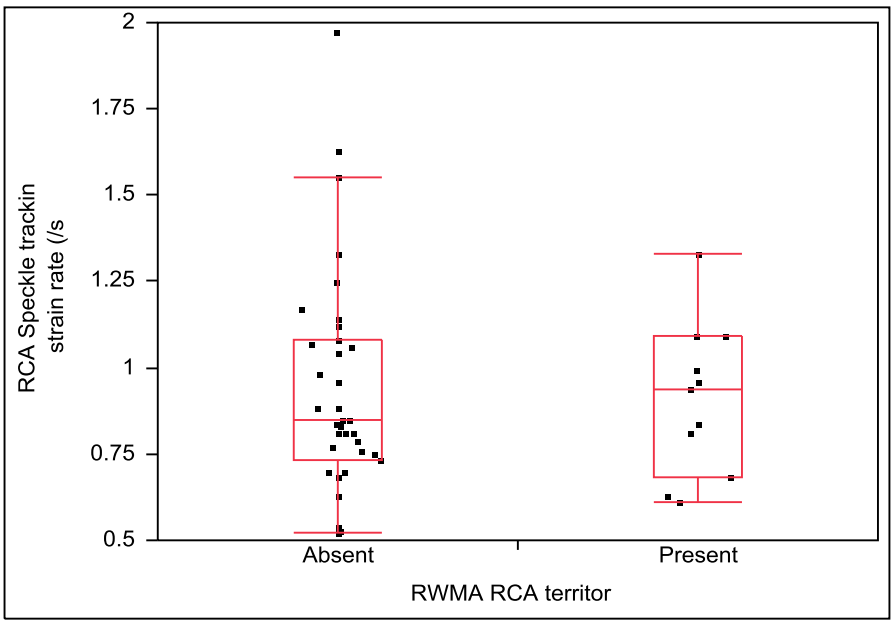
Where: LAD = left anterior descending coronary artery territory; RWMA = regional wall motion abnormality

Graph 18: One-way Analysis of Cx Speckle tracking strain rate (/s) By RWMA Cx territory



Where: Cx = circumflex coronary artery territory; RWMA = regional wall motion abnormality

Graph 19: One-way Analysis of RCA Speckle tracking strain rate (/s) By RWMA RCA territory



Where: RCA = right coronary artery territory; RWMA = regional wall motion abnormality

5.4 Coronary Artery Territory Disease

Univariate correlations between territorial strain from the advanced echocardiography imaging modalities - TVI and ST derived velocity (cm/s), strain (%) and strain rate (/s) - and the presence and absence, of CAD in the three major vessel territories - LAD, Cx and RCA - were assessed. Correlations were reduced compared to those for RWMA. Of the advanced echocardiography modalities, strain and strain rate performed generally equivocally.

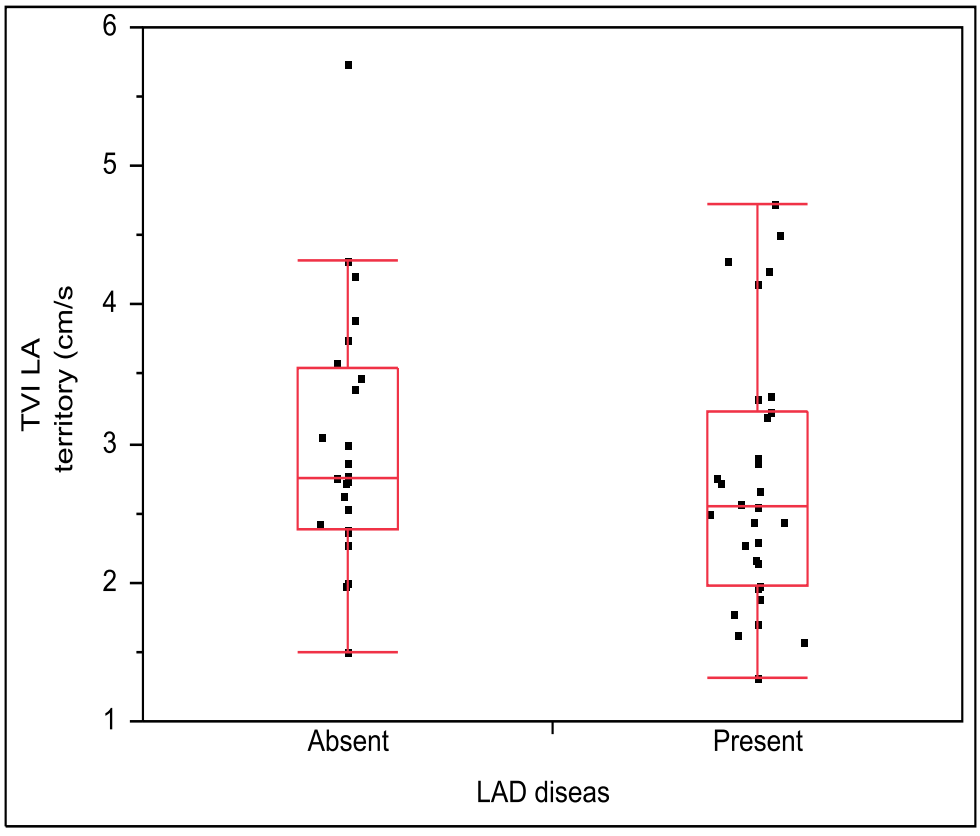
5.4.1 Tissue Velocity Imaging

Below are the results from analysis between CAD and TVI derived velocity, strain and strain rate. For each modality a comparison was made between the group of patients with and without CAD identified with coronary angiography. In general, there was overlap between the groups, although significant group mean differences were observed.

5.4.1.1 TVI Derived Velocity for CAD

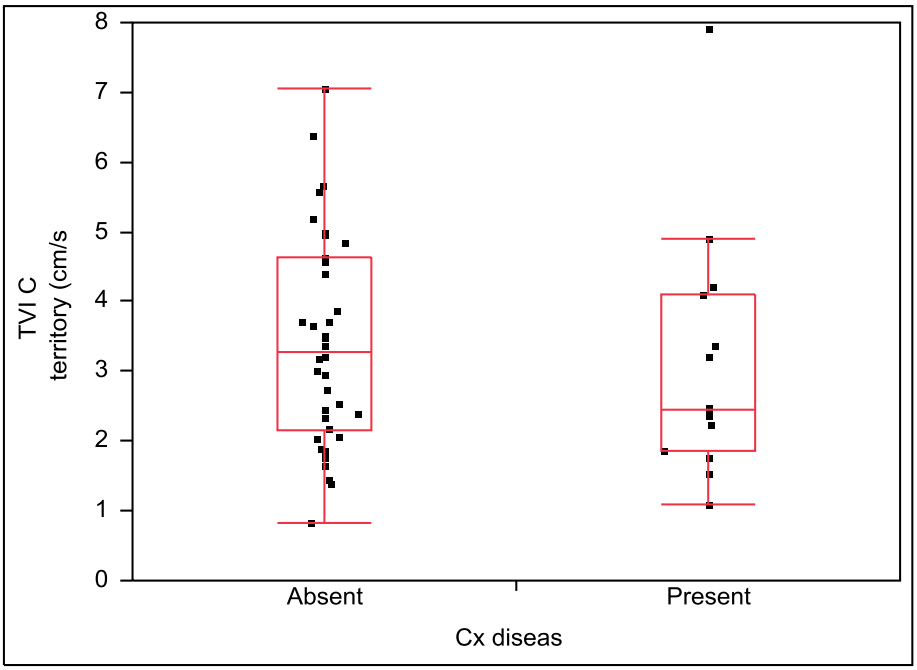
TVI derived velocity (cm/s) was not different between those with or without CAD (determined by angiography), in any of the three major vascular territories: p=0.17 for LAD disease (Graph 20), p=0.27 for Cx disease (Graph 21), and p=0.71 for RCA disease (Graph 22). There was no statistical significance.

Graph 20: One-way Analysis of TVI LAD territory (cm/s) By LAD disease



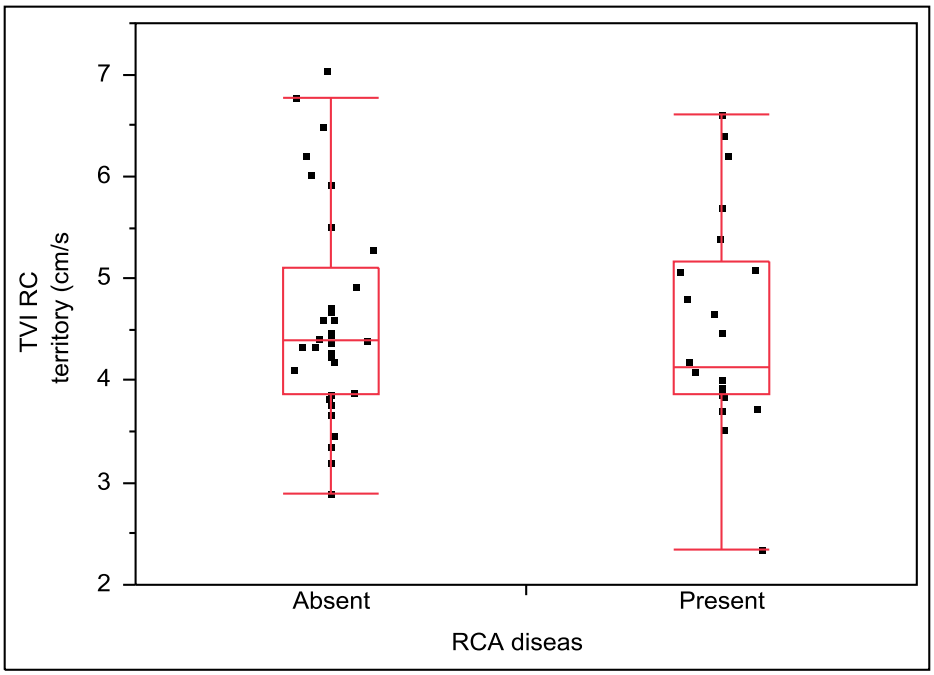
Where: TVI = tissue velocity imging; LAD = left anterior descending coronary artery

Graph 21: One-way Analysis of TVI Cx territory (cm/s) By Cx disease



Where: TVI = tissue velocity imaging; Cx = circumflex coronary artery

Graph 22: One-way Analysis of TVI RCA territory (cm/s) By RCA disease

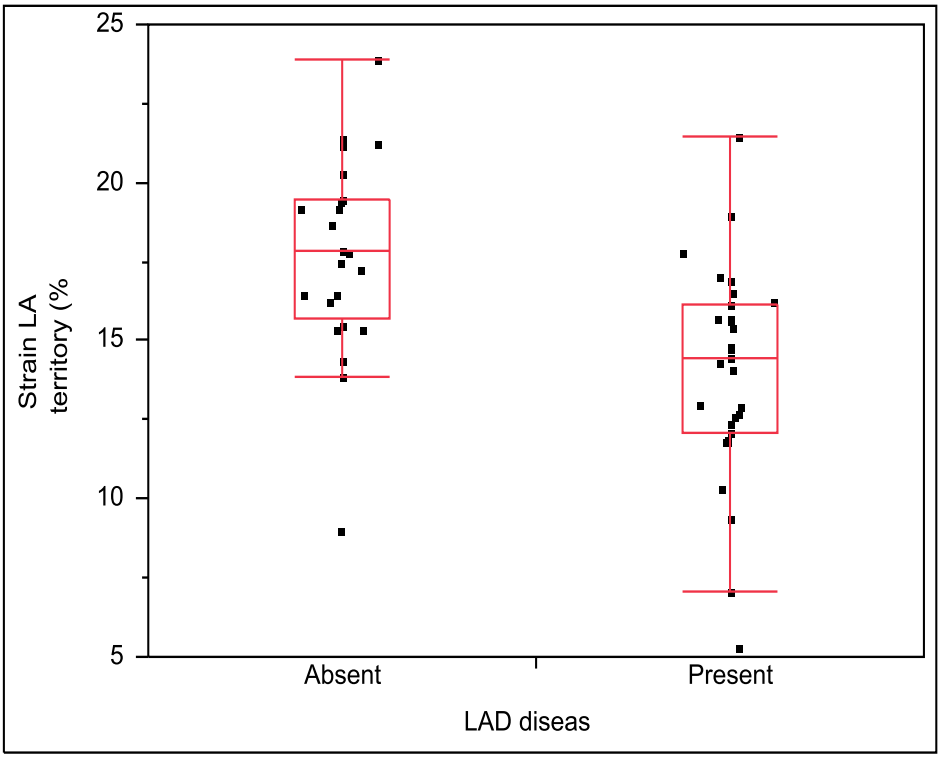


Where: TVI = tissue velocity imaging; RCA = right coronary artery

5.4.1.2 TVI Derived Strain for CAD

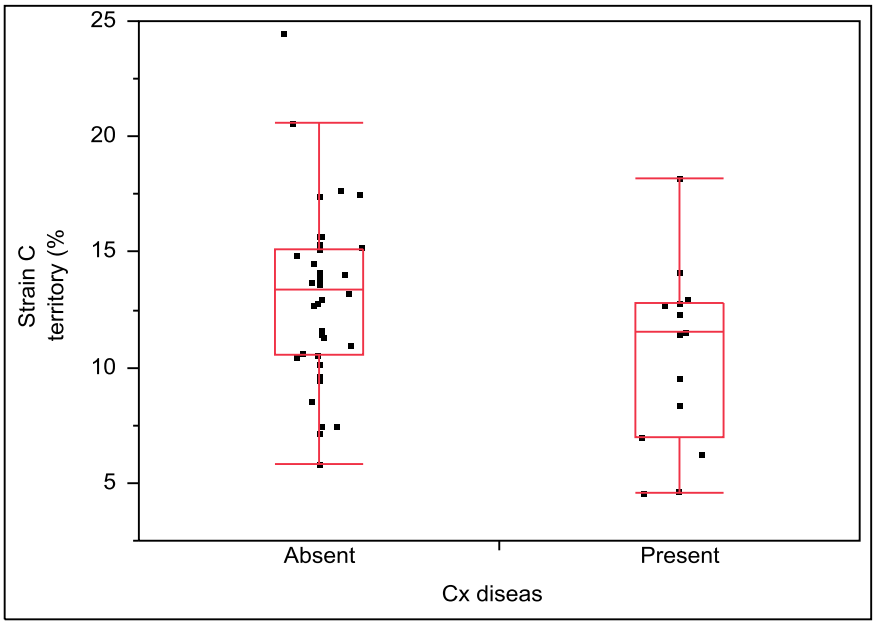
TVI derived strain (%) correlated the presence and absence, of CAD (identified by coronary angiography) in all three of the major vascular territories. TVI derived strain (%) obtained the highest correlation. Strain values were decreased (closer to the baseline), in territories where CAD was evident on a coronary angiogram: $p<0.0001$ for LAD disease (Graph 23), $p=0.03$ for Cx disease (Graph 24), and $p=0.001$ for RCA disease (Graph 25). All territories were statistically significant.

Graph 23: One-way Analysis of Strain LAD territory (%) By LAD disease



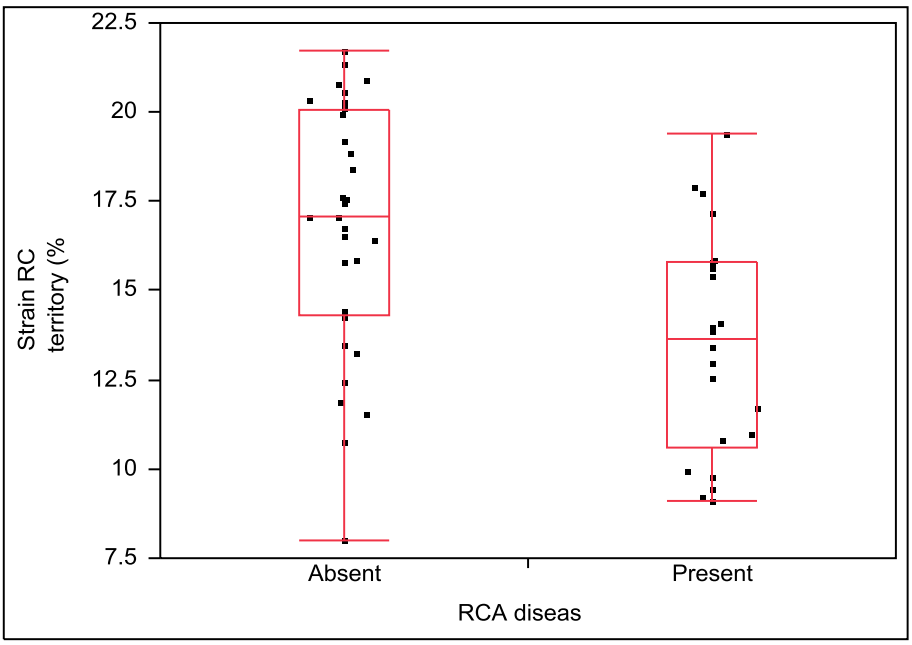
Where: LAD = left anterior descending coronary artery

Graph 24: One-way Analysis of Strain Cx territory (%) By Cx disease



Where: Cx = circumflex coronary artery

Graph 25: One-way Analysis of Strain RCA territory (%) By RCA disease

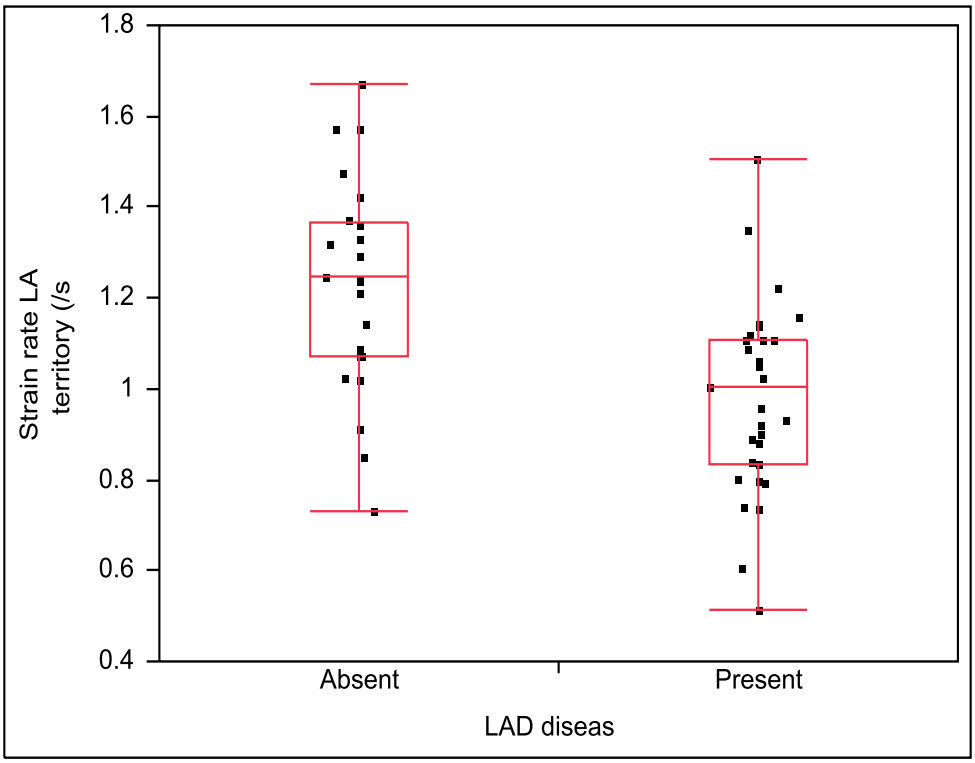


Where: RCA = right coronary artery

5.4.1.3 TVI Derived Strain Rate for CAD

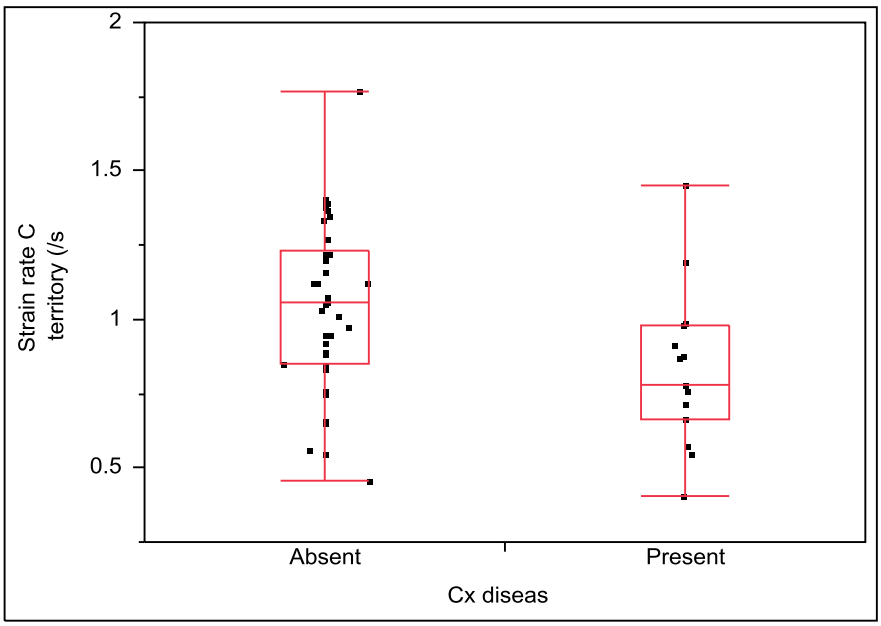
TVI derived strain rate (/s) correlated with the presence and absence, of CAD (identified by coronary angiography) in two of the major vascular territories. Strain rate values were decreased (closer to the baseline), in territories where CAD was evident on a coronary angiogram: p=0.0003 for LAD disease (Graph 26), p=0.01 for Cx disease (Graph 27), and p=0.21 for RCA disease (Graph 28). The LAD and Cx territories were statistically significant.

Graph 26: One-way Analysis of Strain rate LAD territory (/s) By LAD disease



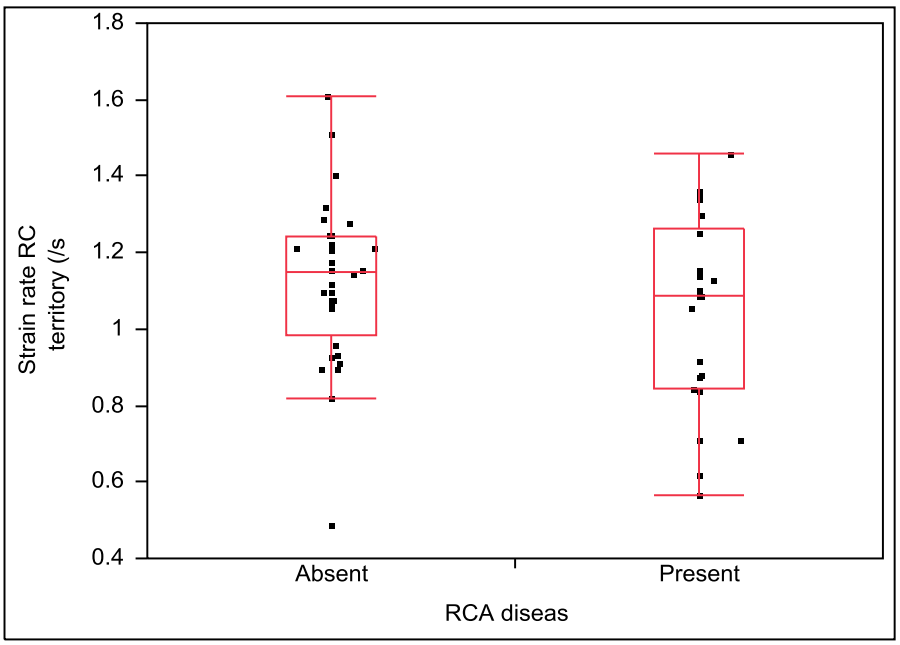
Where: LAD = left anterior descending coronary artery

Graph 27: One-way Analysis of Strain rate Cx territory (/s) By Cx disease



Where: Cx = circumflex coronary artery

Graph 28: One-way Analysis of Strain rate RCA territory (/s) By RCA disease



Where: RCA = right coronary artery

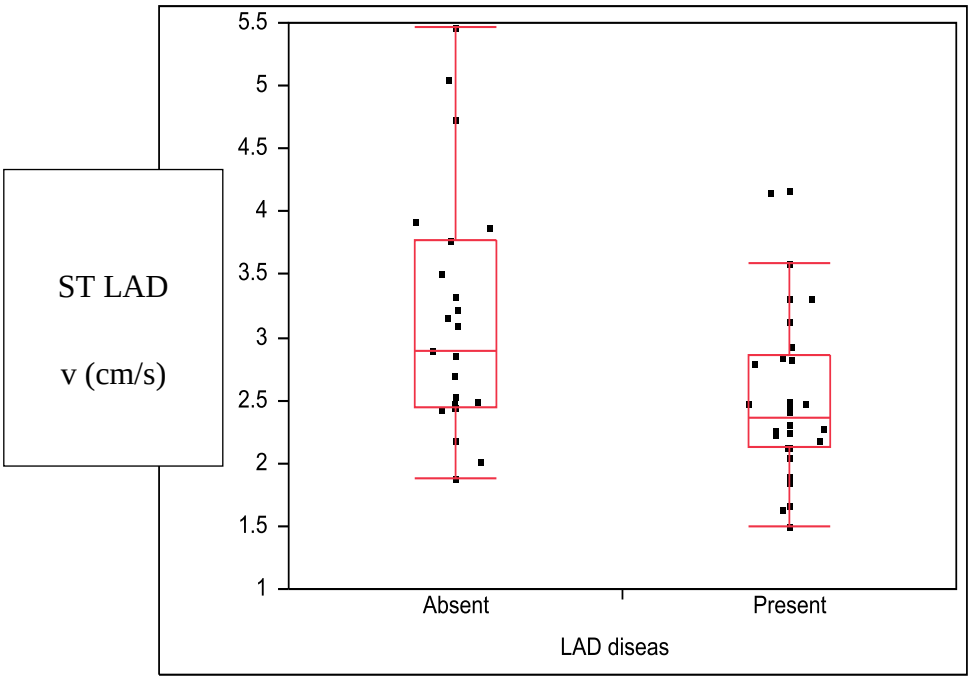
5.4.2 Speckle Tracking Imaging

Below are the results from analysis between CAD and ST derived velocity, strain and strain rate. For each modality a comparison was made between the group of patients with and without CAD identified with coronary angiography. In general, there was overlap between the groups, although group mean differences were observed.

5.4.2.1 ST Imaging Derived Velocity for CAD

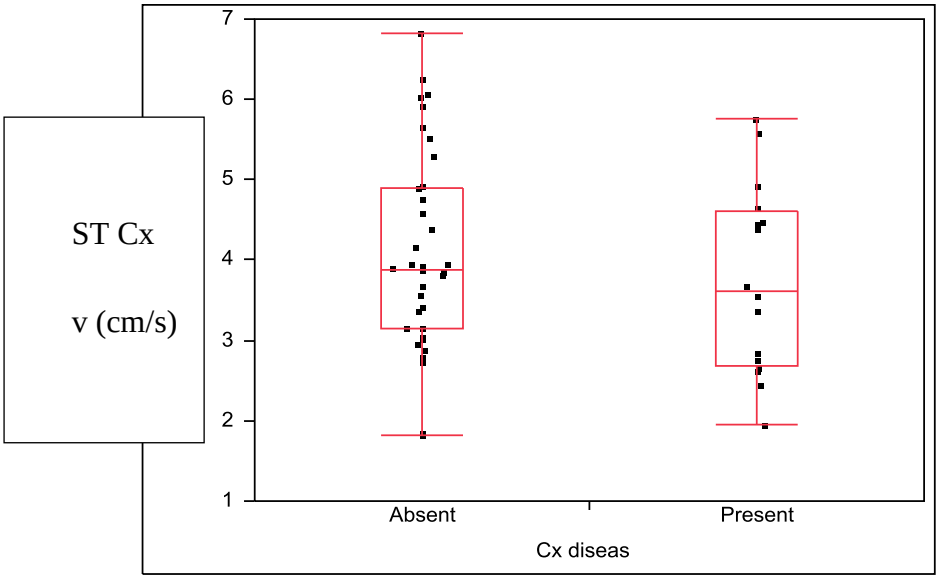
ST derived velocity (cm/s) was not different between those with or without CAD (identified with angiography) in the RCA and Cx territories. However, correlation was noted between the presence and, absence of CAD (identified by coronary angiography) in the LAD territory: p=0.008 for LAD disease (Graph 29), p=0.30 for Cx disease (Graph 30), and p=0.64 for RCA disease (Graph 31). The LAD territory was statistically significant.

Graph 29: One-way Analysis of LAD Speckle tracking derived velocity (cm/s) By LAD disease



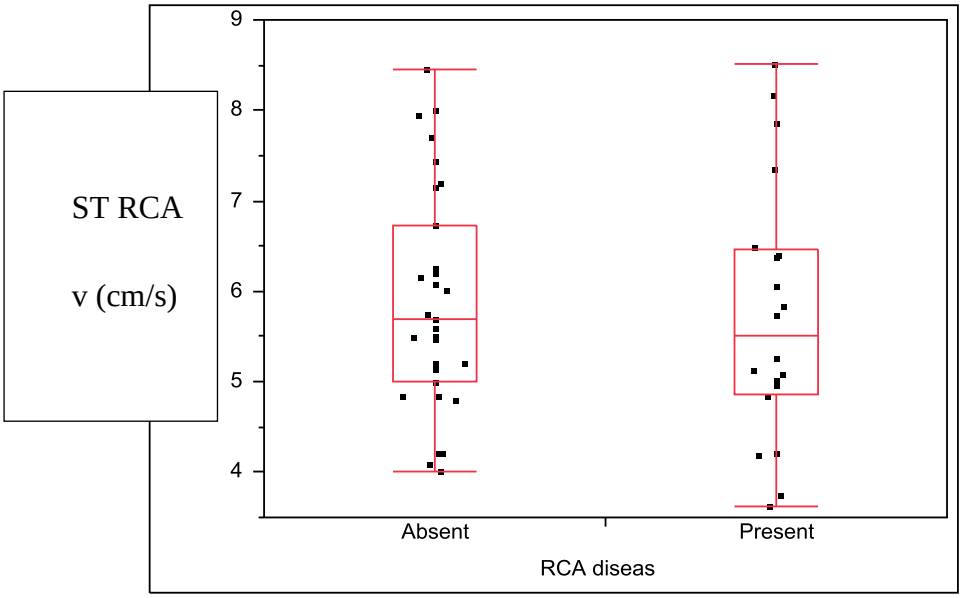
Where: ST = speckle tracking; v = velocity; LAD = left anterior descending coronary artery

Graph 30: One-way Analysis of Cx Speckle tracking TVI (cm/s) By Cx disease



Where: ST = speckle tracking; v = velocity; Cx = circumflex coronary artery

Graph 31: One-way Analysis of RCA Speckle tracking TVI (cm/s) By RCA disease

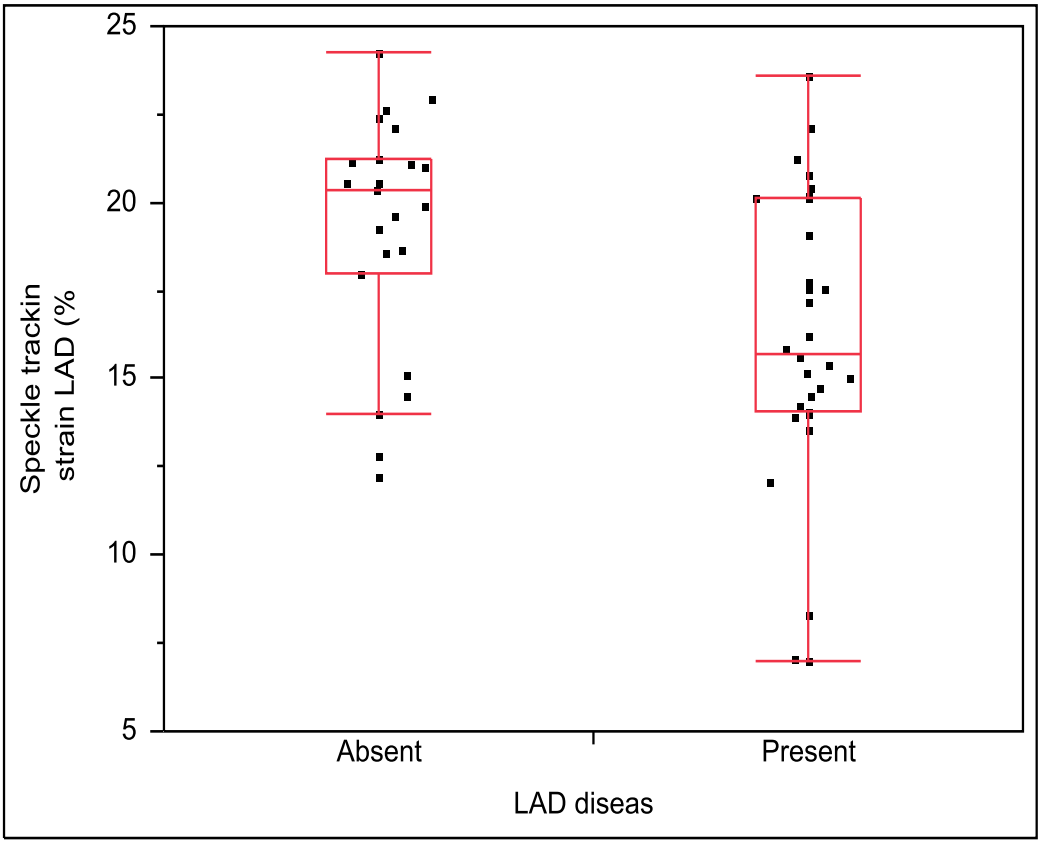


Where: ST = speckle tracking; v = velocity; RCA = right coronary artery

5.4.2.2 ST Imaging Derived Strain for CAD

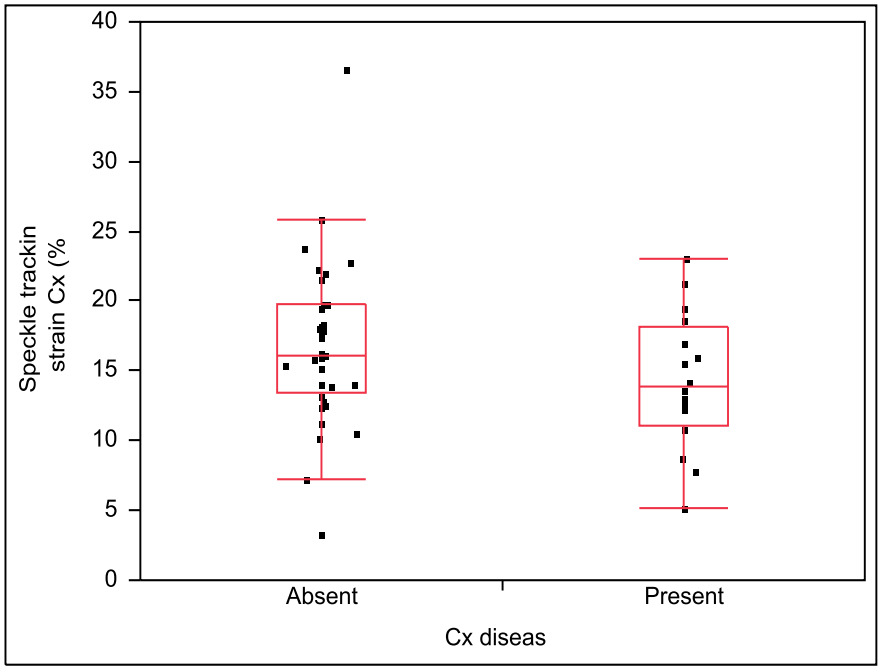
ST derived strain (/s) was not different between those with or without CAD (identified with angiography) in the Cx territory. However, correlation was noted between the presence and, absence of CAD (identified by coronary angiography) in the LAD and RCA territories: p=0.006 for LAD disease (Graph 32), p=0.14 for Cx disease (Graph 33), and p=0.007 for RCA disease (Graph 34). The LAD and RCA territories were statiscally significant.

Graph 32: One-way Analysis of Speckle tracking strain LAD (%) By LAD disease



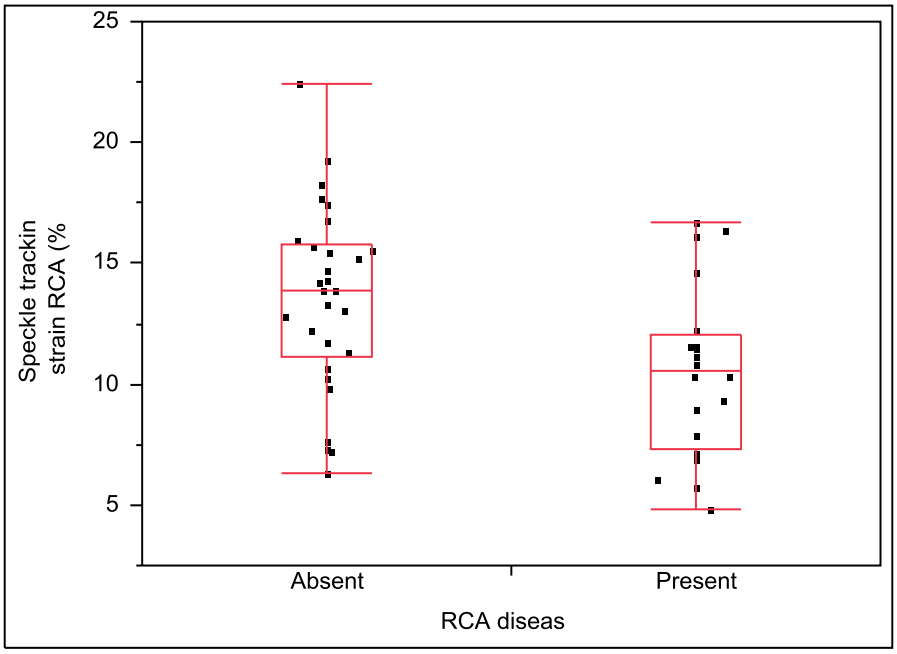
Where: LAD = left anterior descending coronary artery

Graph 33: One-way Analysis of Speckle tracking strain Cx (%) By Cx disease



Where: Cx =circumflex coronary artery

Graph 34: One-way Analysis of Speckle tracking strain RCA (%) By RCA disease

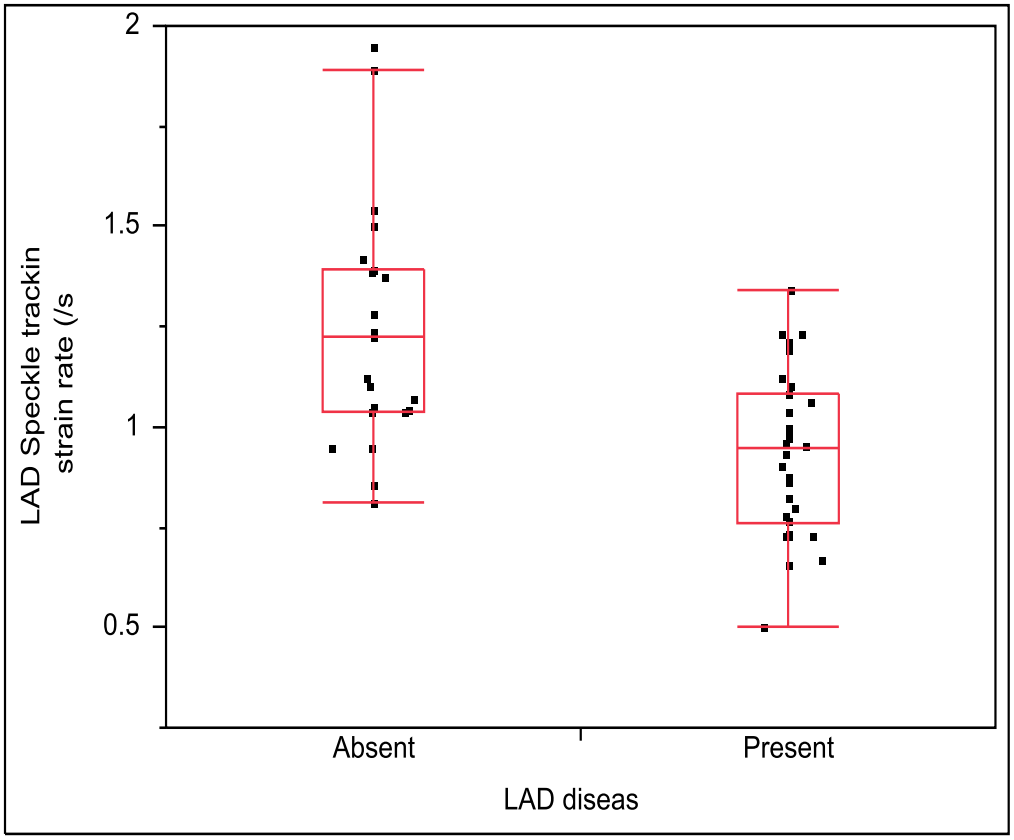


Where: RCA = right coronary artery

5.4.2.3 ST Imaging Derived Strain Rate for CAD

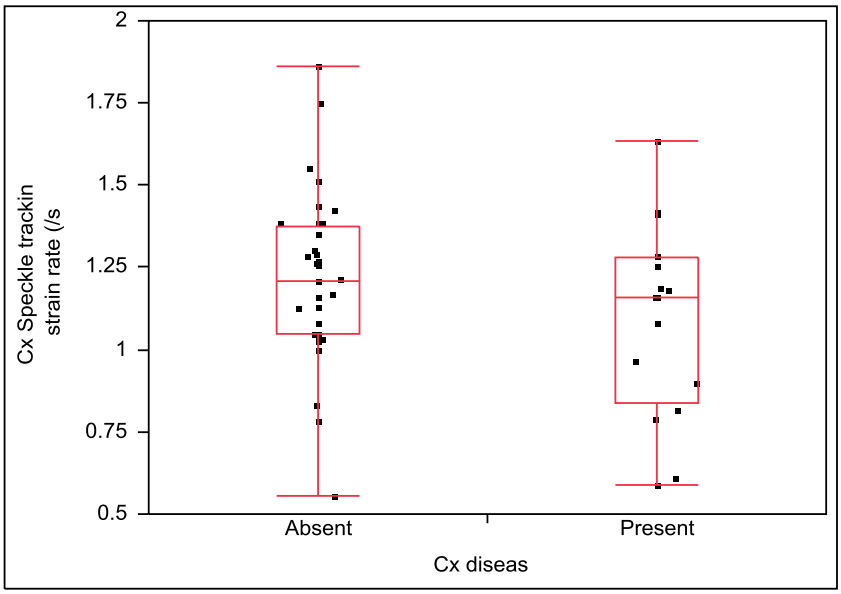
ST derived strain rate (/s) correlated less well than TVI derived strain rate (/s). ST derived strain rate (cm/s) was not different between those with or without CAD (identified with angiography) in the RCA and Cx territories. However, correlation was noted between the presence and absence, of CAD (identified by coronary angiography) in the LAD territory: p=0.0001 for LAD disease (Graph 35), p=0.23 for Cx disease (Graph 36), and p=0.33 for RCA disease (Graph 37). The LAD territory was statistically signficant.

Graph 35: One-way Analysis of LAD Speckle tracking strain rate (/s) By LAD disease



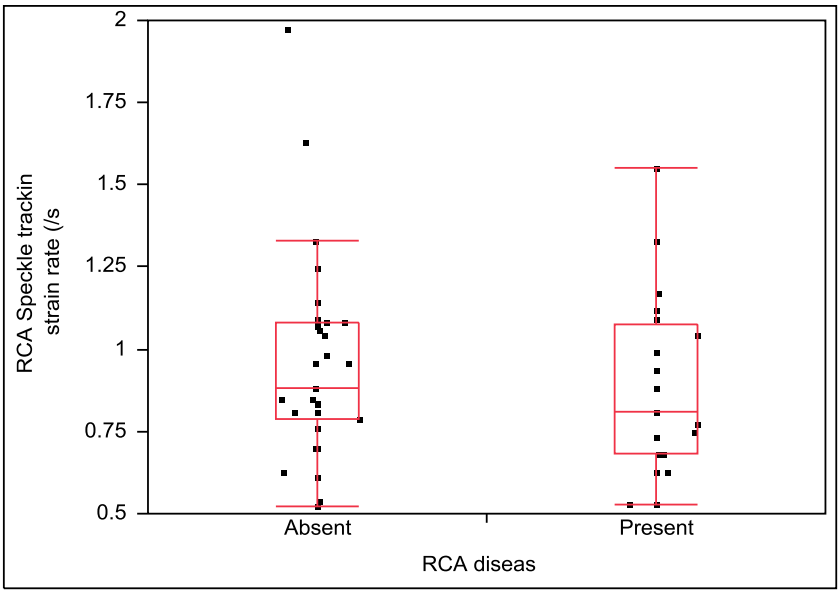
Where: LAD = left anterior descending coronary artery

Graph 36: One-way Analysis of Cx Speckle tracking strain rate (/s) By Cx disease



Where: Cx = circumflex coronary artery

Graph 37: One-way Analysis of RCA Speckle tracking strain rate (/s) By RCA disease



Where: RCA = right coronary artery

Table 19: Quick Reference Table: Vascular Territory Distribution and the Correlation Between Advanced Imaging Modalities and the Presence and Absence of RWMA or CAD (p values)

Vascular Territory Distribution and the Correlation Between Advanced Imaging Modalities and the Presence and Absence of RWMA or CAD

		LAD		Cx		RCA	
		RWMA	CAD	RWMA	CAD	RWMA	CAD
TVI	**Velocity (p)**	0.36	0.17	0.58	0.27	0.50	0.71
	Strain (p)	0.0002	<0.0001	0.002	0.03	0.06	0.001
	Strain Rate (p)	0.0007	0.0003	0.01	0.01	0.009	0.21
ST	**Velocity (p)**	0.23	0.008	0.78	0.30	0.46	0.64
	Strain (p)	0.01	0.006	0.001	0.14	0.25	0.007
	Strain Rate (p)	0.002	0.0001	0.03	0.23	0.97	0.33

Where: TVI = tissue velocity imaging; RWMA = regional wall motion abnormalities; CAD = coronary artery disease; LAD – left anterior descending coronary artery; RCA = right coronary artery; Cx = circumflex and p = p value (statistical significance was taken as p<0.05)

Table 20: Quick Reference Table of Statistical Significance: Vascular Territory Distribution and the Correlation between Advanced Imaging Modalities and the Presence and Absence of RWMA or CAD

Table of Statistical Significance: Vascular Territory Distribution and the Correlation Between Advanced Imaging Modalities and the Presence and Absence of RWMA or CAD

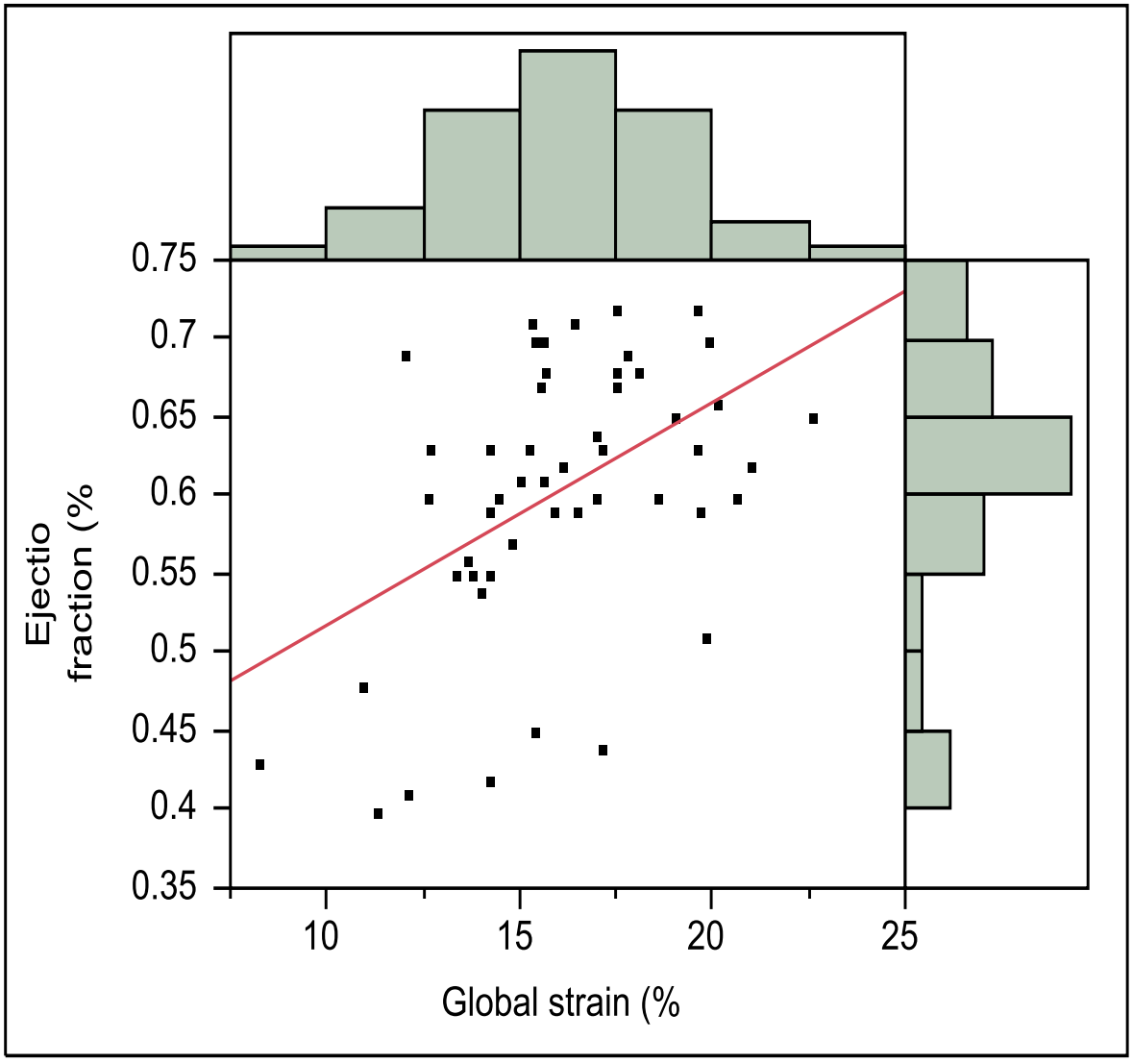
		LAD		Cx		RCA	
		RWMA	**CAD**	**RWMA**	**CAD**	**RWMA**	**CAD**
TVI	**Velocity**	N	N	N	N	N	N
	Strain	SS	SS	SS	SS	N (trend SS)	SS
	Strain rate	SS	SS	SS	SS	SS	N
ST	**Velocity**	N	SS	N	N	N	N
	Strain	SS	SS	SS	N	N	SS
	Strain rate	SS	SS	SS	N	N	N

Where: TVI = tissue velocity imaging; ST = speckle tracking; LAD = left anterior descending; Cx = circumflex; RCA = right coronary artery; SS = statistically significant; N = not statistically significant and trend SS = trend towards statistical significance

5.5 Global Strain

Global strain was assessed from the ST modality (also called 2D strain), in the apical four chamber view, as an indicator of overall left ventricular systolic function (Graph 38). The bivariate fit of ejection fraction to the global strain R square value was 0.2 (20% of the variation can be explained), which suggests there is a weak correlation between global strain and LVEF.

Graph 38: Bivariate Fit of Ejection fraction (%) By Global strain (%)



5.6 Summary: Advanced Echocardiography Results

In summary, TVI derived velocity did not significantly correlate with any of the three major vascular territories and the presence, nor absence, of RWMA or CAD.

TVI derived strain and strain rate was statistically significant for RWMA and CAD in all territories, apart from strain rate in the RCA territory to determine underlying CAD and strain in the RCA territory to determine RWMA. However strain in the RCA territory did trend towards statistical significance (p value = 0.06).

There was good correlation noted in the LAD territory with strain and strain rate (with both TVI and ST modalities) with the presence and absence, of RWMA (identified with standard echocardiography) and CAD (identified with angiography). There was also good correlation noted with TVI derived strain and strain rate and the presence and absence of RWMA and CAD in the Cx territory.

ST derived strain and strain rate were statistically significant with the presence and absence of RWMA in the Cx territory. The RCA was only statistically significant with ST derived strain when determining the presence and absence of CAD.

The bivariate fit of ejection fraction to global strain R square value was 0.2 (20% of the variation can be explained), which suggests there was a weak correlation between global strain and LVEF.

Chapter Six:

Discussion - Part II

Advanced Echocardiography Techniques

6 Chapter Six: Discussion Part II – Advanced Echocardiography Techniques

6.1 Introduction

Echocardiography, although a quick, affordable and effective diagnostic tool, relies upon individual interpretation of wall motion (contraction) to determine systolic dysfunction of a left ventricle after an AMI. This makes the test reasonably observer dependent (even though standardised training and guidelines attempt to minimise the effects of inter-observer variability). Furthermore, there may only be very subtle changes to systolic function, invisible to the human eye. For these reasons, the advanced echocardiographic modalities of tissue velocity imaging (TVI) and speckle tracking (ST) derived velocity, strain and strain rate are proposed as sensitive, quantitative, less observer dependent determinants of regional dysfunction, with the ability to detect significant underlying CAD.

This chapter determines the viability and accuracy of utilising TVI and ST derived velocity, strain and strain rate as a diagnostic tool in a clinical (non-research) setting. This study was performed with the same set of 55 NSTEMI patients as used in *Results I/Discussions I*, admitted to Christchurch Hospital, New Zealand between June 2011 and April 2012. Using territorial strain of the three major vascular territories (LAD, RCA and Cx), trends between the presence and absence, of RWMAs (with echocardiography) and CAD (with coronary angiography) and their correlation with TVI and ST derived velocity, strain and strain rate values were assessed.

6.2 Validity of Performing and Analysing TVI and ST in a Non-Research Clinical Laboratory

6.2.1 Acquisition

The process of performing, analysing and interpreting TVI and ST waveforms is time consuming. This is especially so, for a routine (non-research) clinical laboratory in a public hospital where there are restraints on the length of an echocardiography examination due to high demand for the procedure. The acquisition of images for advanced modality analysis took approximately five minutes (described in detail in *Chapter Two: Methodology*). The images were stored digitally and sent to EchoPac (GE Vingmed Ultrasound System, Horten, Norway). A disadvantage of using the 2007 version of EchoPac (GE Vingmed Ultrasound System, Horten, Norway) was the need for its own workstation. The new version of EchoPac (GE Vingmed Ultrasound System, Horten, Norway) may be uploaded and combined with ProSolv (ProSolv CardioVascular Client 4.0.2), which would significantly speed up the process (announced in 2009 [157]) – this is not currently used at Christchurch Hospital, New Zealand. Production and analysis of TVI and ST derived velocity, strain and strain rate waveforms may be performed on the GE Vivid 7 (GE Vingmed Ultrasound System, Horten, Norway) machine itself; however, this method was not used for this research due to procedure time constraints for each patient.

All patients admitted with NSTEMI underwent additional imaging. From the additional images, advanced imaging modality analysis was performed to determine the usefulness of these tests in a routine clinical (non-research) setting. The patient images (windows) ranged from borderline to excellent (as a result of individual patient image quality) and although Simpson's Biplane was possible in all patients, not all segments were perfectly visualised due to various factors (drop-out, reverberation artefact, etc.). No patients were excluded for poor acoustic window quality. If required, segments or entire walls were discarded. This study population, therefore, resembles a normal patient population in a clinical (non-research)

setting. A study published in 2011 by Marcon et al. [158] determined the accuracy of using longitudinal strain with ST in patients with suboptimal window quality (defined as three or more suboptimal segments). They found that longitudinal strain data was still accurate and reproducible. This suggests, that in this CESTEMI study, although some segments of suboptimal quality were discarded, the final data set should be accurate and reproducible, and moreover, representative of a true clinical population in a routine (non-research) cardiac clinical setting.

6.2.2 Analysis

Offline analysis of the five walls with TVI and two walls with ST derived velocity, strain and strain rate took approximately 20-40 minutes. Angiography for this patient cohort was performed on average 1.4 ± 1.1 days after the echocardiogram. This means that time permits for advanced modality analysis and interpretation prior to angiography if required.

TVI velocity waveforms were used to determine the suitability for segmental interpretation as they represent primary, least processed data [85, 159]. Waveforms with excessive noise or aliasing were excluded as they precluded further analysis with strain and strain rate.

For this study, territorial ‘strain’ was utilised as a method for determining RWMAs and underlying CAD correlation with the advanced modalities. This method was used instead of analysing individual segmental values. The segments were averaged for each theoretical vascular distribution (as described in the methods section), resulting in territorial data (velocity, strain and strain rate) for the LAD, RCA and Cx coronary artery territories according to established recommendations [160]. Studies have used this method in the past with favourable results [100, 161]. Research published in 2010 by Grenne et al. [161] found, of 105 patients presenting with NSTEMI, territorial circumferential strain was reduced in

those with significant CAD. A study published in 2007 by Gjesdal et al. [100] found 35 STEMI patients displayed reduced territorial strain values, which correlated with significant CAD, infarct size and infarct mass. The territorial strain method used in this CENSTEMI study enabled the assessment of trends within the data set between the presence and absence of RWMAs and CAD and their correlation with velocity, strain and strain rate values (at the level of the theoretical coronary artery distribution). The averaged territorial strain value may, therefore, reflect a mixture of normal and diseased myocardium, hence, territorial strain values containing infarcted segments may not be as low as that measured from a single infarcted segment. This means that the resulting territorial strain value variations may not be as obvious as those found with single segmental analysis, with the possibility of greater overlap. This method may not be suitable for a clinical setting as it is time consuming to average the data from each vascular distribution, although if required, the data may be collected then analysed retrospectively when time permits (which was performed in this study).

Territorial strain provided the necessary information required to analyse and determine trends within the data set of this study. Greater or more obvious trends may be observed if a larger patient cohort was used; however, the modalities must work on an individual basis in a clinical (non-research) setting, not as a collective. Therefore, if the modalities were to work well, we would see promising results in a majority of the patients in this study. Individual coronary artery distribution was not accounted for in this study; however, in a clinical setting, this information is also unknown so it reflects real life practise.

6.2.3 TVI Analysis

The sample volume was positioned, blinded to any RWMAs present and moved marginally if artefact was noted (reverberation/drop out etc.) or if the trace was obviously nonsensical. Of 825 possible segments for interrogation, 754 (91%) were found suitable for analysis.

A study published in 2001 by Stoylen A. [162] determined the viability of using TVI derived strain rate to determine regional dysfunction in 30 patients. Of 480 possible segments, 473 (98%) could be analysed with standard echocardiography, while 454 (95%) could be analysed with strain rate. Stoylen A. [162] did not comment on the quality of segments in their study, however, did mention that the patients were randomly selected and not excluded for poor window quality. The proportion of segments suitable for analysis in the Stoylen A. study [162], was equivalent to the number determined suitable for analysis in this CENSTEMI study.

In this study, the inferoseptal and inferior walls were most suitable for interrogation (165 and 164 of 165 possible segments respectively). The author found that these segments aligned best with the cursor, reducing the angle of insonation. The anterior and anterolateral segments were found least suitable for interrogation (130 and 146 of 165 possible segments respectively). Reverberation artefacts and drop-out were often noted in regions of the anterior and anterolateral walls. This, as well as the pronounced curve of the anterolateral wall (which increased the angle of insonation, a limitation of TVI [85]) reduced the potential segments available for interrogation/analysis.

6.2.4 ST Analysis

Of 330 segments for possible interrogation, 305 (92%) were suitable for analysis. The septal wall was the most suitable for analysis (157 of a possible 165 segments), followed by the anterolateral wall (148 of a possible 165 segments). Stoylen A. [85] suggests discarding the entire wall if reverberation artefact or drop-out is noted. This was not performed in this CENSTEMI study.

A feasibility study performed by Sagberg et al. [163], published in 2004 found reverberation artefacts were noted in up to 80% of patients. They suggested that studies reporting 80% of segments for analysis may be feasible, but those reporting 90% or greater may have a high number of artefacts in their data. 92% of segments were determined feasible for analysis in this CENSTEMI study which raised the possibility of a small number of artefacts within the data set. Information obtained from the Sagberg et al. study [163] suggests that, when performing ST imaging, more emphasis should be placed on the determination of segment quality with consideration of discarding the whole segment/wall if artefact is noted.

When performing Simpson's Biplane ejection fraction with standard echocardiography it is recommended to start the trace at the mitral annulus, follow the anterolateral wall to the apex, along the inferoseptal wall to the opposite mitral annulus [107]. This is because there is reduced delineation of the anterolateral endocardial border, which makes tracking of the blood/tissue interface difficult when the image is frozen. This means that both standard echocardiography and advanced imaging modalities are influenced by window quality.

6.2.5 Coronary Angiography Analysis

Analysis with coronary angiography was performed by averaging segmental data into the respective coronary artery territories - LAD, Cx and RCA - resulting in territorial values as described earlier. Significant correlations in the data set were observed when trends were noted between decreased values (of no particular arbitrary value) in the coronary artery territories when related to the presence and absence of RWMAs or underlying CAD. A study published in 2004 by Maniar et al. [164] used this method to assess ventricular function after CABG with myocardial strain imaging using MRI. Average regional circumferential strain for each region was determined with favourable results. They found this approach suitable for their research as it enabled detection of trends within the data. As this CENSTEMI study also wished to assess trends within the data, to determine whether the modalities actually worked or not in a clinical (non-research) laboratory setting, this method was, therefore, decided suitable for use.

This CENSTEMI study did not determine, nor take into consideration normal nor abnormal values for the presence and absence of significant CAD as these have been shown and well validated in previous studies [86, 165] – see *Appendix*: Table 21 p.186.

The analysis of underlying CAD by TVI and ST did not take into account RWMAs identified with echocardiography. The resulting data, therefore, represents patients with RWMAs and CAD, not just underlying CAD. When Choi et al. [91] examined correlation between strain and underlying CAD, they recruited patients with suspected ACS who had no visual RWMAs as determined by standard echocardiography. This reduced the possibility of segments with hypokinetic contraction biasing the results. In future studies, if the presence of underlying CAD is to be evaluated, the patient cohort should have no visible RWMAs with standard echocardiography.

6.3 Interpretation

6.3.1 Tissue Velocity Imaging

TVI derived velocity involves interrogating the motion between two points (the sample volume and the transducer), moving toward or away from each other [86]. In this study, territorial TVI derived strain and strain rate values were superior to velocity when correlating with RWMAs or CAD. Territorial TVI derived velocity did not correlate (was not statistically significant) with the presence of RWMAs and CAD for any of the coronary regions. There was high statistical significance and excellent correlation noted between the LAD region and TVI derived strain and strain rate. There was statistical significance and good correlation noted between the Cx region and TVI derived strain and strain rate. Statistical significance was not noted with the presence of CAD determined by strain rate in the RCA territory. Nor with the presence of RWMA determined by strain in the RCA region, however, a trend towards statistical significance was noted here. Although there was correlation between strain/strain rate and RWMAs/CAD, there was also variation and overlap. This is significant in a clinical setting as it would reduce the validity of performing the test routinely - refer to the graphs (*Chapter Five: Results II*) for visual cues as to the spread of the data with the modalities and indices for the 55 patients.

While TVI derived velocity is well validated and provides least processed waveforms and data [166-168], there are significant regional level differences in the distribution of myocardial velocities. A study published in 2000 by Palmes et al. [169] performed TVI on 20 healthy patients, and 16 patients with AMI analysed waveforms from the basal, mid and apical segments. They found decreased S and E velocities correlated with regional dysfunction, velocity differences between walls (the lateral and septal walls in healthy subjects showed lower velocities) and at different levels of the myocardium (the apical velocities were lower than the basal velocities). Animal based studies have related these variances to non-homogenous contraction of longitudinal, circumferential and radial fibres with an apex which is thickening, yet stationary, hence the low velocities [170].

6.3.1.1 Explanations for the Reduced Statistical Significance between TVI Derived Velocity and RWMAs/CAD

Velocity is indicative of tissue motion and is position dependent [86]. TVI derived velocity involves interrogating the motion between two points (the sample volume and the transducer) moving toward or away from each other [171]. For this reason, TVI derived velocity is influenced by translational motion and tethering of adjacent tissue and indicative only of a single point not fully capturing intricate myocardial mechanics. As velocity increases from apex to base, contraction at the apex of the heart may affect passive segments at the base resulting in motion shown when there is none [86]. These issues may contribute to the low correlation and lack of statistical significance noted between TVI derived velocity and the presence and absence of RWMAs or CAD. The method used for this study – obtaining territorial data – may possibly be incorrect for analysis of trends with TVI derived velocity. In a normal examination, values will differ slightly from the base (lower values) to the apex (higher values) because of the gradient, as explained above. Because this research involved averaging segments from theoretical coronary distributions, data was gathered from these theoretical coronary distributions at the base, mid and apex of the left ventricle. The averaged values are, therefore, incorporating a normal gradient of difference between the levels of the heart, which is not distributed normally for the coronary territories. This may result in values which appear incorrectly significant or insignificant.

6.3.1.2 Reasons for Improved Statistical Significance between TVI Derived Strain and Strain Rate and RWMA/CAD

While velocity is indicative of wall motion, strain and strain rate are measures of tissue deformation [86]. Strain is a measure of tissue deformation; the change in length during myocardial contraction and relaxation normalised to the original length; an estimate obtained from paired velocity points along a single scan line separated by a fixed distance [172]. Strain rate is the rate at which the deformation occurs; the rate to which paired velocity points along

a scan line move toward or away from one another [173] and has been well validated in literature as a method superior to that of TVI derived velocity as it is angle independent [174-176]. Data is now compared between paired internal velocity points, rather than an internal point (sample volume) and an external point (the transducer). This principle overcomes the issues that overshadow TVI derived velocity. Strain and strain rate data, although still angle dependent, overcome the effects of tethering and translation and provide greater correlation with the presence and absence of RWMAs or CAD as shown in literature [85, 86, 171].

A study published in 2001 by Stoylen, A. [162] used 20 patients admitted with AMI for coronary angiography to compare strain rate values to standard echocardiography regional analysis. The presence and absence, of CAD with angiography correlated well with strain rate peak S data ($p<0.001$), confirming the feasibility of this method. Stoylen, A. [162] did also not correct for patients with pre-existing RWMAs so perhaps there is also an element of bias in their study. However, Stoylen, A. [162] concluded that although correlations were present, significant overlap and wide standard deviations meant strain rate analysis was not sufficient for standard clinical laboratory use. The CENSTEMI study agrees with the above research, as significant correlations and trends within the CENSTEMI data sets were noted; however, equally significant overlap between the data sets suggests these values may be unreliable for clinical (non-research) laboratory use.

6.3.1.3 Limitations of TVI Derived Velocity, Strain and Strain Rate

TVI derived velocity, strain and strain rate is observer dependent and requires an experienced user with extensive training in the field. Interpretation of waveforms is often not black and white and there is occasional difficulty in correctly identifying waveforms as multiple peaks may be present [177]. Stoylen, A. [85] has previously described echocardiography as a craft, not an exact science, which concisely sums TVI analysis. As stated earlier, the sample volume was placed in pre-defined locations and moved marginally,

if required. The author noted very minor movements often drastically changed the waveforms for analysis. A user more experienced in the field may feel comfortable altering the positioning of the sample volume to an extent not carried out in this study resulting in more accurate waveforms. However protocol was followed in this study by putting the sample volume in the pre-defined locations ensuring consistency and reproducibility.

Echocardiography performed on NSTEMI patients can often be challenging. These patients are acute admissions, often older with increased body habitus. These factors often result in difficult acoustic images, which make interpretation of cardiac function and advanced modality imaging challenging. Because no patient was excluded from this study for poor image quality, this was a frequent problem faced. This may also contribute to the variation noted within these modalities.

Strain and strain rate data are derived from velocity based measurements which are one dimensional, whereas cardiac tissue deforms in three dimensions [86]. The modality of three dimensional strain (speckle tracking) may overcome this issue in the future, however, current state of knowledge results is significant differences between manufacturers so further clinical validity is required. Moreover, studies of inter-observer variability with the advanced imaging modalities in previous literature were variable. Some found TVI derived indices highly reproducible [178, 179], others suggest variability ranges 10-15% [86], while further studies suggest that TVI derived indices have low reproducibility rates [86, 171].

6.3.1.4 TVI Summary

This study shows that TVI derived strain and strain rate are more promising modalities than TVI derived velocity for identifying the presence of RWMAs and CAD. However, although there is significant correlation within the data sets, there is also significant overlap which reduces the validity of using this modality in a clinical (non-research) laboratory setting.

6.3.2 Speckle Tracking Imaging

ST involves tracking natural acoustic markers frame by frame throughout one cardiac cycle and has been well validated [105, 180-182]. ST overcomes the angle of insonation and the effects of cardiac translation by applying the sum of absolute differences algorithm [178]. Territorial ST derived velocity did not correlate well with the presence of RWMAs, or CAD in the Cx or RCA territories therefore was not statistically significant. ST derived velocity was only statistically significant with the presence and absence of CAD in the LAD region. Territorial ST derived strain and strain rate values correlated well with the presence of RWMAs and CAD in the LAD region, therefore, were statistically significant and outperformed analysis with ST in both the Cx and RCA. The remaining values were varied; while territorial strain and strain rate correlated well and were statistically significant with RWMAs in the Cx region, there was no correlation (no statistical significance) noted in the RCA region; and while territorial strain correlated well with the presence of CAD in the RCA region (there was statistical significance), no correlation was noted with velocity and strain rate in the RCA or Cx region (there was no statistical significance) for CAD.

6.3.2.1 Reasons for Reduced Statistical Significance between ST and RWMAs/CAD

This study used ST to assess velocity, strain and strain rate in the apical four chamber view. Territorial strain was determined (as described earlier) by averaging velocity, strain and strain rate data from the three coronary regions - LAD, Cx and RCA. The apical four chamber view receives coronary flow from all three arteries; one segment via the RCA (basal inferoseptal), three via the LAD (mid and distal inferoseptal and the distal anterolateral segment), and two via the Cx (basal and mid anterolateral segments). The Cx (represented by two segments) and moreover the RCA (represented by one segment) are the least represented regions in the apical four chamber view. The RCA segment is likely misrepresented in this study. Using the technique of averaging data sets to obtain territorial velocity, strain and strain rate data (average values for the theoretical coronary distribution) may be an incorrect

method of analysis when using only the apical four chamber view as in this study. Individual segmental analysis would be the best method for analysis when using only the apical four chamber view. If territorial strain is to be used in the future, this study suggests that all three imaging planes (apical four chamber, apical two chamber and apical long axis) should be analysed. However, as explained earlier, the aim of this study was to ascertain trends within the data set. If there were significant correlations between the RCA and the presence and absence of RWMAs and CAD, these trends would show in the data. This, in general, was not the case.

It is surprising that the RCA region did not (in general) correlate well with RWMAs and underlying CAD as the inferoseptal wall was found to align with the transducer most of all the cardiac walls (reducing the angle of insonation) and there were never any significant artefacts in the region.

Moreover, a study published in 2009 by Gustafsson et al. [183] further confirmed the complexity of the intrinsic mechanics of the left ventricle. Using 40 healthy patients, they used circumferential ST to assess left ventricular motion. They found that the basal inferoseptum segments rotated significantly more clock-wise than both the basal anterolateral segments and the segments at the mid and distal levels of the myocardium. They also noted significant differences concerning the duration of twist within the left ventricle (the basal segments duration of un-twisting was much longer than that of the apical segments). These differences in regional contraction play important roles in left ventricular filling and function. The motion of the basal inferoseptum noted in the above study with circumferential ST may further explain the lack of statistical significance noted between ST and the presence/absence of RWMAs/CAD in the RCA segment in this CENSTEMI study. It is possible, that the accentuated motion of the basal inferoseptum counteracts a hypokinetic myocardium to some extent. Future studies may confirm this.

6.3.2.2 Limitations of ST Derived Velocity, Strain and Strain Rate

Although ST is a quicker and less observer dependent process than TVI [184], there are various pitfalls to this technique which could contribute to the varied correlations and overlap noted in this study. ST relies upon a high frame rate (50-70 fps [99]) which can be difficult in individuals with borderline image quality.

The author found frame rates were often difficult to perfect, due to the reduced quality of patients individual images (frame rates ranged from 36 to 109 frames per second). An increased frame rate reduces under-sampling, however, results in decreased spatial resolution (the ability of a system to distinguish two points as separate in space), which results in less than optimal tracking of the region of interest [185]. Decreased frame rates, increase spatial resolution. But, because the software searches and tracks individual speckles frame-by-frame, this may mean that, owing to the low frame rate, a speckle is outside of the search area, once again resulting in less than optimal tracking of the region of interest [181]. There is a chance, therefore, that variations in frame rates may contribute to underestimated or overestimated values. However, Edvasden et al. [89] used frame rates ranging from 56-134 fps with excellent results, furthermore, studies have suggested that frame rates >30fps allow for reliable and reproducible software operation [186, 187]. This means that the frame rates used in this CENSTEMI study were acceptable.

ST is a two dimensional measurement, whereas cardiac motion is three dimensional [99]. This means that the modality may not capture the full motion of the left ventricle. Therefore, areas may be under or over estimated. Values are variable with age and sex, so there is a possibility that a normal value for one patient may be borderline or abnormal for another [188, 189]. This study was looking for trends in a predominantly older subset of predominantly male patients, so these factors, although still relevant, should be minimised.

6.3.2.3 Statistical Significance between the LAD Territory and ST Derived Velocity Strain and Strain Rate

The strain and strain rate values for the LAD region correlated best (were statistically significant) with the presence and absence of RWMAs and underlying CAD for both the TVI and ST modalities. This may be due to a large number of LAD infarcts in this research (15 patients had LAD single vessel CAD, compared with 5 patients with RCA single vessel CAD and no patients with Cx single vessel CAD). It may also be explained by less individual variation in the LAD coronary artery distribution [190]. Good cursor alignment and visualisation of LAD regional segments may also have assisted with the favourable results.

6.3.2.4 Benefits of the Utilising of Speckle Tracking over Tissue Velocity Imaging

Unlike TVI, which requires user to determine sample volume positioning and waveform measurement, ST requires only a user defined region of interest which is optimised to follow the endocardium throughout one cardiac cycle. The result is automated analysis of segments which are less influenced by the user. Although, an average of three measurements is recommended to ensure reproducibility.

This CENSTEMI study found ST much quicker to perform, which agrees with literature in the field [105, 191]. When the region of interest was optimised, automated analysis resulted in velocity, strain and strain rate waveforms. Values for peak velocity, strain and strain rate were analysed, pre-measured and displayed automatically in a box below the waveforms. Although a high frame rate was required for ST analysis, only one cardiac cycle was required. The need for just one cardiac cycle meant that the traces were less likely to contain incidental movement or inspiration. Hoyt et al [103] suggested ST to be less time consuming as it is a semi-automated process, beneficial over TVI as studies suggest increased reproducibility, increased signal to noise ration and no angle dependency.

6.3.2.5 ST Summary

This study shows that ST of the apical four chamber view correlated well with strain and strain rate with the presence of both RWMAs and underlying CAD in the LAD region. However, less correlation was noted in the Cx region, and lesser still in the RCA region.

This may be due to limitations with the study methodology such as theoretical coronary artery distribution assumptions, difficult patient image quality, the complex mechanics of the left ventricle, or perhaps reflects the real-world application of ST.

6.4 Inter-Observer Variability

No inter-observer or test re-test variation assessment was performed for this research, which is a limitation to the reproducibility of TVI and ST derived velocity, strain and strain rate values obtained in this study. Future studies would benefit from adding the calculation of inter-observer variability to their methodology to ensure the reproducibility of their obtained values.

6.5 Global Strain

Global strain is an average of all segmental values (six segments) in the apical four chamber views. Global strain was assessed by ST, resulting in an automated value. An r^2 of 0.22 suggested weak correlation between LVEF and global strain. Studies such as Brown et al. [192] and Mistry et al. [193] found that global strain an effective quantifier of LVEF, especially in patients with extensive RWMAs. However, in this CENSTEMI study, the correlation between LVEF and global strain was weak, suggesting that in a clinical (non-research) laboratory setting, Simpson's Biplane ejection fraction is superior to ST derived global strain when determining LVEF.

A study published in 2010 and performed by Eek et al. [101] identified 61 patients with NSTEMI, and performed echocardiography prior to angiography. They found good correlation between global strain and infarct size ($r=0.68$ and $p<0.001$), with a global strain >-13.8% identifying patients with significant infarction, who may benefit from urgent angioplasty. The results of the above study were compared to the raw CENSTEMI global strain data set on EXCEL. Nine patients had a global strain values >-13.8%, with average LVEFs of 49 ± 7%. In comparison, 42 patients had global strain values of ≤-13.8%, with average LVEFs of 59 ± 11%. This raw data agrees with that obtained in the Eek et al [101] study, as global strain values in the CENSTEMI data set >-13.8% also had lower LVEFs suggestive of significant infarction.

In this CENSTEMI study, as global strain showed only weak correlation, it is unlikely to be clinically useful. Above all, the advanced imaging modality of real-time three-dimensional echocardiographic quantification is regarded as an excellent indicator of LVEF. It is rapid, accurate and reproducible [194] and especially useful for patients with asymmetrical ventricles [195, 196]; however, also remains highly reliant on patient image quality.

6.6 Clinical Application

On the basis of this study, and existing literature, it is doubtful whether the addition of TVI and ST derived information to a clinical report would alter the clinical pathway of an ACS patient at Christchurch Hospital, New Zealand. This is because although correlation and statistical significance was noted, there was also significant overlap and variation - refer to the graphs (*Chapter Five: Results II*) for visual cues as to the spread of the data with the modalities and indices for the 55 patients. It is unlikely that including data such as this into a clinical report would alter the patient's requirement for stress echocardiography and/or angiography when the patient had otherwise normal left ventricular function and an absence of RWMAs.

However, these modalities may, with further refinement, detect underlying CAD that may otherwise be overlooked, in patients with no regional or global dysfunction, both within the NSTEMI population and the general population. Further testing with adjusted methodologies would clarify this. As novel indices, there is hope that in the future these will prove useful for quantifying RWMAs and detecting underlying CAD. The author will continue to use these modalities, when time permits, in clinical (non-research) situations in an attempt to further refine the technique, with the aim to provide supplementary information to future routine echocardiography studies.

Conclusion: Advanced Echocardiography Discussion

Velocity derived from TVI was not statistically significant with the presence and absence of RWMAs and underlying CAD in any of the coronary regions. In general, strain and strain rate imaging derived from both TVI and ST modalities were statistically significant with the presence and absence of RWMAs and underlying CAD. There was especially excellent correlation noted between the LAD region and strain and strain rate derived indices. There was, however, overlap between patients with and without RWMAs/CAD, such that it is unlikely that the additional information from the new modalities would currently be clinically useful for the management of individual patients.

This study found that TVI was generally superior to ST when assessing the presence of RWMAs and CAD in all of the coronary regions. However, ST was quicker and less operator dependent. The clinical use of these modalities would be useful if there was less variation and overlap noted within the data sets. ST would be the method of choice as it was much quicker, less observer dependent and provides a lot of additional information, however, in this study TVI generally portrayed greater correlation with the presence and absence of RWMAs abd underlying CAD.

Further refinement is required both technically and clinically. This study found the results were highly reliant on patient window quality, which was considered a significant limitation of these modalities clinically. TVI (specifically of the LAD territory) and ST (specifically strain and strain rate of the LAD territory for both RWMAs and CAD and strain and strain rate of the Cx territory for RWMAs) derived indices give quantifiable values which would be useful for future comparison to determine contractile improvement.

There was weak correlation between global strain and LVEF, suggesting that global strain is unlikely to be useful clinically. Moreover, real-time three-dimensional LVEF quantification is now suggested as an excellent indicator of LVEF.

Chapter Seven:

Study Limitations

7 Chapter Seven: Study Limitations

7.1 Clinical Limitations

This research was conducted in one hospital with a small randomly selected sample population (n=55), suggesting the resulting data may not be statistically indicative of a true population. Several values in the TVI and ST derived velocity, strain and strain rate chapter overlapped and were not statistically different. Increasing the patient sample size may reduce the effects of a Type I error (incorrect rejection of the null hypothesis). There may also be failure to identify a true difference due to the small sample size (Type II error – failure to reject the false null hypothesis). However, data heterogeneity and overlap in this study between patients suggests that increasing the patient sample size would have no significant effect on the results. The main aim of this research was to provide further information on NSTEMI characteristics and management. This is a relatively under studied area compared to that of STEMI.

Note should also be made that a GE echocardiography machine was used for this study. The results may not extrapolate to other manufacturers machines, hence clinical relevance may be limited to centres with GE machines.

A limitation of this research was the exclusion criteria, suggesting the results may not be indicative of a true population. However, the exclusion criteria provided consistency between patients. Furthermore, the patients were randomly recruited (as discussed in the *Chapter Two: Methodology*).

7.1.1 Technical Limitations

Observer variability is an important issue in echocardiography because all of the measurements are generally observer-dependent. To minimise this variability, the echocardiography images and advanced imaging modality analysis was performed by one sonographer, but the possibility of intra-observer variation remains. For this research, a single operator provided consistency between patients with any bias likely to be systematic rather than random. We did not formally assess intra-observer variability, but the sonographer employed holds appropriate qualifications (trained formally through Queensland University of Technology - Post Graduate Diploma of Cardiac Ultrasound) and has experience in obtaining images for advanced modality analysis in occasional national and international research projects based at Christchurch Hospital, New Zealand.

An attempt was made to minimise these technical limitations by initiating a prospective study of patient data collection after developing a clear echocardiographic protocol. All images, analysis and interpretations were performed according to this protocol, and clinical interpretation, RWMA and coronary angiography assessment was performed by a single cardiologist. Other studies in this field have used a retrospective approach with multiple researchers performing images and analysis. The methodology used in this CENSTEMI study ensured consistency between patients.

Chapter Eight:

Conclusion

8 Chapter Eight: Conclusion

Although echocardiography is a valuable tool in the setting of ACS management for detecting structural and functional cardiac abnormalities, and it is recommended in the 2012 ACS guidelines, it remains under-utilised. The cohort studied in this thesis was a randomly selected set of 55 NSTEMI patients, typical of a New Zealand hospital setting. We have demonstrated the usefulness of echocardiography for identification of systolic and diastolic dysfunction, also, that the degree of TnI elevation cannot be used to select a subset of patients for echocardiography.

In this study, we examined the characteristics of 55 NSTEMI presentations with echocardiography. One fifth of the patients had diabetes, while over fifty per cent were current or prior smokers. These patients had a higher incidence of CAD and were nine fold more likely to require CABG.

There was no correlation between LVEF and TNI elevation, suggesting that TNI elevation should not be used to determine AMI severity, or the extent of myocardial damage.

The highest incidence of single vessel CAD was noted in the LAD territory, followed by the RCA. No Cx arteries were single vessel culprits. Over one third of the patients had low-normal LVEFs (<60%), while just under one fifth of the patients had at least mild systolic impairment (<50%), which substantially affects patient medical management.

Just over one eighth of patients had moderate to severe diastolic impairment. They were more likely to have impaired LVEFs and CAD. Moderate to severe diastolic dysfunction has been associated with poor prognostic outcome in previous literature, despite the underlying cause.

Almost one quarter of the patients admitted with NSTEMI had no CAD. This may be the result of false positive diagnosis on admission, or perhaps symptoms and TnI elevations which align with other conditions. Of the patients with CAD, just over two fifths had RWMAs, with around three quarters correctly identifying the culprit artery.

This study found that echocardiography, which is cost effective and quick, plays a very useful role in identification of systolic and diastolic dysfunction with NSTEMI presentations. Systolic and diastolic dysfunction are useful indicators for patient management and prognostic outcome.

We also examined the feasibility of utilising the advanced imaging modalities TVI and ST derived velocity, strain and strain rate to quantitatively determine regional function and detect underlying CAD. The process of performing TVI was time consuming, while performing ST was very quick in comparison.

This study found, that of the modalities TVI derived strain and strain rate were superior to velocity when identifying RWMA and underlying CAD, especially in the LAD region, and to a lesser extent, the Cx region. However, noted that, when placing the sample volumes, minor movements often significantly altered the waveforms and waveforms could be created by placing the sample volume outside the cardiac region. Furthermore, interpretation of the waveforms was often difficult. ST derived strain and strain rate was highly statistically significant and correlated best with the LAD segment when identifying RWMAs and underlying CAD.

This study found ST had an advantage over TVI because it was quick and after defining the region of interest, the waveforms were created and measured by the machine, making analysis easier. However, it did not correlate as well with the presence and absence of RWMAs and underlying CAD as the TVI derived indices. Both TVI and ST were highly

reliant on patient image quality which, along with the utilisation of territorial strain analysis, may have been limitations of this study.

From this study, it is therefore recommended that patients require good to excellent image quality for both TVI and ST. Territorial strain was useful in this study for identifying overall trends in the data, however, for clinical use, individual analysis of segments is likely quicker. Individual analysis of segments is more efficiently performed with ST as the waveforms for each imaging plane (apical four chamber, apical two chamber and apical long axis) are displayed on one graph, with peak velocity, strain and strain rate values automatically measured allowing comparisons between segments and walls.

These advanced modalities, with further technical and clinical refinement, may prove useful in clinical situations. Furthermore, the author will continue to use these modalities, especially ST, in the hope of further refining both technical and clinical technique, as quantification of RWMAs would supplement future echocardiographic comparisons while a novel, non-invasive approach to identifying underlying CAD with no visual RWMAs would be of interest in a clinical laboratory.

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9 References

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Appendix

10 Appendix

Table 21: Normal Values: Differences in TVI Derived Velocity, Strain and Strain Rate Values between Cardiac Walls

Normal Values: Differences in TVI Derived Velocity, Strain and Strain Rate Values between Cardiac Walls

	Anteroseptal	Anterior	Anterolateral	Inferolateral	Inferior	Inferoseptal
TVI velocity (cm/s)		8.3 (1.9)	8.8 (1.8)		8.6 (1.4)	8.0 (1.2)
SR (s^{-1})	-0.99 (0.27)	-1.02 (0.28)	-1.05 (0.28)	-1.07 (0.27)	-1.03 (0.26)	-1.01 (0.25)
Strain (%)	-16.0 (4.1)	-16.8 (4.3)	-16.6 (4.1)	-16.5 (4.1)	-17.0 (4.0)	-16.8 (4.0)

'Results from the HUNT study with normal values based on 1266 healthy individuals. Values are mean values (SD in parentheses). Velocities are taken from the four points on the mitral annulus in four chamber and two chamber views, while deformation parameters are measured in 16 segments, and averaged per wall'.

Table and caption reproduced from Stoylen, A. [85]

Ethics Approval

Health and Disability Ethics Committees

Upper South B Regional Ethics Committee
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8 February 2011

Ms Nicola Smith
Echocardiography Department
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Dear Ms Smith

Ethics ref: **URB/11/EXP/002** (please quote in all correspondence)
Study title: Echo in non ST elevation myocardial infarction, Modalities for regional wall assessment in acute coronary syndrome NSTEMI non-diabetic and diabetic patients
Investigator: Nicola Smith
Supervisor: Paul Bridgman

Thank you for the above application for expedited review. The **Chairperson** and the **Deputy Chairperson** of the Upper South B Regional Ethics Committee have declined to review the application as it is an audit or related activity and under the *Ethical Guidelines for Observational Studies: Observational Research, Audits and Related Activities, NEAC, December 2006*, no ethics committee review is required.

Please note, however, that the organisation in which you wish to carry out the study may specify their own processes regarding notification or approval.

Yours sincerely

Diana J. Whipp

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