The Clinical Applications of Cardiogoniometry in Cardiovascular Disease.

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Abstract

Cardiogoniometry (CGM) is a method of 3-dimensional electrocardiographic assessment which has primarily been investigated to evaluate its role in diagnosing patients with suspected coronary artery disease (CAD). Previous work has suggested it has considerable diagnostic ability at identifying patients with both stable CAD and those with acute coronary syndrome (ACS). However, previous studies which investigated the diagnostic performance of CGM in stable CAD did not use robust measures to accurately identify patients with physiologically significant coronary ischaemia. Furthermore, although the ability of CGM to identify specific lesions in stable CAD has been evaluated, to the best of our knowledge no research has been performed to assess the ability of CGM to detect the site of the culprit lesion in patients with non-ST elevation myocardial infarction. The first two studies of this thesis aim to address these two questions about the role of CGM in patients with CAD.

Cardiac resynchronisation therapy (CRT) is a treatment used in patients with heart failure and left bundle branch block which attempts to restore synchronous contraction of the ventricles by pacing both the left and right ventricle together. Unfortunately, 25% of patients do not gain a clinical benefit from CRT, such patients are classed as 'non-responders'. Many methods have been proposed to optimise CRT for 'non-responders', however, no specific optimisation method has yet been identified which significantly improves the long term benefit of CRT in non-responders. The detailed spatial and temporal information on cardiac electrical activity that CGM provides suggests that CGM may have a role in the optimisation of CRT. The aim of the third study in this thesis is to evaluate whether CGM can detect changes to CRT pacing settings, in view of developing a method of CRT optimisation using CGM.

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Declaration

When these studies were first developed we planned on using optical coherence tomography (OCT), a relatively new imaging technique which uses catheter probes that emit near-infrared light to provide cross-sectional high resolution (10-15μm) images of the coronary arteries, as the gold standard method of identifying the culprit lesion in our patients in the COGNITION study. However, although we were successful in sourcing funding to pay for the individual OCT catheters needed for each study participant, the hospital trust did not approve the use of the OCT in time to use in our study. In light of this set back, we decided to use coronary angiography alone to determine the location of the culprit lesion and the location of the lesion was made by the operating cardiologist performing the case. The operating cardiologist remained blind to the results of the CGM in an attempt to reduce the influence of bias in our study.

I confirm that this work is original and that if any passage(s) or diagram(s) have been copied from academic papers, books, the internet or any other sources these are clearly identified by the use of quotation marks and the reference(s) is fully cited. I certify that, other than where indicated, this is my own work and does not breach the regulations of HYMS, the University of Hull or the University of York regarding plagiarism or academic conduct in examinations. I have read the HYMS Code of Practice on Academic Misconduct, and state that this piece of work is my own and does not contain any unacknowledged work from any other sources. I confirm that any patient information obtained to produce this piece of work has been appropriately anonymised'.

Abbreviations

ACEi – Angiotensin converting enzyme inhibitor

ACS – Acute coronary syndrome

AH – Angela Hoye

ALC – Andrew Lawrence Clark

ARB – Angiotensin receptor blocker.

AV - Atrioventricular

CAD – Coronary artery disease

CAV – Cardiac allograft vasculopathy.

CABG – Coronary artery bypass graft

CGM- Cardiogoniometry

COPD – Chronic obstructive pulmonary disease

CRT – Cardiac resynchronisation therapy

CT – Computed tomography

D – Diagonal artery.

DS – Diameter stenosis

ECG – Electrocardiography

eGFR – Estimated glomerular filtration rate

ESC – European Society of Cardiology

FFR – Fractional flow reserve.

JAR – Jennifer Ann Rossington

LBBB – Left bundle branch block.

LMWH – Low molecular weight heparin

LAD – Left anterior descending artery

LCx – Left circumflex artery

LV – Left ventricle

MI – Myocardial infarction

MPI – Myocardial perfusion imaging

MRI – Magnetic resonance imaging.

NICE – National Institute for Clinical Excellence.

NPV – Negative predicative value.

NSTE-ACS – Non-ST elevation acute coronary syndrome.

NSTEMI – Non-ST elevation myocardial infarction

OCT – Optical coherence tomography.

OIB – Oliver Ian Brown

OM – Obtuse marginal artery

PCI – Percutaneous coronary intervention

PPV – Positive predicative value.

QCA – Quantitative coronary angiography.

RCA – Right coronary artery

ROC – Receiver operating characteristic

RV – Right ventricle

SD – Standard deviation.

SOB – Shortness of breath

SPECT – Single photon emission computed tomography

STEMI – ST elevation myocardial infarction.

TIMI – Thrombolysis in Myocardial Infarction

TN – Theodora Nikolaidou

VCG – Vectorcardiography

VV - Interventricular

Chapter 1

Introduction

1 - Introduction

Recording the heart's electrical activity using a standard 12 lead electrocardiogram (ECG) is almost universally used in the investigation of possible cardiovascular disease. However, other techniques for recording cardiac electrical activity are potentially useful.

Vectorcardiography (VCG) was in popular use up until the late 1980s. It displays individual components of the electrical complexes (i.e. P, QRS and T waves) as graphical loops which represent continuous recording of electrical activity throughout the cardiac cycle.[1] VCG was most commonly used for the investigation of suspected coronary artery disease (CAD), but it was notoriously difficult to interpret in comparison to the simpler 12-lead ECG. Simonson et al reviewed the literature on VCG in 1966 and found that all 13 published articles showed VCG to be superior to ECG in diagnosing acute myocardial infarction in 2182 cases confirmed by autopsy.[2] However, in the majority of these studies, the investigators were not blinded, as they analysed the results of a VCG with knowledge of the result of the ECG. Simonson et al went on to conduct a large study which kept the study investigators blind to the results of each test and found that there was no significant difference in detection of cases of acute myocardial infarction between VCG and ECG.[2]

Cardiogoniometry (CGM) is a method of vectorcardiographic assessment.[3,4] The Cardiologic Explorer (Enverdis GmBH, Jena, Germany) is the only commercially available device. It uses five electrodes arranged to make a recording from three virtual bipolar leads. A heart vector can be plotted between the leads over time, resulting in vector loops being constructed in three dimensions for the P, QRS and T waves. Further development and computed scoring systems have resulted in a device with automated data

analysis, giving each CGM recording a numerical score indicating whether myocardial ischaemia is present or not, making CGM an easy technique to perform and interpret.[5]

The aim of this MSc by thesis is to evaluate potential clinical applications of CGM.

1.1. Background to the studies

1.1.1 Principles of Cardiogoniometry

Four electrodes are placed on the chest as shown in figure 1.1. The electrode configuration is based around the Wilson precordial electrode configuration used for conventional 12-lead ECG recordings. Electrode 1 (green) is placed in the 5th intercostal space in the mid clavicular line, in Wilson position V4; electrode 2 (white) is placed directly posterior to electrode 1 in Wilson position V8; electrode 3 (yellow) is placed directly superior to electrode 1, at a distance 0.7 times the distance between electrode 1 and 2; electrode 4 (red) is placed directly right from the position of electrode 3 at the same distance between electrode 1 and 3. A fifth electrode, not shown in the figure, placed on the patient's left thigh, is used as an earth lead.

The electrode placement generates recordings from five bipolar leads defined by the following electrodes: anterior (A) by electrode 4→1; horizontal (Ho) by electrode 4→3; vertical (Ve) by electrode 3→1; inferior (I) electrode 2→1 and diagonal (D) by electrode 4→2 (see figure 1.1A). By manipulation of the leads using trigonometry, x-, y- and z- axes can be defined (figure 1.1B) which are approximately orientated to the axes of the heart in the chest. Three planes can then be created by combining the axes: oblique sagittal plane

(defined by the x- and y- axes); frontal plane (defined by the y- and z- axes); sagittal plane (defined by x- and z- axes).

A heart vector is then constructed by the vectorial summation of the potentials measured between the x, y and z axes at millisecond intervals, resulting in three electrocardiographic traces from which vector loops are plotted (figure 1.1C). The same procedure separately plots loops: the P wave (grey loop), QRS complex (blue loop) and T wave (green loop).

In addition to this, the largest vector of each of the P, QRS and T loops can be plotted using Cartesian system coordinates based on the x, y and z axes. As the x, y and z axes are orientated to the position of the heart in the thorax, an imaginary globe of coordinates around the heart is constructed which is then divided into hemispheres and octants which represent different surfaces of the heart. This allows for visualisation of cardiac depolarisation and repolarisation in space and time. It is easy to recognise if the maximal vector is outside the normal range (see figure 1.2). The position and length of the maximal vector represent the overall direction and strength (measured in mV) of the electrical field respectively.

There are up to 350 CGM variables generated by the Cardiologic Explorer. For each of the P, QRS and T loops, the outputs can be categorised as: 1) angles – the longitude and latitude of the maximal vectors (relative to the origin) and the angles between each loop; 2) amplitudes – the minimal and maximal amplitudes of each loop and the ST segment; 3) shapes and eccentricities – of the course of each loop and 4) velocities – the maximal difference in mV between two points separated by 10ms, given as absolute values and as ratios of the P, QRS and T loops. All these variables are automatically analysed by the

device and deviation from expected values of these variables is indicative of ischaemia. The device then automatically attributes a score to the recording with any score ≠ 0 defined as abnormal.

Since CGM was first described, an automated scoring system has been created to allow easy recognition of coronary ischaemia. Schupbach et al[6] created this scoring system by retrospectively analyzing 461 patients who had had diagnostic coronary angiography, and had also undergone CGM recordings. The authors classified the patients as either having CAD or not having CAD based on the results of their diagnostic angiogram. CAD was classified as the presence of ≥50% diameter stenosis in one or more epicardial coronary artery. The CGM recordings of patients with and without CAD were compared, and CGM variables which were significantly outside the normal reference range when CAD was present were selected and incorporated into an automated diagnostic algorithm. This algorithm was then prospectively assessed in patients undergoing diagnostic coronary angiography, to see if the algorithm could identify patients with CAD present.[6]

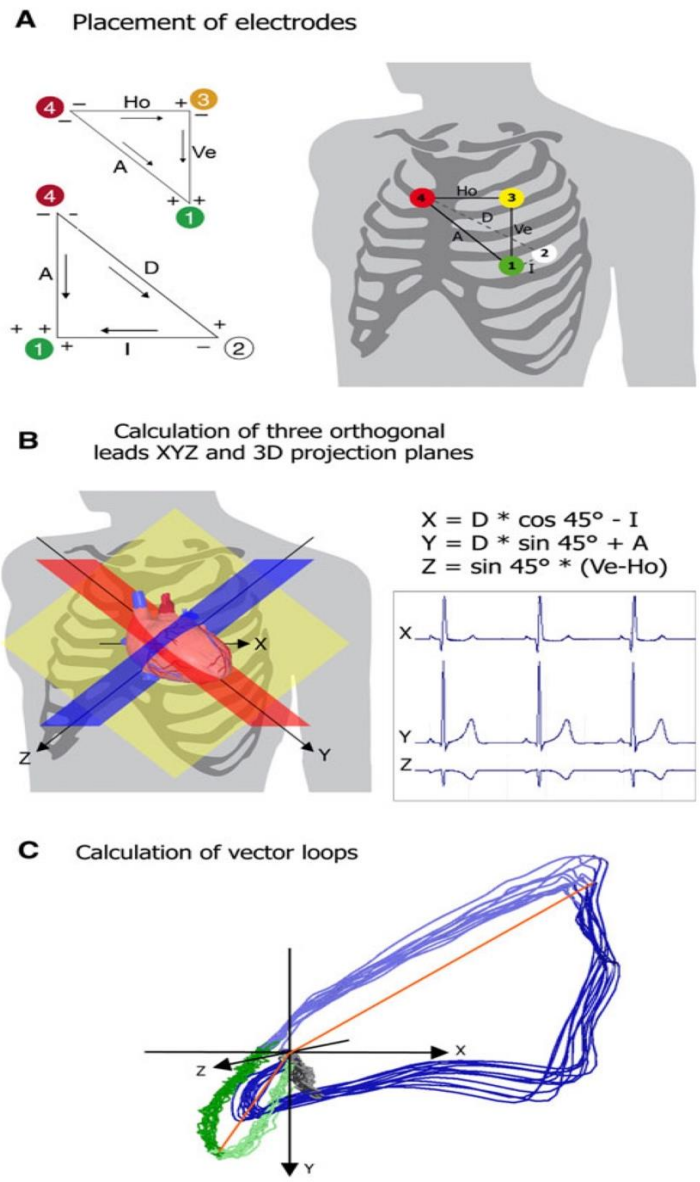

Figure 1.1. – *Principles of Cardiogoniometry (figure reproduced from Tolg et al*[7]*): A - Showing electrode placement: electrode 1 (green), Wilson position V4; electrode 2 (white), Wilson position V8; electrode 3 (yellow), directly superior to electrode 1 at a distance 0.7 times the distance between electrode 1 and 2; electrode 4 (red), directly right of electrode 3 at a distance the same as between electrode 1 and 3. The following leads are defined by the following electrodes: Anterior (A) by electrode 4⟶1; Horizontal (Ho) by electrode 4⟶3; Vertical (Ve) by electrode 3⟶1; Inferior by electrode 2⟶1 and Diagonal (D) by electrode 4⟶2 (see figure 2A). Triangles left of the thorax show the direction of the aforementioned leads. B – Showing the orientation of orthogonal axes X, Y and Z in the thorax (left panel) and trigonometric equations defining their formation (right panel); C – Showing the formation of vector loops by plotting of the heart vector at every millisecond for the P (grey), QRS (blue) and T waves (green), with maximum vectors for the P and QRS loop (orange lines) being shown. Figure reproduced from Tolg et al.*[7]

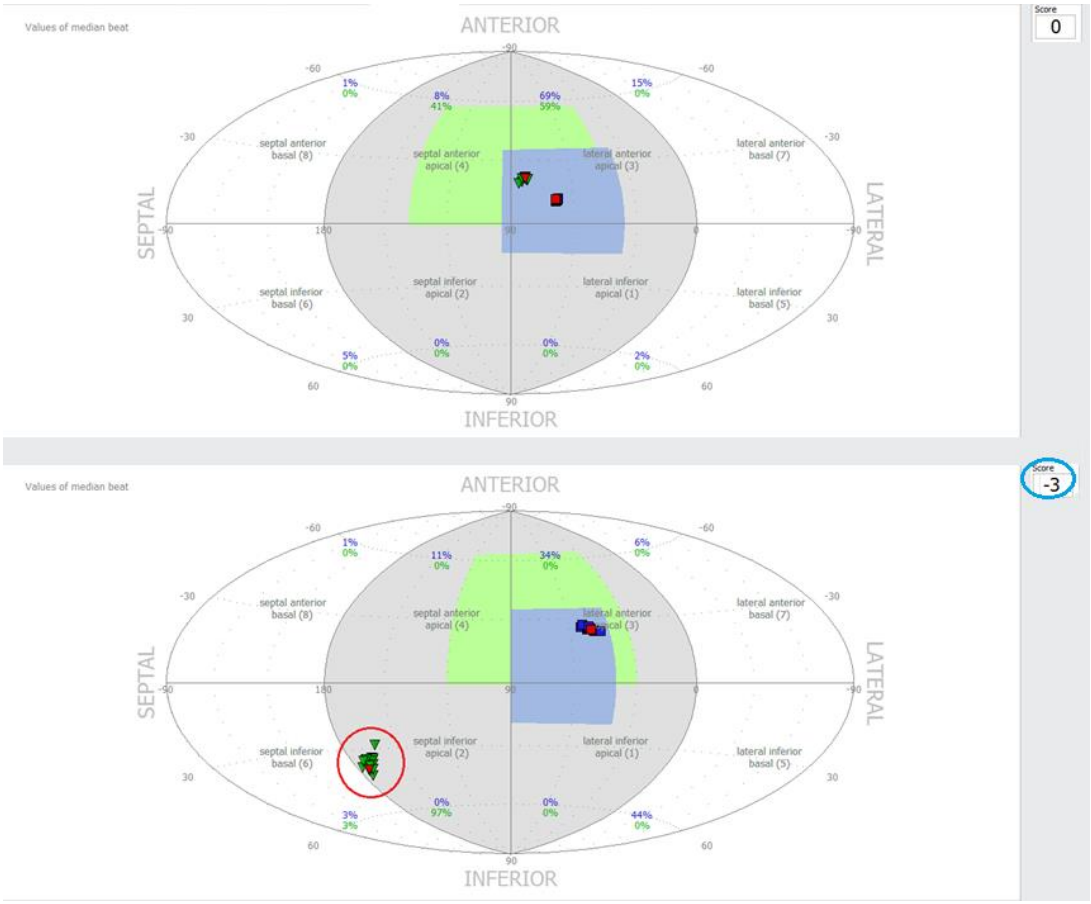

Figure 1.2. - *Cartesian coordinate system of the heart vectors. Blue square represents normal reference range for maximal vector direction of QRS complex; green square represents the normal range of the maximal vector direction of the T waves. The maximal vector direction for the QRS complex is the plotted blue square, with each square representing an individual QRS complex; the maximal vector direction for the T wave is the plotted green triangle with each triangle representing an individual T wave. The ischaemia score is shown at the top of the right sided column. Upper panel shows a normal CGM recording, with the direction of the maximal vectors for both QRS and T waves within the reference ranges. Lower panel shows an abnormal CGM recording, the direction of the maximal vector of the T waves is outside the normal reference range (red circle) plotted in the septal inferior area which indicates ischaemia in the territory opposite, the lateral anterior area. The ischaemia score (blue circle) is <0, indicating the presence of coronary artery disease.*

1.1.2. Coronary artery disease

1.1.2.1. Stable coronary artery disease

Current NICE guidance provides advice about how to initiate initial investigation of patients with chest pain and suspected stable CAD.[8]

In patients whom have a clear clinical history of stable CAD it is appropriate to commence patients on optimal medical therapy before undergoing any investigation. If symptoms are controlled by optimal medical therapy, patients should be considered for functional myocardial imaging (e.g. myocardial perfusion imaging or stress echocardiography) or non-invasive anatomical investigation with CT coronary angiography. If these investigations indicate the presence of significant ischaemia (left main stem or proximal three vessel disease), patients should undergo additional investigation with invasive coronary angiography to decide whether revascularisation with coronary artery bypass grafting surgery (CABG) may offer the patient a potential survival gain. For those patients in whom optimal medical therapy does not achieve symptomatic control, they should be offered invasive coronary angiography as first line to determine their best method of revascularisation with percutaneous coronary intervention (PCI) and CABG being considered.

In patients who do not have a clear clinical history of stable CAD, they should be risk stratified by calculating the likelihood of having stable CAD based on their age, risk factors and symptomology (see table 1.1).[8] If patients are deemed to be low risk (10-29% chance of having stable CAD), they should be offered CT calcium scoring based on CT

coronary angiography and if they score highly, be offered invasive coronary angiography. If patients are at moderate risk (30-60% chance of having stable CAD), they should be offered non-invasive functional testing in the form of nuclear perfusion scanning, stress echocardiography or cardiac MRI. Finally, if they are deemed to be high risk (60-90% chance of having stable CAD) they should be offered invasive coronary angiography.

	Non-anginal chest pain				Atypical angina				Typical angina			
	Men		Women		Men		Women		Men		Women	
Age (years)	Lo	Hi	Lo	Hi	Lo	Hi	Lo	Hi	Lo	Hi	Lo	Hi
35	3	35	1	19	8	59	2	39	30	88	10	78
45	9	47	2	22	21	70	5	43	51	92	20	79
55	23	59	4	25	45	79	10	47	80	95	38	82
65	49	69	9	29	71	68	20	51	93	97	56	84

For men older than 70 with atypical or typical symptoms, assume an estimate of >90%.

For women older than 70, assume an estimate of 61-90% EXCEPT women at high risk AND with typical symptoms where a risk of >90% should be assumed.

Hi = High risk = Diabetes, smoking and hyperlipidaemia (total cholesterol >6.47 mmol/litre)

Lo = Low risk = None of these 3.

The shaded area represents people with symptoms of non-anginal chest pain who would not be investigated for stable angina routinely.

Note:

These results are likely to overestimate coronary artery disease in primary care populations.

If there are resting ECG ST-T changes or Q waves, the likelihood of coronary artery disease is higher in each cell of the table.

Table 1.1. - *Table showing the likelihood of a patient having stable coronary artery disease stratified by age, sex, symptomology and risk factors (table adapted from NICE).*[8]

1.2.2.2. Acute coronary syndrome

ACS is an umbrella term which can be further classified into three additional syndromes based on ECG changes and the presence or absence of a rise in serum troponin (see figure 1.4[9]): Unstable angina; non-ST segment elevation myocardial infarction (NSTEMI) and ST segment elevation myocardial infarction (STEMI). As seen in figure 1.3, the ECG is a key tool in distinguishing between types of ACS, with its most important role being to identify those patients with STEMI who require immediate percutaneous coronary intervention to save myocardium from further infarction. In STEMI there is complete occlusion of the coronary blood supply which results in an area of transmural infarction distal to the occlusion site unless blood supply is not rapidly restored. In these patients (with the exception of those with left bundle branch block) the 12 lead ECG is helpful at localising the coronary artery occluded, as ECG changes are present in all cases and ST elevation in specific ECG leads correspond to infarction in specific vascular territories. For example, if the 12 lead ECG demonstrates ST elevation in the leads corresponding to the anterior territory of the heart (Leads V_1 –V_4), it would indicate that the culprit lesion is the left anterior descending coronary artery.

It is regrettable that same cannot be said for patients with NSTEMI, as electrocardiographic changes do not occur in the majority of these patients, and if present they are often not specific for a certain vascular territory. This has been augmented by the increasing use of highly sensitive troponins, with more patients being correctly diagnosed with NSTEMI, rather than being classified as having unstable angina.[10] Furthermore, work by Mills et al recently demonstrated that highly sensitive troponins also identified patients at high risk of recurrent MI and death.[11] Specifically, those patients with small troponin

rises (0.05-0.19 ng/mL) were at greater risk than those patients with larger troponin rises (≥0.20 ng/mL). The authors surmise that those patients with smaller troponin rises were less likely to received adequate treatment for acute MI due to inadequate diagnostic information.

Furthermore, a significant proportion of these patients demonstrate considerable multi-vessel disease on coronary angiography, making it unclear which is the culprit vessel responsible for the acute event. Interventionists will frequently target the most severe stenosis when treating these patients even though this is not necessarily the culprit lesion; and due to the poor sensitivity and specificity of 12 lead ECG in NSTEMI, it can only assist interventionists in the minority of cases. As ECG changes specific for coronary ischaemia in a certain vascular territory do not occur in all patients.

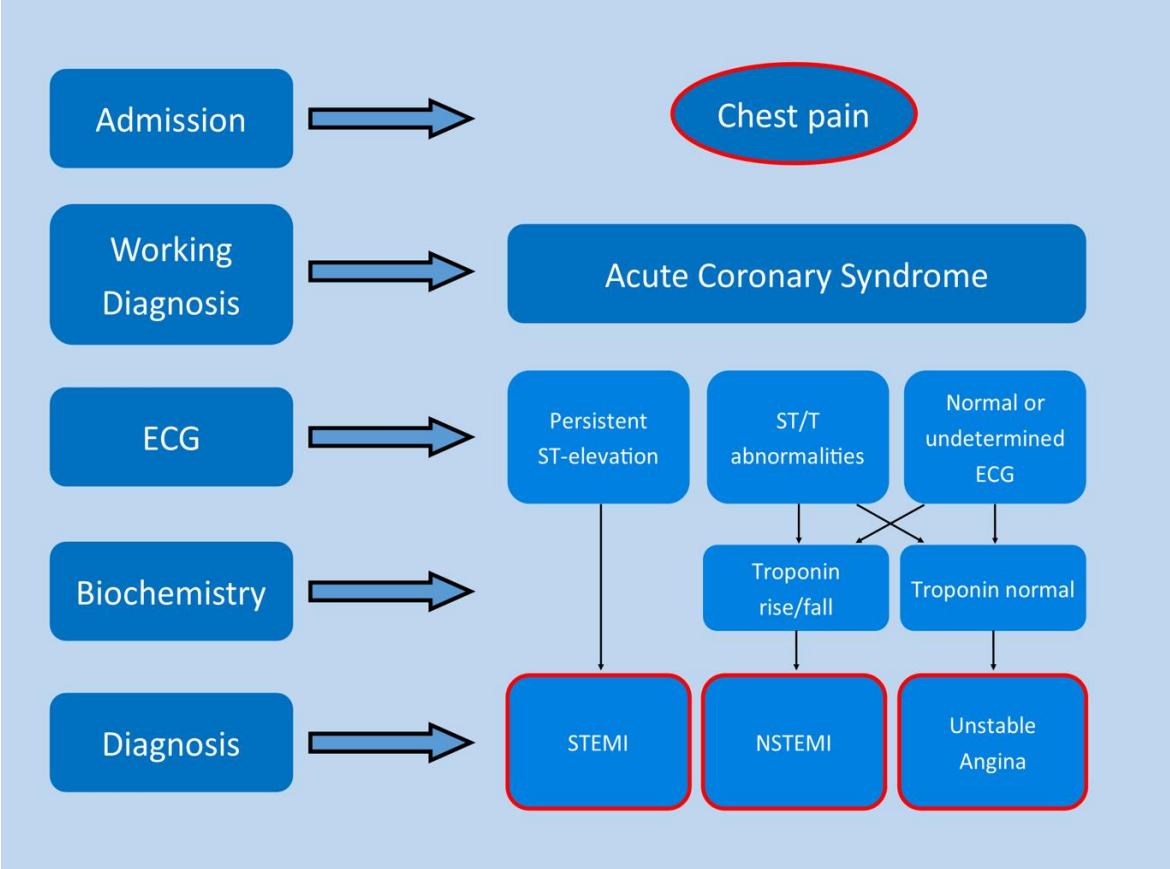

Figure 1.3. - *Flow diagram showing the classification of acute coronary syndrome (figure adapted from the European Society of Cardiology[9]).*

1.1.3. Fractional flow reserve

Fractional flow reserve (FFR) is a technique used in cardiac catheterisation to assess the physiological significance of coronary artery stenoses and is defined as the ratio of maximal blood flow in a stenotic artery to normal maximal flow.[12,13] It is performed by passing a guide wire with an inbuilt pressure transducer into a coronary artery with angiographic evidence of stenosis and administering an intravenous infusion of adenosine to induce hyperaemia. Its function is to measure the pressure gradient across the stenosis and represents the fraction of the normal maximal coronary flow that can be achieved despite the presence of coronary stenosis.[14]

FFR was first validated by Pijls et al in 1993, who successfully modeled coronary pressure to coronary flow in a dog model, showing significant correlation between the two variables and confirming the theoretical basis of FFR.[13] Previous techniques of trying to relate the trans-stenotic pressure of lesions to functional significance had shown poor correlation,[15,16] as the majority of the pressure measurements in these studies had been made in a basal state where coronary flow is predominantly determined by distal vessel auto-regulation. Unfortunately, the two predominant factors involved in coronary auto-regulation (epicardial and myocardial vascular resistance) are constantly changing under metabolic and haemodynamic demands and therefore it is impossible to accurately relate coronary flow to pressure unless both these factors are kept constant. Fortunately, both epicardial and myocardial vascular resistance can be overcome by the administration of a vasodilator such as intravenous adenosine, which opens up the vascular bed and leaves the resistances negligible and as close to constant as possible allowing accurate assessment of FFR.[13]

However, FFR does come with several assumptions; first it assumes that flow from collateral vessels remains constant throughout the procedure; secondly it assumes microvascular resistance is minimal and constant during the administration of adenosine; thirdly it assumes that coronary wedge pressure is small and constant so has little to no effect.

Historically, the decision on whether to revascularise with PCI or not was based on diameter stenosis determined by the operator at the time of angiography, and was either subjectively assessed visually or, in the minority of cases, measured from a single image by quantitative coronary angiography (QCA).[17] However it is well documented that this is not an accurate measure of flow limiting coronary disease.[12] The FAME study was a landmark trial which investigated how basing revascularisation decisions on FFR and angiography vs angiography alone affected the prognosis of patients with stable multivessel coronary artery disease undergoing PCI. Multivessel coronary artery disease was defined as >50% stenosis in at least two of the three major epicardial coronary arteries. When using an FFR treatment threshold of ≤0.8, the authors found that at one year, the incidence of the composite endpoint (death, recurrent myocardial infarction and revascularisation) was significantly reduced by 5.1% ($p=0.02$),[12] in patients who had their management decision made based on FFR and angiography vs those patients who had their management decision based on angiography alone. The treatment threshold of ≤0.8 has since become routinely used as the gold standard cut off in clinical practice. Subsequent follow up of this cohort at 2 years, has shown that FFR based revascularisation still significantly reduces the risk of death and recurrent myocardial infarction when compared to angiographically based revascularisation alone.[18] Although this difference was not significant at 5 years,[19] European guidelines now advocate the use of FFR to assess

physiological significance of coronary stenoses, with class 1 level A evidence supporting its use.[20] Importantly, FFR has not only just been seen to have a benefit in terms of patient outcome but it has also been shown to be resource saving in multiple cost-effectiveness analyses.[21,22] The reason behind this is that it reduces the number of stents implanted for lesions not causing coronary ischaemia. In a system with finite resources such as the National Health Service, this had led to saving of cost which means valuable resources can be allocated elsewhere.

When looking specifically at the relationship between operator visually defined diameter stenosis and FFR, FAME demonstrated that only 35% of coronary stenoses which were classed as 50-75% diameter stenosis were physiologically significant.[23] Further still, only 80% of all stenoses with estimated 71-90% diameter stenosis were shown to be physiologically significant when based on FFR.[24] A big limitation of coronary angiography is that it is only a 2-dimensional representation of a 3-dimensional structure and therefore may under or over-estimate the significance of a coronary stenosis, explaining why although a lesion may appear moderate or severe on coronary angiography it may not be physiologically significant when assessed by FFR. The work on FFR in the RIPCORD study by Curzen et al has further examined the effect FFR has on management based on coronary angiography alone.[25] The investigators enrolled 203 patients across 10 UK centres who were undergoing diagnostic coronary angiography for stable cardiac sounding chest pain and were found to have coronary stenoses of ≥30% severity in any epicardial vessel of ≥2.25 mm diameter. The cardiologist supervising their care was then asked to record the presence of significant stenoses (≥70% by eyeball) and an overall management plan for each patient using the following options: 1) medical treatment alone; 2) PCI, 3) coronary artery bypass grafting (CABG) and 4) more information required. A second interventional cardiologist then performed FFR assessment of all epicardial vessels or

major branches of ≥2.25 mm diameter which had Thrombolysis in Myocardial Infarction 3 flow (complete perfusion),[26] this was performed in the vessels regardless of the presence of ≥30% severity coronary stenosis. The FFR assessment was performed when maximal hyperaemia was achieved using two intracoronary boluses of ≥50mcg adenosine. Coronary stenoses were recorded as functionally significant if the FFR readings were <0.8. The 1st cardiologist was then invited to look at the results of the FFR assessment and invited to consider a revised management plan to the first one made. The authors demonstrated that the management plan changed in 26% of participants and the number and localisation of significant stenoses also changed in 32% of patients enrolled, when their coronary vasculature were assessed by FFR rather than operator visually defined diameter stenosis. Interestingly the management plans of 72 cases in which medical therapy was recommended after coronary angiography were subsequently revised to revascularisation after the addition of FFR data.[25] The RIPCORD study therefore succinctly demonstrates the need for routine functional assessment in the investigation of patients with suspected stable coronary disease and a move away from defining the severity of coronary stenosis on visual assessment alone.

Although the use of FFR has been shown to be cost effective, the cost of the pressure wires is not negligible. In addition to this, the requirement of adenosine for the accurate assessment of FFR gives rise to several problems. Firstly, it means certain patient groups are contraindicated for undergoing FFR assessment, such as those with severe obstructive lung disease and 2nd degree or complete heart block. Furthermore, adenosine is not well tolerated in those patients that receive it, with the majority of patients complaining of flushing, shortness of breath, nausea and chest discomfort whilst it is being administered. A cheap, reliable method of physiological assessment of stable CAD which does not

require the administration of adenosine would therefore be of unquestionable value in the investigation of patients with suspected stable CAD.

1.1.4 *Cardiac resynchronisation therapy (CRT)*

Around a third of patients with heart failure due to left ventricular systolic dysfunction have left bundle branch block (LBBB). In patients with LBBB, the ventricles depolarize more slowly than normal, and depolarize in an uncoordinated manner. In particular, the inter-ventricular septum depolarizes tens of milliseconds before the free wall of the left ventricle. A consequence is that left ventricular contraction is, in turn, uncoordinated: in some patients, the left ventricular free wall is still contracting after the aortic valve has closed.

Cardiac resynchronisation therapy (CRT) is a method of cardiac pacing which attempts to restore mechanical efficiency to the left ventricle. With a standard pacemaker, pacing leads are implanted in the right ventricle (RV) (usually in the apex) and, when indicated, in the right atrium. The lead in the right ventricle can then track the heart's natural heart rate as detected by the lead in the atrium, or, if the natural rate is too slow, the pacemaker can sequentially pace the atrium and then the ventricle.

A CRT system is similar, but with the addition of an extra lead positioned in a vein overlying the left ventricle which is accessed via the coronary sinus (which drains into the right atrium). Now, the pacemaker is able to stimulate both left and right ventricles simultaneously, an action called biventricular pacing (BIV), restoring synchronous ventricular contraction.

CRT improves both the symptoms and the prognosis of patients with chronic heart failure, [27] and is indicated in people with heart failure and left bundle branch block (LBBB) on the electrocardiogram (ECG).

Unfortunately, approximately 25% of patients do not gain significant clinical benefit with CRT.[28] Such patients are termed "non-responders", and lack of response is typically measured as a failure to improve exercise capacity with CRT, or a failure of left ventricular function to improve on echocardiography. The reasons for non-response have been extensively investigated, and include poor positioning of the left ventricular lead (especially in relation to the right ventricular lead – the leads should be as far apart as possible[29]). One method to improve response to CRT may be to optimise the CRT device by adjusting its settings based on clinical variables (such as ECG and echocardiography findings): typically optimisation involves altering both atrioventricular (AV) and interventricular (VV) timing intervals. Manufacturers of different CRT devices have developed device algorithms to simplify and automate the optimisation process.

An extensive review on the different methods of CRT optimisation was published in 2012 and found that although acute haemodynamic benefits can be gained from optimising AV and VV intervals, no specific technique is clearly superior to another and that the long term clinical benefit of each technique is unclear.[30] Furthermore, if AV and VV intervals were inappropriately altered, it could result in a loss of diastolic filling and clinical deterioration for the patient. The authors concluded that simple and rapid methods of CRT optimisation, such as optimising settings to maximal aortic velocity-time integral on echocardiography, were the most practical and beneficial.

Two simple methods of CRT optimisation were recently evaluated in a small randomised control trial.[31] Patients were randomised to undergo VV optimisation by either electrocardiographic or echocardiographic methods. Patients in the electrocardiographic group had their VV pacing delays adjusted until the delay producing the narrowest QRS complex was found. Echocardiographic optimisation was based on tissue Doppler imaging, with patients classed as being optimised when the VV pacing delay leading to the largest degree of superposition between the displacement curves of the lateral and septal walls and of the anterior and inferior walls was found. The authors concluded that both electrocardiographic and echocardiographic optimisation gave similar results in terms of clinical response to CRT (based on a six minute walk test and Minnesota Living with Heart Failure questionnaire);[31] however, patients who had their CRT optimised electrocardiographically were more likely to have a reduction in left ventricular end-systolic volume by at least 10%.[31]

The direction of cardiac electrical activity after CRT implantation predicts improvement in left ventricular ejection fraction (LVEF).[32] Bode et al demonstrated that patients with an 'optimal' paced QRS morphology (defined as R/S ratio ≥1 in lead V_1 and/or R/S ratio ≤1 in lead I) after CRT implantation had a significant improvement in LVEF compared to those who did not have 'optimal' paced QRS morphology (14.3% *vs.* 2.6%, p=0.0001).[32]

VCG has been used to optimise CRT in a dog model.[33] However, the study computed a form of VCG from conventional 12-lead ECG, using only one plane. In humans, VCG can identify patients with delayed activation of the left ventricular lateral wall (LVLW), a cause of ventricular mechanical dysfunction which is amenable to CRT therapy.[34] The three planes (XY, YZ, XZ) constructed by CGM potentially give far more spatial detail

about cardiac depolarisation and therefore might be of greater use in optimising CRT settings than other forms of VCG.

1.1.5 *Measures of diagnostic performance*

Measures of diagnostic performance are based around the ability of a test to discriminate between the presence or absence of a disease state. A perfect test would have the ability to identify everyone who had the disease and exclude everyone who did not have the disease present.

Sensitivity and specificity are the two most commonly used measures to assess the diagnostic performance of a test, as they are independent of the prevalence of the disease in the population being investigated. To understand these measures the following terms must be understood (see appendix 1):

- True positive – The patient has the disease and the test is positive.
- True negative – The patient doesn't have the disease and test is negative.
- False positive – The patient doesn't have the disease and the test is positive.
- False negative – The patient has the disease and the test is negative.

The sensitivity of a test is the ability of the test to identify patients who do not have disease and is defined as:

$$\frac{True\ Positive}{True\ Positive + False\ Negative}$$

For example, in a population of one hundred patients with a disease, a test with 95% sensitivity will correctly identify 95 patients with the disease but 5 patients will go

undetected. A highly sensitive test is therefore good at ruling out patients with disease, as if a patient has a negative test result it is highly unlikely that they have the disease.

Conversely, the specificity of a test is the test's ability to correctly identify patients who do have the disease and is defined as:

$$\frac{True\ Negative}{True\ Negative + False\ Positive}$$

For example, in a population of one hundred patients without a disease, a test with a 95% specificity will correctly identify 95 patients without the disease but 5 patients will be incorrectly classified by the test as having the disease. A highly specific test is therefore good at ruling in patients with disease, as if a patient undergoing testing has positive test result it is highly unlikely they do not have the disease.

Two related concepts to sensitivity and specificity are positive predictive value (PPV) and negative predictive value (NPV). The PPV of a test represents the chance that the patient with a positive test result actually has the disease and is defined as:

$$\frac{True\ Positive}{True\ Positive + False\ Positive}$$

Whereas, the NPV of a test represents the chance that a patient with a negative test result actually does not have the disease and is defined as:

$$\frac{True\ Negative}{True\ Negative + False\ Negative}$$

However, unlike sensitivity and specificity, both PPV and NPV are affected by disease prevalence. When disease prevalence in the population increases, the PPV also increases and NPV decreases. The converse relationship is true when disease prevalence in the population falls.

Kappa statistic for agreement is another measure used to assess diagnostic performance and assesses the agreement between two tests.[35] It is defined by the following equation:

$$\kappa = \frac{P(A)-P(E)}{1-P(E)}$$

Where P(A) represents the number of times observed where the two tests agree and P(E) represents the number of times the two tests would be expected to agree by chance alone.

Furthermore, the magnitude of the statistical agreement of κ can be classified as no agreement (<0), slight (0-0.2), fair (0.21-0.40), moderate (0.41-0.60), substantial (0.61-0.8) and almost perfect (0.81-1) depending on its value as described by Landis and Koch.[36] A p value can then be attributed to the value of κ, to identify the likelihood the observed value of κ was based on chance alone. For example if the value of κ between two tests equalled 0.45 it would indicate there was moderate agreement between the two tests. However, if its p value was 0.65 it would mean that the observed agreement was due to chance rather than true agreement.

1.2 - Governance

1.2.1. *Confidentiality*.

All patients involved in the studies were attending Castle Hill Hospital as part of their routine care. Furthermore, to be able to be recruited into a study, a participant had to have capacity to consent to their involvement. To have capacity, a patient had to be able to understand the information about the study, retain that information, weigh up and communicate a response.

Only essential information required for the study was accessed from the patient's medical records and consent was gained from each participant before this was done. Information was stored in a secure encrypted database and was only accessible by investigators who were directly involved in the study.

1.2.2. *Personal input*

Organisation and planning of all three studies was done by OIB under the supervision of AH and ALC, beginning 12 months before the start date of the MSc.

Study protocols, patient information leaflets, consent forms and other study documentation were all written by OIB and reviewed by a local patient group before submission to the regional ethics committee.

The ethics application for each project was composed and submitted by OIB who met the regional ethics committee in June 2015. A successful grant application was made to the

Hull and East Riding Cardiac Trust Fund by OIB with AH, who were awarded £27 409 for the conduction of the research. In addition to this, OIB was also awarded the prestigious Wolfson Intercalated Award by the Royal College of Physicians on behalf of the Wolfson Foundation. This is a competitive scheme open nationally to all intercalating medical students and included £4996 in funding to support OIB.

Data collection for all studies was performed by OIB between August 2015 and April 2016 TN provided supervision to the HF-CGM study in terms of data analysis. All statistical analysis was done by OIB with assistance by Jufen Zhang and Alan Rigby.

The manuscript was drafted and written by OIB before undergoing revision by AH and ALC.

1.3 - Aims and Objectives

1.3.1. *COGNITION study*

The primary aim of the COGNITION study was to assess the diagnostic performance of CGM to identify the culprit vessel in patients with non-ST elevation myocardial infarction in comparison to the 12 lead ECG.

We had the specific objectives to assess the aim:

a) What is the sensitivity of CGM at detecting NSTEMI?
b) What is the sensitivity and specificity of CGM to identify the culprit vessel in NSTEMI?

c) What is the negative/positive predictive power of CGM to identify the culprit vessel in NSTEMI?
d) Is the diagnostic performance of CGM significantly better than the 12-lead ECG at identifying the culprit vessel in NSTEMI?

1.3.2. *CARDIOFLOW study*

The primary aim of the CARDIOFLOW study was to assess the diagnostic performance of CGM to identify physiologically significant coronary stenosis defined by FFR.

We had the specific primary objectives to assess the aim:

a) What is the sensitivity and specificity of CGM to detect physiologically significant coronary stenoses?
b) What is the negative/positive predictive power of CGM to detect physiologically significant stenoses?

1.3.3. *HF-CGM study*

The primary aim of the study was to investigate the relation between CGM variables and different pacing site in patients with chronic heart failure and a CRT device *in situ*. The

main outcome measure was the mean QRS axis in each CGM plane.

We wanted to investigate:

a) What is the range of cardiac axis in patients with heart failure with LBBB when in native rhythm, paced from the right ventricle alone, left ventricle alone, and both ventricles together?
b) Is there a statistically significant difference in the range of cardiac axis for different pacing sites?

In addition, secondary aims of the study included

a) To investigate the relation between the frontal CGM axis plane (YZ) and the conventional 12-lead ECG axis plane.
b) To identify 'optimal' QRS morphology from CGM recordings (defined by Bode et al[32] as an R/S ratio ≥ 1 in V_1 and/or R/S ratio ≤ 1 in lead I).

Chapter 2

Literature Review

2 - Literature review

2.1. **Aims and Objectives**

The aim of this review was to identify all the currently published literature investigating the clinical application of CGM in cardiovascular disease.

2.2. **Methods**

We searched electronic databases (MEDLINE and Embase) and conference proceedings for original articles published between 1948 and June 2015 using only the term "cardiogoniometry", limited to human and adult (>18 years of age) studies. Duplicates were excluded and titles along with their abstracts were reviewed by OIB and JAR as to their suitability for inclusion. The articles had to be original research articles that investigated the clinical application of CGM. Review articles and case reports were excluded. Reference lists of retrieved articles were also searched for further publications.

The methodological quality of the included studies was assessed using the QUADAS-2 tool.[37] Data on diagnostic performance was extracted and pooled, where possible. Statistical analysis was performed using SPSS (IBM SPSS Statistics for Macintosh, Version 23.0), which we used to compare sensitivity and specificity between CGM and its comparators and to produce pooled data.

2.3. **Results**

2.3.1. *Search results for the literature review*

We identified 18 articles (figure 2.1), of which four were excluded because they were not original research articles.[3,38–40] A further article[41] was excluded as a more recent publication by the same author had been published with the complete data set.[7] Three studies were excluded as they investigated different CGM variables without directly reporting diagnostic performance.[5,42,43] Finally, a small early paper could not be accessed.[44]

Of the remaining nine studies, seven investigated the value of CGM in patients with stable CAD,[4,6,45–48] one investigated the value of CGM in patients with non-ST segment elevation ACS (NSTE-ACS),[7] and one study explored CGM as a screening tool for cardiac allograft vasculopathy (CAV) in patients with a heart transplant.[49] Of the 7 studies in patients with stable CAD, two[6,47] used up-to-date scoring methods and were suitable for data collation.

Four additional conference abstracts were identified.[50–53] One conference abstract was excluded as the final full text article has subsequently been published[53] and a review article abstract was excluded.[50] The remaining two abstracts reported data on the use of specific cardiogoniometric variables to identify CAD,[51,52] without directly reporting diagnostic performance, and were thus excluded.

The risk of bias in one paper[4] was unclear due to the lack of methodological information. The published abstract by Spiliopoulos et al[49] also did not contain enough information to assess its methodological quality. All the other studies had low risk of bias (table 1).

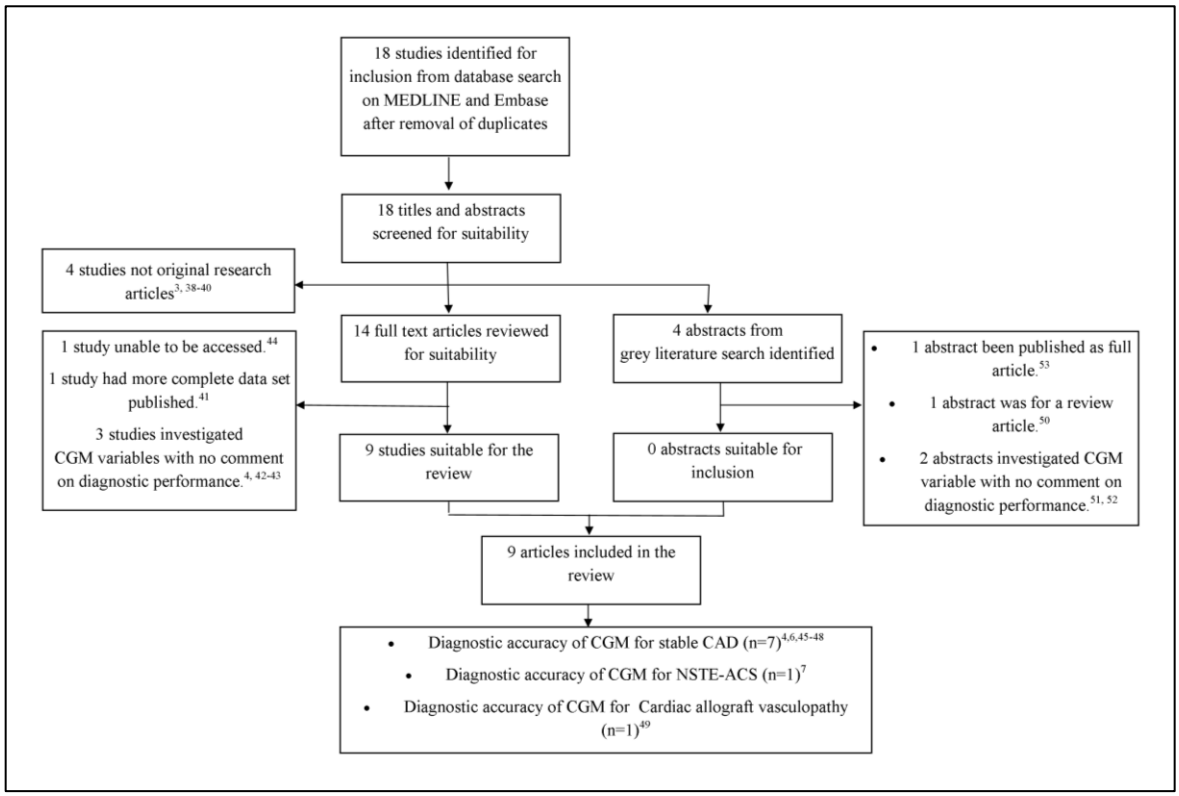

Figure 2.1. – *Flow chart showing search results from the literature review.*

Study	Patient selection	Reference standard	Index test	Flow and timing	Overall
Saner et al[4]	Low	Low	Low	Low	Low
Meier et al[15]	Low	Low	Low	Low	Low
Vontobel et al[18]	Unclear	Unclear	Unclear	Unclear	Unclear
Schüpbach et al[6]	Low	Low	Low	Low	Low
Birkemeyer et al[16]	Low	Low	Low	Low	Low
Weber et al[9]	Low	Low	Low	Low	Low
Ghadrdoost et al[17]	Low	Low	Unclear	Low	Low
Tolg et al[7]	Low	Low	Unclear	Low	Low
Spiliopoulous et al[49]	Unclear	Unclear	Unclear	Unclear	Unclear

Table 2.1. *Table showing methodological quality of included studies – For each category studies were classed as having low, unclear or high risk of bias.*

Study	Year	Population	Number of participants	Gold standard	Diagnostic Accuracy (CGM)		Comparator(s)	Diagnostic Accuracy (Comparator)	
					Sensitivity (%)	Specificity (%)		Sensitivity (%)	Specificity (%)
Saner et al[4]	1983	Stable CAD	50	Coronary angiography[a] (≥70% diameter stenosis)	79	82	Resting ECG	56	91
Meier et al[45]	1987	Stable CAD	48	Coronary angiography[b] (≥50% diameter stenosis)	63	67	Exercise ECG	50	78
							Thallium 201	82	72
Vontobel et al[48]	1988	Stable CAD	85	Coronary angiography[b] (≥50% diameter stenosis)	89	64	Resting ECG	76	18
							Exercise ECG	58	36
Schüpbach et al[6]	2008	Stable CAD	332*	Coronary angiography[b] (≥50% diameter stenosis)	64	82	Resting ECG	53	75
Birkemeyer et al[46]	2012	Stable CAD	40	Cardiac MRI[c]	70	95	Resting ECG	35	90

Table 2.2. – *Table showing characteristics of included studies in the literature review*

**Only prospective data included.*

Study	Year	Population	Number of participants	Gold standard	Diagnostic Accuracy (CGM)		Comparator(s)	Diagnostic Accuracy (Comparator)	
					Sensitivity (%)	Specificity (%)		Sensitivity (%)	Specificity (%)
Weber et al[54]	2014	Stable CAD	21	Myocardial Scintigraphy[d]	71	70	Resting ECG	24	95
Ghadrdoost et al[47]	2015	Stable CAD	390	Coronary angiography[e] (≥70% diameter stenosis or ≥50% in LMS)	84	81	Resting ECG	29	67
Tölg et al[7]	2012	non-ST-segment elevation ACS	216	Coronary angiography[a] (≥70% diameter stenosis)	69	54	Resting ECG	28	78
							First Troponin	34	98
							Serial Troponin	49	96
Spiliopoulous et al[49]	2013	Cardiac allograft vasculopathy	30	Coronary angiography (diagnostic criteria unknown)	100	81	n/a	n/a	n/a

Table 2.2. continued – *Table showing characteristics of included studies in the literature review*

[a] *Defined as ≥70% coronary artery stenosis.*

[b] *Defined as ≥50% luminal diameter stenosis in one or more major coronary vessel.*

[c] *With adenosine perfusion (140μg/kg/min) and late gadolinium enhancement (0.2mmol/kg of gadoteridol)*

[d] *250-300MBq of technetium-99m tetrofosmin and adenosine stress perfusion (140mcg/kg/min)*

[e] *Defined as >70% luminal diameter stenosis in one more major coronary vessel or >50% for left main stem.*

2.3.2. *CGM in stable CAD*

Five of the seven studies of CGM in stable CAD compared CGM to the 12-lead ECG, using coronary angiography as a gold standard reference. Detailed information on study design is given in table 2.2. The majority of studies regarded an automated CGM ischaemia score of <0 as abnormal.[6,47,53,54] No studies gave specific data on the ability of CGM to localise the site of any coronary stenosis.

The sensitivity of CGM varied between 64 and 89% and the specificity between 64 and 82%. Despite the wide range, the sensitivity of CGM was consistently greater than for the 12-lead ECG whilst specificity was similar: sensitivity was between 29 and 76% and specificity between 18 and 95% for ECG.

There was significant clinical heterogeneity between studies. Firstly, the criteria for defining CAD between studies varied; with two using functional imaging and five using coronary angiography. Secondly, in the studies which used coronary angiography to confirm a diagnosis of CAD, there was further heterogeneity in the definitions of CAD: three used a definition of >50% luminal diameter stenosis[6,45,48] and two used >70% luminal diameter stenosis.[4,47] Finally, the definition of a 'positive' CGM result also varied between studies, with only the two most recent publications[6,47] using a contemporary method of CGM interpretation (ischaemia score <0). We thus used only the recent data from the studies by Schupbach et al[6] and Ghadrdoost et al[47] in our pooled analysis. Although Schupbach et al defined CAD as >50% diameter stenosis, over 96% of the patients recruited had stenoses ≥75% or multiple 50% stenoses. The pooled data included 772 patients of whom 473 had CAD on angiography.[6,47] CGM was both more sensitive and

more specific then resting ECG in identifying stable CAD (Table 2.3).

Compared with exercise ECG, and again using coronary angiography as the gold standard (>50% diameter stenosis), CGM had greater sensitivity (63-89%) and comparable specificity (64-67%).[45,48] However, CGM had lower specificity and sensitivity than myocardial perfusion scanning using thallium-201 at peak exercise.[45]

Compared with resting 12-lead ECG, but using cardiac MRI with adenosine stress perfusion as the gold standard, CGM had greater sensitivity (70 *v*s 35%) and specificity (95 *v* 90%).[46] Compared with resting 12-lead ECG, and using rest and stress single positive emission computer tomography [SPECT] using technetium-99m tetrofosmin as the gold standard, CGM had greater sensitivity (71 *vs* 24%) but lower specificity (70 *vs* 95%) than 12-lead ECG.[54]

Diagnostic Accuracy of CGM (%)		**Diagnostic Accuracy of ECG (%)**	
Sensitivity	Specificity	Sensitivity	Specificity
70	82	44	70

Table 2.3 – *Collated data of cardiogoniometry vs the 12-lead ECG to diagnose stable CAD.*

2.3.3. CGM in acute coronary syndrome

The multicentre prospective observational CGM@ACS trial[7] investigated the performance of CGM performed on admission, in 216 patients with acute chest pain or dyspnoea. Patients with ST-segment elevation, bundle branch block or atrial fibrillation were excluded. Following an angiogram within 72 hours of admission, and blind to the results of

CGM, the investigators classified the patients as having either (a) non ST-elevation acute coronary syndrome (NSTE-ACS), which included unstable angina or non ST-elevation myocardial infarction;[55] or (b) cardiac symptoms but no diagnosis of NSTE-ACS.

CGM had greater sensitivity (69%) for identifying NSTE-ACS than other measured variables, including 12 lead ECG and troponin (using standard sensitivity assays), but had a significantly lower specificity (54%; Table 1). CGM had a sensitivity of 74% and specificity of 51% for detecting coronary stenosis of >70% on angiography.

2.3.4. Other clinical applications of CGM published in the literature

An abstract reporting the value of CGM in detecting CAV amongst 30 heart transplant recipients reported a sensitivity of 100% and specificity of 88% compared with coronary angiography. The full paper has not yet been published.

2.4. **Discussion**

We have found that CGM is more sensitive than a 12 lead ECG in identifying patients with stable CAD and NSTE-ACS. The specificity of CGM is comparable to that of a 12-lead ECG in patients with stable CAD, but has lower specificity in patients with NSTE-ACS.

A large limitation of all the work published on CGM is that it has been mainly compared with 12-lead ECG in identifying patients with stable CAD. However, the 12-lead ECG is not used to diagnose patients as having stable CAD and using it as the comparator is therefore questionable as the performance of the 12-lead ECG is bound to be poor.

Although the diagnostic performance of cardiogoniometry may be superior to that of 12-lead ECG, it is not sufficiently sensitive or specific to have a role as a routine screening tool in patients with suspected stable CAD. Other methods of VCG have also been proposed[56] however they too are limited as they have used 12-lead ECG as their comparator. The Vectraplex ECG system uses five electrodes and complex mathematical modelling to derive a "cardiac electrical biomarker". In a study of 367 patients it was shown to be non-inferior to the 12 lead ECG in recognising 'acute myocardial ischemic injury'.[56] However the study 'validating' this technique has major limitations, as 'acute myocardial ischaemic injury' was only based on ECG changes (i.e. did not include coronary angiography or serum troponin) and the ECG changes it used were not specific for myocardial ischaemia.

The sensitivity of CGM tended to be better when a greater % diameter coronary stenosis is used to define CAD at angiography. However, operator defined diameter stenosis is not an accurate measure of flow limiting coronary disease.[12] Fractional flow reserve (FFR) is a method of assessing the physiologically significance of coronary stenosis by measuring the pressure gradient across a stenosis.[12] The FAME study demonstrated the relatively poor ability of angiography to detect lesions of physiological significance.[23] In the study, 509 patients with multivessel disease were randomized to a strategy of FFR-guided angioplasty, with an FFR $\leq$0.80 taken to indicate a significant lesion. The results showed that only 35% lesions with an angiographic diameter stenosis of 50-70% were significant on FFR. This increased to 82% for lesions with a diameter stenosis >70%. None of the studies included in our review used FFR assessment to define CAD.

Birkemeyer et al[46] and Weber et al[54] tried to generate more robust data and address the problem of defining CAD angiographically by using functional imaging techniques to confirm physiologically significant CAD; however this gave rise to another problem. A large proportion of the patients in Birkemeyer's study[46] who had a pathological adenosine stress perfusion test also showed late gadolinium enhancement on MRI, making it unclear whether the detection of CAD in this study was driven by the detection of myocardial scarring or of chronic reversible ischaemia. It is plausible that CGM cannot differentiate between these two entities, reducing its ability to diagnose chronic reversible ischaemia[54] which is of greater clinical significance.

Although the CGM@ACS trial[7] suggested that there might be a role for CGM in the diagnosis of acute coronary syndromes, the advent of the new high-sensitive troponin assays[57] render it redundant. In one study of 1,320 patients admitted with acute chest pain, the baseline measurement of high-sensitivity troponin had an overall sensitivity and specificity for the diagnosis of acute myocardial infarction of 92.1% and 79.4% respectively. [58] When high-sensitivity troponin was repeated at 1 hour, the sensitivity to identify patients without MI further increased to 99.6%. This is clearly far greater than the sensitivity of CGM and makes it a far more clinically useful investigation.

One remaining possible utility of CGM could be its ability to identify the site of ischaemia. Huebner et al[5] showed that stenoses in each major coronary vessel were associated with a specific pattern of cardiogoniometric abnormality. If shown to be accurate, this could theoretically help to guide revascularisation if the location of the culprit lesion is not obvious at the time of angiography.

2.4.1. Potential non-coronary application of CGM

Although CGM may have little clinical utility in the contemporary management of CAD, there may be other possibilities based on exploratory work that has been performed with VCG. Recently, a research group in the Netherlands evaluated the potential utility of VCG to optimise cardiac resynchronisation therapy (CRT), by performing a preliminary study in a dog model.[33] The authors demonstrated that QRS vector angle of the maximum QRS vector amplitude could predict optimal timing of LV stimulation. However, the study computed a form of VCG from conventional 12-lead ECG, using only one plane. This research group has subsequently shown, that when measured with VCG, patients with the smallest QRS vector area had the greatest haemodynamic response to CRT[59] and that patients with a larger QRS vector area also have delayed activation of the left ventricular lateral wall,[34] a common cause of cardiac mechanical dysfunction for which CRT is indicated. The three planes (XY, YZ, XZ) constructed by CGM could potentially give far more spatial detail on cardiac depolarisation and therefore might be of greater use in optimising CRT settings than other forms of VCG, due to the basis of their alignment of it's axes around the position of the heart in the thorax.

2.4.2. *Limitations*

There was significant clinical heterogeneity between the studies we identified for the review. We were thus unable to pool all the studies we identified in a single meta-analysis. Most studies excluded patients with atrial fibrillation, limiting the value of CGM to patients in sinus rhythm. Most of the research published on CGM was produced in Germany and Switzerland and we may have missed some German language publications.

2.5. **Conclusions**

There is no convincing evidence to support the use of CGM in routine clinical practice. Further studies are needed to assess the technique's value in localising coronary artery lesions in patients with acute or chronic ischaemia; and to assess its potential role in guiding CRT therapy in patients with chronic heart failure.

Chapter 3

The COGNITION study: The ability of cardiogoniometry to identify the culprit vessel in patients with non-ST elevation myocardial infarction as compared to the 12-lead ECG.

3. **COGNITION study**

3.1. **Methodology**

3.1.2. *Study design*

The COGNITION study was a prospective, double blind, observational study which aimed to assess the diagnostic performance of CGM to identify the site of the culprit vessel in comparison to the 12-lead ECG in patients admitted with non-ST elevation myocardial infarction (NSTEMI).

3.1.3. *Study participants*

Thirty patients admitted to a single tertiary centre with a diagnosis of NSTEMI were recruited consecutively between January 2016 and March 2016. The presence of NSTEMI was defined as a patient with chest pain, with a rise in serum troponin +/- the presence of ischaemic changes on their ECG.[9] Patients were identified on the cardiology ward, where they were approached for enrolment into the study by a member of the clinical team, given a patient information leaflet and time to consider if they wished to be involved in the study. If at this point they decided they did not wish to be involved in the study they were thanked for taking the time to read the patient information leaflet and treated as per routine clinical practice. For inclusion, patients had to be aged 18 or over with diagnosis of NSTEMI and have had been consented for coronary angiography +/- PCI as part of their routine care by their clinician. Major exclusion criteria included patients with STEMI; patients with ongoing chest pain at rest; patients with haemodynamic instability; patients

unable to perform a good quality CGM; patients with atrial fibrillation and patients with previous coronary artery bypass graft surgery (for a full list of exclusion criteria see Appendix 2). OIB then returned to the patients and answered any questions they may have had, and if they were happy to get involved their written consent was taken by OIB on the cardiology ward before they had undergone coronary angiography. Once enrolled into the study, patient baseline characteristics were collected by OIB. Prior MI was defined as a previous diagnosis of myocardial infarction on a hospital letter or discharge summary.

3.1.4. *Ethics*

The study protocol along with all other documentation was approved by a local patient group before being approved by the regional ethics committee (12/YH/0271). The research project was conducted in accordance with the Declarations of Helsinki. All subjects provided written informed consent. The study was registered on www.clinicaltrials.gov, unique identifier: NCT02803931.

3.1.5. *Study protocol*.

Four CGM electrodes were placed on the patient's thorax and the patient's details were computed into the Cardiologic Explorer software in preparation for a CGM recording. A CGM recording was then performed whilst the patient held their breath for 15 seconds. OIB then took the CGM recording for interpretation. Anonymised copies of all 12-lead ECGs recorded during the patient's admission were then collected from the patient's notes and given to an independent cardiologist for interpretation. As per clinical practice, patients underwent coronary angiography. Radial or femoral access was gained and

patients were anticoagulated with 100 U/kg of heparin and received a 200mg bolus of intra-arterial glyceryl trinitrate. A guide catheter was advanced to the coronary ostia and coronary angiograms of the right and left coronary systems were taken. The interventional cardiologist performing the angiogram was asked to identify what they felt to be the culprit vessel and this was recorded onto a separate database, so the interventional cardiologist remained blind to the information from CGM. The interventional cardiologist had access to the patient's clinical history, electrocardiographic and echocardiographic results, so their judgment of the culprit lesion site was based off a combination of these investigations with angiography rather than angiography alone. Further management of the patient with regards to proceeding to PCI was decided by the operating interventional cardiologist as part of the patient's usual clinical care and was not influenced by the patient's involvement in the study.

If there was no angiographic evidence of the location of the culprit lesion and no other diagnoses were being considered (i.e. Takosubo's cardiomyopathy or myocarditis), the study participant's echocardiogram was reviewed by an independent cardiologist for evidence of regional wall abnormality which may indicate the location of the coronary ischaemia. Additionally, the patient's medical records were checked to see if they had subsequently undergone a cardiac MRI scan to look for evidence of myocardial scarring.

3.1.6. *Data analysis*

CGM data was recorded onto the Patient Explorer software version 2.1 [Enverdis, Jena, Germany. All CGM recordings were interpreted by OIB, who remained blind to the result of coronary angiography. The data from the CGM recordings was recorded as a

dichotomous result, i.e. either negative (ischaemia score = 0) or positive (ischaemia score < 0) for coronary ischaemia. The software automatically detected any irregular or ectopic beats in the recording and excluded them from the analysis. In addition to this, OIB also recorded which territory of the heart the ischaemia was localised to. This was using a number of ways: 1) the patient explorer software locates the ischaemia automatically if certain variables are deviated and this is calculated by the software; 2) OIB looked at the global coordinate window to see if the direction of the T wave axis was outside the normal range. If the T wave axis was located outside the normal range, it indicates ischaemia in the opposite territory (see figure 1.2). The CGM results were stored in an encrypted electronic database, separate to the results of the 12-lead ECG and coronary angiogram.

An independent cardiologist analysed the 12-lead ECGs of each study participant. Ischaemic ECG changes were defined as ST segment depression and/or T wave inversion (present in >2 contiguous leads). The location of the ischaemic changes in relation to the ECG territory was recorded. ECG territories were defined as anterior (leads V1-V4); lateral (leads I, aVL, V5 and V6) and inferior (II, III and aVF). Each ECG territory corresponded to a vascular territory: Anterior changes corresponded to the LAD, lateral changes corresponded to the LCx and inferior changes to the RCA (note: if a patient was found to have left dominant coronary vasculature on angiography, inferior ECG changes in that patient were classed as corresponding to the LCx). If there were not any ECG changes present, the location of the culprit vessel was classed as indeterminate. The final decision regarding the location of the culprit lesion determined by the 12-lead ECG was left at the discretion of the independent cardiologist.

To investigate whether infarct size influenced the diagnostic performance of CGM, the

population was stratified and a subset analysis was performed in those participants with a serum troponin level >500ng/L.

3.1.6. *Statistical analysis*

IBM SPSS Statistics for Macintosh, Version 23.0 was used for statistical analysis. Descriptive statistics were used to summarise the data. Baseline continuous variables are expressed as mean +/-SD or median with interquartile range, categorical data was expressed as numbers/percentages. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were used to measure the diagnostic accuracy of CGM in identifying the culprit vessel. Statistical agreement between CGM and coronary angiography was calculated by the Kappa statistic. P values < 0.05 were considered significant. Missing data was not imputed.

3.2. **Results**

Of the thirty patients recruited in our study, twenty-five demonstrated angiographic evidence of a culprit lesion. One patient did not demonstrate angiographic evidence of a culprit lesion on coronary angiography but was found to have myocardial scaring when they underwent a cardiac MRI. Four patients had no evidence of myocardial infarction on either cardiac MRI or echocardiogram and were therefore excluded from our analysis.

Baseline and angiographic characteristics for the study participants are shown in table 3.1 and table 3.2, respectively. Study participants had a mean age of 67.5 years and 76.7% were male, 13.3% of participants had previously had a myocardial infarction and 13.3% had previously received PCI. All patients had a serum potassium level within the normal

reference range. The majority of culprit lesions evident on coronary angiography were located in the LAD artery (42.3%) and angiographic evidence of thrombus was present in 26.7% of study participants. Coronary revascularisation was performed in 73.1% of study participants, 15 patients received PCI and 4 patients received CABG. The mean delay between clinical presentation and angiography was 68.8 hours.

CGM reported a score positive for coronary ischaemia in nineteen participants and gave site specific information for coronary ischaemia in fifteen of those patients.

Demographics	
N	26
% Male	20 (76.9)
Age (SD)	67.5 (10.8)
Body mass index (SD)	28.3 (4.4)
Past medical history (%)	
Myocardial infarction	2 (7.7)
Percutaneous coronary intervention	2 (7.7)
Stroke/Transient ischaemic attack	2 (7.7)
Heart failure	0 (0.0)
Chronic kidney disease	2 (7.7)
Diabetes Mellitus	5 (19.2)
Hypertension	12 (46.2)
Hypercholesterolaemia	15 (57.7)
Smoking (Never/Ex/Current)	8 (30.8) / 10 (38.5) / 7 (26.9)
Chronic obstructive pulmonary disease	1 (3.8)
Asthma	0 (0)
Peripheral artery disease	1 (3.8)

Table 3.1. – *Showing baseline characteristics for participants in COGNITION study. Continuous data is expressed with its mean and standard deviation (SD).*

Medication at enrollment (%)	
Aspirin	92.3 (24)
Clopidogrel	2 (7.7)
Ticagrelor	23 (88.5)
Prasugrel	0 (0)
Glycoprotein 2_b3_a inhibitor	1 (3.8)
Low molecular weight heparin	17 (68.0)
Angiotensin converting enzyme inhibitor	20 (76.9)
Angiotensin receptor blocker	0 (0)
β-blocker	20 (76.9)
Ca^{2+}channel blocker	4 (15.4)
Lipid lowering drug	23 (88.5)
Baseline blood results	
Haemoglobin, g/L (SD)	134.6 (16.4)
Sodium, mmol/L (SD)	136.4 (3.4)
Potassium, mmol/L (SD)	4.2 (0.3)
Urea, mmol/L (SD)	7.7 (7.5)
Creatinine, mmol/L (SD)	88.7 (31.0)
Glucose, mmol/L (SD)	11.2 (18.3)
Pre-procedural troponin, ng/L, median (IQR)	630 (239-2245)

Table 3.1. continued – *Showing baseline characteristics for participants in COGNITION study. Continuous data apart from pre-procedural troponin is expressed with its mean and standard deviation (SD). Pre-procedural troponin is expressed with its median and inter-quartile range (IQR).*

Angiographic details		
Number of diseased vessels (0/1/2/3)		1/6/12/7
Culprit lesion site (%)	LAD	11 (42.3)
	RCA	7 (26.9)
	LCX	7 (26.9)
Time between clinical presentation and angiography, hours (SD)		68.8 (48.0)
Baseline TIMI flow (0/1/2/3)		2/2/2/20
Angiographic evidence of thrombus (% Yes)		8 (30.8)
Revascularisation (% Yes)		19 (73.1)
Reference vessel diameter (±SD)		3.06 ± 0.72mm
Minimal luminal diameter (±SD)		4.95 ± 0.70mm
% Diameter stenosis (±SD)		66.15 ± 20.6

Table 3.2. - *Showing the angiographic characteristics of participants in the COGNITION study. Culprit lesion site is categorised into left anterior descending artery (LAD); right coronary artery (RCA); left circumflex artery (LCx). All continuous data is expressed with its mean and standard deviation (SD).*

3.2.1 *Diagnostic performance of CGM.*

In patient diagnosed with NSTEMI, CGM was positive in 73.1% of patients. When study participants were classified according to whether they had single or multi-vessel coronary disease, CGM was positive in 57.1% and 78.9% of patients respectively.

CGM was able to provide ischaemia localising information in 15 (57.7%) of patients. The diagnostic performance of CGM to detect operator determined culprit lesion site is shown in table 3.3. There was moderate agreement between the location of the culprit lesion

identified by CGM and coronary angiography for all three lesion sites, which was statistically significant ($p<0.05$) for all three lesion sites.

When study participants were stratified by serum troponin results so that only participants with a serum troponin result over 500 ng/L were included (n=14), the sensitivity of CGM was 78.6%. Furthermore, CGM was able to provide ischaemia localising information for 10 (71.4%) study participants in this population.

Site of culprit lesion	**LAD**	**RCA**	**LCX**
Sensitivity	63.6%	42.9%	42.9%
Specificity	93.3%	100.0%	94.7%
Positive predicative value	87.5%	100.0%	75.0%
Negative predicative value	77.8%	82.6%	81.8%
Kappa statistic for agreement	0.59 p=0.002	0.52, p=0.002	0.44, p=0.02

Table 3.3. *Showing the diagnostic performance of CGM to identify the culprit lesion site in patients with NSTEMI. Culprit lesion site is categorised into left anterior descending artery (LAD); right coronary artery (RCA); left circumflex artery (LCx).*

3.2.2. *Diagnostic performance of the 12-lead ECG*.

In patients diagnosed with NSTEMI, the 12-lead ECG was positive in 57.7% of patients. When study participants were classified according to whether they had single or multi-vessel coronary disease, the 12-lead ECG was positive in 28.6% and 68.4% of patients respectively.

The diagnostic performance of the 12-lead ECG to detect operator determined culprit lesion sites it shown in table 3.4. There was slight, moderate and fair agreement for culprit lesions located in the LAD, RCA and LCx respectively when comparing the 12-lead ECG to coronary angiography. However, agreement was only statistically significant for the RCA analysis ($p<0.001$), suggesting the observed κ statistic for the LCx and LAD analyses were due to chance alone.

Site of culprit lesion	**LAD**	**RCA**	**LCX**
Sensitivity	36.4%	57.1%	33.3%
Specificity	93.3%	100.0%	80.0%
Positive predicative value	80.0%	100.0%	33.3%
Negative predicative value	66.7%	86.4%	80.0%
Kappa statistic for agreement	0.32, p=0.06	0.66, p<0.001	0.08, p=0.69

Table 3.4. *Showing the diagnostic performance of the 12-lead ECG to identify the culprit lesion site in patients with NSTEMI. Culprit lesion site is categorised into left anterior descending artery (LAD); right coronary artery (RCA); left circumflex artery (LCx).*

3.3. **Discussion**

Our results have demonstrated that CGM is more frequently positive than the 12-lead ECG in patients with diagnosed NSTEMI. In addition to this we have demonstrated that CGM has considerable diagnostic ability at identifying the location of the culprit vessel in NSTEMI.

Interestingly the percentage of patients in which CGM was positive in our study population of patients with a diagnosis of NSTEMI, was very similar to the sensitivity of CGM published in the only other known trial evaluating the diagnostic performance of CGM to identify NSTE-ACS.[7] This study enrolled 210 patients and reported a sensitivity of CGM to be 69% to detect NSTE-ACS. However, it should be stated that this study included patients with unstable angina, as well as NSTEMI.

CGM had the highest sensitivity at detecting the culprit lesion when it was located in the LAD, having a poorer diagnostic performance when the lesion was in either the RCA or the LCx arteries. Nevertheless, CGM still surpassed the diagnostic performance of the 12-lead ECG to detect the site of the culprit lesion in 2 out of 3 lesion sites. Importantly, there was a statistically significant level of statistical agreement between the site of the culprit lesion located by CGM and coronary angiography for all three lesion sites. This level of statistical agreement was not seen with the 12-lead ECG for all lesions sites, only reaching statistical significance ($p<0.05$) when the culprit lesion was in the RCA.

A benefit of CGM compared to a 12-lead ECG is that it is able to give an indication if coronary ischaemia is present, irrespective of whether it is able to localise the ischaemia.

This may explain why CGM was more commonly positive than the 12-lead ECG in our study population of patients with NSTEMI, due to the extra information gained from the automated ischaemia score. However, it should be stated that the derivation of the ischaemia score which CGM calculates was based on the ability of CGM to detect lesions with >50% diameter stenosis in patients with suspected stable CAD.

The benefit gained from the increased sensitivity of CGM compared to the 12-lead ECG is unclear. As previously discussed, due to the development of new highly sensitive 1 hour troponins the role of electrocardiographic assessment, albeit apart from excluding the presence of STEMI, when investigating for the presence of NSTEMI is questionable,[10,11] as the need for quick recognition of NSTEMI is no longer reliant on an ECG. The value of electrocardiographic assessment is further diminished by the fact that not only are these new troponin assays highly sensitive, but when serial serum troponin results are measured, the new troponin assays also demonstrate high specificity.

Multiple studies have shown that the 12-lead ECG is poor at identifying ST segment changes associated with myocardial infarction.[60,61] Kornreich et al used body surface potential mapping to identify which ECG leads offered the best information about the presence of acute myocardial infarction (classifying myocardial infarctions as anterior, inferior and posterior). The authors demonstrated ST segment changes often occur in the direction of thorax which is not well interrogated by the 12-lead ECG (notably the right lateral and left posterior aspect of the thorax) and therefore ischaemia localising ST segment changes are not well represented by this modality of electrocardiographic assessment.[60] Furthermore, evidence from a multicentre prospective trial has shown that when posterior and right ventricular leads are added to the conventional 12-lead ECG, the

sensitivity of the 12-lead ECG to detect acute myocardial infarction significantly increases, with a concomitant reduction in specificity being observed.[62] Although in this study, the investigators were using ST-segment elevation as their electrocardiographic marker of acute myocardial infarction, a similar principle applies for other electrocardiographic changes relating to ischaemia. This may explain why CGM showed a statistically significant agreement with all three culprit lesion sites unlike the 12-lead ECG, as CGM offers extra spatial information, due to the fact it contains an additional dimension to that of the 12-lead ECG.

The mean time delay between clinical presentation and angiography of study participants was 68.8 hours. This is within the updated NICE recommended timescale of 72 hours (previously 96 hours) from first admission to hospital and angiography for patients with intermediate to high risk of adverse cardiovascular events.[63,64] Unfortunately, the data need to calculate the GRACE ACS risk score for study participants was not collected at baseline, so we cannot comment how many of the study participants were at intermediate to high risk of adverse cardiovascular events. Eight (30.7%) of the study participants included in the analysis had been referred from a district general hospital to our centre, which may explain the wide variance in the delay in time from clinical presentation and angiography for some of the participants. However, the participants who had been referred from a district general hospital had received angiography at their original centre before coming to our centre. The delay in time from clinical presentation to angiography may have affected the thrombus burden in the culprit vessel which may have influenced which vessel was identified by the interventional cardiologist as containing the culprit lesion.

Most study participants had evidence of a significant myocardial infarction (serum troponin >500ng/L), so we can be confident that the diagnostic performance of CGM assessed in our study is a reasonable representation of the ability of CGM to identify significant infarction. As if the majority of study participants only had small troponin rises it could be argued that the diagnostic performance of CGM was low as the study participants had not undergone significant infarction.

It is unclear why CGM was unable to identify and distinguish the site of the culprit lesion in some study participants. However, this is not dissimilar to what is seen when performing a 12-lead ECG in patients with NSTEMI, where 'ischaemic changes' are only present on some, if not the minority, of patients. This phenomenon is supported by our results where the 12-lead ECG was able to provide ischaemia localising information in only 15 (57.7%) of participants. It is important to clarify however, that although CGM was superior to the 12-lead ECG in terms of achieving significant statistical agreement for all three culprit lesion sites, CGM itself could only provide ischaemia localising information for 15 (57.7%) of study participants. Interestingly, these 15 participants for whom CGM could provide ischaemia localising information, differed to those participants in whom the 12-lead ECG could localise the site of ischaemia.

3.3.1. *Study Limitations*

A major limitation of our study is that the gold standard we used (coronary angiography) may not have correctly identified the culprit lesion in all of our patients. A more robust gold standard we could have used would have been OCT as this has the ability to determine the characteristics of lesions. However as previously mentioned, this was unavailable for us to use in our study.

In addition to this, the operator who determined the culprit lesion was not blind to the result of the 12-lead ECG. The reason for this being, that it was deemed unethical to withhold information which could influence patient care. This may bring bias into the results of analysis of the diagnostic performance of the 12-lead ECG. However, it should not have influenced the primary aim of our study, the diagnostic performance of CGM, as the study investigator analysing the CGM data remained blind to both the results of the 12-lead ECG and coronary angiography.

The sample size in our study was small. Moreover, the number of each specific lesion site was particularly small. A larger sample size may have given us a more representative picture of the true diagnostic performance of CGM to detect lesions in specific sites.

We could only report on the sensitivity, not the specificity, of both CGM and the 12-lead ECG to detect NSTEMI. The reason for this was that patients had to have an NSTEMI for inclusion into the study. It would have been of interest if we had included patients with chest pain but without NSTEMI so the specificity of both CGM and the 12-lead ECG could have been reported.

3.3.2. *Conclusions*

CGM is more frequently positive than a 12-lead ECG in patients with NSTEMI. In addition to this, although CGM outperformed the 12-lead ECG in terms of its ability to accurately locate the culprit lesion site in patients with NSTEMI, it is only able to provide ischaemia localising information in a similar proportion of patients with NSTEMI as that of the 12-lead ECG.

Chapter 4

The CARDIOFLOW study: The ability of cardiogoniometry compared to flow fractional reserve to evaluate the significance of a physiologically significant coronary stenosis.

4. CARDIOFLOW Study

4.1 **Methodology**

4.1.1 *Design and Objectives*

The CARDIOFLOW study, was a prospective single centre, double blinded observational study which aimed to assess the diagnostic accuracy of CGM to recognise physiologically significant coronary stenosis (based on FFR assessment) in patients being investigated for stable CAD.

4.1.2. *Study participants*

Forty patients with single vessel CAD admitted for elective PCI were recruited consecutively in a single tertiary centre between August 2015 and March 2016. All patients had been referred for elective PCI, with the decision to perform FFR being made by the cardiologist in charge of their clinical care. Patients were first identified once they had had a diagnostic angiogram as part of investigation for suspected stable angina and had been found to have single vessel disease on coronary angiography.

Patients were then approached to be invited to the study at their cardiology pre-assessment appointment, given a patient information leaflet and time to consider if they wished to be involved. When the patient returned to the department (approximately 1-2 weeks later) and had been admitted to the cardiology day ward for their procedure, they were approached for enrolment by OIB and any questions they had were answered. If they agreed to be

enrolled into the study, they were then consented by the cardiologist supervising their clinical care. For inclusion, patients had to be aged 18 years or over and have provided informed consent to undergo coronary angiography +/- PCI. Major exclusion criteria included patients with an acute coronary syndrome (as defined by the ESC[11]); patients unable to tolerate adenosine; patients unable to perform a good quality CGM; patients with atrial fibrillation; patients with haemodynamic instability and patients with previous coronary artery bypass graft surgery (for a full list of exclusion criteria see Appendix 3). Once enrolled into the study, patient baseline characteristics were collected. Prior MI was defined as a prior diagnosis of myocardial infarction on a hospital letter or discharge summary.

4.1.3. *Ethics*

The study protocol along with all other documentation was approved by the local patient group before being approved by the regional research ethics committee (12/YH/0271). The research project was conducted in accordance with the Declarations of Helsinki. All subjects provided written informed consent. The study was registered on www.clinicaltrials.gov, unique identifier: NCT02815631.

4.1.4. *Catheter laboratory protocol*

Four CGM electrodes were placed on the patient's thorax and the patient's details were computed into the Cardiologic Explorer software in preparation for a CGM recording. A baseline CGM recording was performed. Radial or femoral access was gained and patients were anticoagulated with 100 U/kg of heparin. A guide catheter was advanced to the

coronary ostia as per usual clinical practice and coronary angiograms of the right and left coronary systems were recorded following administration of 200mcg bolus of intra-coronary glyceryl trinitrate. The coronary pressure wire was advanced down the guide catheter until the pressure sensor was aligned with the tip of the guide catheter, and was then normalised to the pressure at the guide catheter (assumed to be the aortic pressure). The coronary pressure wire was then advanced down the affected coronary artery being investigated and through the stenosis, where a bolus of 200mcg of intracoronary glyceryl trinitrate was administered. Baseline FFR and a second baseline CGM recording were then performed. An intravenous adenosine infusion (180mg/kg/min) was administered through a peripheral venous cannula in the antecubital fossa for 3 minutes or until maximal hyperaemia had been achieved. During maximal hyperaemia, peak FFR and CGM recordings were made. OIB then left the room to remain blind to the result of the FFR assessment and took the CGM recordings for interpretation. The operating interventional cardiologist recorded the results of the FFR assessments and managed the patient as per clinical practice.

4.1.5. *Data analysis*

CGM data was recorded onto the Patient Explorer software version 2.1 [Enverdis, Jena, Germany. All CGM recordings were interpreted by OIB, who remained blind to the result of FFR, and was recorded as a dichotomous result, i.e. either negative (ischaemia score = 0) or positive (ischaemia score < 0). This was done for both baseline and maximal hyperaemia recordings. The software automatically detected any irregular or ectopic beats in the recording and excluded them from the analysis. The CGM results were stored in an encrypted electronic database, separate to the results of the FFR.

The FFR results for each patient were recorded by the operating interventional cardiologist into a separate electronic database. FFR was classified dichotomously as negative (FFR > 0.80) or positive (FFR ≤ 0.80) at baseline and at maximal hyperaemia. At the end of participant recruitment, blinding was broken and OIB analysed the results of CGM in comparison to FFR. Quantitative coronary angiographic (QCA) analysis was performed using Centricity Explorer system. The reference vessel diameter, minimal lumen diameter (MLD), percent (%) diameter stenosis and lesion length were measured before FFR assessment. Reference vessel diameter was taken as the diameter of the normal vessel proximal to the lesion.

Previous work investigating the diagnostic performance of CGM to identify patients with stable CAD has suggested that its diagnostic ability has been driven by detection of scarring from myocardial infarction, rather than detection of chronic reversible ischaemia.[5446] Therefore, a pre-specified subgroup analysis for the diagnostic performance of CGM was patients without previous myocardial infarction.

To allow comparison between our study and previous studies, the diagnostic performance of CGM was calculated when % diameter stenosis (both ≥50% and ≥70% DS) was used as the gold standard.

Finally, the diagnostic performance of diameter stenosis (DS) to identify physiologically significant coronary stenoses (based on FFR) was calculated.

4.1.6. *Statistical analysis*

IBM SPSS Statistics for Macintosh, Version 23.0 was used for statistical analysis. Descriptive statistics were used to summarise the data. Baseline continuous variables are expressed as mean+/-SD or median with interquartile range, categorical data was expressed as numbers/percentages. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were used to measure the diagnostic accuracy of CGM in comparison to FFR; CGM to ≥50% DS, and CGM to ≥70% DS. Statistical agreement between CGM and FFR; CGM to ≥50% DS and ≥70% DS was calculated by the Kappa statistic. Additionally the diagnostic performance of DS (both ≥50% and ≥70% DS) to FFR was assessed using the identical diagnostic markers for which CGM was assessed. Finally, a receiver operating characteristic (ROC) curve was used to further evaluate the diagnostic performance of DS to identify physiological significant stenosis. Missing data was not inputted.

4.2. **Results**

Of the forty patients recruited in our study, sixteen (40%) were found to have significant coronary artery disease when assessed by FFR.

Baseline and angiographic characteristics for the study participants are shown in table 4.1 and table 4.2. respectively. Study participants had a mean age of 61.1 years and 60.0% were male, 27.5% of participants had previously had a myocardial infarction and 40.0% had previously received PCI. All patients had a serum potassium level within the normal reference range. The majority of lesions were located in the LAD artery (75%). Mean

diameter stenosis was 56.9% ± 15.34, mean lesion length was 18.49 ± 13.61mm and mean MLD was 1.27 ± 0.48mm. QCA was able to be performed in 36 (90%) of patients. At baseline, the majority of patients had a negative CGM result (ischaemia score = 0) with only 14 (35%) participants having a positive CGM result (ischaemia score ≤ -1). At maximal hyperaemia the number of patients with a positive CGM result increased to 18 (45%). At baseline, 3 (7.5%) participants had a positive FFR result (≤0.80) whilst at maximal hyperaemia 16 (40.0%) participants had a positive FFR.

Demographics	
N	40
Male (%)	24 (60)
Age (SD)	61.1 (11.0)
Body mass index (SD)	30.3 (6.1)
Past medical history (%)	
Myocardial infarction	11 (27.5)
Percutaneous coronary intervention	16 (40.0)
Stroke/Transient ischaemic attack	2 (5.0)
Heart failure	0
Chronic kidney disease	0
Diabetes Mellitus	8 (20.0)
Hypertension	22 (55.0)
Hypercholesterolaemia	22 (55.0)
Smoking (Never/Ex/Current)	14 (35.0) / 16 (40.0) / 10 (25.0)
Chronic obstructive pulmonary disease	1 (2.5)
Asthma	3 (7.5)
Peripheral artery disease	1 (2.5)

Table 4.1. – *Baseline characteristics of participants in CARDIOFLOW. Continuous data is expressed with its mean and standard deviation (SD).*

Medication at enrollment (%)	
Aspirin	37 (92.5)
Clopidogrel	9 (22.5)
Ticagrelor	7 (17.5)
Prasugrel	0.0
LMWH	0.0
ACEi	13 (32.5)
ARB	7 (17.5)
β-blocker	29 (72.5)
Ca^{2+}channel blocker	9 (22.5)
Lipid lowering drug	32 (80.0)
Baseline blood results	
Haemoglobin, g/L (SD)	142.5 (11.8)
Sodium, mmol/L (SD)	137.3 (2.2)
Potassium, mmol/L (SD)	4.3 (0.3)
Urea, mmol/L (SD)	5.8 (1.6)
Creatinine, mmol/L (SD)	78.2 (17.9)

Table 4.1. continued – *Baseline characteristics of participants in CARDIOFLOW.*

Continuous data is expressed with its mean and standard deviation (SD).

Angiographic details		
Stenosis Site (%)	LAD	30 (75.0)
	RCA	4 (10.0)
	LCX	3 (7.5)
	OM	1 (2.5)
	D	2 (5.0)
Stent implanted (% Yes)		15 (37.5)
Reference vessel diameter (±SD)		2.96 ± 0.68mm
Minimal luminal diameter (±SD)		1.27 ± 0.48mm
% Diameter stenosis (±SD)		56.90 ± 15.34
Lesion length (±SD)		18.49 ± 13.61mm
FFR details		
Baseline FFR (±SD)		0.90 ± 0.12
Peak hyperaemia FFR (±SD)		0.81 ±0.13
Positive FFR at baseline (%)		3 (7.5)
Positive FFR during hyperaemia (%)		16 (40.0)

Table 4.2. - *Showing the angiographic and fractional flow reserve (FFR) characteristics of study participants. Stenosis site is categorised into left anterior descending artery (LAD); right coronary artery (RCA); left circumflex artery (LCx); obtuse marginal artery (OM) and diagonal artery (D). Continuous data is expressed with its mean and standard deviation (SD).*

	CGM at rest (n=40)	**CGM during maximal hyperaemia** (n=40)
Sensitivity	31.3%	68.8%
Specificity	62.5%	54.2%
Positive predicative value	35.7%	50.0%
Negative predicative value	57.7%	72.2%
Kappa statistic for agreement	-0.06, p=0.64	0.21, p=0.15

Table 4.3. – *Diagnostic performance of cardiogoniometry (CGM) to detect physiologically significant coronary stenosis.*

	CGM at rest		CGM during maximal hyperaemia	
Definition of stable CAD	**≥50% DS (n=36)**	**≥70% DS (n=36)**	**≥50% DS (n=36)**	**≥70% DS (n=36)**
Sensitivity	38.5%	16.7%	61.5%	50.0%
Specificity	70.0%	56.7%	50.0%	40.0%
Positive predicative value	76.9%	14.3%	76.2%	14.3%
Negative predicative value	30.4%	77.3%	33.3%	80.0%
Kappa statistic for agreement	0.06, p=0.64	-0.174 p=0.22	0.10, p=0.53	-0.05 p=0.65

Table 4.4. – *Diagnostic performance of cardiogoniometry (CGM) to detect stable coronary artery disease defined as either ≥50% diameter stenosis (DS) or ≥70% DS.*

4.2.1 *Diagnostic performance of CGM*

The diagnostic performance of CGM to detect physiologically significant stenosis is shown in table 4.3. At rest, the diagnostic performance of CGM to detect physiologically significant stenosis was poor across all measures. During maximal hyperaemia the sensitivity of CGM was significantly increased compare to that found at rest (31.3 vs 68.8%), however a concomitant reduction in specificity was also observed (62.5 vs 54.2%). PPV and NPV were also increased at maximal hyperaemia compared to at rest. No significant statistical agreement between CGM and FFR was found at rest (κ=-0.06, p=0.64); however a fair agreement between CGM and FFR was seen during maximal hyperaemia, but this was not statistically significant (κ=0.21, p=0.15).

When excluding patients with previous MI, the majority of the measures of diagnostic performance of CGM were overall, similar to those in the total population (see table 4). In this subgroup, the sensitivity of CGM was slightly higher at rest than the total population (40.0 vs 31.3%) and the sensitivity of CGM during maximal hyperaemia was slightly lower (68.8 vs 60%).

When % diameter stenosis was used as the gold standard to define stable CAD, the diagnostic performance of CGM at rest and during maximal hyperaemia was equally poor if not worse than FFR defined CAD (see table 4.4). The sensitivity and specificity of CGM to detect stable CAD was greater when 50% DS was used instead of 70% DS to define stable CAD. During maximal hyperaemia, the sensitivity and specificity of CGM increased and decreased respectively, when stable CAD was defined at both ≥50% DS and ≥70% DS. CGM showed no significant statistical agreement with either ≥50% DS or ≥70% DS

defined stable CAD, either at rest or during maximal hyperaemia.

	CGM at rest (n=29)	**CGM during maximal hyperaemia** (n=29)
Sensitivity	40.0%	60.0%
Specificity	63.2%	52.6%
Positive predicative value	36.3%	40%
Negative predicative value	66.6%	71.4%
Kappa statistic for agreement	0.03	0.113

Table 4.5. – *Diagnostic performance of cardiogoniometry (CGM) to detect physiologically significant coronary stenoses when patients with previous myocardial infarction are excluded.*

4.2.2 *Diagnostic performance of % DS.*

The sensitivity and specificity of ≥50% DS identifying physiologically significant coronary stenoses was 86.7% and 38.1% respectively (see table 4.6). Statistical agreement between ≥50% DS and FFR was fair, but not statistically significant (κ=0.22, p=0.102). Sensitivity of ≥70% DS identifying physiologically significant coronary stenosis was 63.3%, whereas specificity was 6.6%. Slight agreement between ≥70% DS and FFR was observed, but this was not statistically significant (κ=0.19, p=0.142). The ROC curve for DS is shown in figure 4.1. The area under the curve of the ROC curve was 0.695.

	≥50% Diameter stenosis (n=36)	**≥70% Diameter stenosis** (n=36)
Sensitivity	86.7%	63.3%
Specificity	38.1%	66.6%
Positive predicative value	50.0%	26.7%
Negative predicative value	80.0%	90.5%
Kappa statistic for agreement	0.22, p=0.102	0.19, p=0.142

Table 4.6. - *Diagnostic performance of ≥50% diameter stenosis and ≥70% diameter stenosis to detect physiologically significant coronary stenosis.*

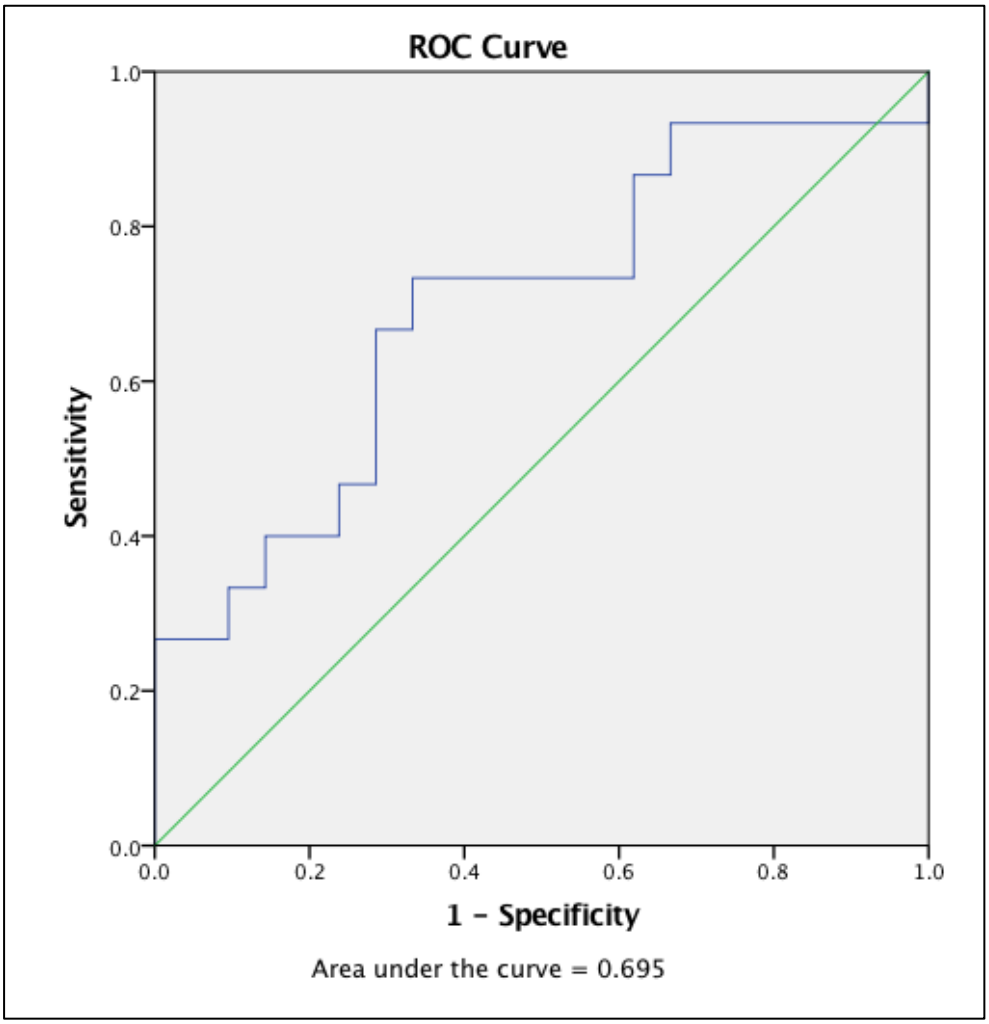

Figure 4.1 – *Receiver operating characteristic (ROC) curve for diagnostic performance of %DS to identify physiologically significant coronary stenoses.*

4.3. **Discussion**

Our results have demonstrated that the diagnostic performance of CGM at rest to detect patients with physiologically significant stable CAD is poor. When patients undergo pharmacological cardiovascular stress using intravenous adenosine, the diagnostic performance of CGM improves. However, it does not reach sufficient levels of diagnostic accuracy to be relied upon to either exclude or diagnose the presence of physiologically significant stable CAD. Furthermore, the diagnostic performance of CGM is as poor, if not worse than FFR defined stable CAD when % diameter stenosis is used to define stable CAD. Our data has demonstrated that although the sensitivity of ≥50% DS to detect physiologically significant stenosis is good, its specificity is lacking. Whereas, the sensitivity and specificity of ≥70% DS is poor. Therefore, overall diagnostic performance of DS is poor.

Non-invasive physiological assessment has an important role in the investigation of patients with suspected stable CAD;[8] however current electrocardiographic based investigations lack sufficient diagnostic accuracy to definitively rule in or out the presence of stable CAD.[65]

One of the main objectives of this study was to see if CGM had adequate sensitivity to have a potential future role as a screening tool. If you could safely stratify which patients did not require FFR assessment, it would avoid the additional cost of the pressure wires which are used during the FFR assessment. As seen in the results, the sensitivity of CGM to detect significant stable CAD increased from 31.3% at rest to 68.8% during pharmacological stress. However even then, the sensitivity of CGM was not great enough

to be trusted, as for every hundred patients with physiologically significant stable CAD tested, CGM would not detect the presence of stable CAD in thirty-one of those patients.

In our study, the specificity of CGM was found to be reduced when patients underwent pharmacological stress as opposed to when at rest. The most probable explanation of this is that patients with 'borderline' CGM results which were classed as negative by the automated algorithm at rest, became positive after adenosine had been administered. This is hardly surprising, as pharmacological stress with adenosine induces myocardial ischaemia. However, these positive CGM results may not have been based on CGM variables which represent physiologically significant stable CAD. One major issue of the automated algorithm used by the CGM device is that when it was originally validated, it was based on data from a study where patients were classified as having stable CAD based only on coronary angiography (defined as ≥50% diameter stenosis).[6] As we and others have demonstrated, this is a fundamental flaw as DS is not a reliable means of detecting significant lesions causing ischemia. In our results, we demonstrated that the specificity of ≥50% DS to detect physiologically significant stenosis was 38.1%. This means that if you used ≥50% DS to classify stable CAD, for every 100 patients with a stenosis greater than ≥50% in diameter, 62 would not have CAD that was physiologically significant. The low specificity seen in this study may be due therefore to an issue in the device algorithm itself, as the cardiogoniometric variables it classes as being present in patients with stable CAD are not sufficiently specific for physiologically significant coronary disease. Nevertheless, it should be clarified that CGM was first developed before the routine use of FFR. Therefore, it is not unreasonable that its initial development was based on the ability of CGM to detect angiographically significant coronary stenoses, and not FFR significant stenosis. The situation is similar for studies which used a definition of ≥70% DS.[23]

The diagnostic performance of CGM in this study was considerably worse than other methods of physiological assessment of coronary ischaemia, including stress echocardiography and myocardial perfusion imaging. When using coronary angiography as the gold standard, the reported figures in the literature of the sensitivity and specificity of stress echocardiography to detect stable CAD are 80% and 84% respectively;[66] whilst the reported figures for sensitivity and specificity of myocardial perfusion imaging to detect stable CAD differ by modality. SPECT have reported figures of 87% and 73% respectively for sensitivity and specificity, and the figures for cardiac MRI were reported at 89% and 87%.[67] However, when these methods of physiological assessment have been assessed using FFR as the gold standard, they have been shown to have poor agreement with FFR to detect physiologically significant stable CAD.[6869] The study by Melkian et al,[68] an observational study where patients with double or triple vessel CAD underwent adenosine/rest myocardial perfusion imaging (MPI) with SPECT and FFR assessment, found that the sensitivity and specificity of MPI was 76% and 38% respectively to identify physiologically significant CAD defined by FFR. In this study, MPI and FFR identified identical physiologically ischaemic areas in only 42% of participants, with MPI overestimating physiological ischaemia in 22% of participants and underestimating it in 36% of participants. Stress echocardiography fairs similarly poorly when compared against FFR, with the sensitivity and specificity of stress echocardiography being shown to be 50% and 90% respectively at identifying patients with physiologically significant CAD.[69] It is therefore difficult to criticise the diagnostic performance of CGM based on comparing it to these other non-invasive methods of physiological ischaemia assessment alone.

The reported figures for the measures of diagnostic performance of CGM in this study are considerably worse than figures previously published. A possible explanation for this is that the population in this study is different from those in previously published work, as we only recruited patients with known coronary anatomy with single vessel disease. All of the previously published work did not limit study participants to having single vessel disease and the diagnostic performance of CGM may be greater in patients with multi-vessel disease as it may represent patients with a greater ischaemic burden. These patients tend to have worse long term outcome, increased procedural risk and significant comorbidities.[70] Nevertheless, this is the only study investigating CGM to determine the presence of physiologically important CAD using a robust method to identify significant myocardial ischaemia.

As previously stated, it has been postulated that the diagnostic performance of CGM could be driven by detection of myocardial scarring, as opposed to chronic reversible ischaemia. However, our results have demonstrated that there is little difference in the diagnostic performance of CGM to detect physiologically significant stable CAD when patients with previous MI are excluded. Specifically, you would expect that the effect of myocardial scarring from previous MI would be to reduce the specificity of CGM at detecting stable CAD. As shown in our results, when patients with previous MI have been excluded the difference in specificity is small at 0.7%. Our results correlate with studies previously published trying to address this question,[54]and we can therefore conclude that myocardial scarring does not have a big influence on the diagnostic performance of CGM.

Another possible explanation of why the sensitivity of CGM was not greater than that observed, is that patients may have undergone myocardial ischaemia preconditioning.

Hence, when the patient underwent pharmacological stress with intravenous adenosine, no ECG changes were observed.

It would have been interesting to see if other stressing agents like dobutamine, may have precipitated more ECG changes which CGM may have been able to detect and hence increased its sensitivity. The reason for this being, that dobutamine, a β_1 adrenergic receptor agonist, acts by directly raising the metabolic demands of the myocardium by increasing heart rate and the force of cardiac contractility. Whereas the mechanisms by which adenosine induces cardiovascular stress resulting in detectable electrocardiographic changes are unclear, but thought to be indirect in nature. Previous work has associated intravenous adenosine infusion with ST depression in patients undergoing MPI.[71] Interestingly, in this study it demonstrated that ST depression during intravenous adenosine infusion was more common in patients with collateral vessels on angiography and hypothesized the ischaemic changes were driven by a coronary steal effect.[72] In addition, experimental dog models of single vessel coronary artery stenosis have demonstrated that coronary dilation with adenosine increases the pressure gradient across the stenosis, resulting in a decrease in distal perfusion pressure.[73] The physiological process behind this 'steal' effect has been proposed as follows: adenosine binds to the A_{2A} receptor, which causes vasodilation and a fall in resistance in the cardiac vascular bed. At rest, the stenotic vessel is maximally dilated to compensate for reduced flow, so when resistance in the vascular bed falls, the perfusion pressure in the collateral vessels also falls. As a consequence of this, there is loss of collateral blood supply to the myocardium distal to the lesion, resulting in worsened myocardial ischaemia.[72] However, this mechanism is unlikely to be the sole explanation, as adenosine also reduces 'afterload' in the coronary vasculature distal to the stenosis – an action which should improve distal

coronary flow distal in the effected vessel. In addition, the coronary steal phenomenon is only thought to occur vessels with critical stenosis. As in the majority of patients, the decrease in flow in the diseased vessel is only relative to the neighbouring healthy vessel, as the healthy vessel has the ability to further dilate.

As study participants were already undergoing pharmacological stress with intravenous adenosine as part of their clinical care, it was felt to be unethical to subject them to an additional CGM stress test and induce the unpleasant side effects associated with dobutamine (nausea, headaches and dyspnoea). In addition to this, almost all of the previous studies investigating CGM have been performed whilst participants have been at rest and therefore 'stress' CGM is a relatively novel concept as it has not fully been investigated before and would add considerable value to the literature. One previous study,[54] has studied the diagnostic performance of CGM during adenosine stress perfusion and reported figures of sensitivity and specificity similar to those seen in this study. Interestingly, this study also showed a reduction in the specificity of CGM, when patients underwent pharmacological stress with intravenous adenosine compared to rest testing.

CARDIOFLOW was designed to make the results as clinically applicable as possible, hence why the interpretation of the CGM result was based solely on the automated ischaemia score alone, and not by review by an experienced CGM reporter. The idea being that if CGM was implemented into routine clinical practice, a recording could be performed by an operator without detailed knowledge of CGM. Furthermore, if CGM was found to be sufficiently accurate, it could be used as non-invasive alternative of myocardial physiological assessment using adenosine, therefore avoiding the need of performing an invasive procedure. Our patients are typical of routine clinical practice, a reflection of our consecutive recruitment of participants and reduction of the risk of selection bias.

Furthermore, as demonstrated by the spread of data in the angiographic table, there was a wide range in both the length and severity of the lesions in the participants recruited in our study. This again mirrors the picture seen in routine clinical practice and increases the external validity of the study.

4.3.1 Study limitations

There are some important limitations to recognise for our study. Firstly, this was a single centre study and only a relatively small number of participants enrolled. In addition to this, patients with multi-vessel disease, atrial fibrillation or previous CABG were excluded, which means the results cannot be applied to that population in clinical practice. The definition of prior MI was based on a previous hospital diagnosis of MI and as a consequence was not very robust. In addition, myocardial scarring was assumed in patients with previous MI and not formally assessed by performing cardiac MRI with late gadolinium enhancement; therefore, patients may have been incorrectly excluded from the subgroup analysis. Further research with more robust inclusion criteria, may help clarify the role of CGM in this particular subgroup. The 12-lead ECG in patients presenting with new onset chest pain who have had a prior MI can be difficult to interpret, so it would be especially pertinent to see how well CGM could perform. Additional testing of participants with stress echocardiography and myocardial perfusion imaging would have allowed direct comparison between CGM and other methods of assessment, however this was not performed as it is not part of their routine clinical care.

4.3.2 Conclusions

The diagnostic performance of CGM to detect physiologically significant stable CAD is poor at rest. Although, the diagnostic performance of CGM improves substantially during adenosine stress testing, it does not reach sufficient levels of accuracy to be used routinely in clinical practice. Angiographically determined diameter stenosis is a poor indicator of physiologically significant CAD.

Chapter 5

The HF-CGM study: Can CGM detect changes to cardiac axis when cardiac resynchronisation therapy device settings are altered?

5. **HF-CGM**

5.1. **Methodology**

5.1.1. Study *design*

We conducted a feasibility study (HF-CGM) to assess the ability of CGM to detect changes in CRT pacing site.

5.1.2. *Study participants*

Eleven patients who were attending pacemaker clinic for routine CRT device checks were consecutively recruited in one month (November 2015). They were identified from the appointment list before the pacing clinic started; they were then approached for enrolment into the study by OIB. Potential participants were given a patient information leaflet and time to consider whether they would like to be involved in the study. For inclusion, patients had to be aged 18 or over, have a functioning CRT device implanted and be able to provide informed written consent. Patients who were pacemaker dependant (i.e. had no intrinsic electrical activity) were excluded from the study, as were those who were non-English speakers due to funding restrictions. All questions were answered and if happy, the participants were consented for enrolment into the study by OIB.

5.1.3. *Ethics*

The study protocol along with all other documentation was approved by the Trans-Humber Consumer Research Panel (local patient group), before being approved by the regional ethics committee (15/NW/0479). All subjects provided written informed consent. The study was registered on http://www.clinicaltrials.gov/, unique identifier: NCT02803879.

5.1.4. *Study protocol.*

For each patient, four CGM electrodes were placed on the patient's thorax, with a fifth CGM electrode placed on the patient's left thigh to act as an earthing electrode. The patient's details were computed into the Cardiologic Explorer software. Each patient then underwent the following sequential CGM recordings whilst lying as still as possible with shallow breathing for 30 seconds whilst the recording was in progress:

a) biventricular pacing (BIV) with no device settings change
b) pacing via the RV lead alone;
c) pacing via the LV lead alone; and
d) both RV and LV leads turned off.

For paced rhythms, traces were obtained at a minimum paced rate of 80bpm (or until intrinsic electrical activity had been overcome) so the recordings taken were a reflection of paced cardiac axis and not intrinsic electrical activity. In addition to having sequential CGM recordings performed, concomitant 12-lead ECGs were recorded to allow comparisons of cardiac axis calculated by both methods. The limb electrodes for the 12-

lead ECG were placed on the patient's wrists and ankles, precordial electrodes were placed in Wilson positions V_1 to V_6. Finally, patients had their CRT settings restored (or optimised using conventional methods if clinically indicated).

5.1.5. *Data analysis*

CGM data were recorded using the Patient Explorer software version 2.1 [Enverdis, Jena, Germany]. CGM analysis was performed by OIB.

For each of the CGM recordings, the mean QRS axis (in degrees) was calculated as follows: the net deflection of the QRS complex (mV) was measured for each of the X, Y and Z axes to produce orthogonal coordinates (figure 2). Polar angles for the oblique sagittal (XY), frontal (YZ), and sagittal (XZ) planes were calculated using formulae previously described by Sanz et al in 1983[3] (Appendix 4). Using the 12-lead ECG recordings the QRS axis was calculated in a similar way to that of CGM. The net deflection of the QRS complex measured in the plane defined by the orthogonal leads I and aVF was used to produce coordinates, which were subsequently transformed to polar angles by trigonometry (Appendix 4). This method is validated as a method for calculating the cardiac axis.[74]

The CGM frontal plane is claimed to be equivalent to the frontal plane calculated by the 12-lead ECG rotated by -45° (figure 5.1), and so we subtracted 45° from the axis calculated from the conventional ECG to allow direct comparison with the axis calculated from CGM.[3]

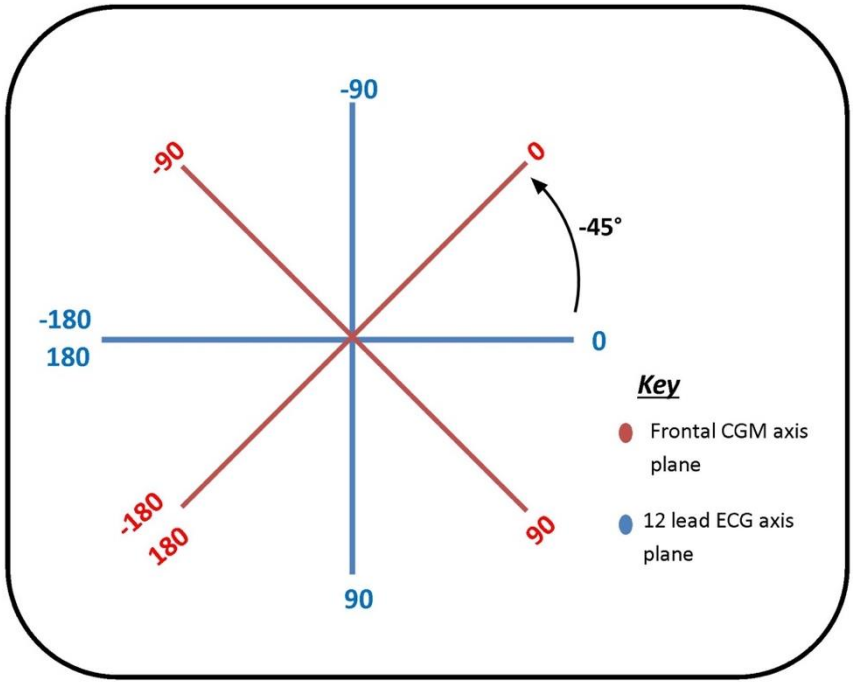

Figure 5.1. – *Demonstrating the relationship of frontal (YZ) CGM plane to the 12-lead ECG plane.*

5.1.6. *Statistical analysis.*

IBM SPSS Statistics for Macintosh, Version 23.0 was used for statistical analysis of baseline clinical characteristics. Descriptive statistics were used to summarise the data. Baseline continuous variables are expressed as mean +/-SD, categorical data are expressed as numbers/percentages.

Statistical analysis for the axis data was performed using RStudio Version 0.99.491 (RStudio Inc, Boston, USA). Values for the cardiac axis were first transformed from linear to circular format, with the scale of degrees going from 0→180→-180→0. The mean value, and 95% confidence interval (based on a Von Mises distribution)[75] for each CRT

pacing site in each plane was calculated and circular scatter plots for each CRT pacing settings were drawn. Differences between pacing sites were assessed with the non-parametric Moore's test for paired circular data, with RV pacing, LV pacing and biventricular pacing compared to no pacing. Statistical significance was pre-defined as $p \leq 0.05$. The equivalence of the frontal CGM plane to the conventional 12-lead ECG plane was assessed by visual comparison of scatterplots.

A secondary analysis was performed based on whether patients had satisfied the 'optimal' QRS morphology defined by Bode et al[32] (R/S ratio ≥1 in V_1 and/or R/S ratio ≤1 in lead I) on their initial ECG with CRT. Circular scatter plots were then plotted to look for any difference in CGM cardiac axes between the 'optimal' and 'non-optimal' groups.

5.2. **Results**

Baseline characteristics for study participants are shown in table 5.1.

5.2.1. *Direction of cardiac axis by pacing settings.*

Mean angles and their 95% confidence interval for each device setting in each plane is shown in table 2 and illustrated in figures 5.2-5.4. Biventricular pacing led to a very wide range of readings in all three planes. The narrowest ranges for axis were in the XY plane, and only in the XY plane were there significant differences in axis between the different pacing modes. There was no significant difference in axis in either YZ or XZ planes between no pacing and biventricular pacing.

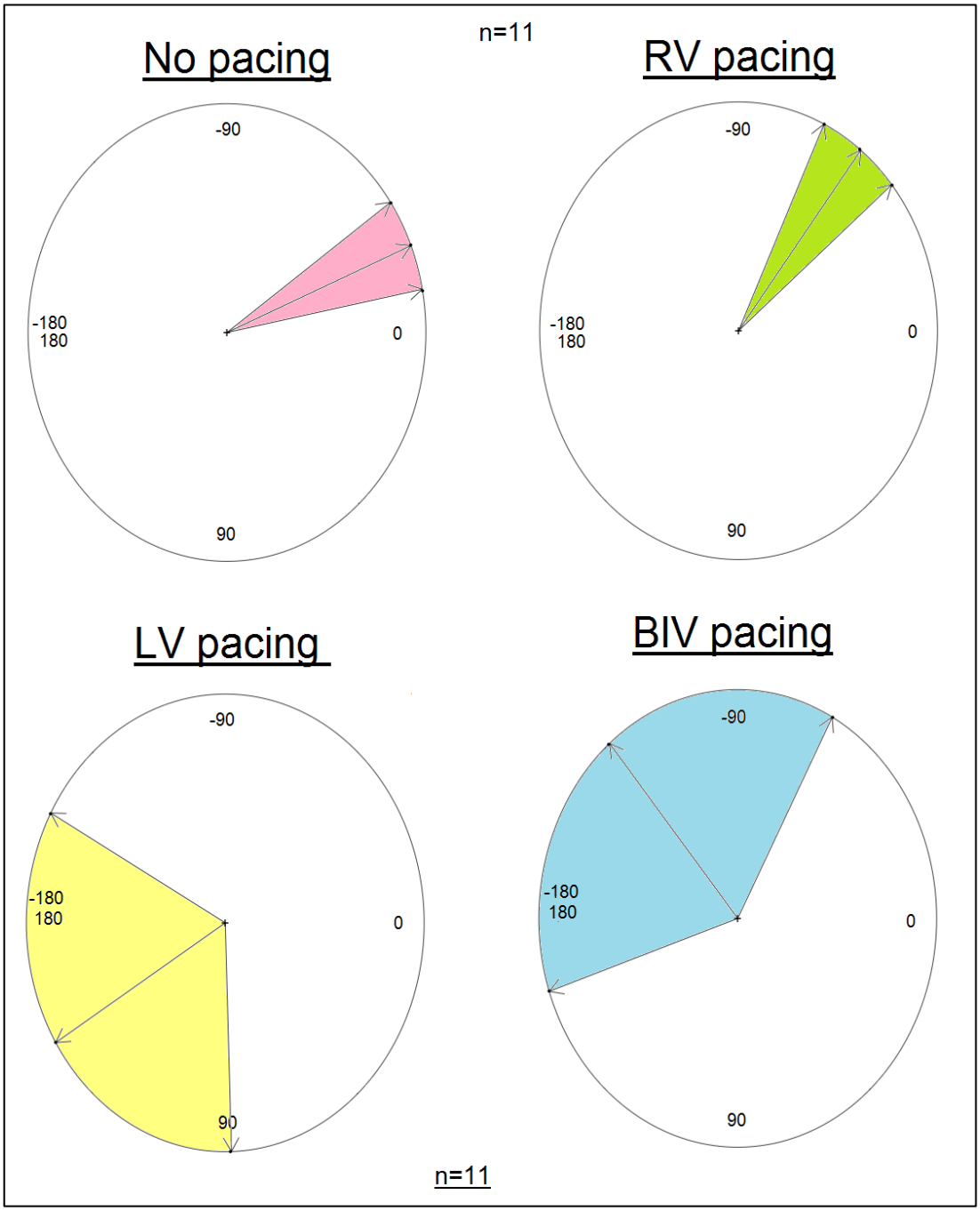

Figure 5.2. – *Graph showing the mean cardiac axis (central arrow) and 95% confidence intervals (peripheral arrows) of study participants for different CRT device settings in the XY plane. Upper left panel – no pacing; upper right panel – right ventricular (RV) pacing; lower left panel – left ventricular (LV) pacing; lower right panel – biventricular (BIV) pacing*

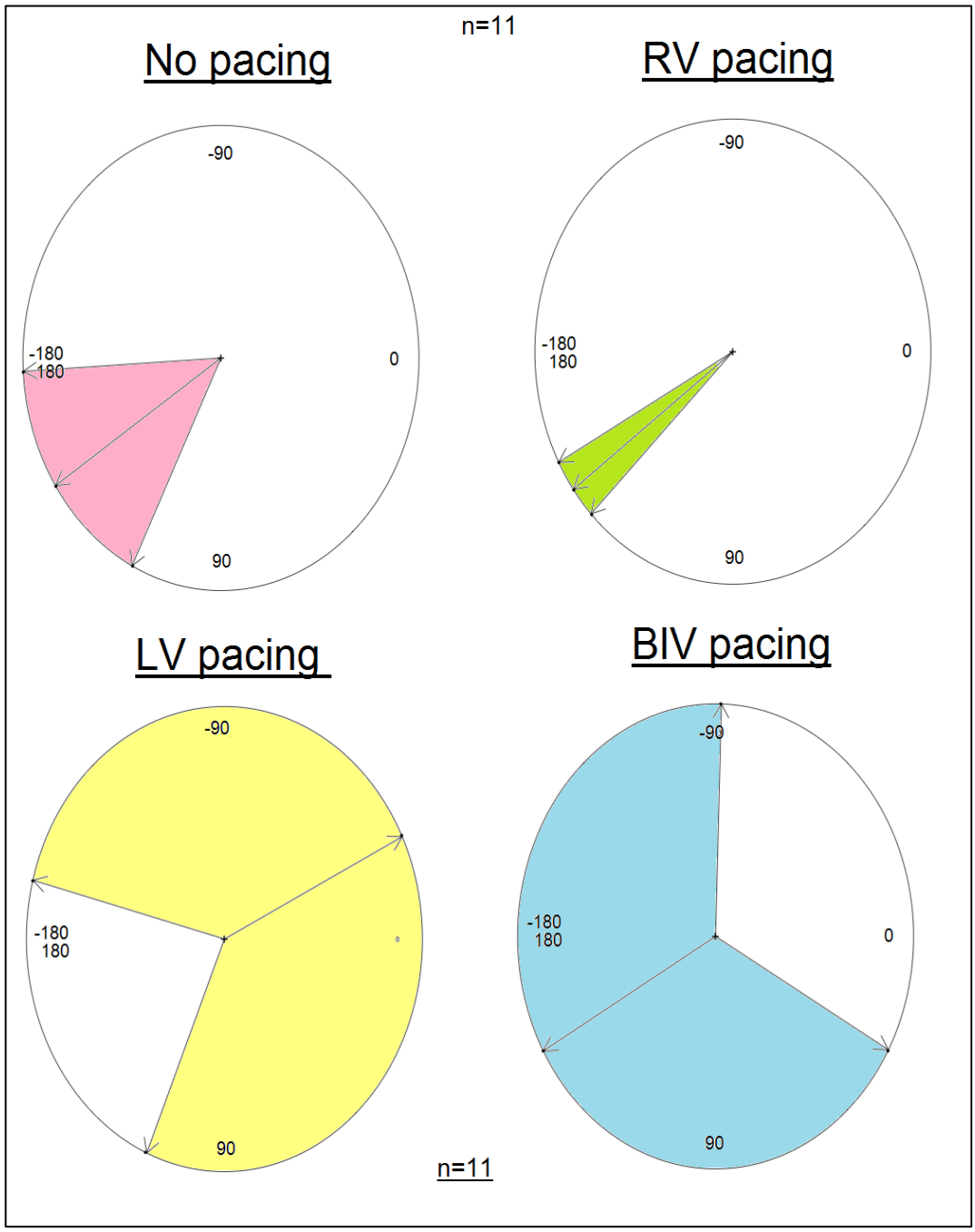

Figure 5.3. - *Graph showing the mean cardiac axis (central arrow) and 95% confidence intervals (peripheral arrows) of study participants for different CRT device settings in the YZ plane. Upper left panel – No pacing; upper right panel – right ventricular (RV) pacing; lower left panel – left ventricular (LV) pacing; lower right panel – biventricular (BIV) pacing.*

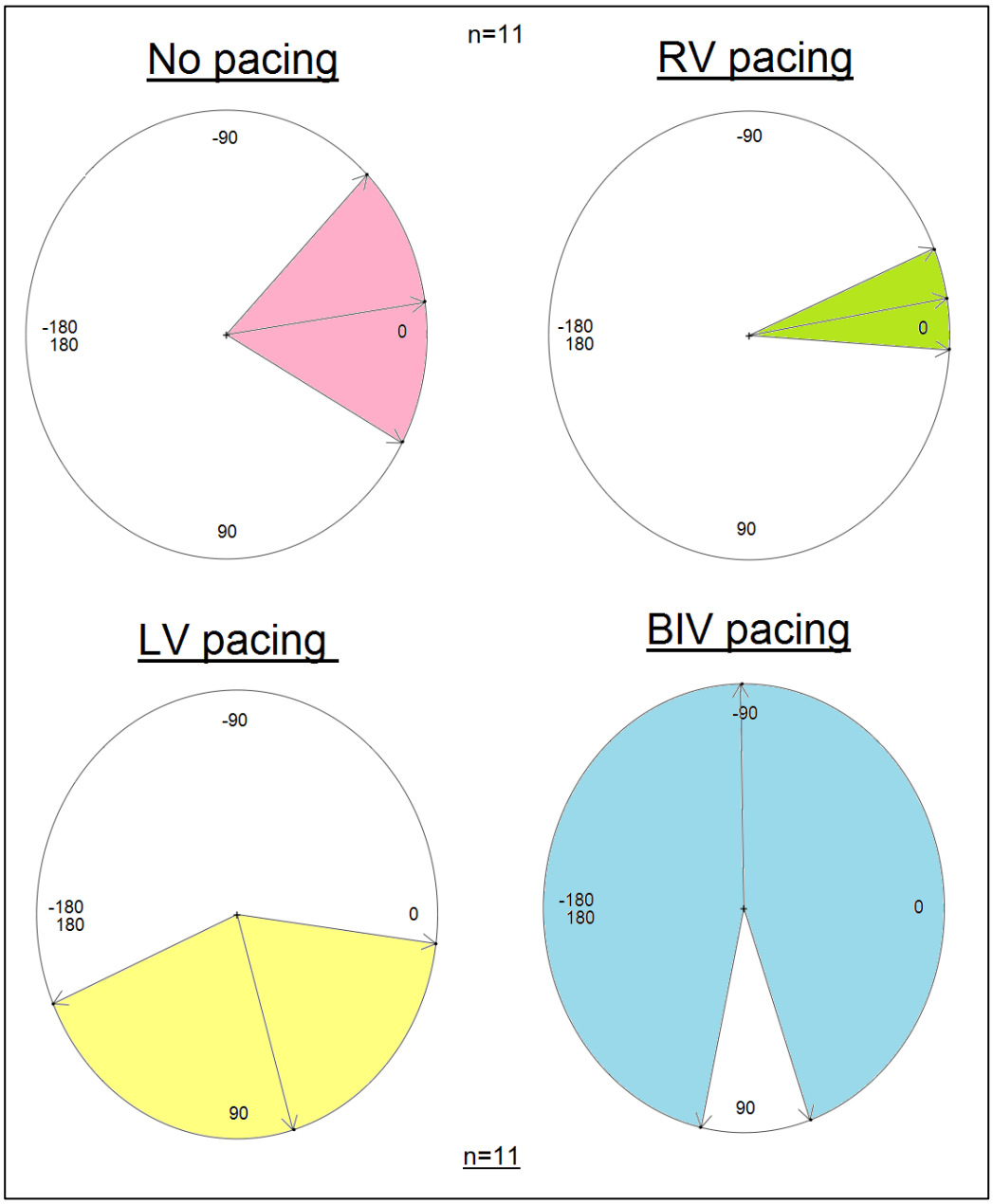

Figure 5.4. – *Graph showing the mean cardiac axis (central arrow) and 95% confidence intervals (peripheral arrows) of study participants for different CRT device settings in the XZ plane. Upper left panel – No pacing; upper right panel – right ventricular (RV) pacing; lower left panel – left ventricular (LV) pacing; lower right panel – biventricular (BIV) pacing.*

5.2.2. *Mean QRS axis: 12 lead ECG plane vs CGM YZ plane*

There was little agreement in the direction of the cardiac axis between the YZ CGM plane and conventional 12-lead plane (see figure 5.5).

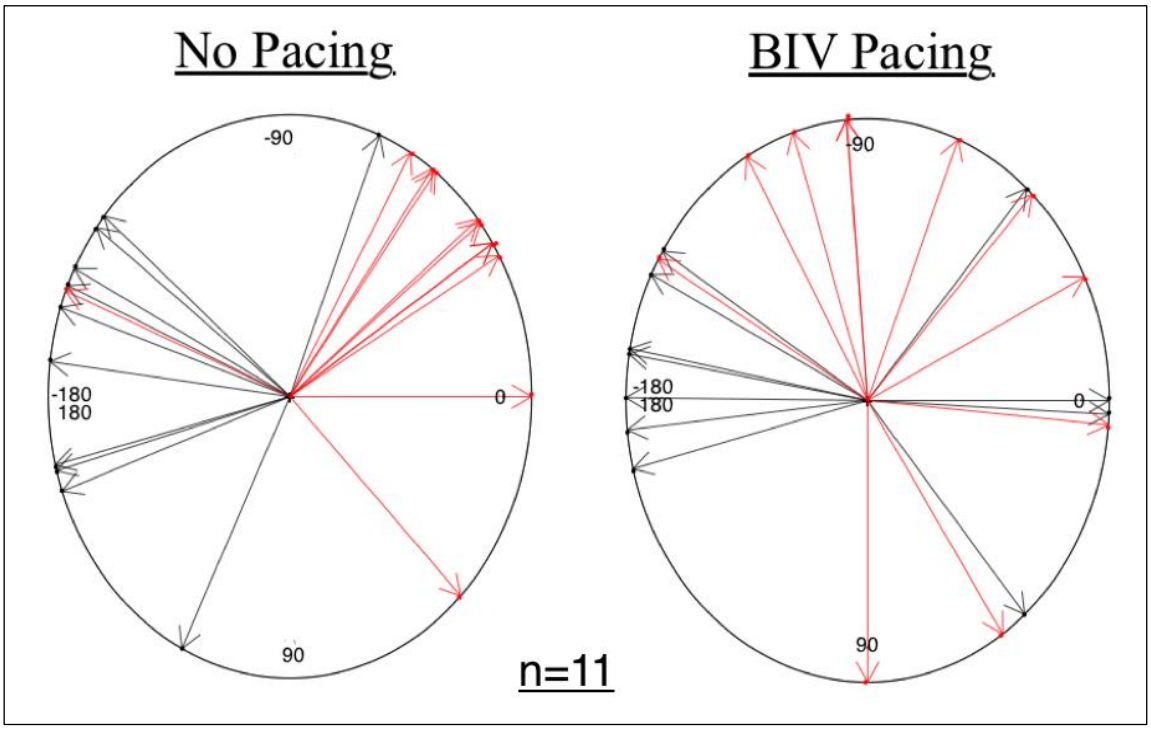

Figure 5.5. – *Circular scatter plot demonstrating individual study participant's cardiac axes. Black arrows represent cardiac axis on CGM YZ plane, red arrows represent cardiac axis on 12 lead ECG frontal plane. Left panel – no pacing. Right panel – biventricular (BIV) pacing.*

5.2.3. *'Optimal' QRS axis vs non-optimal QRS axis morphology.*

Figure 5.6 shows scatter plots for patients with optimal vs non-optimal paced QRS morphology in each CGM plane. There was a marked difference between the two groups in the axis measured in the XY plane, but a large amount of overlap between the two in the other planes.

In the XY and YZ planes, the axis in patients with optimal paced QRS morphology was directed basally.

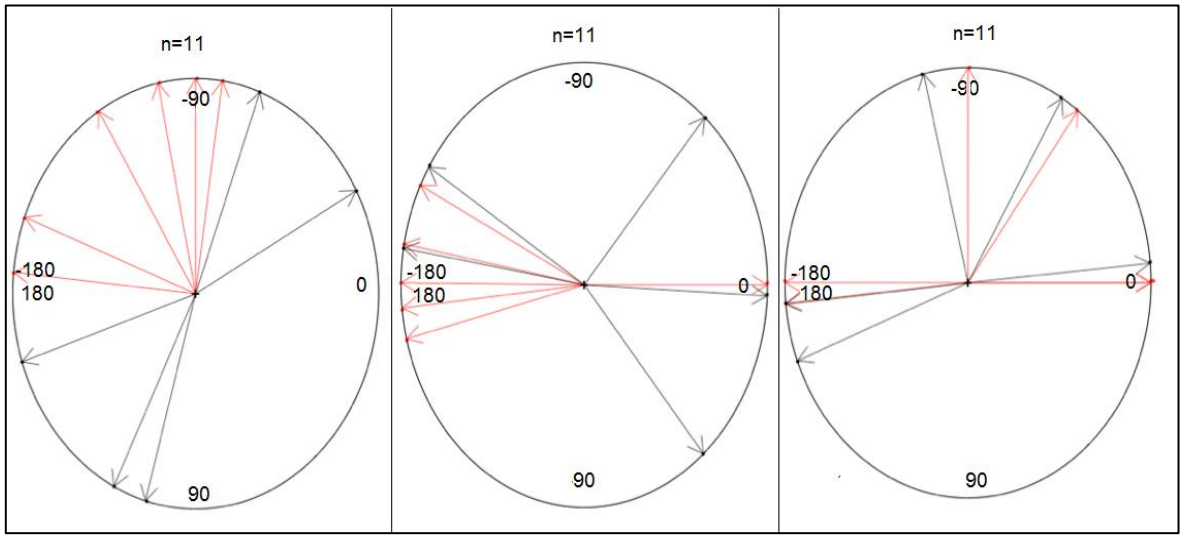

Figure 5.6. – *Circular scatter plots showing the direction of cardiac axis of patients with 'optimal' paced QRS morphology (red arrows) vs 'non-optimal' paced QRS morphology (black arrows). Left panel – cardiac axes in the XY plane, centre panel – cardiac axes in the YZ plane, right panel – cardiac axes in the XZ plane.*

Demographics	
N	11
Male (%)	7 (63.6)
Age (SD), years	77.4 (11.5)
Body mass index (SD)	28.1 (5.9)
NYHA class (I/II/III/IV)	0/4/7/0
Ejection fraction (SD), %	31.0 (6.2)
Native QRS duration (SD), ms	165 (7.3)
Type of device fitted:	
PROTECTA CRT-D	7 (63.6)
ANTHEM RF CRT-P	4 (36.4)
Length of CRT implantation (SD), months	49.8 (18.9)
Past medical history (%)	
Myocardial Infarction	4 (36.4)
Percutaneous coronary intervention	7 (63.6)
Atrial fibrillation	1 (9.1)
Stroke/Transient ischaemic attack	4 (36.4)
Chronic kidney disease	7 (63.6)
Diabetes Mellitus	7 (63.6)
Hypertension	10 (90.9)
Hypercholesterolaemia	7 (63.6)
Smoking (Never/Ex/Current)	4 (36.4) / 6 (54.5) / 1 (9.1)
Chronic obstructive pulmonary disease	2 (18.2)
Asthma	0 (0)
Peripheral artery disease	0 (0)

Table 5.1. – *Table showing the baseline characteristics of study participants in the HF-CGM study. Continuous data is expressed with its mean and standard deviation (SD).*

Medications (%)	
Aspirin	4 (36.4)
Clopidogrel	2 (18.2)
Angiotensin converting enzyme inhibitor	4 (36.4)
Angiotensin receptor blocker	5 (45.5)
β-blocker	7 (63.6)
Mineralocorticoid antagonist	5 (16.7)
Loop diuretic	9 (81.8)
Digoxin	4 (36.4)
Lipid lowering drug	6 (54.5)
Blood results (SD)	
Haemoglobin, g/L	120.0 (10.1)
Sodium, mmol/L	136.0 (4.6)
Potassium, mmol/L	4.6 (0.4)
Chloride, mmol/L	101.8 (6.2)
Urea, mmol/L	25.9 (27.6)
Creatinine, μmol/L	88.7 (27.2)
NT proBNP, ng/L	1028.0 (368.6)

Table 5.1. continued – *Table showing the baseline characteristics of study participants in the HF-CGM study. Continuous data is expressed with its mean and standard deviation (SD).*

Table 5.2. – *Mean direction and 95% confidence intervals of cardiac resynchronisation (CRT) device settings in each cardiogoniometry (CGM) plane.*

	XY plane	YZ plane	XZ plane
No pacing	-23° (95% CI: -35° →11°)	147° (95% CI: 117° →177°)	-8° (95% CI: -45° →29°)
RV pacing	-52° (95% CI: -66° → -40°)	144° (95% CI: 136° →152°)	-10° (95% CI: -23° →4°)
LV pacing	148° (95% CI: 88° → -152°)	-24° (95% CI: -166° →113°)	74° (95% CI: 7° →157°)
BIV pacing	-130° (95% CI: 161° →-62°)	150° (95% CI: 29° →-88°)	-91° (95% CI: 102° →71°)

Table 5.3. – *P values calculated for mean differences for cardiac axis between device settings; no pacing vs RV, LV and BIV pacing for each plane.*

	XY plane	YZ plane	XZ plane
None vs RV	0.06	0.29	0.362
None vs LV	0.005	0.022	0.108
None vs BIV	0.001	0.368	0.062

5.3. **Discussion**

We have found that different CRT device settings lead to differences in CGM recordings, and that the most consistent patterns are seen with recordings in the XY plane. We have also shown that the electrical activity recorded in the YZ plane using CGM is not the same as the mean frontal QRS axis recorded in the frontal plane using the 12-lead ECG as previously thought, even after rotating by 45˚. Finally, we have demonstrated that the XY plane has the ability to identify the direction of electrical activity which is associated with an "optimal" paced QRS morphology.

The XY plane is aligned with the long axis of the heart (see figure 5.7), and we saw a statistically significant difference in the direction of electrical activity between no pacing and all three pacing modes in this plane. RV pacing causes the heart to depolarise from the apex of the RV and therefore depolarisation moves basally. LV pacing by and large causes the heart to depolarise from the LV free wall, and therefore the depolarisation is directed towards the RV. During BIV pacing the direction of electrical activity varies depending on the timing delays and location of the LV and RV leads. Nevertheless, the overall cardiac depolarisation during BIV pacing should be directed basally, due to the origin of electrical activity arising towards the apex of the heart.

The XY plane includes large areas of both RV and LV, which may explain why recordings in this plane were significantly different between each of the pacing modes. Although the YZ plane is aligned to the long axis of the heart to some degree, the section it takes through the heart predominantly contains LV (see figure 5.8). The electrical information represented in the YZ plane is therefore primarily obtained from the LV and therefore it is

a poor representation of biventricular electrical activity. Similarly, although the XZ plane contains similar amounts of both RV and LV, it takes a section through the short axis of the ventricles (figure 5.9). Information contained in the XZ plane therefore does not reflect depolarisation from apex to base, but rather relates to depolarisation from the endocardium to epicardium.

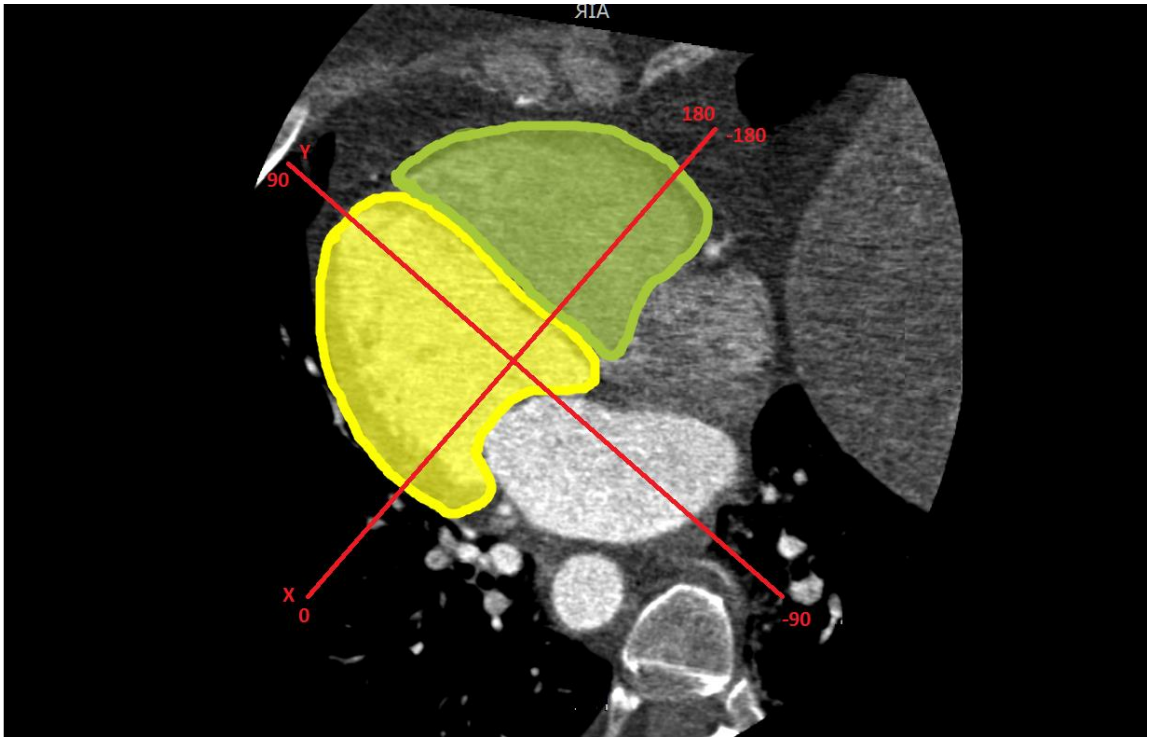

Figure 5.7. – *Cardiac CT section taken in the same plane as the CGM XY plane, demonstrating the orientation of the XY plane in relation to the heart in the thorax. Green shading represents the right ventricle; yellow shading represents the left ventricle. Note that the XY plane takes a long axis view through the heart, and the plane contains similar amounts of both the left ventricle and the right ventricle.*

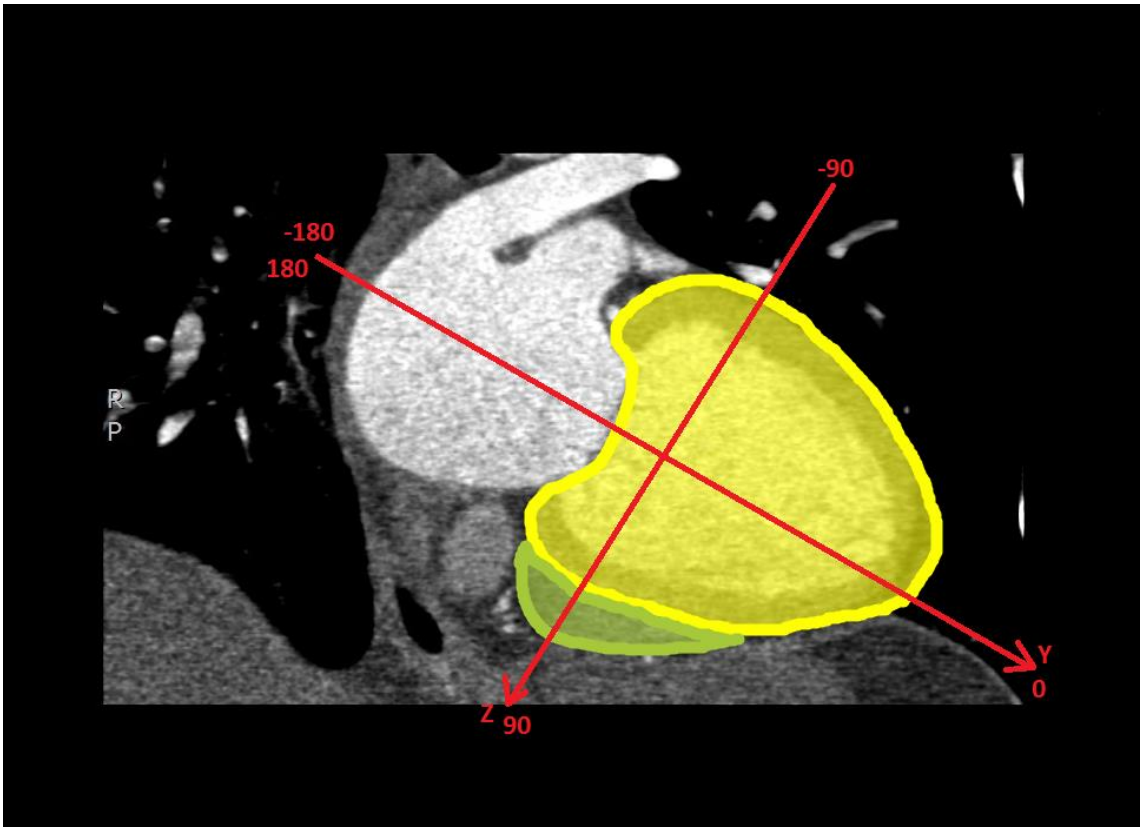

Figure 5.8. – *Cardiac CT section taken in the same plane as the CGM YZ plane, demonstrating the orientation of the YZ plane in relation to the heart in the thorax. Green shading represents the right ventricle; yellow shading represents the left ventricle. Note that the YZ plane takes a long axis view through the heart, but the plane predominately contains the left and not the right ventricle.*

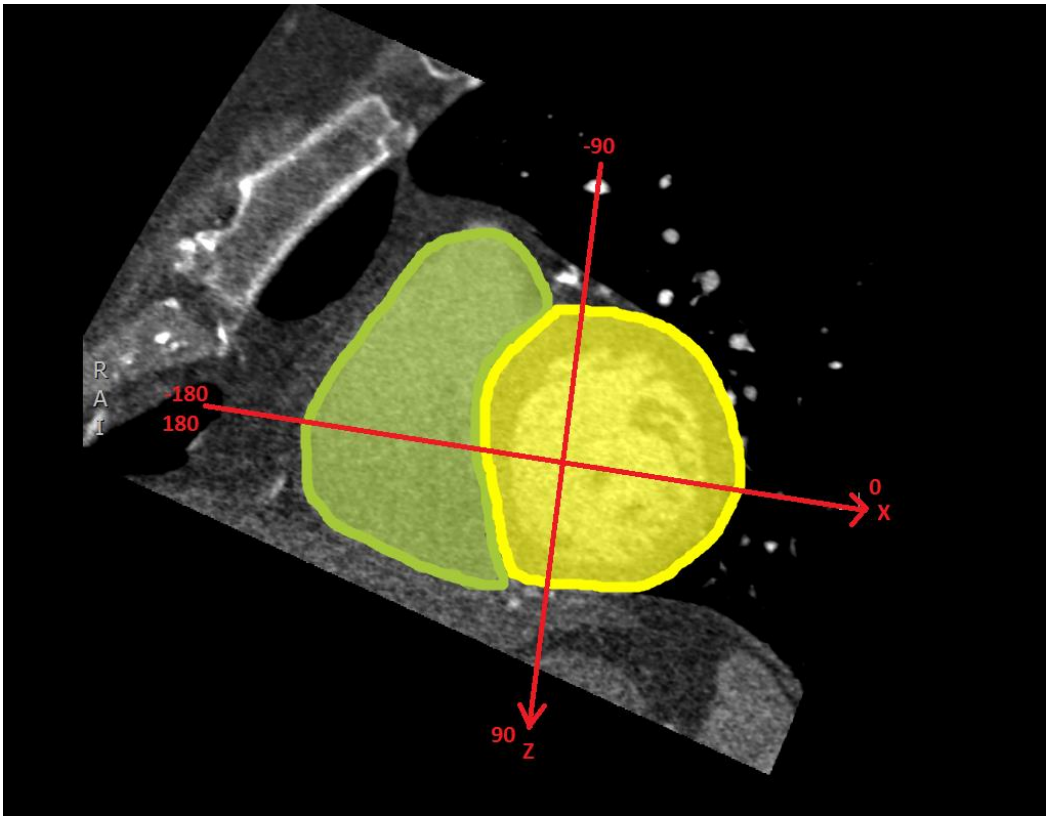

Figure 5.9. – *Cardiac CT section taken in the same plane as the CGM XZ plane, demonstrating the orientation of the XZ plane in relation to the heart in the thorax. Green shading represents the right ventricle; yellow shading represents the left ventricle. Note that the XZ plane takes a short axis view through the heart and the plane contains similar amounts of both the left and right ventricle.*

Depolarisation in the XY plane also better discriminated between "optimal" CRT delivery and sub-optimal. Of course, the definition of "optimal" is to some degree arbitrary and based on analysis of 12 lead electrocardiograms. It might be that CGM provides additional information which may prove more helpful, especially if an 'optimal' range of paced QRS axis can be determined.

The trigonometric construction of the CGM YZ and the frontal ECG planes both take a coronal slice through the heart: and, not surprisingly, previous reports have suggested that the two are equivalent.[3] However, we have demonstrated that the two are not the same. A possible explanation is that the reference points for the CGM and the 12-lead ECG are different. The difference in cardiac axis based on lead placement can be explained by using the example of the 12-lead ECG. In the 12-lead ECG, Wilson's central terminal (WCT) is the central reference point from which the augmented leads (aVR, aVL and aVF) are constructed. The position of WCT itself is determined by the position of the electrodes on the left arm, right arm and left leg, with WCT being calculated using Einthoven's triangle.

Einthoven's triangle assumes that the distance between each pair of electrodes is identical and that leads I, II and III form an equilateral triangle. The limb electrodes are thus normally placed on the wrists and ankles, but potentially small deviations can markedly alter the cardiac axis. For example, if the upper limb electrodes are placed on the shoulders and the lower limb electrodes kept on the ankles, the triangle is then isosceles and the site of WCT changes. The resistance between the electrodes is also altered, as there is now a different amount of body tissue through which the electrical current has to run. By changing the position of WCT, the direction of the augmented leads is altered and thus the cardiac axis will change. The construction of the CGM YZ plane is fundamentally

different: it uses information from an electrode on the back (electrode 2) which does not happen in the 12-lead ECG. Although the YZ plane runs coronally, the plane is fundamentally different from the frontal plane in a 12-lead ECG.

Our method of statistical analysis specific for circular data is novel, and has never been used before in cardiovascular research. There is only a limited amount of work published on its use in other disciplines. Previous work on cardiac axes in CRT has not used statistical methods specific for circular data and thus their findings should be interpreted with caution.[33]

Whether CGM has anything to offer in clinical practice needs to be tested further. Does pacing from different points on a multipolar LV lead alter the CGM readings? One potential study would be to relate CGM findings to clinical response in a larger sample of patients using, say, a 6-minute walk test, a disease-specific quality of life score and left ventricular end systolic volume. Is there a relation between CGM variables and "response"? A randomised study might then explore whether there is any clinical benefit to manipulating pacing sequences based on their effect on CGM variables.

5.3.1. *Study Limitations*

The sample size of the study was small. However, the study was designed as a pilot and the fact we were able to demonstrate statistically significant differences suggests CGM might have something to offer. Cardiac axes for both CGM and ECG were calculated by hand which could bring a degree of human error into our results. Participants had different CRT devices with different atrioventricular and interventricular programmed settings and the devices had been implanted at different time-points.

It might be possible in future to analyse further aspects of the CGM recordings, such as the area within the vector loops for different pacing settings.[59] In addition to this, we only looked at direction of the axis of ventricular depolarisation, and information may be gained from the axes of atrial depolarisation and ventricular repolarisation.

The position of the ventricular pacing wires may also explain the variability of cardiac axes, particularly for the variation in cardiac axes during LV pacing. There can be considerable differences in the location of the LV pacing wires between patients, depending on each individual's coronary venous anatomy.

5.3.2. *Conclusion*

CGM can detect differences between ventricular pacing sites. It is able to identify patients with a paced QRS morphology associated with improvement in clinical endpoints. CGM should further be evaluated to explore whether CGM-derived axes might help guide CRT lead placement and pacing timing intervals to improve patient outcomes.

Chapter 6

Summary and future directions

Chapter 6 – Summary and future directions

6.1. **Summary of results**

6.1.1. *CGM in coronary artery disease*.

The scope of this thesis was to evaluate the diagnostic performance of CGM at identifying patients with physiologically significant stable CAD. In addition to this, we wished to evaluate the ability of CGM to identify the culprit lesion in patients with NSTEMI.

We have demonstrated that the diagnostic performance of CGM to identify physiologically significant stable CAD at rest is poor. When 'stress' CGM is performed using an intravenous adenosine infusion, the sensitivity of CGM significantly increases by almost 40%. However, it does not reach a level of sufficient sensitivity to be used in routine clinical practice. We believe our work represents the most robust evidence about the true ability of CGM to identify patients with physiologically significant CAD as it is the only study using a robust method to quantify physiological significance.

Our work in patients with NSTEMI, is the first study to formally assess the diagnostic performance of CGM at identifying the site of the culprit lesion. We have demonstrated that CGM is more frequently positive than a 12-lead ECG in patients with NSTEMI. In addition to this, we demonstrated that although CGM is superior to the 12-lead ECG in terms of diagnostic performance, it is only able to provide ischaemia localising information in a similar proportion of patients to that of the 12-lead ECG.

6.1.1.1. *Limitations and future directions.*

The main limitation of the CARDIOFLOW study is that the study population was not a true reflection of the general population. The reason for this being, that it was a requirement that the coronary anatomy of study participants was known prior to enrolment as only patients with single vessel disease were included. If the inclusion criteria were expanded to include all patients who were referred for coronary angiography regardless of their coronary anatomy, it would increase the external validity of the study. Patients referred for coronary angiography could have both a rest and stress CGM performed at their pre-assessment appointment. Following this, when the patients underwent coronary angiography, FFR would be performed on any vessels demonstrating a visible coronary stenosis. The results of CGM and angiography +/- FFR would then be compared to calculate the diagnostic performance of CGM.

As previously discussed, the gold standard measure used in the COGNITION study may not have accurately identified the culprit lesion site in all participants. This could have been overcome by using a more robust method to classify the lesion site such as OCT. By using OCT as the gold standard measure, it would give greater certainty as to whether the identify of the culprit lesion suggested by coronary angiography was truly the culprit, especially in those patients with multi-vessel disease. This would increase the internal validity of our results and give us more confidence as to whether our results were a true reflection of the diagnostic performance of CGM to identify the culprit lesion.

6.1.2. *CGM in cardiac resynchronisation therapy.*

Our work investigating the role that CGM may have in the optimisation of CRT therapy in patients with heart failure is completely novel. With a sample size of only eleven patients we were able to demonstrate the CGM has the ability to distinguish different pacing modes to a degree of statistical significance. Further still, our work has suggested that CGM is able to identify patients with a QRS morphology which has been previously been shown to predict response to CRT therapy. We believe that the preliminary work we have performed gives us a strong indication that there could be a possible role for the use of CGM in patients with CRT therapy, which could lead to an improvement in patient outcomes.

6.1.2.1. *Limitations and future directions.*

The main limitation in the HF-CGM study was that data extraction from the CGM traces was performed by hand as it was unable to be done electronically. If this problem could be overcome, it would alleviate the risk of human error in our analysis and mean additional CGM variables could be analysed (such as QRS area or P and T wave axis).

Future study design evaluating the role CGM may have in the optimisation of CRT therapy in heart failure patients has been addressed in the previous chapter. In summary, it would involve trying to correlate CGM findings to clinical outcomes in a larger cohort of patients. A final study could then be performed where patients were randomised to receive CRT optimisation by CGM methods vs conventional methods to see if there was a difference in patient outcomes.

References

1. Burch GE. The history of vectorcardiography. *Med Hist Suppl*. 1985; **5**:103–31.

2. Simonson E, Tuna N, Okamoto N, Toshima H. Diagnostic accuracy of the Vectorcardiogram and the Electrocardiogram - a cooperative study. *Am J Cardiol*. 1966; **17**: 829–878.

3. Sanz E, Steger JP, Thie W. Cardiogoniometry. *Clin Cardiol*. 1983; **6**:199–206.

4. Saner H, Baur HR, Sanz E, Gurtner HP. Cardiogoniometry: a new noninvasive method for detection of ischemic heart disease. *Clin Cardiol*. 1983; **6**: 207–210.

5. Huebner T, Schuepbach WMM, Seeck A, Sanz E, Meier B, Voss A, Pilgram R. Cardiogoniometric parameters for detection of coronary artery disease at rest as a function of stenosis localization and distribution. *Med Biol Eng Comput*. 2010; **48**: 435–446.

6. Schüpbach WMM, Emese B, Loretan P, Mallet A, Duru F, Sanz E, Meier B. Non-invasive diagnosis of coronary artery disease using cardiogoniometry performed at rest. *Swiss Med Wkly*. 2008; 138: 230–238.

7. Tölg R, Zeymer U, Birkemeyer R, Wessely R, Eggebrecht H, Bocksch W, Schneider S, Richardt G, Hamm C. Cardiogoniometry as a diagnostic tool in patients with acute coronary syndromes: results of the CGM@ACS trial. *Clin Res Cardiol.* 2012; **101**: 727–736.

8. National Institute for Health and Clinical Excellence (2012). Managing stable angina. NICE guidelines (CG126).

9. Hamm CW, Bassand J-P, Agewall S, Bax J, Boersma E, Bueno H, Caso P, Dudek D, Gielen S, Huber K, Ohman M, Petrie MC, Sonntag F, Uva MS, Storey RF, Wijns W, Zahger D, et al. ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: The Task Force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevatio. *Eur Heart J*. 2011; **32**: 2999–3054.

10. Keller T, Zeller T, Peetz D, Tzikas S, Roth A, Czyz E, Bickel C, Baldus S, Warnholtz A, Frohlich M, Sinning C, Eleftheriadis MS, Wild PS, Schnabel RB, Lubos E, Jachmann N, Genth-Zotz S, Post F, Nicaud V, et al. Sensitive troponin I assay in early diagnosis of acute myocardial infarction. *N Eng J Med*. 2009; **361**: 868–877.

11. Mills NL, Churchhouse AMD, Lee KK, Anand A, Gamble D, Shah AS, Paterson E, MacLeod M, Graham C, Walker S, Fox KAA, Newby DE. Implementation of a sensitive troponin I assay and risk of recurrent myocardial infarction and death in patients with suspected acute coronary syndrome. *JAMA*. 2011; **305**:1210–1216.

12. Tonino PAL, De Bruyne B, Pijls NHJ, Siebert U, Ikeno F, van 't Veer V. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. *N Eng J Med.* 2009; **360**: 213–224.

13. Pijls NH, van Son JA, Kirkeeide RL, De Bruyne B, Gould KL. Experimental basis of determining maximum coronary, myocardial, and collateral blood flow by pressure measurements for assessing functional stenosis severity before and after percutaneous transluminal coronary angioplasty. *Circulation*. 1993; **87**:1354–1367.

14. Pijls NHJ, De Bruyne B, Peels K, van der Voort PH, Bonnier HJRM, Bartunek J, Koolen J. Measurement of fractional flow reserve to assess the functional severity of coronary-artery stenoses. *N Eng J Med*. 1996; **334**: 1703–1708.

15. MacIssac H, Knudtson M, Robinson V, Manyari D. Is the residual translesional pressure gradient useful to predict regional myocardial perfusion after percutaneous transluminal coronary angioplasty? *Am J Cardiol*. 1989; **117**: 783–790.

16. Rothman M, Baim D, Simpson J, Harrison D. Coronary haemodynamics during PCTA. *Am J Cardiol*. 1982; **39**:1615–1622.

17. Serruys PW, Reiber JH, Wijns W, van den Brand M, Kooijman CJ, ten Katen HJ, Hugenholtz PG. Assessment of percutaneous transluminal coronary angioplasty by quantitative coronary angiography: diameter versus densitometric area measurements. *Am J Cardiol*. 1984; **54**: 482–488.

18. Pijls NHJ, Fearon WF, Tonino PAL, Siebert U, Ikeno F, Bornschein B, van't Veer M, Klauss V, Manoharan G, Engstrom T, Oldroyd KG, Ver Lee PN, Maccarthy PA, de Bruyne B. Fractional flow reserve versus angiography for guiding patients with

multivessel coronary artery disease. *J Am Coll Cardiol*. 2010; **56**:177–184.

19. van Nunen LX, Zimmermann FM, Tonino PAL, Barbato E, Baumbach A, Engstrom T, Klauss V, Maccarthy PA, Manoharan G, Oldroyd KG, Ver Lee PN, van't Veer M, Fearon WF, De Bruyne B, Pijls NHJ. Fractional flow reserve versus angiography for guidance of PCI in patients with multivessel coronary artery disease (FAME): 5-year follow up of a randomised controlled trial. *Lancet*. 2015; **386**: 1853-1860.

20. Windecker S, Kolh P, Alfonso F, Collet JP, Cremer J, Falk V, Filippatos G, Hamm C, Head SJ, Juni P, Kappetein AP, Kastrati A, Knuuti J, Landmesser U, Laufer G, Neumann FJ, Richter DJ, Schauerte P, Uva MS, Stefanini GG, Taggart DP, Torracca L, Valgimigli M, Wijns W, Witkoswki A. 2014 ESC/EACTS Guidelines on myocardial revascularization. *Eur Heart J*. 2014; **35**: 2541–619.

21. Fearon WF, Shilane D, Pijls NHJ, Boothroyd DB, Tonino PAL, Barbato E, Juni P, De Bruyne B, Hlatky MA. Cost-effectiveness of percutaneous coronary intervention in patients with stable coronary artery disease and abnormal fractional flow reserve. *Circulation*. 2013; **128**:1335–1340.

22. Siebert U, Arvandi M, M. Gothe R, Bornschein B, Eccleston D, L. Walters D, Rankin J, De Bruyne B, F. Fearon W, H. Pijls N, Harper R. Improving the Quality of Percutaneous Revascularisation in Patients with Multivessel Disease in Australia: Cost-Effectiveness, Public Health Implications, and Budget Impact of FFR-Guided PCI. Hear Lung Circ. Australian and New Zealand Society of Cardiac and Thoracic Surgeons (ANZSCTS) and the Cardiac Society of Australia and New Zealand (CSANZ); 2014; **23**:527–533.

23. Tonino PAL, Fearon WF, De Bruyne B, Oldroyd KG, Leesar MA, Ver Lee PN, MacCarthy PA, van't Veer M, Pijls NHJ. Angiographic Versus Functional Severity of Coronary Artery Stenoses in the FAME Study. Fractional Flow Reserve Versus Angiography in Multivessel Evaluation. *J Am Coll Cardiol*. 2010; 55: 2816–2821.

24. Lotfi A, Jeremias A, Fearon WF, Feldman MD, Mehran R, Messenger JC, Grines CL, Deans LS, Kern MJ, Klein LW. Expert consensus statement on the use of fractional flow reserve, intravascular ultrasound, and optical coherence tomography. *Catheter Cardiovasc Interv*. 2014; **83**: 509-518.

25. Curzen N, Rana O, Nicholas Z, Golledge P, Zaman A, Oldroyd K, Hanratty C, Banning A, Wheatcroft S, Hobson A, Chitkara K, Hildick-Smith D, McKenzie D, Calver A, Dmitrov BD, Corbett S. Does routine pressure wire assessment influence management strategy at coronary angiography for diagnosis of chest pain? Circ Cardiovasc Interv. 2014; **7**: 248–255.

26. Chesebro JH, Knatterud G, Roberts R, Borer J, Cohen LS, Dalen J, Dodge HT, Francis CK, Hillis D, Ludbrook P. Thrombolysis in Myocardial Infarction (TIMI) Trial, Phase I: A comparison between intravenous tissue plasminogen activator and intravenous streptokinase. Clinical findings through hospital discharge. *Circulation*. 1987; **76**: 142–54.

27. Cleland JGF, Daubert JC, Erdmann E, Freemantle N, Gras D, Kappenberger L, Tavazzi L. The Effect of Cardiac Resynchronization on Morbidity and Mortality in Heart Failure. *N Eng J Med.* 2005; **352**: 1539–49.

28. Auricchio A, Prinzen FW. Non-Responders to Cardiac Resynchronization Therapy. *Circ J.* 2011; **75**: 521–527.

29. Singh JP, Klein HU, Huang DT, Reek S, Kuniss M, Quesada A, Barsheshet A, Cannom D, Goldenberg I, McNitt S, Daubert JP, Zareba W, Moss AJ. Left ventricular lead position and clinical outcome in the multicenter automatic defibrillator implantation trial-cardiac resynchronization therapy (MADIT-CRT) trial. *Circulation*. 2011; **123**:1159–1166.

30. Cuoco FA, Gold MR. Optimization of cardiac resynchronization therapy: Importance of programmed parameters. *J Cardiovasc Electrophysiol*. 2012; **23**:110–118.

31. Tamborero D, Vidal B, Tolosana JM, Sitges M, Berruezo A, Silva E, Castel M, Matas M, Arbelo E, Rios J, Villacastín J, Brugada J, Mont L. Electrocardiographic versus echocardiographic optimization of the interventricular pacing delay in patients undergoing cardiac resynchronization therapy. *J Cardiovasc Electrophysiol*. 201; **22**:1129–1134.

32. Bode WD, Bode MF, Gettes L, Jensen BC, Mounsey JP, Chung EH. Prominent R wave in ECG lead V1 predicts improvement of left ventricular ejection fraction after cardiac resynchronisation therapy in patients with or without left bundle branch

block. *Heart Rhythm*. 2015; **12**: 2141–2147.

33. van Deursen C, Strik M, Rademakers L, van Hunnik A, Kuiper M, Wecke L, Crijns H, Vernooy K, Prinzen FW. Vectorcardiography as a tool for easy optimization of cardiac resynchronization therapy in canine left bundle branch block hearts. Circ Arrhythm Electrophysiol. 2012; **5**: 544–552.

34. Mafi Rad M, Wijntjens GWM, Engels EB, Blaauw Y, Luermans JGLM, Pison L, Crijns HJ, Prinzen FW, Vernooy K. Vectorcardiographic QRS area identifies delayed left ventricular lateral wall activation determined by electroanatomic mapping in candidates for cardiac resynchronization therapy. *Heart Rhythm*. 2016; 13: 217-225.

35. Carletta J. Assessing Agreement on Classification Tasks: The Kappa Statistic. *Computational linguistics.* 1993; **22**: 249-254.

36. Landis J, Koch G. The measurement of observer agreement for categorical data. *Biometrics*. 1977; **33**:159–174.

37. Whiting PF, Rutjes AW, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, Leeflang MM, Sterne JA, Bossuyt PM. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. *Ann Intern Med.* 2011; **155**: 529–536.

38. Tolg R. Early diagnosis of heart infarction: Cardiogoniometry - An alternative to ECG? *Dtsch Apotheker Zeitung*. 2011; **151**:80–83.

39. Huebner T, Goernig M, Schuepbach M, Sanz E, Pilgram R, Seeck A, Voss A. Electrocardiologic and related methods of non-invasive detection and risk stratification in myocardial ischemia: state of the art and perspectives. *Ger Med Sci*. 2010; **8**: 1–19.

40. Spiliopoulos S, Wald C, Hergesell V, Dimitriou AM, Koerfer R, Tenderich G. Diagnosis of obstructive coronary artery disease by cardiogoniometry: A field test in a real-life setting. *J Electrocardiol*. 2015; **48**: 420–422.

41. Tölg R, Wölken M, Schneider S, Boksch W, Wessely R, Birkemeyer R, Eggebrecht H, Zeymer U, Richardt G, Hamm CW. Early discrimination of non-ST-segment elevation acute coronary syndromes (NSTE-ACS) by cardiogoniometry - results of the CGM @ ACS trial. In: European Society of Cardiology Annual Congress 2010; 25-29 August 2010; Munich, Germany: European Society of Cardiology. P1687.

42. Herrmann H, Meier A. Does the cardiogoniogram change following revascularisation? *Schweiz Med Wochenschr*. 1988; **118**: 1609–1611.

43. Vontobel H, Schmidd J, Steinbrunn W. The Sanz method of cardiogoniometry. *Schweiz Med Wochenschr*. 1988; **118**: 1603–8.

44. Sanz E, Kinser J. Cardiogoniometry as a method for the diagnosis of coronary disease. Comparison with myocardial scintigraphy. *Schweiz Rundsch Med Prax*. 1984; **73**: 1169–1173.

45. Meier A, Höflin F, Herrmann HJ, Wolf C, Gurtner HP, Rösler H. Comparative diagnostic value of a new computerized vectorcardiographic method (cardiogoniometry) and other noninvasive tests in medically treated patients with chest pain. *Clin Cardiol.* 1987; **10**: 311–316.

46. Birkemeyer R, Toelg R, Zeymer U, Wessely R, Jäckle S, Hairedini B, Lübke M, Aßfalg M, Jung W. Comparison of cardiogoniometry and electrocardiography with perfusion cardiac magnetic resonance imaging and late gadolinium enhancement. Europace. 2012; **14**: 1793–1798.

47. Ghadrdoost B, Haghjoo M, Firouzi A. Accuracy of Cardiogoniometry Compared With Electrocardiography in the Diagnosis of Coronary Artery Disease. *Res Cardiovasc Med*. 2015; **4**:1–5.

48. Vontobel H, Tartini R, Steinbrunn W. Kardiogoniometrie, bei koronarerHerzkrankheitf. *Schweiz Med Wochenschr.* 1988; **44**: 1609–1611.

49. Spiliopoulos S, Krueger U, Hergesell V, Tenderich M, Dogan G, Guersoy D, Koerfer R, Tenderich G. Cardiogoniometry: A potential non-invasive screening tool for the diagnosis of cardiac allograft vasculopathy in heart transplant patients. In: Annual Congress of the German Transplant Association; 24-26 October 2013, Frankfurt, Germany: German Transplant Assocation.

50. Seeck A, Huebner T, Schuepbach M, Sanz E, Voss A. Nichtinvasive Diagnostik der koronaren Herzerkrankung mittels Kardiogoniometrie. In: 41st DGBMT Annual Meeting, Proceedings BMT 2007. Biomed Tech 2007; **52**(suppl): 47439.

51. Seeck A, Garde A, Schuepbach M, Giraldo B, Sanz E, Huebner T, Caminal P, Voss A. Diagnosis of Ischemic Heart Disease with Cardiogoniometry - Linear discriminant analysis versus Support Vector analysis. In: Vander Sloten J, Verdonck P, Marc Nyssen M, Haueisen J (eds). 4th European Conference of the International Federation for Medical and Biological Engineering 2008. IFMBE Proc. Berlin, Heidelberg: Springer; 2009.

52. Huebner T, Pilgram R, Schuepbach M, Sanz E, Seeck A, Voss A. Suitability of spatial orientation of the electrocardiologic T-loop for detecting coronary artery disease at rest. In: Biomed Tech Conference, 5-8th October 2010. The German Society for Biomedical Engineering. Rostock, Germany; 2010.

53. Birkemeyer R, Jackle S, Hajredini B, Lubke M, Tolg R, Wolken M, Wessely R, Zeymer U, Jung W. Direct comparison of cardiogoniometry with perfusion cardiac magnetic resonance and late gadolinium enhancement. Clin Res Cardiol. 2010; 100 (suppl 1).

54. Weber S, Birkemeyer R, Schultes D, Grewenig W, Huebner T. Comparison of Cardiogoniometry and ECG at Rest versus Myocardial Perfusion Scintigraphy. *Ann Noninvasive Electrocardiol*. 2014; **19**: 462–470.

55. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, Katus H a, Apple FS, Lindahl B, Morrow D a, Chaitman B a, Clemmensen PM, Johanson P, Hod H, Underwood R, Bax JJ, Bonow RO, Pinto F, Gibbons RJ, et al. Third universal definition of myocardial infarction. *Eur Heart J*. 2012; **33**: 2551–2567.

56. Schreck D, Fishberg R. Diagnostic Accuracy of New Cardiac Electrical Biomarker for Detection of Electrocardiogram Changes Suggestive of Acute Myocardial Ischemic Injury. *Ann Noninvasive Electrocardiol*. 2014; **19**:129–144.

57. Neumann JT, Sörensen NA, Schwemer T, Ojeda F, Bourry R, Schäfer S, Waldeyer C, Sinning C, Renné T, Than M, Wildi K, Makarova N, Schnabel RB, Landmesser U, Mueller C, Greenslade J, Zeller T, Blankenberg S, Karakas M, et al. Accurate and Rapid Diagnosis of Myocardial Infarction Using a High-Sensitivity Troponin I 1-Hour Algorithm. In: European Society of Cardiology Annual Congress 2015; 29 August - 02 September 2015; London, United Kingdom: European Society of Cardiology.

58. Reichlin T, Schindler C, Drexler B, Twerenbold R, Reiter M, Zellweger C, Moehring B, Ziller R, Hoeller R, Rubini Gimenez M, Haaf P, Potocki M, Wildi K, Balmelli C, Freese M, Stelzig C, Freidank H, Osswald S, Mueller C. One-Hour Rule-Out and Rule-In of Acute Myocardial Infarction Using High-Sensitivity Cardiac Troponin T. *Arch Intern Med*. 2012; **172**:1211–1218.

59. Van Deursen CJM, Vernooy K, Dudink E, Bergfeldt L, Crijns HJGM, Prinzen FW, Wecke L. Vectorcardiographic QRS area as a novel predictor of response to cardiac resynchronization therapy. *J Electrocardiol*. 2015; **48**: 45–52.

60. Kornreich F, Montague T, Rautaharju P. Body surface potential mapping of ST segment changes in acute myocardial infarction. *Circulation*. 1993; **87**: 773–782.

61. Kornreich F, Rautaharju P, Warren J, Montague T, Horacek B. Identification of best electrocardiographic leads for diagnosing myocardial infarction by statistical analysis of body surface potential maps. *Am J Cardiol*. 1985; **56**: 852–856.

62. Zalenski R, Rydman R, Sloan E, Hahn K, Cooke D, Fagan J, Fligner D, Hessions W, Justis D, Kampe L, Shah S, Tucker J, Zwicke D. Value of posterior and right ventricular leads in comparison to the standard 12-lead electrocardiogram in evaluation of ST-segment elevation in suspected acute myocardial infarction. *Am J Cardiol*. 1997; **79**: 1579–1585.

63. National Institute for Health and Clinical Excellence (2010). Unstable angina and NSTEMI: early management. NICE guidelines (CG94).

64. National Institute for Health and Clinical Excellence (2014). Acute coronary syndromes in adults. NICE Quality Standard (QS68).

65. Banerjee A, Newman DR, Van Den Bruel A, Heneghan C. Diagnostic accuracy of exercise stress testing for coronary artery disease: A systematic review and meta-analysis of prospective studies. *Int J Clin Pract*. 2012; **66**:477–492.

66. Geleijnse ML, Fioretti PM, Roelandt JRTC. Methodology, Feasibility, Safety and Diagnostic Accuracy of Dobutamine Stress Echocardiography. *JACC*. 1997; **30**: 595–606.

67. Salerno M, Beller GA. Noninvasive Assessment of Myocardial Perfusion. *Circ Cardiovasc Imaging*. 2009; **2**: 412–424.

68. Melikian N, De Bondt P, Tonino PAL, De Winter O, Wyffels E, Bartunek J, Heyndrickx GR, Fearon WF, Pijls NHJ, Wijns W, De Bruyne B. Fractional flow reserve and myocardial perfusion imaging in patients with angiographic multivessel coronary artery disease. *JACC Cardiovasc Interv.* 2010; **3**: 307–314.

69. Kamiya K, Sakakibara M, Asakawa N, Yamada SS, Yoshitani T, Iwano H, Komatsu H, Naya M, Chiba S, Yamada SS, Manabe O, Kikuchi Y, Oyama-Manabe N, Oba K, Tsutsui H. Cardiac Magnetic Resonance Performs Better in the Detection of Functionally Significant Coronary Artery Stenosis Compared to Single-Photon Emission Computed Tomography and Dobutamine Stress Echocardiography. *Circ J.* 2014; **78**: 2468–2476.

70. Casey C, Faxon DP. Multi-vessel coronary disease and percutaneous coronary intervention. *Heart*. 2004; **90**: 341–346.

71. Abbott B, Afshar M, Berger A, Wackers F. Prognostic significance of ischemic electrocardiographic changes during adenosine infusion in patients with normal myocardial perfusion imaging. *J Nucl Cardiol*. 2003;**10**: 9–16.

72. Botvinick EH. Current Methods of Pharmacologic Stress Testing and the Potential Advantages of New Agents. *J Nucl Med Technol.* 2009; **37**: 14-25..

73. Gross G, Warltier D. Coronary steal in four models of single or multiple vessel obstruction in dogs. *Am J Cardiol*. 1981; **48**: 84–91.

74. Spodick DH, Frisella M, Apiyassawat S. QRS Axis Validation in Clinical Electrocardiography. *Am J Cardiol.* 2008; 101: 268–269.

75. Zar J. 27. Circular Distributions: Hypothesis Testing. In: Biostatistical analysis 5th edition. Upper Saddle River, New Jersey, USA: Prentice-Hall Inc; 2010. p. 665-713.

Appendices

Appendix 1 – General appendix

Appendix 1.1 – Showing methodology of calculating sensitivity, specificity, positive predictive value and negative predictive value

	Test positive	**Test negative**
Disease positive	True positive	False negative
Disease negative	False positive	True negative

Sensitivity = True positive / (True positive + false negative) * 100

Specificity = True negative / (True negative + false positive) * 100

Positive predictive value = True positive / (True positive + false positive) * 100

Negative predictive value = True negative / (True negative + false negative) * 100

Appendix 2 - COGNITION study

Appendix 2.1. Inclusion/exclusion criteria for the COGNITION study.

Inclusion Criteria	Exclusion criteria

• Patients admitted with NSTEMI defined in accordance with the ESC guidelines [9].
• Patients who have been consented to undergo coronary angiography +/- PCI as part of their routine care by their clinician.
• Aged 18 or over.
• The patient has been informed of the nature of the study and has provided full written informed consent.
	• Patients unable to give informed consent including those with communication difficulties due to poor English.
	• Patients with on-going chest pain at rest despite medical therapy
	• Patients with haemodynamic instability and / or cardiogenic shock (defined as a sustained blood pressure of <90mmHg +/- the need for inotropic support)
	• Patients with STEMI
	• Those unable to perform a good quality CGM
	  ○ Patients who are SOB at rest
	  ○ Patients with very frequent ectopic beats
	  ○ Patients in atrial fibrillation
	  ○ Patients with a heart rate >150 beats/min
	  ○ Patients with a permanent pacemaker implanted
	• Patients with previous coronary artery bypass graft surgery
	• Patients who are unable to receive treatment with heparin
	• Patients with significant renal impairment (defined as eGFR<30ml/min)
	• Females who are or could be pregnant

Appendix 2.2. Tables showing the diagnostic performance of CGM to detect NSTEMI: a) total population, b) single vessel disease and c) multi-vessel disease.

a)

	CGM positive	CGM negative	
NSTEMI positive	19	7	26

b)

	CGM positive	CGM negative	
NSTEMI positive	4	3	7

c)

	CGM positive	CGM negative	
NSTEMI positive	15	4	19

Appendix 2.3. Showing the 2x2 tables showing the diagnostic performance of the 12-lead ECG to detect NSTEMI: a) total population, b) single vessel disease and c) multi-vessel disease.

a)

	ECG positive	ECG negative	
NSTEMI positive	15	11	26

b)

	ECG positive	ECG negative	
NSTEMI positive	2	5	7

c)

	ECG positive	ECG negative	
NSTEMI positive	13	6	19

Appendix 2.4. Showing the 2x2 tables used to calculate the diagnostic performance of CGM at detecting the culprit lesion in patients with NSTEMI:

1) Culprit lesion located in the LAD

	LAD	Not LAD	
CGM positive	7	1	8
CGM negative	4	14	18
	11	15	26

2) Culprit lesion located in the RCA

	RCA	Not RCA	
CGM positive	3	0	3
CGM negative	4	19	23
	7	19	26

3) Culprit lesion located in the LCx

	LCx	Not LCx	
CGM positive	3	1	4
CGM negative	4	18	22
	7	19	26

Appendix 2.5. Showing the 2x2 tables used to calculate the diagnostic performance of the 12-lead ECG at detecting the culprit lesion in patients with NSTEMI:

1) Culprit lesion located in the LAD

	LAD	Not LAD	
ECG positive	4	1	8
ECG negative	7	14	18
	11	15	26

2) Culprit lesion located in the RCA

	RCA	Not RCA	
ECG positive	4	0	4
ECG negative	3	19	22
	7	19	26

3) Culprit lesion located in the LCx

	LCx	Not LCx	
ECG positive	2	4	6
ECG negative	4	16	20
	6	20	26

Appendix 3 – CARDIOFLOW study

Inclusion Criteria	Exclusion Criteria

• Patients admitted with stable CAD for elective PCI
• Patients who have been consented to undergo coronary angiography +/- PCI as part of their routine care by their clinician.
• Aged 18 or over.
• The patient has been informed of the nature of the study and has provided full written informed consent.
• FFR will be performed on study participants who demonstrate visible single vessel coronary stenosis on coronary angiography.
	• Patients unable to give informed consent including those with communication difficulties due to poor English.
	• Patients with haemodynamic instability and / or cardiogenic shock (defined as a sustained blood pressure of <90mmHg +/- the need for inotropic support)
	• Patients with an ACS (as defined by the ESC[9])
	• Those unable to perform a good quality CGM
	  o Patients who are SOB at rest
	  o Patients with very frequent ectopic beats
	  o Patients in atrial fibrillation
	  o Patients with a heart rate >150 beats/min
	  o Patients with a permanent pacemaker implanted.
	• Those patients unable to tolerate adenosine
	  o Patients with severe asthma, especially if taking oral theophylline.
	  o Patients with second or third degree heart block (without a pacemaker in situ).
	  o Patients with sick sinus syndrome.
	  o Patients with Long QT syndrome.
	  o Patients with severe hypotension (systolic pressure) <100mmHg).
	  o Patients with decompensated heart failure.
	• Patients with previous coronary artery bypass graft surgery
	• Patients who are unable to receive treatment with heparin
	• Patients with a chronic total occlusion
	• Patients with extremely tortuous or calcified vessels that are unfavorable for assessment with FFR.
	• Patients with severe stenosis of the left main stem
	• Patients with significant renal impairment (defined as eGFR<30ml/min)
	• Females who are or could be pregnant

Appendix 3.1. Inclusion/exclusion criteria for the CARDIOFLOW study.

Appendix 3.2. Showing the 2x2 tables used to calculate the diagnostic performance of the CGM at detecting stable CAD (defined by both FFR and % diameter stenosis) in the total study population:

1) Definition of stable CAD is a coronary stenosis with an FFR ≤0.80

Baseline accuracy

	FFR Positive	FFR negative	
CGM positive	5	9	14
CGM negative	11	15	26
	16	24	40

Maximal hyperaemia accuracy

	FFR Positive	FFR negative	
CGM positive	11	11	22
CGM negative	5	13	18
	16	24	40

2) Definition of stable CAD is ≥50% DS.

Baseline accuracy

	50% DS positive	50% DS negative	
CGM positive	10	4	14
CGM negative	16	6	22
	26	10	36

Maximal hyperaemia accuracy

	50% DS Positive	50% DS negative	
CGM positive	16	5	21
CGM negative	10	5	15
	26	10	36

3) Definition of stable CAD is ≥70% DS.

Baseline accuracy

	70% DS positive	70% DS negative	
CGM positive	1	13	14
CGM negative	5	17	22
	6	30	36

Maximal hyperaemia accuracy

	70% DS Positive	70% DS negative	
CGM positive	3	18	21
CGM negative	3	12	15
	6	30	36

Appendix 3.3. - Showing the 2x2 tables used to calculate the diagnostic performance of the CGM at detecting stable CAD (defined by both FFR and % diameter stenosis) in the study population with patients with previous MI excluded:

Baseline accuracy

	FFR Positive	FFR negative	
CGM positive	4	7	11
CGM negative	6	12	18
	10	19	29

Maximal hyperaemia accuracy

	FFR Positive	FFR negative	
CGM positive	6	9	15
CGM negative	4	10	14
	10	19	29

Appendix 3.4. Showing the 2x2 tables used to calculate the diagnostic performance of the % diameter stenosis at detecting stable CAD (defined by FFR) in the total study population:

1) Definition of stable CAD is a coronary stenosis with an FFR ≤0.80

50% DS accuracy

	FFR Positive	FFR negative	
50% DS positive	13	13	26
50% DS negative	2	8	10
	15	21	36

70% DS accuracy

	FFR Positive	FFR negative	
70% DS positive	4	2	6
70% DS negative	11	19	30
	15	21	36

Appendix 4 - HF-CGM study.

Appendix 4.1 – Formulae for the calculation of CGM polar angles from CGM orthogonal coordinates.

Oblique sagittal plane (XY)

(1) x = positive, y = positive $\alpha = \tan^{-1}\frac{+y}{+x}$

(2) x = negative, y = positive $\alpha = \tan^{-1}\frac{+y}{-x} + 180°$

(3) x = negative, y = negative $\alpha = \tan^{-1}\frac{-y}{-x} - 180°$

(4) x = positive, y = negative $\alpha = \tan^{-1}\frac{-y}{+x}$

Frontal plane (YZ)

(5) y = positive, z = positive $\alpha = \tan^{-1}\frac{+z}{+y}$

(6) y = negative, z = positive $\alpha = \tan^{-1}\frac{+z}{-y} + 180°$

(7) y = negative, z = negative $\alpha = \tan^{-1}\frac{-z}{-y} - 180°$

(8) y = positive, z = negative $\alpha = \tan^{-1}\frac{-z}{+y}$

Sagittal plane (XZ)

(9) x = positive, z = positive $\alpha = \tan^{-1}\frac{+z}{+x}$

(10) x = negative, z = positive $\alpha = \tan^{-1}\frac{+z}{-x} + 180°$

(11) x = negative, z = negative $\alpha = \tan^{-1}\frac{-z}{-x} - 180°$

(12) x = positive, z = negative $\alpha = \tan^{-1}\frac{-z}{+x}$

Appendix 4.2 – Formulae for the calculation of ECG polar angles from ECG orthogonal coordinates.

12-lead ECG axis plane

(1) I = positive, aVF = positive $\alpha = \tan^{-1}\frac{+aVF}{+I}$

(2) I = negative, aVF = positive $\alpha = \tan^{-1}\frac{+aVF}{-I} + 180°$

(3) I = negative, aVF = negative $\alpha = \tan^{-1}\frac{-aVF}{-I} - 180°$

(4) I = positive, aVF = negative $\alpha = \tan^{-1}\frac{-aVF}{+I}$