“The effect of coronary calcifications on interpretation of non-invasive investigations for coronary artery disease in patients with typical chest pain”

By

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Dedicated to

My father and mother for their continual encouragement, prayers and support:

thank you both for being my inspiration.

My wife Basma for her understanding, patience and support all the time. My lovely daughter Norayn, and my sons Aoab, Aban and Ayan for their happy company which cheered me up during times of difficulty.

ABSTRACT

Coronary artery disease (CAD) is the most common cause of mortality. Invasive coronary angiography remains the gold standard for the diagnosis of patients with stable CAD and acute coronary syndromes (ACS). However, the accurate diagnosis of CAD is complex and may involve a number of different investigations, including non-invasive techniques, primarily based on patient symptoms. The aim of this thesis was to investigate the prediction of CAD from coronary calcium scoring using multi-detector computed tomography (MDCT) against exercise treadmill testing (ETT [n=360]), myocardial perfusion imaging using magnetic resonance imaging (CMR [n=120]), and myocardial ischaemia assessed using Dobutamine stress echocardiography (DSE [n=35]) in a retrospective cohort of patients with typical chest pain. All 515 patients underwent conventional coronary angiography within 1-month of their non-invasive investigations. The results of this thesis demonstrated that MDCT is more accurate than ETT in identifying significant CAD, whereas a negative ETT was accurate in excluding CAD, as such the two investigations are complementary. Compared to CMR, MDCT was more accurate in detecting significant CAD. However, the burden of perfusion defects during stress was associated with a progressive increase in CAC in patients with non-obstructive CAD only. Finally, DSE was abnormal in patients with non-significant coronary stenosis but with high CAC and a positive ETT, which may suggest microvascular disease. In addition, resting wall motion abnormalities on echocardiography was associated with coronary calcification by MDCT. Non-invasive techniques for the assessment, diagnosis and treatment of CAD remains an integral component for the investigation of chest pain. Future research is required to investigate the relative importance of non-invasive assessments of CAD with respect to coronary intervention, adverse cardiovascular outcomes and all-cause mortality.

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ABBREVIATIONS

CAD	=	Coronary Artery Disease.
MDCT	=	Multi-Detector Computed Tomography.
CAC	=	Coronary Artery Calcification.
MI	=	Myocardial Infarction.
CMR	=	Cardiac Magnetic Resonance imaging.
CABG	=	Angiotensin Converting Enzyme Inhibitors.
ETT	=	Exercise Treadmill Test.
ECG	=	Electro-Cardio-Graph.
DSE	=	Dobutamine Stress Echocardiography.
BP	=	Blood Pressure.
SBP	=	Systolic Blood Pressure.
DBP	=	Diastolic Blood Pressure.
LV	=	Left Ventricular.
RV	=	Right Ventricular.
LA	=	Left Atrium.
RA	=	Right Atrium.
EF	=	Ejection Fraction
ACS	=	Acute Coronary Syndrome
S’	=	Systolic Velocities.
E’	=	Diastolic Velocities.
A’	=	Late Diastolic Velocity.

SD = Standard Deviation.

TDI = Tissue Doppler Imaging.

TAPSE = Tricuspid annular plane systolic excursion.

MAPSE = Mitral annular plane systolic excursion.

FFR = Fractional Flow Reserve

RWMA = Reginal wall motion abnormality.

WMA = Wall motion abnormality.

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CHAPTER ONE

GENERAL INTRODUCTION AND LITERATURE REVIEW

Coronary artery disease (CAD) is the commonest cardiovascular disease and the leading single cause of morbidity and mortality. Each year around 70.000 individuals die from CAD in the UK (British Heart Foundation, 2016). Angina is a symptom associated with obstruction or spasm of the coronary arteries. It is characterised by chest pain or discomfort, squeezing, burning or fullness, arm, neck, jaw, shoulder or back pain accompanying chest pain. Sometimes it is presented by nausea, breathlessness, dizziness, sweating and fatigue. There are many types of angina, including stable angina, which is produced by exertion and relieved by rest or medications, and unstable angina, which can occur at rest and has a more adverse prognosis than stable angina. The last one is variant angina or Prinzmetal's angina, which is microvascular angina. It may occur at rest due to either microvascular disease or due to vasospasm, and it is improved by medications (Sani et al., 2015).

One in seven women and one in five men die from CAD (British Cardiovascular Intervention Society, 2020). CAD is the most common cause of death in people aged more than 35 years, and it is the most common cause of death in the European Union (Townsend et al., 2016). In Europe, more than 335,000 men and more than 297,000 women die yearly due to CAD (British Heart Foundation, 2017). The conventional gold standard for diagnosing CAD is based on coronary artery luminal stenosis characterised by coronary angiography (Libby and Theroux, 2005).

Pathophysiology of coronary artery disease

CAD is characterized by atherosclerosis within the wall of coronary arteries, which is due to deposits of cholesterol (plaque) in the arteries. The atheromatous plaque grows progressively leading to narrowing of the arterial lumen, which may develop into angina.

The non-modifiable risk factors for CAD include age, male gender, ethnicity and family history of CAD, which is associated with early development of CAD. Modifiable risk factors, such as high cholesterol, hypertension, diabetes mellitus (DM), smoking, obesity, and physical inactivity can be changed and can be controlled. (Rosamond et al., 2008). Importantly, these risk factors can accelerate low-grade inflammation of the inner lining (intima) of medium-sized arteries.

Atherosclerosis progresses slowly leading to gradual thickening of the intima (figure 1). The plaque consists of inflammatory cells, cellular debris, smooth muscle cells, and different amounts of cholesterol and cholesterol ester. When plasma cholesterol increases, the arterial endothelial permeability changes, and this allows the LDL-C particles to move into the arterial wall, and the formation of intraluminal thrombus may occur.

This thrombus may dissolve spontaneously or grow and progress to occlude a coronary artery and result in an acute coronary accident. All these stages depend on a number of factors, such as plaque composition, plaque volume, the degree of luminal narrowing, and the size of the cap tear (Nakahara et al., 2017).

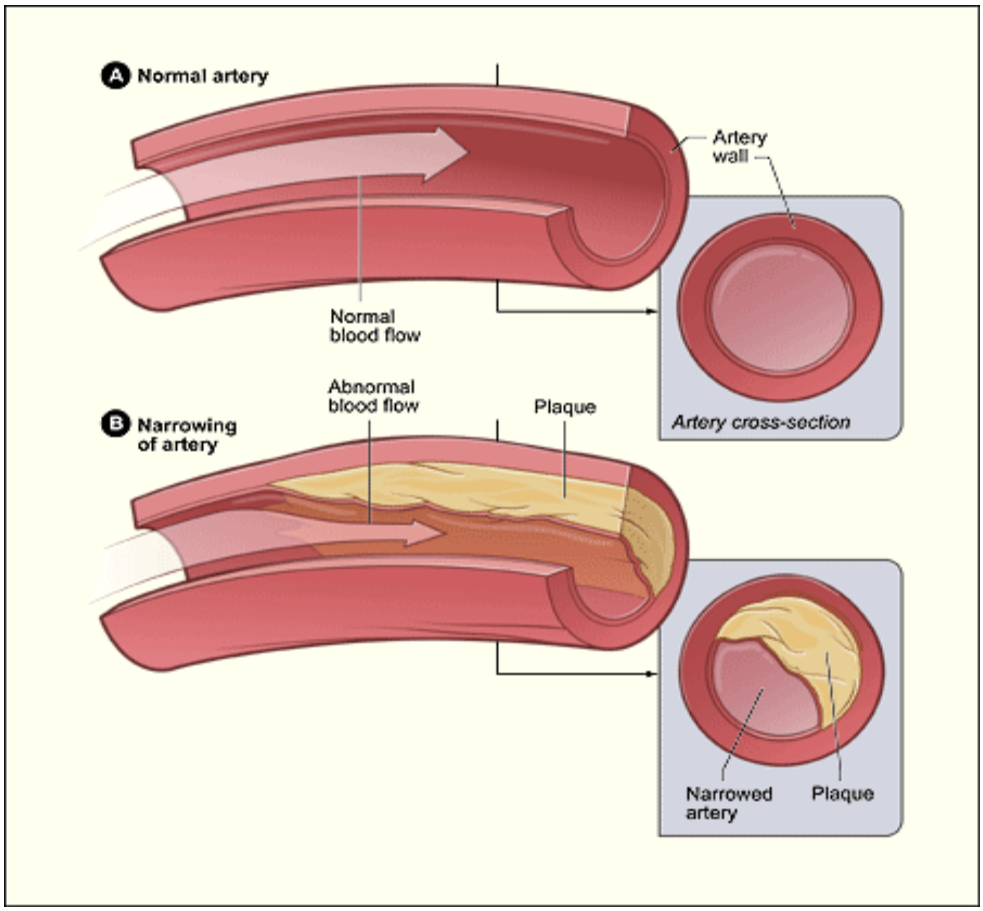

Figure 1: Normal artery and narrowed artery due to plaque. (Permitted)

According to the American College of Cardiology (ACC) and American Heart Association (AHA), coronary atherosclerosis is defined when there is calcification in the epicardial coronary arteries (O'Rourke et al., 2000). However, calcification is not only found in advanced lesions, but it may appear in small amounts in early stage lesions in people in their second and third decade of life (Wexler et al., 1996).

Impaired arterial compliance may affect the ability of an artery to dilate, particularly during exercise, which may compromise the blood supply to the myocardium, leading to ischaemia and symptoms.

In females, low indexed arterial compliance is associated with high coronary artery calcification (Coutinho et al., 2017). The coronary arterial stiffness measurements are strongly associated with the presence of CAD and its progression (Hack-Lyoung Kim, 2016). A reduction in arterial compliance is due to changes in the arterial wall, and this may come before the symptoms of the arterial disease (Glasser et al., 1997). Cardiac risk factors such as hypertension, DM, age, and atherosclerosis attenuate arterial compliance. The early detection of vascular abnormalities such as a decrease in arterial compliance may lead to increased risk of clinical events (Glasser et al., 1997).

During vasospasm of as coronary artery, vasoconstrictors such as angiotensin II and endothelin 1 are elevated compared to acetylcholine and nitric oxide (Yasue et al., 2008). Many studies have shown that nitric oxide deficiency is associated with coronary vasospasm (Kaneda et al., 2006). On the other hand, other studies reported that nitric oxide levels are not decreased during coronary vasospasm (Egashira et al., 1996). Moreover, enhanced phospholipase C activity and the increase in thioredoxin, C-reactive protein (CRP), and monocyte levels are associated with coronary vasospasm (Nakano et al., 2002). Anxiety, panic disorder, and type A personality also have been associated with coronary vasospasm (Stern and Luna, 2009). One other indicator of the presence of arterial disease is a reduction in arterial compliance (Glasser et al., 1996). Cardiovascular medications, such as vasodilators have an effect on arterial compliance (Safar et al., 1983).

Syndrome X

Syndrome X is a form of angina-like chest pain associated with ST depression on exercise; however, patients have normal coronary arteries when viewed using conventional coronary angiography.

Physiological mechanism of syndrome X:

The physiological mechanism(s) of syndrome X remain unclear and the optimum management of this patient population remains a clinical challenge (Crea and Lanza, 2004). These patients are diagnosed with other non-cardiac diagnoses, such as psychiatric and gastrointestinal disorders (Phan et al., 2009). There are some proposed causes such as endothelial dysfunction, estrogen deficiency, insulin resistance, and abnormal autonomic control (Kaski, 1999, Rosano et al., 1994, Roqué et al., 1998, Bøtker et al., 1993). Other (Agrawal et al., 2014) proposed criteria of syndrome X include:

1. Chest discomfort on exertion.
2. ST-segment depression during the anginal symptoms.
3. Normal coronary arteries at angiography.
4. Inducible coronary artery spasm upon egonovine or acetylcholine provocation
5. Absence of any systemic diseases associated with microvascular dysfunction.

Myocardial bridging is when the epicardial coronary vessel enters into the myocardium, it is associated with microvascular endothelial dysfunction in those patients with non-obstructive CAD, and it is investigated by intravascular ultrasound.

Endothelial dysfunction is characterised by a decrease in epicardial coronary artery diameter >20% after intracoronary acetylcholine and microvascular dysfunction when the index of microcirculatory resistance ≥25 (Sara et al., 2020, Pargaonkar et al., 2019). Other syndrome X patients may present with features of the metabolic syndrome such as hyperlipidaemia and hypertension (Jadhav et al., 2006).

Syndrome X in clinical studies:

Many studies suggested that the main cause of syndrome X is coronary microvascular dysfunction and microvascular angina (Crea and Lanza, 2004). Patients with Syndrome X remain a clinical challenge in their management. The exact mechanism behind symptoms in Syndrome X patients remains disputable (Agrawal et al., 2014). In general, syndrome X is still not fully understood, and there are no clear guidelines for its treatment (Agrawal et al., 2014). Another important cause of chest pain is the constriction of the coronary artery smooth muscles (coronary artery vasospasm).

Patients at intermediate risk of CAD might present with typical or atypical angina-like symptoms. For these patients, current guidelines recommend MDCT for the assessment of CAC score for optimum risk stratification (De Backer et al., 2003, Greenland et al., 2010).

There is no difference between 0 CAC and >0 CAC patient with the cardiac risk factor of age, male gender and smoking. However, patients with DM and hypertension have significantly higher CAC. It has been shown that diabetic patients always have a CAC greater than zero (Shipman et al., 2015). In terms of lipid profile, there is an association between hyperlipidemia and the extended CAC in more than one coronary artery (Abd Alamir et al., 2018). In addition, there is a strong association between age and gender with the presence of CAC. (Pletcher et al., 2004b)

The process of coronary calcification due to hypertension is not just because of hypertension, but it might be multifactorial (Megnien et al., 1996). Patients with a CAC >0 and diastolic blood pressure <60 mmHg have a high risk of CAD events (Rahman et al., 2017). Extra high CAC patients have a high risk of developing hypertension (Aladin et al., 2018). In diabetic patients, the mortality rate is expected to be high in patients with high CAC (Agarwal et al., 2013). Asymptomatic diabetic patients with zero CAC have good 5 year prognosis; however, the mortality rate increases significantly after 5 years (Valenti et al., 2016). Zero CAC is associated with good prognosis in older smokers. However, the presence of CAC is associated with a high predictive mortality rate, even in the absence of other cardiac risk factors (Schulman-Marcus et al., 2014). People with a family history of CAD and CAC of zero have a high risk of CAD events (Cohen et al., 2014).

The direct relationship between the extent of CAC and the functional status of the coronary circulation remains controversial (Henneman et al., 2008). Although CAC is perceived as a sub-clinical form of atherosclerosis, severe forms exist in the asymptomatic general population, while zero CAC has been reported in patients with acute coronary syndrome (Henneman et al., 2008, Schuijf et al., 2009).

Clinical investigations for CAD:

There are invasive and non-invasive techniques to diagnose CAD in patients with angina like symptoms. Invasive coronary angiography continues to be the gold standard in the diagnosis of coronary artery disease.

Although ETT is not recommended by NICE guideline but remains a practical investigation for excluding CAD as an explanation for exertional angina-like symptoms, and with a negative stress test often being used to rule out the need for coronary angiography (Desideri et al., 2005) or other non-invasive investigations. According to NICE guidelines, the current first line investigation for patients with typical / stable chest pain is CT angiography (Koo et al., 2011). The cardiac risk factors should be taken into account, including, age, gender, smoking history, diabetes, hypertension, dyslipidaemia and family history of premature CAD. NICE guidelines also recommend taking a resting 12-lead ECG as soon as possible in these patients. CT angiography should be used if the clinical assessment suggests typical and atypical angina, or 12-lead resting ECG demonstrates ST/T wave changes or Q waves. Patients should be offered other non-invasive functional imaging for myocardial ischaemia such as DSE or CMR if CT angiography has non-diagnostic results. Conventional coronary angiography may be considered as a third-line when the results of non-invasive functional imaging are non-conclusive. In terms of medical treatment, according to NICE guidelines, clinicians should consider a short-acting nitrate for preventing and treating episodes of angina. For secondary prevention, aspirin 75 mg daily, angiotensin-converting enzyme (ACE) inhibitors, statin and treat hypertension. Offer either beta blockers or a calcium channel blocker as first-line treatment for stable angina. Beta-blocker or calcium channel blocker pharmacotherapy should be based on contraindications and the individual's preference and comorbidities. Consider adding a third anti-anginal drug only when there is persistent chest pain or waiting for coronary revascularisation.

For male patients with a normal resting electrocardiograph (ECG) who are able to exercise, the 1997 ACC/AHA guidelines for exercise testing, as modified in 2002, recommend risk factor assessment and ETT, because of its simplicity, low cost and the widespread familiarity with its performance and interpretation, to determine whether the patient is at low, intermediate or high risk (Gibbons et al., 2002).

It is recognised that ETT is of less value in women due to a poorer accuracy of ECG changes as a result of more frequent resting ST-T-wave changes, lower ECG voltage and hormonal factors (Mieres et al., 2005).

Cardiac magnetic resonance imaging (CMR) myocardial perfusion has high diagnostic accuracy for CAD, even superior to single-photon emission computed tomography (Greenwood et al., 2012), however, it is known for its limitations.

The diagnosis of CAD by the two techniques is based on different concepts; while CMR assesses myocardial perfusion as a consequence of coronary disease, MDCT analyses the arterial disease morphology and allows for quantification of coronary wall calcification. In addition, MDCT non-invasive coronary angiography has shown higher accuracy than CMR in determining coronary stenosis (Schuijf et al., 2006). CAC score assessed by MDCT has also been shown to have high specificity in excluding obstructive CAD (Nieman et al., 2009b)

Coronary calcification itself generally reflects atherosclerosis and its extent correlates with the overall plaque burden, in the form of luminal stenosis (Rennenberg et al., 2009). However, many symptomatic patients might present with coronary calcification in the absence of significant luminal stenosis, suggesting that arterial wall hardening could be associated with ischaemia and compromised myocardial blood supply as a cause of symptoms.

Dobutamine stress echocardiography is an accurate non-invasive technique for detecting coronary artery disease (Senior et al., 2005). Currently, the clinical idea of the technique is based solely on the detection of ischaemia-induced wall motion abnormalities.

Multi-detector Computed Tomography (MDCT)

Non-invasive imaging techniques may enable early detection of CAD before significant luminal stenosis. Cardiac CT for CAC is a non-invasive technique for obtaining information about the location and extent of calcified plaque in the coronary arteries that cause narrowing of the coronary arteries or even block blood flow to the heart. CAC is a marker of CAD (American College of Radiology (ACR) and the Radiological Society of North America (RSNA), 2020). In 1994 a two-slice scanner was introduced, followed by a four-slice scanner in 1999. Then 16-slice, 32-slice, and 40-slice scanners have been introduced, with the latest being a 64-slice scanner in 2004 (Mittal et al., 2006, Flohr et al., 2003). In the future, MDCT coronary angiography is expected to become an alternative to invasive angiography for the diagnosis of significant coronary artery occlusions. Invasive coronary angiography assesses just the arterial lumen, detecting the location and severity of lumen narrowing, but is unable to give information about the arterial wall.

MDCT for CAC is a non-invasive way of evaluating the coronary arteries, after the technique no radiation remains in a patient's body. The CAC provides information about whether CAD is present even if the patient is asymptomatic or is likely to develop CAD in the next few years. The cardiac CT can suggest the presence of CAD even when the coronary arteries are less than 50 percent narrowed (Mittal et al., 2006, Agatston et al., 1990, Callister et al., 1998, Ferencik et al., 2003, Hong et al., 2002, Matthew Budoff and Jerold Shinbane, 2016, Alan Boyar, 2020).

CAC is indicated in the screening of young people with risk factors of CAD such as family history of CAD, diabetes, hypercholesterolemia, hypertension, obesity, and smoking (Saad et al., 2018). Also, CAC should be checked annually in all asymptomatic patients with high CAC. In dilated cardiomyopathy, CAC can be used to determine the presence and extent of CAD. It may be helpful in assessing whether the cardiomyopathy is due to ischaemic heart disease.

A very low CAC would indicate that the cardiomyopathy is of unknown origin, so invasive coronary angiography would be unnecessary. When CAC is 0, the probability of finding coronary artery stenosis is about 0% for women and 0.7% for men (American College of Radiology (ACR) and the Radiological Society of North America (RSNA), 2020, Matthew Budoff and Jerold Shinbane, 2016). MDCT is contraindicated in patients with arrhythmias, pregnant women, iodinated contrast material allergy, renal failure, and hyperthyroidisms (American College of Radiology (ACR) and the Radiological Society of North America (RSNA), 2020, Alan Boyar, 2020).

There are several methods of measuring CAC. The Agatston scoring scale is rule-based and uses the weighted sum of all lesions with a density above 130 Hounsfield Units (HU) and multiplying the area of calcium by a factor related to maximum plaques attenuation (density factor).

Partial volume effects lead to higher peak values only for small lesions (Agatston et al., 1990). The volume method of (Callister et al., 1998) resolves the issue of slice thickness and spacing by computing a volume above threshold. The calcium mass score consists of an integration of the signal for pixels above a given threshold. This score however, has not been clinically validated (Ferencik et al., 2003, Hong et al., 2002). Rumberger et al (2003) data showed that the Agatston, Volume, and Mass scores could provide similar but not exactly the same characterization. CAC levels and its relations to the presence of plaques and their severity are shown in table 1.

The Coronary Calcium Score (CAC) Interpretations is as follows:

Table 1: Coronary Calcium Score Interpretations (American College of Radiology (ACR) and the Radiological Society of North America (RSNA), 2020)

Calcium Score	Presence of Plaque
0	No evidence of plaque
1-10	Minimal evidence of plaque
11-100	Mild evidence of plaque
101-400	Moderate evidence of plaque
Over 400	Extensive evidence of plaque

Table 2 shows the impact of CAC level on the presences of CAD, and cardiovascular risk, and the clinical recommendations in each CAC levels.

Table 2: Calcium Score Guidelines (Alan Boyar, 2020)

EBCT Calcium Score	Plaque Burden	Probability of Significant CAD	Implications for Cardiovascular Risk	Recommendations
0	No identifiable plaque burden	Very low (generally <5% likelihood)	Very low CV risk	Reassure patient while discussing general public guidelines for primary CV prevention.
0-10	Minimal identifiable plaque burden	Very unlikely (generally <10% likelihood)	Low CV risk	Discuss general public health guidelines for primary CV prevention.
11-100	Definite (at least mild)	Mild or minimal coronary stenoses likely	Moderate CV risk	Counsel patient on risk factor modification, with strict adherence to NCEP ATP II primary prevention cholesterol guidelines.
101-400*	Definite (at least moderate atherosclerotic plaque burden)	Nonobstructive CAD highly likely, although obstructive disease possible	Moderate to high CV risk	Institute risk factor modification and secondary prevention NCEP ATP II guidelines. Consider stress testing for further risk stratification.
>400* (*Greater clinical significance if calcium score is >75th percentile for age and sex.)	Extensive	High likelihood (>90%) of at least one "significant" coronary stenosis	High CV risk	Very aggressive risk factor modification and stress imaging to evaluate inducible ischemia.

People with higher CAC have greater plaque burden and high risk for myocardial infarction (MI) regardless of their symptoms. The presence of MI is well described with retrospective 64-slice CT (Francone et al., 2007). For asymptomatic people, a CAC of 0 indicates the absence of CAD, whereas CAC over 400 is associated with high cardiac event rates (Matthew Budoff and Jerold Shinbane, 2016, Alan Boyar, 2020). The disadvantage of the MDCT is that it exposes the patient to radiation. The dose is similar to 50-180 chest x-rays and about similar to that received during a diagnostic cardiac catheterisation procedure. The effective radiation dose for cardiac CT for CAC is around 3 Sub-millisievert (mSv) (depending on dose modulation strategies), whereas effective radiation dose for cardiac catheterisation average 8 to 10 mSv. From 2007 to 2017, the MDCT radiation dose decreased by around 80%, the median effective dose decreased from 12.4 mSv to 2.7 mSv (Stocker et al., 2018). The combination of adaptive iterative reconstruction algorithms, tube current modulation, tube voltage reduction, heart rate reduction, prospective electrocardiogram-gating and high-pitch helical acquisition are responsible for reduction in the radiation doses during the coronary computed tomography angiography in the diagnosis of CAD (Richards and Obaid, 2019).

Radiation exposure of cardiac MDCT is approximately the same as a CT scan of the chest or abdomen; however, it is slightly higher than invasive coronary angiography. The approximate radiation dose exposure during 64-slice CT was 13 mSv and 18 mSv for men and women respectively (Raff et al., 2005). The increase in spatial and temporal resolution with 64-slice CT is associated with an increased radiation dose (Pitcher et al., 2007). The radiation dose significantly decreases with increasing heart rates (Stolzmann et al., 2008). The radiation dose exposure during 16-slice CT is reduced by 30%-50% (according to heart rate) with ECG pulsing (Flohr et al., 2003).

MDCT is a reliable test to detect coronary artery stenosis in patients with sinus rhythm, presenting with atypical chest pain, stable or unstable angina (Rubinshtein et al., 2007, Mollet et al., 2005, Cademartiri et al., 2006).

Emergency department MDCT has a high positive predictive value for ACS diagnosis. Coronary 32-slice CT excludes coronary stenosis of 50% in patients with high CAC and advanced CAD (Cordeiro et al., 2006). Normal cardiac MDCT has an excellent prognosis (Gaemperli et al., 2008). Schlosser et al (Schlosser et al., 2007) reported that MDCT may overestimate the severity of coronary stenosis. MDCT is able to evaluate the nature and severity of arterial wall disease in patients presented with cardiac chest pain (Pitcher et al., 2007).

Meta-analysis data showed that MDCT has shortcomings, which are difficult to overcome in daily practice (Hamon et al., 2006). Niemann et al (2001) found that only 76% of coronary segments could be evaluated by MDCT. However, most published studies illustrate that CAC predicts CAD events regardless of risk factors. The ability of the CAC to estimate total plaque burden is the most important predictor for future myocardial events (Hasdai et al., 1997). A negative CAC (0 calcium score) is associated with a 0.1% per year risk for a hard coronary event (Secci et al., 1997, O'Rourke et al., 2000).

Greenland et al (2004) data showed that patients with CAC >300 are considered as high risk. Arad et al (2000) illustrated that a CAC >160 was highly predictive of nonfatal MI and death due to CAD. CAC predicted events independently of age, gender, and other cardiovascular risk factors. The lack of calcium does not completely rule out CAD (Wong et al., 2000). A four-year follow-up study (Arad et al., 2005) showed a higher incidence of adverse cardiovascular events in patients aged between 50 and 70 years old with no symptoms and CAC of ≥100.

Cooper Clinic Study (LaMonte et al., 2005) investigated more than ten thousand adults, aged between 22 and 96 years unknown for CAD and the study demonstrated a strong association between CAC and incident coronary heart disease events.

A meta-analysis showed the risk of CAD events increased 2.1-fold for CAC from 1 to 100 and 10-fold for CAC >400 (Pletcher et al., 2004a). People with very high CAC without cardiac symptoms have a 25% higher risk annually of having an MI or dying due to cardiovascular causes (Wayhs et al., 2002).

The presence and extent of CAC are greater in young patients with acute MI (Pohle et al., 2003) and MDCT angiography provides promise to reduce the number of invasive angiography investigations in symptomatic patients with suspected CAD. However, calcium scoring alone was less appropriate as a filter before angiography (Haberl et al., 2005). Elevation of CAC ≥1000 is associated with increasing age and with a likelihood of coronary artery occlusion (Almeda et al., 2004). The Multi-Ethnic Study of Atherosclerosis (MESA) (McClelland et al., 2006) examined the spread of CAC based on age, gender, and ethnicity in clinical cardiovascular disease and treated diabetes. The study showed that men had higher calcium levels than women. In addition, CAC increases steadily with the age. Moreover, there were significant differences in CAC by race.

In diabetic patients, any increase in CAC was associated with an increase in mortality when compared with non-diabetic patients (Raggi et al., 2004).

There is no evidence that a high CAC would be attenuated following cessation of smoking or with effective blood pressure control and diabetes management (Pearson et al., 2002). CAC is superior to most of the cardiac risk factors such as gender, DM, hypercholesterolemia, hypertension, age and family history, in identifying significant CAD (Nicoll et al., 2016).

MDCT in clinical practice

A large meta-analysis study comparing MDCT with ETT showed high sensitivities, specificities, and accuracy for the ETT in the range of 68%, 77%, and 73%, respectively; 89%, 80%, and 89% for myocardial perfusion; and 85%, 84%, and 87% for stress echocardiography compared with 91%, 49%, and 70% for CT (O'Rourke et al., 2000).

Other studies (Dennis et al., 1995, Fleischmann et al., 1998, Detrano et al., 1989) demonstrated lower and variable sensitivity and specificities of 84% to 44% for treadmill testing, 85% to 77% for stress echocardiography, and 87% to 63% for myocardial scintigraphy. Cardiac CT is more sensitive than ETT for the identification of patients with occluded CAD (Shavelle et al., 2000). CAC for occluded CAD is superior to ETT in asymptomatic high-risk patients (Geluk et al., 2007).

Berman et al (2004) studied 1195 patients who underwent cardiac CT for CAC measurement and CMR single photon emission assessment. The study showed that CAC was frequently present in the absence of abnormalities in CMR. Other reports have supported this study (Brindis et al., 2005). Ischaemic CMR is associated with a likelihood of atherosclerosis by CAC of >100 (Berman et al., 2004). A meta-analysis comparing MDCT to CMR showed higher diagnostic accuracy for MDCT than CMR (Schuijf et al., 2006). The sensitivity of cardiac CT was slightly higher than stress echocardiography, whereas the specificity was lower (Myers et al., 2002). The CAC was significantly lower in syndrome X patients than in CAD patients. CAC could differentiate between syndrome X and CAD in patients with chronic stable angina (Chen et al., 2001).

Coronary artery wall calcification is a sensitive marker for the presence of atherosclerosis (Rumberger et al., 1995). 30% of the elderly male and 15% of the elderly female, without cardiac risk factors, had extensive coronary calcification (Oei et al., 2004).

The sensitivity of detecting CAD declines and the specificity increases with increasing CAC (Agatston et al., 1990, Budoff et al., 1996). Asymptomatic individuals with CAC >400 but have no cardiac risk factors may have a poorer prognosis than those who have zero CAC but have three or more cardiac risk factors (Nasir et al., 2012). In the future, CAC with other non-invasive cardiac investigation will play a very important role in daily clinical practice in the diagnosis of CAD (Piers et al., 2008). Recently, there is no medical treatment to stop the progress of coronary calcification or reduce the CAC (Liu et al., 2015).

Exercise Treadmill Test (ETT)

Exercise testing is the most widely used and relatively inexpensive method for the evaluation of suspected CAD and its severity (Kligfield and Okin, 1994, Detry et al., 1970).

ST depression during ischaemia is due to spatial and non-spatial factors. The spatial factor is the myocardial ischaemic area, and the non-spatial factor is the physiological severity of ischaemia of the myocardium. The non-spatial factor becomes greater during exercise and it is responsible for the ST changes during the exercise test. Another non-spatial factor that may affect ST-segment depression during exercise is changing intra-ventricular conductance (Wilson et al., 1991, Holland and Arnsdorf, 1977). ST depression during exercise-induced ischaemia is not only due to the presence of coronary occlusion but also due to the increase in excess myocardial oxygen demand (Detry et al., 1970, Mirvis et al., 1986).

Heart rate normally increases during exercise. The first increase in heart rate early in exercise is due to a central withdrawal of parasympathetic inhibition and an increase in sympathetic tone. Then there is a further increase in central nervous system sympathetic stimulation and increase in levels of circulating catecholamines (Lauer, 2004, Lauer, 2001).

Heart rate decrease during the first 30 seconds to 1 minute after exercise due to parasympathetic reactivation (Imai et al., 1994). ETT is indicated as a diagnostic test in suspected coronary artery disease patients, chest pain assessment, high-risk patients to identifying documented CAD, evaluate patients after CABG or angioplasty, and assessment of arrhythmia (Hill and Timmis, 2002).

ETT is contraindicated in:

1-Acute MI (4 to 6 days).

2-Unstable angina at rest within 48 hours.

3-Recent aortic surgery.

4-Arrhythmia.

5-Acute myocarditis or pericarditis.

6-SBP >220 mm Hg or diastolic >120 mm Hg.

7-Severe aortic stenosis.

8-Uncontrolled heart failure.

9-Hypertrophic obstructive cardiomyopathy (HOCM).

10-Dissecting aneurysm (Hill and Timmis, 2002).

The ACC and the AHA performed a meta-analysis of the diagnostic accuracy of ETT for patients who underwent conventional coronary angiography and ETT. The sensitivity and the specificity were 68%, and 77%, respectively.

When the meta-analysis excluded the studies of patients with previous MI, the sensitivity and the specificity were 67%, 72%, respectively, for diagnosing CAD (Gibbons et al., 2002). The ADORE trial (Babapulle et al., 2007) divided ETT results to positive, indeterminate, and negative. They found that after PCI there is no significant difference in clinical events between patients with positive and negative ETT. This result supports the ACC/AHA guidelines that ETT should not be used routinely after PCI.

Silent ischaemia during ETT is associated with an increased risk of stroke and cardiovascular disease in men with cardiac risk factors, such as hyperlipidaemia, hypertension, and smoking (Kurl et al., 2003). In patients following an uncomplicated MI who had a negative ETT before discharge, have less cardiac events at one year follow up (Desideri et al., 2005). Curzen et al (1996) showed that a negative ETT in older women with cardiac risk factors have a very low predictive value. In patients with cardiac risk factors, ETT is a reliable and important investigation to detect CAD.

In diabetic patients, a positive ETT is better than a positive thallium scan for detecting CAD in asymptomatic patients (Koistinen et al., 1990). Chest pain during ETT is strongly associated with nonfatal cardiac hospitalisations (Ho et al., 2007). Young women with the absence of chest pain during ETT are associated with a high negative predicted value (Curzen et al., 1996). During ETT, hypertensive patients with left ventricular hypertrophy may be associated with myocardial ischaemia in the absence of CAD (Manolis et al., 1997). Patients presenting with chest pain, hypertension, and insignificant ECG changes, had a higher risk of CAD (Conti et al., 2000).

Exaggerated increases of systolic blood pressure (SBP) by >20 mmHg during ETT were associated with cardiovascular mortality, and risk of acute MI and stroke (Huang et al., 2008). SBP may increase during ETT in women with hyperlipidaemia (Kolovou et al., 2007).

Hypertensive patients with positive ETT had higher minimum coronary resistance and lower arterial compliance (Kozàkovà et al., 2003). Normotensive men with normal resting ECG and strong positive ETT are more likely to have CAD. The same study reported that hypertensive women with ischaemic resting ECG are more likely to have a false-positive ETT (Faisal et al., 2007). ST segment depression on a resting ECG does not impair the detection of ischaemia by ETT but may be associated with a false-positive ETT (Kalaria and Dwyer, 1998).

ST depression ≥2 mm during ETT is a predictor of reversible ischaemia, whereas ST depression 1 mm during ETT was not a predictor of ischaemia (Yap et al., 2005). Prolonged ST-segment depression of more than five min in recovery does not relate to the severity of CAD (Desai et al., 2003). However, there is a strong association between ST-segment depression during ETT and the magnitude of ischaemia (Hauser et al., 2004).

Other ECG changes during exercise

In 1986, Ahnve et al (1986) showed the prolonged QRS duration during exercise could be a marker of myocardial ischaemia. The QRS score provides complementary diagnostic information to ST-segment depression during ETT (Koide et al., 2001). The differences in QRS duration from rest to exercise may work as a marker of myocardium ischaemia (Kligfield and Lauer, 2006, Koide et al., 2001). Another study (Michaelides et al., 1995) showed that the QRS score was directly related to the number of occluded coronary arteries and to exercise-induced reversible myocardial perfusion defects. During ETT, transient abnormal Q waves are rare, as Q waves indicate an old MI (Alameddine and Zafari, 2004). In asymptomatic CAD patients, ETT is an acceptable technique in clinical follow-up (Guerreiro et al., 2017).

Increases in the duration of the P-wave together with ST depression during ETT is associated with high sensitivity in identifying three vessels CAD (Kuch, 2017). In men, ST depression during exercise with low cardiorespiratory fitness is associated with a high risk of sudden cardiac death (Hagnäs et al., 2017). MDCT is more accurate than ETT in the diagnosis and assessment of CAD (Yin et al., 2016).

Cardiac Magnetic Resonance Imaging (CMR)

Cardiac magnetic resonance imaging myocardial perfusion has high diagnostic accuracy for CAD, even superior to single-photon emission computed tomography (Greenwood et al., 2012); however, it is known for its limitations. CAC score assessed by MDCT has also been shown to have high specificity in excluding obstructive CAD (Nieman et al., 2009b). The diagnosis of CAD by the two techniques is based on different concepts; while CMR assesses myocardial perfusion as a consequence of coronary disease, MDCT analyses the arterial disease morphology and allows for quantification of coronary wall calcification. In addition, MDCT non-invasive coronary angiography has shown higher accuracy than CMR in determining coronary stenosis (Schuijf et al., 2006).

Coronary calcification itself generally reflects atherosclerosis and its extent correlates with the overall plaque burden, in the form of luminal stenosis (Rennenberg et al., 2009). However, many symptomatic patients might present with coronary calcification in the absence of significant luminal stenosis, suggesting that arterial wall hardening could be associated with ischaemia and compromised myocardial blood supply as a cause of symptoms.

Jaarsma et al (2012) meta-analysis showed that stress CMR has better diagnostic accuracy than DSE and MDCT.

CMR has more advantages than MDCT in the diagnosis and assessment of CAD, as CMR is not affected by the CAC which limit the benefits of MDCT in patients with advanced atheroma.

(Kim et al., 2001) showed that CMR has very high sensitivity in identifying obstructed CAD, however, the specificity is low. In addition, meta-analysis illustrated that the overall sensitivity and specificity of CMR in detecting significant CAD were 87% and 70%, respectively (Schuetz et al., 2010).

Dobutamine Stress Echocardiography (DSE)

DSE is an accurate non-invasive technique for detecting coronary artery disease and has been shown sensitive even in demonstrating evidence for subendocardial ischaemia before transmural disturbances appear. DSE is more accurate than ETT in the diagnosis of CAD (Mahenthiran et al., 2005). In the setting of a normal ECG and resting echocardiogram, DSE is an effective and safe investigation in the detection of early stages of CAD (Bedetti et al., 2005). DSE has more advantages than the other non-invasive investigations and recommended in the assessment of patients referred to invasive coronary angiography (Scherhag et al., 2005).

In routine clinical practice, DSE has higher sensitivity and lower specificity in detection CAD (Geleijnse et al., 2009). In symptomatic outpatients, DSE is superior to ETT and should be performed in all symptomatic patients to clarify the cause (Leischik et al., 2007). DSE has average results for the diagnosis of CAD, with high sensitivity and specificity, but these results are not too different to MDCT (Mordi et al., 2017).

Both DSE and MDCT together have high sensitivity in the diagnosis of CAD, but DSE alone has lower sensitivity but high specificity than MDCT (Nixdorff et al., 2008). Most patients with high CAC have normal wall motion during DSE (Ramakrishna et al., 2006).

Patients with diastolic dysfunction are more likely to have positive DSE, and obstructive CAD by MDCT (Mansour et al., 2017).

In symptomatic patients with normal ECG and negative troponin, MDCT is more accurate than DSE to assess patient symptoms (Durand et al., 2017). DSE is superior to CMR in a chest pain assessment emergency department (Davies et al., 2016).

In women who presented with chest pain, DSE is a more reliable and practical investigation compared to ETT in identifying CAD (Kim et al., 2016). DSE has high specificity and average sensitivity in detecting CAD in females (Geleijnse et al., 2007). In patients with left bundle branch block, DSE has more specificity than CMR in assessing CAD, but lower sensitivity mainly in patients with abnormal wall motion abnormalities at rest (Cortigiani et al., 2001, Sicari, 2009). There are more false positive DSE results in patients who developed systolic blood pressure >220 mmHg during the test (Ha et al., 2002). Patients who had ST elevation during DSE has a higher risk of future cardiovascular events (Arruda et al., 2006).

AIM

The aim of this thesis is to assess symptomatic patients with typical chest pain, particularly those with typical angina. This thesis will compare the different levels of CAC by MDCT with the findings on ECG responses of the heart using ETT, myocardium perfusion using CMR, and heart muscle function in terms of wall motion abnormalities and other measures such as M-mode and tissue Doppler imaging (TDI) using DSE. Moreover, this work aims to evaluate the potential association between CAC assessed by MDCT with other non-invasive investigations, including ETT, CMR, and DSE in a group of symptomatic patients, irrespective of the presence of luminal stenosis. The list of thesis aims and hypothesis are listed below:

Study 1 Aim (Chapter 3). This study aims to compare the diagnostic accuracy of MDCT with ETT for significant coronary artery disease in patients with typical chest pain.

Study 1 Hypothesis (Chapter 3). This study hypothesises that MDCT is more accurate in identifying the presence and absence of significant coronary artery disease compared to ETT in patients with typical chest pain.

Study 2 Aim (Chapter 4). This study aims to compare the diagnostic accuracy of MDCT with CMR for significant coronary artery disease in patients with typical chest pain.

Study 2 Hypothesis (Chapter 4). This study hypothesises that MDCT is more accurate in identifying the presence and absence of significant coronary artery disease compared to CMR in patients with typical chest pain.

Study 3 Aim (Chapter 5). This study aims to compare the diagnostic accuracy of MDCT with DSE for significant coronary artery disease in patients with syndrome X.

Study 3 Hypothesis (Chapter 5). This study hypothesises that MDCT is more accurate in identifying the presence and absence of significant coronary artery disease compared to DSE in patients with syndrome X.

CHAPTER TWO

General methods

A retrospective study investigating 515 patients (360, 120, and 35 for ETT, CMR, and DSE respectively), (311 male, age 63 ± 8.4 years), presenting with angina-like symptoms to Bethanien Hospital Frankfurt, Germany between 2007 and 2010, or Umea Heart Centre, Umea, Sweden between 2009 and 2011, and had conventional risk factors assessed. From Umea medical centre and Bethanien hospital, patient data was collected from each hospitals database. Patients with a full data set, including CAC results, ETT results, CMR results at rest and stress, DSE results at rest and stress and full images and reports of invasive coronary angiography were used in this thesis. Patients with incomplete data were excluded. Umea medical Ethics Committee approved the study (see Appendix section) and Bethanien hospital's Ethics Committee provided a waiver to use retrospective de-identified and anonymised patient data for the thesis. When performing routine clinical tests, patients provide signed informed consent to sign that they agree to being contacted with regard to clinical registries and future ethically approved research studies.

All patients included were stable with a normal LV ejection fraction (>55%), RV size and diameter (<3.6 cm). The exclusion criteria included acute coronary syndrome patients, heart failure, valvular heart disease, thyroid and parathyroid diseases, inflammatory disease or chronic kidney disease (creatinine >130mmol/L). All patients subsequently underwent conventional coronary angiography, which was performed not more than one month after their ETT, MDCT, CMR, and/or DSE. The Judkin's technique was used with at least four views of the left system and two views of the right coronary system.

Significant obstructive coronary disease was considered present when there was clear evidence for at least one vessel stenosis of ≥50% lumen narrowing on invasive angiography. Although it is acknowledged other researchers consider significant CAD when the stenosis is ≥70% on coronary angiography, we considered ≥50% as previously performed (Meijboom, W.B 2008; JACC 52; 2135-44) and due to the fact that the majority of plaque ruptures and resultant MI's occur in coronary arteries with <70% stenosis (Maddox, TM 2014 JAMA, 312; 1754-63). All patients age, gender, presence or absence of hypercholesterolemia, hypertension, diabetes, obesity, smoking history and family history of CAD was recorded.

Interobserver variability was performed using SPSS to all the echo measurements during rest and stress. The interobserver variability is highly agreed with results between 0.81 and 1.0.

With variability of CAC measurements depending on the MDCT system used.

Figure 2 illustrates the patients flow for each study.

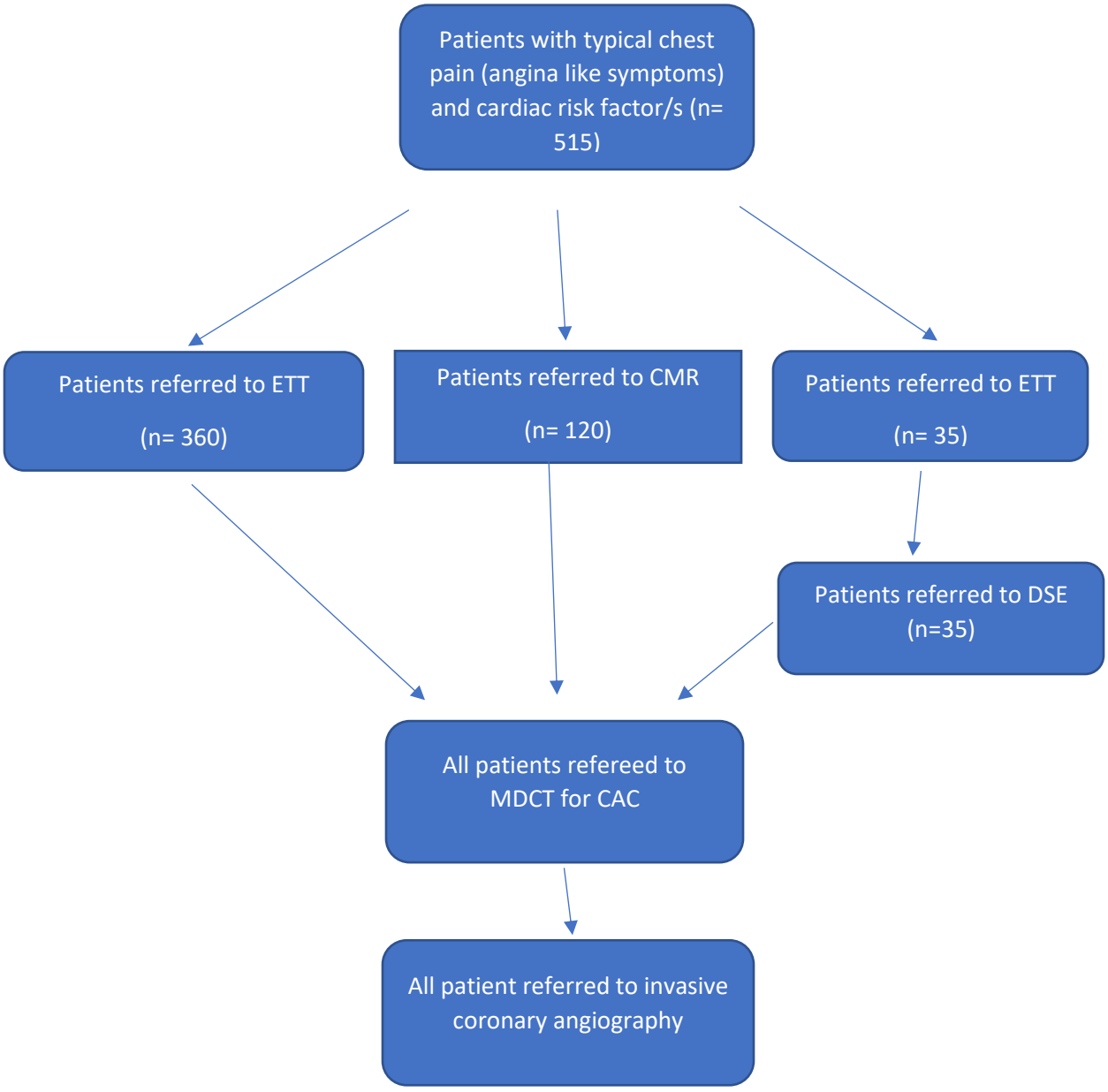

Figure 2 Flow chart of cardiac investigation flow chart for typical chest pain patients.

Calcium screening

Computed tomography was used to determine coronary calcium. The scanner operated in the high-resolution volume mode. All patients had sinus rhythm at the time of CT and none had renal failure, hyperthyroidism or allergy. CT was performed using a 64-detector-row scanner (Somatom Sensation Cardiac 64; Siemens Medical Solutions, Forchheim, Germany) (Figure 3) with a gantry rotation time of 330 ms (collimation 64 x 0.6 mm, reconstruction increment 0.3 mm).

Figure 3: Somatom Sensation Cardiac 64; Siemens Medical Solutions, Forchheim, Germany.

Image acquisition was performed during inspiratory breath-hold. To familiarize a patient with the protocol, breath-holding was practiced before the examination.

Patients whose heart rates were >60 beats/min received 5 mg bisoprolol or 50 mg of metoprolol orally 1 hour before CT examination. For an insufficient decrease in heart rate, up to 6 vials (30 mg) of metoprolol was injected intravenously. The calcium scan was performed using prospective electrocardiographic triggering usually at 70% of the RR interval. The collimation was set to 30 x 0.6 mm, and the reconstructed slice thickness was 3 mm (adapted field of view depending on heart size, matrix 512 x 512, pixel size usually 0.5 x 0.5 mm). Calcium was defined as the presence of >2 contiguous pixels with >130 Hounsfield Units.

These lesions were automatically identified and marked in colour by the workstation. All lesions were added to calculate the total Agatston score (Becker et al., 2001), which was computed by summing the CACs of all foci in the epicardial coronary system (Matthew Budoff and Jerold Shinbane, 2016) (Figure 4).

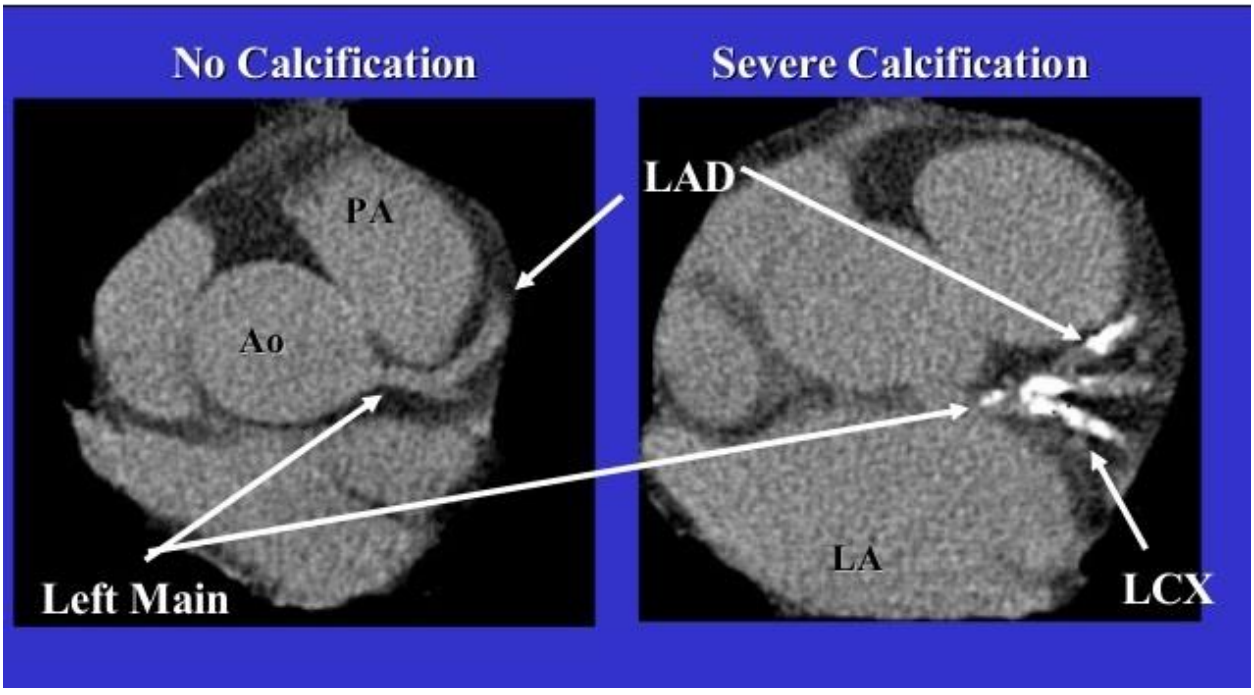

Figure 4: CAC and CT angiography for normal and sever calcified coronary arteries (182)

Recently, coronary CT angiography fractional flow reserve (FFR_{CT}) is increasingly used in patients with coronary artery disease, and is likely to expand in the future with the use of coronary CT angiography as a first-line investigation in patients with suspected CAD. This technology was not available when the PhD data was collected. Invasive FFR has been shown as a useful technique to identify the probability of a coronary narrowing that hinds the myocardial ischemia. FFR_{CT} is a non-invasive technique that calculating fluid dynamics to assess the physiological significance of CAD. It calculates the rest and hyperemic pressure fields in coronary arteries without modifying the protocols of the CT acquisition imaging, or adding any other images or medications. The FFR_{CT} ratio obtained by dividing the mean pressure distal to the coronary stenosis by the mean aortic pressure (Koo et al., 2011, Kim et al., 2010). Patients with FFRCT ≤0.80 is considered positive for coronary ischemia, and may benefit from coronary revascularization. However, patients with FFRCT >0.80 can be treated medically (Nørgaard et al., 2018, Ihdayhid et al., 2019). There are many studies comparing the invasive FFR with the non-invasive $FFR_{CT.}$

Coronary angiography

The Judkin's technique was used with at least four views of the left system and two views of the right system. The decision to perform coronary angiography was not influenced by the CAC score but was based on the clinical assessment of the patient's symptoms. Angiography was performed blindly within one month after the CT scan in all patients. Analysis of the coronary angiograms was performed by an independent experienced observer. Invasive coronary angiography was performed, and multiple views were stored on a CD-ROM.

According to the AHA, the coronary arteries were segmented as the following: the right coronary artery (RCA) was divided in a proximal, middle, and distal parts; the left anterior descending artery (LAD) was divided into proximal, middle, and distal parts; the left circumflex artery (LCX) was divided into proximal and distal parts. Significant stenosis was defined as ≥50% lumen narrowing of any epicardial coronary artery.

Exercise Tolerance Testing (ETT)

All patients underwent exercise ECG using conventional treadmill method and Bruce protocol (Figure 5). ECG changes, blood pressure and symptoms were monitored throughout the test. There are seven stages of exercise, each stage of 3 minutes (maximum 21 minutes). In the first stage, the patient walks at 2.7 km up a 10% incline. Energy consumption is estimated to be 4.8 METs during this stage.

Figure 5: Treadmill Stress ECG machine.

The speed and incline increase with each stage. A 12-lead ECG was recorded during the test by the physiologist, before exercise (Figure 6), during peak exercise (Figure 7), and after the exercise during the recovery (Figure 8). ST-segment was observed continuously during the test to check if there were any ST segment changes. The patient should achieve at least 85% of maximum heart rate, otherwise, the test is not conclusive.

Maximum heart rate is 220 minus age for men and 210 minus age for women (Hill and Timmis, 2002). Each patient underwent ETT that was interpreted as positive when >1.5 mm ST depression after the J point (Ellestad and Wan, 1975).

Exercise endpoints were chest pain or breathlessness, ischaemic ECG changes or arrhythmia. All our patients exercised for 9 mins or more, none of these patients had developed chest pain during the exercise, and all managed to reach the target heart rate. None of our patients were excluded due to developed chest pain before the 9 mins exercise.

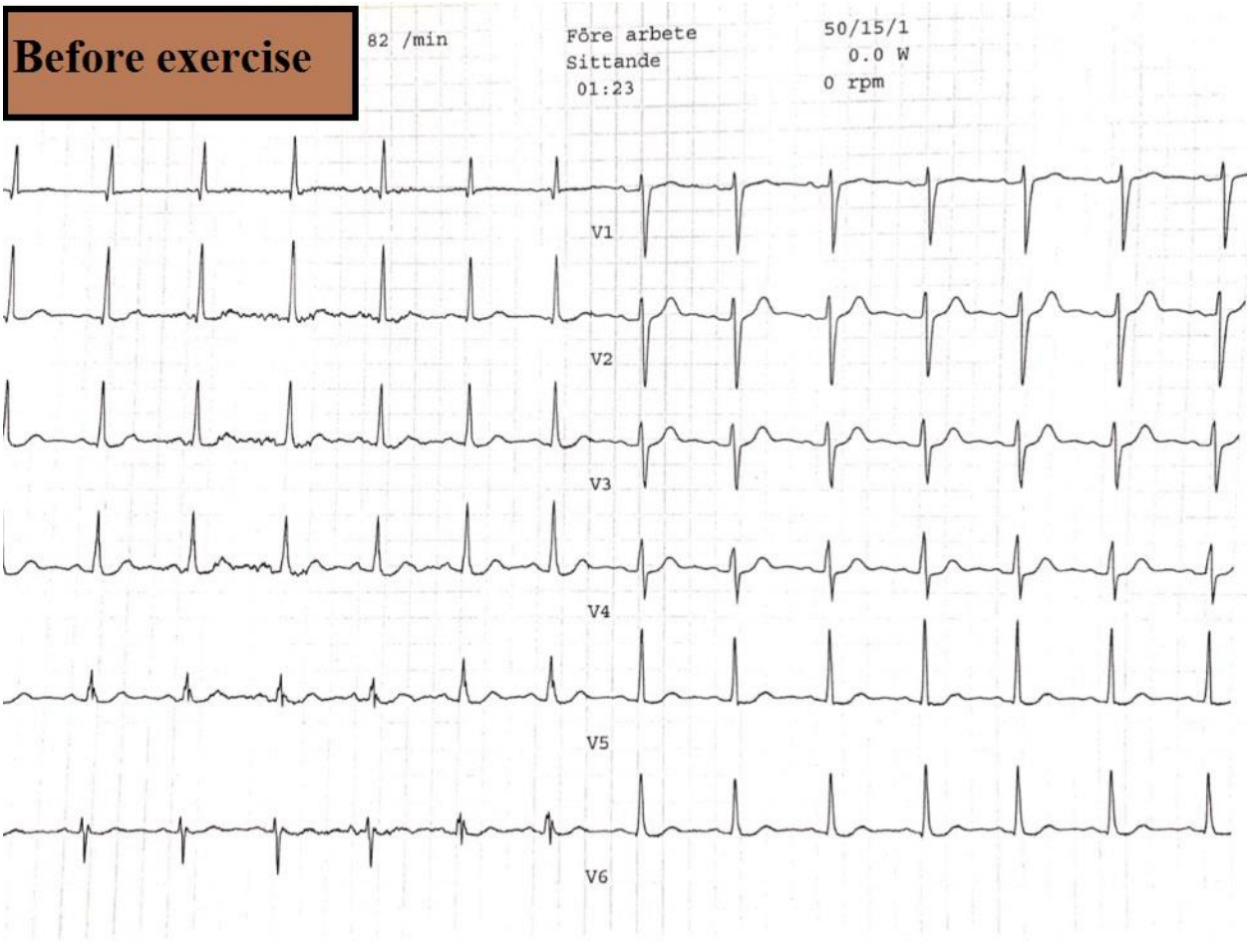

Figure 6: Normal 12 lead ECG before exercise.

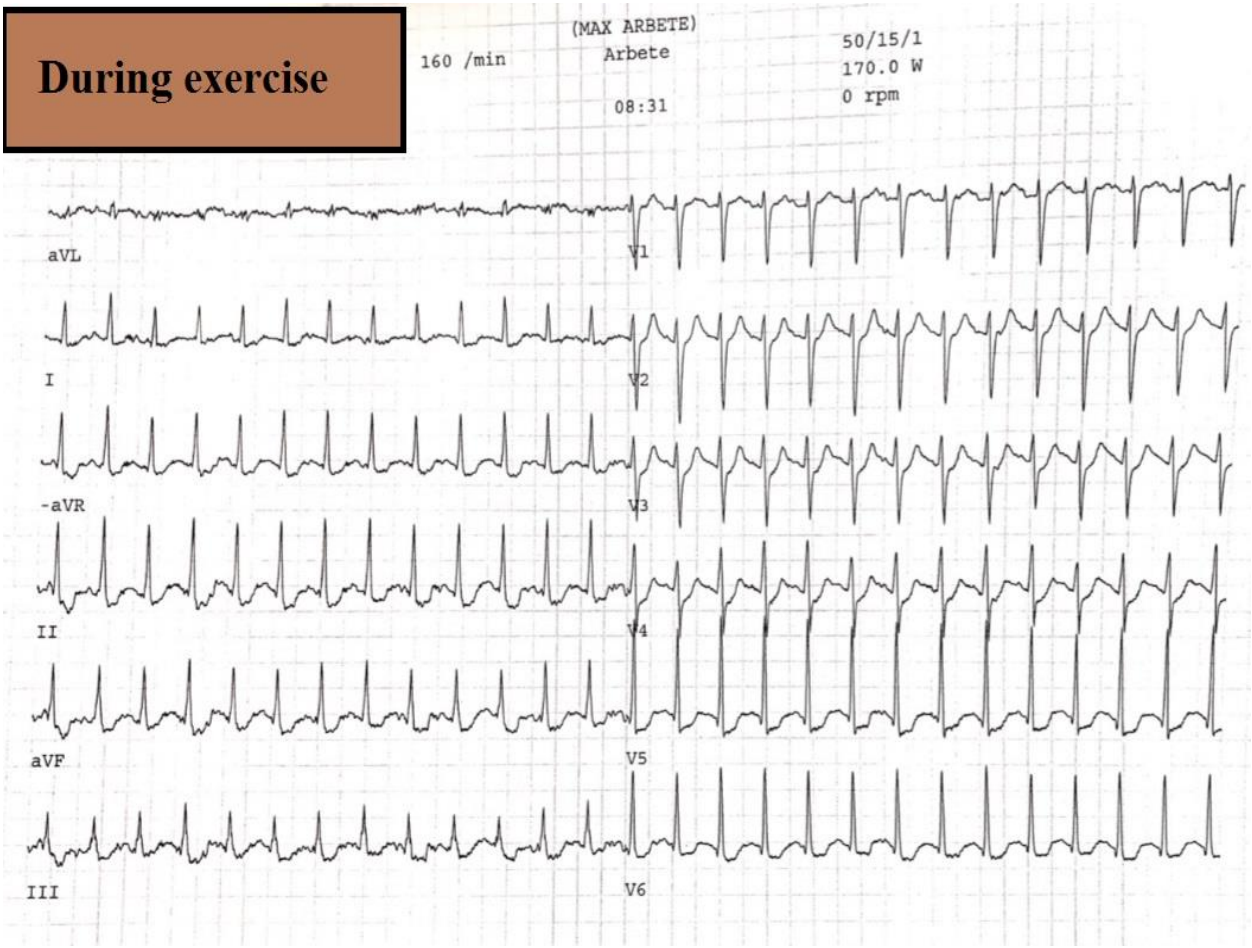

Figure 7: 12 lead ECG during exercise with ST changed (peak exercise).

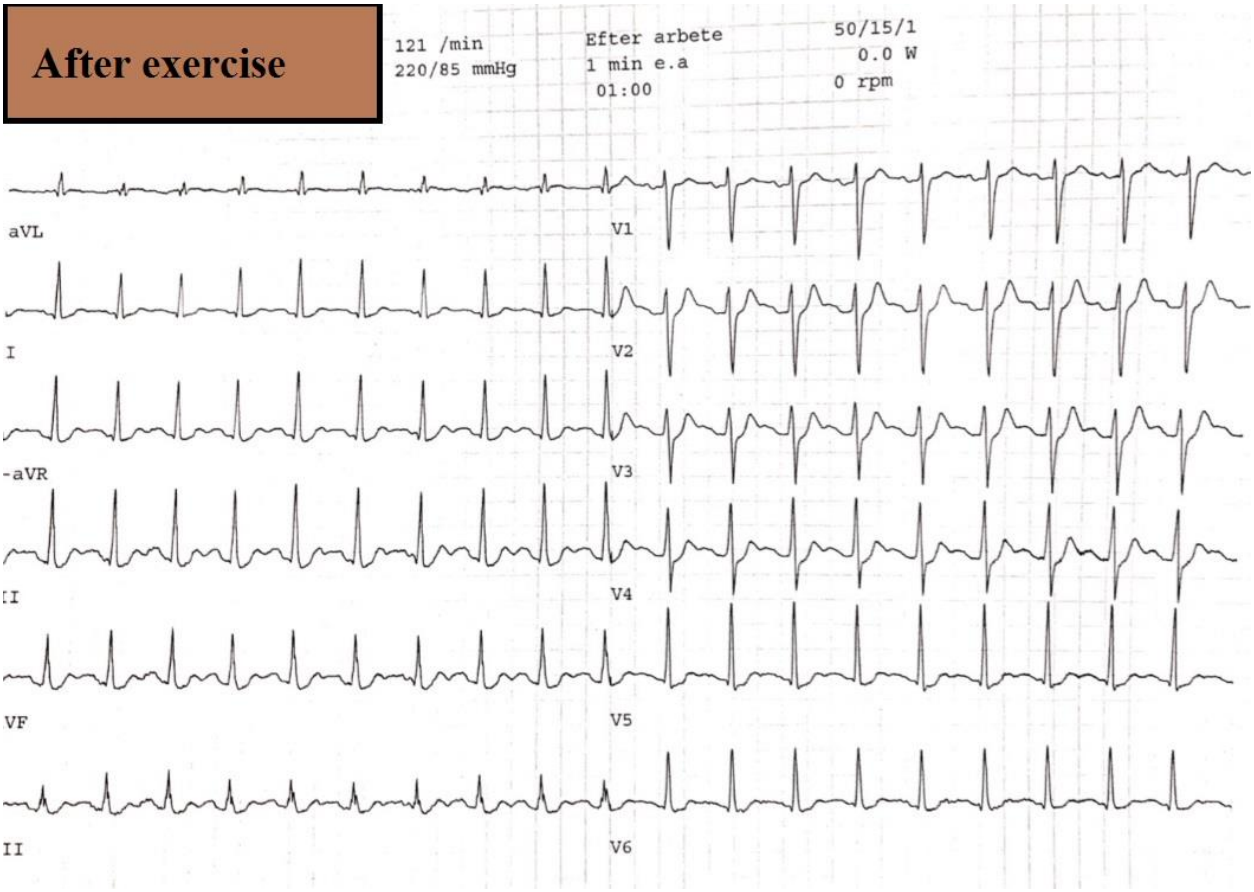

Figure 8: 12 lead ECG after exercise (recovery).

CMR perfusion scan

CMR studies were performed using a 1.5 Tesla MRI system (Magnetom Sonata Maestro Class, Siemens AG, Erlangen, Germany) (Figure 9), with the patient in the supine position, and additional ECG electrodes connected with external system (Magnitude 3150, In Vivo Research Inc., Orlando, FL, U.S.A.) for continuous heart rate monitoring (Al-Saadi et al., 2000).

Figure 9: Magnetom Sonata Maestro Class, Siemens AG, Erlangen, Germany

Blood pressure was also monitored. Both a six-channel body phased-array coil and a two-channel spine phased-array coil were used. Sequences acquired during breath-hold were performed during quiet expiration.

After localizers and anatomical images, perfusion imaging was performed. Typically, 3 short axis slices were acquired at the basal, mid papillary and apical levels of the left ventricle. Patients were stressed using a conventional adenosine protocol.

Adenosine stimulates A2 receptors in the microvasculature, leading to relaxation of the arterioles. In normal myocardium, this leads to increased perfusion without changes in blood volume (Jayaweera et al., 1999). With coronary stenosis, the magnitude of the increased perfusion during vasodilation is compromised (Jayaweera et al., 1999).

The pressure drops results in capillary closure and reduced perfusion and blood volume, which is demonstrated as slower arrival and lower contrast agent concentration in the ischaemic segment (Jayaweera et al., 1999). A single shot prospectively gated balanced Turbo Field Echo (TFE) sequence with a typical in-plane resolution of 2.5 x 2.5mm was used.

Patients were then allowed to rest until the haemodynamic effects of the adenosine had subsided (typically 5 minutes). The location and distribution of myocardial perfusion defects in the left ventricle were described using the AHA 16 segment model (Cerqueira et al., 2002). For the stress study, intravenous adenosine was started 3 minutes before contrast injection.

Twenty short-axis images were taken at every level of myocardium before, during and after contrast injection. Myocardial perfusion was measured during adenosine infusion using a high dose of Gadolinium-DTPA (0.06 mmol/kg).

Adenosine was injected at a rate of 0.14 mg/kg/min, for 3–6 minutes for a total dose of 0.48 to 0.84 mg/kg. To avoid the risk of large bolus drug, adenosine and contrast were administered through separate IVs (Gerber et al., 2008). Acquired images were subsequently transferred to a dedicated computer for analysing changes in the myocardial signal intensity (Cullen et al., 1999).

Two experienced observers reported results by the visual assessment of the myocardial perfusion and the blood supply of the 6 conventionally studied segments. Rest and adenosine stress scans were magnified and displayed at the same time for visual assessment (Hamon et al., 2010).

In normal scans, the first pass into the myocardium changed its colour uniformly from black to grey. A slowly changing colour to grey suggested impaired perfusion and hence was considered as a perfusion defect either at rest or induced if it occurred at peak stress. The CMR system employed quantitative parametric tissue analysis (Jayaweera et al., 1999). Figure 10 details the comparison between MDCT perfusion and CMR perfusion during rest and during stress. During stress, there is perfusion defects in the basal inferior and infero-septal walls marked with the yellow arrows (Dweck et al., 2016).

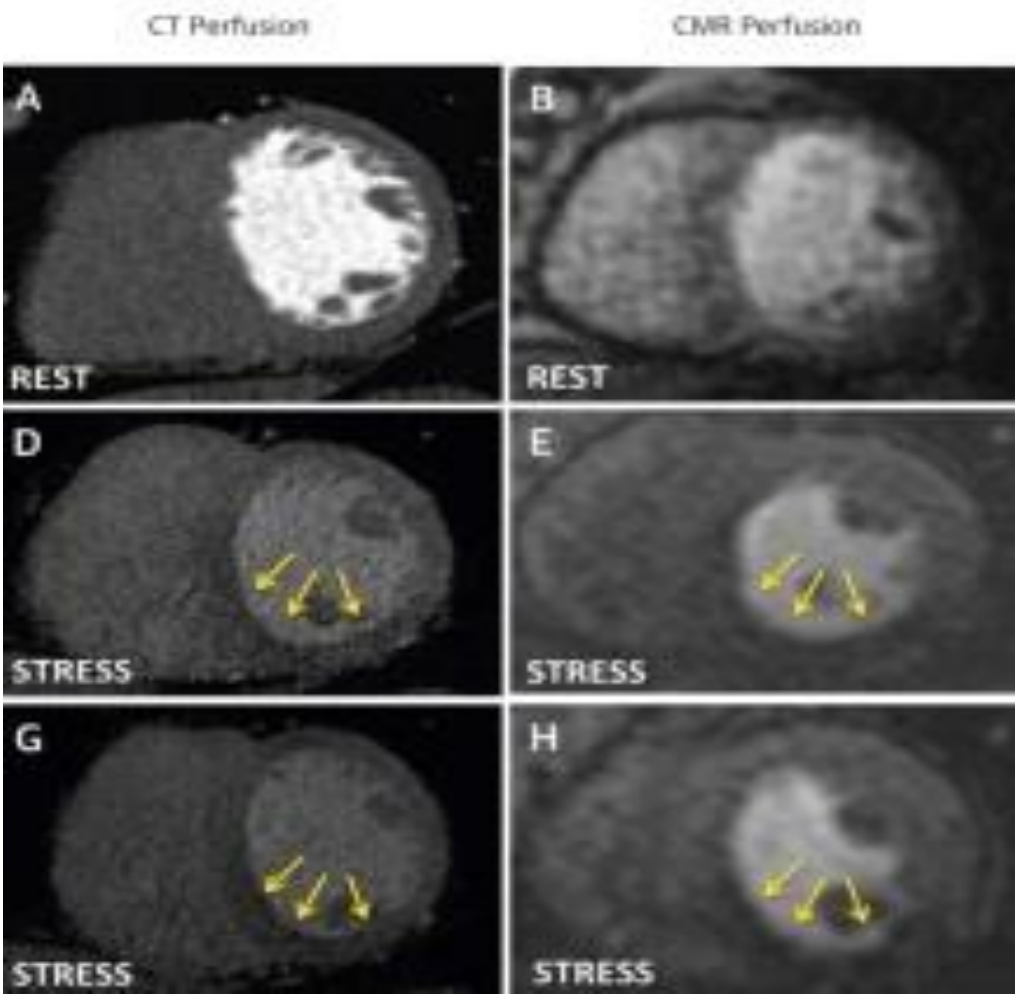

Figure 10: Comparison between CT perfusion and CMR perfusion during rest and stress (Dweck et al., 2016) (Permitted from the author)

According to the coronary angiography results, patients were divided into two groups: High Grad (HG) stenosis (≥50% stenosis) group (n=67, mean age 65.1±9.4 years) and no-HG stenosis (<50% stenosis) group (n=53, mean age 65.1±8.6 years).

The significant obstructive coronary disease was considered present when there was clear evidence for at least one HG stenosis with ≥50% lumen narrowing on the conventional angiogram. For compatibility the radiologists who analysed, interpreted and reported the CMR data have published work demonstrating high reliability (Voigtländer et al., 2011, Hunold et al., 2005).

Echocardiographic examination

All patients underwent rest and DSE. A Philips Intelligent E-33 system (Figure 11) with a multi-frequency transducer was used for all echocardiographic examinations.

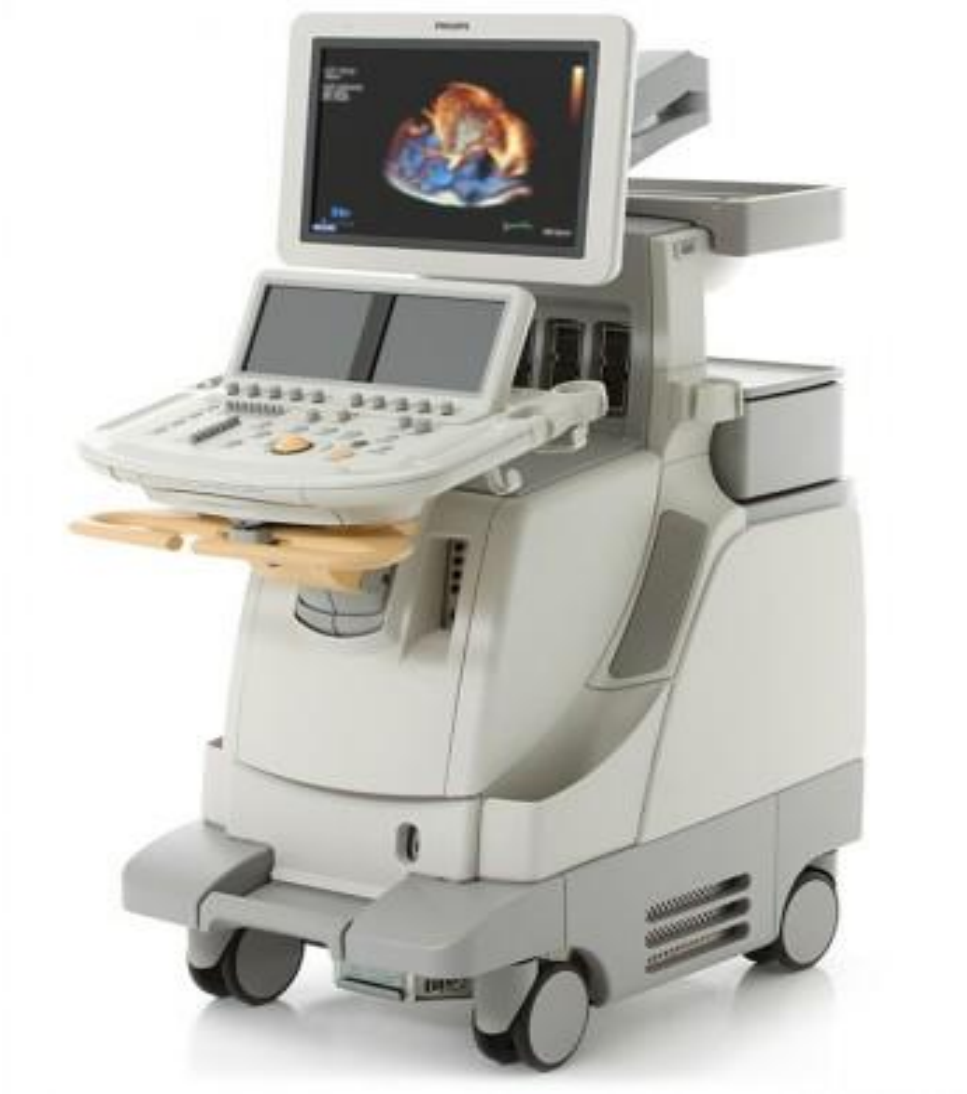

Figure 11: Echocardiography, Philips Intelligent E-33 system.

A standard protocol (McNeill et al., 1992) was used with dobutamine infusion, increasing every 3 min with 10 μg/kg/min to a maximum dose of 40 μg/kg/min. If the target heart rate was not reached, atropine (0.25 mg - 2 mg) was used. The images were obtained with the patient in the left lateral decubitus position and during expiration.

Left ventricular (LV) segmental wall motion was assessed using a 17-segment model. A global wall motion score was calculated using the segmental scoring system (1 = normal, 2 = hypokinetic, 3 = akinetic, 4 = dyskinetic). (Table 3). RWMAs considered when confirmed by a minimum of two expert (senior) reviewers.

Table 3 The segmental scoring system

Score:

1 = Normal/Hyperkinetic: normal/increased systolic wall motion and thickening

2 = Hypokinetic: decreased systolic wall motion and thickening

3 = Akinetic: absent systolic wall motion and thickening

4 = Dyskinetic: outward systolic wall motion and thickening

With two-dimensional echocardiography from the four-chamber view, ventricular long axis motion was studied by M-mode with the cursor positioned at the LV septal (Figure 12, 13) and lateral (Figure 14, 15) annulus and recorded mitral annular plane systolic excursion (MAPSE) and then positioned at the RV free wall annulus (Figure 16, 17) to measure tricuspid annular plane systolic excursion (TAPSE). The total long-axis amplitude of motion was measured from the annular displacement between the outermost point at the onset of the Q wave and the innermost part shortly after the end of ejection. In addition, at the same sites, pulse wave myocardial tissue Doppler velocities were acquired to record systolic (s') and early (e') and late (a') diastolic velocities. All M-mode and pulse-wave myocardial tissue Doppler velocity measurements were recorded at rest and peak stress (at speeds of 100 and 50 mm/s, respectively).

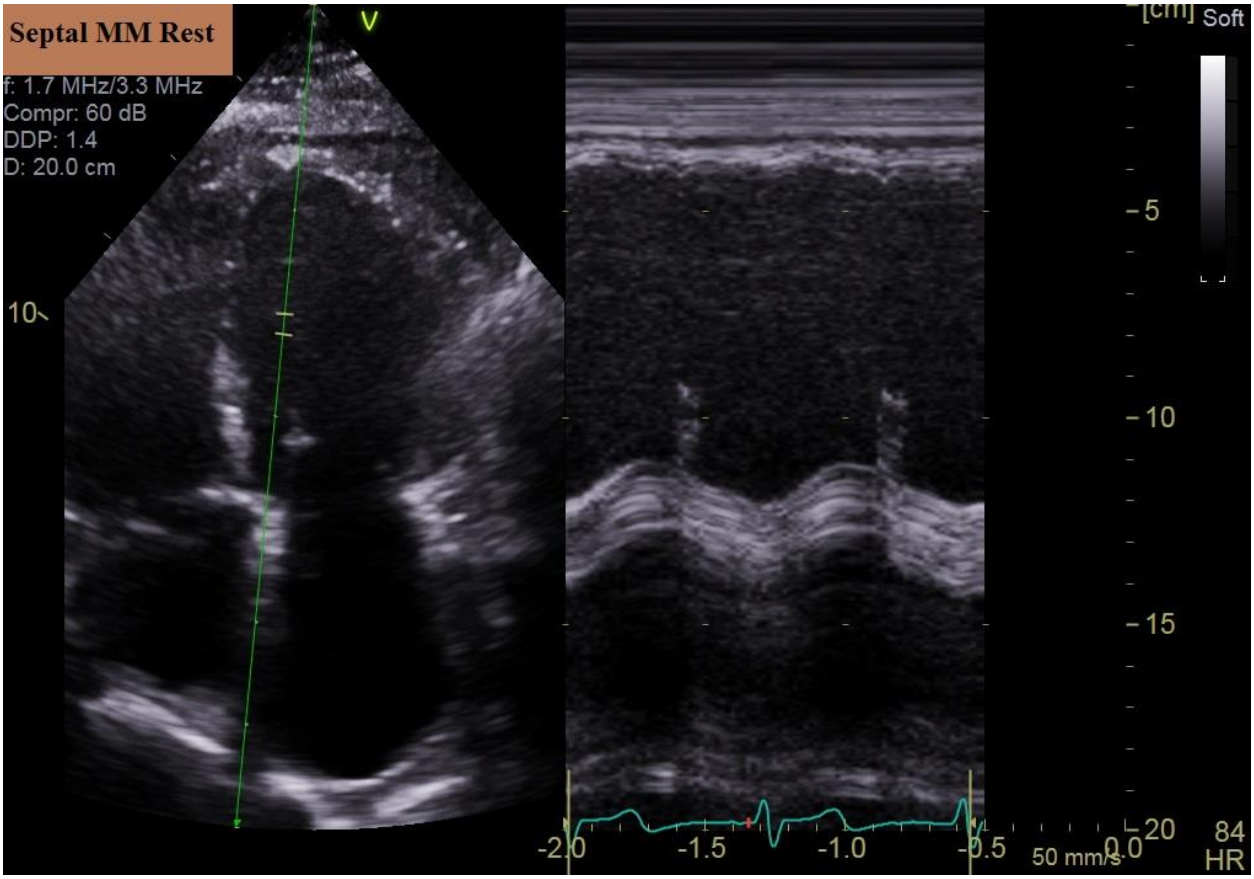

Figure 12: Trans-thoracic echocardiography, Septal M-mode at rest.

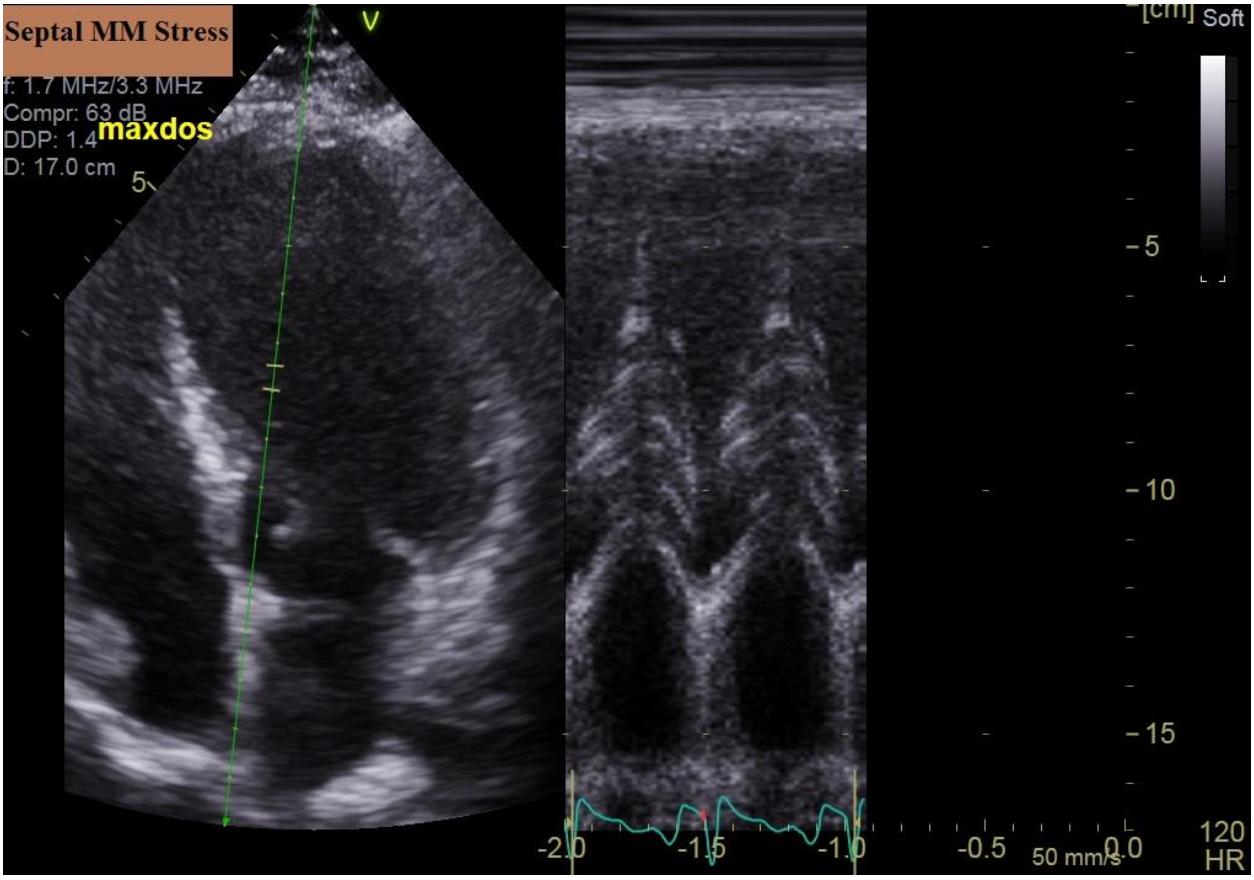

Figure 13: Trans-thoracic echocardiography, Septal M-mode at peak stress.

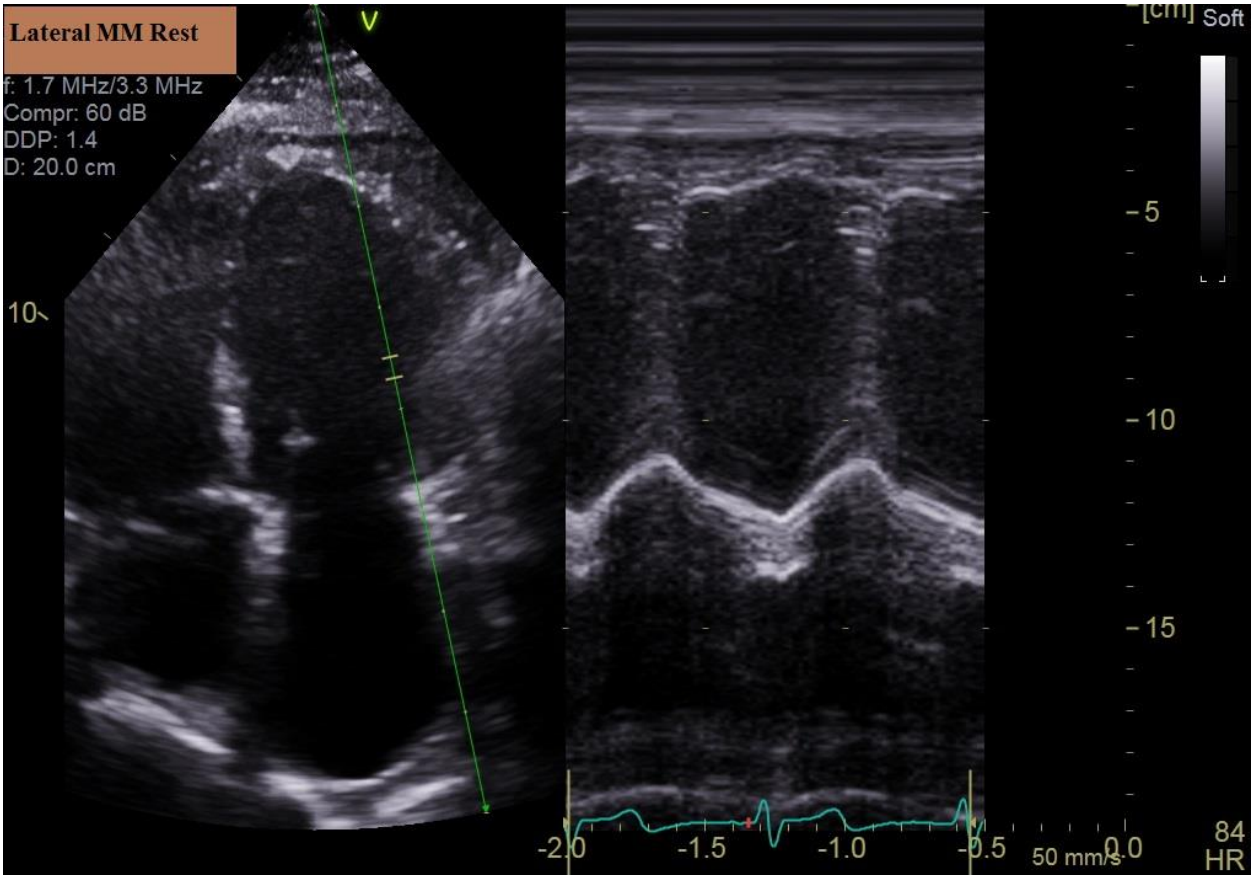

Figure 14: Trans-thoracic echocardiography, Lateral M-mode at rest.

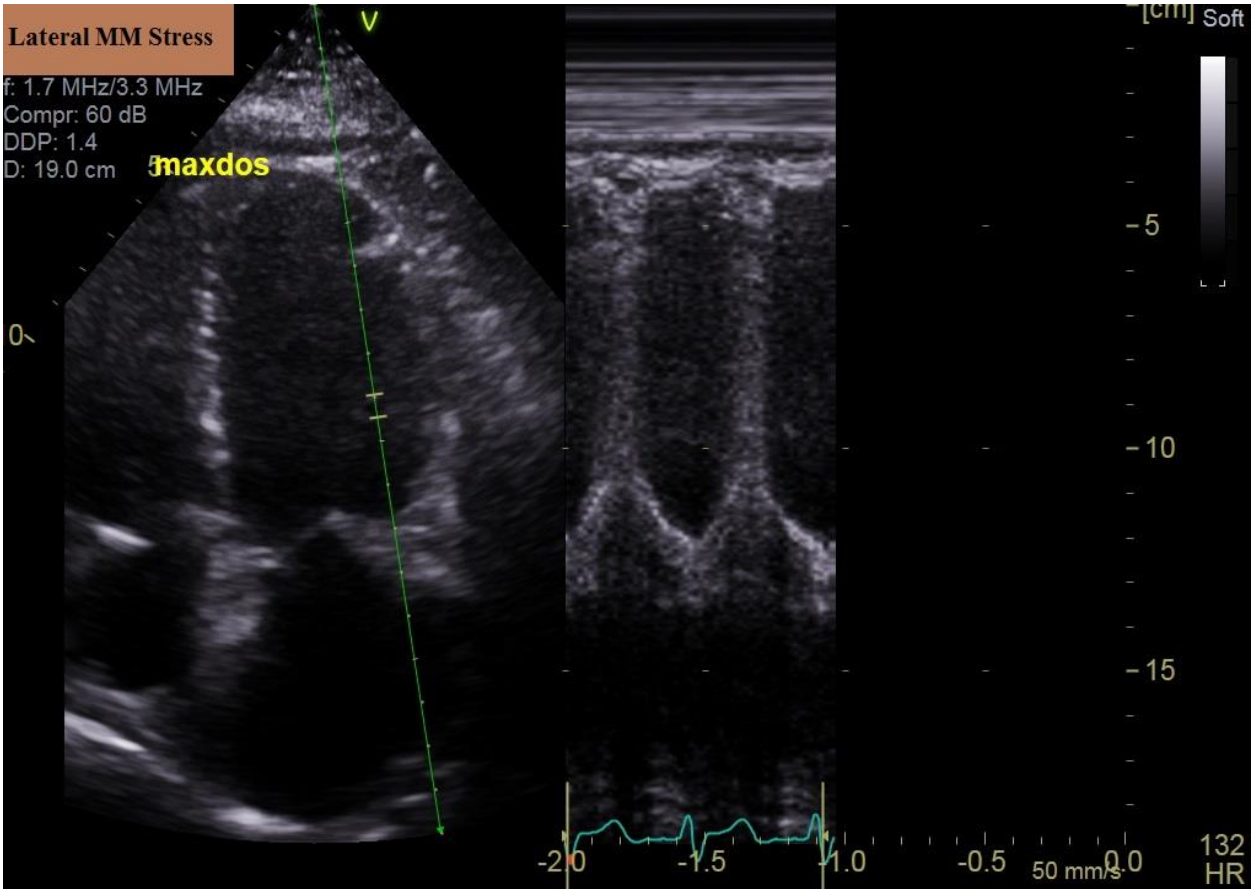

Figure 15: Trans-thoracic echocardiography, Lateral M-mode at peak stress.

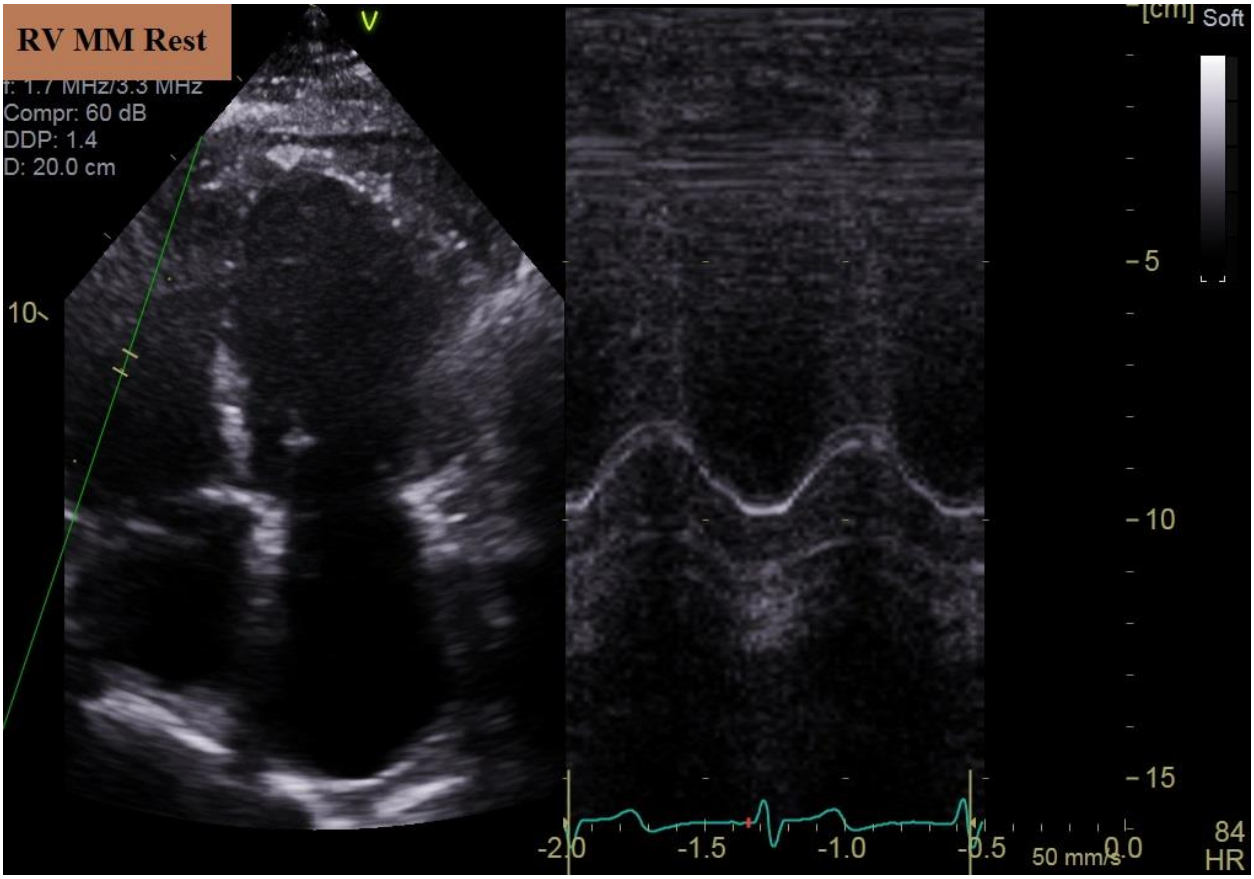

Figure 16: Trans-thoracic echocardiography, Right Ventricle M-mode at rest.

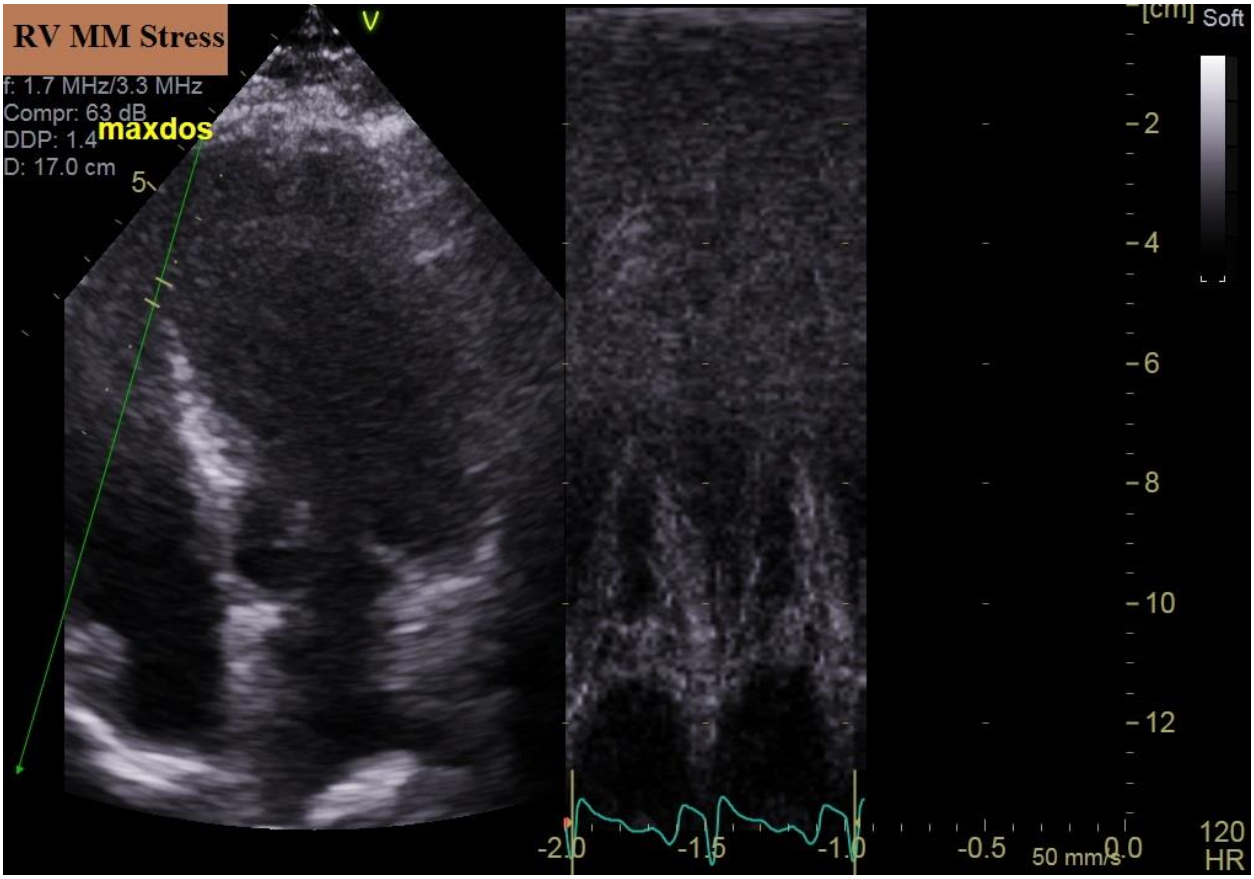

Figure 17: Trans-thoracic echocardiography, Right Ventricle M-mode at peak stress.

Tissue Doppler imaging assess myocardial motion linked to blood flow. Global and regional systolic and diastolic velocities can be displayed at rest and under stress.

RV peak systolic and early diastolic velocities were measured. LV myocardial velocities were recorded using Tissue Doppler Imaging (TDI). With tissue Doppler, the velocities of myocardial segments can be measured. In tissue Doppler, the cursor is positioned over the tissue we want to examine. The probe will send pulses to the selected area, the pulses reflect with different frequency, and then the machine calculates the velocity of the reflection.

During systole of the heart moves toward the apex (toward the probe), (s') will appear above the baseline as it is positive and called systolic deflection, whereas, during diastole the heart base moves away from the apex (away from the probe), (e') and (a') will appear as two negative deflections below baseline (e') and (a') are equivalent to e/a of mitral filling.

We measured systolic (s') and early and late (e' and a') diastolic myocardial velocities in the lateral (Figure 18) and septal (Figure 19) segments of the LV, and at the RV free wall (Figure 20).

In addition, we measured Peak LV and RV early (e wave), and late (a wave) diastolic velocities, and calculated the e/a ratios.

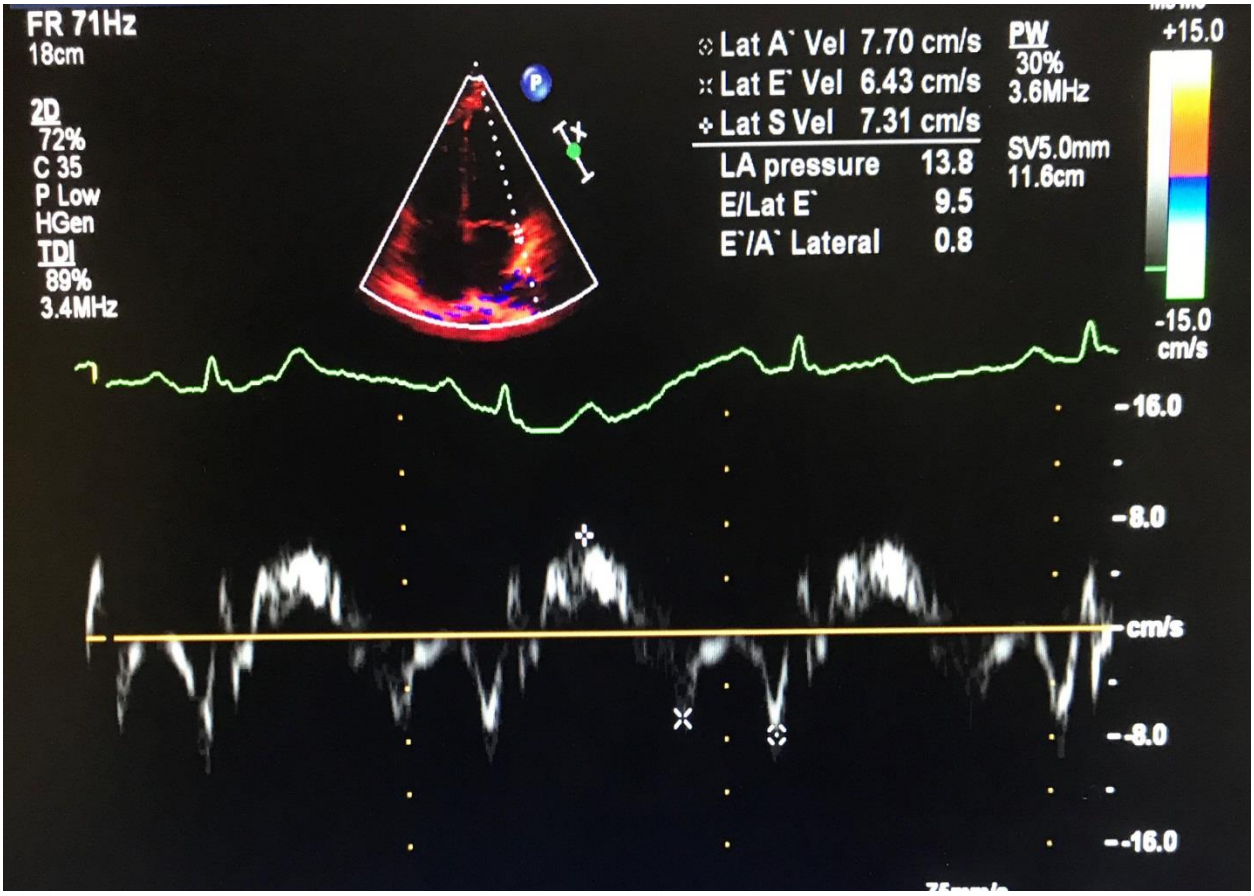

Figure 18: Tissue Doppler imaging of lateral segment of LV during rest.

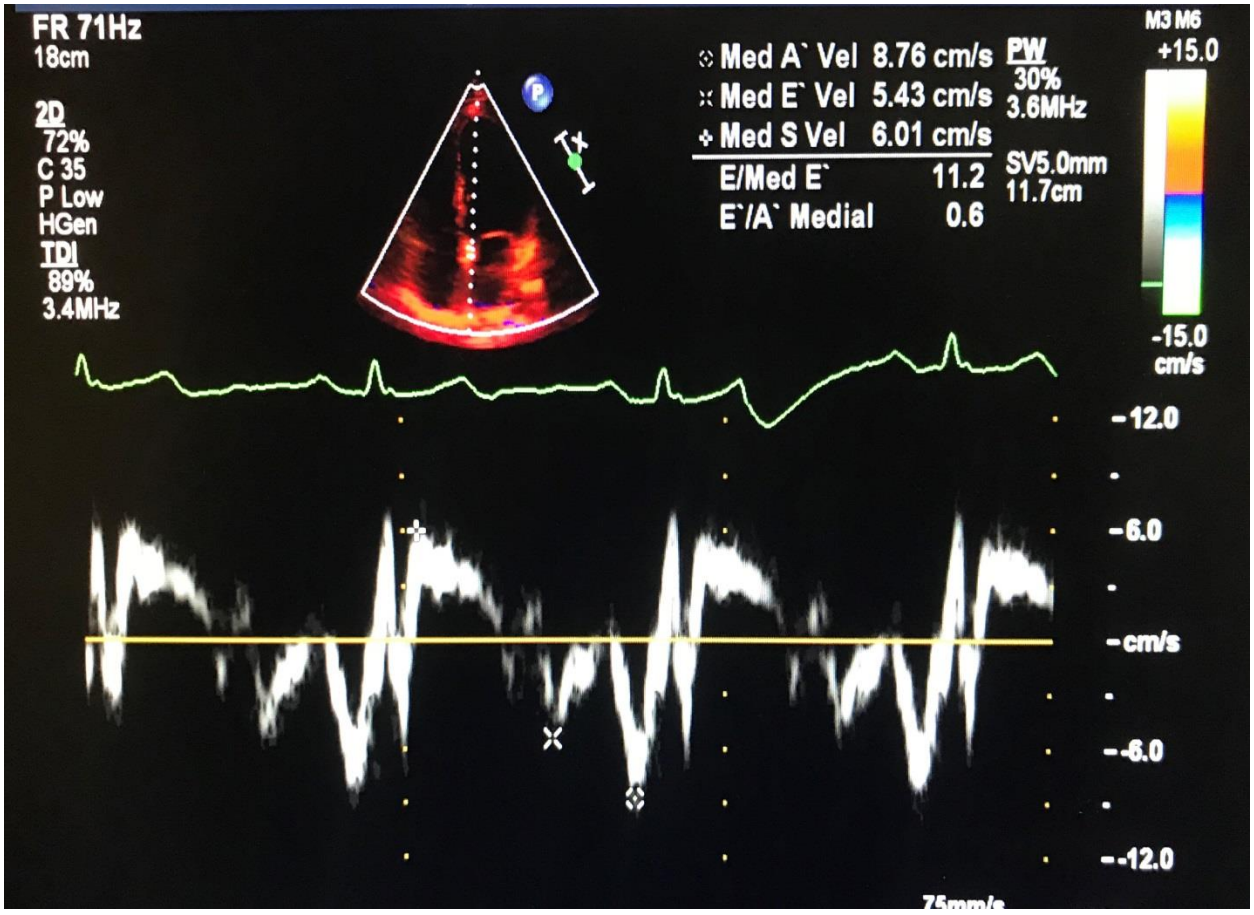

Figure 19: Tissue Doppler imaging of septal segment of LV during rest.

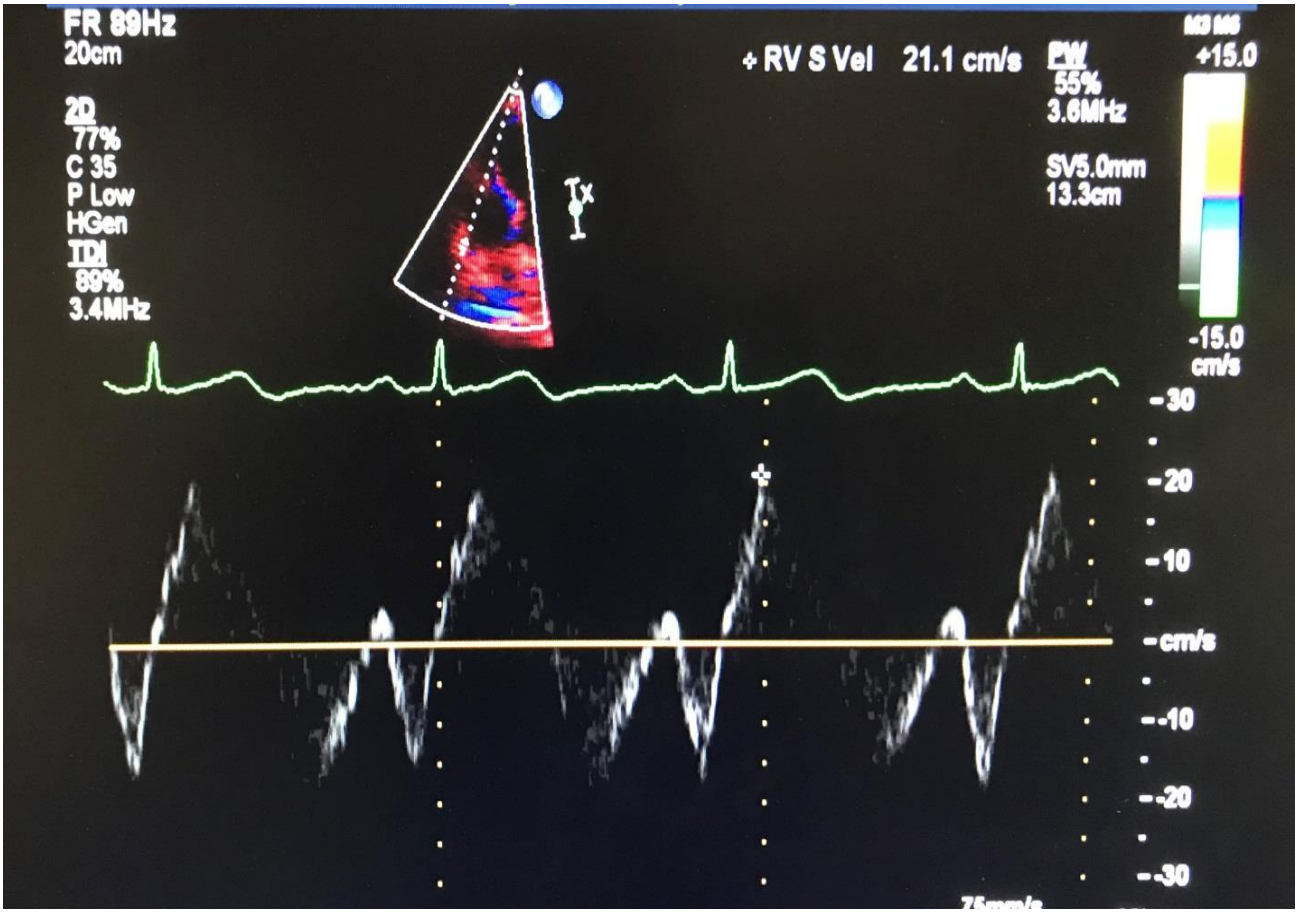

Figure 20: Tissue Doppler imaging of RV during rest.

Dobutamine infusion was performed with an IVAC pump. Starting with a dose of 10µg/kg/min and increasing by similar increments every 3 minutes to a maximum of 40 µg/kg/min. Stress endpoints in controls were achieving 85% of the predicted target heart rate (220 minus age) or maximum Dobutamine dose. Atropine was used in some patients who did not reached the target heart rate after the maximum Dobutamine dose. Stress endpoints in patients were a development of symptoms (chest pain or breathlessness), systolic blood pressure decreased by 20 mmHg, ischaemic ECG changes such as ST changes or T wave inversion, and arrhythmia.

Blood pressure (systolic and diastolic) was measured automatically at rest and at the end of each stage of stress. 12 lead ECG and oxygen saturation were recorded at the end of each stress stage.

Tissue Doppler velocities of all the LV segments measured during stress and compared with rest.

All the recruited patients complained of exertional angina-like symptoms, had >1mm ST shift on exercise test, but no obstructive disease on conventional angiography. All had normal LV ejection fraction (>55%), RV size and inlet diameter (<3.6 cm). All patients underwent DSE including M-mode and tissue Doppler of LV and RV free wall, and CT CACS using a MDCT system. Based on CT findings patients were divided into Group I with CACS<100 and Group II with CACS >100.

When patients are referred for DSE and the echo images are suboptimal due to lung problems or obesity, this may result in inaccurate assessment of LV function. As such contrast enhanced echo improves image quality and endocardial border definition during rest and stress. However, in this study, contrast was not available and as a result a number of studies were excluded due to poor image quality.

Conventional risk factors

A family history of premature CVD was defined as CAD in a first-degree relative (men <55 years and women <65 years). DM was defined as fasting glucose level of at least 126 mg/dl (7.0 mmol/l), use of hypoglycemic medications or self-reported previous physician diagnosis. Hypertension was defined as the use of antihypertensive medications or known but untreated hypertension. Dyslipidaemia was defined as the use of cholesterol-lowering medications or having known but untreated total serum cholesterol >200mg/dl (5.2 mmol/L). Current smokers and those who stopped smoking less than 30 days prior to the CT scan were included in the smoking category, whereas the remainder was characterized as non-smokers. Obesity was defined as body mass index (BMI) $\geq 30 kg/m^2$, calculated from standardized measurements of height and weight.

Statistics

The statistical analysis was undertaken using a standard statistical software package (SPSS 18.0, SPSS Inc.). Categorical variables were expressed as an absolute number and percentage (%). Normally distributed continuous data were expressed as the mean ± standard deviation. The sensitivity, specificity and ratio comparison were analysed using Chi-square test. A p-value of less than 0.05 was considered statistically significant. Unpaired Student t-test was used to compare the difference between the two groups.

Statistical measures of performance

Sensitivity is a test, which measures the proportion of true positives (disease correctly identified) and specificity is a test, which measures the proportion of true negatives (no disease correctly identified).

These measures provide the relative accuracy of an investigation when compared to the reference standard. Sensitivity is calculated by dividing the number of diseased patients who have positive tests by all the diseased patients and specificity is calculated by dividing the number of normal patients who have negative tests by the number of all the normal patients. The positive predictive value (PPV) is a positive test result and the patient truly has disease and the negative predictive value (NPV) is a negative test result and the patient truly does not have disease. PPV is calculated by dividing the number of diseased patients who have a positive test by the number of all the patients who have a positive test (true and false positive); however, the NPV is calculated by dividing the number of the non-diseased patients who have positive tests (false positive) by all the patients with a positive test. Ideally, measurements should be both accurate and precise. Both accuracy and precision reflect how close a measurement is to an actual value, but they are not the same. Accuracy reflects how close a measurement conforms to the correct value, whereas, precision reflects how close two or more measurements are to each other, regardless of whether those measurements are accurate or not. A Receiver Operator Characteristic (ROC) curve is a graphical plot used to show the diagnostic ability of binary classifiers, which is a plot of the sensitivity against the specificity for the different possible cut-points of a diagnostic test. The best cut-off values for sensitivity and specificity were determined.

CHAPTER THREE

STUDY ONE

Coronary calcium score is superior to exercise tolerance testing in predicting significant coronary artery stenosis

Backgroud

Coronary artery disease is one of the most common causes of death. Coronary calcium with CT scan measuring Agatston score, has been shown to be a reliable non-invasive investigation for screening patients with cardiac risk factors and for assessment of CAD. Coronary artery calcium detected with EBCT and MDCT is a sensitive marker of coronary artery calcifications. These scans measure the amount of calcium accumulated in the coronary arteries (Oudkerk et al., 2008, Agatston et al., 1990). The identification of CAC by MDCT or EBCT studies can be performed within 10 minutes (Budoff et al., 2006). CAC score increases with age and are known to be higher in males (McClelland et al., 2006). According to the ACC and the AHA guidelines, a heart scan by MDCT is generally not recommended for males under the age of 40 and females under the age of 50 (as it is unlikely to detect calcium at these age cut-offs), and to those who have low cardiac risk factors and people who are known to have CAD (Greenland et al., 2010). The severity of atherosclerosis is associated with the amount of calcium detected in the coronary arteries. A CAC score >400 is a severe form of coronary calcifications, and >1000 is very severe calcification (Azevedo et al., 2012). Calcium is not present in all the atherosclerotic plaque, therefore there is a possibility to find people with zero CAC and have obstructed CAD (Villines et al., 2011).

There is a recommendation from the American College of Cardiology Foundation/American Heart Association (ACC-AHA) guidelines to screen asymptomatic patients with intermediate risk of CAD (Greenland et al., 2010).

On the other hand, ETT is a safe and inexpensive technique; however, it has limited positive predictive value for detecting CAD. During the exercise, if there are no ECG changes and there are no symptoms at maximum exercise, this indicates that the patient is less likely to have CAD. Any ECG changes with or without cardiac symptoms suggest a need for further investigations to confirm and determine the severity of CAD (Gershlick et al., 2007). The ACC-AHA guidelines recommend exercise ECG as the initial diagnostic test in patients at intermediate cardiac risk who are able to exercise (Fihn et al., 2012). Exercise-induced ST depression is a strong predictor of cardiac events (Mark et al., 1987). In patients with long-term cardiac risk factors, the CAC score by MDCT is the first line of investigation (Chang et al., 2015). Asymptomatic individuals with cardiac risk factors can be detected by the appearance of CAC, and positive ETT for those patients predicts cardiac events (Greenland et al., 2004). 50% of asymptomatic patients with a CAC of zero have less coronary events, even when they have a positive ETT. Patients with zero CAC score and positive ETT are more likely to have a false positive ETT result (Grossman et al., 2015). ETT has low sensitivity and specificity in predicting cardiac events in asymptomatic patients (Gibson, 1991).

In patients with cardiac chest pain, CAC is a trusted first investigation to rule out occluded CAD when compared to ETT and can be performed on all patients presenting with chest pain (Dedic et al., 2013). In stable patients with chest pain and intermediate cardiac risk factors, both CAC by MDCT and ETT investigations give high diagnostic accuracy in predicting CAD (Versteylen et al., 2013).

On the other hand, ETT is a safe and inexpensive technique; however, it has limited positive predictive value for detecting CAD. During the exercise, if there is no ECG change and there are no symptoms at maximum exercise, as detailed above, this indicates that the patient is less likely to have CAD. Any ECG changes with or without cardiac symptoms suggest a need for further investigations to confirm and determine the severity of CAD (Gershlick et al., 2007). The ACC-AHA guidelines recommend exercise ECG as the initial diagnostic test in patients at intermediate cardiac risk who are able to exercise (Fihn et al., 2012). Exercise-induced ST depression is a strong predictor of cardiac events (Mark et al., 1987). In patients with long-term cardiac risk factors, the CAC score by MDCT is the first line of investigation (Chang et al., 2015). Asymptomatic individuals with cardiac risk factors can be detected by the appearance of CAC, and positive ETT for those patients predicts cardiac events (Greenland et al., 2004). 50% of asymptomatic patients with a CAC of zero have less coronary events, even when they have a positive ETT. Patients with zero CAC score and positive ETT are more likely to have a false positive ETT result (Grossman et al., 2015). ETT display low sensitivity and specificity in predicting cardiac events in asymptomatic patients (Gibson, 1991). In patients with cardiac chest pain, CAC is a trusted first investigation to rule out occluded CAD when compared to ETT and can be performed on all patients presenting with chest pain (Dedic et al., 2013). In stable patients with chest pain and intermediate cardiac risk factors, both CAC by MDCT and ETT investigations give high diagnostic accuracy in predicting CAD (Versteylen et al., 2013).

Aim

The aim of this study is to compare the sensitivity and specificity of CAC and ETT in predicting significant coronary artery stenosis in a group of symptomatic patients at intermediate risk of CAD.

METHODS

This was a retrospective study investigating 360 patients presenting with angina-like symptoms to Bethanien Hospital Frankfurt, Germany between 2007 and 2010, or Umea Heart Centre, Umea, Sweden between 2009 and 2011. Patients with chronic kidney disease (creatinine>130mmol/L or eGFR < 45 mL/min/1.73 m^2), significant heart valve disease, heart failure, thyroid disease, parathyroid disease and severe inflammatory disease were excluded from the study. These patients underwent firstly ETT, then CT scanning for calcium scoring and finally conventional coronary angiography. All the patients had cardiac conventional risk factors assessed.

Conventional risk factors

Family history for premature disease was defined as CAD in a first-degree relative (men <55 years and women <65 years). Diabetes mellitus was defined as fasting glucose level of at least 126 mg/dl (7.0 mmol/l), use of hypoglycaemic medications or self-reported previous physician diagnosis. Hypertension was defined as the use of antihypertensive medications or known but untreated hypertension. Dyslipidaemia was defined as the use of cholesterol-lowering medications or having known but untreated total serum cholesterol >200mg/dl (5.2 mmol/L). Current smokers and those who stopped smoking less than 30 days prior to the CT scan were included in the smoking category, whereas the remainder was characterized as non-smokers. Obesity was defined as body mass index (BMI) ≥30kg/m^2, calculated from standardized measurements of height and weight.

Intermediate risks factors can be assessed in primary health care and can suggest an increased risk of developing a heart attack, heart failure and other cardiac complications.

Exercise Tolerance Testing (ETT)

All patients underwent exercise ECG using conventional treadmill method utilizing the Bruce protocol. A positive exercise ECG was taken as >1.5 mm ST depression after the J point with more information in chapter “2”.

Calcium screening

Computed tomography was used to determine coronary calcium. The scanner operated in the high resolution volume mode. CT was performed using a 64-detector-row scanner (Somatom Sensation Cardiac 64; Siemens Medical Solutions, Forchheim, Germany), explained in detail in chapter “2”.

Coronary angiography

The Judkin’s technique was used with at least four views of the left system and two views of the right system. More details in chapter “2”.

Statistics

The statistical analysis was undertaken using a standard statistical software package (SPSS 18.0, SPSS Inc.). Categorical variables were expressed as an absolute number and percentage (%). Normally distributed continuous data were expressed as mean ± standard deviation.

The sensitivity, specificity and ratio comparison were analysed using Chi square test. As the two methods use same group of patients, the McNemar test was used. A *p*-value less than 0.05 was considered statistically significant.

Results

Population characteristics

Table (4) shows the population characteristics of age, gender and coronary atherosclerosis risk factors (hypertension, dyslipidaemia, smoking, obesity, family history of CAD, and DM). The total population numbered 360 out of 515 patients, mean age 64.7±9.8years, 208 (59%) were males. There were 241 (67%) patients <70 years, and the remaining 119 (33%) patients were ≥70 years. Two thirds of the patients (68%) had hypertension and around 50% had dyslipidaemia and/or family history of CAD. We excluded all patients who did not have all the required data. Moreover, we excluded patients who had inconclusive ETT and/or MDCT results, and accordingly those who did not get referred for invasive angiography. The mean CAC score for the whole patient group was 295±561. There were 142 (39.4%) out of 360 patients who had a positive ETT, 70 of these were males. All the patients exercised ≥9 mins, and most of them reached the target heart rate.

Those who failed to reach their target HR had ST segment changes suggesting a positive ETT. All the ETT results were reviewed by two investigators and confirmed by Professor N. Patel (second supervisor).

Table 4: Population characteristics of the 360 patients

	Percentage/mean age	+VE ETT
Mean age	64.7±9.8	
Males	208 (57.8%)	70 (33.65%)
Hypertension	246 (68.3%)	93 (37.8%)
Hypercholesterolemia	190 (52.8%)	69 (36.31%)
Smoking	106 (29.4%)	38 (35.84%)
Obesity	103 (28.6%)	33 (32.0%)
Family history	169 (46.9%)	63 (37.27%)
Diabetes mellitus	38 (10.6%)	14 (36.84%)
Mean CAC score	295±561	

CAC presence/score and ETT in the prediction of CA stenosis (Table 4 and figure 20)

Table 5 shows that the presence of CAC >0 had a sensitivity of 97% in predicting both ≥50% and ≥70% CA stenosis and a sensitivity of 96% in predicting single- and multi-vessel disease (SVD and MVD). The negative (-ve) predictive value of the presence of CAC >0 for ≥50% CAD, ≥70% CAD, single CAD and multiple CAD was 96%, 97%, 79% and 92%, respectively, but the specificity was generally poor.

Compared to CAC >0, a CAC ≥400 had higher specificity for CA stenosis ≥50%, ≥70% and MVD ($p<0.001$) and for SVD ($p=0.05$) but lower sensitivity which fell to <50% ($p<0.001$ for CA stenosis ≥50%, ≥70% and SVD; $p=0.01$ for MVD) and -ve predictive value, although only the difference in SVD was significant ($p=0.01$). ETT sensitivity was significantly lower for CAC >0 ($p<0.001$ for CA stenosis ≥50%, ≥70% and SVD, $p=0.01$ for MVD) and not different from CAC ≥400 for all degrees of stenosis.

ETT specificity was higher than CAC >0 ($p<0.001$ for CA stenosis ≥50%, ≥70% and MVD, $p=0.62$ for SVD) but lower than for CAC ≥400 ($p=0.015$ and $p=0.027$ for CA stenosis ≥50% and ≥70%; SVD and MVD not significant), while the –ve predictive value was not significantly different from any measure of CAC >= 0 or CAC ≥400 except for SVD with CAC >0 ($p<0.001$). (Figure 21).

Table 5: The sensitivity and specificity for CAC and ETT to predict coronary stenosis (CS)

	%	CS ≥50%	CS ≥70%	Single vessel	Multi Vessel
CAC>0 (276)	Sensitivity	97.2 (91.5-99.3)	97.4 (90.1-99.5)	96.3(91.1-98.6)	96.6 (87.2-99.4)
	Specificity	26.2 (20.6-31.7)	23.3 (18.6-28.8)	46.3 (40.1-62.4)	19.0 (13.1-28.2)
	Positive value	35.9 (30.5-41.8)	25.7 (20.9-31.2)	85.4 (78.6-90.4)	37.7 (30.1-46.0)
	Negative value	95.6 (86.8-98.9)	97.1 (88.8-99.5)	79.2 (57.3-92.1)	91.7 (72.5-98.6)
CAC≥400 (84)	Sensitivity	41.7 (32.4-51.6)	37.7 (27.1-49.4))	42.5 (34.1-51.4)	45.8 (33.5-63.0)
	Specificity	84.5 (79.3-88.6)	80.6 (75.4-84.9)	92.7 (79.0-98.1)	71.6 (62.6-79.5)
	Positive value	53.6 (42.4-64.4)	34.5 (24.7-45.8)	95.0 (85.2-98.7)	45.0 (32.3-58.3)
	Negative value	77.1 (71.6-81.8)	82.6(77.5-86.8)	33.0 (24.7-42.5)	72.2 (63.8-80.7)
ETT positive	Sensitivity	38.9 (29.8-48.8)	39.0 (28.3-50.8)	41.0 (32.7-49.9)	45.8 (32.0-58.4)
	Specificity	60.3(54.0-66.3)	60.4 (54.4-66.1)	56.1 (39.9-71.2)	60.3 (50.3-68.7)
	Positive value	29.6 (22.4-37.9)	21.5 (14.9-28.9)	75.3 (63.6-84.4)	37.0 (25.0-47.8)
	Negative value	69.7 (63.1-75.7)	78.4 (72.3-83.6)	22.5 (15.1-32.1)	68.6 (58.6-77.3)

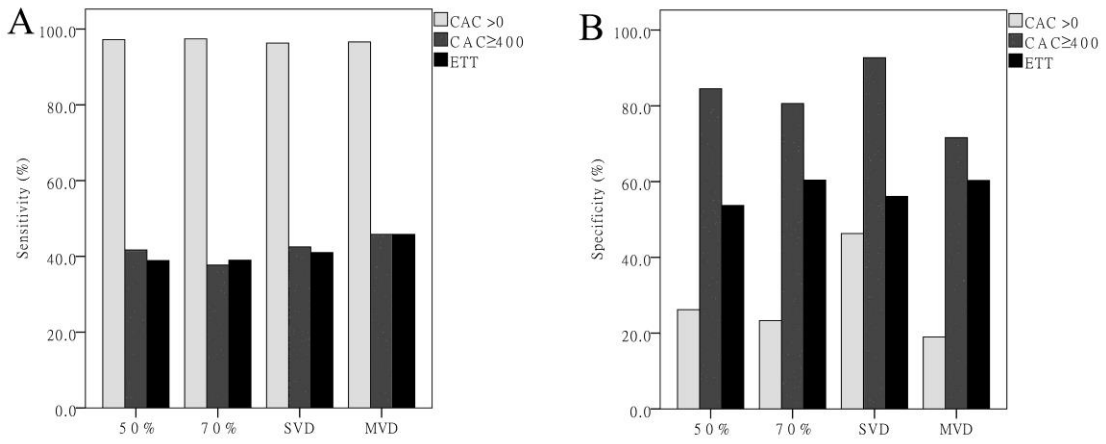

Figure 21: The Sensitivity (A) and Specificity (B) of CAC and ETT to predict CAD. A: CAC >0 sensitivity is higher than CAC≥400 and ETT (p<0.01), CAC≥400 and ETT is not different. B: CAC >0 specificity is lower than CAC≥400 (p<0.01) and ETT (p<0.01)

The effect of age on CAC and ETT in the prediction of CA stenosis (Table 6 and figure 22):

Comparison between CAC >0, CAC ≥400 and ETT within the two age groups:

In patients aged ≥70, sensitivity for CAC >0 was higher than for ETT (p=0.009 for CA stenosis ≥50%, p=0.045 for CA stenosis ≥70%, p=0.004 for SVD and p=0.08 for MVD) but not different between CAC >0 and CAC ≥ 400. Specificity is lower for CAC >0 than for both CAC ≥ 400 (p<0.01 for all) and ETT (p<0.001 for CA stenosis ≥50%, ≥70% and MVD, p=0.04 for SVD), and there was no difference in specificity between CAC ≥400 and ETT.

The –ve predictive value was not different between CAC >0, CAC≥ 400 and ETT.

In patients aged <70y, the sensitivity for CAC >0 was greater compared to both CAC ≥400 and ETT ($p<0.01$ for CA stenosis ≥50%, ≥70% and SVD and $p<0.05$ for MVD), but there was no difference in sensitivity between CAC ≥ 400 and ETT. Specificity was generally lower for CAC >0 than for both CAC ≥400 and ETT ($p<0.01$ for CA stenosis ≥50%, ≥70% and MVD) except for SVD, where there was no difference, while specificity for ETT was lower than for CAC ≥400 ($p<0.01$ for CA stenosis ≥50%, ≥70% and MVD, no difference for SVD). The –ve predictive value of CAC >0 was higher than for CAC ≥ 400 and ETT.

Comparison between age ≥70 and <70:

Compared to age <70, the sensitivity was higher in age ≥70 when using CAC ≥ 400 in predicting CA stenosis ≥50% ($p=0.018$), ≥70% ($p=0.06$), SVD ($p=0.008$) and MVD ($p=0.039$) but not when using CAC >0 and ETT. The specificity was lower in age ≥70 when using CAC >0 to predict CA stenosis ≥50% ($p<0.001$), ≥70% ($p<0.001$), SVD ($p=0.052$) and MVD ($p=0.018$), but not for CAC ≥400 and ETT. The –ve predictive value was not different between age ≥70 and <70 for any category of stenosis.

Table 6: The sensitivity and specificity for CAC and ETT to predict coronary stenosis (CS) in patients above and those below 70 years

		%	CS ≥50%	CS ≥70%	Single vessel	Multi vessel
≥70ys	CAC>0	Sensitivity	97.9 (97.3-99.9)	100 (87.0-100)	100 (82.2-100)	98.1 (88.4-99.9)
		Specificity	5.6 (1.8-14.3)	5.8 (2.2-13.7)	5 (0.9-18.2)	9.1 (0.5-42.8)
		Positive value	40.4 (31.4-50.0)	28.9 (21.0-38.3)	37.7 (25.9-51.1)	83.6 (71.5-91.4)
		Negative value	80.0 (29.9-98.9)	100 (46.3-100)	100 (19.8-100)	50 (0.3-97.3)
	CAC≥400	Sensitivity	61.7 (46.4-75.1)	57.6 (39.4-74.0)	73.9 (51.3-88.9)	65.4 (50.8-77.7)
		Specificity	75 (63.2-84.1)	67.4 (56.4-76.9)	57.5 (41.0-72.6)	100 (67.9-100)
		Positive value	61.7 (46.4-75.1)	40.4 (26.7-55.7)	50 (32.8-67.2)	100 (87.4-100)
		Negative value	75 (63.2-84.1)	80.6 (69.2-88.6)	79.3 (59.7-91.3)	37.9 (21.3-57.6)
	ETT positive	Sensitivity	40.4 (26.7-55.7)	45.5 (28.5-63.4)	43.5 (23.9-65.1)	38.5 (25.6-53.0)
		Specificity	66.7 (54.5-77.1)	67.4 (56.4-76.9)	67.5 (50.8-80.9)	72.7 (39.3-92.7)
		Positive value	44.2 (29.4-60.0)	34.9 (21.5-51.0)	43.5 (23.9-65.1)	87 (65.3-96.6)
		Negative value	63.2 (51.3-73.7)	76.3 (64.9-85.0)	67.5 (50.8-80.9)	20 (9.6-36.1)
<70ys	CAC>0	Sensitivity	96.7 (87.6-99.4)	95.5 (83.3-99.2)	94.4 (83.4-99.9)	95.1 (87.3-98.4)
		Specificity	33.9 (27.1-41.4)	31 (24.7-38.0)	26.3 (18.0-38.8)	60 (40.8-76.8)
		Positive value	33.1 (26.4-40.6)	23.6 (17.7-30.6)	37.8 (28.0-48.7)	86.7 (77.5-92.6)
		Negative value	96.8 (88.0-99.4)	96.8 (88.0-99.4)	90.9 (75.1-99.8)	81.8 (59.0-94.0)
	CAC≥400	Sensitivity	26.2 (16.2-39.3)	22.7 (12.0-38.2)	27.8 (15.2-46.5)	28 (19.0-39.2)
		Specificity	88.3 (82.5-92.5)	86.3 (80.1-90.6)	78.9 (68.2-87.3)	90 (72.3-97.4)
		Positive value	43.2 (27.5-60.4)	27 (14.4-44.4)	38.5 (20.9-59.3)	88.5 (68.7-97.0)
		Negative value	77.9 (71.5-83.3)	83.3 (77.3-88.0)	69.8 (60.0-79.9)	31.4 (22.1-42.4)
	ETT positive	Sensitivity	37.7 (25.9-51.1)	34.1 (20.9-50.0)	47.2 (29.2-63.1)	42.7 (32.0-54.1)
		Specificity	57.8 (50.2-65.0)	57.4 (50.1-64.3)	56.6 (44.1-66.9)	50 (31.7-68.3)
		Positive value	23.2 (15.6-33.0)	15.2 (9.0-24.1)	34 (20.0-46.8)	70 (55.2-81.7)
		Negative value	73.2 (65.0-80.2)	79.6 (71.8-85.7)	69.4 (56.2-80.1)	24.2 (14.6-37.0)

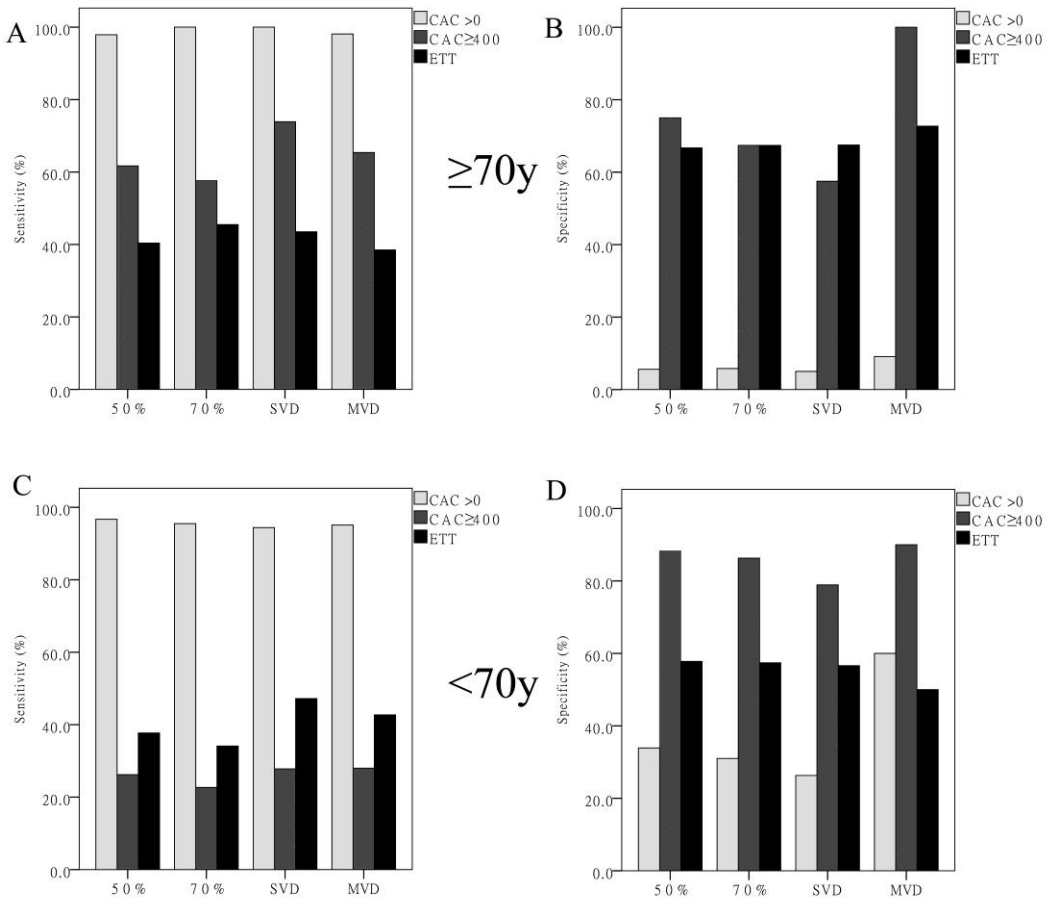

Figure 22: The Sensitivity and specificity of age≥70 (A, B) and age<70 (C,D) on CAC and ETT in the prediction of CA stenosis

The effect of gender on CAC and ETT in the prediction of CA stenosis (Table 7)

Comparison between CAC >0, CAC ≥400 and ETT according to gender:

In females, sensitivity for CAC >0 was higher than for CAC ≥400 ($p<0.01$ for CA stenosis ≥50%, ≥70% and SVD, $p=0.11$ for MVD) but not different from ETT and there was no difference in sensitivity between CAC ≥400 and ETT. Specificity for CAC >0 was lower than for CAC ≥400 ($p<0.01$ for CA stenosis ≥50%, ≥70% and MVD, $p=0.1$ for SVD) and modestly lower than for ETT ($p<0.05$ for CA stenosis ≥50% and ≥70%, $p=0.76$ for SVD, $p=0.10$ for MVD). CAC ≥400 had higher specificity than ETT in predicting CA stenosis ≥50% and ≥70% ($p<0.01$ for both) but not for SVD or MVD. In males, sensitivity for CAC >0 was higher than for both CAC ≥400 and ETT ($p<0.01$ for CA stenosis ≥50%, ≥70% and SVD, $p<0.05$ for MVD) but specificity for CAC>0 was lower than for CAC ≥400 and ETT in predicting CA stenosis ≥50%, ≥70% and MVD ($p<0.001$ for all) but not for SVD. Neither sensitivity nor specificity were different between CAC ≥400 and ETT and the –ve predictive value was similarly unchanged between CAC >0, CAC ≥400 and ETT for all categories except SVD. CAC >0 had higher -ve predictive value than CAC ≥400 ($p=0.02$) and ETT ($p=0.001$).

Comparison between females and males:

Table 7 shows that the sensitivity between females and males was not different for all categories of stenosis for CAC >0, CAC ≥400 and ETT. Compared to females, males had lower specificity in predicting CA stenosis ≥70% ($p=0.02$) when considering CAC >0 and had a lower -ve predictive value for SVD when considering CAC ≥400 ($p=0.01$) or ETT ($p=0.001$).

Table 7: The sensitivity and specificity for CAC and ETT to predict coronary stenosis (CS) in female and male patients.

		%	CS ≥50%	CS ≥70%	Single vessel	Multi vessel
CAC>0	Female	Sensitivity	93.5 (77.2-98.9)	95.2 (74.1-99.8)	90.9 (57.1-99.5)	91.9 (77.0-97.9)
		Specificity	33.1 (24.9-42.2)	31.3 (23.6-40.1)	28.3 (18.4-43.8)	48.1 (29.2-67.6)
		Positive value	26.4 (18.6-35.8)	18.2 (11.7-26.9)	20.8 (10.9-35.4)	70.8 (55.7-82.6)
		Negative value	95.2 (82.6-99.2)	97.6 (85.9-99.8)	93.8 (69.2-99.7)	81.3 (53.7-95.0)
	Male	Sensitivity	98.7 (92.0-99.9)	98.2 (89.2-99.9)	97.9 (87.5-99.9)	97.9 (92.0-99.6)
		Specificity	19.1 (12.9-27.1)	16.4 (11.1-23.5)	11.1 (5-22.2)	42.9 (18.8-70.4)
		Positive value	41.8 (34.6-49.3)	30.2 (23.8-37.5)	45.6 (35.9-55.7)	92.2 (84.8-96.3)
		Negative value	96.2 (78.4-99.8)	96.2 (78.4-99.8)	87.5 (46.7-99.3)	75 (35.6-95.5)
CAC≥400	Female	Sensitivity	29 (14.9-48.2)	19 (6.3-42.6)	27.3 (8.1-64.6)	29.7 (16.4-27.2)
		Specificity	95 (89.1-98.0)	91.6 (85.1-95.5)	83.0 (70.2-91.6)	96.3 (76.1-99.8)
		Positive value	60 (32.9-84.5)	26.7 (8.9-55.2)	25 (6.7-57.2)	91.7 (59.8-99.6)
		Negative value	83.9 (76.5-89.5)	87.6 (80.6-92.4)	84.6 (73.6-93.9)	50 (36.0-64.0)
	Male	Sensitivity	46.8 (35.4-58.4)	44.6 (31.6-58.4)	50 (35.4-64.6)	47.4 (37.3-57.8)
		Specificity	74.8 (66.3-81.8)	71.1 (63.1-78.0)	61.9 (48.8-73.6)	85.7 (56.2-97.5)
		Positive value	52.2 (39.9-64.2)	36.2 (25.3-48.8)	50 (35.4-64.6)	95.8 (84.6-99.3)
		Negative value	70.5 (62.1-77.8)	77.7 (69.7-84.1)	61.9 (48.8-73.6)	19 (10.6-31.3)
ETT positive	Female	Sensitivity	54.8 (36.3-72.2)	57.1 (34.4-77.4)	81.8 (41.8-96.8)	59.5 (44.2-74.8)
		Specificity	54.5 (45.3-63.5)	54.2 (45.3-62.9)	52.8 (38.8-66.5)	55.6 (35.6-74.0)
		Positive value	23.6 (14.7-35.3)	16.7 (9.3-27.7)	26.5 (13.5-44.7)	64.7 (46.5-79.9)
		Negative value	82.5 (72.0-89.8)	88.8 (79.2-94.4)	93.3 (76.5-98.8)	50 (31.7-68.3)
	Male	Sensitivity	32.5 (22.5-44.2)	32.1 (20.6-46.1)	37.5 (24.3-52.7)	34 (24.9-44.4)
		Specificity	65.6 (56.8-73.6)	65.8 (57.6-73.2)	66.7 (53.6-77.7)	57.1 (29.6-81.2)
		Positive value	35.7 (24.9-48.1)	25.7 (16.3-37.8)	46.2 (30.4-62.6)	84.6 (68.8-93.6)
		Negative value	62.3 (53.6-70.3)	72.5 (64.1-79.6)	58.3 (46.1-69.6)	11.1 (5.3-21.3)

ROC curve analysis for prediction of CA stenosis (Figure 23):

The optimum cut-off value for CAC in predicting ≥50% CA stenosis was 46.5, giving an area under the curve (AUC) of 76%, a sensitivity of 83% and specificity of 62% (p<0.001). Exclusion of patients with extensive calcification (CAC >1000) resulted in a sensitivity of 81%, specificity of 53% and AUC of 71.1%.

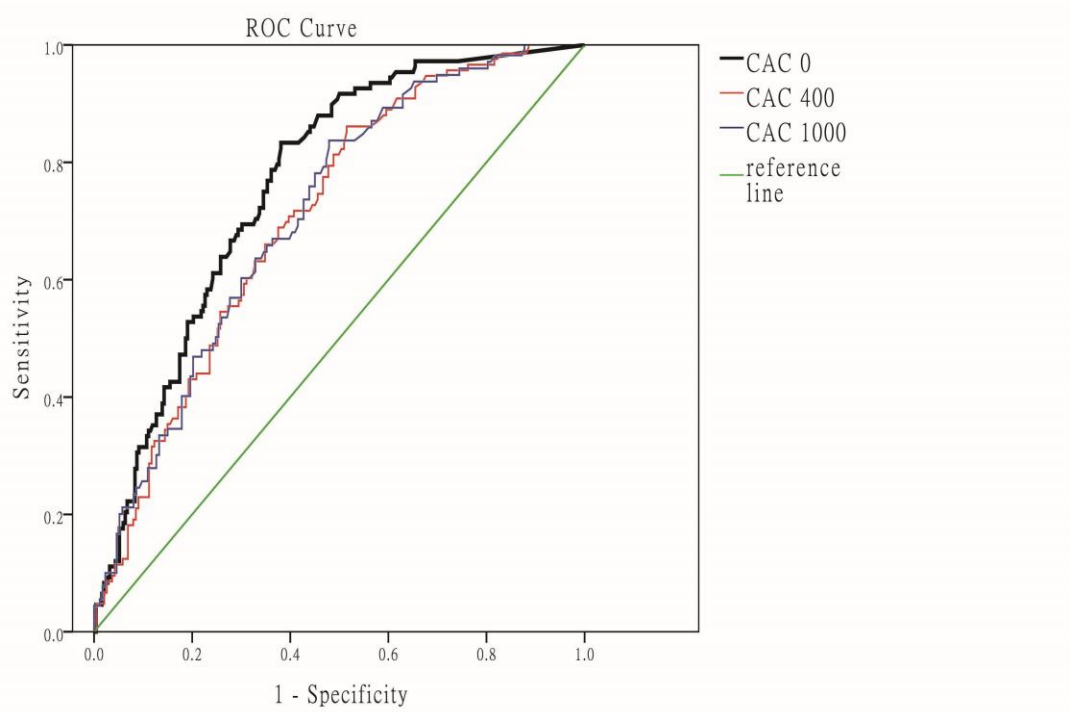

Figure 23: ROC Curve showing the highest sensitivity and specificity for prediction of coronary artery stenosis

CAC 0 = the analysis includes all patients. AUC=0.763, cut-off = 46.5, sensitivity = 83.3%, specificity = 61.9%.

CAC 400 = the analysis includes patients with CAC ≥ 400. AUC=0.706, cut-off = 46.5, sensitivity = 85.7%, specificity = 48.7%.

CAC 1000 = the analysis includes patients with 0<CAC<1000. AUC=0.711, cut-off = 46.5, sensitivity = 83.3%, specificity = 52.3%.

Discussion

Findings

In our symptomatic group of patients, the results show that a CAC score of 46.5 is the best predictor of the presence of significant CA stenosis, having a sensitivity of 83% and specificity of 62%. This accuracy is irrespective of whether severity of CA stenosis was taken as ≥50% or ≥70%. In addition, ETT proved to be the poorer predictor of CA stenosis, except for its high -ve predictive value in predicting multi-vessel disease. In the study population the fact that a CAC score of 46.5 is the best predictor of severe CA stenosis is remarkable for two reasons. Firstly, it is a relatively low score; many individuals above the age of 65 would have a similar, if not a higher score. Secondly, the conventional approach is to take a CAC score of ≥200 as a significant marker for CA stenosis. In addition, our study shows definitively that severe CA stenosis does not equate to a severe CAC.

Analysis of age showed that for CAC scores >0 and ≥400, age ≥70 gives a more accurate sensitivity but lower specificity, while -ve predictive values are not different between age groups. For ETT, age ≥70 gives a marginally higher sensitivity and specificity but lower –ve predictive value. Furthermore, analysis of gender showed that for a CAC score >0, there was little difference between results for males and females but for a CAC score ≥400, accuracy for males was higher for sensitivity but lower for specificity and –ve predictive value. Similarly, for ETT, accuracy in males was higher for both sensitivity and specificity, although lower for –ve predictive value.

Data Interpretation

In this study, two non-invasive methods of predicting significant CA stenosis were compared in a group of symptomatic patients. CAC is an anatomical pathology which is considered as a marker of subclinical atherosclerosis.

Although it is well known that not all plaques become calcified, in most cases plaques are 'mixed' type (partly calcified and partly un-calcified). We managed to demonstrate a moderately close relationship between the presence of CAC and coronary stenosis, although evidence exists showing that in some forms of atherosclerotic CA disease this association does not exist, such as in acute coronary syndrome, where a significant percentage of patients have no evidence of CAC on the culprit lesion (Henneman et al., 2008, Schuijf et al., 2009). It is possibly that these lesions were calcified, but by very small micro-particles of calcium, which cannot feasibly be measured by the conventional Agatston score.

On the other hand, evidence also exists that patients with stable angina might present with severe calcification but no flow-limiting lesions (Nicoll and Henein, 2010), as was the case with some of our patients. Studies consistently show that patients with extensive calcification have a lower probability of acute coronary syndrome compared to those with zero CAC (Nicoll and Henein, 2013).

CAC presence and extent is known to correlate with cardiac events and all-cause mortality (Rennenberg et al., 2009, Polonsky et al., 2010, Budoff et al., 2010), and can approximate the total atherosclerosis plaque burden (Mieres et al., 2007), although not all studies found a close linear relationship between CAC area and degree of luminal stenosis (Mieres et al., 2007, Hamon et al., 2006).

As with ours, most studies show a very high sensitivity but poor specificity of the CAC score for angiographic obstructive disease (Greenland et al., 2007, Budoff and Gul, 2008, Simons et al., 1992, Ardehali et al., 2007, Nieman et al., 2009b), possibly because of arterial remodelling. This has led several authors to conclude that CAC screening in stable symptomatic patients is a reliable means of excluding obstructive CAD (Nieman et al., 2009b). Even in asymptomatic patients, Geluk et al (2007) found that CAC was significantly more reliable than ETT in predicting ≥50% CA stenosis.

On the other hand, ETT is a functional test, the value of which is based on the demonstration of electrical evidence for myocardial ischaemia. It is the most commonly used investigation in open access chest pain clinics, as well as in post-myocardial infarction prognosis clinics (Sami et al., 1979). Our results show that ETT has significantly lower sensitivity and specificity in predicting significant CA stenosis compared to CAC. This of course does not refute the significant value of ETT in providing good prognostic value in patients with multi-vessel CAD (Bartel et al., 1974). Since it is based on the assessment of overall cardiac muscle function and its response to severity of ischaemia rather than simply the presence of calcium deposition in the arterial wall, therefore it seems that the two investigations should be seen as complimentary rather than in competition.

Despite the fact that ETT has long been used in the work-up of patients with suspected CAD (Greulich et al., 2012) and is prediction of cardiac events (Versteylen et al., 2013, Dedic et al., 2011), a number of recent large studies have failed to show a strong predictive value in symptomatic intermediate risk patients, with ETT having between a 30%-50% sensitivity to detect ≥50% stenosis (Greulich et al., 2012, Blankstein et al., 2012, Maffei et al., 2010a, Maffei et al., 2010b, Pundziute et al., 2009, Lewis et al., 2005). Our result of 38.9% is entirely consistent with this.

Only one study has shown a sensitivity of 71% for ≥50% stenosis (Lewis et al., 2005), while in another, sensitivity increased to 83% for detection of ≥70% stenosis (Blankstein et al., 2012); we found sensitivity to predict ≥70% narrowing remained at 39%. ETT specificity varies wildly, with study results ranging between 17% and 93% for detection of ≥50% stenosis (Bartel et al., 1974, Blankstein et al., 2012, Lewis et al., 2005, Larghat et al., 2013, Nieman et al., 2009a) we found specificity of 53.7%. A meta-analysis showed that ETT was more useful at excluding CAD than predicting it but a positive test may be more predictive in younger patients (Banerjee et al., 2012).

ETT is also known to be generally less accurate in women (Mieres et al., 2005). A meta-analysis showed that in women ETT had sensitivity of 61% (vs 72% in men) and specificity of 70% (vs 77% in men), although the –ve predictive value is high for ETT (Gibbons et al., 2002).

Our findings, however, showed that sensitivity was more accurate in women than men (54.8% vs 32.5%) for prediction of ≥50% stenosis and ≥70% stenosis (57.1% vs 32.1%).

Where predictive accuracy of ETT is compared against other imaging techniques, magnetic resonance imaging stress testing and stress echocardiography proved to be significantly more accurate (Banerjee et al., 2012, Greulich et al., 2012).

Clinical implications

Although our results clearly show that CAC screening is a better predictor of coronary stenosis than ETT, we find that the using of the two methods together, is better than either alone, since one is anatomical and the other is functional.

Particularly in symptomatic patients with extensive CAC, we illustrated that ETT might be more informative in confirming myocardial ischaemic as an explanation of symptoms than a coronary angiogram which might not show any significant stenotic lesions and may give false reassurance.

Conclusions

Coronary calcification and exercise stress testing provide different information with regards to the presence of CA stenosis. While calcification is more sensitive in predicting its presence, exercise testing is more accurate in excluding it. The two tests then should be seen as complementary rather than competing.

CHAPTER FOUR

STUDY TWO

Coronary Calcification Compromises Myocardial Perfusion Irrespective of luminal stenosis

Background

A myocardial perfusion scan assesses blood flow to the myocardium, and it is a gold standard cardiac non-invasive investigation for assessing cardiac function. CMR is used to detect myocardial ischaemia with a high diagnostic accuracy, and it used to evaluate rest and stress perfusion (Greenwood et al., 2012). In patients with triple vessels disease, CMR is more accurate than SPECT in identify CAD (Schwitter et al., 2012, Keijer et al., 2000). During stress CMR, myocardial perfusion, and left ventricular contractility are assessed (Nagel et al., 1999). The sensitivity of CMR perfusion in identifying CAD increased with both MDCT and CMR together, whereas the specificity slightly decreased from 88% to 83%. In general, the combination of CMR and MDCT are more accurate than CMR alone in the diagnosis of CAD (Falcão et al., 2013). In patients with an inconclusive MDCT result, CAD can be ruled out by stress CMR (Sicari et al., 2007). One of the important advantages of CMR is that it does not use ionizing radiation. There is an expectation that the use of CMR would reduce the requirements and the demand of invasive coronary angiography (Hartlage et al., 2012). There is an association between a negative stress CMR perfusion scan and very good two years prognosis with no major cardiac events (Nandalur et al., 2007).

Aim

The aim of this study was to evaluate the relationship between CAC assessed by MDCT and myocardial perfusion assessed by CMR in a group of symptomatic patients.

Methods

This is a retrospective analysis of 120 patients (mean age 65.1±8.9 years, 88 males) who presented with typical chest pain, defined as consistent exertional chest discomfort, to Bethanien Hospital, Frankfurt, Germany, between 2007 and 2010 and who underwent firstly CAC scoring using MDCT followed by myocardial perfusion scanning using CMR for those patients with persistent chest pain and who had inconclusive MDCT results. All patients subsequently underwent conventional coronary angiography. Invasive coronary angiography was performed not more than one month after the MDCT and CMR perfusion scans. None of the patients had acute coronary syndrome, heart failure, significant valvular heart disease, thyroid and parathyroid diseases, inflammatory disease or chronic kidney disease (creatinine>130mmol/L). Significant obstructive coronary disease was considered present when there was clear evidence for at least one high grade (HG) stenosis with ≥50% lumen narrowing on the conventional angiogram. According to the coronary angiography results, patients were divided into two groups: HG stenosis group (n=67, mean age 65.1±9.4 years) and no-HG stenosis group (n=53, mean age 65.1±8.6 years).

CMR perfusion scan

CMR studies were performed using a 1.5 Tesla MRI system (Magnetom Sonata Maestro Class, Siemens AG, Erlangen, Germany). The location and distribution of myocardial perfusion defects in the left ventricle was described using the AHA 16 segment model (Cerqueira et al., 2002).

Intravenous adenosine was started 3 minutes before contrast injection. Twenty short-axis images were taken at every level of myocardium before, during and after contrast injection (Gerber et al., 2008). Rest and adenosine stress scans were magnified and displayed at the same time for visual assessment (Hamon et al., 2010). In normal scans, the first pass into the myocardium changed its colour uniformly from black to grey. A slowly changing colour to grey suggested impaired perfusion and hence was considered as a perfusion defect either at rest or induced, if it occurred at peak stress (Cullen et al., 1999). More details are available in chapter "2".

Coronary artery calcium (CAC) score

CAC was measured using a 64 MDCT (Somatom Sensation Cardiac 64; Siemens Medical Solutions, Forchheim, Germany). The individual lesion scores were automatically summed to calculate the total Agatston score for each of the epicardial coronary artery territories as well as for the total coronary tree. Technique explained in detail in chapter "2".

Coronary angiography

The Judkin's technique was used with at least four views of the left system and two views of the right system. Significant stenosis was defined as ≥50% lumen narrowing.

Statistical analysis

A standard statistical software package (SPSS 20, IBM, Armonk, NY, USA) was used for the statistical analyses. Categorical variables were expressed as absolute number and percentage (%). Normally distributed continuous data were expressed as mean ± standard deviation.

The comparison between HG stenosis and no-HG stenosis group was analysed using Chi square test. The Spearman Rank Correlation was used to define the correlation between different CAC levels and myocardial perfusion on CMR. The null hypothesis was rejected on p-values <0.05.

Result

Of 120 patients, there were 67 in the group with high-grade stenosis and 53 in the group with no high-grade stenosis, based on invasive coronary angiography. Coronary risk factor distribution in the total study population and subgroups are listed in Table 8. The cardiovascular risk factors did not differ between the two groups, except for a higher proportion of males in the HG lesions group (p=0.015), and those with previous MI (p=0.014).

Table 8: Risk factor distribution in the total study population divided into those with HG stenosis and no HG stenosis

Risk factors	**Total n=120**	**HG stenosis n=67**	**no-HG stenosis n=53**	**p-value**
Males, n (%)	88(73.3)	55(82.1)	33(62.3)	0.015
Age Group (over 60 Y) n (%)	86 (71)	49 (73.1)	37 (69.8)	0.421
Hypertension, n (%)	45(37.5)	24(35.8)	21(39.6)	0.669
Smoking, n (%)	18(15.0)	11(16.4)	7(13.2)	0.625
Diabetes, n (%)	14(11.7)	8(11.9)	6(11.3)	0.916
Obesity, n (%)	3(2.5)	1(1.5)	2(3.8)	0.427
Family history of CVD, n (%)	20(16.7)	11(16.4)	9(17.0)	0.934
Prior MI, n (%)	34 (28.3)	25 (37.3)	9 (17)	0.014

CMR perfusion between HG-stenosis and no HG-stenosis (Table 9 and figure 24):

50% percent (60 patients) had CMR perfusion defect, either at rest or stress. Perfusion defect at rest indicate the high possibility of the presence of coronary HG-stenosis. The percentage and number of perfusion segments were significantly higher in patients with HG stenosis with more than 1 segment perfusion defect at rest (p=0.014) but there was no difference with stress (p=0.83).

This implies that the more segments showing perfusion defect, the more patients had HG stenosis. In contrast, at peak stress there was no relationship between the number of segments with the perfusion defect and HG stenosis by conventional coronary angiography.

Thirty four patients had myocardial perfusion abnormalities at rest and twenty six patients developed perfusion defects with stress. Stress-induced myocardial perfusion defects were 22.4% sensitive and 79.2% specific for detecting HG coronary stenosis. Combining resting and stress induced myocardial perfusion defect correlated linearly with the presence of HG stenosis.

Table 9: The difference in myocardial perfusion between the two groups at rest and with stress

	CMR perfusion defect (n, %)		
	0 segment	**> 1 segment**	**p-value**
At rest			
HG stenosis	42 (62.7)	25 (37.3)	0.014
No HG stenosis	44 (83.0)	9 (17)	
At stress			
HG stenosis	52 (77.6)	15 (22.4)	0.83
No HG stenosis	42 (79.2)	11 (20.8)	

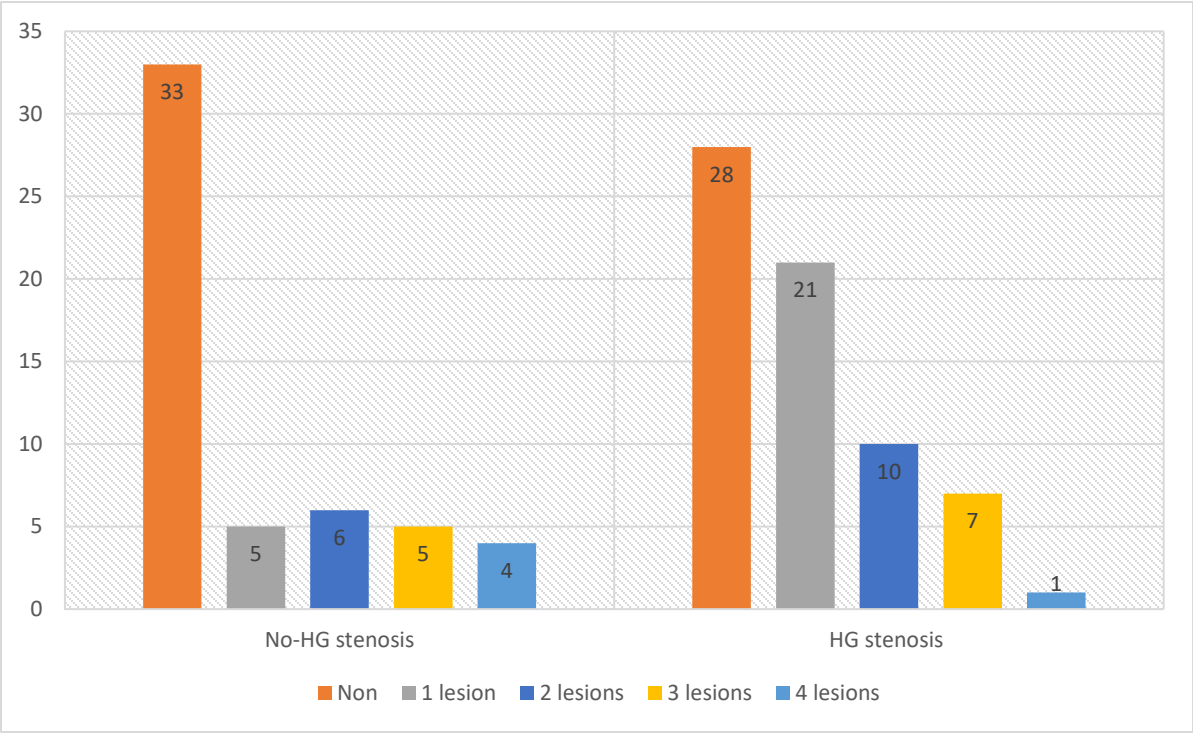

Figure 24: The difference in myocardial perfusion between the two groups at rest and with stress

CAC score between HG stenosis and no-HG-stenosis (Table 10 and figure 25 and 26):

There was a significant different between the two groups with a lower CAC score in patients with no-HG stenosis and a higher CAC score in those with HG stenosis ($p<0.0001$). On the ROC curve, the CAC cut-off value of 293 had a sensitivity of 71.6% and specificity of 83% in predicting HG coronary stenosis, giving an area under the curve of 0.80 (p-value <0.0001).

Using the Chi-square test, the p-value of <0.0001 means that the CAC distribution between HG stenosis and No HG-stenosis are significantly different. Our purpose here is only to see the CAC distribution between the two groups.

Table 10: The difference in CAC between the two groups

	CAC (n)				
	0-99	100-399	400-999	⩾1000	Total
HG stenosis	12	12	20	23	67
No HG-stenosis	29	17	4	3	53
Total	41	29	24	26	120

Figure 25 showed the different cut-off points of CAC and their relations to the presence or absence of significant CAD by invasive coronary angiography. We noticed that those who have >0 CAC have more patients with significant CAD. Also, the cut-off point of 400 shows that the higher the CAC the more likely to have CAD, and the less the CAC the less likely to have CAD.

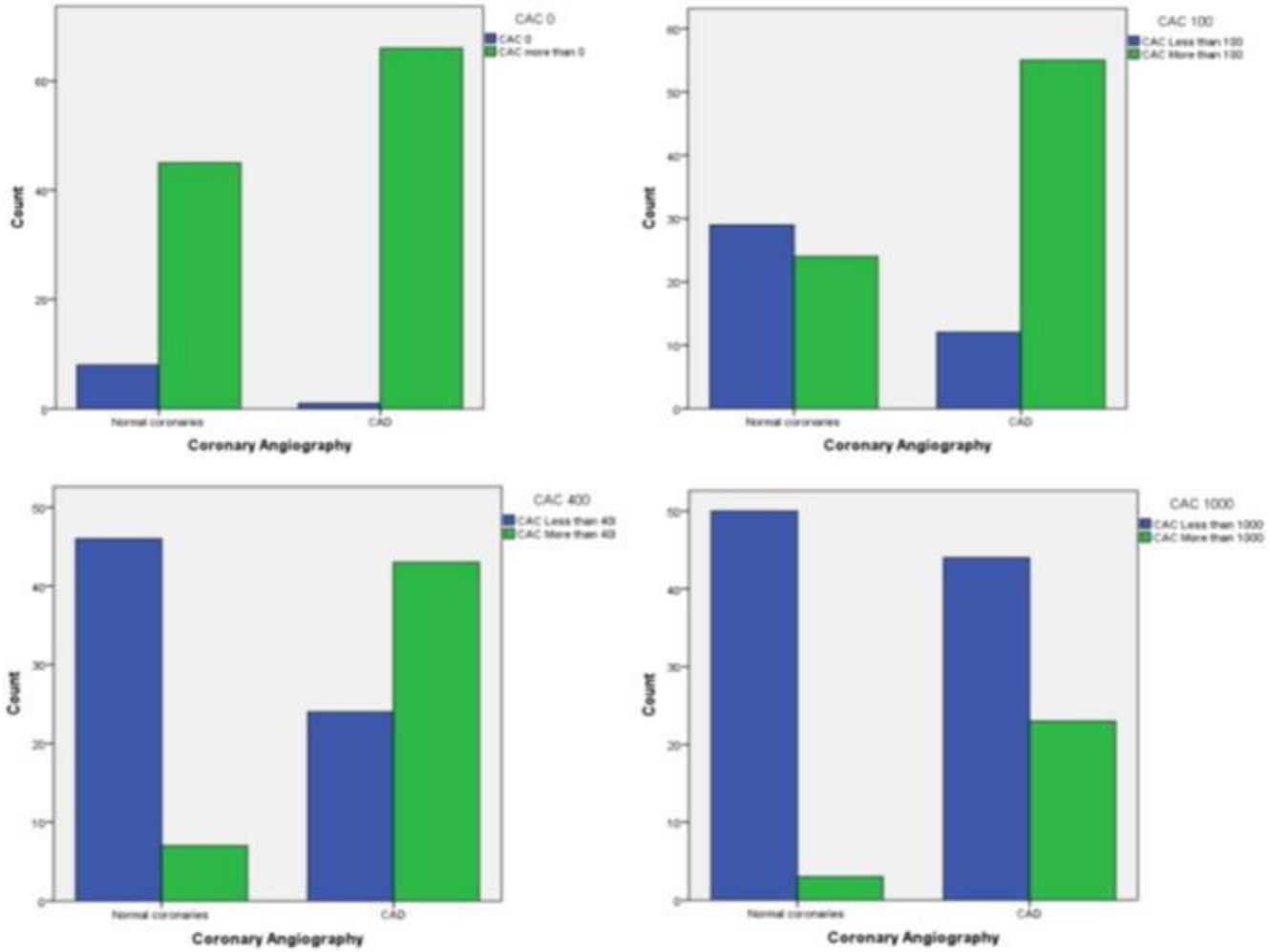

Figure 25: The difference in CAC between the HG stenosis and no HG stenosis groups.

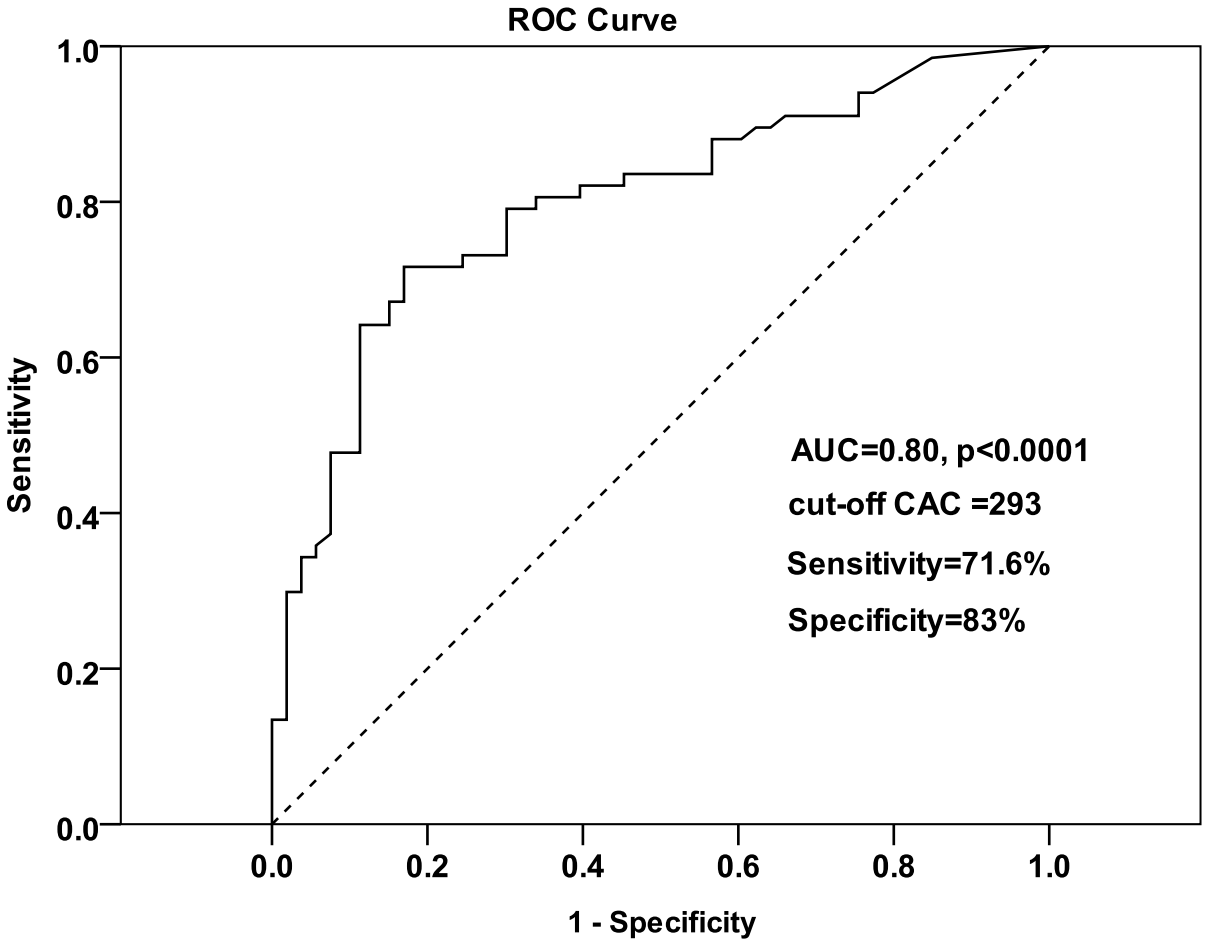

Figure 26: The ROC curve for calcium score to predict the CAD, AUC=0.80 (95% CI 0.82-0.88, p<0.0001), cut-off value is CAC=293 with sensitivity 71.6% and specificity 83%.

CAC or/and myocardial perfusion in predicting HG coronary stenosis:

A CAC score of 293 or the presence of at least 1 segment showing a myocardial perfusion abnormality was 74.6% sensitive and 71.7% specific in detecting HG stenosis. The respective values for the two abnormalities combined were 19.4% sensitivity and 90.6% specificity.

CAC score versus CMR myocardial perfusion (Table 11, and 12):

As shown in table 11, the severity of CAC correlated with the extent of myocardial perfusion in the patient group as a whole with stress (r=0.22, p=0.015), particularly in patients with no-HG stenosis (r=0.31, p=0.022). A CAC score cut-off value of 293 was 31.6% sensitive and 87.3% specific in detecting myocardial perfusion abnormalities. CAC score >0 was associated with a higher incidence of CMR perfusion defect compared to CAC score = 0. Furthermore, CAC >1000 was associated with higher incidence of CMR perfusion defects compared to a CAC score <1000 with stress, but not with CAC score > 0 or < 400 either at rest or stress.

Table 11: The relationship between CAC level and the number of segments showing myocardial perfusion, particularly in patients with no HG stenosis

	Rest		**Stress**	
All	r=0.066	p=0.476	r=0.221	p=0.015
HG-stenosis	r=0.049	p=0.696	r=0.189	p=0.125
No HG-stenosis	r=0.149	p=0.288	r=0.314	p=0.022

Table 12: CAC with variable cut off points and the CMR perfusion segments defects

CMR defect segments	CAC				P	P
	0-99	100-399	400-999	≥1000	(Pearson X^2)	(Linear by Linear Association)
Defect only at rest						
0 segments	32	20	18	16		
1 segment	2	4	5	7	0.192	0.700
2 segments	1	2	1	2		
> 3 segments	6	3	0	1		
Defect only at stress						
0 segments	37	21	20	16		
1 segment	1	4	1	3	0.236	0.042
2 segments	1	2	2	5		
> 3 segments	2	2	1	2		
Defect either at rest or at stress						
0 segments	28	13	14	6		
1 segment	13	7	4	5		
2 segments	14	6	3	1	0.006	0.189
> 3 segments	6	10	7	3		

Discussion

CMR myocardial perfusion has been shown to have high accuracy in detecting coronary artery disease and related events (Nandalur et al., 2007, Gargiulo et al., 2013, Nagel et al., 1999, Falcão et al., 2013, Sicari et al., 2007, Hartlage et al., 2012, Takahashi et al., 2004, Schwitter et al., 2012, Keijer et al., 2000). This has been superseded by the greater accuracy of MDCT in excluding significant CAD (Schuijf et al., 2006).

In fact, a subgroup of patients with either severe calcification but no HG stenosis or with impaired myocardial perfusion but no HG stenosis remains a clinical dilemma. There is currently no study that has shown an ideal way of describing these patients or proposed a strategy for managing them. The purpose of this study was to assess the relationship between CAC and CMR myocardial perfusion in patients with insignificant coronary stenosis.

Findings

Our study results concur with some of the above findings in showing only a modest relationship between the presence of HG stenosis and myocardial perfusion abnormalities by CMR. On the other hand, the CAC score was much more sensitive and specific in detecting HG stenosis, giving an area under the ROC curve of 80%.

In addition, our findings highlight the relationship between CAC and stress myocardial perfusion defects, with an incremental increase in the number of myocardial segments showing perfusion defects, with stress, parallel to the progressive increase in CAC score, only in patients with no-HG stenosis.

This suggests potential development of myocardial ischaemia and symptoms associated with arterial wall hardening rather than luminal narrowing by a stenosis, suggesting that the CAC score might be reflecting the extent of plaque burden, irrespective of luminal narrowing (Bajraktari et al., 2013). We believe that we are the first to demonstrate that extensive CAC correlates with the diffuse pattern of myocardial perfusion defect in the absence of significant coronary stenosis, again suggesting association between a perfusion defect and arterial hardening. Pellika et al (2006) had shown a relationship between CAC and left ventricular wall motion abnormalities using stress echo but made no comment on the extent of obstructive lesions. We too have recently shown parallel subendocardial abnormalities at peak stress in symptomatic patients with no coronary stenosis, particularly in those with significant calcification (Palmerini et al., 2014).

This evidence suggests that CAC, particularly with high scores, is likely to be associated with compromise coronary blood flow reserve and hence myocardial perfusion at the time of increased demand (peak stress).

Clinical implications

The coronary calcium score remains more accurate in detecting HG luminal stenosis over and above myocardial perfusion defects by CMR. Absolute reliance on luminal narrowing by either MDCT or conventional coronary angiography is likely to miss an important group of patients with limiting angina who do not demonstrate evidence for HG stenosis but suffer from wall hardening which compromises myocardial perfusion.

This finding suggests an important role for the routine measurement of the CAC score in angina patients, particularly those with unexplained symptoms by conventional angiography.

Limitations

There was a gender difference between patients with HG stenosis and those without, but this does not seem to have influenced our results, since the relationship between CAC and CMR myocardial perfusion defects was shown in those with no-HG stenosis, negating the potential imbalance of males, who generally have higher incidence of CAC (Erbel et al., 2008). Assessment of CMR perfusion was semi-quantitative but followed the international recommendations (Dweck et al., 2016). This study was retrospective in its design therefore subject to potential bias in patient selection. A larger sample size would have strengthened the relevance of our findings, particularly with the subgroup of patients with extensive calcification who showed clear evidence for myocardial perfusion abnormalities. We relied in our data interpretation on the accuracy of the CAC measurements as previously reported by Achenbach et al (2001) who showed non-significant results in the variability of repeating CAC measuring by EBCT as well as the known low variability of the system we used 64-MDCT (Horiguchi et al., 2008). Further investigation of coronary flow such as Fractional Flow Reserve (FFR) is required for an accurate assessment of the coronary flow and confirm the severity of coronary stenosis. However, this information is not available.

Finally, we did not assess MRI reproducibility, having considered the long experience of the radiologist reported and the lack of potential competitor.

Conclusion

In a group of patients with exertional limiting angina, coronary calcification is more accurate in detecting high grade luminal stenosis than myocardial perfusion defects. In addition, in patients with no stenosis the incremental relationship between coronary calcium score and the extent of myocardial perfusion suggests association with coronary wall hardening as an additional mechanism for stress-induced angina other than luminal narrowing. Also, there is an association between a perfusion defect and HG stenosis in patients with previous MI. These preliminary findings might have a clinical impact on management strategies of these patients other than conventional therapy.

CHAPTER FIVE

STUDY THREE

Effect of coronary calcium score on left and right ventricular response to stress in patients with syndrome "X"

Background

Cardiac syndrome X is typical chest pain with evidence of myocardial ischaemia but in the absence of flow-limiting CAD on angiography. The physiological mechanism(s) of syndrome X remain unclear and the optimum management of this patient population remains a clinical challenge (Agrawal et al., 2014). Myocardial bridging is when the epicardial coronary vessel enter down into the myocardium, it is associated microvascular endothelial dysfunction in those patients with non-obstructive CAD, and it is investigated by intravascular ultrasound. Endothelial dysfunction is characterised by a decrease in epicardial coronary artery diameter >20% after intracoronary acetylcholine, microvascular dysfunction when the index of microcirculatory resistance ≥25. (Sara et al., 2020, Pargaonkar et al., 2019). Since patient symptoms are usually exertional and one of the diagnostic criteria of the syndrome is 1 mm ST depression on exercise ECG, exercise treadmill testing is routinely used to assess functional capacity and to better understand the mechanisms of symptoms (Jadhav et al., 2006). Some patients who present with angina-like symptoms and have no signs of obstructive CAD usually have non-cardiac disease such as gastrointestinal or psychiatric disorders (Crea and Lanza, 2004). Other syndrome X patients may present with features of the metabolic syndrome such as hyperlipidaemia and hypertension (Agrawal et al., 2014).

Such co-morbidities can limit a patient's ability to perform an exercise treadmill test. Dobutamine stress echocardiography is a useful functional assessment for CAD in patients unable to exercise.

Assessing myocardial function at rest and during stress using echocardiography, including M-mode and tissue Doppler analysis, is a useful tool for the assessment of myocardial ischaemia through the assessment of stress induced wall motion abnormalities. There is association between RWMA and cardiac risk factors, such as obesity, hypertension, and male gender. Most patients who have high CAC have resting RWMAs (Agrawal et al., 2014). When assessing subclinical CAD individuals, a RWMA is more possible in those who have high CAC (Tsao et al., 2011).

A meta-analysis of 55 studies including 3,714 patients, demonstrated that DSE has a sensitivity of 81% and specificity of 84% in identifying CAD (Heijenbrok-Kal et al., 2007). Based on >11000 patients, a normal stress echocardiogram gives an annual risk of 0.4–0.9% (Metz et al., 2007) and importantly, DSE has a higher specificity than ETT in predicting CAD (Tsao et al., 2011).

Prior research has demonstrated that there is a significantly elevated risk of adverse cardiac events in syndrome X patients with non-obstructive coronary artery disease compared to syndrome X patients with normal coronary arteries.

However, no study has examined the association of coronary calcium score with DSE outcomes in syndrome X patients with non-obstructive coronary artery disease. Therefore, the aim of this study is to compare resting and stress echocardiography parameters with coronary artery calcium score in higher risk syndrome X patients.

The results may provide important clinical information surrounding syndrome X patient management.

Method:

We examined thirty-five patients with Syndrome X (24 female, mean age 62 years), who complained of exertional angina like symptoms, had ≥1mm ST shift on exercise test but no obstructive disease on conventional angiography.

No patient had a prior coronary event, coronary intervention, significant valvular heart disease, heart failure or atrial fibrillation. All patients had normal LV ejection fraction (>55%), RV size and inlet diameter (<3.6 cm). Patients underwent DSE including M-mode and tissue Doppler of LV and RV free wall long axis, and CT CACS using a MDCT scanner. Based on the CT findings patients were divided into: Group I with CACS<100 and Group II with CACS ≥100. Although it is recommended to use a CAC score > 400, many international studies have shown that CAS of 100 or more is an important change point, and it indicates that a plaque is present.

All ETT and echocardiography measurements were analysed by two investigators blinded to participant order and blind to the other investigations.

Table 13 Provides information about the modifiable and non-modifiable cardiac risk factors of the study population.

Table 13Modifiable and non-modifiable cardiac risk factors

Risk factors	Number of patients (%)
Age>60	23 (65.7%)
DM	5 (14.3%)
Hypertension	23 (65.7%)
Hypercholestolemia	19 (54%)
Smoking	18 (51.4%)
Family history	22 (62.9%)

Echocardiographic examination

All patients underwent rest and stress echocardiography. Two-dimensional echocardiography was used to acquire the apical 4 chamber view and M-mode and TDI measures were performed at the LV mitral annulus and RV free wall, at rest and during peak stress.

Moreover, RWMA was assessed by four, two and three chamber views and rest and stress images were reviewed by two senior cardiologists.

From the myocardial Doppler recordings, three velocities were made, the s', an antegrade velocity during systole and two retrograde velocities, e' during early diastole and a' during late diastolic filling. Stress echocardiography was performed using Dobutamine.

DSE results were reported as follows (Sicari and Cortigiani, 2017):

- Normal, if there is normal wall motion at rest and increased myocardial thickening during stress.
- Ischaemic, if normal at rest and wall motion abnormalities occur during stress.
- Necrotic, wall motion abnormalities at rest, which remain during stress.
- Viable, myocardial abnormalities at rest, which improve during stress.

More details of the procedure in chapter “2”.

Coronary calcium scoring

Computed tomography was used to assess coronary calcium. The CT was performed using a 64-detector-row scanner (Somatom Sensation Cardiac 64; Siemens Medical Solutions, Forchheim, Germany).

All lesions were added to calculate the total Agatston score (Becker et al., 2001), which was computed by summing the CACs of all foci in the epicardial coronary system.

According to the CAC score, patients were classified into two groups; Group I with CAC <100 and Group II with CAC >100.

Coronary angiography

The Judkin’s technique was used with at least four views of the left system and two views of the right coronary system. More details in chapter “2”.

Statistical analysis

Statistical analysis was undertaken using a standard statistical software package (SPSS 18.0, SPSS Inc.). All continuous variables were expressed as mean ± SD. A paired Student t-test was used to compare the difference between the two groups. A p-value less than 0.05 was considered statistically significant.

The below flow chart shows the patient pathway within the research design (Figure 27)

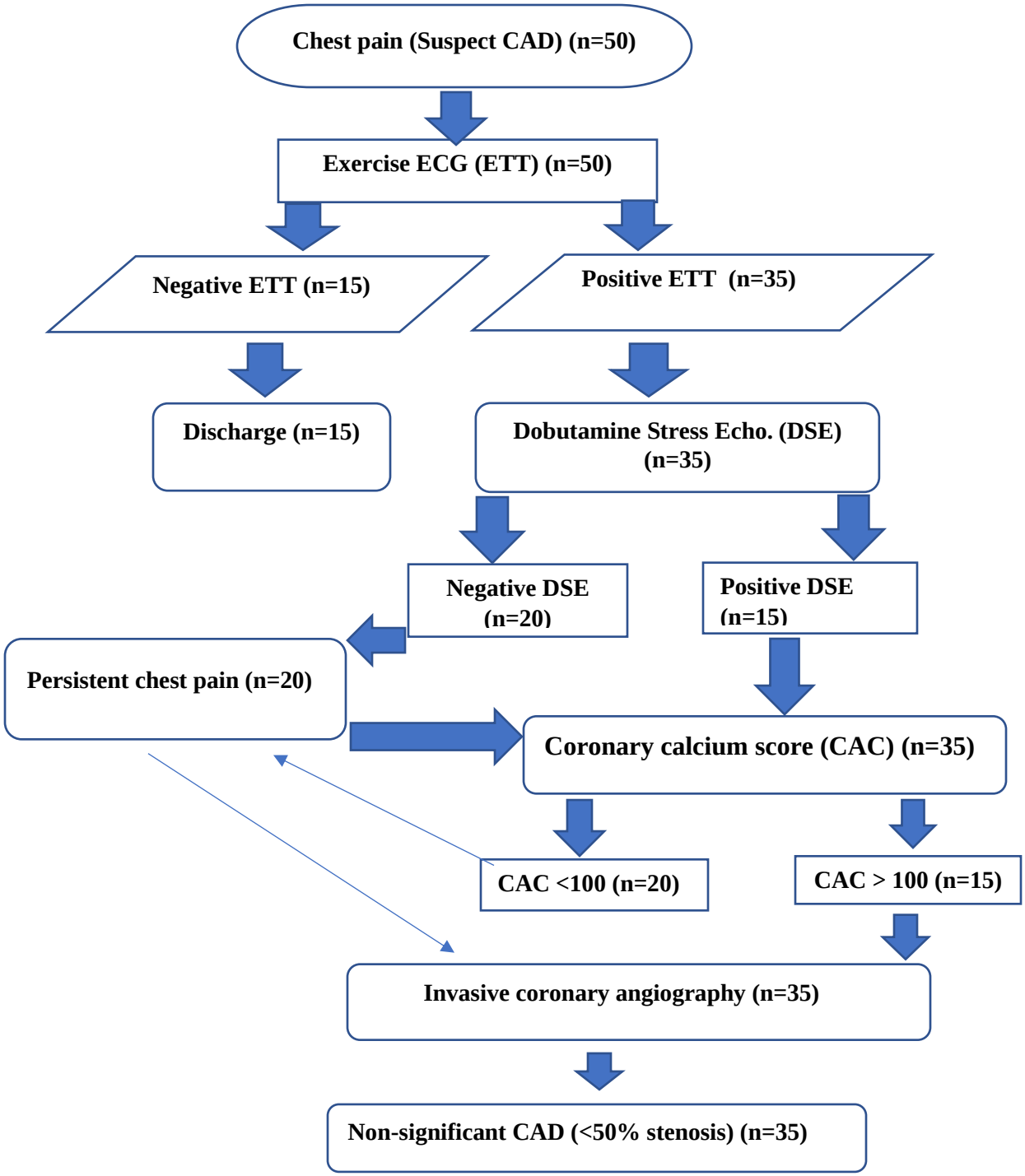

Figure 27 flow chart of the chest pain patients.

Results

We aimed to illustrate the relationship between the presence of cardiac risk factors and its association with RWMA. We used the Chi-Square Distribution Calculator to obtain the p-values.

When we compared the cardiac risk factors with the presence of RWMAs, >60 years old, male gender and hypertensive patients are linked to the presence of RWMAs during DSE, with significant p-values of 0.026, 0.002 and 0.003, respectively. The other risk factors such as age, DM, hypercholesterolemia, smoking and family history of CAD have no association with RWMAs during DSE, as shown in table 14

Table 14 Cardiac risk factors with the presence of RWMAs during DSE.

Risk factors	Number of patients (%)	Positive DSE (RWMAs) (%)	Mean CAC	P-value
Age>60	23 (65.7%)	13 (56.52%)	133	0.026
Male	11 (31.4%)	9 (81.81%)	363	0.002
DM	5 (14.3%)	3 (60%)	530	0.360
Hypertension	23 (65.7%)	14 (60.86%)	289	0.003
Hypercholestolaemia	19 (54%)	10 (52.63%)	290	0.176
Smoking	18 (51.4%)	8 (44.44%)	214	0.558
Family history	22 (62.9%)	9 (40.90%)	232	0.516

In terms of a positive or negative DSE and despite the number of segments which have wall motion abnormalities, we impact these results on CAC. When CAC of 400 and 100 are used as cut off values, the sensitivities of detecting peak RWMAs when the CAS is either ≥100 or ≥400 are very high, especially with CAC of 400, with a significant P-value of 0.001. In addition, the specificities are 100% and 90% for CAC of 400 and 100 respectively (Table 15 and 16).

At rest, before starting the Dobutamine infusion, all the patients had normal wall motion. During stress, 15 patients developed a peak RWMA in different myocardial segments, and tables 17 and 18 compare the presence of peak RWMAs against CAC with two different cut-off points. The results demonstrate a statistically significant association between the presence of CAC and stress induced ischaemia ($p<0.001$).

Table 15: CAC cut-off point 400 against RWMAs by DSE.

		DSE			P-value
		Negative (No RWMAs)	Positive (RWMAs)	Total	
CAC<400	Count (%)	20 (57.1)	7 (20)	27 (77.1)	
CAC≥400	Count (%)	0 (0.0)	8 (22.9)	8 (22.9)	
Total	Count	20 (57.1)	15 (42.9)	35 (100)	0.001

Table 16: CAC cut-off point 100 against RWMAs by DSE.

		DSE			P-value
		Negative (No RWMAs)	Positive (RWMAs)	Total	
CAC<100	Count (%)	18 (51.4)	2 (5.7)	20 (57.1)	
CAC≥100	Count (%)	2 (5.7)	13 (37.1)	15 (42.9)	
Total	Count	20 (57.1)	15 (24.9)	35 (100)	0.001

The LV long axis MAPSE significantly increased at the septal site (from 13.1±1.9 to 14.1±2.9 mm, P=0.012), but failed to do so at the lateral site (from 14.8±2.5 to 15.2±3.4 mm, P=0.48). Systolic velocities (s') significantly increased (from 7.2±1.7 to 11.9±2.9 cm/s, and from 7.9±2.4 to 12.5±3.8 cm/s, P<0.0001 for both), at the septal and lateral sites, respectively. However, early diastolic velocities (e') only increased in the lateral site (from 9.0±2.7 to 10.3±2.4 cm/s (P=0.008) and not in the septal site (from 7.7±1.8 to 8.1±2.4 cm/s, P=0.35). Atrial contraction (a') increased in both lateral and septal sites with significant p-value as shown in table 18 and figures (28, 29 and 30). CAC range was 0-1356 (mean 205.49). Paired student's T-test was used for comparison between rest and stress parameters.

Table 17: Compare the variables between rest and stress echocardiography.

		Rest	Stress	P
Lateral	S	7.9±2.4	12.5±3.8	<0.0001
	E	9.0±2.7	10.3±2.4	0.008
	A	9.9±2.9	12.5±3.5	<0.0001
	M-Mode	14.8±2.5	15.2±3.4	0.48
Septal	S	7.2±1.7	11.9±2.9	<0.0001
	E	7.7±1.8	8.1±2.4	0.35
	A	9.4±1.9	12.2±2.6	<0.0001
	M-Mode	13.1±1.9	14.1±2.9	0.012

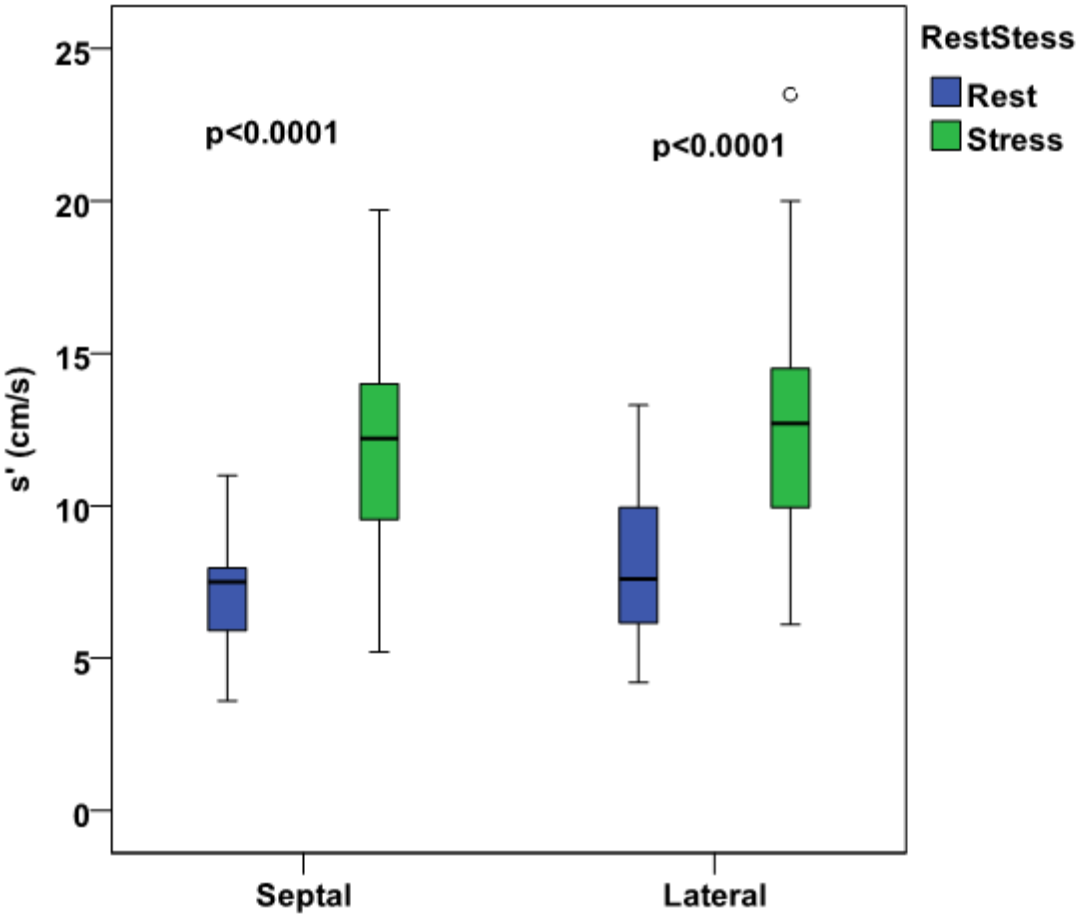

Figure 28: The s' increased both in septal and lateral site at stress.

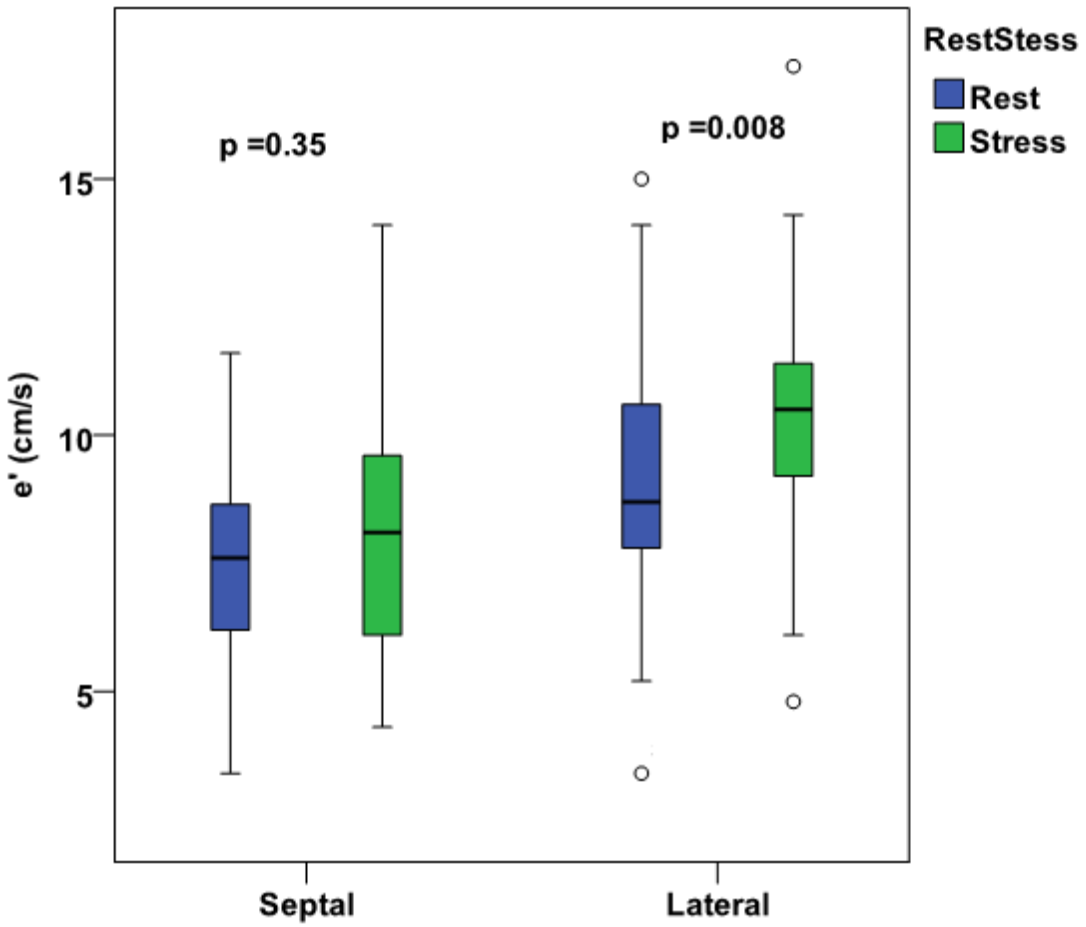

Figure 29: The e' only increased in later site (p=0.008) but not in septal site (p=0.35) at stress.

On peak stress, systolic velocities of septal wall significantly increased in 20 patients out for 35, (p=0.012), whereas 22 patients out 35 failed to increase in the lateral wall (p=0.48).

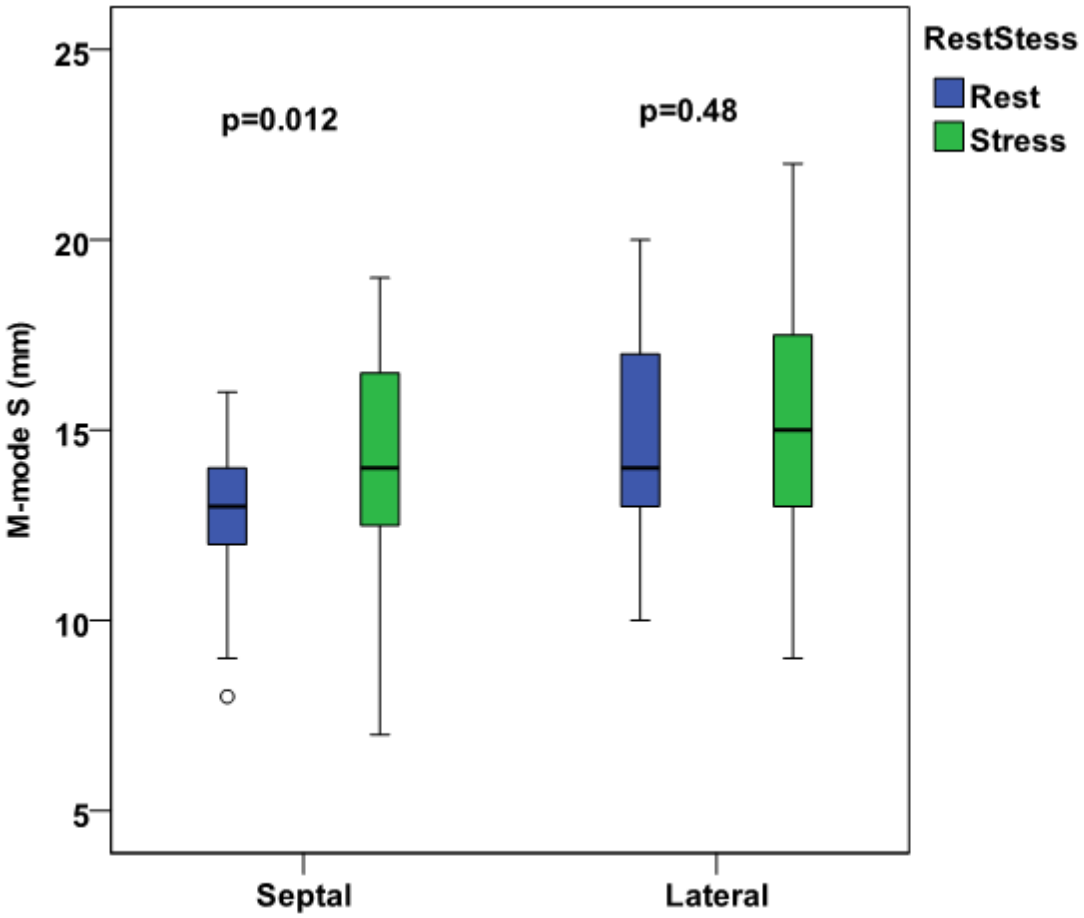

Figure 30: The M-mode S only increased in septal site (p=0.012) but not in lateral site (p=0.48) at stress.

There is no relationship between CAC score and any of the long axis measurements during rest and stress. However, TDI at different levels of the RV may have different results. Resting RV long axis amplitude, s' was not different between the two groups. At peak stress, long axis amplitude did not significantly increase in Group I 22.3±3.2 to 24.2±3.5mm (P=0.12), and it even fell in Group II from 23.2±3.3 to 19.5±3.9 mm (P=0.05). RV s' significantly increased from 10.9±1.9 to 17.6±3.2 cm/s (P<0.0002) in Group I but to a lesser extent from 12.6±2.8 to 17.2±4.9 cm/s (P=0.013) in Group II. However, RV e' failed to increase in group I 8.2±2.0 vs 10.1±3.3 cm/s (p=0.08), but increased in group II 7.1±1.5 vs 11.7±6.0 cm/s (P=0.04), as seen in table 18 and figure 31.

Table 18: The comparison between Group I and -Group II for RV rest and stress.

		Group 1 CACS<100			Group 2 CACS≥100		
		Rest	Stress	P	Rest	Stress	P
RV M-mode		22.3±3.2	24.2 ±3.5	0.12	23.2±3.3	19.5±3.9	0.05
RV TDI	S	10.9±1.9	17.6±3.2	<0.0001	12.6±2.8	17.2±4.9	0.013
	E	8.2±2.0	10.1±3.3	0.08	7.1±1.5	11.7±6.0	0.04
	A	13.4±3.4	18.8±3.9	0.001	14.0±4.7	18.9±4.8	0.003

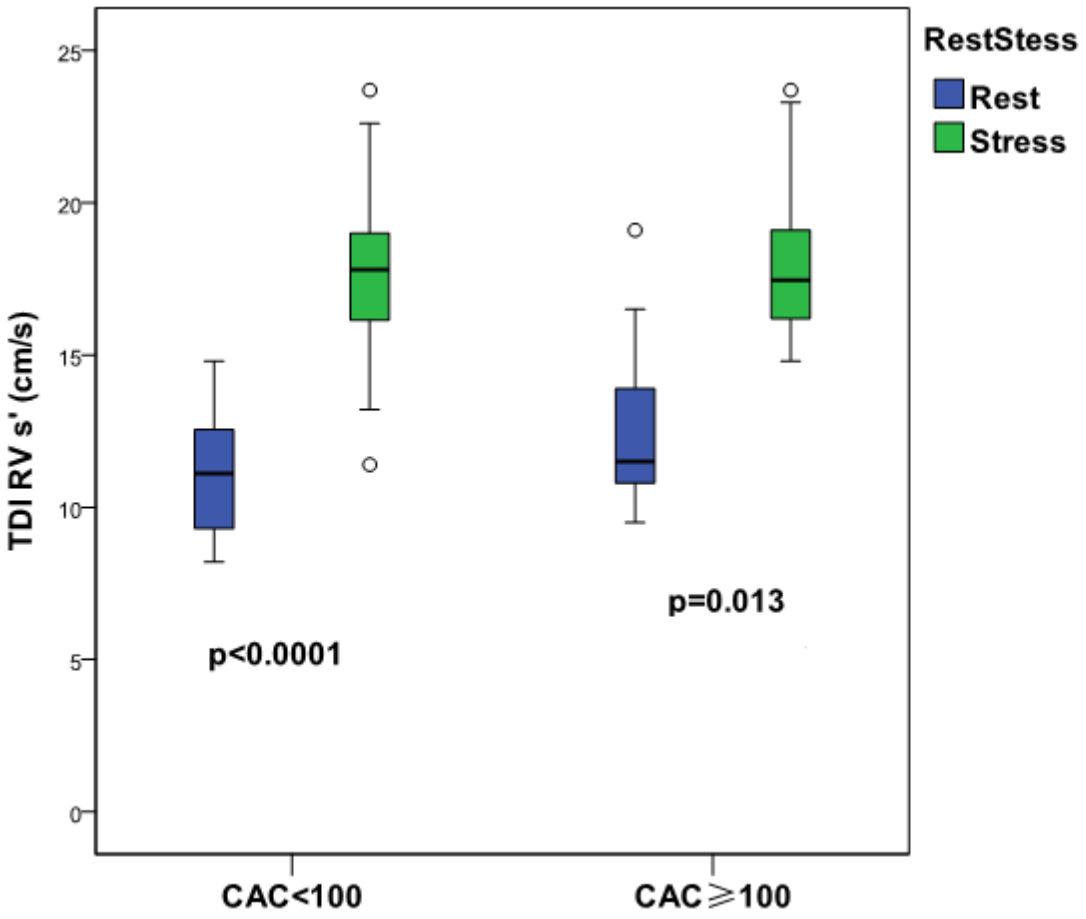

Figure 31: To show the RV s' increased both in group 1 and group 2, but with a less extent in group 2

In diastole, in the lateral segment, early diastolic velocities (e') and late diastolic velocity (a') significantly increased with stress (p=0.008 and p=0.001, respectively), whereas, only septal a' (not septal e') increased with stress. In group II (CAC ≥ 100) the systolic velocity increased with stress in lateral and septal segments. When we compared the lateral, septal, and RV separately, during rest and stress in group I, group II and both groups together, we find that in the lateral segment, apart from long axis M-mode, which is very slightly increased with stress (p-value 0.47), tissue Doppler s', e' and a' increased significantly with stress.

In group I patients, tissue Doppler velocity have the same changes in all the patients, whereas in group II a' insignificantly increased (p-value 0.077), Tables 19, Figures (32, 33 and 34).

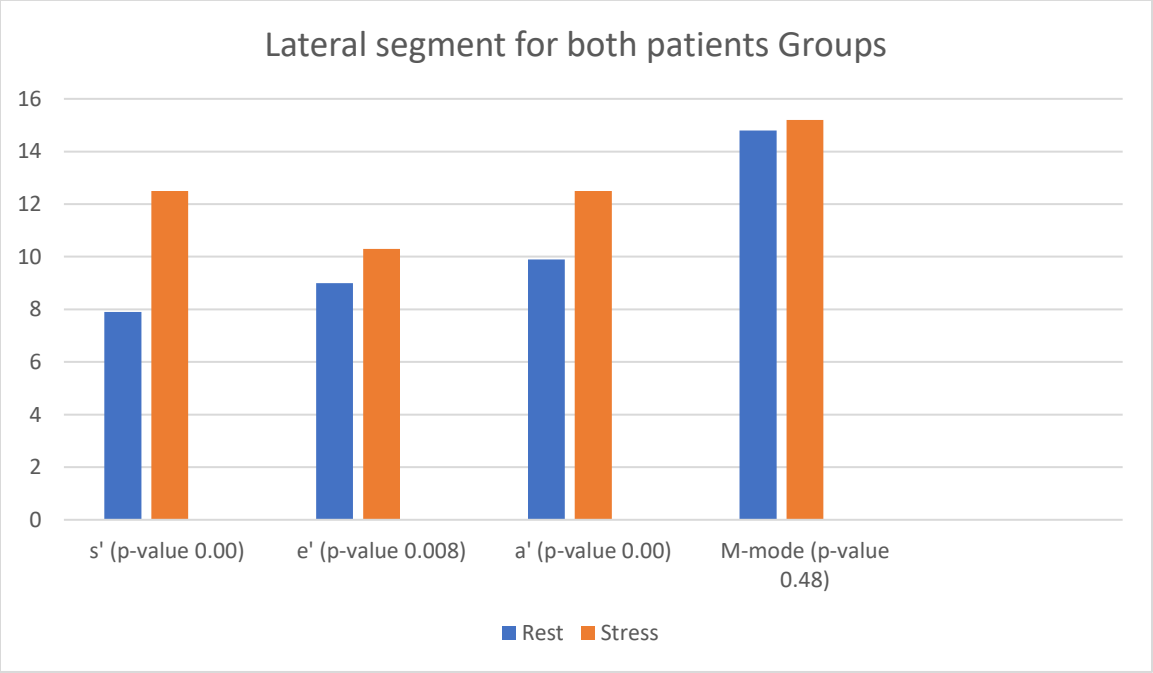

Figure 32: Tissue Doppler and long axis m-mode of lateral segment during rest and stress for both patients group together.

Table 19 Tissue Doppler and long axis m-mode for lateral and septal segments during rest and stress in group I (n=20)

		Rest	Stress	P
Lateral	S	7.9±2.6	12.8±3.5	<0.0001
	E	9.6±2.9	10.5±2.6	0.204
	A	9.3±2.6	12.3±2.9	<0.0001
	M-Mode	14.7±2.8	15.2±3.5	0.508
Septal	S	7.2±1.5	12.4±2.2	<0.0001
	E	8.2±1.6	8.1±2.2	0.851
	A	9.4±1.7	12.5±2.4	<0.0001
	M-Mode	13.1±2.0	14.8±2.6	0.003

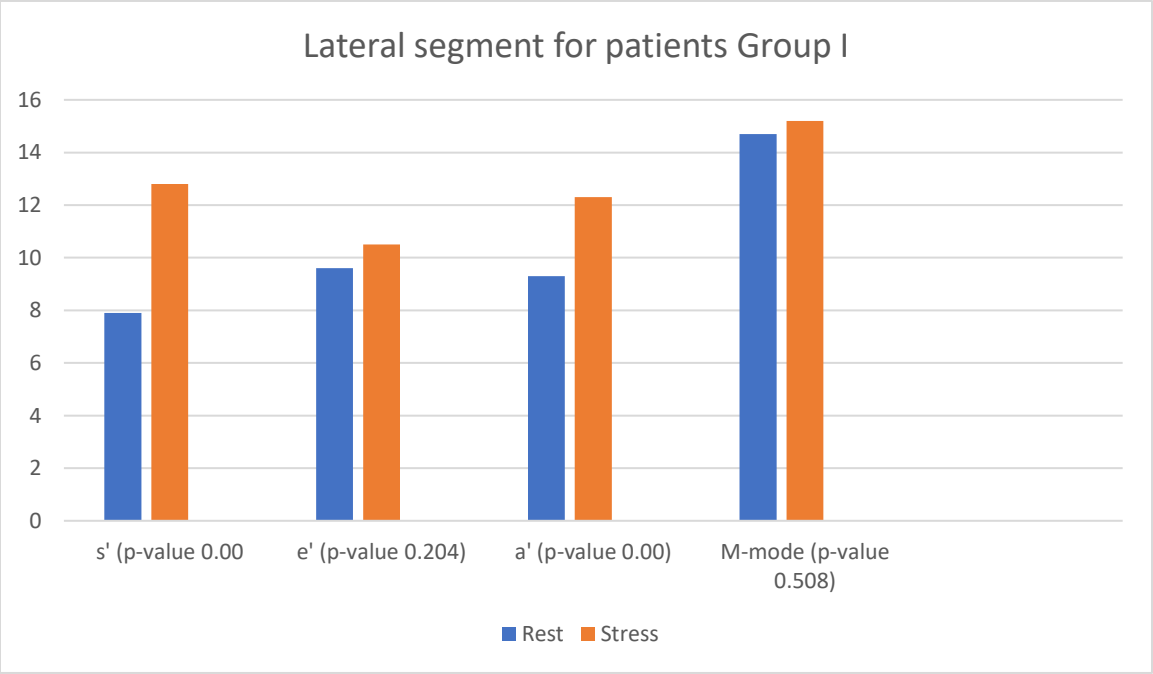

Figure 33: Tissue Doppler and long axis m-mode of lateral segment during rest and stress for patients group I.

Table 20 Tissue Doppler and long axis m-mode for lateral and septal segments during rest and stress in group II (n=15)

		Rest	Stress	P
Lateral	S	7.9±2.2	12.2±4.2	<0.0001
	E	7.9±2.3	9.9±2.0	0.001
	A	10.6±3.3	12.7±4.3	0.077
	M-Mode	15.0±2.2	15.3±3.3	0.741
Septal	S	7.2±2.0	11.3±3.6	0.001
	E	6.9±1.8	8.2±2.8	0.148
	A	9.3±2.1	11.7±2.8	0.008
	M-Mode	13.0±1.6	13.3±3.1	0.617

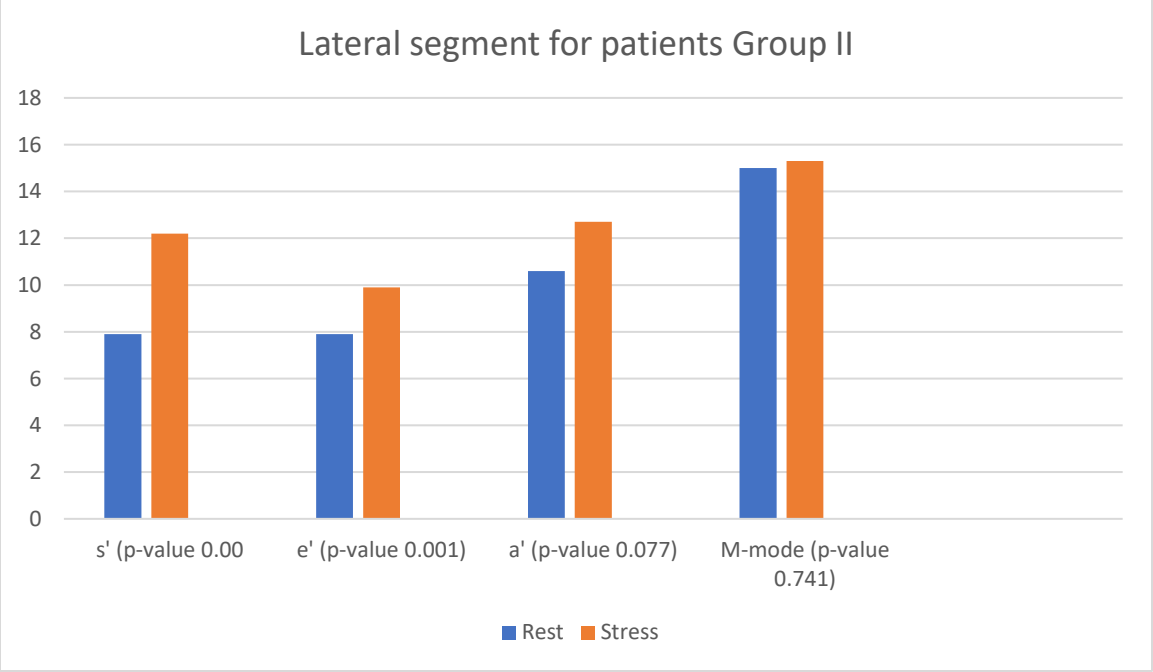

Figure 34: Tissue Doppler and long axis m-mode of lateral segment during rest and stress for patients group II.

In both groups, the tissue Doppler s’ and a’ of the septal segment increased significantly during stress, whereas, e’ did not significantly increase from 7.7±1.8 to 8.1±2.4, (p=0.35). Similarly, M-mode long axis increased significantly on peak stress, and e’ increased slightly. Septal e’ did not change during stress in group II patients, and even decreased in group I. On the other hand, M-mode long axis septal increased in group I but not in group II. (Figures 35, 36 and 37).

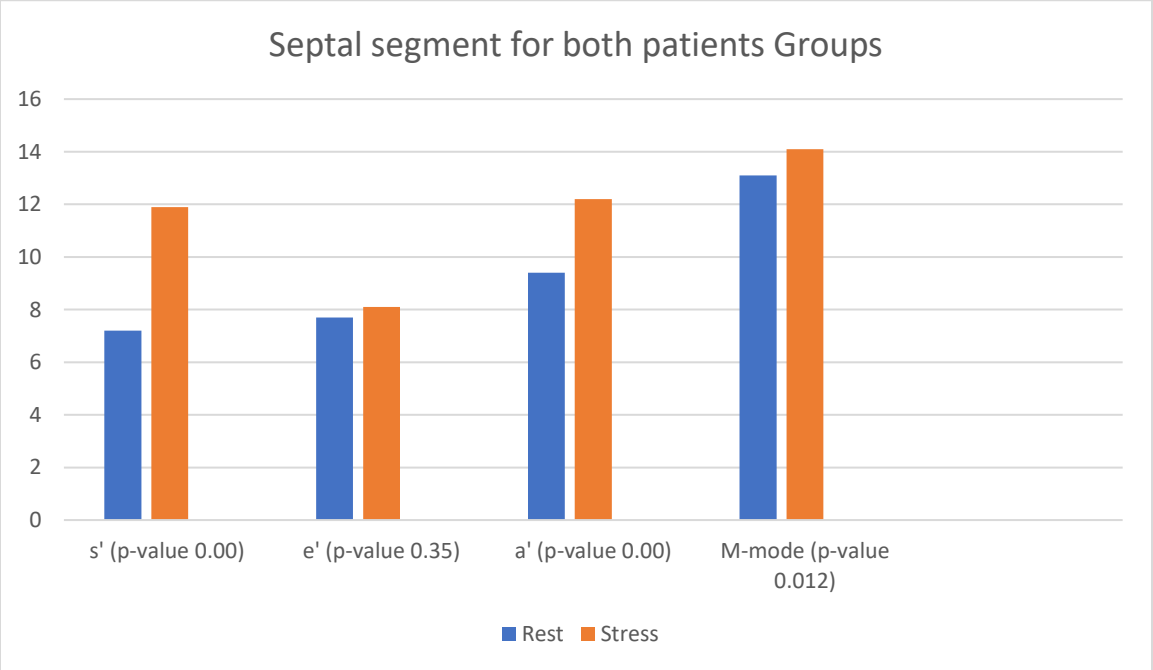

Figure 35: Tissue Doppler and long axis m-mode of septal segment during rest and stress for both patients groups.

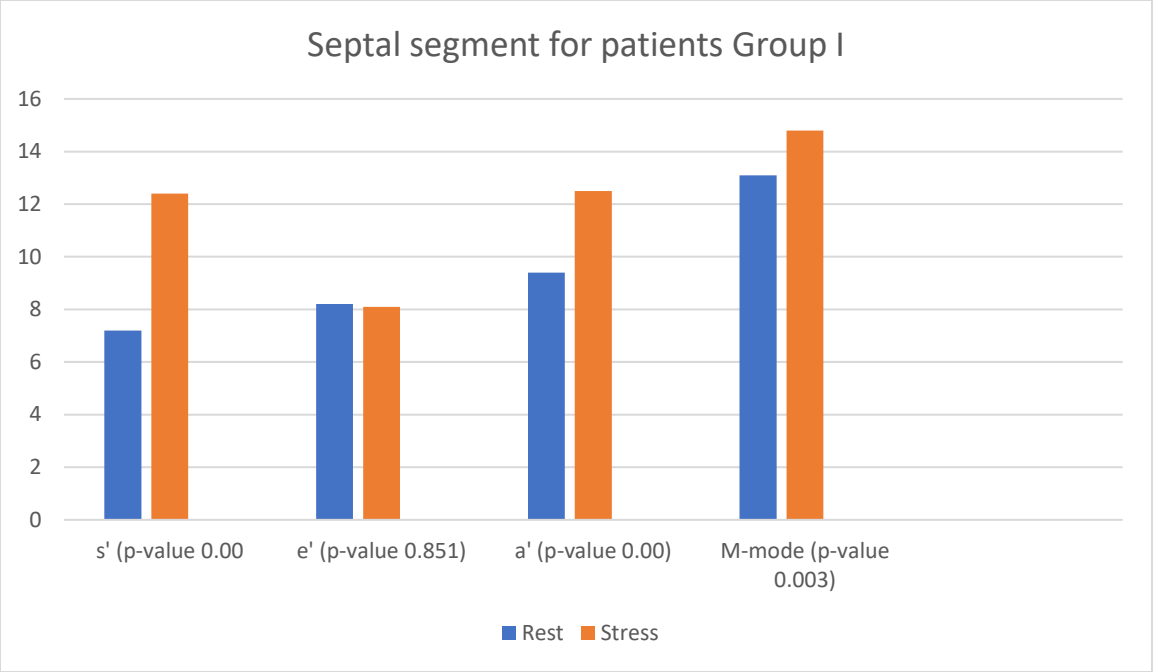

Figure 36: Tissue Doppler and long axis m-mode of septal segment during rest and stress for patients group I.

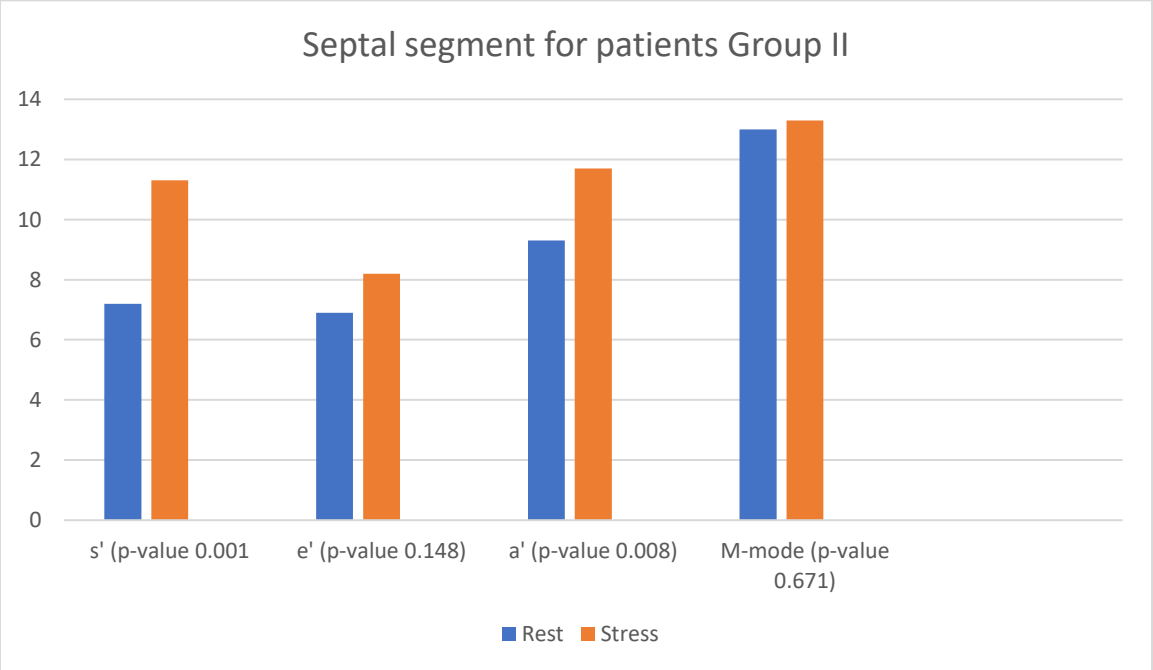

Figure 37: LV Tissue Doppler and long axis m-mode of septal segment during rest and stress for patients group II.

In the RV, s' and a' increased significantly in both patient groups with stress from 12.1±2.6 to 18.2±4.1 and from 13.6±3.9 to 18.9±4.2, respectively (p-<0.0001 for both), whereas, e' and TAPSE failed to significantly increase, as shown in table 21 and figure 38

Table 21 The TDI and TAPSE of RV during rest and stress for both groups

		Rest	Stress	P
RV for both groups	S	12.1±2.6	18.2±4.1	<0.0001
	E	11.0±2.9	10.8±4.4	0.75
	A	13.6±3.6	18.9±4.2	<0.0001
	M-Mode	23.4±4.6	22.7±5.1	0.440

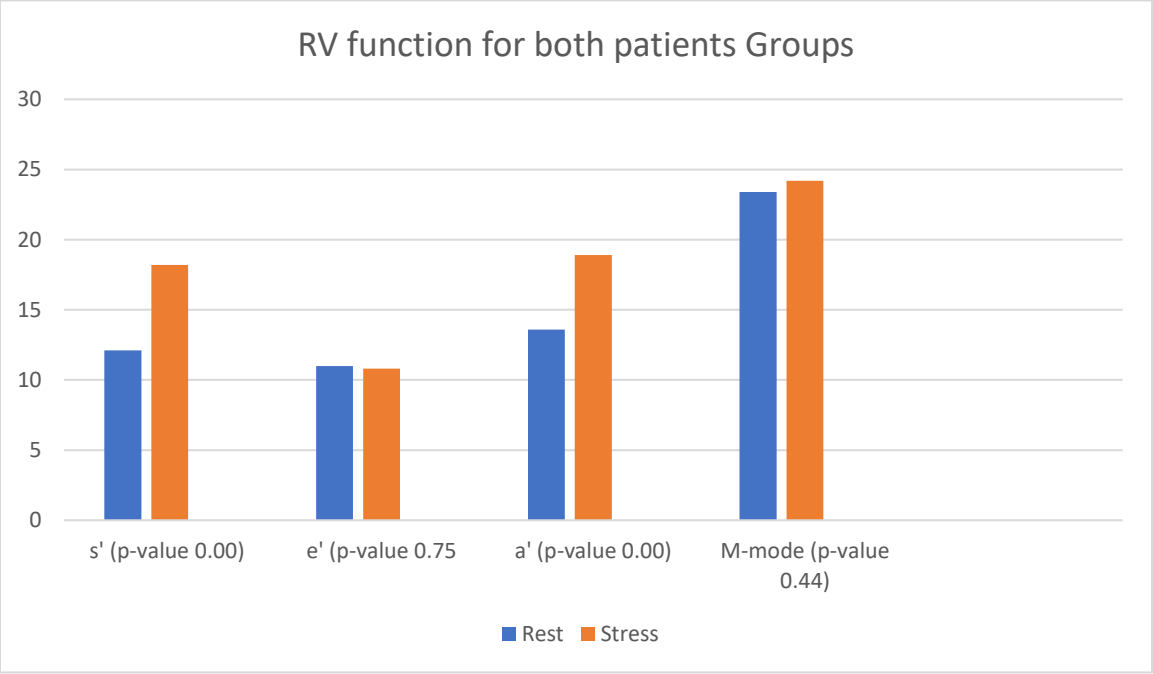

Figure 38: Tissue Doppler and long axis m-mode of RV during rest and stress for both patients groups.

In group I which has CAC is <100, the systolic velocity s' and the late filling velocity a' increased significantly with stress from 10.9±1.9 to 17.6±3.2 and from 13.4±3.4 to 18.8±3.9, respectively. In the same group, the early filling velocity in tissue Doppler (e') and the TAPSE of the RV did not increase significantly. In group II, which has CAC ≥100, the tissue Doppler of the RV increased as in the first group, whereas the TAPSE decreased from 23.2±3.3 to 19.5±3.9. (Figures 39, 40).

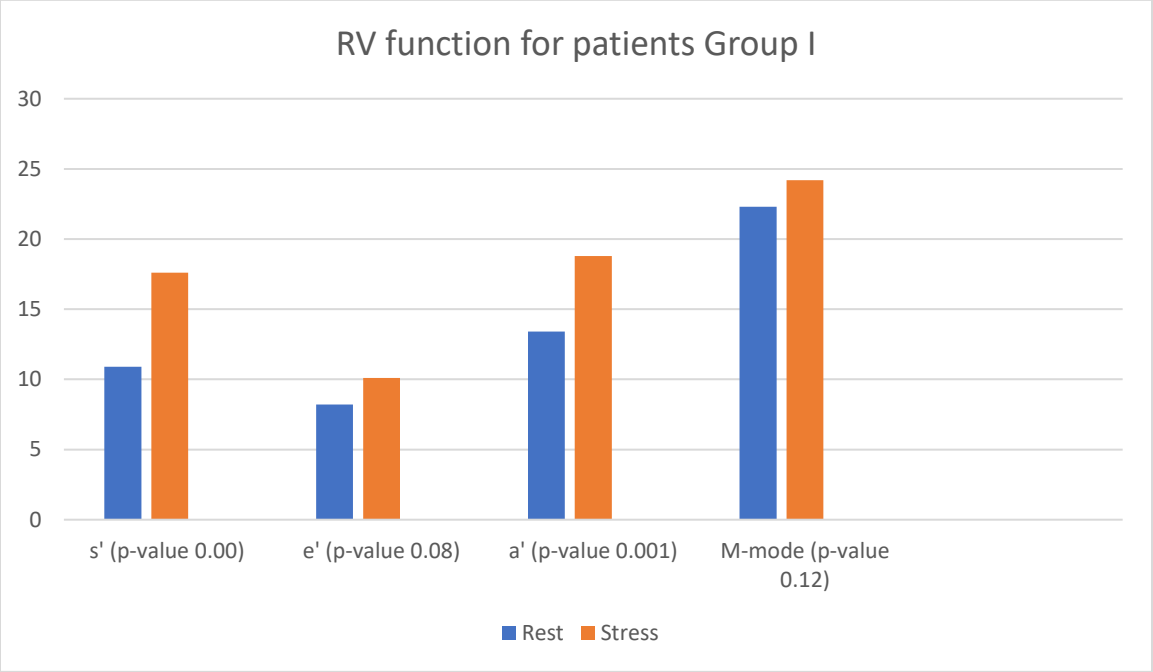

Figure 39: Tissue Doppler and long axis m-mode of RV during rest and stress for patients group I.

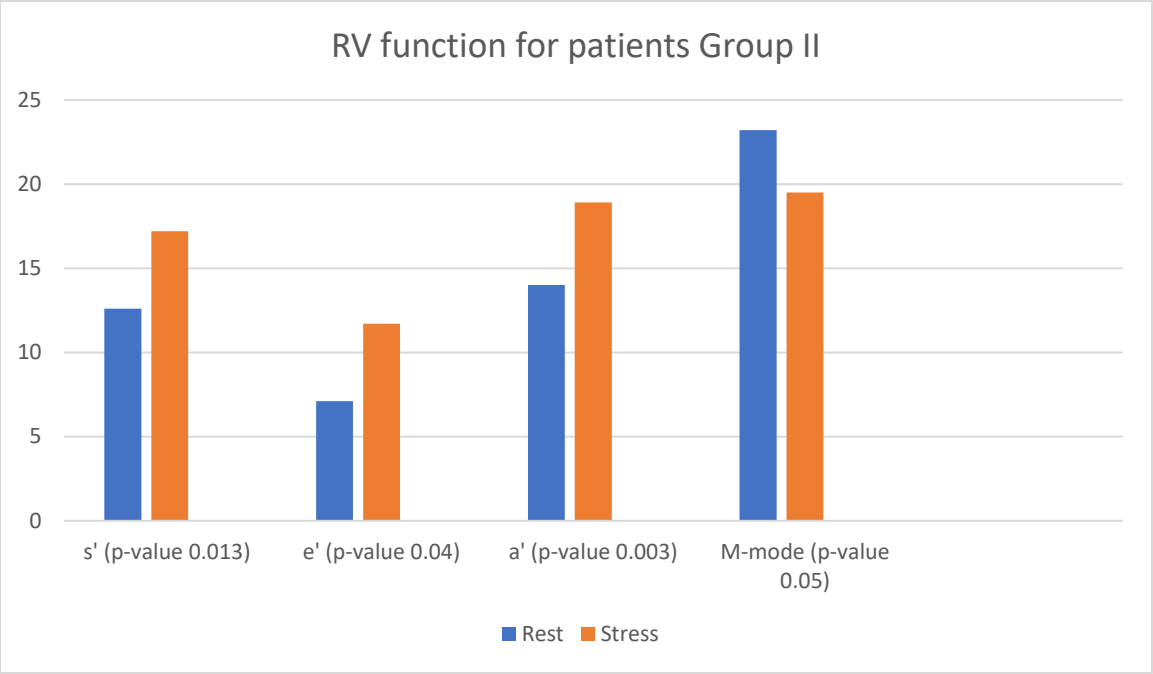

Figure 40: (Tissue Doppler and long axis m-mode of RV during rest and stress for patients group II.)

When the same patients were examined using invasive angiography, those patients who have mild atheroma or non-obstructive CAD (less than 50% stenosis) were compared with the presence of RWMAs by DSE results. The result show that DSE has a very high specificity of 95% and reasonably high sensitivity of 60% in identifying non-obstructed coronary stenosis, with a significant p-value of 0.001. More details in table 22.

Table 22: Compare invasive coronary angiography with RWMAs by DSE.

Angiography		DSE Negative (No RWMAs)	DSE Positive (RWMAs)	Total
Mild atheroma	Count	1	9	10
	% of Total	2.9%	25.7%	28.6%
Normal	Count	19	6	25
	% of Total	54.3%	17.1%	71.4%
Total	Count	20	15	35
	% of Total	57.1%	42.9%	100%

Discussion

Fifty patients with typical chest pain presented to the cardiology department for cardiac investigations and all passed through different non-invasive cardiac investigations before undergoing invasive coronary angiography. Fifteen patients were excluded due to a negative or inconclusive ETT. Chest pain investigations started with the most practical and cheaper test until reaching the most expensive technique. All patients had a positive ETT with ST depression regardless of the presence of chest pain during the test. All patients were subsequently referred for a DSE to investigate the presence or absence of ischaemic heart disease via the assessment of stress induced RWMAs. This also provided the opportunity to measure TDI, TAPSE, and MAPSE during rest and stress. All positive and negative DSE patients who had persistent chest pain were referred to perform MDCT for CAC, then referred to invasive coronary angiography.

In this study, DSE results impacted the results of CAC by MDCT and invasive coronary angiography results. Conventional coronary angiography is the gold standard test for identifying CAD, but if the diameter of coronary micro-vessels is less than 0.5 mm, it will be difficult for the cardiologist to visualise the small vessels (Berry et al., 2019).

Our findings show that in patients with a positive ETT with ECG signs of ischaemia, but no significant luminal stenosis, coronary calcification determine the behaviour of the sub-endocardial function of the left and right ventricles by long axis studies. Unlike this study, nearly all the other studies compared the presence of RWMAs by DSE with the presence of coronary calcifications; however, this study added more valuable measurements during rest and stress to support the results. Patients with mild coronary calcification (score <100) had a greater increase in long axis amplitude and velocities than those with more than mild coronary calcium calcification (score >100). The significant increases were seen in all RV TDIs and M-mode. Moreover, significant increases were seen in LV TDIs and M-mode, including the lateral s'& a' and septal M-mode, s'& a'. These findings suggest that the higher the calcium score the harder the wall and the more compromised the coronary flow reserve during stress, hence the development of markers of subendocardial ischaemia.

Conventional investigation of coronary artery disease for angina is the demonstration of luminal stenosis by either conventional angiography or CT coronary angiography. Syndrome X patients, however, do not show any signs of significant stenosis (<50%) hence the clinical dilemma they present. We and others have (Nikolaou et al., 2004, Schuetz et al., 2010) previously demonstrated that symptomatic patients with significant calcification may show myocardial perfusion abnormalities as a sign of compromised blood supply, even in the absence of significant stenosis.

Some patients had mild coronary atheroma/calcification with non-significant stenosis, this can help in identifying early stages of CAD, and can be treated medically, and slow progression of advanced CAD by periodic follow-up.

In those who do not have any atheroma by invasive angiography or any calcifications by MDCT but still have persistent chest pain, these are considered to have microvascular disease. In such patients, MDCT together with myocardial perfusion positron emission tomography (PET) imaging may help in the assessment of non-obstructive CAD which is related to the microvascular coronary flow obstruction. In women with cardiac chest pain and non-obstructed CAD, PET imaging can detect coronary microvascular dysfunction (Campisi and Marengo, 2017).

Although we did not study myocardial perfusion in our cohort, the above findings mirror those but in a mechanical fashion in showing abnormal systolic and diastolic subendocardial function in syndrome X patients. These abnormalities were not limited to the left ventricle as is the case with myocardial perfusion but extended to the right ventricle too, as has previously been shown in patients with significant coronary disease. Thus, they demonstrate biventricular ischaemic subendocardial dysfunction. Although in this study we did not measure LVEF (contractile reserve) or global/segmental longitudinal, radial or circumferential strain or strain rate using speckle tracking like some other studies, we measured other important parameters, which demonstrate significant results, especially when added to the presence of RWMAs.

Utsunomiya et al (2015) showed that RWMAs by DSE has high specificity but mild sensitivity for detecting CAD, Similarly, our study provides very high specificity and high sensitivity of identifying coronary atheroma or mild calcifications with less than 50% narrowing (non-obstructive CAD).

The presence of RWMAs may be an early singe of progressive CAD, which can be treated medically or by angioplasty ± stenting and avoid bypass surgery. Utsunomiya el al (2015) also showed that both inducible RWMAs and coronary calcifications provided a very high sensitivity for ischemia in identifying CAD than the RWMAs alone. These results support our study, which showed that the combination of RWMAs and high CAC showed early calcified CAD or microvascular calcifications.

There are few studies (Li et al., 2016, Geraiely et al., 2019), which compared the TDI of RV and LV systolic and/or diastolic functions with the presence of CAD but not CAC by MDCT. Most TDI studies assessed LV diastolic and not systolic function (Agarwal et al., 2012). We are the first team who compared both RWMAs and TDI measurements during rest and stress and which impact both CAC and invasive coronary angiography.

Meta-analysis (Agarwal et al., 2012) showed that TDI systolic velocity can be used to identify CAD at rest, and the accuracy can be improved by adding RWMAs to the TDI. We are different, as all our patients had syndrome-X (non-obstructive CAD) with different levels of CAC by MDCT and different DSE results. At peak stress, systolic and diastolic function of the RV are impaired, mainly in patients with high CAC. TAPSE was impaired at peak stress whereas s' was not. Although we consider this as impaired longitudinal function because of impaired TAPSE, the maintained s' is contradictory and this may be due to measurement inaccuracies and the small sample size. Future research is required to investigate this association further.

Conclusion

In a group of patients with syndrome X and normal resting LV size and function, systolic and diastolic long axis ‘subendocardial’ function including amplitude and diastolic velocities, at peak stress were significantly abnormal.

Since these disturbances are independent of the extent of CAC calcification, they may suggest evidence for microvascular disease, which is likely to compromise early diastolic coronary circulation. In the same group, patients with RWMAs have more chance of having coronary calcifications by MDCT than those with no inducible RWMA. Moreover, syndrome X patients exhibit clear evidence for TAPSE and diastolic right ventricular dysfunction at a fast heart rate, particularly with worsening coronary calcification. The small sample size may have influenced the outcome of the study.

CHAPTER SIX

GENERAL DISCUSSION

The overall aim of this thesis was to assess patients who were refereed to cardiology with stable cardiac chest pain. Conventional angiography is considered the gold standard for the diagnosis of significant and non-significant CAD. Although NICE guidelines currently recommend CT angiography as a first line investigation for patients presenting with stable chest pain, CT angiography was not commonly used when this thesis began and therefore CAC by MDCT was selected. As such, this thesis aimed to compare the diagnostic accuracy of MDCT with ETT, CMR and DSE. This thesis showed MDCT is more sensitive than ETT and CMR in predicting CAD, whereas ETT is more accurate in excluding CAD. Moreover, we find that there is association between MDCT and perfusion defect by CMR in patient with non-obstructive CAD. In addition, DSE is positive in patients with non-significant coronary stenosis but with high CAC and a positive ETT. We hypothesised that the presence of coronary calcifications could explain the patient's symptoms through compromising blood flow to the myocardium (coronary circulation) particularly the distal circulation. There were three investigational pathways, which firstly included chest pain patients screened by ETT and MDCT, then by invasive coronary angiography; a second group of patients investigated using CMR before invasive angiography and thirdly, DSE was performed before invasive coronary angiography. The results of this thesis demonstrated that MDCT is more accurate than ETT in identifying significant CAD, whereas a negative ETT was accurate in excluding CAD, as such the two investigations are complementary.

Compared to CMR, MDCT was more accurate in detecting significant CAD. However, the burden of perfusion defects during stress was associated with a progressive increase in CAC in patients with non-obstructive CAD only. Finally, DSE was abnormal in patients with non-significant coronary stenosis but with high CAC and a positive ETT, which may suggest microvascular disease. In addition, resting wall motion abnormalities on echocardiography was associated with coronary calcification by MDCT.

A CAC score of 46.5 was the best predictor of the presence of significant CA stenosis, with a sensitivity of 83% and specificity of 62%. This accuracy is irrespective of whether the severity of CA stenosis was taken as ≥50% or ≥70%. ETT proved to be a poorer predictor of CA stenosis, except for its high -ve predictive value. This finding is remarkable for two reasons. Firstly, it is a relatively low score; compared to what has been detected in asymptomatic populations, suggesting that even a small score but with symptoms should highlight the potential presence of significant stenosis. Secondly, our study shows that severe CA stenosis does not equate to severe CAC.

For ETT, the predictive value increased with the presence of cardiac risk factors. Analysis of age showed that for CAC scores >0 and ≥400, age ≥70 gives a more accurate sensitivity but lower specificity, while the -ve predictive values are not different between age groups. For ETT, age ≥70 gives a marginally higher sensitivity and specificity but lower –ve predictive value.

Furthermore, analysis of gender showed that for a CAC score >0, there was little difference between results for males and females but for a CAC score ≥400, accuracy for males was higher for sensitivity but lower for specificity and –ve predictive value. Similarly, for ETT, accuracy in males was higher for both sensitivity and specificity, although lower for the –ve predictive value.

In ETT and CAC study, we compared two non-invasive methods of predicting significant CA stenosis in a group of symptomatic patients.

CAC is an anatomical pathology which is considered a marker of subclinical atherosclerosis. Although it is well known that not all plaques become calcified, in most cases plaques are 'mixed' type (partly calcified and partly un-calcified). We managed to demonstrate a moderately close relationship between the presence of CAC and a coronary stenosis, although evidence exists showing that in some forms of atherosclerotic CAD this association does not exist, such as in acute coronary syndrome, where a significant percentage of patients have no evidence of CAC on the culprit lesion (Henneman et al., 2008, Schuijf et al., 2009). Possibly these lesions were calcified but by very small micro-particles of calcium, which cannot feasibly be measured by the conventional Agatston score.

On the other hand, evidence also exists that patients with stable angina might present with severe calcification but no flow-limiting lesions (Blankstein et al., 2012), as was the case with some of our patients.

Although not all studies found a close linear relationship between CAC area and degree of luminal stenosis (Mieres et al., 2007, Maffei et al., 2010a) as with ours, most studies show a very high sensitivity but a poor specificity of the CAC score for angiographic obstructive disease (Greenland et al., 2007, Budoff and Gul, 2008, Simons et al., 1992, Ardehali et al., 2007, Nieman et al., 2009b), possibly associated with arterial remodelling. This has led several authors to conclude that CAC screening in stable symptomatic patients is a reliable means of excluding obstructive CAD (Nieman et al., 2009b).

Even in asymptomatic patients, Geluk et al (2007) found that CAC was significantly more reliable than ETT in predicting ≥50% CA stenosis. On the other hand, ETT is a functional test, the value of which is based on the demonstration of electrical evidence for myocardial ischaemia. It is the most commonly used investigation in open access chest pain clinics, as well as in post-myocardial infarction prognosis clinics (Sami et al., 1979).

Our results show that the sensitivity and specificity of the ETT in predicting significant CA stenosis are significantly low compared to CAC. This, of course, does not refute the significant value of ETT in providing good prognostic value in patients with multi-vessel CAD (Bartel et al., 1974), since it is based on the assessment of overall cardiac muscle function and its response to the severity of ischaemia rather than simply the presence of calcium deposition in the arterial wall. Therefore, it seems that the two investigations should be seen as complementary rather than in competition.

Despite the fact that ETT has long been used in the workup of patients with suspected CAD (Greulich et al., 2012) and is predictive of cardiac events (Versteylen et al., 2013, Dedic et al., 2011), a number of recent large studies have failed to show a strong predictive value in symptomatic intermediate-risk patients, with ETT having between a 30%-50% sensitivity to detect ≥50% stenosis (Greulich et al., 2012, Blankstein et al., 2012, Maffei et al., 2010a, Maffei et al., 2010b, Pundziute et al., 2009, Lewis et al., 2005).

Our result of 38.9% is entirely consistent with this. Only one study has shown a sensitivity of 71% for ≥50% stenosis (Hagnäs et al., 2017), while in another, sensitivity increased to 83% for detection of ≥70% stenosis (Blankstein et al., 2012); we found sensitivity to predict ≥70% narrowing remained at 39%. ETT specificity varies wildly, with study results ranging between 17% and 93% for detection of ≥50% stenosis (Hagnäs et al., 2017, Greulich et al., 2012, Blankstein et al., 2012, Maffei et al., 2010b, Lewis et al., 2005) we found a specificity of 53.7%.

A meta-analysis showed that ETT was more useful at excluding CAD than predicting it but a positive test may be more predictive in younger patients (Banerjee et al., 2012). ETT is also known to be generally less accurate in women (Mieres et al., 2005).

A meta-analysis showed that in women ETT had a sensitivity of 61% (vs 72% in men) and specificity of 70% (vs 77% in men), although the –ve predictive value is high for ETT (Gibbons et al., 2002). Our findings, however, showed that sensitivity was more accurate in women than men (54.8% vs 32.5%) for prediction of ≥50% stenosis and ≥70% stenosis (57.1% vs 32.1%), where predictive accuracy of ETT is compared against other imaging techniques, magnetic resonance imaging stress testing and stress echocardiography proved to be significantly more accurate (Banerjee et al., 2012, Greulich et al., 2012).

In myocardium perfusion, when the myocardial perfusion impacted on coronary calcification, the result showed the relation between coronary calcification and the extent of myocardial perfusion in respect of the presence of coronary stenosis.

CMR myocardial perfusion has been shown to have high accuracy in detecting CAD and related events (Nandalur et al., 2007, Gargiulo et al., 2013, Nagel et al., 1999, Falcão et al., 2013, Sicari et al., 2007, Hartlage et al., 2012, Takahashi et al., 2004, Schwitter et al., 2012, Keijer et al., 2000).

A subgroup of patients with either severe calcification but no HG stenosis or with impaired myocardial perfusion but no HG stenosis remains a clinical dilemma. There is currently no study that has shown an ideal way of describing these patients or proposed a strategy for managing them. The purpose of the CMR study was to assess the relationship between CAC and CMR myocardial perfusion in patients with HG coronary stenosis.

The CMR study results concur with some of the findings in showing only a modest relationship between the presence of HG coronary stenosis and myocardial perfusion abnormalities by CMR.

On the other hand, the CAC score was much more sensitive and specific in detecting HG stenosis, giving an area under the ROC curve of 80%.

In addition, our findings highlight the relationship between CAC and stress myocardial perfusion defects, with an incremental increase in the number of myocardial segments showing perfusion defects, with stress, parallel to the progressive increase in CAC score, only in patients with no-HG stenosis.

This suggests the potential development of myocardial ischaemia and symptoms is associated with arterial wall hardening rather than luminal narrowing by a stenosis, suggesting that the CAC score might be reflecting the extent of plaque burden, irrespective of luminal narrowing. We believe that we are the first to demonstrate that extensive CAC correlates with the diffuse pattern of myocardial perfusion defect in the absence of significant coronary stenosis, again suggesting an association between a perfusion defect and arterial hardening.

Pellika et al (2006) have shown a relationship between CAC and left ventricular RWMAs using stress echo but made no comment on the extent of obstructive lesions

We too have recently shown parallel subendocardial abnormalities at peak stress in symptomatic patients with no coronary stenosis, particularly in those with significant calcification. This evidence suggests that CAC, particularly with high scores, is likely to be associated with compromise coronary blood flow reserve and hence myocardial perfusion at the time of increased demand (peak stress).

Our findings in the DSE study show that in patients with angina-like symptoms but no significant luminal stenosis, coronary calcification is associated with the behaviour of the subendocardial function as shown by long axis studies of the left and right ventricles.

Patients with mild coronary calcification (score <100) had a better increase in long axis amplitude and velocities than those with more than mild coronary calcium calcification (score >100).

These findings suggest that a higher calcium score may be association with hardening of the arterial wall and a more compromised coronary flow reserve during stress, hence the development of markers of subendocardial ischaemia. Conventional investigation of CAD for angina is the demonstration of luminal stenosis by either conventional angiography or CT coronary angiography.

Syndrome X patients, however, do not show any signs of significant stenosis (>50%) hence the clinical dilemma they present.

We and others have (Gibson, 1991, Dedic et al., 2013) previously demonstrated that symptomatic patients with significant calcification may show myocardial perfusion abnormalities as a sign of compromised blood supply, even in the absence of significant stenosis.

Although we did not study myocardial perfusion in our cohort, the DSE findings mirror those but in a mechanical fashion in showing abnormal systolic and diastolic subendocardial function in syndrome X patients. These abnormalities were not limited to the left ventricle as is the case with myocardial perfusion but extended to the right ventricle too, as has previously been shown in patients with significant coronary disease.

Mild coronary atheroma / calcification patients with non-obstructive CAD noticed in our study, this can help in identifying early stages of CAD, and can be treated medically, and delay progression of advanced CAD by periodic follow-up. In those who do not have any atheroma by invasive angiography or any calcifications by MDCT but still have persistent chest pain, this can be considered as microvascular disease.

In such patients, MDCT together with myocardial perfusion positron emission tomography **(**PET) imaging may help in the assessment of non-obstructive CAD which is related to the microvascular coronary flow obstruction. In women with cardiac chest pain and non-obstructed CAD, PET imaging can detect coronary microvascular dysfunction (Campisi and Marengo, 2017).

Clinical implications

In the ETT study, although our results clearly show that CAC screening is a better predictor of coronary stenosis than ETT, we would recommend using the two methods together, rather than either alone, since one is anatomical and the other is functional.

Particularly in symptomatic patients with extensive CAC, ETT might be more informative in confirming myocardial ischaemia as an explanation of symptoms than a coronary angiogram which might not show any flow-limiting lesions and would give false reassurance. In myocardium perfusion, the coronary calcium score remains more accurate in detecting HG luminal stenosis over and above myocardial perfusion defects by CMR.

Absolute reliance on luminal narrowing by either MDCT or conventional coronary angiography is likely to miss an important group of patients with limiting angina who do not demonstrate evidence for HG stenosis but suffer from wall hardening which compromises myocardial perfusion. This finding suggests an important role for the routine measurement of the CAC score in angina patients, particularly those with unexplained symptoms by conventional angiography.

Limitations

There was a gender difference between patients with HG stenosis and those without, but this does not seem to have influenced our results, since the relationship between CAC and CMR myocardial perfusion defects was shown in those with no-HG stenosis, negating the potential imbalance of males, who generally have higher incidence of CAC (Erbel et al., 2008).

Assessment of CMR perfusion was semi-quantitative but followed the international recommendations (Larghat et al., 2013). This study was retrospective in its design therefore subject to potential bias in patient selection. A significantly larger sample volume would have strengthened the relevance of our findings, particularly with the subgroup of patients with extensive calcification who showed clear evidence for myocardial perfusion abnormalities. Prospective study, however, would reduce potential selection and information bias.

We relied on our data interpretation on the accuracy of the CAC measurements as previously reported by Achenbach et al (2001) who showed non-significant results in the variability of repeating CAC measuring by EBCT as well as the known low variability of the system we used (64-MDCT).

Interobserver variability was performed in a retrospective way to all the echo measurements during rest and stress. Differences in intra and interobserver variability were assessed using SPSS. The interobserver variability is between 0.81 and 1.0, which means the measures are highly agreed.
None of the patients we studied was clinically felt to need an FFR assessment and as such this information is not available.

Finally, we did not assess CMR reproducibility, having considered the long experience of the radiologist reported and the lack of the potential competitor. With variability of CAC measurements depending on the MDCT system used.

CONCLUSIONS

Coronary calcification and exercise stress testing provide different information with regards to the presence of CA stenosis. While calcification is more sensitive in predicting its presence, exercise testing is more accurate in excluding it. The two tests should be seen as complementary rather than competing. In term of myocardium perfusion, in a group of patients with exertional limiting angina, coronary calcification is more accurate in detecting high-grade luminal stenosis than myocardial perfusion defects. In addition, in patients with no stenosis, the incremental relationship between coronary calcium score and the extent of myocardial perfusion suggests association with coronary wall hardening as an additional mechanism for stress-induced angina other than luminal narrowing. These preliminary findings might have a clinical impact on the management strategies of these patients other than conventional therapy.

In regard to DSE, syndrome X patients with normal resting LV size and function, systolic and diastolic long axis amplitude and diastolic velocities were significantly abnormal at peak stress. Since these disturbances are independent of the extent of CAC, this may suggest evidence of microcirculation disease, which is likely to compromise early diastolic coronary circulation. In the same group, patients with RWMAs have more chance of having coronary calcifications by MDCT than those with no inducible RWMA. Moreover, syndrome X patients exhibit clear evidence for reduced TAPSE and diastolic right ventricular dysfunction at a fast heart rate, particularly with worsening coronary calcification. The low sample size may have influenced the outcome of the study.

CHAPTER SEVEN

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APPENDIX

Regionala
etikprövningsnämnden
i Umeå
Avdelningen för medicinsk
forskning

BESLUT
2016-06-20

Michael Henein
Hjärtcentrum
Norrlands universitetssjukhus
901 85 Umeå

Ändringsansökan

Dnr 2016-66-32M (Tillägg till 08-118M)
Förkalkning i kranskärlen hos patienter med bröstsmärta och positivt arbetsprov men avsaknad av ateroskleros vid kranskärlsröntgen.

Projektet är tidigare godkänt.

Ansökan inkom till myndigheten 2016-02-22, komplett 2016-05-26.

Inkommen ansökan om ändring, som även omfattar eventuella begärda och inkomna kompletteringar, **godkänns** efter granskning av vetenskaplig sekreterare Bruno Hägglöf i samråd med ordföranden Anders Iacobaeus.

Ett godkännande enligt denna lag medför inte att forskningen får utföras, om den strider mot någon annan författning. (6§ EPL)

Initialt inkommen skrivelse bifogas som bilaga.

Anders Iacobaeus, ordförande
Regionala etikprövningsnämnden i Umeå
Avdelningen för medicinsk forskning
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Table 23 ICC (intraclass correlation coefficient) for intra-observer reliability and inter-observer reliability.

	Intra-observer ICC	Inter-observer ICC
REST		
Lateral S	0.997	0.998
Lateral E	1	0.999
Lateral A	1	0.999
Septal S	0.997	0.996
Septal E	0.997	0.996
Septal A	0.998	0.997
RV S	1	0.998
RV E	1	0.997
RV A	1	0.999
M-lateral (MAPSE)	0.908	0.889
M-septal	0.833	0.851
M-RV (TAPSE)	0.992	0.988
STRESS		
Lateral S	1	0.999
Lateral E	0.999	0.999
Lateral A	0.999	1
Septal S	1	0.997
Septal E	0.998	0.998
Septal A	0.999	0.998
RV S	1	0.999
RV E	0.999	1
RV A	1	0.999
M-lateral (MAPSE)	0.989	0.973
M-septal	0.956	0.964
M-RV (TAPSE)	0.978	0.993

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Letter to the Editor

Coronary calcium score is superior to exercise tolerance testing in predicting significant coronary artery stenosis

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Coronary artery calcification (CAC) scoring is recommended [1] for improving cardiovascular risk stratification but its relationship with the status of the coronary circulation remains controversial, being absent in some patients with acute coronary syndrome [2]. Exercise tolerance testing (ETT) remains a conclusive investigation for excluding significant obstructive CAD [3] but is known for its limitations. When patient is classified as intermediate risk, US and European guidelines then recommend CAC assessment [4], where zero calcification can be used to rule out obstructive CAD [5], particularly with an equivocal stress test [6].

We sought to compare the sensitivity and specificity of CAC and ETT in predicting significant coronary artery stenosis in 360 symptomatic patients at intermediate risk, presenting with angina-like symptoms to Bethanien Hospital Frankfurt, Germany, between 2007 and 2010 or to Umeå Heart Centre, Umeå, Sweden between 2009 and 2011. No patient had chronic kidney disease (creatinine >130 mmol/L), valve disease, heart failure, parathyroid disease or severe inflammatory disease. Patients received coronary angiography, ETT, CT scanning for calcium scoring using conventional techniques and had conventional risk factors assessed.

Patients mean age was 64.7 ± 9.8 years, 241 (67%) being aged <70, 208 (59%) were male, 68% had hypertension and around 50% had dyslipidaemia and/or family history for CAD. The mean CAC score for the whole patient group was 295 ± 561. Table 1 shows the sensitivity and specificity for CAC and ETT to predict CA stenosis. CAC > 0 had a sensitivity of 97% in predicting both ≥50% and ≥70% CA stenosis and a sensitivity of 96% in predicting single- and multi-vessel diseases (SVD and MVD). The negative predictive value (NPV) of the presence of CAC > 0 was 96%, 97%, 79% and 92%, respectively, but the specificity was generally poor. Compared to CAC > 0, CAC ≥400 had higher specificity for CA stenosis ≥50%, ≥70% and MVD ($p < 0.001$) and for SVD ($p = 0.05$) but lower sensitivity, which fell to <50% ($p < 0.001$ for CA stenosis ≥50%, ≥70% and SVD; $p = 0.01$ for MVD) and NPV, although only the difference in SVD was significant ($p = 0.01$). ETT sensitivity was lower than for CAC > 0 ($p < 0.001$ for all degrees of stenosis and $p = 0.01$ for MVD) and not different from CAC ≥ 400 for all degrees of stenosis. ETT specificity was higher than for CAC > 0 ($p < 0.001$ for all degrees of stenosis except SVD) but lower than that for CAC ≥ 400 ($p = 0.015$ and $p = 0.027$ for CA stenosis ≥50% and ≥70%), while NPV was not different from any measure for CAC ≥ 0 or CAC ≥ 400 except for SVD with CAC > 0 ($p < 0.001$).

Compared to age <70, sensitivity was higher in age ≥70 when using CAC ≥ 400 in predicting CA stenosis ≥50% ($p = 0.018$), ≥70% ($p = 0.06$), SVD ($p = 0.008$) and MVD ($p = 0.039$) but not when using CAC > 0 and ETT (Table 2). The specificity was lower in age ≥70 when using CAC > 0 to predict CA stenosis ≥50% ($p < 0.001$), ≥70% ($p < 0.001$), SVD ($p = 0.052$) and MVD ($p = 0.018$), but not for CAC ≥ 400 and ETT. The NPV was not different between age ≥70 and <70 for any category of stenosis. The sensitivity between females and males (Table 3) was not different for all categories of stenosis for CAC > 0, CAC ≥ 400 and ETT. Compared to females, males had lower specificity in predicting CA stenosis ≥70% ($p = 0.02$) when considering CAC > 0 and had a lower NPV for SVD when considering CAC ≥ 400 ($p = 0.01$) or ETT ($p = 0.001$).

Table 1
The sensitivity and specificity for CAC and ETT to predict coronary stenosis (CS).

	%	CS ≥ 50%	CS ≥ 70%	Single vessel	Multi vessel
CAC > 0	Sensitivity	97.2	97.4	96.3	96.6
	Specificity	26.2	23.3	46.3	19.0
	Positive value	35.9	25.7	85.4	37.7
	Negative value	95.6	97.1	79.2	91.7
CAC ≥ 400	Sensitivity	41.7	37.7	42.5	45.8
	Specificity	84.5	80.6	92.7	71.6
	Positive value	53.6	34.5	95.0	45.0
	Negative value	77.1	82.6	33.0	72.2
ETT positive	Sensitivity	38.9	39.0	41.0	45.8
	Specificity	53.7	60.4	56.1	60.3
	Positive value	29.6	21.5	75.3	37.0
	Negative value	69.7	78.4	22.5	68.6

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Table 2
The sensitivity and specificity for CAC and ETT to predict coronary stenosis (CS) in patients ≥70 years and <70 years.

		%	CS ≥ 50%	CS ≥ 70%	Single vessel	Multi vessel
≥70 years	CAC > 0	Sensitivity	97.9	100	100	98.1
		Specificity	5.6	5.8	5	9.1
		Positive value	40.4	28.9	37.7	83.6
		Negative value	80.0	100	100	50
	CAC ≥ 400	Sensitivity	61.7	57.6	73.9	65.4
		Specificity	75	67.4	57.5	100
		Positive value	61.7	40.4	50	100
		Negative value	75	80.6	79.3	37.9
	ETT positive	Sensitivity	40.4	45.5	43.5	38.5
		Specificity	66.7	67.4	67.5	72.7
		Positive value	44.2	34.9	43.5	87
		Negative value	63.2	76.3	67.5	20
<70 years	CAC > 0	Sensitivity	96.7	95.5	94.4	95.1
		Specificity	33.9	31	26.3	60
		Positive value	33.1	23.6	37.8	86.7
		Negative value	96.8	96.8	90.9	81.8
	CAC ≥ 400	Sensitivity	26.2	22.7	27.8	28
		Specificity	88.3	86.3	78.9	90
		Positive value	43.2	27	38.5	88.5
		Negative value	77.9	83.3	69.8	31.4
	ETT positive	Sensitivity	37.7	34.1	47.2	42.7
		Specificity	57.8	57.4	56.6	50
		Positive value	23.2	15.2	34	70
		Negative value	73.2	79.6	69.4	24.2

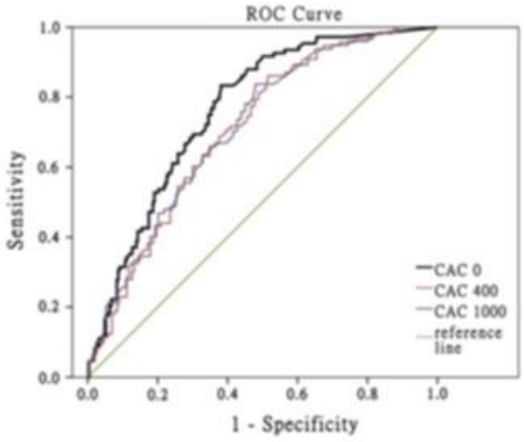

Fig. 1. ROC curve showing the highest sensitivity and specificity for prediction of coronary artery stenosis. CAC 0 = the analysis include all patients. AUC = 0.763, cut-off = 46.5, sensitivity = 83.3%, specificity = 61.9%. CAC 400 = the analysis include patients with CAC ≥ 400. AUC = 0.706, cut-off = 46.5, sensitivity = 85.7%, specificity = 48.7%. CAC 1000 = the analysis include patients with 0 < CAC < 1000. AUC = 0.711, cut-off = 46.5, sensitivity = 83.3%, specificity = 52.3%.

ROC curve analysis (Fig. 1) showed that the optimum cut-off value for CAC in predicting ≥50% CA stenosis was 46.5, with area under the curve (AUC) of 76%, a sensitivity of 83% and specificity of 62% ($p < 0.001$). The respective values for patients with CAC < 1000 were 71.1%, 81% and 53%. In addition, AUC was 71% for males with CAC > 0 and 79% for females with CAC > 46 in predicting CA stenosis. Conventional risk factors did not influence CAC sensitivity.

Our results show that CAC does not equate to coronary stenosis, in keeping with previous findings, which showed no CAC in ACS culprit lesions [2]. Our results also support the existing evidence that some patients with stable angina might have severe CAC but no flow-limiting lesions [7]. CAC presence and extent are known to correlate with cardiac events and all-cause mortality [8], although not all studies found a close linear relationship between CAC area and degree of luminal stenosis [6]. As with ours, most studies show a high sensitivity but poor specificity of the CAC score for angiographic obstructive disease [4,9], possibly because of arterial remodelling. This has led to the conclusion that CAC screening in stable and unstable symptomatic patients is a more reliable means of excluding obstructive CAD than ETT [9].

Furthermore our results show that ETT has significantly lower sensitivity and specificity in predicting significant CA stenosis compared to CAC, though not underestimating its value in patients with multi-vessel CAD [10], since it is based on the assessment of overall cardiac muscle function and its response to severity of ischemia rather than simply the presence of calcium deposition in the arterial wall.

Although our results clearly show that CAC screening is a better predictor of coronary stenosis than ETT, we would recommend using the two methods together, rather than either alone, since one is anatomical and the other is functional. Particularly in symptomatic patients with extensive CAC, ETT might be more informative in confirming myocardial ischaemic burden as an explanation of symptoms than a coronary angiogram which might not show any flow-limiting lesions and would give false reassurance. We recommend that the two investigations should be seen as complimentary rather than in competition.

Table 3
The sensitivity and specificity for CAC and ETT to predict coronary stenosis (CS) in female and male patients.

		%	CS ≥ 50%	CS ≥ 70%	Single vessel	Multi Vessel
CAC > 0	Female	Sensitivity	93.5	95.2	90.9	91.9
		Specificity	33.1	31.3	28.3	48.1
		Positive value	26.4	18.2	20.8	70.8
		Negative value	95.2	97.6	93.8	81.3
	Male	Sensitivity	98.7	98.2	97.9	97.9
		Specificity	23.6	16.4	11.1	42.9
		Positive value	41.8	30.2	45.6	92.2
		Negative value	96.2	96.2	87.5	75
CAC ≥ 400	Female	Sensitivity	29	19	27.3	29.7
		Specificity	95	91.6	83.0	96.3
		Positive value	60	26.7	25	91.7
		Negative value	83.9	87.6	84.6	50
	Male	Sensitivity	46.8	96.2	50	47.4
		Specificity	74.8	71.1	61.9	85.7
		Positive value	52.2	36.2	50	95.8
		Negative value	70.5	77.7	61.9	19
ETT positive	Female	Sensitivity	54.8	57.1	81.8	59.5
		Specificity	54.5	54.2	52.8	55.6
		Positive value	23.6	16.7	26.5	64.7
		Negative value	82.5	88.8	93.3	50
	Male	Sensitivity	32.5	32.1	37.5	34
		Specificity	65.6	65.8	66.7	57.1
		Positive value	35.7	25.7	46.2	84.6
		Negative value	62.3	72.5	58.3	11.1

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Coronary calcification compromises myocardial perfusion irrespective of luminal stenosis

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ABSTRACT

Aim: The aim of this study was to evaluate the relationship between coronary artery calcification (CAC) assessed by multi-detector computed tomography (MDCT) and myocardial perfusion assessed by cardiac magnetic resonance imaging (CMR) in a group of symptomatic patients.

Method: Retrospective analysis of 120 patients (age 65.1 ± 8.9 years, 88 males) who presented with atypical chest pain to Bethanien Hospital, Frankfurt, Germany, between 2007 and 2010 and who underwent CAC scoring using MDCT, CMR, and conventional coronary angiography. Patients were divided into those with high-grade (HG) stenosis (n = 67, age 65.1 ± 9.4 years) and those with no-HG stenosis (n = 53, age 65.1 ± 8.6 years).

Results: There were more males with HG stenosis (82.1% vs. 62.3%, $p = 0.015$), in whom the percentage and number of abnormal perfusion segments were higher at rest (37.3% vs. 17%, $p = 0.014$) but not different with stress ($p = 0.83$) from those with no-HG stenosis. Thirty-four patients had myocardial perfusion abnormalities at rest and 26 patients developed perfusion defects with stress. Stress-induced myocardial perfusion defects were 22.4% sensitive and 79.2% specific for detecting HG stenosis. The CAC score was lower in patients with no-HG stenosis compared to those with HG stenosis ($p < 0.0001$). On the ROC curve, a CAC score of 293 had a sensitivity of 71.6% and specificity of 83% in predicting HG stenosis [(AUC 0.80 ($p < 0.0001$)]. A CAC score of 293 or the presence of at least 1 segment myocardial perfusion abnormality was 74.6% sensitive and 71.7% specific in detecting HG stenosis, the respective values for the 2 abnormalities combined being 19.4% and 90.6%. The severity of CAC correlated with the extent of myocardial perfusion in the patient group as a whole with stress ($r = 0.22$, $p = 0.015$), particularly in those with no-HG stenosis ($r = 0.31$, $p = 0.022$). A CAC score of 293 was 31.6% sensitive and 87.3% specific in detecting myocardial perfusion abnormalities.

Conclusion: In a group of patients with exertional angina, coronary calcification is more accurate in detecting high-grade luminal stenosis than myocardial perfusion defects. In addition, in patients with no stenosis, the incremental relationship between coronary calcium score and the extent of myocardial perfusion suggests coronary wall hardening as an additional mechanism for stress-induced angina other than luminal narrowing. These preliminary findings might have a clinical impact on management strategies of these patients other than conventional therapy.

1. Introduction

Cardiac magnetic resonance imaging (CMR) myocardial perfusion has high diagnostic accuracy for coronary artery disease (CAD), even superior to single-photon emission computed tomography [1]; however, it is known for its limitations. Coronary artery calcium (CAC) score assessed by multi-detector computed tomography (MDCT) has also been shown to have high specificity in excluding obstructive CAD [2]. The diagnosis of CAD by the two techniques is based on different concepts; while CMR assesses myocardial perfusion as a consequence of coronary disease, MDCT analyzes the arterial disease morphology and allows for quantification of coronary wall calcification. In addition, MDCT non-invasive coronary angiography has shown higher accuracy than CMR in determining coronary stenosis [3].

Coronary calcification itself generally reflects atherosclerosis and its extent correlates with the overall plaque burden, in the form of luminal stenosis [4]. However, many symptomatic patients might present with coronary calcification in the absence of significant luminal stenosis, suggesting that arterial wall hardening could be associated with ischemic and compromised myocardial blood supply as a cause of symptoms. The aim of this study was to evaluate the potential relationship between CAC assessed by MDCT and myocardial perfusion assessed by CMR in a group of symptomatic patients, irrespective of the presence of luminal stenosis.

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2. Methods

This is a retrospective analysis of 120 patients (mean age 65.1 ± 8.9 years, 88 males) who presented with atypical chest pain, defined as inconsistent exertional chest discomfort, to Bethanien Hospital, Frankfurt, Germany, between 2007 and 2010 and who underwent CAC scoring using MDCT and myocardial perfusion scanning using CMR. All patients subsequently underwent conventional coronary angiography, which was performed not more than 1 month after the MDCT and CMR perfusion scans. None of the patients had acute coronary syndrome, heart failure, valvular heart disease, thyroid and parathyroid diseases, inflammatory disease, or chronic kidney disease (creatinine > 130 mmol/L). Significant obstructive coronary disease was considered present when there was clear evidence for at least one high-grade (HG) stenosis with ≥50% lumen narrowing on the conventional angiogram.

According to the coronary angiography results, patients were divided into two groups: HG stenosis group (n = 67, mean age 65.1 ± 9.4 years) and no-HG stenosis group (n = 53, mean age 65.1 ± 8.6 years). Being a retrospective comparison of imaging methods which had been ordered due to clinical indications by the cardiologists responsible for the patients' management. Therefore, an ethical vote did not appear to be necessary, according to the hospital policy.

2.1. CMR perfusion scan

CMR studies were performed using a 1.5-Tesla MRI system (Magnetom Sonata Maestro Class, Siemens AG, Erlangen, Germany), with the patient in the supine position, and additional ECG electrodes connected with external system (Magnitude 3150, InVivo Research Inc., Orlando, FL, USA) for continuous heart rate monitoring [5]. Blood pressure was also monitored. Both a six-channel body phased-array coil and a two-channel spine phased-array coil were used. Sequences acquired during breath-hold were performed during quiet expiration.

After localizers and anatomical images, perfusion imaging was performed. Typically, 3 short-axis slices, each with 10 mm slice thickness, were acquired at the basal, mid papillary, and apical levels of the left ventricle. Patients were stressed using conventional adenosine protocol. Adenosine stimulates A2 receptors in the microvasculature, leading to relaxation of the arterioles. In normal myocardium, this leads to increased perfusion without changes in blood volume [6]. With coronary stenosis, the magnitude of the increased perfusion during vasodilation is compromised [6]. The pressure drop results in capillary closure, reduced perfusion, and reduced blood volume, which is demonstrated as slower arrival and lower contrast agent concentration in the ischemic segment [6].

A single shot prospectively gated balanced Turbo Field Echo (TFE) sequence with a typical in-plane resolution of 2.5 × 2.5 mm was used. Patients were then allowed to rest until the hemodynamic effects of the adenosine had subsided (typically 5 min). The location and distribution of myocardial perfusion defects in the left ventricle were described using the American Heart Association 16-segment model [7].

For the stress study, intravenous adenosine was started 3 min before contrast injection. Twenty short-axis images were taken at every level of myocardium before, during, and after contrast injection. Myocardial perfusion was measured during adenosine infusion using high dose of Gadolinium-DTPA (0.06 mmol/kg). Adenosine was injected at a rate of 0.14 mg/kg/min, for 3–6 min for a total dose of 0.48–0.84 mg/kg. To avoid risk of large bolus drug, adenosine and contrast were administered through separate IVs [8].

Acquired images were subsequently transferred to a dedicated computer for analyzing changes in the myocardial signal intensity [9]. Two experienced observers, blinded to the MDCT results, decided by visual assessment on the myocardial perfusion and the blood supply of the 6 conventionally studied segments.

Rest and adenosine stress scans were magnified and displayed at the same time for visual assessment [10]. In normal scans, the first pass into the myocardium changed its colour uniformly from black to gray. A slowly changing colour to gray suggested impaired perfusion and hence was considered as a perfusion defect either at rest or induced, if it occurred at peak stress. The CMR system employed quantitative parametric tissue analysis [5].

2.2. Coronary artery calcium (CAC) score

CAC was measured using 64 MDCT (Somatom Sensation Cardiac 64; Siemens Medical Solutions, Forchheim, Germany) with a gantry rotation time of 330 ms (collimation 64 × 0.6 mm, reconstruction increment 0.3 mm). Images were acquired with the patient in quiet expiratory pause. Oral beta-blockers (bisoprolol 5 mg or metoprolol 50 mg) were given 1 h before the scan if the resting heart rate was > 60 beats/min. Calcification was described as the presence of > 2 contiguous pixels with > 130 Hounsfield Units. The workstation software automatically detected calcified areas and marked it in colour. The individual lesion scores were automatically summed to calculate the total Agatston score for each of the epicardial coronary artery territories as well as for the total coronary tree [4].

2.3. Coronary angiography

The Judkin's technique was used with at least four views of the left system and two views of the right system. Angiography was performed within 1 month after the CT scan in all patients. Analysis of the coronary angiograms was performed by an independent experienced observer. Significant stenosis was defined as ≥50% lumen narrowing of any epicardial coronary artery.

2.4. Statistical analysis

A standard statistical software package (SPSS 20, IBM, Armonk, NY, USA) was used for the statistical analyses. Categorical variables were expressed as absolute number and percentage (%). Normally distributed continuous data were expressed as mean ± standard deviation. The comparison between the HG stenosis and the no-HG stenosis groups was analyzed using chi-squared test. Spearman rank correlation was used to define the correlation between different CAC levels and myocardial perfusion on CMR. The null hypothesis was rejected on p values <0.05.

3. Results

Coronary risk factor distribution in the total study population and subgroups are listed in Table 1. The cardiovascular risk factors did not differ between the two groups, except for a higher proportion of males in the HG lesions group ($p = 0.015$).

Table 1
Risk factor distribution in the total study population divided into those with HG stenosis and no-HG stenosis

Risk factors	Total n = 120	HG stenosis n = 67	no-HG stenosis n = 53	p value
Males, n(%)	88 (73.3)	55 (82.1)	33 (62.3)	0.015
Age group (over 60 y) n(%)	86 (71)	49 (73.1)	37 (69.8)	0.421
Hypertension, n(%)	45 (37.5)	24 (35.8)	21 (39.6)	0.669
Smoking, n(%)	18 (15.0)	11 (16.4)	7 (13.2)	0.625
Diabetes, n(%)	14(11.7)	8(11.9)	6(11.3)	0.916
Obesity, n(%)	3(2.5)	1(1.5)	2(3.8)	0.427
Family history of CVD, n(%)	20(16.7)	11(16.4)	9(17.0)	0.934
Prior MI, n(%)	34 (28.3)	25 (37.3)	9 (17)	0.014

3.1.1. CMR perfusion between HG stenosis and no-HG stenosis (Table 2 and Fig. 1)

The percentage and number of perfusion segments were significantly higher in patients with HG stenosis with more than 1 segment perfusion defect at rest ($p = 0.014$), but there was no difference with stress ($p = 0.83$). Thirty-four patients had myocardial perfusion abnormalities at rest, and 26 patients developed perfusion defects with stress. Stress-induced myocardial perfusion defects were 22.4% sensitive and 79.2% specific for detecting HG coronary stenosis.

3.1.2. CAC score between HG stenosis and no-HG stenosis (Table 3 and Fig. 2)

The patient number and percentage were significantly different between the two groups with a lower CAC score in patients with no-HG stenosis and a higher CAC score in those with HG stenosis ($p < 0.0001$). On the ROC curve, the CAC cut-off value of 293 had a sensitivity of 71.6% and specificity of 83% in predicting HG coronary stenosis, giving an area under the curve of 0.80 ($p < 0.0001$) (Fig. 3).

3.1.3. CAC or/and myocardial perfusion in predicting HG coronary stenosis

A CAC score of 293 or the presence of at least 1 segment showing myocardial perfusion was 74.6% sensitive and 71.7% specific in detecting HG coronary stenosis. The respective values for the two abnormalities combined were 19.4% sensitivity and 90.6% specificity.

3.1.4. CAC score versus CMR myocardial perfusion (Table 4)

As shown in Table 4, the severity of CAC correlated with the extent of myocardial perfusion in the patient group as a whole with stress ($r = 0.22$, $p = 0.015$), particularly in patients with no-HG stenosis ($r = 0.31$, $p = 0.022$). A CAC score cut-off value of 293 was 31.6% sensitive and 87.3% specific in detecting myocardial perfusion abnormalities.

4. Discussion

CMR myocardial perfusion has been shown to have high accuracy in detecting coronary artery disease and related events [10–19]. This has been superseded by the greater accuracy of CTCA in excluding significant CAD [3]. The exact accuracy of the two techniques in identifying significant CAD (>50%) coronary stenosis in daily practice remains controversial [20]. Although CMR perfusion is considered a factual reflection of myocardial blood supply, as an accurate functional test, CTCA demonstrates the anatomical phenotypic manifestation of the disease and its implications on the coronary circulation. However, the main limitation of CTCA accuracy is in patients with severe calcification because of its masking of the true plaque size and relative narrowing of the lumen [3,21]. In fact, current guidelines recommend conventional angiography in patients with more than intermediate degree of coronary calcification and a calcium score >200. Despite that, a subgroup of patients with either severe calcification but no significant stenosis or with impaired myocardial perfusion but no significant stenosis remains, representing a clinical dilemma. There is currently no study that has shown an ideal way of describing these patients or proposed a strategy for managing them. The purpose of this study was to assess the relationship between CAC and CMR myocardial perfusion in patients with insignificant coronary stenosis.

Table 2
The difference in myocardial perfusion between the two groups at rest and with stress

	CMR perfusion defect (n, %)		
	0 segment	>1 segment	*p* value
At rest			
HG stenosis	42 (62.7)	25 (37.3)	0.014
no-HG stenosis	44 (83.0)	9 (17)	
At stress			
HG stenosis	52 (77.6)	15 (22.4)	0.83
no-HG stenosis	42 (79.2)	11 (20.8)	

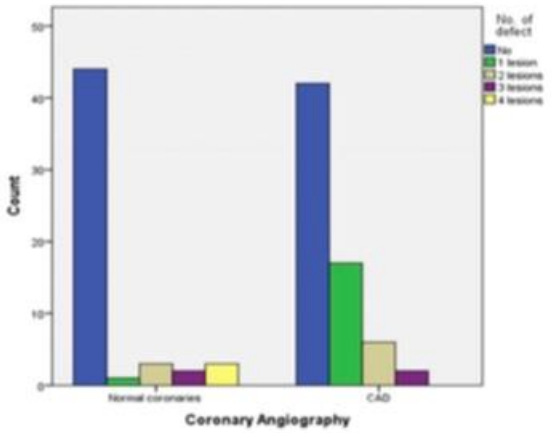

Fig. 1. The difference in myocardial perfusion between the two groups at rest and with stress

4.1.1. Findings

Our study results concur with some of the above findings in showing only a modest relationship between the presence of significant coronary stenosis and myocardial perfusion abnormalities by CMR. On the other hand, the CAC score was much more sensitive and specific in detecting HG stenosis, giving an area under the ROC curve of 80%. In addition, our findings highlight the relationship between CAC and stress myocardial perfusion defects, with an incremental increase in the number of myocardial segments showing perfusion defects, with stress, parallel to the progressive increase in CAC score, only in patients with no-HG stenosis. This suggests potential development of myocardial ischemia and symptoms as a result of the arterial wall hardening rather than luminal narrowing by a stenosis, suggesting that the CAC score might be reflecting the extent of plaque burden, irrespective of luminal narrowing [22]. We believe that we are the first to demonstrate that extensive CAC correlates with the diffuse pattern of myocardial perfusion defect in the absence of significant coronary stenosis, again suggesting a potential causative relationship. Pellika et al has shown a relationship between CAC and left ventricular wall motion abnormalities using stress echo but made no comment on the extent of obstructive lesions [23]. We too have recently shown parallel subendocardial abnormalities at peak stress in symptomatic patients with no coronary stenosis, particularly in those with significant calcification [24]. This evidence suggests that CAC, particularly with high scores, is likely to compromise coronary blood flow reserve and hence myocardial perfusion at the time of increased demand (peak stress).

4.1.2. Clinical implications

The coronary calcium score remains more accurate in detecting HG luminal stenosis over and above myocardial perfusion defects by CMR. Absolute reliance on luminal narrowing by either CTCA or conventional coronary angiography is likely to miss an important group of patients with limiting angina who do not demonstrate evidence for HG stenosis but suffer from wall hardening which compromises myocardial perfusion. This finding suggests an important role for the routine measurement of the CAC score in angina patients, particularly those with unexplained symptoms by conventional angiography.

Table 3
The difference in CAC between the two groups.

	CAC (n, %)				
	0–99	100–399	400–999	≥1000	*p*
HG stenosis	12 (17.9)	12 (17.9)	20 (29.9)	23 (34.3)	<0.0001
No-HG stenosis	29 (54.7)	17 (32.1)	4 (7.5)	3 (5.7)	

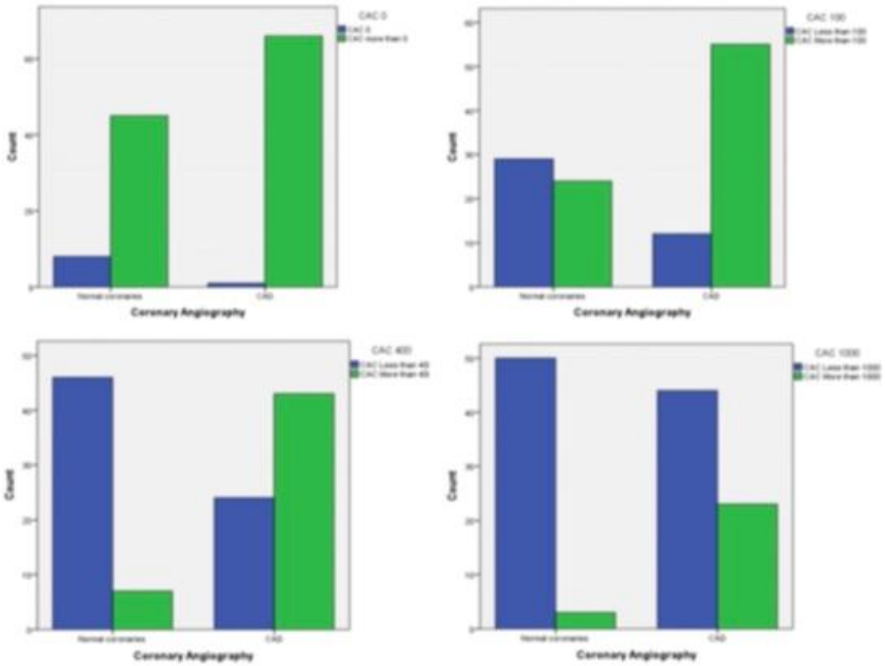

Fig. 2. The difference in CAC between the two groups

4.1.3. Limitations

There was a gender difference between patients with HG stenosis and those without, but this does not seem to have influenced our results, since the relationship between CAC and CMR myocardial perfusion defects was shown in those with no-HG stenosis, negating the potential imbalance of males, who generally have higher incidence of CAC [25]. Assessment of CMR perfusion was semi-quantitative but followed the international recommendations [26]. This study was retrospective in its design therefore subject to potential bias in patient selection. A significantly larger sample volume would have strengthened the relevance of our findings, particularly with the subgroup of patients with extensive calcification who showed clear evidence for myocardial perfusion abnormalities. We relied in our data interpretation on the accuracy of the CAC measurements as previously reported by Achenbach et al [27], who showed non-significant results in the variability of repeating CAC measuring by EBCT as well as the known low variability of the system we used (64-MSCT) [28]. None of the patients we studied was clinically felt to need an FFR assessment, this information is not available. Finally, we did not assess MRI reproducibility, having considered the long experience of the radiologist reported and the lack of potential competitor.

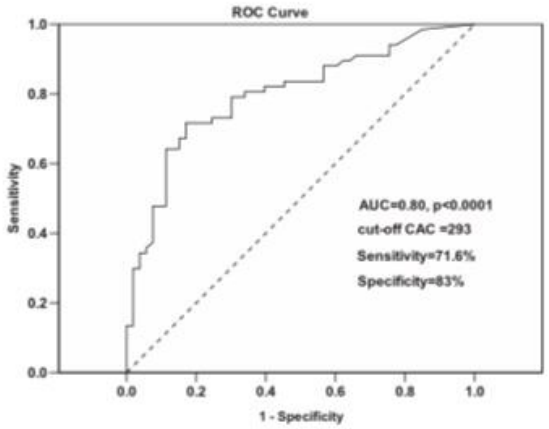

Fig. 3. the ROC curve for calcium score to predict the coronary artery stenosis, AUC = 0.80 (95% CI 0.82–0.88, $p < 0.0001$), cut-off value is CAC = 293 with sensitivity 71.6% and specificity 83%.

4.1.4. Conclusion

In a group of patients with exertional limiting angina, coronary calcification is more accurate in detecting high-grade luminal stenosis than myocardial perfusion defects. In addition, in patients with no stenosis, the incremental relationship between coronary calcium score and the extent of myocardial perfusion suggests coronary wall hardening as an additional mechanism for stress-induced angina other than luminal narrowing. These preliminary findings might have a clinical impact on management strategies of these patients other than conventional therapy.

Table 4
The relationship between CAC level and the number of segments showing myocardial perfusion, particularly in patients with no-HG stenosis.

	Rest		Stress	
All	$r = 0.066$	$p = 0.476$	$r = 0.221$	$p = 0.015$
HG stenosis	$r = 0.049$	$p = 0.696$	$r = 0.189$	$p = 0.125$
No-HG stenosis	$r = 0.149$	$p = 0.288$	$r = 0.314$	$p = 0.022$

Conflict of interest

None of the authors have any financial or conflict of interest to disclose.

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Coronary calcium score is superior to exercise tolerance testing in predicting significant coronary artery stenosis

Tarek Bengrid, Rachel Nicoll, Ying Zhao, Axel Schmermund and Michael Y Henein

ABSTRACT Aim: To determine whether coronary calcification is more predictive of significant coronary artery stenosis than exercise tolerance testing in symptomatic patients.

Methods: We retrospectively studied 360 patients, mean age 64.7±9.8y, 59% males, who presented to Bethanien Hospital, Frankfurt, Germany with angina-like symptoms and who underwent conventional angiography, CT scanning for coronary artery calcification (CAC) and exercise tolerance testing (ETT).

Results: A CAC score >0 was superior to ETT for prediction of significant coronary artery stenosis (≥50% narrowing), with sensitivity 97% vs. 39% ($p<0.001$) but specificity was only 26% vs. 54% ($p<0.001$). Patients aged ≥70 had higher sensitivity for CAC ≥400 in predicting CA stenosis compared to those aged <70 (62% vs. 26%, $p=0.018$) and in predicting single vessel disease (SVD) (74% vs. 28%, $p=0.008$) and multivessel disease (MVD) (65% vs. 28%, $p=0.039$). The respective specificities for CAC >0 were significantly lower in those aged ≥70 compared to age <70 for SVD (5% vs. 26%, $p=0.052$) and MVD (9% vs. 60%, $p=0.018$). ROC curve analysis showed a CAC score of 46.5 as having the highest sensitivity and specificity (83% and 62%, respectively, $p<0.001$) for predicting ≥50% CA stenosis with an area under the curve of 76%.

Conclusion: In symptomatic patients, coronary artery calcium score is more accurate in predicting the presence of significant coronary stenosis but exercise tolerance testing is more specific in excluding significant multivessel disease.

CORONARY CALCIFICATION COMPROMISES MYOCARDIAL PERFUSION IRRESPECTIVE OF LUMINAL STENOSIS

Michael Y. Henein, Tarek Bengrid, Rachel Nicoll, Ying Zhao, Bengt Johansson and Axel Schmermund

ABSTRACT

Aim: The aim of this study was to evaluate the relationship between coronary artery calcification (CAC) assessed by multi-detector computed tomography (MDCT) and myocardial perfusion assessed by cardiac magnetic resonance imaging (CMR) in a group of symptomatic patients.

Method: Retrospective analysis of 120 patients (age 65.1±8.9 years, 88 males) who presented with atypical chest pain to Bethanien Hospital, Frankfurt, Germany, between 2007 and 2010 and who underwent CAC scoring using MDCT, CMR and conventional coronary angiography. Patients were divided into those with high grade (HG) stenosis (n=67, age 65.1±9.4 years) and those with no HG stenosis (n=53, age 65.1±8.6 years).

Results: There were more males with HG stenosis (82.1% vs. 62.3%, p=0.015), in whom the percentage and number of abnormal perfusion segments were higher at rest (37.3% vs. 17%, p=0.014) but not different with stress (p=0.83) from those with no-HG stenosis. Thirty four patients had myocardial perfusion abnormalities at rest and twenty six patients developed perfusion defects with stress. Stress-induced myocardial perfusion defects were 22.4% sensitive and 79.2% specific for detecting HG stenosis. The CAC score was lower in patients with no-HG stenosis compared to those with HG stenosis (p<0.0001). On the ROC curve, a CAC score of 293 had a sensitivity of 71.6% and specificity of 83% in predicting HG stenosis [(AUC 0.80 (p<0.0001)]. A CAC score of 293 or the presence of at least 1 segment myocardial perfusion abnormality was 74.6% sensitive and 71.7% specific in detecting HG stenosis, the respective values for the two abnormalities combined being 19.4% and 90.6%. The severity of CAC correlated with the extent of myocardial perfusion in the patient group as a whole with stress (r=0.22, p=0.015), particularly in those with no-HG stenosis (r=0.31, p=0.022). A CAC score of 293 was 31.6% sensitive and 87.3% specific in detecting myocardial perfusion abnormalities.

Conclusion: In a group of patients with exertional angina, coronary calcification is more accurate in detecting high grade luminal stenosis than myocardial perfusion defects. In addition, in patients with no stenosis the incremental relationship between coronary calcium score and the extent of myocardial perfusion suggests coronary wall hardening as an additional mechanism for stress-induced angina other

than luminal narrowing. These preliminary findings might have a clinical impact on management strategies of these patients other than conventional therapy.

Effect of coronary calcium score on subendocardial function in patients with Syndrome X: A tissue Doppler dobutamine stress echocardiography study

Tarek Bengrid, Ying Zhao, and Michael Y Henein

Background and Aim: Patients with Syndrome X remain a clinical challenge in their management. We aimed in this study to determine the relationship between coronary calcification, measured by Agatstaon score and stress changes in subendocardial function as shown by left ventricular (LV) long axis amplitude and systolic and diastolic velocities.

Method: We examined 35 patients with Syndrome X (24 female, mean age 62 years), all complained of angina like symptoms, had > 1mm ST shift on exercise but no obstructive coronary disease on conventional angiography. No patient had prior coronary event, valve disease or LVEF <55%. All patients underwent dobutamine stress echocardiography (DSE) including M-mode and tissue Doppler and CT coronary calcium scoring CAC) using a multidetector CT system

Results: LV long axis amplitude increased at septal site (from 13.1±1.9 to 14.1±2.9 mm, P=0.012), but failed to do so at the lateral site (from 14.8±2.5 to 15.2±3.4 mm, P=0.48). Systolic velocities (s') increased (from 7.2±1.7 to 11.9±2.9 cm/s, and from 7.9±2.4 to 12.5±3.8 cm/s, P<0.0001 for both), at the two sites, respectively. However, early diastolic velocities (e') only increased in lateral site (from 9.0±2.7 to 10.3±2.4 cm/s (P=0.008) but not in septal site (from 7.7±1.8 to 8.1±2.4 cm/s, P=0.35). CAC range was 0-1356 (mean 205.49). There was no relationship between CAC score and any of the long axis measurements.

Conclusion: In a group of patients with syndrome X and normal resting LV size and function systolic and diastolic long axis 'subendocardial' function including amplitude and diastolic velocities, at fast heart rate were significantly abnormal. Since these disturbances are independent of the extent of CAC calcification, they may suggest an evidence for microcirculation disease, which is likely to compromise early diastolic coronary circulation.

Disturbed right ventricular function response to dobutamine stress in Syndrome X patients: A potential effect of coronary calcification.

Tarek Bengrid, Ying Zhao, Michael Y Henein

Background and Aims: The exact mechanism behind symptoms in Syndrome X patients remains disputable. We aimed in this study to assess in detail right ventricular (RV) function response to heart rate increase with dobutamine and compare it with the extent of coronary artery calcification score (CACS).

Methods: Thirty five patients with Syndrome X (24 female, mean age 62 years), who complained of angina like symptoms, had > 1mm ST shift on exercise but no obstructive coronary disease on conventional angiography were recruited. All patients had normal LV ejection fraction (>55%) and RV size, inlet diameter (<3.6 cm) who underwent dobutamine stress echocardiography (DSE) including M-mode and tissue Doppler of RV free wall and CACS using a multidetector CT system. Based on CT findings patients were divided into: Group I with CACS<100 and Group II with CACS >100.

Results: Resting RV long axis amplitude, s' was not different between the two groups. At peak stress, long axis amplitude did not increase (as it does in normal) in Group I 22.3±3.2 to 24.2±3.5mm (P=0.12), and it even fell in Group II from 23.2±3.3 to 19.5±3.9 mm (P=0.05). RV s' increased from 10.9±1.9 to 17.6±3.2 cm/s (P<0.0002) in Group I but to a lesser extent from 12.6±2.8 to 17.2±4.9 cm/s (P=0.013) in Group II. However RV e' failed to increase in the group I 8.2±2.0 vs 10.1±3.3 cm/s (p=0.08), but increased in group 2 7.1±1.5 vs 11.7±6.0 cm/s (P=0.04).

Conclusion: Syndrome X patients exhibit clear evidence for systolic and diastolic right ventricular dysfunction at fast heart rate, particularly with worsening coronary calcification.

SOCIETY OF CARDIOVASCULAR COMPUTED TOMOGRAPHY

December 15, 2017 Via Email

Dear Dr. Ben Grid,

We are pleased to inform you that your presentation, entitled "Effect of coronary calcium score on subendocardial function in patients with Syndrome X: A tissue Doppler dobutamine stress echocardiography study" has been accepted by the Society of Cardiovascular Computed Tomography as a POSTER presentation for the SCCT London 2018 Winter Meeting. Additional information about the date and time of your sessions, as well as guidelines for poster presentations (ie, poster dimensions, set-up times, etc.) will be made available to you soon. If you are not the presenter for the abstract, you are responsible for making sure the presenter receives all information from SCCT. *Please confirm that you will be attending by sending an email to abstracts@scct.org.*

As a reminder, all abstract presenters need to register for the SCCT London 2018 Winter Meeting. Please go to this link to register for the meeting and reserve hotel rooms https://www.rsm.ac.uk/events/rsm-professionals.aspx.

If you need additional assistance regarding registration or hotel rooms, please contact Gemma Lamb at the RSM at gemma.lamb@rsm.ac.uk.

We look forward to seeing you in London!

Sincerely,

Ed Nicol, MD, FSCCT Todd C. Villines, MD, FSCCT Jonathon Leipsic, MD, FSCCT

The SCCT 2018 London Winter Meeting Program Directors

For questions about registration, meeting arrangements, or for any other society related matters please contact: info@scct.org or visit www.scct.org for more information.

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Acceptance

16 February 2014 at 16:23

Moderated Poster Scheduling Notification
82nd European Atherosclerosis Society Congress
Madrid, Spain May 31st – June 3rd, 2014

Dear Dr Tarek Bengrid,

On behalf of the Scientific Programme Committee, we are pleased to inform you that your Abstract EAS-0077 entitled **EXTENSIVE CORONARY CALCIFICATION COMPROMISES MYOCARDIAL PERFUSION IN THE ABSENCE OF HIGH GRADE STENOSIS** has been selected for **POSTER PRESENTATION WITH DISCUSSION** at the 82nd European Atherosclerosis Society Congress.

Each Moderated Poster Session will consist of up to 8 posters and you will be allocated 3 minutes presentation time plus 3 minutes for discussion. Further details of the exact time of your poster presentation with discussion will be available in due course.

Instructions on how to prepare posters can be found on the congress website via this link. Please be sure to keep to these specifications.

Poster Scheduling Notification
82nd European Atherosclerosis Society Congress
Madrid, Spain May 31st-June 3rd, 2014

Dear Dr Tarek Bengrid,

On behalf of the Scientific Programme Committee, we are pleased to inform you that your Abstract EAS-0027 entitled **DISTURBED RIGHT VENTRICULAR FUNCTION RESPONSE TO DOBUTAMINE STRESS IN SYNDROME X PATIENTS: A POTENTIAL EFFECT OF CORONARY CALCIFICATION** has been selected for **POSTER PRESENTATION** at the 82nd European Atherosclerosis Society Congress.

Instructions on how to prepare posters can be found on the congress website via this link. Please be sure to keep to these specifications.

Your poster should be displayed as per the poster board number in the final programme that you will receive at the congress. Posters may be mounted from 15:30 on Saturday, May 31st, 2014 and should remain on display until the end of sessions on Tuesday, June 3rd, 2014. Authors are asked to actively participate in both poster sessions which will take place on Sunday, June 1st from 12:30-15:00 and Monday, June 2nd from 12:30-15:00. These events give you the unique chance to discuss your work with other scientists, they are located surrounding the Exhibition area where lunch boxes will be served.

CME/CPD Certificate

This is to certify that

Dr. Tarek Bengrid

Participated in the

82nd Congress of the European Atherosclerosis Society

Madrid, Spain
May 31 - June 3, 2014

and received 13 credits

Alberico L. Catapano
President
European Atherosclerosis Society

European Board for Accreditation in Cardiology (EBAC)

The 82nd Congress of the European Atherosclerosis Society (EAS 2014) has been accredited by the European Board for Accreditation in Cardiology (EBAC) for 13 hours of external CME credits. Each participant should claim only those hours of credit that have actually been spent in the educational activity. EBAC works according to the quality standards of the European Accreditation Council for Continuing Medical Education (EACCME), which is an institution of the European Union of Medical Specialists (UEMS).

The European Board for Accreditation in Cardiology is responsible for Accreditation of international CME programmes in cardiology for the European medical community. EBAC is one of the European Specialty Accreditation Boards (ESAB) of UEMS and belongs to ECSF (European Cardiology Section Foundation), a foundation of UEMS – Cardiology Section.

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Estonia Estonian Society of Cardiology/ on behalf of the Ministry of Social Affairs of the Republic of Estonia

Germany (Aerztekammer Nordrhein) 06/01/2014, VNR 2760512014138011795, 5 CME point[s] - 06/02/2014, VNR 2760512014138011787, 5 CME point[s] – 06/03/2014, VNR 2760512014138011779, 3 CME point[s]

Switzerland Valid for FMH Fortbildungsprogramm Kardiologie according to Voraussetzungskatalog, IA

List of institutions officially recognising the competence of EBAC in international accreditation:

CardioVasculair Onderwijs Instituut (NL), Österreichische Akademie der Ärzte (AT).

Dear Tarek Mohamed Ben Grid

on behalf of the EuroCMR 2016 Organizers and the Program/Abstract Committee I have the pleasure to inform you that your following Abstract has been accepted for presentation at EuroCMR 2016:

ID 1358

CORONARY CALCIFICATION COMPROMISES MYOCARDIAL PERFUSION IRRESPECTIVE OF LUMINAL STENOSIS

An final decision about **ORAL or POSTER PRESENTATION will be made as soon as possible**. As soon as we know the oral or poster presentation schedule we will inform you and invite you to prepare your oral presentation or how you can print/upload your poster presentation.

Please note that for either presentation the author (or any of his/her co-authors) must be present at the meeting and have a valid registration. Early registration fee still applies until February 14.

Thank you and looking forward to seeing you in Florence in May.

Mit freundlichen Grüßen/Best Regards

Franz J. Ganser
Congress Manager EuroCMR 2016

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