# On Stable Coronary Artery Disease. Diagnostic Aspects of Stress-induced Myocardial Ischemia.

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# On Stable Coronary Artery Disease

## Diagnostic Aspects of Stress-induced Myocaridal Ischemia

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# On Stable Coronary Artery Disease

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## Diagnostic Aspects of Stress-induced Myocardial Ischemia

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LUND
UNIVERSITY

Thesis for the degree of Doctor of Philosophy
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Faculty opponent: Prof. Jan Engvall

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Abstract
Stable coronary artery disease (CAD) is characterized by presence of stress-induced myocardial ischemia, in the myocardial territory supplied by a flow-limiting stenosis. Currently, many patients are treated with elective revascularizations based on findings on a coronary angiogram, without prior assessment of stress-induced myocardial ischemia. This is despite the recommendation by current guidelines to use imaging methods which assess the presence of stress-induced myocardial ischemia, as guidance in treatment decision-making. The overall aim of this thesis was to further elucidate the pathophysiologic mechanisms associated with stable CAD using different clinical methods, with a focus on their performance in diagnosing stress-induced myocardial ischemia. This is clinically important when identifying which patients would benefit from an elective revascularization.

**Paper I** demonstrated the difference between the pathophysiology underlying exercise-induced ST elevation and exercise-induced ST depression on an exercise-ECG. In contrast to exercise-induced ST depression, ST elevation at stress was predictive of presence, amount and location of exercise-induced ischemia, as determined by myocardial perfusion single photon emission computed tomography (SPECT).

In **Paper II**, the diagnostic performance of exercise-induced ST depression in determining exercise-induced ischemia was further explored, with a focus on gender differences. Myocardial perfusion SPECT was used as reference standard. The limited diagnostic performance of exercise-induced ST depression, especially in females, was highlighted. Furthermore, the need to go beyond the ST response interpretation, to enhance the diagnostic performance of an exercise stress test, was demonstrated.

**Paper III** revealed the limited performance of qualitative assessment of myocardial perfusion by cardiac magnetic resonance imaging and coronary angiography, when related to quantitative positron emission tomography.

**Paper IV** showed that unnecessary revascularizations could be performed or stenotic arteries in need of revascularization might be left untreated, if stress-induced myocardial ischemia is not assessed.

In summary, this thesis highlights the need to use diagnostic methods which assess the presence and amount of stress-induced myocardial ischemia, in patients with suspected stable CAD, as guidance in treatment decision-making. This could reduce the amount of unnecessary coronary interventions performed in this patient group.

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# On Stable Coronary Artery Disease

## Diagnostic Aspects of Stress-induced Myocardial Ischemia

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A doctoral thesis at a university in Sweden takes either the form of a single, cohesive research study (monograph) or a summary of research papers (compilation thesis), which the doctoral student has written alone or together with one or several other author(s).

In the latter case the thesis consists of two parts. An introductory text puts the research work into context and summarizes the main points of the papers. Then, the research publications themselves are reproduced, together with a description of the individual contributions of the authors. The research papers may either have been already published or are manuscripts at various stages (in press, submitted, or in manuscript).

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**Cover illustration front:** Image reflecting the imbalance between blood supply by the coronary arteries and the metabolic demand of the myocardium during stress, in the presence of stress-induced myocardial ischemia. (Credits: My sister-in-law Fatima Shdeed)

**Cover illustration back:** Shahnaz in Disneyland, Paris.



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*To my parents, husband and sons...*

# Contents

# List of publications

This thesis is based on the following papers, which in the text will be referred to by their Roman numerals.

I was responsible for the writing of the manuscripts in all studies. My contribution to Paper I was to take part in data collection and data analysis. My contribution to Papers II-IV was to write the ethical application, take part in design, perform the data collection and data analysis.

I. **Stress-induced ST elevation with or without concomitant ST depression is predictive of presence, location and amount of myocardial ischemia assessed by myocardial perfusion SPECT, whereas stress-induced ST depression is not**. **S. Akil**, L. Sunnersjö, F. Hedeer, B. Hedén, M. Carlsson, L. Gettes, H. Arheden, H. Engblom. Journal of Electrophysiology, vol. 49 pp. 307–315 (2016)

II. **Gender aspects on exercise-induced ECG changes in relation to scintigraphic evidence of myocardial ischemia**. **S. Akil**, B. Hedén, O. Pahlm, M. Carlsson, C. Hindorf, J. Jögi, D. Erlinge, H. Arheden, H. Engblom. Journal of Clinical Physiology and Functional Imaging. 2017 Nov 8 (epub ahead)

III. **Qualitative perfusion assessment by cardiac magnetic resonance imaging and invasive coronary angiography is not enough when evaluating patients with coronary artery disease - a cardiac positron emission tomography study**. **S. Akil**, F. Hedeer, J. Oddstig, M. Carlsson, H. Arheden, H. Engblom. Journal of the American College of Cardiology- Cardiovascular Imaging. *Submitted*

IV. **Need for assessment of myocardial perfusion prior to revascularization in patients with stable coronary artery disease**. **S. Akil**, F. Hedeer, J. Oddstig, T. Olsson, J. Jögi, M. Carlsson, C. Hindorf, H. Arheden, H. Engblom. *Manuscript*

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*"When you reach a peak, look down to see who helped you reach it and look up to thank God."*

— Unknown

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# Summary

Stable coronary artery disease (CAD) is characterized by presence of stress-induced myocardial ischemia, in the myocardial territory supplied by a flow-limiting stenosis. Currently, many patients are treated with elective revascularizations based on findings on a coronary angiogram, without prior assessment of stress-induced myocardial ischemia. This is despite the recommendation by current guidelines to use imaging methods which assess the presence of stress-induced myocardial ischemia, as guidance in treatment decision-making. The overall aim of this thesis was to further elucidate the pathophysiologic mechanisms associated with stable CAD using different clinical methods, with a focus on their performance in diagnosing stress-induced myocardial ischemia. This is clinically important when identifying which patients would benefit from an elective revascularization.

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In **Paper II**, the diagnostic performance of exercise-induced ST depression in determining exercise-induced ischemia was further explored, with a focus on gender differences. Myocardial perfusion SPECT was used as reference standard. The limited diagnostic performance of exercise-induced ST depression, especially in females, was highlighted. Furthermore, the need to go beyond the ST response interpretation, to enhance the diagnostic performance of an exercise stress test, was demonstrated.

**Paper III** revealed the limited performance of qualitative assessment of myocardial perfusion by cardiac magnetic resonance imaging and coronary angiography, when related to quantitative positron emission tomography. Furthermore, the need for fully quantitative non-invasive assessment of myocardial perfusion as well as for increased use of invasive flow reserve measurements during coronary angiography, in patients with suspected stable CAD, was emphasized.

**Paper IV** showed that unnecessary revascularizations could be performed or stenotic arteries in need of revascularization might be left untreated, if stress-induced myocardial ischemia is not assessed.

In summary, this thesis highlights the need to use diagnostic methods which assess the presence and amount of stress-induced myocardial ischemia, in patients with suspected stable CAD, as guidance in treatment decision-making. This could reduce the amount of unnecessary coronary interventions performed in this patient group.

# Populärvetenskaplig sammanfattning

Kärl som försörjer hjärtat med blod kallas för kranskärl. Vid en förträngning i ett kranskärl blir blodtillförseln till hjärtmuskeln otillräcklig. Detta resulterar i syrebrist i det området i hjärtmuskeln som försörjs av det drabbade kärlet (ischemi). Stabil kranskärlssjukdom karakteriseras av syrebrist i hjärtmuskeln vid arbete. Sjukdomen kan behandlas genom att vidga det förträngda kranskärlet. Idag behandlas flera patienter med kranskärlsvidgning, utan någon utvärdering av närvaro och utbredning av den arbetsutlösta syrebristen i hjärtmuskeln. Detta trots riktlinjer som rekommenderar användandet av diagnostiska metoder som utvärderar den arbetsutlösta syrebristen i hjärtmuskeln, hos patienter med misstänkt stabil kranskärlssjukdom. Denna avhandling syftar till att, med befintliga kliniska metoder, undersöka de mekanismer som ligger bakom stabil kranskärlssjukdom, med fokus på metodernas diagnostiska ackuratess vid utvärdering av den arbetsutlösta syrebristen i hjärtmuskeln. Detta är viktigt vid selektion av patienter som kommer att gynnas av en kranskärlsvidgning.

**Delarbete I** belyser skillnaden i bakomliggande mekanismer mellan två olika elektrokardiografiska (EKG) mönster (ST höjning och ST sänkning) som uppstår under arbete, vid närvaro av stabil kranskärlssjukdom. Detta delarbete visar att den arbetsutlösta ST höjningen på ett arbets-EKG kan förutsäga förekomst, utberedning och lokalisation av syrebristen i hjärtmuskeln vid arbete.

**Delarbete II** fördjupar analysen avseende betydelsen av arbetsutlöst ST sänkning samt arbetsprovets prestanda som helhet vad gäller förekomst av syrebrist i hjärtmuskeln vid arbete. Delarbetet påvisar att EKG mönstret som nämns ST sänkning, har ett begränsat diagnostiskt värde för arbetsutlöst syrebrist, speciellt hos kvinnor. Dessutom påvisas vikten av att använda andra variabler som fås från ett arbetsprov, för att utöka metodens prestanda vid diagnostik av stabil kranskärlssjukdom.

**Delarbete III** belyser behovet av att kunna kvantifiera blodflödet till hjärtmsukeln, vid diagnostik av arbetsutlöst syrebrist.

**Delarbete IV** påvisar att bristen på utvärdeing av den arbetsutlösta syrebristen i hjärtat, i samband med behandlingsbeslut, kan resultera i onödiga kranskärlsvidgningar och obehandlande kranskärl med förträngningar.

Sammmanfattningsvis betonar denna avhandling vikten av att behandlingsbeslut guidas av diagnostiska metoder som utvärderar närvaro och utbredning av arbetsutlöst syrebrist i hjärmuskeln, hos patienter med misstänkt stabil kranskärlssjukdom. Detta för att minska antalet onödiga kranskärlsvidgningar som görs i denna patientgrupp.

# Abbreviations

**CABG** coronary artery by-pass graft surgery

**CAD** coronary artery disease

**CFR** coronary flow reserve

**CT** computed tomography

**DTPA** diethylenetriamine penta-acetic acid

**ECG** electrocardiogram

**ESC** european society of cardiology

**EST** exercise stress test

**Gd** gadolinium

**HR** heart rate

**LAD** left anterior descending coronary artery

**LCx** left circumflex coronary artery

**LGE** late gadolinium enhancement

**LV** left ventricle

**MI** myocardial infarction

**MRI** magnetic resonance imaging

**NPV** negative predictive value

**PET** positron emission tomography

**PCI** percutaneous coronary intervention

**PPV** positive predictive value

**RCA** right coronary artery

**SPECT** single photon emission computed tomography

**SSS** summed stress score

**S-TPD** stress total perfusion deficit

**99mTc** Technetium-99m

*Like a small boat*
*On the ocean*
*Sending big waves*
*Into motion*
*Like how a single word*
*Can make a heart open*
*I might only have one match*
*But I can make an explosion...*
— Fight song by Rachel Platten

*Choosing what is right over what is easy*
*gives an undepictable pain in the heart*
*but has the best long-term outcome*
— Shahnaz Akil

# Chapter 1

# Inroduction

*"We cannot conceive of matter being formed of nothing,*
*since things require a seed to start from..."*

— William Shakespeare

## 1.1 Coronary artery disease

Coronary artery disease (CAD), also known as ischemic heart disease, includes a wide spectrum of clinical presentation, from stable angina pectoris to acute coronary syndrome. This thesis will focus on stable CAD. Globally, CAD is the leading cause of mortality and is considered to be the primary cause of heart failure [1;2]. In 2015, about 8.8 million people (52% males and 48% females) died from CAD, which represented 16% of all global deaths during that year [1]. The prevalence of the disease is higher among males than females and increases with increasing age in both genders [1]. Furthermore, CAD has burdened the health care economy with several billion dollars a year [3]. The high health care costs and mortality rates of the disease can be decreased by accurate treatment resulting from reliable diagnosis. This can be achieved by understanding different aspects of the pathophysiology underlying the disease.

### Atherosclerosis in the coronary arteries

Stable CAD is mainly characterized by development of stress-induced myocardial ischemia. Stress-induced myocardial ischemia is defined as an imbalance between the arterial supply of blood and the myocardial metabolic demand, during stress. In the presence of stress-induced myocardial ischemia, the coronary flow reserve (CFR), defined as the maximum increase of blood flow from rest to stress, is decreased. The main cause of stress-induced ischemia is presence of a flow-limiting stenosis, in the wall of one or several epicardial coronary arteries.

**The epicardial coronary arteries.** The coronary arteries are situated on the surface of the myocardium. The left main coronary artery divides into the left anterior descending artery (LAD) and the left circumflex coronary artery (LCx). The LAD delivers blood to the anterior, septal and apical part of the left ventricle (LV), while the LCx supplies the lateral part of the LV. The LAD further branches into diagonals and the LCx into marginals. Furthermore, the right coronary artery (RCA) supplies the inferior part of the LV, in addition to the right atrium and right ventricle. The wall of the coronaries consists of three layers, with the *Tunica externa* being the outermost layer. The *Tunica media* is the middle layer and consists of smooth muscle cells. The *Tunica interna* is the layer closest to the lumen and it consists of endothelial cells and a basal membrane. Stenosis can form from atherosclerotic plaques in the wall of the epicardial coronary arteries.

**Atherosclerosis.** Atherosclerosis is a complex process which begins at early age and develops over decades[4]. Risk factors including smoking, hypertension, diabetes and hyperlipidemia might catalyze the rate of the process. Several components including lipoproteins, cells of the immune- system, smooth muscle cells and signaling molecules are involved in the development of atherosclerotic plaques. In summary, when T-lymphocytes and monocytes pass through the endothelial layer to reach the intima of the artery wall, they transform into macrophages. During this process, the macrophages become "foam cells" forming "fatty streaks". An inflammatory process occurs parallel to the building-up of the lipid storage, creating a necrotic inner core in the built-up lipid storage. A fibroartheroma, composed of type I collagen, lymphocytes, macrophages and smooth muscles cells, is formed on the outer layer of the necrotic lipid, resulting into atherosclerotic plaques. The plaques create a lumen-narrowing stenosis which limits the myocardial blood flow.

**Myocardial blood flow.** In normal coronary arteries, myocardial blood flow is mainly regulated by the resistance of the arterioles. Epicardial coronary arteries contribute with very little resistance to the coronary blood flow. The equations below show that Ohm's Law of physics (equation 1) and Poiseuille's equation (equation 2) are combined (equation 3) to describe the relationship between blood flow, vessel radius and resistance (Q= flow, $\Delta$P= difference in pressure, R= resistance, r= radius of the vessel, L= length of the vessel, $\eta$= viscosity of blood).

$$Q = \frac{\Delta P}{R} \tag{1}$$

$$R = \frac{8L\eta}{\pi r^4} \tag{2}$$

$$Q = \frac{\Delta P \pi r^4}{8L\eta} \tag{3}$$

Thus, a decrease in the radius of a vessel, when a stenosis is present, increases the

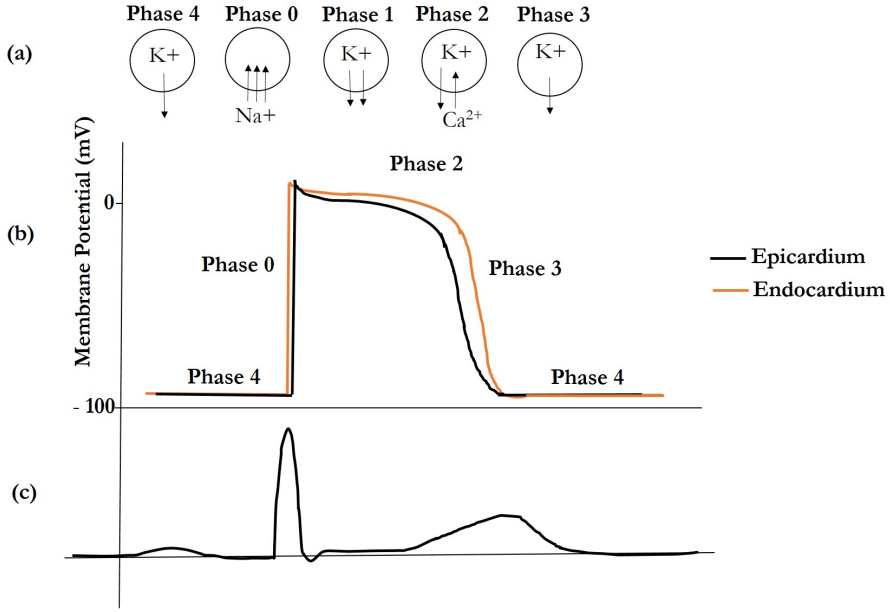


FIGURE 1.1: The **(a)** in- and out-flow of ions during the five phases of a normal myocyte action potential, the **(b)** resulting endo- and epicardial action potential curves illustrated during normal conditions with the **(c)** resulting waves on a normal electrocardiogram.

resistance and thereby decreases the blood flow, through the coronary artery, with a power of 4. In the case of stable CAD, myocardial blood flow is affected predominantly during stress. When the blood supply to a certain myocardial territory does not meet the required demand, the oxygen supply to the myocytes in that territory decreases. This affects important cellular processes.

**Ischemia at the myocyte level.** Both nutrients and oxygen are needed to produce enough energy for contraction and relaxation of the myocytes. Energy in the form of adenosine triphosphate (ATP) is produced by synthesizing ATP from adenosine diphosphate (ADP). Normally, approximately 60% of the energy is produced from fatty acids, while the rest comes from glucose and lactate. In the presence of ischemia, the aerobic oxidative phosphorylation process in the mitochondria is inhibited or slowed down. Thus, the amount of ATP produced is decreased. This affects the contraction and relaxation of the myocytes, which are guided by an energy-demanding electrophysiological process where an action potential is created.

## The action potential

Both chemical and electrical gradients work together to create the action potential. Transportation of ions in and out of the myocytes, through channels in the cellular membrane, produces a chemical gradient across the membrane. The difference in the charges between the interior and the exterior of the cell produces an electrical gradi-

ent. The charge of the interior and exterior of the cell is decided by the intra- and extracellular concentrations of $K^+$ (negative equilibrium potential) and $Na^+$ (positive equilibrium potential). Normally, the $K^+$ concentrations are higher in the intracellular space (140 mmol/L)[5], compared to the extracellular space (4.0 mmol/L)[5]. $Na^+$ is however found in higher concentrations in the extracellular space (140 mmol/L)[5] compared to the intracellular space (10 mmol/L)[5]. Thus, during adequate blood flow, the interior of the cell has a negative charge while the extracellular space is positively charged. The resting action potential of the myocytes normally ranges between -85 mV and -90 mV and is maintained by the active pumping of $K^+$ into the cell and $Na^+$ out of the cell, through the energy-demanding $Na^+/K^+$-ATPase pump.

**Phases of the action potential.** The action potential is usually divided into five phases (Phases 0-4). The transport of ions during the different phases and the resulting endo- and epicardial action potential curves are illustrated in Fig. 1.1. *Phase 0* is the depolarization phase and involves inflow $Na^+$, into the intracellular space, through the voltage-dependent $Na^+$ channels. Thus, the action potential switches from being negative into being positive. Furthermore, a slight inflow of $Ca^{2+}$ occurs through calcium channels. *Phase 1* is characterized by a "notch" caused by the outflow of $K^+$ and the decay of $Na^+$ current. A plateau is then created, in *Phase 2*, by the passive outflow of $K^+$ and inflow of $Ca^{2+}$. A slight inflow of $Na^+$ also occurs, to stabilize the action potential. A rapid repolarization of the myocytes takes place in *Phase 3* where there is a fast outflow of $K^+$ and a decay of $Ca^{2+}$ intracellularly. The regained resting negative action potential is stabilized in *Phase 4* by the active pumping of $Na^+$ and $K^+$ across the membrane, together with a slight outflow of $K^+$ passively.

**Ischemia and the action potential.** Ischemia is classified based on its extent and severity. Subendocardial ischemia is localized in the endocardium while transmural ischemia extends across the myocardial wall thickness, from the endocardium to the epicardium. Thus, in contrast to subendocardial ischemia, transmural ischemia involves changes in both the epicardial and endocardial action potential[6;7]. Subendocardial ischemia, however, decreases the maximum action potential amplitude (Phase 2) and makes repolarization occur earlier (Phase 3) in the endocardium only, as illustrated in Fig. 1.2. In the case of stable CAD, the ischemia is mostly subendocardial and the action potential changes during ischemia are induced by stress. Ischemia does not only affect the action potential, but also triggers a cascade of events in the body.

## The ischemic cascade

The ischemic cascade summarizes a sequence of events occurring over time, ranging from reversible (stable) ischemia to myocardial infarction[8]. Thus, possible consequences of not treating the stable CAD can be reflected by this cascade.

**Ischemia.** The first step in the cascade is ischemia. Ischemia is caused by a decrease in the myocardial perfusion to a myocardial territory. The affected myocardial territory is either supplied by an occluded coronary artery (acute coronary syndrome) or a coronary artery with a stenosis limiting myocardial blood flow only during stress (stable CAD).

**Diastolic dysfunction.** Ischemia is followed by diastolic dysfunction, which is the second step in the cascade. Diastole is an energy-demanding process where the relaxation of the myocardium requires ATP for the pumping of $Ca^{2+}$ from the cytosol back into the sarcoplasmatic reticulum or out to the extracellular space. In ischemic myocytes, a dysfunction in the relaxation process occurs due to lack of oxygen for the oxidative phosphorylation. Oxidative phosphorylation is the process by which the highest amount of energy, in the form of ATP, is produced [9].

**Systolic dysfunction.** If the ischemia remains untreated, systolic dysfunction occurs, which is the third step of the ischemic cascade.

**Changes on the electrocardiogram (ECG).** In the next step of the cascade, ECG changes start appearing mainly in the form of ST segment deviations.

**Angina pectoris.** The fifth step of the cascade involves development of chest pain, also named angina pectoris, which is caused by the accumulation of metabolites. The chest pain is experienced together with radiating pain to the jaw, back, shoulder, arm or neck [10].

**Myocardial infarction (MI).** MI, caused by an occluded coronary artery, occurs when the duration of untreated ischemia has persisted long enough. MI, the final step of the ischemic cascade, results into necrosis and thus irreversible injury. The subendocardium is the first myocardial area to be affected by the necrosis. If the blood flow remains impaired, the extent of MI increases over time as the wavefront of necrosis progresses from the subendocardium across the myocardial wall [11]. Transmural MI evolves when the extent of MI has covered the entire myocardial wall thickness. To prevent patients with CAD from developing MI, it is important with early detection of ischemia and subsequent accurate treatment.

## Treatment

Patients with stable CAD are treated by medication and/or an elective revascularization [12;13]. Medical treatment is aimed to improve patient prognosis by preventing the progression of the disease. The normally prescribed medicines include statins, anticoagulants, angiotensin converting enzyme inhibitors/angiotensin II receptor blockers, beta blockers and nitrates. Some patients with stable CAD are treated with a revascularization in combination with a medical treatment. Elective revascularization is an invasive procedure aimed to treat coronary stenosis causing stress-induced myocardial ischemia. Revascularization can be performed either by way of percutaneous coronary intervention (PCI) or coronary artery bypass graft surgery (CABG). Today, a PCI is mostly performed in conjunction with an invasive cardiac imaging examination named coronary angiography [14].

TABLE 1.1: Summary of the diagnostic methods used in this thesis.

| | Detected energy or signal | Utility | Cost[a] | Radiation dose (mSv)[b] |
|---|---|---|---|---|
| **Coronary angiography** | Transmitted photons produced in X-ray tube | Coronary stenosis | Very high | 5-15 |
| **Exercise-ECG** | Electrical changes in the myocardium over time | Stress-induced ischemia and infarct | Low | None |
| **Myocardial perfusion SPECT** | Photons from gamma-emitting radiopharmaceutical | Relative perfusion | Medium | 4 |
| **Cardiac PET** | Photons from positron-emitting radiopharmaceutical | Quantitative perfusion | High | 4 |
| **Cardiac MRI** | Signal from externally stimulated tissue | Relative perfusion, viability and left ventricular function | Medium | None |

[a] Rating of cost is relative
[b] Dose includes low-dose CT for PET and stress as well as rest examination for both SPECT and PET, using the radiopharmaceuticals $^{99m}$Tc-tetrofosmin and $^{13}$N-$NH_3$

## 1.2 Cardiac imaging

Currently, several cardiac imaging methods are available for the assessment of patients with suspected stable CAD. These methods include coronary angiography, exercise testing (EST), myocardial perfusion single photon emission computed tomography (SPECT), cardiac magnetic resonance imaging (MRI), cardiac positron emission tomography (PET), diagnostic computed tomography (CT) and echocardiography. Diagnostic CT and echocardiography were not used in the papers included in this thesis and will therefore not be described in this section. The methods used in this thesis are summarized in Table 1.1 and they are based on different techniques, allowing them to assess different aspects of the pathophysiology of stable CAD.

### Coronary angiography

Coronary angiography is a widely used invasive examination which is considered the reference standard for assessing presence of stenosis in the coronary arteries.

**Generating an angiogram.** The coronary arteries are accessed by inserting a small catheter through an artery, typically in the arm or groin. An iodinated contrast agent is also injected intravenously during the examination. Real-time images, named angiograms, are obtained using X-ray fluoroscopy. The emitted X-rays are a type of ionizing electromagnetic radiation. The discovery of X-rays in 1895 by Wilhelm Conrad Röntgen awarded him the first Noble Prize in Physics in 1901. The invasive nature of the examination allows acquisition of images, of the lumen of the coronary arteries, with excellent temporal and spatial resolutions.

**Invasive flow reserve measurements.** Fractional flow reserve (FFR) and instantaneous wave-free ratio (iFR) are two types of invasive flow reserve measurements performed during coronary angiography. The invasive measurements are used to assess the functional significance of a coronary stenosis detected on an angiogram. Using catheters with pressure sensitive tips, FFR can be obtained by calculating the ratio of the pressure measured distal to the stenosis and the pressure measured in the aorta, at rest as well as during adenosine stress. To obtain iFR, however, the pressure difference across a stenosis is measured during a wave-free period in diastole where flow is linearly proportional to the pressure. IFR is thus measured at rest and does not require the use of the vasodilator adenosine.

**Limitations of the technique.** Coronary angiography is a costly examination which involves the use of ionizing radiation. X-ray fluoroscopy only provides 2- dimensional images of the inside of the coronary arteries. Furthermore, possible complications of the invasive procedure include in-stent stenosis, endothelial damage, myocardial infarction, stroke and death. Complications related to the contrast agent used include kidney damage and acute allergic reactions.

## Exercise stress testing

Due to its availability and low cost, bicycle or treadmill EST is the most widely used stress-test in patients with suspected stable CAD. The analysis of an EST is to a large extent dependent on stress-induced ECG changes [15]. Observations such as exercise capacity, blood pressure- and heart-rate (HR) response are analyzed in addition to the ST response in certain ECG leads [16]. An ECG records the electrical activation of the myocardium (depolarization and repolarization) over time, from different angles. In 1887, the first ECG was performed by a British named August Waller. The different waves (P, Q, R, S and T) of the ECG were however named by Willem Einthoven, in 1891, which made him earn the Noble Prize in medicine 1924. In Sweden, the first ECG was performed in Lund 1908.

**The standard 12-lead ECG.** A standard 12-lead ECG is comprised of six percordial leads (V1-V6) and six limb leads (I, II, III, aVF, aVL, aVR), obtained by correctly placing a total of 10 electrodes on the body (six on the chest, three on the limbs and one earth electrode), as previously described [17]. The output shown in each ECG lead is generated when an electrode or combination of electrodes record the summed vector of the electrical activation of the heart, pointing towards or away from them, at a given time. The summed vector is the resulting vector of the size and direction of an electrical impulse at a given time. When the summed vector is pointing towards the recording electrode, a positive deflection is obtained on the ECG. A summed vector pointing away from the recording electrode gives a negative deflection on the ECG. The limb leads show the electrical activation of the heart in the frontal plane (superior, inferior, lateral and septal) while the percordial leads present the electrical activation of the heart in the horizontal plane (anterior, posterior, lateral and septal). The ECG output shows the voltage of the recorded summed vector, of the electrical activation of the heart, over

time, with 1mV=1mm on paper. Atrial depolarization is represented by the P-wave, ventricular depolarization by the QRS-complex and ventricular repolarization by the T-wave. The PQ line is referred to as the ECG baseline and is iso-electric. The ECG machines set the zero point at the baseline.

**ST segment deviations.** The ST segments before, during and after exercise are mainly used to assess the presence of stress-induced myocardial ischemia[15]. Stress-induced ST segment deviation, typically ST depression on the 12-lead ECG, is usually considered to be a sign of stress-induced ischemia[15]. Exercise-induced ST segment depression is commonly attributed to subendocardial or non-transmural ischemia. Occasionally, patients demonstrate elevation of the ST segment during the EST, and this has been suggested to indicate more severe ischemia than that associated with ST segment depression[18;19]. The performance of exercise-induced ST deviations, in diagnosing stress-induced ischemia, has been shown to be limited[16], especially in females[20;21;22], which could partly be explained by more frequent atypical ST responses during EST in females compared to males. However, no gender-specific diagnostic criteria for findings during an EST exist.

**Cause of ST segment deviations.** The electrical changes during repolarization and depolarization, in the presence of either transmural or subendocardial ischemia, are illustrated in Fig 1.2.

In the case of subendocardial ischemia, the changes in the endocardial action potential (lower amplitude and earlier repolarization) create a difference in electrical potential between the ischemic subendocardium and the normal epicardium (Fig.1.2). This causes a depression of the ST segment.

In the case of transmural ischemia, which extends over the entire thickness of the myocardial wall, the $Na^+/K^+$-ATPase pump in the myocytes is impaired. Thus, the outside of the myocytes within the ischemic area becomes negatively charged. Myocytes in the normal myocardial area are, however, completely repolarized and the outside of cells is therefore positively charged. The difference in extracellular electrical charges between the ischemic and non-ischemic myocardial areas generates an injury current at the boundary between the two areas. This affects the PQ interval of the ECG by shifting it downwards. Given that the ECG machines set the zero point (baseline) at the PQ interval, the ST segment appears elevated relative to the depressed ECG baseline (new zero point). The position of the rest of the waves of the ECG is, however, mainly not affected by the presence of the ischemia.

ST depressions are known to be poor markers of the location of ischemia[23] compared to ST elevations[24]. The diagnostic meaning and the underlying pathophysiological basis for appearance of exercise-induced ST elevation on the ECG are much less studied compared to exercise-induced ST depression.

**Exercise capacity.** Evaluation of exercise capacity has been shown to be of prognostic significance in patients with suspected or established stable CAD[25;26]. Exercise capacity can be measured in Watts and % of expected achieved exercise capacity. In the absence of lung disease, the exercise capacity can be evaluated by determining the peak oxygen uptake ($VO_2$ peak)[17]. $VO_2$ peak can be determined from an EST combined

with simultaneous gas analysis. This type of EST is also named a cardiopulmonary stress test and requires the placement of an airtight mask on the face of the patient. This allows, breath by breath, continuous recording of the inspired oxygen ($O_2$) and the expired carbon dioxide ($CO_2$).

**Limitations of the technique.** As previously mentioned above, the location of subendocardial ischemia from ST depressions on an exercise ECG is known to be poor [23]. Furthermore, the amount and extent of the subendocardial ischemia can not be assessed from an exercise ECG. Other limitations include motion artifacts on the exercise ECG, making the assessment of exercise-induced ECG changes more difficult.

## Myocardial perfusion single photon emission computed tomography (SPECT)

Myocardial perfusion SPECT is a non-invasive nuclear medicine examination involving an intravenous injection of a radiopharmaceutical and subsequent image acquisition by a gamma camera. The acquired images allow assessment of the relative LV myocardial perfusion distribution during exercise or pharmacological stress and during resting conditions [27].

**Exercise versus pharmacological stress.** The chosen stress method during myocardial perfusion SPECT examination depends on the patient's clinical history and the clinical routine at each center. Both exercise and pharmacological stress tests are aimed to increase the myocardial blood flow through vasodilation of the coronary arteries. The two stress methods, however, differ in the way by which they induce the vasodilation.

Exercise, either by way of bicycle stress test or treadmill test, is expected to cause a 2- to 3-fold increase in myocardial blood flow through an endothelium-dependent flow-mediated process, triggered by the increased oxygen demand during exercise [28]. Thus, the increase in myocardial blood flow during exercise is demand-driven. Inadequate increase in blood flow during exercise is mainly caused by presence of one or several flow-limiting stenoses.

A pharmacological stress test uses vasodilators to cause a 3.5-to 4-fold increase in myocardial blood flow [29]. Several vasodilators exist (dipyridamole, regadenoson, adenosine and dobutamine) [29], but adenosine is the one used in the papers included in this thesis. The binding of adenosine to A2A receptors activates dilation of the coronary arterioles. The increase in myocardial flow, when adenosine is used, is supply-driven because it is triggered by how much the blood supply can be increased given the diameter of the coronary artery. Adenosine can also activate other receptors which cause bronchospasm and is therefore recommended to not be used in patients with asthma or severe chronic obstructive lung disease. Flushing, dyspnea and chest pain are common side-effects which disappear shortly after the administration of adenosine, given the short half-life (<10s) of this vasodilator. Caffeine is an adenosine receptor-antagonist. Patients are thus instructed to refrain from caffeine intake 24 hours before the adenosine stress test.

**Radiopharmaceutical.** Properties of an optimal radiopharmaceutical for imaging myocardial perfusion include 1) linear relation between its uptake in the myocardium and perfusion 2) high first-pass uptake by the myocardium 3) kinetics unaltered by the metabolism of the myocyte and 4) stable retention within the myocytes throughout the imaging procedure[30;31]. Several radiopharmaceuticals exist for myocardial perfusion SPECT imaging (Thallium-201,$^{99m}$Tc-sestamibi,$^{99m}$Tc-tetrofosmin)[32]. $^{99m}$Tc labeled radiopharmaceuticals have a shorter half-life (6 hours) and a higher photon energy (140 keV) than Thallium-201 (80 kev), yielding images with higher resolution[32]. $^{99m}$Tc-tetrofosmin is the radiopharmaceutical used in the studies included in this thesis. Tetrofosmin is a lipophilic cation. This property allows it to diffuse passively across the cell membrane and accumulate in the mitochondria. A total of 1.2% of the injected dose of $^{99m}$Tc-tetrofosmin is taken up by the myocardium, 5 minutes after injection, and it is cleared out of the blood mainly through the urine[31]. The extraction of $^{99m}$Tc-tetrofosmin (54%) decreases at higher flows, causing an underestimation of the myocardial uptake. All SPECT radiopharmaceuticals emit gamma rays consisting of photons.

**Gamma cameras.** The gamma camera was developed in 1957 by the American electrical engineer and biophysicist Hal Anger. Images of the relative myocardial perfusion distribution, at the time of radioisotope injection, can be acquired using either a conventional or a cadmium zinc telluride (CZT) gamma camera.

A conventional gamma camera consists of a moving gantry containing a parallel-hole collimator, NaI scintillation detectors and photomultiplier tubes, as illustrated in Fig. 1.3. In a conventional gamma camera, the gamma rays are absorbed by the NaI detectors and are converted to ultra-violet photons. The ultra-violet photons then release electrons when directed to the photomultiplier tubes. There, the electrons are accelerated and multiplied to create a signal.

A CZT gamma camera, however, consists of a stationary gantry, as illustrated in Fig. 1.3, containing 19 semi-conductor detectors with a total of 19 multi-pinhole collimators. Thereby, 19 views of the heart can be acquired simultaneously. In a CZT, direct conversion of gamma rays, emitted from the radioisotope, into electric charge occurs when they are absorbed by the semi-conductor detectors. Applied electric fields cause movement of the charges and induce signals which are amplified by integrated circuits and electronics to create images with high spatial resolution. Correct position of the patient in a CZT camera is important, because image resolution is affected by the distance between collimator and the patient. The difference in detectors and collimators between the two SPECT cameras allows acquisition of images with higher spatial resolution with a CZT camera compared to a conventional camera. An ECG-gated image acquisition allows reconstruction of time-resolved images which can be used for the assessment of myocardial function.

**Limitations of the technique.** The limited spatial resolution achieved with SPECT makes it difficult to detect subendocardial perfusion defects. Given that myocardial perfusion SPECT only allows assessment of the relative perfusion distribution, 3-vessel diseases caused by balanced ischemia are often missed. Mild to moderate stenosis are more difficult to detect with SPECT, given the loss in the linear relation between myocardial blood flow and uptake of radioisotope at higher flows. Furthermore, motion

artifacts due to respiration and attenuation artifacts are other limitations with SPECT. Post-processing software can however correct for motion artifacts. Cardiac images acquired when the patient is placed in prone position in the camera can exclude perfusion defects caused by attenuation.

## Positron emission tomography (PET)

The PET technique was developed n 1973 by a team led by Edward J. Hoffman and Michael Phelps at Washington University in St. Louis, Missouri, USA. Today, PET is a non-invasive nuclear medicine examination which is mostly used for the assessment of possible spread of cancers in the body, using an intravenously injected radiopharmaceutical. Furthermore, PET also allows assessment of myocardial viability, function and perfusion, but is not widely clinically used for this purpose. What can be assessed with PET depends on which radiopharmaceutical is used. When it comes to assessment of myocardial viability with PET, the use of the radiopharmaceutical $^{18}$F-FDG is required instead of the other radiopharmaceuticals used for qualitative and quantitative assessment of myocardial perfusion.

**Radiopharmaceuticals.** Several cardiac PET radiopharmaceuticals exist for the assessment of myocardial perfusion, including $^{15}$O water, $^{32}$Rb, $^{13}$N-$NH_3$ and the novel radiopharmaceutical $^{18}$F-flurpiridaz[33]. $^{13}$N-$NH_3$ is the radioisotope used for quantification of the absolute myocardial perfusion in the studies included in this thesis. Myocardial uptake of $^{13}$N-$NH_3$ occurs through passive diffusion of the radiopharmaceutical across the cellular membrane[33]. There it equilibrates to form $^{13}NH_4^+$ and then accumulates inside the cell as $^{13}$N-glutamine, after being converted by the enzyme glutamine synthetase. The physical half-life of $^{13}$N-$NH_3$ is 10 min, which requires presence of an on-site or nearby cyclotron.$^{13}$N-$NH_3$ has a myocardial extraction fraction of 80%, which is higher than $^{32}$Rb (65%) but lower than that of $^{15}$O water (100%) and $^{18}$F-flurpiridaz (94%)[33]. The positron range of $^{13}$N-$NH_3$ (2.5 mm) is, however, better than that of $^{32}$Rb (8.6 mm) and $^{15}$O water (4.1 mm), resulting in intermediate to high image resolution. All PET radiopharmaceuticals are positron-emitters[33].

**Positron-emission.** Image acquisition with a PET scanner is based on the ability of the radiopharmaceutical to emit positrons. The intravenously injected PET radiopharmaceutical emits positrons as it undergoes a positive beta decay, where a proton is converted into a neutron. When the emitted positron travels through the tissue, it loses energy and interacts with an electron by colliding with it. This process is named annihilation and produces a pair of 180° oppositely directed photons, each with a photon energy of 511 MeV. The next step is detection of these photons.

**Detection of photons.** The pair of photons are co-registered from different angles by a 360° ring of detectors surrounding a patient placed in the PET camera. The detectors and their components are illustrated in Fig. 1.2. The co-registration of photons by the detectors is named coincidence. The PET system must accurately measure the time when the photon pair hit the detector to ensure that they were produced from the same

annihilation. In this way, the PET system can distinguish noise caused by random coincidences from the desired signal.

**Generating an image.** Co-registration of photons produced from the same annihilation defines a straight line on which the collision took place. This allows spatial location of the annihilation in the organ. Information about spatial location of the annihilation along many lines in space is used to produce an image. An ECG-gated image acquisition allows reconstruction of time-resolved images which can be used for the assessment of myocardial function.

**Limitations of the technique.** Costly on-site cyclotrons are needed for the production of most PET radiopharmaceuticals, given their short half-lives. PET is thus not a widely available technique. Furthermore, PET has a limited spatial as well as temporal resolution and involves the use of ionizing radiation.

**Myocardial perfusion.** Acquisition of static PET images allows assessment of the relative myocardial perfusion distribution. Performing a low-dose CT enables accurate anatomical positioning of the heart as well as correction for attenuated photons registered by the detectors. For the quantification of absolute myocardial perfusion in ml/min/g, dynamic images must be acquired during simultaneous intravenous injection of the radiopharmaceutical. To get a quantitative number in ml/min/g, the information from the dynamic images must enter a compartment model.

**Compartment models.** Compartment models are mathematical models which depict the distribution of material (such as $^{13}$N-$NH_3$) or energy between at least two different compartments. In pharmacokinetics, the compartments represent different parts of the body, such as myocardial tissue and blood pool. Different compartment models for $^{13}$N-$NH_3$ exist, ranging from simple 2-compartment models to more complex 3-compartment models. These models are integrated in the different softwares available for the analysis of cardiac PET images. The mathematics behind the different compartment models for $^{13}$N-$NH_3$ is based on the pharmacokinetics of the radioisotope. As previously discussed above, $^{13}$N-$NH_3$ diffuses freely across the cellular membrane. The accumulation of its metabolic product, $^{13}$N-glutamine, in the tissues increases with time. The accumulation of $^{13}$N-glutamine contaminates the quantification of myocardial perfusion and must therefore be corrected for by the models. The DeGrado 2- compartmental model, taking into account the spill-over of activity from the right ventricle and the left ventricle [34], is used in the studies included in this thesis. Information from only the first four minutes of dynamic acquisitions is used by the DeGrado compartment model. This is due to the inability of the model to correct for the increase in accumulation of $^{13}$N-glutamine, trapped in the myocardial tissue, after the 4 minutes of image acquisition. Other 3-compartment models, including Hutchins [35], have a separate tissue compartment for the trapped $^{13}$N-glutamine.

## Magnetic Resonance Imaging (MRI)

MRI is a radiation-free examination which is used to acquire images of the human body in different planes and in different ways. Cardiac MRI is considered the reference method for assessing LV mass and volumes. Furthermore, myocardial viability and stress/rest myocardial perfusion can also be assessed when a contrast agent is used. The MRI technique has generated four noble prizes: In physics (1952) to Felix Bloch and Edward Purcell, in chemistry (1991) to Richard Ernst, in chemistry (2002) to Kurt Wüthrich and in medicine (2003) to both Paul C. Lauterbur and Sir Peter Mansfield. To understand how an image is created with MRI, a discussion of the basic underlying physics of the technique is needed.

**Basic MRI physics.** Two-thirds of the mass of the human body consists of water. Thus, the most abundant atom in the body is hydrogen ($^1$H), which consists of a nuclei with one proton. All protons possess a unique physical property named spin. The underlying physics of MRI is based on these spins. A proton rotates (precesses) around its own axis, which gives rise to different spin vectors. This means that the electrical charge of the proton moves which creates an electric current and induces a magnetic field. Therefore, protons are considered to be tiny magnets which can be used to obtain a signal. When an external magnetic field is applied to this tiny magnet, the proton will most probably align with the magnetic field and precess around the axis of the field. The frequency of the precession of the proton, when placed in the external magnetic field, is named the Larmour frequency ($\omega$). The following equation shows the relation between the Larmour frequency, the gyromagnetic ratio ($\gamma$) and the external static magnetic field (B).

$$\omega = \gamma \times B$$

The gyromagnetic ratio is constant for each element. Thus, the Larmour frequency, ($\omega$), is proportional to the magnetic field. For $^1$H, the $\gamma$ is 43 MHz/Tesla (T). Thereby, the precession of $^1$H occurs at a frequency of 64 MHz in a 1.5 T scanner.

These underlying basic principles are used for the acquisition of images with the MRI scanner.

**Generating an image.** The basics behind generating an anatomical image is the following. In summary, when a patient is placed in the MRI scanner $^1$H spin vectors align with the main magnetic field (B). Therefore, a net magnetization vector (M) is created along the direction of B. B is generated by the main magnet of the scanner. The main magnet consists of a metal wire which is most often rapped around a circular gantry. The metal wire is superconductive and has a resistance of almost zero, because it is cooled down by Helium. A strong magnetic field, with a typical strength of 1.5 T for cardiac imaging, is generated when an electric current flows through the wire. However, the aligning of M in the direction of B causes difficulties in the detection of the signal from M. To create a detectable signal, the direction of M is manipulated by applying a radio frequency (RF) pulse at the Larmour frequency of $^1$H. The continuous precession of the protons creates varying magnetic fields which generate electrical signals (echoes). These echoes are detected by a receiver RF coil. An interpretable anatomical image is generated by applying a mathematical operation named the Fourier transformation to

raw signal data which are acquired in the k-space. Gradient systems are used to generate images of tissue in a specific slice through the body. The use of contrast agents aids in the assessment of presence of different pathologies.

**Contrast agents.** Contrast agents are used during perfusion and viability imaging but are not needed for the assessment of myocardial function. Gadolinium (Gd)- pentaacetic acid (DTPA) is the contrast agent used in the studies included in this thesis and is the most widely used MRI contrast agent. Gd must be binded to a carrier molecule such as DTPA, because Gd ions are toxic in their free form[36]. The intravenously injected Gd is distributed in the extracellular space and reaches a steady state after about 20 min[37]. Given that Gd is a paramagnetic contrast agent, it affects the tissue it passes through by shortening its T1 relaxation time[38]. T1 is a constant defined as the time when M has regained 63% of its original component in the direction of B and ranges between 300-1500 ms in humans.

Gd-DTPA is then secreted through the kidneys. Gd-DTPA is recommended to not be used in patients with a glomerular filtration rate of <30 ml/min, because it has been reported to cause a serious condition, named nephrogenic systemic fibrosis, in these patients.

**Myocardial perfusion.** In the current clinical routine, the myocardial perfusion distribution is qualitatively assessed from first-pass perfusion images. First-pass imaging is mostly performed by acquisition of single shots of short-axis images, simultaneously with the intravenous injection of Gd-DTPA. The acquisition is performed at rest and during pharmacological stress. The inflow of the contrast agent causes hyper-enhancement of the perfused territories in the myocardium, while territories with decreased perfusion appear as hypo-enhanced areas. Recent sequence development has enabled quantification of stress/rest absolute myocardial perfusion[39].

**Myocardial viability.** MR images where viable myocardium can be distinguished from non-viable myocardium enable qualitative and quantitative assessment of presence and extent of myocardial infarction (MI). The acquisition of viability images is not initiated until the intravenously injected Gd-DTPA has reached a steady state, as it distributes itself in the extracellular space. The steady state is usually reached 15-20 min post-injection. The amount of Gd-DTPA is proportional to the amount of extracellular space[40;41;42;43]. Given that gadolinium shortens the T1 relaxation time, tissue containing more Gd-DTPA will appear more hyper-enhanced in relation to tissue with less Gd-DTPA.

**Myocardial function.** For the assessment of cardiac function, dynamic short-axis MRI images, named cine-images, must be acquired. The cine short-axis images cover the entire LV, from base to apex.

**Limitations of the technique.** Patients with non-MR compatible pacemakers and intra-cardiac converters can not be examined with MRI. Examination of claustrophobic patients with MRI can be problematic. Currently used perfusion pulse sequences can generate images with dark-rim artifacts, which can increase the rate of false positive

first-pass CMR images. Dark-rim artifacts can have multiple causes including myocardial motion during the acquisition and limitations in resolution. ECG triggering in patients with arrhythmias, such as atrial fibrillations, is problematic.

## 1.3 Diagnosis of stress-induced myocardial ischemia

As discussed in the previous section, the underlying pathophysiology of stable CAD is mainly based on presence of stress-induced myocardial ischemia in the territory supplied by a coronary artery with a flow-limiting stenosis. The relationship between visual assessment of degree of coronary stenosis and presence of stress-induced ischemia has been shown to be weak[44]. Therefore, it is important to assess the effect that a stenosis has on the myocardial perfusion, before taking therapeutic decisions. This section will focus on the diagnosis of stress-induced myocardial ischemia with the stress-imaging methods used in this thesis.

### Guidelines on revascularization

Current European Society of Cardiology (ESC) and American Heart Association (AHA) guidelines on revascularization, in patients with low to intermediate risk of stable CAD, strongly recommended the assessment of the presence and amount of stress-induced myocardial ischemia, before the decision regarding revascularization therapy is made[45;46] Only men >70 years presenting with typical angina symptoms should, according to guidelines, perform coronary angiography without prior non-invasive imaging. Furthermore, current ESC guidelines also state that stress-induced myocardial ischemia <5% of the left ventricle can be treated with medication while stress-induced myocardial ischemia >10% of the left ventricle should be revascularized[46]. Therefore, diagnostic methods which allow assessment of presence and extent of stress-induced myocardial ischemia should be used.

### Invasive and non-invasive assessment

Currently, revascularizations are usually performed based on presence of an anatomically significant stenosis on a coronary angiogram and without prior assessment of stress-induced ischemia[47;48]. Coronary angiography performed, without invasive flow measurements, allows for qualitative assessment of presence of an anatomically significant stenosis (>50% of the vessel diameter) and not its functional significance. Therefore, qualitative invasive coronary angiography has been shown to have the lowest diagnostic accuracy in detecting stable CAD (sensitivities/specificity: 70/78%) compared to stress-imaging methods[49].

**Invasive flow measurements during coronary angiography.** The functional significance of a coronary stenosis can however be assessed during coronary angiography, if invasive flow reserve measurements, such as FFR or iFR, are performed. Currently, invasive flow reserve measurements are used as the reference standard for the physiologic assessment of a coronary stenosis[48;49]. The use of FFR in guiding treatment decisions

in patients with stable CAD has been shown to improve patient outcome[50].

**EST.** Diagnosis of stress-induced myocardial ischemia from an EST is mainly focused on analysis of ST-T changes before, during and after exercise. A positive EST is usually defined by presence of horizontal or down-sloping exercise-induced ST depressions of typically $\geq$1 mm, 60 ms after the J-point. The accuracy of ST depressions in detecting presence or absence of stress-induced myocardial ischemia is limited, with reported sensitivities ranging between 45-50% and specificities between 85-90%[46]. The number of false positive tests is higher 1) in the presence of digitalis 2) in females compared to males[51] and 3) in the presence of resting changes such as left ventricular hypertrophy[52], atrial fibrillation[53] and ST deviations[54]. An EST is not useful in the presence of left bundle branch block and paced rhythm on the resting ECG as well as in patients who are unable to achieve $\geq$85% of their maximum HR. Other parameters obtained from an EST, including exercise capacity, HR response, blood-pressure and pulse-response, are usually added to the interpretation of the EST to increase its accuracy in diagnosing stress-induced myocardial ischemia[55;56]. The additional parameters are, however, only useful in the absence of anti-ischemic medication.

**Myocardial perfusion SPECT.** Qualitative assessment of stress/rest images of the LV regional myocardial perfusion distribution are used in the diagnosis of stress-induced myocardial ischemia with myocardial perfusion SPECT. The extent and severity of stress-induced ischemia can also be assessed. Recently sensitivities/specificities of 70/78%[49] have been reported for myocardial perfusion SPECT in detecting absence or presence of stress-induced ischemia. Adding information, regarding LV function, from the gated-image has been shown to be of prognostic benefit[57]. Myocardial perfusion SPECT is known to have limited ability in detecting three-vessel disease.

**Cardiac PET.** Similar to myocardial perfusion SPECT, static cardiac PET allows qualitative assessment of the stress/rest regional myocardial perfusion distribution, but with a higher image quality due to the higher spatial resolution provided by PET. Reported sensitivities and specificities for the qualitative assessment of stress-induced ischemia by PET range between 81-97% and 74-91%[58;59] respectively. Furthermore, dynamic cardiac PET allows quantification of stress/rest absolute myocardial perfusion in ml/min/g from which the coronary flow reserve (CFR) can be calculated. CFR depicts the coronary circulation from the main epicardial coronary arteries to the microcirculation[60]. Thus, CFR also assesses microvascular disease in addition to epicardial coronary disease. Although not widely clinically used, dynamic cardiac PET is still considered to be the reference method for quantification of myocardial perfusion[30;61]. The quantitative ability of dynamic cardiac PET facilitates the detection of 3-vessel disease.

**Cardiac MRI.** In the current clinical routine, stress/rest first-pass CMR images are qualitatively assessed for the diagnosis of stress-induced myocardial ischemia. Reported sensitivities/specificities for the qualitative assessment of CMR have recently been shown to be 90/94%[49]. Adding information about viability (late-gadolinium enhancement images) and function (cine-images) has been shown to facilitate the diagnosis

of stress-induced myocardial ischemia. Furthermore, first-pass CMR imaging also allows semi-quantitative assessments of stress-induced ischemia[62;63;64]. Recently fully-quantitative assessments of the absolute myocardial perfusion in ml/min/g have been shown to be possible with first-pass MR[39;65].

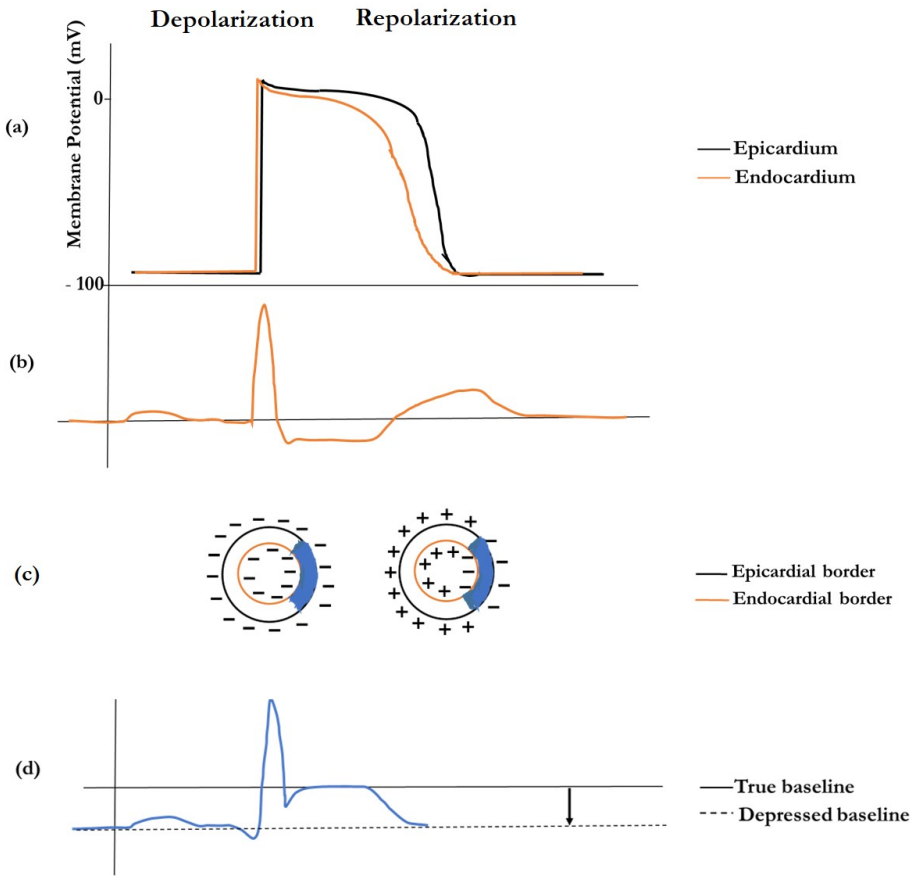


FIGURE 1.2: Electrical changes between the endo- and epicardium in the presence of **(a)** subendocardial ischemia and the **(b)** resulting waves on the electrocardiogram. Note the lowered action potential amplitude and the earlier repolarization occurring in the endocardium, in the presence of subendocardial ischemia. Extracellular electrical charges in the normal and ischemic myocardial area during depolarization and repolarization in the presence of **(c)** transmural ischemia (blue area) and the **(d)** resulting waves on an electrocardiogram are also illustrated.

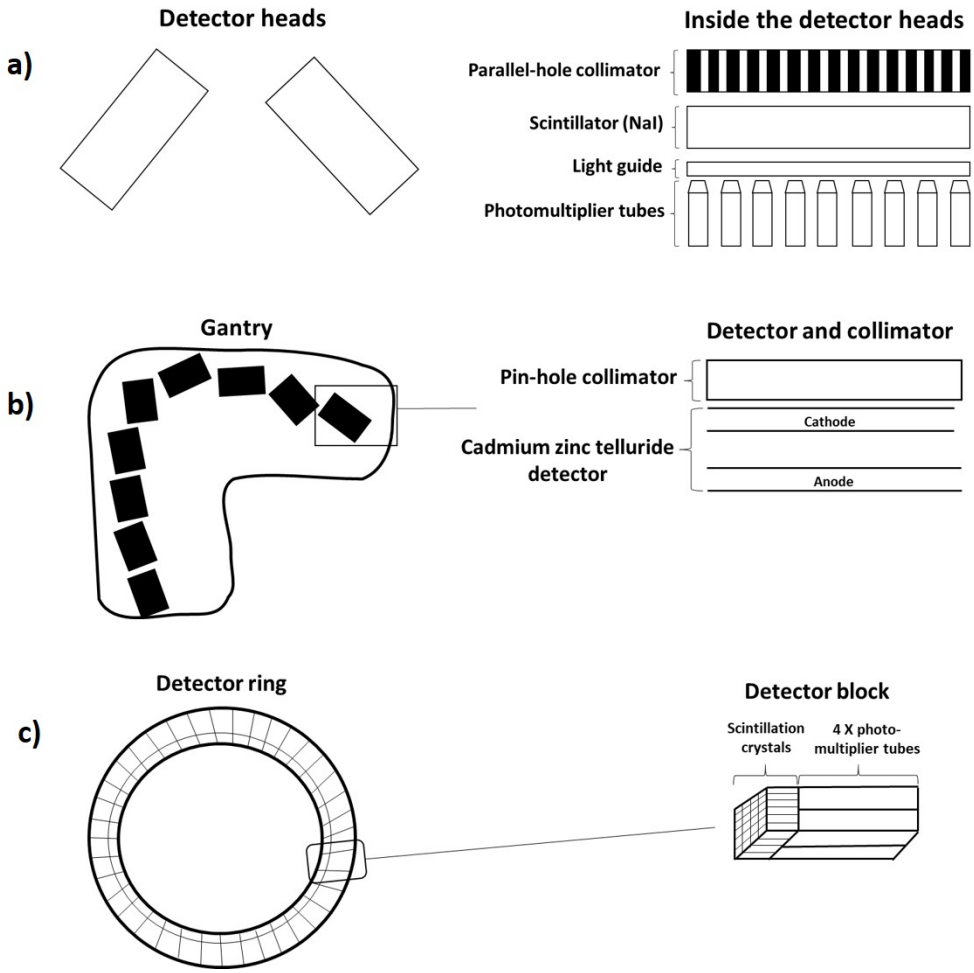


FIGURE 1.3: Schematic illustration of detectors and their components in a **(a)** conventional single photon emission computed tomography (SPECT), **(b)** cadmium zinc telluride SPECT and **(c)** positron emission tomography camera.

# Chapter 2

# Aims

The general aim of the thesis is to further elucidate the pathophysiologic mechanisms associated with stable CAD using different clinical methods, with a focus on their performance in diagnosing stress-induced myocardial ischemia. This is clinically important when identifying which patients will benefit from an invasive intervention. The specific aims of the included papers were the following:

I. To assess the pathophysiological correlate of stress-induced ST elevation and stress-induced ST depression on an exercise stress test, specifically with regard to the presence, amount and location of myocardial ischemia as determined by MPS, in patients with suspected coronary artery disease.

II. To determine the diagnostic performance of exercise-induced ST response for the absence or presence of exercise-induced myocardial ischemia as assessed by MPS, with special focus on gender differences, in patients with suspected or established stable ischemic heart disease.

III. To show the diagnostic accuracy of qualitative evaluation of first-pass perfusion CMR and anatomical evaluation on coronary angiography to the reference standard of quantitative perfusion, cardiac PET, in patients with suspected stable CAD.

IV. To investigate to what extent patients improve in exercise capacity, global left ventricular ejection fraction, regional wall thickening, myocardial perfusion assessed by both qualitative first-pass CMR and quantitative cardiac PET, following elective revascularization performed according to clinical routine.

# Chapter 3

# Materials and Methods

*"It was the best of times, it was the worst of times, it was the age of wisdom, it was the age of foolishness, it was the epoch of belief, it was the epoch of incredulity, it was the season of light, it was the season of darkness, it was the spring of hope, it was the winter of despair."*

— Charles Dickens, A Tale of Two Cities

## 3.1 Study populations

All protocols and procedures were approved by the Regional Ethical Committee, Lund, Sweden. Patients included in Paper I and II were retrospectively enrolled at Skane University Hospital, Lund, Sweden. Patients included in Paper III and IV were prospectively recruited at Skane University Hospital, Lund, Sweden. A written informed consent was obtained from all patients, except for the retrospectively included patients examined before 2004. Instead, the ethical board waived informed consent for those patients.

### Paper I

The study included a total of 226 patients (101 females) with suspected or known stable CAD, who were referred for a clinical myocardial perfusion SPECT. Of these patients, 198 (97 females) were consecutively enrolled between 1 July and 31 December 2008. The remaining 28 patients (4 females) had a clinical myocardial perfusion SPECT exercise test performed between January 2000 and December 2013, where exercise-induced ST elevation was described in their clinical report. Coronary angiograms were available for 17/28 ST elevation patients. Patients who were pharmacologically stressed and patients in the ST elevation group not meeting the ST elevation criteria were excluded.

### Paper II

The study included a total of 1 021 patients (518 females) with suspected or known stable CAD, who were referred for a clinical myocardial perfusion SPECT between 2 June 2008 and 30 April 2011. Patients who were pharmacologically stressed were excluded.

### Paper III and IV

The studies included patients with suspected stable CAD, clinically referred for coronary angiography in conjunction with possible elective PCI, from November 2013 to December 2016. Patients with atrial fibrillation, claustrophobia, asthma, severe chronic obstructive lung disease, glomerular filtration rate $< 30$ ml/min were excluded. In both paper III and IV, patients had performed adenosine stress/rest first-pass perfusion CMR, adenosine stress/rest $^{13}$N-$NH_3$ PET (same day as CMR, 4-5 hours apart) and a cardiopulmonary exercise testing at a mean of 4 weeks before undergoing coronary angiography. In paper IV, the patients were also followed-up, with same examinations, at mean 5 months after undergoing coronary angiography with or without elective revascularization. Forty-one patients (9 females) were included in Paper III while 33 patients (10 females) were included in paper IV.

## 3.2 Exercise-induced ischemia using exercise stress test

### Exercise stress test

An EST, in conjunction with the myocardial perfusion SPECT examination, was performed in both Paper I and II using the same protocol. Patients were stressed using an electronically braked ergometer (Siemens Ergomed 940 before 2009 and Monark 939 E after 2009). A specific workload was applied according to gender, mass, age and self-estimated physical fitness, aiming for a total stress time of 8–10 min. The workload was progressively increased, and the perceived exertion was rated by the patient using the 6-to-20 Borg scale. The heart rate was continuously acquired during the examination, while the blood-pressure was measured before, during and after exercise. Averaged ECG complexes were recorded every other minute before, during and until 4 min after exercise for the 12 leads (avL, I, -aVR, II, aVF, III, V1-V6) with digital ECG recorders.

### ECG analysis

**Presence of stress-induced ischemia.** The consecutively enrolled ESTs in paper I and all ESTs included in paper II were analyzed by experienced physicians. Physicians were blinded to all patient history and medication. The classification of the ST response during exercise as normal, abnormal or indeterminate was not evaluated using specific millimeter-thresholds. Instead, the ST response was classified based on a holistic interpretation of the ST response. The parameters included in the holistic interpretation of the ST response are summarized in Fig. 3.1. For the 28 ST elevation patients, included

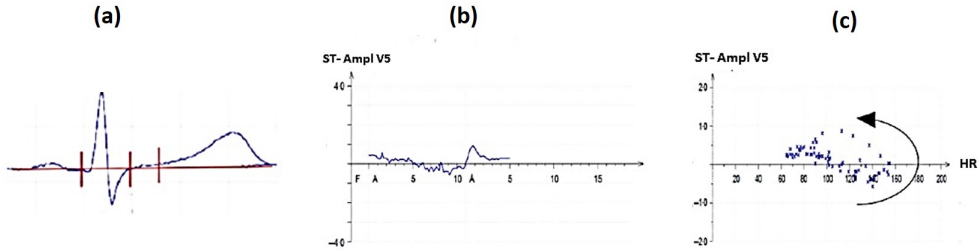


FIGURE 3.1: Parameters used in the holistic interpretation of the ST response during an exercise stress test, including **(a)** the ECG, **(b)** the ST trend and **(c)** the ST-heart rate (HR) loops. Changes in lead V5 are used in this example. ST response at rest, max stress and 4 min of recovery is interpreted from the ECG, with a horizontal or down-sloping depression of $\leq$ 1 mm, in relation to the PQ baseline, being normal. ST trends, defined as change in ST amplitude as a function of time, are normal in this example. ST-HR loop, defined as ST response over different heart rates, is normal in this example.

i paper I, the presence of exercise-induced ST elevation, stated in the clinical report, was confirmed by experienced physicians.

**Additional variables.** Presence of stable CAD based on an overall assessment of the EST was evaluated in paper II. In addition to the ST response, other variables including blood pressure and HR response as well as exercise capacity (in W and % of expected exercise capacity) were also analyzed by an experienced physician. Blood-pressure and pulse response were related to previously described normal values[66]. HR response was considered normal when $\geq$85% of the patient's maximal HR (220 - age) was achieved. Based on this overall assessment, the EST was classified as normal, abnormal or non-interpretable.

**Amount of exercise-induced ischemia.** In Paper I, the amount of stress-induced ischemia was determined from the exercise ECGs by calculating the sum as well as the maximum significant exercise-induced ST elevations/ST depressions. The ST depression at stress was measured at 60 ms after the STJ-point. A horizontal or down-sloping depression of $\geq$ 1 mm, in relation to the PQ baseline, was considered significant. The exercise-induced ST elevation was measured at the STJ-point and was considered significant if the elevation, in relation to the PQ baseline, was $\geq$ 2.0 mm in men and $\geq$1.5 mm in women in leads V2-V3 or $\geq$ 1.0 mm in other leads[67]. The maximum ST elevation/depression at stress was defined as the magnitude (in mm) of ST deviation in the lead with the most pronounced elevation/depression. The sum of exercise-induced ST elevations/depressions was obtained by adding the ST deviation amplitude in the leads with significant exercise-induced ST elevations/depressions. In patients with exercise-induced ST elevation in lead V1 and ST depression at stress in leads –aVR and V4-V6, the sum of ST changes was determined in the leads with ST depression.

**Location of exercise-induced ischemia.** In Paper I, the location of stress-induced ischemia was determined from the exercise ECG based on which leads the significant

ST deviations appeared in (RCA: II, III, aVF; LAD: V2-V4; LCX: negative V1-V2 with or without concomitant changes in leads V5 and V6 or I and aVL). The following was taken into consideration when determining the location. 1) If stress-induced ST changes occurred in more than one vessels territory, the lead with the most pronounced ST change was used to designate the main location of stress-induced ischemia 2) In patients with exercise-induced ST elevation in lead V1 and ST segment depression in leads –aVR and V4-V6, the location of stress-induced ischemia was assigned to LAD. The ECG localization of ischemia was then compared with the location of ischemia determined with myocardial perfusion SPECT.

**Simultaneous gas analysis.** In Paper IV, the peak oxygen uptake in ml/min ($VO_2$ peak) was determined from a cardiopulmonary exercise stress test. A cardiopulmonary exercise stress test is an exercise stress test with simultaneous gas analysis. During this examination, the patient was placed on a bicycle with an airtight mask for measurement of $O_2$ and $CO_2$ concentrations. The same protocol as for a conventional EST was used.

## 3.3 Stress-induced ischemia using myocardial perfusion SPECT

### Myocardial perfusion SPECT imaging

MPS was performed in Paper I and II using the same protocol. Stress and rest imaging were performed either on the same day ($\geq$ 2 hours apart) or on separate days after intravenously injecting $^{99m}$Tc- tetrofosmin. The doses of the radiopharmaceutical depended on the patient's weight and the type of imaging (rest or stress). Rest imaging was obtained only in patients whose exercise myocardial perfusion SPECT images were considered to be abnormal. All images were acquired with the patient placed in supine position, but also in prone position if exclusion of defects in the image, caused by attenuation artifacts, was needed. All images were gated with ECG using eight bins per cardiac cycle acquisition. Stress/rest myocardial perfusion SPECT images, of the consecutively enrolled patients in Paper I as well as of all patients included in Paper II, were acquired using a dual-headed gamma camera (Ventri, GE Healthcare Buckinghamshire, UK). Images were acquired in 32 projections over an 180° orbit, using a 64 X 64 matrix. Iterative reconstruction was performed using maximum-likelihood expectation maximization (MLEM) with a post-filtration using a butterworth filter (cut-off 5.0 mm). The ST elevation patients in Paper I were either imaged using another dual-headed gamma camera (n= 11 patients with ADAC Vertex, Milpitas, CA, USA) or a CZT gamma camera (n= 6 patients with Discovery NM 530c, GE Healthcare), depending on which year they were examined. For images acquired with a CZT gamma camera, iterative reconstruction of gated images was made using Ordered Subset Expectation Maximization (OSEM).

### Image analysis

**Presence of exercise-induced ischemia.** In Paper I and II, a visual assessment of the reconstructed myocardial perfusion SPECT images, analyzed in the QPS software

(version 4.0; Cedars-Sinai Medical Centre, Los Angeles, CA), was performed by the clinician responsible for writing the clinical report and confirmed by a second observer. Presence of exercise-induced myocardial ischemia was reported if there was a decreased radioisotope uptake seen in the supine stress image but not in the rest image. Defects caused by breast or diaphragmatic artifacts were excluded using the prone images[68].

**Location of exercise-induced ischemia.** The location of the exercise-induced ischemia on the myocardial perfusion SPECT images was determined in Paper I. The location of exercise-induced ischemia was assigned to LAD for ischemia in the anterior, septal and apical LV wall, to LCx for ischemia in the lateral LV wall and to RCA for ischemia in the inferior LV wall. If exercise-induced ischemia was found in more than one vessel territory, the coronary artery supplying the region with the most severe exercise-induced ischemia and/or a fixed perfusion defect was chosen for the main location of the exercise-induced ischemia.

**Amount of exercise-induced ischemia.** The amount of exercise-induced ischemia (extent and severity) was calculated both in Paper I and II, but using two different methods. In Paper I, the summed stress score (SSS) was automatically generated from all included stress images using the QPS software (version 4.0; Cedars-Sinai Medical Centre, Los Angeles, CA). According to the Cedars- Sinai scoring system, the extent and severity of ischemia is increased with an increasing SSS. In paper II, the amount of exercise-induced ischemia was determined, in images where exercise-induced ischemia was present, by calculating the difference in total perfusion deficit (D-TPD) between stress and rest images. D-TPD was generated using an automated validated algorithm in the freely available software Segment version 2.0 (http://segment.heiberg.se), as previously described[69].

## 3.4 Quantification of myocardial perfusion using PET

### PET imaging

PET imaging was performed in Paper III and IV using the same protocol. Rest and stress imaging was performed on the same day (1 hour apart) with rest imaging first. For positioning, a scout view over the chest was performed, followed by a low-dose CT for attenuation correction (120 kV; 10 mAs; rotation time 0.5 s). Both stress and rest PET image acquisitions were started simultaneously with the injection of $^{13}$N-$NH_3$ (525±78 MBq at both stress and during rest). During the stress examination, $^{13}$N-$NH_3$ was injected 3 minutes after the beginning of adenosine infusion (140 $\mu$g/kg/min). Adenosine infusion continued for another 4 minutes after radiopharmaceutical injection. Images were acquired using a GE Discovery 690 PET/CT, with a total dynamic PET acquisition time of 4 min for both stress and rest. Before reconstructing the images, evidence for patient motion was checked between the CT and PET images and manual adjustments were made. Stress/rest dynamic PET were reconstructed into 15 time-frames (12x10s, 2x30s and 1x60s) using Ordered Subset Expectation Maximization (3 iterations, 12 subsets) and a 5 mm post-filter.

### Image analysis

Analysis of the dynamic PET images is aimed to generate a quantitative value of the rest and stress absolute myocardial perfusion (global and regional) in ml/min/g, in each of the three vessel territories (LAD, LCX, RCA). The steps performed during the analysis of the reconstructed dynamic images in the software Carimas (version 2.7, Turku, Finland) are summarized in Fig. 3.2. The analysis included automatic delineation of the left ventricle, with manual adjustment when needed, and insertion of input information into the deGrado compartment model for $^{13}$N-$NH_3$ [34]. A CFR was calculated by dividing the stress by the rest regional MP. CFR $< 2.0$ was considered pathologic, in both Paper II and IV, as previously suggested [17;71].

## 3.5 Myocardial perfusion, function and viability using MRI

### MR imaging

MR imaging was performed in Paper III and IV using the same protocol. Images were acquired using either 1.5 T Philips Achieva (Best, The Netherlands) or Siemens Aera (Erlangen, Germany), depending on the time of the examination. Three short-axis slices (basal, mid-ventricular and apical) were acquired at rest and after 3 min of adenosine infusion (140 $\mu$g/kg/min), during the first-pass of 0.05 mmol/kg bolus of the Gd-based contrast agent Dotarem (Guerbet, Roissy, France). For the Philips scanner spatial resolution was 2 x 2 x 10 mm reconstructed to 1.4 x 1.4 x 10 mm and accelerating factor 3. For the Siemens scanner spatial resolution was 1.9 x 2.4 x 8 mm reconstructed to 1.9 x 1.9 x 8 mm and accelerating factor 3. Late gadolinium enhancement imaging (LGE) was performed to evaluate presence of infarct.

### Image analysis

All CMR analysis in Paper III and IV was performed using the freely available software Segment version 2.0 (http://segment.heiberg.se).

**Presence of stress-induced ischemia.** Visual assessment of the stress/rest first-pass perfusion images was performed by an experienced physician. Stress-induced ischemia was indicated if there was a hypo-enhanced area at stress, present during at least three heart cycles, but not present at rest and not corresponding to contrast enhancement on LGE. The stress-induced ischemia was assigned to one of the three vessel territories (LAD, LCX and RCA).

**Myocardial function.** In Paper IV, the left ventricular ejection fraction and regional wall thickening were calculated. First, the endo- and epicardial borders in end-diastole (ED) and end-systole (ES), in the cine short-axis images covering the entire LV, were manually delineated. To guide the algorithm in the rotation of the short-axis images, right ventricular insertion points were placed in ES in the most basal image, with LV myocardium present for the entire circumference. An automated algorithm was then

used to obtain the ED and ES regional wall thickness in millimeters. The regional wall-thickening in % was calculated using the following formula: (ES wall thickness – ED wall thickness)/ED wall thickness, for each of the three vessel territories (LAD, LCX, RCA), according to the 17-segment model[70]. The calculations were performed in short axis slices with myocardium throughout the circumference in systole. Thus, the most basal slices with myocardium not present throughout the circumference were excluded.

**Myocardial viability.** In Paper III and IV, LGE images were qualitatively assessed for presence of infarct or fibrosis. Scar size was determined, in paper III, from the LGE short-axis images using a recently described automated algorithm for scar quantification. The algorithm takes signal intensity distribution, coronary vessel territory and partial volume effects into consideration[72].

## 3.6 Coronary stenosis and myocardial perfusion during coronary angiography

Coronary angiographies in Paper I, III and IV were performed using the national protocol used in clinical routine, where invasive flow reserve measurements are performed at the angiographer's request. According to clinical routine, instant flow reserve (iFR) $> 0.89$ and fractional flow reserve (FFR) $> 0.80$ were considered normal, as previously suggested[73;74]. The decision to perform a revascularization in conjunction with the coronary angiography was based on available clinical data and coronary angiography findings in each of the three vessels (LAD, RCA, LCX).

## 3.7 Statistical analyses

Results are presented in mean $\pm$SD unless otherwise is specified. Confidence intervals (CI) are presented at 95% confidence level (Paper II). A p-value of less than 0.05 was considered statistically significant in all papers. Non-paired t-tests were used to test variations between normally distributed data (Paper I-III). The Wilcoxon signed-rank test for dependent data (Paper IV) and the Mann-Whitney test for independent data (Paper III) was used to test the variation between non-normally distributed data. A chi-squared test or a Fisher's exact test was used to compare the frequency of a variable in two independent populations (Paper I and II). The correlation between two normally distributed variables was assessed by a linear regression analysis using Pearson's correlation coefficient (Paper I). Level of agreement between two variables was assessed using Cohen's Kappa (Paper I and II).

In Paper I, the diagnostic performance of exercise-induced ST depressions was assessed by calculating the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV). The diagnostic performance of exercise-induced ST elevation was assessed by calculating the PPV. The correlation between SSS and the ST change measures (maximum ST depression/elevation, sum of significant ST elevations/depression) was assessed using Pearson's correlation coefficient. The level of agreement between location of exercise-induced ischemia with exercise ECG and myocardial perfusion SPECT was evaluated using Cohen's Kappa.

In Paper II, the diagnostic performance of exercise-induced ST depressions alone and in addition to other EST variables was assessed by calculating the sensitivity, specificity and PPV for each gender.

In Paper III, differences in regional CFR, by PET, between normal vessels and vessels requiring revascularization by coronary angiography, as well as between normal vessel territories and territories with stress-induced ischemia by first-pass MRI were assessed using a non-paired t-test.

In Paper IV, differences between baseline and follow-up for $VO_2$ peak, global LV ejection fraction, regional wall thickening, global and regional CFR were assessed using a Wilcoxon signed-rank test.

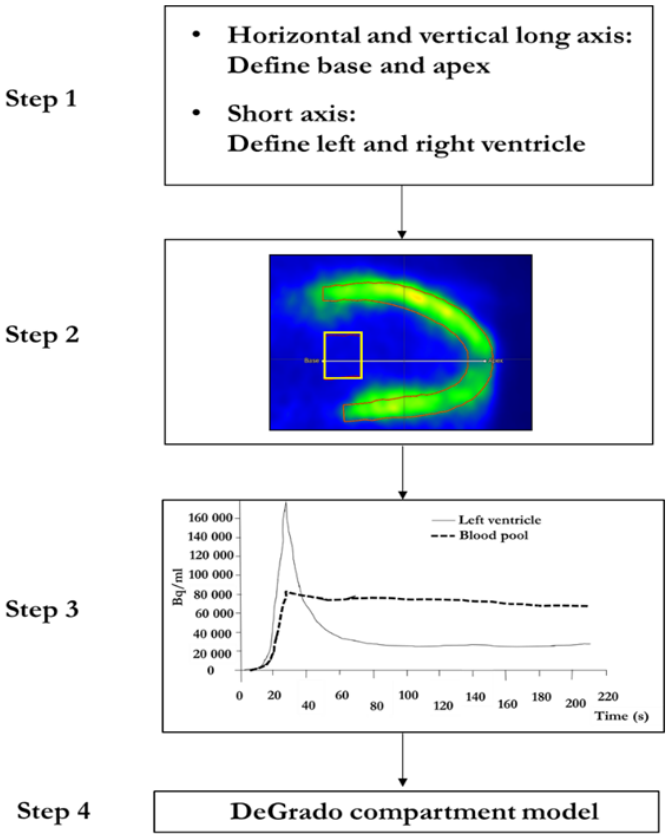


FIGURE 3.2: Steps performed during the PET image analysis in the software Carimas. In **Step 1**, the apex, base, right and left ventricle are defined in reconstructed short and long axis images of the myocardium. **Step 2** involves automatic delineation of the left ventricular myocardium with manual adjustments when needed. The image in step 2 shows an example of a delineation of a horizontal long axis slice of the left ventricular myocardium. The yellow small box in the basal part of the myocardium represents the blood pool volume of interest. The volume of interest of the myocardium is the red tracing drawn around it. The green color represents the activity in the myocardium. In **Step 3**, time-activity curves for the blood pool and myocardial tissue are created using the volume of interests obtained in step 2. The time activity curves are then used as input information for the Degrado compartmental model chosen in **Step 4**. The output is quantitative values of the regional and global myocardial perfusion in ml/min/g in each vessel territory and in each of the previously described 17-segments of the left ventricle [70].

# Chapter 4

# Results and Comments

*"And you'll sit beside me, and we'll look, not at visions, but at realities."*

— Edith Wharton, The Age of Innocence

## 4.1 Diagnostic performance of exercise-induced ST deviations (Paper I)

The rare prevalence (2-8%[75;76]) of exercise-induced ST elevation might be a reason for why the mechanism behind their appearance is less well studied than that of exercise-induced ST depression. Therefore, the underlying pathophysiology and diagnostic meaning of exercise-induced ST elevations were explored in Paper I. It has been known for decades that exercise-induced ST elevations are a sign of a more severe ischemia[24;75]. This is reflected by Fig. 4.1 which shows a higher PPV for exercise-induced ST elevations in detecting presence of exercise-induced ischemia by myocardial perfusion SPECT compared to exercise-induced ST depressions. The following possible explanations for the appearance of exercise-induced ST elevations were deduced from findings in Paper I. 1) Stress-induced transmural ischemia underlying the leads with ST elevation during exercise 2) Extensive left ventricular subendocardial ischemia, if elevations are present in V1 with concomitant depressions in V4-V6 and -aVR 3) Reciprocal to the ST depressions if the elevation at stress was present in leads with evidence of prior infarction, such as pathological Q waves 4) Left ventricular dysfunction or aneurysm.

Furthermore, the study in Paper I is to the best of our knowledge the first to show that exercise-induced ST elevation does not only correlate to presence and location of exercise-induced ischemia, but also to its amount as assessed by SSS from $^{99m}$Tc-tetrofosmin myocardial perfusion SPECT. Fig. 4.2 shows that the SSS by myocardial perfusion SPECT correlated with the maximum as well as sum of significant exercise-induced ST elevations and not ST depressions. SSS by myocardial perfusion SPECT is a widely accepted measure of the amount of ischemia at stress. To further assess the validity of the automatically generated SSS as a measure of amount of ischemia, we related SSS to an in-house developed alternative measure of amount of exercise-induced

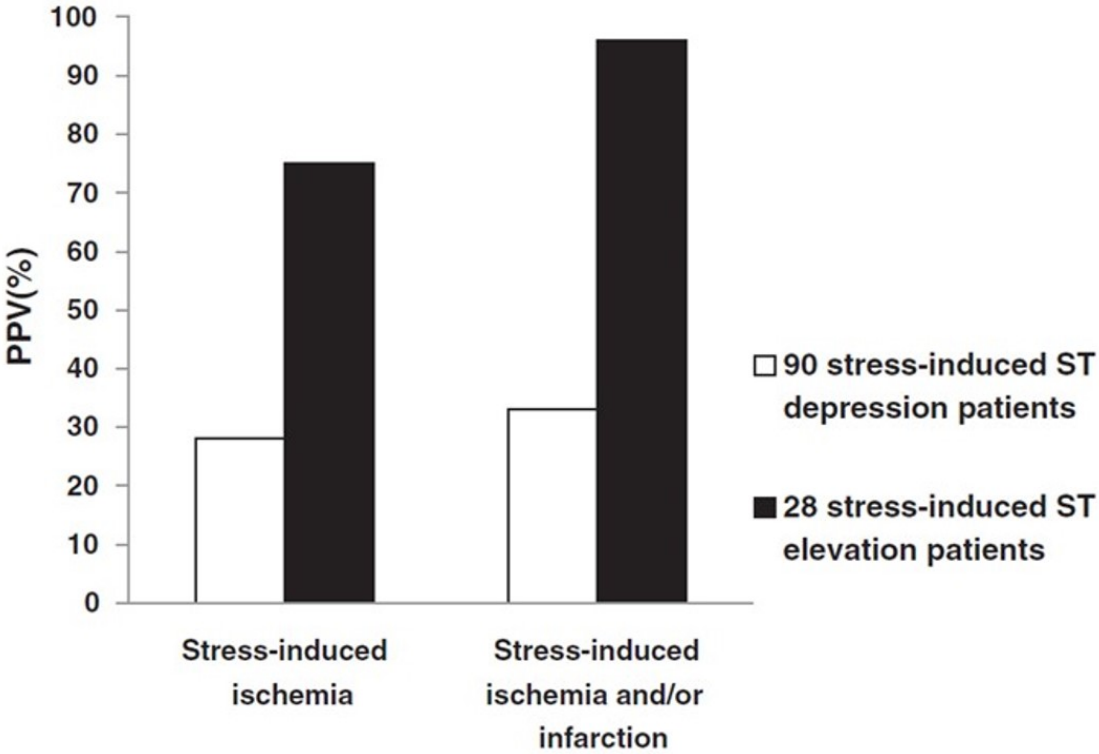


FIGURE 4.1: Positive predictive values (PPV) of ST changes at stress for presence of exercise-induced and/or fixed perfusion defect on myocardial perfusion SPECT, in patients with exercise-induced ST depression (n= 90) and in ST elevation patients (n= 28). Note that exercise-induced ST elevation had a higher PPV compared to exercise-induced ST depression

ischemia by myocardial perfusion SPECT named stress total perfusion deficit (S-TPD). S-TPD, automatically generated from another software named Segment as previously described[69], has been well-validated against the manual scoring of experienced physicians. Fig. 4.3 shows that SSS from QPS correlated well with S-TPD from Segment with acceptable bias. S-TPD is, however, not a widely used measure and was therefore not used instead of SSS in Paper I.

Moreover, coronary angiography findings were available for 17/28 ST elevation patients. The coronary angiography findings confirmed findings of exercise-ECG and myocardial perfusion SPECT in 15 out of the 17 ST elevation patients. In the remaining two patients, the coronary arteries were described by the angiographer as being normal.

In summary, findings in Paper I indicate that presence of significant ST elevations on the exercise ECG, especially in the inferior leads or in V1 with concomitant depressions in V4-V6 and -aVR, is a finding that signals the need of urgent treatment.

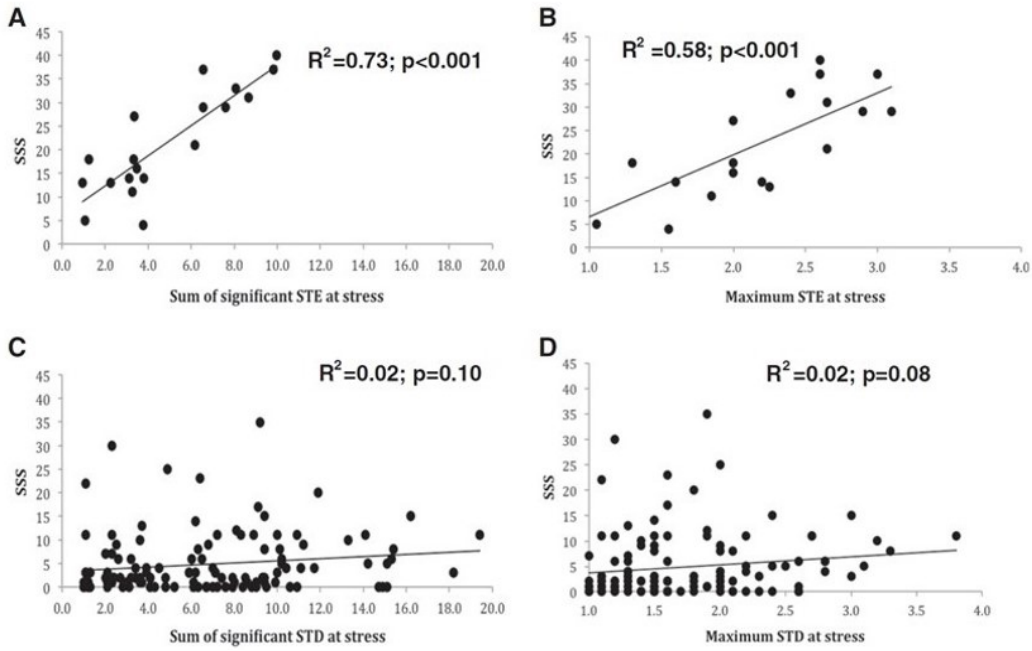


FIGURE 4.2: The relationship between the amount of exercise-induced ischemia by myocardial perfusion SPECT and the amount of exercise-induced ST elevation (at the top) as well as exercise-induced ST depression (at the bottom). At the top left, the correlation between summed stress score (SSS) on myocardial perfusion SPECT and the sum of significant ST elevations (STE) during bicycle stress test (BST) is shown. At the top right, the correlation between SSS on myocardial perfusion SPECT and the lead with maximum STE during BST is shown. At the bottom left, the correlation between SSS on myocardial perfusion SPECT and the sum of significant ST depressions (STD) during BST is shown. At the bottom right, the correlation between SSS on myocardial perfusion SEPCT and the lead with maximum STD during BST is shown.

## 4.2 Gender aspects on the diagnostic performance of an exercise stress test (Paper II)

The diagnostic accuracy of exercise-induced ST depressions in determining presence or absence of exercise-induced ischemia is known to be limited [16], especially in females [20;21]. Previous studies investigating the diagnostic accuracy of ST depressions in females compared to males has however used coronary angiography as gold standard and a cut-off of of typically 1 mm to define a pathological ST response [20;77]. Therefore, we sought to investigate the diagnostic accuracy of exercise-induced ST depressions in males compared to females, using a different study design. Thus, the study design in Paper II included $^{99m}$Tc-tetrofosmin myocardial perfusion SPECT as the gold standard for exercise-induced ischemia and a pathologic ST response defined using a holistic interpretation by an experienced physician. The findings presented in Table 4.1 show that the

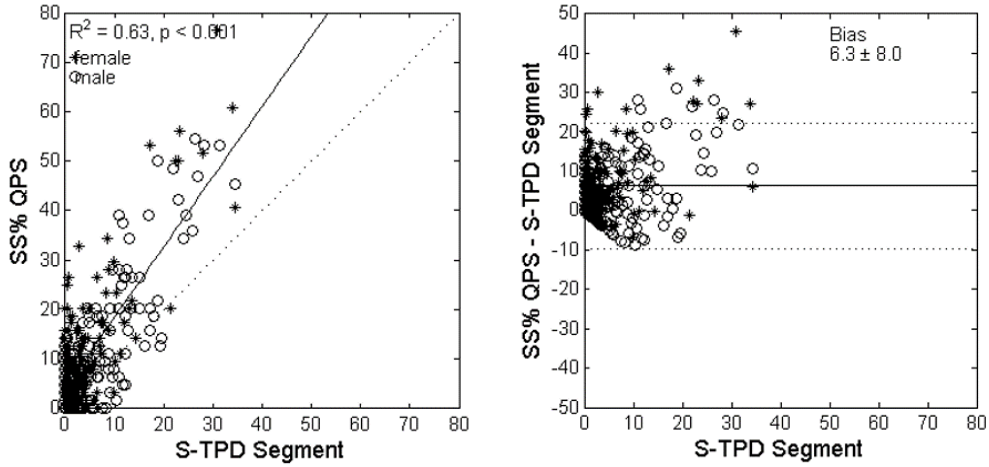


FIGURE 4.3: Correlation plot (to the left) and bland-altman plot (to the right) for the normalized summed stress score (SS) automatically generated from the QPS software (%) and stress. total perfusion deficit (S-TPD) obtained from the software segment as previously described [69].

PPV and sensitivity of ST depressions at stress, in detecting exercise-induced ischemia by myocardial perfusion SPECT is lower in females compared to males. Thus similar findings were found in Paper II, as in previous studies, even when using a different study design. The main reason behind the more frequent false positive exercise-induced ST depressions in females compared to males is not known. Previous studies have discussed various explanations for this difference between genders, including digoxin-like effect of estrogen, haemoglobin concentrations and different chest wall anatomy in females [20;78].

Furthermore, Table 4.1 also shows that adding the exercise capacity, blood-pressure and HR-response to the interpretation of the ST response at stress increases the specificity and PPV both in each gender. Low exercise capacity and slow HR recovery have been shown to be valuable prognostic risk factors of CAD, both in addition to and independent of exercise-induced ST depression [25;26]. In summary, false positives are more frequent in females compared to males, even when $^{99m}$Tc-tetrofosmin myocardial perfusion SPECT is used as reference standard and no specific millimeter thresholds are used when interpreting the ST response. In addition, it is important to go beyond the ST response interpretation when diagnosing exercise-induced ischemia from an exercise-ECG.

## 4.3 Qualitative coronary angiography and MRI in relation to quantitative PET (Paper III)

Despite recommendation of current guidelines, coronary interventions are still performed in many patients based on the presence of anatomically significant stenosis on the coronary angiography, clinical status and risk factors, without any prior assessment of stress-induced ischemia [47;48]. Furthermore, in the current clinical routine, qualitative

TABLE 4.1: Performance of variables from an exercise stress test in diagnosing exercise-induced myocardial ischemia in both genders.

| | **ST response at stress (Adding other variables[a])** | |
|---|---|---|
| | **Females** | **Males** |
| **Sensitivity%[b]** | 48 (44) | 70 (51) |
| **Specificity%[b]** | 67 (84) | 64 (83) |
| **NPV%[b]** | 93 (93) | 87 (85) |
| **PPV%[b]** | 13 (22) | 38 (48) |
| **n** | 495 (507) | 469 (488) |

[a] Exercise capacity, blood-pressure and pulse response
[b] Using myocardial perfusion SPECT as reference method

assessments of presence or absence of stress-induced ischemia with MRI are performed. Therefore, in Paper III, we aimed to show the performance of qualitative assessments of stable CAD with coronary angiography and qualitative MRI compared to that of quantitative PET.

## Coronary angiography vs coronary flow reserve by PET

Table 4.2 demonstrates the limited diagnostic accuracy of qualitative coronary angiography, in assessing presence of stable CAD, when related to CFR by PET. A lower specificity for the per-patient analysis and a lower sensitivity for the per-vessel analysis was found in Paper III, compared to previously reported diagnostic accuracies[49]. In contrast to previous studies, a positive coronary angiography finding, in Paper III, was based on the angiographer's decision on whether to revascularize or not and not on specific cut-off value of % diameter stenosis[79;80]. Fig. 4.4 shows that a significantly lower CFR was found in vessel territories supplied by coronary arteries evaluated to have significant stenosis (1.9 $\pm$0.6) compared to arteries with no significant stenosis (2.4 $\pm$0.8) ($p<0.001$). However, note that several vessels (n=12) that underwent revascularization had a normal CFR, suggesting unnecessary revascularizations of these vessels. No invasive flow reserve measurements were performed in these vessels. The angiographer decided to perform invasive flow reserve measurements in only 17 of the 123 vessels evaluated in Paper III, with complete agreement between CFR and iFR/FFR found in 16 of the 17 vessels. Thus, findings in Paper III further emphasize what has previously been shown about the importance of performing invasive flow reserve measurements during coronary angiography, to enhance the limited diagnostic accuracy of the examination in detecting stable CAD[48;49].

## CMR vs CFR by PET

Table 4.2 also shows that the diagnostic accuracy of qualitative assessment of first-pass MRI images is also limited, when related to CFR by PET. Higher sensitivities and NPV for the per-patient analysis have been reported by previous studies, where $\geq$50% stenosis on a coronary angiogram was instead used as the reference standard[79;80;81]. Figure 4.4 shows that a significantly lower CFR in vessel territories with stress-induced

TABLE 4.2: Diagnostic accuracy of coronary angiography vs MRI, on a per-patient and per-vessel or -vessel territory analysis.

| | Per-patient | | Per-vessel | |
|---|---|---|---|---|
| | **CA** | **MRI** | **CA** | **CMR** |
| **Sensitivity%[a]** | 76 | 47 | 39 | 27 |
| **Specificity%[a]** | 54 | 75 | 83 | 96 |
| **PPV%[a]** | 54 | 57 | 63 | 82 |
| **NPV%[a]** | 76 | 67 | 66 | 65 |

CA= coronary angiography, CMR= magnetic resonance imaging
[a] Using coronary flow reserve by PET as reference standard

myocardial ischemia by MRI (1.6±0.5) compared to those with no regional stress-induced ischemia (2.4 ±0.8) ($p<0.001$) was found in Paper III. However, note that a CFR<2 was found in several territories with normal first-pass MRI which can be explained either by presence of multi-vessel or micro-vessel disease. A recent study, validating the ability of MRI in quantifying perfusion, has shown good correspondence between findings of quantitative MRI and PET [65]. This implies that implementation of the newly validated quantitative MRI in the clinical routine could provide the same diagnostic information as PET. Moreover, Figure 4.4 also reveals that 3 vessels with normal CFR had a pathologic first-pass MRI. Presence of dark-rim artifacts and poor image quality in the first-pass MRI images might explain the false positive findings by CMR [30].

In summary, we should strive towards more quantitative approaches in the assessment of stress-induced myocardial ischemia. Furthermore, invasive flow reserve methods should be performed more frequently during coronary angiography.

## 4.4 Additive value of assessing stress-induced ischemia (Paper IV)

Currently, the recommendation by current guidelines to assess stress-induced ischemia [45;46] prior to revascularization decisions is not always followed in clinical practice. Furthermore, the extent to which findings on coronary angiography can be used to guide decisions on whether to revascularize a patient with stable CAD or not is debated [82;83;84;85;86;87]. Thus, in Paper IV we investigated the effect of revascularizations or non-revascularizations on different parameters, in a cohort where decisions on whether to revascularize or not was mainly based on angiographic findings.

### Assessment of stress-induced ischemia with non-invasive imaging

Nine of the 33 included patients were found to be normal by angiographic findings, but also normal by non-invasive first-pass MRI and PET. This finding in Paper IV thus suggests that unnecessary invasive angiographies could have been avoided in the nine patients if non-invasive imaging was performed. Thus, this is in line with findings of the recently published CE-MARC II study [88]. In this way, patients can be spared from the known complications of the invasive procedure (i.e. endothelial damage, in-stent

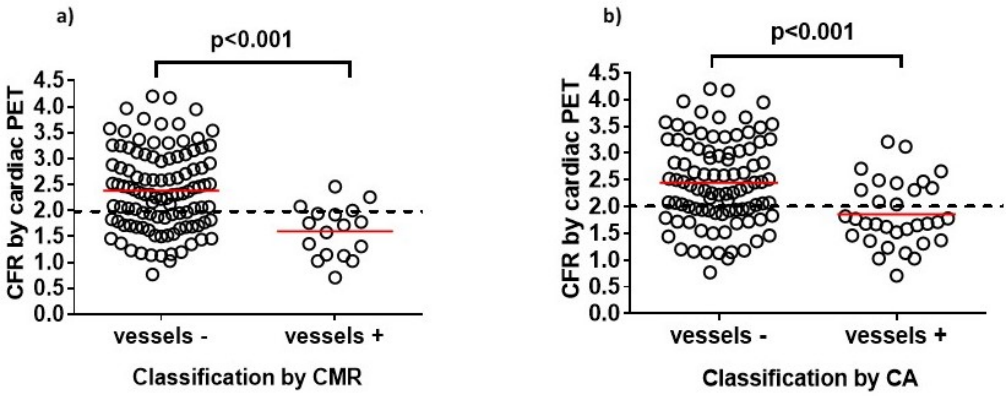


FIGURE 4.4: Coronary flow reserve (CFR) by cardiac positron emission tomography (PET) for a total of 123 coronary arteries (41 patients X 3) classified by **a)** cardiac magnetic resonance imaging (CMR) as normal (vessels -) or supplying territories with stress-induced myocardial ischemia (vessels +) **b)** coronary angiography (CA) as normal/ having non-significant stenosis (vessels -) or as having significant stenosis that was electively revascularized (vessels +). Red lines indicate mean CFR and the dashed line indicates CFR cut-off at 2.0.

stenosis) with no negative effect on major adverse cardiac events[88;89]. In addition, invasive procedures are known to be associated with treatment-related risks such as induction of myocardial infarction, as was found for one of the patients in Paper IV.

## Assessment of stress-induced ischemia with invasive imaging

An abnormal MRI or PET was found in one or more coronary territories in five of the 14 patients not undergoing PCI. No invasive flow reserve measurements were performed in these patients during coronary angiography. Moreover, complete agreement between iFR/FFR and CFR by PET was found in 12/13 vessels where invasive flow reserve measurements were performed during coronary angiography. Thus, the findings in Paper IV further emphasize what has also been shown in Paper III about the importance of performing invasive flow reserve measurements during all coronary angiographies.

## Effect of angio-guided revascularization or non-revascularization on myocardial perfusion

A significant improvement in regional CFR was found following revascularization (2.2 [1.6-2.9] vs 2.0 [1.3-2.2], p=0.01). However, Fig. 4.5 shows that in 41% (11/27) of the revascularized vessel territories, a normal regional CFR (CFR<2) was found prior to the PCI and no improvement in CFR was found at follow-up (p=0.9). However, vessel

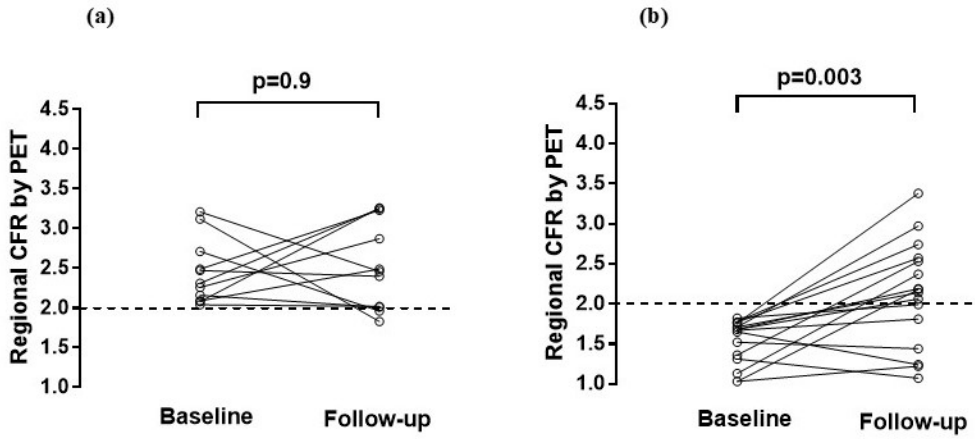


FIGURE 4.5: Effect of revascularization (follow-up) on myocardial perfusion, as assessed by PET, in vessel territories with **a)** regional coronary flow reserve (CFR) >2.0 (n=11) and **b)** regional CFR <2.0 (n=16), before revascularization (baseline). Note the significant improvement in CFR for the vessel territories with decreased CFR prior to revascularization not seen in vessel territories with normal CFR at baseline. The dashed line represents the cut-off value of regional CFR at 2.0.

territories with regional CFR<2 at baseline improved significantly after PCI (p=0.003). These findings in Paper IV further emphasize the previously shown limited diagnostic accuracy of qualitative coronary angiography in determining presence of stable CAD[49]. Both findings in Figure 4.5 and the example case presented in Fig. 4.6 strengthen the need to assess presence of stress-induced myocardial ischemia prior to revascularization, to decrease the amount of unnecessary revascularizations.

Furthermore, increase in regional CFR between baseline and follow-up was not only seen in the revascularized patients but also in 50% (7/14) of the non-revascularized patients. This supports the recent study by Al-Lamee et al.[82] showing similar outcome in revascularized and non-revascularized patients with stable CAD.

In summary, for appropriate revascularizations, stress-induced ischemia needs to be assessed either by non-invasive cardiac imaging or by performing invasive flow reserve measurements during coronary angiography.

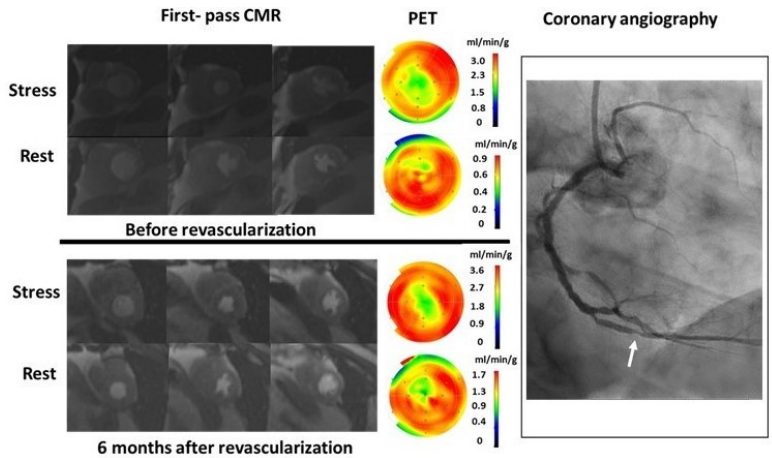


FIGURE 4.6: An example of non-invasive cardiac imaging findings in a patient undergoing revascularization in the RCA based on coronary angiography findings (arrow). The cardiac positron emission tomography (PET) bull's eye plots represent the distribution of the quantified absolute myocardial blood flows (ml/min/g tissue) in the left ventricle. The color scales to the right of the bull's eyes represent the flow ranges, with yellow-red colors indicating higher flows and blue-green colors lower flows. In this case, the patient had normal findings in the RCA territory by first-pass CMR, before and after revascularization. The regional coronary flow reserve by cardiac PET was normal in the RCA territory before revascularization (2.7), but decreased to 2.0 after revascularization. No significant effect of revascularization on the regional wall-thickening (82% at baseline and 88% during follow-up) was found in the RCA territory.

# Chapter 5

# Conclusions and future directions

*"I wanted you to see what real courage is, instead of getting the idea that courage is a man with a gun in his hand. It's when you know you're licked before you begin, but you begin anyway and see it through no matter what."*

— Harper Lee, To Kill a Mocking Bird

The major conclusions of the four papers are as follows:

I. Exercise ECGs with ST elevation, either concomitant or non-concomitant to ST depression, correlates to presence, location as well as amount of myocardial ischemia assessed by myocardial perfusion SPECT. Exercise-induced depression without concomitant ST elevation is, however, a poor predictor of myocardial ischemia.

II. In patients who have performed bicycle EST in conjunction with myocardial perfusion SPECT, there is a gender difference in the diagnostic performance of ST response at exercise for the presence or absence of myocardial ischemia as determined by myocardial perfusion SPECT, with a significantly lower PPV of exercise-induced ST depression in females compared to males. For both genders, specificity can be significantly improved, and a higher PPV can be obtained while the sensitivity might be compromised, by considering blood pressure and heart rate response as well as exercise capacity in addition to the ST response, for the EST interpretation.

III. The limited performance of qualitative assessment of the presence of stable CAD with MRI and coronary angiography, when related to quantitative $^{13}$N-$NH_3$ cardiac PET, shows the need for fully quantitative assessment of myocardial perfusion and the use of invasive flow reserve for coronary angiography, to confirm the need of elective revascularization.

IV. Appropriate coronary revascularization in stable CAD can be accomplished if invasive flow measurements during coronary angiography or non-invasive cardiac imaging is used to guide treatment decision. If not, unnecessary angiographies

could be performed or stenotic arteries in need of revascularization left untreated.

This thesis gives rise to two questions: 1) Do revascularizations guided by non-invasive imaging provide a better patient outcome compared to those guided by invasive methods? 2) Which non-invasive cardiac imaging method should a clinical center invest in, for accurate diagnosis of stable CAD?

The recently published CE-MARC II[88] study and the findings in paper IV in this thesis show that the number of unnecessary revascularizations can be decreased if stress-induced myocardial ischemia is assessed by non-invasive imaging. In addition, the use of non-invasive imaging has been shown to decrease the number of unnecessary angiographies, with no negative effect on major adverse cardiac events[88;89]. However, no prospective study has shown if revascularizations guided by non-invasive imaging provides better patient prognosis than those guided by invasive imaging. Thus, a future prospective study designed so that cardiologists decide whether to revascularize a patient or not based on findings of non-invasive imaging is needed. This is important to spare patients from the possible complications of the invasive procedure (endothelial damage, in-stent stenosis). There are, however, several non-invasive diagnostic methods available for the assessment of stable CAD.

A clinical center must weigh in cost and utility of the available diagnostic methods, when deciding which one they should invest in for diagnosis of stable CAD. A bicycle or treadmill EST is the cheapest and most widely available method among the existing modalities for the diagnosis of stable CAD. However, a subendocardial ischemia cannot be localized from an exercise ECG and the reliability of the results obtained are dependent on whether the patient has been maximally exerted or not. Thus, the value of EST to detect ischemia in patients with stable CAD is debated, and the NICE guidelines[90] advises against the use of EST in the diagnosis of patients with stable CAD.

The most expensive and least available non-invasive diagnostic method is cardiac PET. In contrast to myocardial perfusion SPECT, cardiac PET allows quantification of the stress/rest absolute myocardial perfusion and assessment of myocardial viability as well as function. However, two different isotopes are used for the assessment myocardial perfusion and viability. This increases the radiation dose to the patient and the already high cost of the examination. Furthermore, the underlying pathophysiology of a CFR<2.0, calculated from the quantified stress/rest myocardial perfusion, needs to be studied in future studies[91;92]. Still, the cut-off value of CFR at <2 is clinically established and has been used in several studies[71;91;93].

Currently, the radiation-free widely available method cardiac MRI is the reference standard for the assessment of myocardial function. Cardiac MRI also allows both qualitative and quantitative assessment of myocardial infarction. Recently, quantification of myocardial perfusion has been shown to be possible with cardiac MRI[65]. The demonstrated good correspondence between findings of quantitative CMR and PET[65] implies that quantitative cardiac MRI perfusion could provide the same diagnostic information as PET.

Thus, cardiac MRI could be the future all-in-one examination which clinical centers might invest in for accurate diagnosis of stable CAD. Still, it must be noted that patients with kidney insufficiency, claustrophobic patients and those with non-MR safe metals or devices in their body cannot be investigated with this examination due to cardiac

MRI safety. Therefore, the availability of alternative nuclear medicine examinations is still important for assessment of stable CAD in patients where MRI is contraindicated.

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# Paper I

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# Stress-induced ST elevation with or without concomitant ST depression is predictive of presence, location and amount of myocardial ischemia assessed by myocardial perfusion SPECT, whereas isolated stress-induced ST depression is not

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**Abstract**

**Background:** Evaluation of stress-induced ST deviations constitutes a central part when interpreting the findings from an exercise test. The aim of this analysis was to assess the pathophysiologic correlate of stress-induced ST elevation and ST depression with regard to presence, amount and location of myocardial ischemia as assessed by myocardial perfusion SPECT (MPS) in patients with suspected coronary artery disease.

**Methods and results:** 226 patients who had undergone bicycle stress test in conjunction with MPS were included. Of these, 198 were consecutive patients while 28 patients were included on the basis of having stress-induced ST elevation mentioned in their clinical report. The amount and location of ST changes were related to MPS findings. Summed stress scores (SSS) from MPS images were used to measure the amount of stress-induced ischemia.

The positive predictive values for detecting stress-induced ischemia were 28% for the consecutive patients with ST depression and 75% for patients with ST elevation. The maximum and sum of stress-induced ST elevations correlated with SSS ($r^2$=0.58, p< 0.001 and $r^2$=0.73, p < 0.001), whereas the maximum and sum of significant ST depressions did not ($r^2$=0.022, p =0.08 and $r^2$=0.024, p = 0.10). The location of ST elevation corresponded to the location of ischemia by MPS (kappa = 1.0), whereas the location of ST depression did not (kappa = 0.20).

**Conclusions:** Stress-induced ST elevation, with or without concomitant ST depression, is predictive of the presence, amount and location of myocardial ischemia assessed by MPS, whereas stress-induced ST depression without concomitant ST elevation is not.



*Keywords:* electrocardiography; exercise; chronic ischemia; myocardial perfusion SPECT

## Introduction

Stress-induced myocardial ischemia is associated with the prognosis of patients with ischemic heart disease [1,2]. Current "European Society of Cardiology" and "European Association for Cardio-Thoracic Surgery" guidelines emphasize the importance of assessing not only the presence but also the amount of stress-induced ischemia, before making clinical decisions regarding revascularization, in patients with suspected ischemic heart disease [1,3].

Various methods are clinically available for diagnosing the presence and the amount of stress-induced ischemia [1]. Exercise stress tests are often used as the first method in patients with suspected stable ischemic heart disease. It provides information on exercise capacity, pulse and blood pressure reactions, patient symptoms and ECG changes during and after exercise [4]. Stress-induced ischemia is typically manifested as stress-induced ST segment depression on the ECG [5]. Such exercise induced ST segment depression is commonly attributed to subendocardial, or non-transmural ischemia in the myocardium supplied by the culprit artery. Occasionally, patients demonstrate elevation of the ST segment during the exercise stress test, and this has been suggested to indicate more severe ischemia than that

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associated with ST segment depression [6,7]. ST depressions at stress are known to be less specific to location of ischemia as compared to ST elevations at stress [8,9]. The diagnostic meaning and the underlying pathophysiological basis for appearance of stress-induced ST elevation on the ECG are much less studied compared to stress-induced ST depression.

Due to its high diagnostic accuracy, myocardial perfusion single photon emission computed tomography (MPS) has been used for decades as the reference standard for evaluation of amount as well as the presence of stress-induced ischemia [10].

Therefore, the aim of this study was to assess the pathophysiological correlate of stress-induced ST elevation and stress-induced ST depression on an exercise stress test, specifically with regard to the presence, amount and location of myocardial ischemia as determined by MPS, in patients with suspected coronary artery disease.

## Methods

### *Study population*

A total of 226 patients (125 males/ 101 females, age range 39–87 years, average 62 years), with suspected or known ischemic heart disease, who were referred for a clinical MPS exercise test at the department of Clinical Physiology in Lund, were retrospectively included. Of these patients, 198 (101 males/ 97 females, age range 39–87 years, average 61 years) were consecutively enrolled between July 1$^{st}$ and December 31$^{st}$ 2008.

The remaining 28 patients (24 males/ 4 females, age range 40–86 years, average 65 years) had a clinical MPS exercise test performed between January 2000 and December 2013, where stress-induced ST elevation was described in their clinical report. Patients with left bundle branch block, ECGs with inadequate signal quality as well as those patients in the ST elevation group not meeting the ST elevation criteria [11] (n= 3), were excluded. Of these 28 patients with stress-induced ST elevation, 17 underwent coronary angiography.

The study was approved by the regional ethics committee and a written informed consent was obtained from all patients examined after 2004. For patients examined before 2004, the ethical board waived informed consent. A health declaration comprising responses to questions about risk factors was attained from the patients. In 3 patients the health declaration was lacking and the risk factors were obtained from their clinical charts.

### *Exercise stress test*

The bicycle stress test (BST) was performed in conjunction with the MPS examination using an electronically braked ergometer (Siemens Ergomed 940 before 2009 and Monark 939 E after 2009) and according to the national standard clinical protocol, including assessment of exercise capacity, pulse and blood pressure reaction, symptoms and ECG. The mean ECG complexes were recorded every other minute before, during and until 4 min after stress for the 12 leads (avL, I, −aVR, II, aVF, III, V1-V6) with a digital sampling rate of 500 Hz (apparatus: Cardiolex, Lexor × 100).

### *MPS examination*

A 1 or 2-day $^{99m}$Tc-tetrofosmin stress/rest MPS protocol, following American Society of Nuclear Cardiology recommendations [12] was performed according to clinical routine. Patients were injected with $^{99m}$Tc-tetrofosmin at approximately 1 min before stopping exercise. Administrated doses of the isotope varied between 400 and 700 MBq at stress depending on the patient's weight. The rest examination was performed at least 2 h after the stress examination, but was only obtained in those patients whose stress MPS images were considered to be abnormal.

### *MPS image acquisition*

For the ST elevation patients examined before 2008 (n= 11), images were acquired at stress and at rest using a dual-headed gamma camera (ADAC Vertex, Milpitas, CA, USA) with the patient placed in supine position and in prone position, after stress injection, if attenuation correction was needed. Iterative reconstruction was performed using maximum likelihood-expectation maximization. Patients examined after 2008 (n = 209) were imaged using a dual-headed gamma camera (Ventri, GE Healthcare Buckinghamshire, UK), with similar camera settings and reconstruction methods as above. Six of the ST elevation patients were examined using a cadmium zinc telluride gamma camera (Discovery NM 530c, GE Healthcare). Iterative reconstruction of gated images was made using Ordered Subset Expectation Maximization. All images were gated with ECG and obtained using 8 bins per cardiac cycle.

### *Exercise stress test analysis*

The exercise stress tests of the 198 consecutive patients were analyzed by two experienced physicians (BH and FH) blinded to all other data. The ST response was classified by the two experienced physicians as being normal or abnormal based on changes during stress and at 4 min of recovery without using any specific millimeter- threshold. An ST elevation at stress was considered as an abnormal response if it occurred in any of the 198 consecutive patients. For the 28 ST elevation patients, the presence of the stress-induced ST elevation was confirmed by two experienced physicians (LG and HE). Signs of prior infarction on the ECG at rest (Q-waves or Q-wave equivalents such as pathologically reduced R-waves in leads with expected dominant R and tall R-waves in V1-V2 as a sign of basolateral infarction) were documented.

For the calculation of sum/maximum significant ST elevations/ST depressions at stress, the ST depression was measured at 60 ms after the STJ-point and ST elevation was measured at the STJ-point, both in relation to the PQ baseline. Measurements of stress-induced ST depressions were performed with automatic computer assistance (Infinity MegaCare; version VF 4.4; Dräger Medical Centre) with manual adjustments done by the experienced physicians when needed. Measurements of stress-induced ST elevations were performed manually. The maximum stress-induced ST elevation/depression was defined as the magnitude (in mm) of ST deviation in the lead with the most pronounced elevation/depression. Leads with stress-induced ST elevation exceeding the limits for ST elevation associated with acute

coronary syndrome [11] (ST-J elevation of ≥ 2.0 mm in men and ≥ 1.5 mm in women in leads V2-V3 or ≥ 1.0 mm in other leads) were designated as having ST elevation at stress. By adding the ST elevation amplitude in these leads, a sum of stress-induced ST elevations was obtained. The sum of significant stress-induced ST depressions was calculated by adding the amplitude in the leads having ≥ 1.0 mm ST depression.

The distribution of ST changes was used to estimate the location of ischemia based on the main coronary artery territories (RCA: II, III, aVF; LAD: V2-V4; LCX: negative V1-V2 with or without concomitant changes in leads V5 and V6 or I and aVL). If stress-induced ST changes occurred in more than one territory, the lead with the most pronounced ST change was used to designate main location of ischemia.

In patients with ST elevation in lead V1 and ST segment depression in leads –aVR and V4-V6, the sum of ST changes and their location was determined in the leads with ST segment depression, because the ST elevation in V1 in this context was considered reciprocal to the ST depression in V4-V6. When ST elevation at stress was in V1, the culprit artery was assigned to LAD if there was a concomitant ST depression at stress in –aVR and leads V4-V6. In the patients with stress-induced ST elevation, either with or without associated ST segment depression, the leads with stress-induced ST elevation were used to determine the sum of the ST segment changes and to designate the location. The ECG localization of ischemia was then compared with the location of ischemia determined with MPS.

### *MPS and coronary angiography analysis*

The MPS images were analyzed using the QPS software (version 4.0; Cedars-Sinai Medical Centre, Los Angeles, CA). If there was a significant difference between the rest and the stress examination, stress-induced ischemia was indicated, regardless of ECG pattern. Presence of ischemia at rest and/or stress and its location was determined by the clinician responsible for writing the clinical report. The MPS findings were confirmed by a blinded second observer (SA). The location of ischemia as assessed by MPS was used to specify the culprit vessel (LAD – ischemia in the anterior, septal and apical left ventricular (LV) wall; LCX – lateral LV wall; RCA – inferior LV wall).

If ischemia was found to be in more than one region, the culprit vessel was determined to be the coronary artery supplying the region with the most severe stress-induced ischemia and/or a fixed perfusion defect.

The summed stress score (SSS) was determined from the stress MPS images. It was calculated automatically by the QPS software and was used as a measure of the amount of ischemia during stress. According to the Cedars- Sinai scoring system, MPS images were classified as normal when SSS < 4, as mildly abnormal when SSS is 4–8, as moderately abnormal when SSS = 9–13 and severely abnormal when SSS > 13.

For the coronary angiographies, presence and location of culprit lesion was determined by the cardiologist responsible for writing the clinical angiography report.

### *Statistical analysis*

Values are expressed as mean ± SD. $\chi^2$ test was used to compare the frequency of risk factors in the two patient populations. Fisher's exact test was instead used in cases where the expected count was less than 5 in a cell. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of stress-induced ST depression for determining presence of ischemia by MPS, were calculated. The PPV of ST elevation for determining presence of ischemia by MPS was also calculated. Pearson's correlation coefficient was used to assess the correlation between SSS and the ST change measures (maximum ST depression/elevation, sum of significant ST elevations/depression) in all 198 consecutive patients and in the 28 patients with stress-induced ST elevation. Cohen's Kappa was used as a measure of level of agreement between ECG and MPS with regard to location of ischemia. Kappa values were interpreted as follows: 0–0.20 poor agreement, 0.21–0.40 fair agreement, 0.41–0.60 moderate agreement, 0.61–0.80 good agreement and 0.81–1.0 excellent agreement. Statistical Package for the Social Sciences (SPSS) v.21.0 (Chicago, Illinois, USA) was used for all statistical analysis. A p value $< 0.05$ was considered to indicate statistical significance.

## Results

Patient characteristics are summarized in Table 1. The incidence of prior PCIs, prior bypass surgeries and prior infarctions was significantly higher in the ST elevation group than in the group with consecutive patients.

### *Myocardial perfusion SPECT findings*

Stress-induced myocardial ischemia was found in 25% (56/226) of all patients. In the 198 patients without ST elevation, 35 (18%) had stress-induced myocardial ischemia while 21 of the 28 patients with ST elevation (75%) had stress-induced myocardial ischemia. In 6 of the 7 patients with stress-induced ST elevation but no stress-induced myocardial ischemia, a fixed perfusion defect was found, indicating prior infarction or hibernating myocardium. The remaining patient did not have stress-induced ischemia or a

Table 1
Patient characteristics.

| Characteristics | Consecutive patients | ST elevation patients | p-value |
|---|---|---|---|
| **Total** | 198 | 28 | |
| **Gender M/F** | 101/97 | 24/4 | |
| **Smoker** | 101 (51%) | 3 (11%) | <0.001 |
| **Previous smoker** | 22 (11%) | 4 (14%) | 0.54 |
| **Previous elective PCI** | 24 (12%) | 16 (57%) | <0.001 |
| **Previous bypass surgery** | 14 (7%) | 10 (36%) | <0.001 |
| **Previous infarction** | 31 (16%) | 12 (43%) | 0.001 |
| **Diabetes** | 17 (9%) | 6 (21%) | 0.047 |
| **Hypertension** | 99 (50%) | 3 (11%) | <0.001 |
| **Hypercholesterolemia** | 67 (34%) | 13 (46%) | 0.19 |
| **Heredity for coronary artery disease** | 65 (33%) | 7 (25%) | 0.41 |

Table 2
Stress-induced ST deviation and myocardial perfusion SPECT (MPS).

| | All patients | Consecutive patients | ST elevation patients |
|---|---|---|---|
| **Total** | 226 | 198 | 28 |
| **Gender (M/F)** | 125/101 | 101/97 | 24/4 |
| **ST segment at stress** | | | |
| **Normal** | 107 (47%) | 107 (54%) | 0 (0%) |
| **Pathologic** | 119 (53%) | 91 (46%) | 28 (100%) |
| **ST depression** | 113 (50%) | 91 (46%) | 22 (79%) |
| **ST elevation** | 28 (12%) | 0 (0%) | 28 (100%) |
| **Resting changes** | | | |
| **ST depression at rest** | 33 (15%) | 32 (16%) | 1 (4%) |
| **Signs of prior infarction*** | 35 (15%) | 18 (9%) | 17 (61%) |
| **Stress induced ischemia** | 56 (25%) | 35 (18%) | 21 (75%) |

* Q-waves and Q-wave equivalent.

fixed perfusion defect and was not further investigated by the patient responsible physician.

*Exercise ECG findings*

Characteristics of the 226 stress tests and MPS are presented in Table 2. A pathologic ST response was found in 46% (91/198) of the consecutive patients. Of the 33 patients with ST depression at rest, 1 patient was in the ST elevation group. 17 of the 35 patients with ECG signs of prior infarction were in the ST elevation group (Table 2).

*Stress-induced ST deviation in relation to presence of myocardial ischemia by MPS*

Fig. 1 shows the sensitivity, specificity, NPV and PPV for ST depression at stress with regards to presence of stress-induced myocardial ischemia on MPS. For the 198 consecutive patients, the NPV of a normal ST response for absence of myocardial ischemia was 91%. For the ST elevation patients with signs of prior infarction on ECG at rest (n = 17), the PPV for stress-induced myocardial ischemia was 65%, whereas those with no signs of prior infarction on the ECG at rest (n = 11) had a PPV of 91%. In patients with signs of prior infarction on their resting ECG, the ST elevation at stress was always found in the leads with Q waves. Of these 17 patients, 6 had a fixed perfusion defect only on MPS, which was always in a region corresponding to the leads with Q waves on the resting ECG.

Fig. 2 shows the PPVs for stress-induced ischemia as well as for stress-induced ischemia and/or fixed perfusion defect in patients with stress-induced ST depression and ST elevation, respectively. The PPV of having stress-induced ischemia and/or fixed perfusion defect on MPS was 33% in patients with stress-induced ST depression at stress and 96% in patients with stress-induced ST elevation.

In the 198 consecutive patients, 32 had ST depression at rest. Of these patients, 25 had further ST depression at stress. In the 166 patients without ST depression at rest, a normal ST response had a NPV of 90% (90/100) and stress-induced ST depression had a PPV of 27% (18/66) for stress-induced myocardial ischemia by MPS. Of the 166 patients without ST depression at rest, 45 had a pathological ST response on exercise ECG. These 45 patients all had a normal MPS and no signs of prior infarction on resting ECG.

*Stress-induced ST deviation in relation to the amount of myocardial ischemia by MPS*

Patients with stress-induced ST elevation and positive MPS (n = 21) had more extensive ischemia (SSS 18 ± 10) compared to the patients with positive MPS and ST depression (SSS 8 ± 6, n = 25; $p < 0.001$) as well as to patients with no ST elevation or ST depression (SSS 9 ± 7, n = 10; p = 0.002).

Fig. 3A-B shows that there was a significant correlation between SSS determined from the MPS and the sum of significant stress-induced ST elevations ($r^2 = 0.73$, $p < 0.001$) as well as between SSS and maximum ST elevation during BST ($r^2 = 0.58$, $p < 0.001$). However, as also shown in Fig. 3, no correlation was found between sum of significant ST depressions and SSS ($r^2 = 0.024$, p = 0.10) or between the maximum ST depressions and SSS ($r^2 = 0.022$, p = 0.08; Fig. 3C-D).

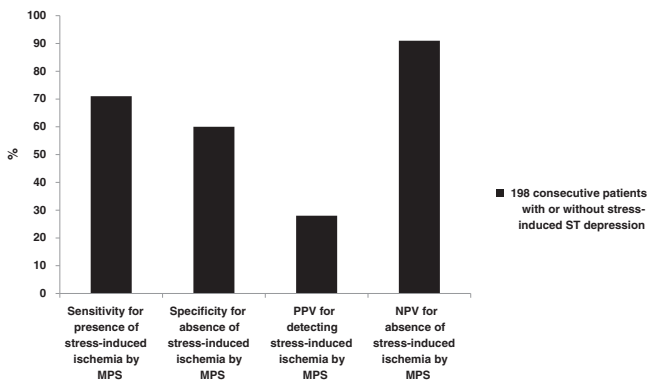


Fig. 1. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for presence/absence of stress-induced ischemia by myocardial perfusion SPECT in the consecutively included patients (n = 198).

*Stress-induced ST deviation in relation to the location of myocardial ischemia by MPS*

In the patients with stress induced ST elevation, there was excellent agreement between the location predicted by the ECG leads showing ST elevation and that determined by the MPS, except in those patients with ST elevation in V1 and ST depression in leads V4-V6 and –aVR. In all of these patients, the MPS determined ischemia was in the LAD territory. For patients with stress-induced ST depression and a positive MPS, the ischemia location on ECG had a poor agreement with the location of the ischemia by MPS (kappa = 0.20).

Coronary angiography was performed in 17 of the patients with stress induced ST elevation. In 88% (15/17) there was complete agreement between the angiographically determined culprit vessel and that predicted by the ECG and the MPS. In the remaining 2 patients, the coronary arteries were described as normal.

Fig. 4 and Table 3 shows characteristics and examples of ST deviation patterns identified among the patients with stress-induced ST elevation. Concomitant ST depressions in leads II, III, aVF occurred in 8 patients in group B and in 5 patients in group C in Table 3. Fig. 4 includes examples of a patient with ST elevation in II, III, aVF without ST depression in lead – aVR or in leads V2-V6 (Fig. 4A), ST elevation in V1 with ST depression in – aVR, V4-V6 as well as II, III, aVF (Fig. 4B) and ST elevation in V1-V3 without ST depression in –aVR (Fig. 4C). In patients with Q waves or QS complex in leads with ST elevation having both a fix defect and stress-induced ischemia on MPS (n = 8), the fix defect and stress-induced ischemia were located in the same vessel territory in 8/8 patients.

## Discussion

The present study is, to the best of our knowledge, the first to show that stress-induced ST elevations, with or without concomitant ST depression, do not only correlate to presence and location of stress-induced myocardial ischemia, but also to its amount as assessed by SSS from MPS. In this study, stress-induced ST depression without concomitant ST elevation was a poor predictor of myocardial ischemia in a group of consecutively included patients. However, the NPV of a normal ST response during stress is high.

*Stress-induced ST changes during bicycle stress test*

Manifestation of stress-induced ST changes has previously been shown to be a sign of stress-induced ischemia and coronary artery disease [4,9,13]. The findings in the present study show that BSTs with stress-induced ST elevation reflect more severe myocardial ischemia as compared to stress-induced ST depression. This result is supported by the high prevalence of critical coronary stenosis (> 90% stenosis) in patients with stress-induced ST elevation [6,9,14]. The ST elevation population in the present study can be divided into two distinct groups: those with (n = 17) and those without signs of prior infarction (n = 11) on the resting ECG. The PPV of stress-induced ST elevation for stress-induced myocardial ischemia by MPS was found to be higher (91%) in patients without signs of prior infarction. Patients with stress-induced ST elevation and no signs of prior infarction are rare, but have previously been shown to have extensive reversible perfusion defects and respond well to revascularization or medical therapy [15,16].

There are several possible explanations for stress-induced ST elevation. Stress-induced transmural ischemia in the myocardium underlying the leads with the ST elevation is one possible pathophysiologic mechanism explaining stress-induced ST elevation. When stress-induced ST elevation occurs in lead V1 and is accompanied by ST depression in leads –aVR and V4–V6, the most likely cause is extensive left ventricular subendocardial ischemia caused by stenosis in the left main artery or severe, proximal LAD stenosis as seen in Fig. 4C. Furthermore, ST elevation in leads with evidence of prior infarction, such as pathological Q waves, might be caused by ST depression in the contra-lateral LV wall locally observed through the electrically silent infarcted myocardium underlying this lead. This mechanism could potentially explain stress-induced ST elevation in patients with signs of prior Q wave myocardial infarction associated with a fixed defect on the MPS in the present study. Stress-induced

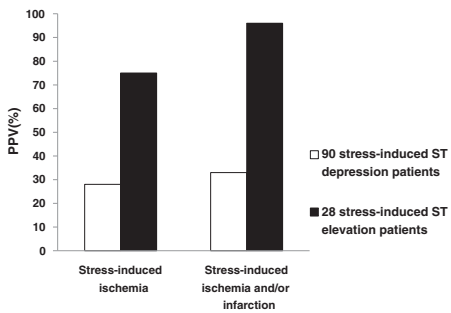


Fig. 2. Positive predictive values (PPV)of stress-induced ST changes for presence of stress-induced and/or fixed perfusion defect on myocardial perfusion SPECT, in patients with stress-induced ST depression (n = 90) and in ST elevation patients (n = 28). Stress-induced ST elevation had a significantly higher PPV compared to stress-induced ST depression.

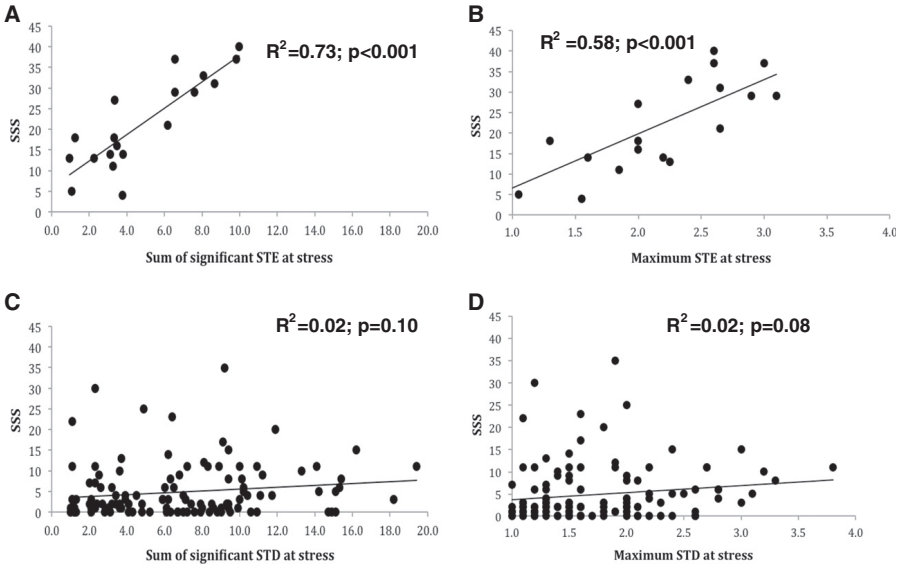


Fig. 3. The relationship between the amount of stress-induced ischemia by myocardial perfusion SPECT (MPS) and the amount of stress-induced ST elevation **(at the top)** and stress-induced ST depression **(at the bottom). At the top left,** the correlation between summed stress score (SSS) on MPS and the sum of significant ST elevations (STE) during bicycle stress test (BST) is shown. **At the top right,** the correlation between SSS on the MPS and the lead with maximum STE during BST is shown.**At the bottom left,** the correlation between summed stress score (SSS) on the MPS and the sum of significant ST depressions (STD) during bicycle stress test (BST) is shown. **At the bottom right,** the correlation between SSS on the MPS and the lead with maximum STD during BST is shown. No correlation was found.

ST elevation in these patients might also be related to stress-induced regional dysfunction and aneurysm as has previously been suggested [17]. Further analysis of other potential mechanisms that could possibly result in stress-induced ST elevation such as drugs, potassium level and presence/absence of left ventricular hypotrophy requires a larger patient cohort and was not performed in the present study.

In this study, 17/28 of the ST elevation patients had a coronary angiogram performed after the MPS examination.

The present study is to the best of our knowledge the first to show the relationship between SSS by $^{99m}$Tc-tetrofosmin MPS and sum of stress-induced ST elevation ($r^2 = 0.73$), which is stronger than previous findings by Gewirtz et al. [18] showing a correlation between sum of stress-induced ST elevation and thallium uptake defect score ($r^2 = 0.40$) in patients with prior anterior myocardial infarction.

In this study, the location of stress-induced ST elevation correlated with the location of ischemia by MPS when the ST elevation occurred in leads II, III and aVF without a Q wave of an old infarction in these leads. When the stress-induced ST elevation was in V1 with concomitant ST depression in V4-V6 and –aVR (interpreted as LAD ischemia), all patients (7/7)showed LAD perfusion defect by MPS which corresponds to findings in previous studies [19,20].

We found that stress-induced ST depression was shown to be a poor marker of the location of stress-induced myocardial ischemia by MPS, even if the patients with ST depression at rest were omitted from the analysis. In the absence of significant coronary artery disease, other confounding factors such as hypertrophy, hypertension, electrolyte abnormalities or pharmacological treatment such as digoxin can cause ST depression [21,22].

### *MPS as reference standard*

In contrast to previous studies where coronary angiography has often been used as reference standard for significant coronary artery disease [8,23], the current study has related stress-induced ECG findings to MPS. Coronary angiography depicts the presence and degree of coronary stenosis, whereas MPS reflects the physiological consequence of a coronary stenosis on myocardial perfusion [10,24]. The correlation between the visual assessment of the degree of stenosis and the severity of stress-induced ischemia has previously been shown to be low [25,26]. Thus, in the present study, MPS was considered to be more relevant as a reference standard for diagnosing stress-induced ischemia in patients with suspected ischemic heart disease.

### *Clinical implications*

The novel clinical information that this study implies is that in patients with ST elevation in leads II, III, aVF, occurring in the absence of Q waves (or QS complex) in these leads, probably indicates severe ischemia of the inferior (diaphragmatic) wall

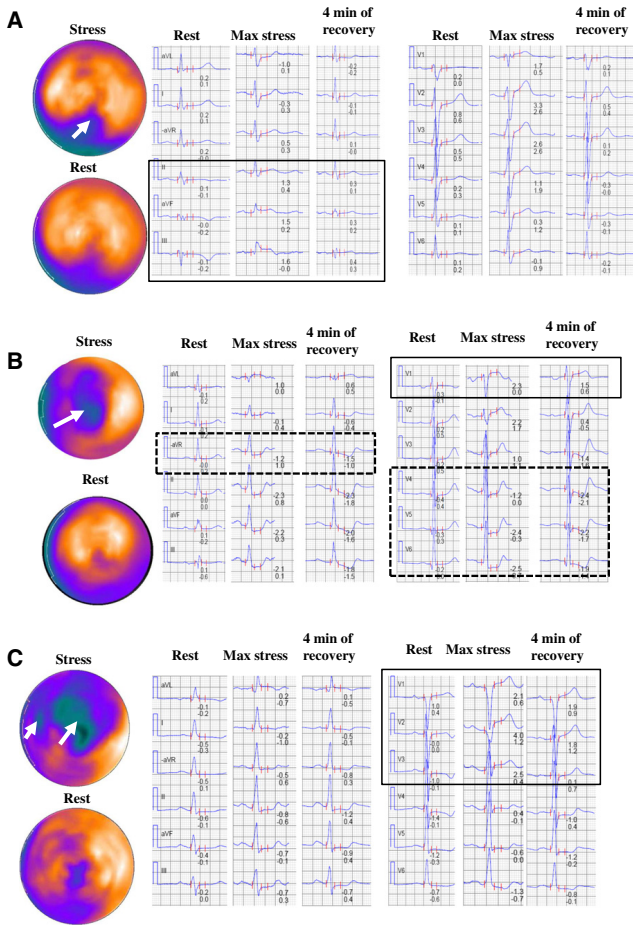


Fig. 4. Example of one case from each of the 3 groups of ST-deviation patterns identified among the patients with stress-induced ST elevation. **To the left,** bull's eye plots (at stress at the top and at rest at the bottom) representing the myocardial perfusion distribution in the left ventricle, with the apex in the center and the basal parts of the LV in the periphery. Warm colors represent good perfusion and cold colors or black represent decreased perfusion. **To the right,** the corresponding ECG response (at rest, max stress and 4 min of recovery) in the 12 leads (50 mm/s, 10 mm/mV).**A)** (n = 7) Stress-induced ST elevation in leads II, III, aVF (box) without ST depression in lead -aVR or in leads V2-V6. This ECG pattern was seen in patients with stress-induced ischemic (arrow) in the RCA perfusion territory and could occur with or without Q waves in these leads.**B)** (n = 9) Stress-induced ST elevation in lead V1 (solid box) with ST depression in leads V4-V6 (dashed box), −aVR (i.e. ST elevation in lead +aVR, dashed box) and II, III, aVF. This correlated with stress-induced ischemia in the LAD perfusion territory (arrow).**C)** (n = 12) Stress-induced ST elevation in lead V1-V3 (box) with no ST depression in lead –aVR which could occur with or without Q waves in these leads. This correlated with stress-induced ischemia in the LAD perfusion territory (arrows).

caused by a tight RCA lesion (or spasm of the RCA). This is an indication of a lesion that requires urgent treatment. Our findings also imply that particular attention should be paid to effect of stress on leads V1 and aVR. The presence of ST elevation in V1 at stress with concomitant stress-induced ST depression in –aVR (or ST elevation in +aVR) and ST depression in any of leads II, aVF, V4-V6 indicates severe LAD coronary disease that needs prompt treatment. More specific clinical outcome studies are needed to confirm these possible clinical implications.

This study also conveys that an MPS done in conjunction with a stress-test enhances the ECG interpretation and impacts subsequent decision-making and treatment, especially in the presence of ST elevation at stress. Given that stress-induced ST elevation is rare, it cannot justify the use of

Table 3
MPS findings in the 3 different groups of ST deviation patterns found in patients with stress-induced ST elevation.

| Group | Exercise ECG | MPS | Culprit vessel MPS | Stress-induced ischemia (mean SSS ± SD) | Fixed defect only (mean SSS ± SD) |
|---|---|---|---|---|---|
| **A (7)** | ST elevation in II, III, aVF without ST depression in -aVR or in leads V2-V6. Absence of Q waves or QS complex in leads with ST elevation. | Fixed defect and stress-induced ischemia (n = 1); only stress-induced ischemia (n = 3) | RCA | 14 (±7) | 0 |
| | As above but with Q waves or QS complex in leads with ST elevation. | Fixed defect and stress-induced ischemia (n = 3)* | | | |
| **B (9)** | ST elevation in V1-V2 with ST depression in– aVR and V4-V6. | Only fixed defect (n = 1); fixed defect and stress-induced ischemia (n = 3); only stress-induced ischemia (n = 5) | LAD | 17 (±9) | 37 (±0) |
| **C (12)** | ST elevation in V1-V5 without ST depression in –aVR. | Only stress-induced ischemia (n = 1); no stress-induced ischemia or fixed defect (n = 1) | LAD | 26 (± 10) | 30 (± 8) |
| | As above but with Q waves or QS complex in leads with ST elevation | Only fixed defect (n = 5); Fixed defect and stress-induced ischemia (n = 5)* | | | |

* Fixed defect and stress-induced ischemia were located in the same area on the MPS.

MPS as a first method of choice in patients with stable coronary artery disease, both with regard to radiation exposure and costs associated with MPS. Our results from this study further emphasize that ST depression alone on the exercise ECG, both in patients with and without resting changes, is a significantly less specific indicator of stress-induced ischemia than is stress-induced ST elevation.

*Limitations*

The findings in the present study should be interpreted in the light of the following limitations. 1) The study population is not representative of a general clinical exercise test population given that the patients have been referred for a MPS examination. Thus, patients with intermediate risk of ischemic heart disease as well as challenging exercise test interpretation were probably overrepresented, affecting the results. 2) The study population is limited, especially with regards to patients with stress-induced ST elevations (n = 28). These patients are, however, not so frequently seen in clinical routine, probably explaining the lack of studies in these patient populations. 3) The ST elevation patients were enrolled on the basis of a clinical report stating the presence of stress-induced elevations, whereas the remaining patients were consecutively included. Thus, there may have been additional patients between the years 2000–2013 with unreported stress-induced ST elevations not included in the study. 4) Given the low number of females included in the ST elevation group, gender aspects of the findings could not be studied. 5) Collateral contribution to the coronary blood flow was not considered in this study. 6) The difference in prevalence of coronary artery disease in the ST elevation patients and the consecutive patients affects the calculated predictive values. 7) MPS, the reference standard used in this study, shows the relative perfusion distribution and has a quite low resolution which makes diffuse subendocardial ischemia hard to localize. 8) Given the retrospective nature of the work, coronary angiography could only be obtained when this was performed on clinical indication.

## Conclusions

Exercise ECGs with ST elevation, either concomitant or non-concomitant to ST depression, correlates to presence, location as well as amount of myocardial ischemia assessed by MPS. Stress-induced depression without concomitant ST elevation is, however, a poor predictor of myocardial ischemia.

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## Disclosure

None. The authors report no relationships that could be construed as a conflict of interest.

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# Paper II

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# Gender aspects on exercise-induced ECG changes in relation to scintigraphic evidence of myocardial ischaemia

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## Summary

*Background* This retrospective study aimed to determine the diagnostic performance of exercise-induced ST response in relation to findings by myocardial perfusion single photon emission computed tomography (MPS), with focus on gender differences, in patients with suspected or established stable ischemic heart disease.

*Methods* MPS findings of 1 021 patients (518 females) were related to the exercise-induced ST response alone (blinded and unblinded to gender) and ST response together with additional exercise stress test (EST) variables (exercise capacity, blood pressure and heart rate response).

*Results* Exercise-induced ischaemia by MPS was found in 9% of females and 23% of males. Diagnostic performance of exercise-induced ST response in relation to MPS findings in females versus males was: sensitivity = 48%,70%; specificity = 67%, 64%; PPV = 13%, 38%; NPV = 93%, 87%. Adding more EST variables to the ST response interpretation yielded in females vs males: sensitivity = 44%, 51%; specificity = 84%, 83%; PPV = 22%, 48% and NPV = 93%, 85%.

*Conclusions* In patients who have performed EST in conjunction with MPS, there is a gender difference in the diagnostic performance of ST response at stress, with a significantly lower PPV in females compared to males. For both genders, specificity can be significantly improved, and a higher PPV can be obtained, while the sensitivity might be compromised by considering more EST variables, in addition to the ST response.

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## Introduction

Ischemic heart disease (IHD) is the number one cause of mortality worldwide. Accurate diagnosis of exercise-induced ischaemia is of importance for choice of treatment and for assessment of patients' prognosis (Candell-Riera *et al.*, 2013; Task Force Members, 2013; Task Force on Myocardial Revascularization of the European Society of C, 2010).

For the diagnosis of exercise-induced ischaemia, exercise stress test (EST) is often the first method of choice at many clinical centres. When interpreting EST, observations such as blood pressure and heart rate (HR) response and exercise capacity are analyzed in addition to the ST response in certain ECG leads. Exercise-induced ST deviation, typically ST depression, on the 12-lead ECG is usually considered to be a sign of exercise-induced ischaemia (Goldschlager *et al.*, 1976). The performance of exercise-induced ST changes alone in diagnosing exercise-induced ischaemia is known to be limited (Detrano *et al.*, 1989) especially in females, which could partly be explained by more frequent atypical ST responses during EST in females compared to males (Sketch *et al.*, 1975; Detry *et al.*, 1977; Barolsky *et al.*, 1979; Shaw *et al.*, 2016). However, the majority of larger studies focusing on gender differences in the diagnostic performance of exercise-induced ST changes have used coronary angiography and not exercise-induced ischaemia, as reference standard (Sketch *et al.*, 1975; Detry *et al.*, 1977; Barolsky *et al.*, 1979).

While some consider invasive coronary angiography, including fractional flow reserve, as a gold standard for diagnosing IHD, current guidelines recommend the usage of invasive investigation only in patients with high pretest likelihood. Patients with intermediate pretest likelihood of stable coronary artery disease should be investigated noninvasively for the presence of exercise-induced ischaemia (Task Force Members, 2013).

Myocardial perfusion single photon emission computed tomography (MPS) is one of the recommended non-invasive methods by the 2013 ESC guidelines on the management of stable coronary artery disease for the diagnosis of exercise-induced ischaemia (Task Force Members, 2013). Due to its

 

high diagnostic accuracy, MPS has been used as the reference standard for evaluation of presence and extent of exercise-induced ischaemia (Underwood *et al.*, 2004). Despite this, studies relating EST findings of exercise-induced ischaemia to MPS findings, with specific focus on gender differences, are limited (Tavel, 1992; Miller *et al.*, 2001).

Therefore, the aim of the study was to determine the diagnostic performance of exercise-induced ST response for the absence or presence of exercise-induced myocardial ischaemia as assessed by MPS, with special focus on gender differences, in patients with suspected or established stable IHD.

## Methods

### Study population

A total of 1 021 patients (518 females, age range 33–88 years, mean 63 years females/ 64 years males), with suspected stable IHD (with the majority (n = 1 011) referred to MPS due to chest pain, experienced decrease in exercise capacity or risk factors for coronary artery disease and the minority (n = 10) referred to MPS due to follow-up after kidney/lung transplantations and adjustment of tambocor treatment) were retrospectively included. All patients were referred for clinical MPS between 2 June 2008 and 30 April 2011 at the department of Clinical Physiology and Nuclear Medicine at Lund University Hospital, Lund, Sweden. Inclusion and exclusion procedure is summarized in Fig. 1. All included patients had performed an MPS examination with exercise on a bicycle being the method of choice for stressing the patient, according to national clinical standard. Patients who were pharmocalogically stressed (adenosine or dobutamine being the stressor) were excluded from the study.

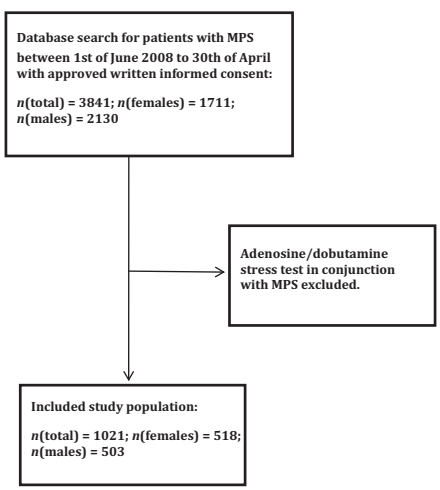


**Figure 1** Flowchart of inclusion and exclusion.

The study was approved by the regional ethics committee, and written informed consent was obtained from each patient. Risk factors were collected from a health declaration form, completed by the patient at the time of the examination, and from the patients' clinical charts.

### Exercise stress test

The bicycle stress test was performed in conjunction with the MPS examination using an electronically braked ergometer (Siemens Ergomed 940 before 2009 and Monark 939 E after 2009) and according to the national standard clinical protocol, including assessment of exercise capacity, HR and blood pressure response, symptoms and ECG. A specific workload was applied according to gender, mass, age and self-estimated physical fitness, aiming for a total stress time of 8–10 min. A 12-lead ECG was acquired before, during and after exercise. Blood pressure was attained at rest in supine position, before exercise on the bicycle in an upright position, during exercise and finally in supine position after exercise. The workload was progressively increased, and the perceived exertion was rated by the patient using the 6-to-20 Borg scale Borg, 1970. Averaged ECG complexes were recorded every other minute before, during and until 4 min after exercise for the 12 leads (avL, I, -aVR, II, aVF, III, V1-V6) with digital ECG recorders: Megacart R/E, sampling rate 500 Hz (Siemens Elema AB, Solna, Sweden) before 14 May 2009 and EC Sense Lexor X100 (Cardiolex AB, Täby, Sweden) after 14 May 2009.

### MPS examination

A 1- or 2-day $^{99m}$Tc- tetrofosmin stress/rest MPS protocol, following American Society of Nuclear Cardiology (ASNC) recommendations (Henzlova *et al.*, 2016) was performed according to clinical routine. Patients were injected with $^{99m}$Tc-tetrofosmin at ≥85% of maximum predicted HR, one minute before the termination of exercise. If a patient experienced chest pain (at least grade 5/10 on the Borg scale) during the bicycle EST, the isotope was injected regardless of achieved HR. Administered doses of the isotope varied between 400 and 700 MBq at stress depending on the patient's weight. The rest examination was obtained only in those patients whose exercise MPS images were considered to be abnormal and was then performed at least 2 h after the stress examination. Administered doses of the isotope for the rest examination were approximately three times higher than the administered doses at exercise.

### MPS image acquisition

Images were acquired using a dual-headed gamma camera (Ventri, GE Healthcare Buckinghamshire, UK) with the patient placed in supine position. Images were also attained in prone

position after stress injection, if needed, to exclude defects on the image caused by attenuation artifacts Heden *et al.*, 2009 Images were acquired in 32 projections over an 180° orbit, using a 64 × 64 matrix. Iterative reconstruction was performed using maximum-likelihood expectation maximization (MLEM) with a postfiltration using a butterworth filter (cut off 5·0 mm). The reconstructed voxel size was 6·4 × 6·4 × 6·4 mm. All images were gated with ECG using eight bins per cardiac cycle acquisition.

### Exercise stress test analysis

The exercise stress tests of the 1 021 patients were analyzed by an experienced physician (BH) who was blinded to all patient history and ongoing medication. In a subset of the ESTs (234 patients, 111 males/123 females, age range 33–88 years, mean 61 years males/64 years females), the ST response alone was re-analyzed by the same experienced physician (BH). The same criteria as when analyzing the ST response in the total population (1 021 patients) was used, but now blinded to gender in addition to being blinded to patient history and ongoing medication. The subset population was selected from the total patient population in a random fashion, but preserving gender distribution and prevalence of stable IHD.

The ST segments at rest were either classified as normal or with resting ST changes such as ST depression/elevation or abnormal ST slope (horizontal or descending). If there were solitary resting ST changes (>1 mm) in leads aVL, V1 or in lead III, but normal resting ST changes in V4-V6, the ST response was considered interpretable. If resting ST changes (>1 mm) were present in V4-V6, the ST response was considered non-interpretable.

The parameters taken into account during the interpretation of the exercise-induced ST response only are summarized in Fig. 2. The ST response at exercise was evaluated by the experienced physician based on a holistic interpretation, which included the visual assessment of the 12-lead ECG (at rest, 1and 4 min after termination of exercise, as well as every second minute during exercise with >1 mm horizontal or downsloping ST depression 60 ms after J-point being pathologic), the ST trends and the ST-heart rate loops (shape and rotational direction), as can be seen in the examples presented in Fig. 2.

Based on the holistic interpretation of ST changes during rest, exercise and at 4 min of recovery, the ST response was classified as being normal (with or without remarks), normal but difficult-to-assess (poor signal quality, resting changes, other reasons), abnormal (borderline abnormal or abnormal), abnormal but difficult-to-assess (poor signal quality, resting changes, other reasons) or non-interpretable (inadequate signal quality, resting changes, other reasons). For calculation of diagnostic accuracy, the five categories were further divided into positive, indeterminate and negative according to the guidelines (Fletcher *et al.*, 2013). The abnormal (borderline abnormal or abnormal) and abnormal but difficult-to-assess were set as positive. The non-interpretable ST response was set as indeterminate. The normal ST responses (with or without remarks) and those which were normal but difficult-to-assess were set as negative.

In addition to the ST segment response, EST variables including blood pressure and HR response as well as exercise capacity (in W and % of expected exercise capacity) were analyzed by the experienced physician (BH). The blood pressure response during exercise (resting blood pressure taken account) and the exercise capacity were analysed in relation to gender and age, using previously described normal values Henderson & O'Flynn, 2012. The HR response was considered normal when ≥85% of the patient's maximal HR (220-age) was reached. Based on this overall assessment, the EST was then classified as normal, abnormal or non-interpretable.

The ST response or the overall EST was considered non-interpretable when at least one of the following findings was present: (i) Missing 4 min of recovery, (ii) changes on resting ECG such as significant ST changes at rest and (iii) inadequate signal quality. The patients' clinical charts were used to find out if β-blocker was taken on the day of the exercise test.

### MPS analysis

Based on the MPS images acquired using the QPS software (version 4·0; Cedars-Sinai Medical Centre, Los Angeles, CA), the presence of ischaemia was determined by a visual assessment of the reconstructed images. Images acquired in prone position were used to exclude defects caused by breast or diaphragmatic artefacts. Exercise-induced ischaemia was reported if there was a decreased isotope uptake seen in the supine stress image but not in the rest image.

The extent and severity of exercise-induced ischaemia was calculated in patients diagnosed with exercise-induced ischaemia. In these patients (n = 166), short-axis (stress and rest) non-gated MPS images were analysed using an automated validated algorithm in the software Segment version 2·0 (http://segment.heiberg.se), as previously described (Fransson *et al.*, 2014). The difference in total perfusion deficit (TPD) between stress and rest images (D-TPD) was automatically obtained and was used as the quantitative measure of the extent and severity of exercise-induced ischaemia. This was performed to investigate whether false-negative ST reaction could be explained by a less pronounced exercise-induced ischaemia found in these patients, compared to those with true-positive ST reactions.

### Statistical Analysis

Values are expressed as mean ± SD. $\chi^2$ test was used to compare the frequency of risk factors in the two patient populations. The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of exercise-induced ST response for determining the presence/absence of

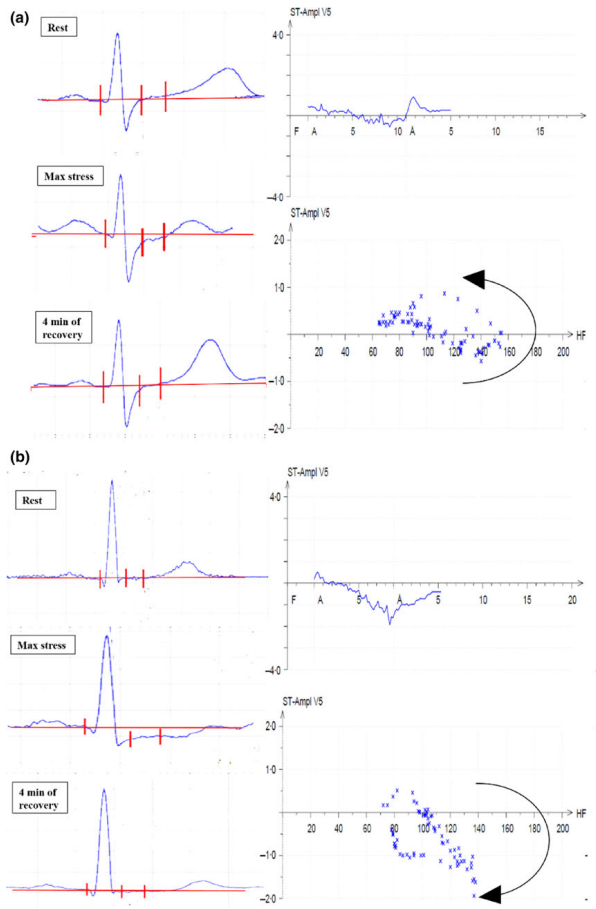


**Figure 2** Examples showing parameters used in the holistic interpretation of the ST response at stress. ECG in lead V5 at rest, max stress and 4 min of recovery (to the left), ST amplitude as a function of time (upper right) and the ST-HR loop (bottom right), in a patient with a ST response interpreted as (a) normal and (b) pathologic. Note in (a) the non-significant ST depression (<1 mm) at max stress, the small change in ST amplitude over time and the counterclockwise ST-HR loop direction. Note in (b) the significant horizontal ST depression (>1 mm) at max stress, the down-sloping ST amplitude during stress and the clockwise ST-HR loop direction, indicating a pathological ST response.

ischaemia by MPS was calculated. The indeterminate ST responses were excluded from the calculation of diagnostic accuracy. Cohen's Kappa was used as a measure of level of agreement between interpretation ST response at exercise blinded and unblinded to gender. Kappa values were interpreted as follows: 0–0·20 poor agreement, 0·21–0·40 fair agreement, 0·41–0·60 moderate agreement, 0·61–0·80 good agreement, and 0·81–1·0 excellent agreement. Statistical Package for the Social Sciences (SPSS) v.21·0 (Chicago, Illinois, USA) was used for all statistical analysis. Results with $P<0·05$ were considered to be statistically significant. Confidence intervals (CI) are presented at 95% confidence level.

## Results

### Characteristics of patients, EST and MPS

Patient characteristics for the included males and females are summarised in Table 1. Prior PCI, prior bypass surgery, prior myocardial infarction, diabetes, heredity for coronary artery

**Table 1** Patient characteristics.

| Characteristics | Gender | | *p*-value |
|---|---|---|---|
| | males n = 503 | females n = 518 | |
| Smoker | 50 (10%) | 39 (8%) | 0·2 |
| Previous smoker | 236 (47%) | 222 (43%) | 0·2 |
| Prior PCI | 122 (24%) | 45 (8%) | <0·001 |
| Prior CABG | 61 (12%) | 23 (4%) | <0·001 |
| Prior myocardial infarction | 110 (22%) | 44 (9%) | <0·001 |
| Diabetes | 81 (16%) | 39 (8%) | <0·001 |
| Hypertension | 236 (47%) | 234 (45%) | 0·6 |
| Hypercholesterolemia | 191 (38%) | 168 (32%) | 0·06 |
| Family history of coronary artery disease | 122 (24%) | 172 (33%) | 0·002 |
| β-blocker | 176 (35%) | 135 (26%) | 0·002 |

disease and medication with β-blocker were all significantly more prevalent in males than in females.

Characteristics of the 1021 ESTs and MPS are presented in Table 2. A total of 83/1021 patients did not reach ≥85% of their maximal HR. Of these, 51 had reached 80%–85% of their maximal HR and were considered by the responsible clinician to be maximally exercised given the preceived exertion. The remaining 32 of 83 patients had all not reached ≥85% of the maximal HR (intervall 52%–78%) and were injected with the isotope due to experiencing chest pain. Exercise-induced ischaemia as determined by MPS was found in 9% (48/518) of the females and 23% (118/503) of the males. An abnormal ST response was found in 33% (172/518) of the females and 41% (208/503) of the males. Of the abnormal ST responses, 34% (59/172) were difficult-to-assess in the females versus 24% (50/208) in the males.

When adding assessment of exercise capacity, blood pressure and HR response to the ST response interpretation, an abnormal EST was found in 19% (96/518) of females and 24% (122/503) of males.

**Table 2** Characteristics of bicycle exercise stress test and myocardial perfusion single photon emission computed tomography.

| | Males | Females |
|---|---|---|
| Total | 503 | 518 |
| Age | 64 (±9) | 63 (±9) |
| ST response | | |
| Normal | 222 (44%) | 263 (51%) |
| Normal (difficult-to-assess) | 39 (8%) | 60 (12%) |
| Abnormal | 158 (31%) | 113 (22%) |
| Abnormal (difficult-to-assess) | 50 (10%) | 59 (11%) |
| Non-interpretable | 34 (7%) | 23 (4%) |
| Other exercise stress test variables added[a] | | |
| Normal | 366 (73%) | 411 (79%) |
| Pathologic | 122 (24%) | 96 (19%) |
| Difficult-to-assess/ non-interpretable[a] | 15 (3%) | 11 (2%) |
| Persistent ST depression after 4 min of recovery | 192 (38%) | 173 (34%) |
| Resting ECG changes | 92 (18%) | 87 (17%) |
| Left bundle branch block | 0 | 0 |
| Left ventricular hypertrophy | 3 (0·6%) | 1 (0·2%) |
| Paced rhythm | 0 | 0 |
| Exercise capacity (% of expected exercise capacity) | 101% (±22) | 96% (±20) |
| Exercise capacity (W) | 154 (±46) | 106 (±30) |
| Blood pressure response | | |
| Normal | 375 (75%) | 387 (75%) |
| Pathologic | 87 (17%) | 90 (17%) |
| Non-interpretable[b] | 41 (8%) | 41 (8%) |
| Heart rate response (peak exercise heart rate) | 148 (±16) | 151 (±17) |
| Heart rate response (% of expected peak exercise heart rate) | 95% (±10) | 96% (±10) |
| β-blocker[c] | 103 (21%) | 73 (14%) |
| Long-term nitrates[d] | 0 | 0 |
| Stress-induced ischaemia | | |
| With fixed defect | 30 (6%) | 21 (4%) |
| Without fixed defect | 88 (17%) | 27 (5%) |
| No stress-induced ischaemia | | |
| Normal | 344 (68%) | 462 (89%) |
| Fixed defect | 41 (8%) | 8 (2%) |

[a]Blood pressure and heart rate response as well as exercise capacity added to the exercise stress test interpretation.
[b]Scarce number of blood pressures taken.
[c]On the same day as the exercise test.
[d]On the day of the exercise test as well as the day before.

## Exercise-induced ST response in relation to the presence of myocardial ischaemia by MPS

For the total population, sensitivity, specificity, negative predictive value (NPV) and positive predictive value (PPV) for ST changes at exercise in diagnosing the presence or absence of exercise-induced myocardial ischaemia on MPS are shown in Fig. 3. For the total patient population, PPV and sensitivity of an abnormal ST response for the presence of exercise-induced ischaemia were 26% (CI: 22%–31%) and 63% (CI: 56%–71%), respectively. The NPV and specificity of a normal ST response for the absence of ischaemia were 90% (CI: 87%–92%) and 65% (CI: 62%–69%), respectively.

The PPV increased to 30% (CI: 24%–36%) while the NPV remained unchanged at 89% (CI: 86%–92%), when excluding ESTs with ST responses interpreted as 'normal with remarks', 'normal but difficult-to-assess', 'borderline abnormal' and 'abnormal but difficult-to-assess' from the total patient population.

## Gender aspects on exercise-induced ST response in relation to the presence of myocardial ischaemia by MPS

For each gender, in the total patient population, sensitivity, specificity and predictive values for ST changes at exercise in diagnosing the presence or absence of exercise-induced myocardial ischaemia on MPS are presented in Table 3. The specificity and NPV of a normal ST response did not differ significantly between females and males (specificity = 67% CI: 62%–71% versus 64% CI: 58%–69% and NPV = 93% CI:

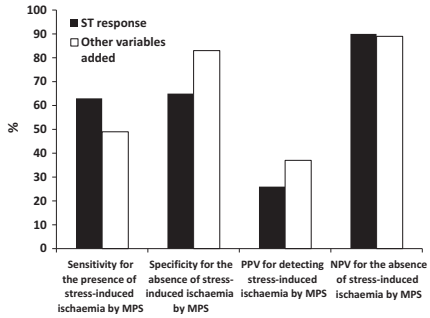


**Figure 3** Sensitivity, specificity, positive predictive value and negative predictive value for the presence or absence of stress-induced ischaemia by Myocardial perfusion single in the total patient population, using ST response alone and when adding factors including blood pressure and HR response as well as exercise capacity to the exercise stress test interpretation.

89%–95% versus 87% CI: 82–91%). There was a trend towards a lower sensitivity when comparing females to males (48% CI: 32%–62% versus 70% CI: 60%–79%). Furthermore, the PPV of exercise-induced ST depression was significantly lower in females than in males (13% CI: 8%–19% versus 38% CI: 31%–44%). The PPV was 42% (CI: 34%–50%) in males and 11% (CI: 10%–18%) in females, when excluding ESTs with ST responses interpreted as 'normal with remarks', 'normal but difficult-to-assess', 'borderline abnormal' and 'abnormal but difficult-to-assess' from the statistical analysis.

For males, a significant difference in D-TPD by MPS was found between patients with and without abnormal ST response (D-TPD: $10 \pm 8$ versus $7 \pm 6$, $P = 0{\cdot}03$). For females, the same trend was seen (D-TPD: $9 \pm 12$ versus $4 \pm 3$, $P = 0{\cdot}08$) but the difference was not statistically significant.

For the subset of patients where the ST response alone was re-analysed blinded to gender and divided into a 2-point scale (normal, abnormal), excellent agreement was found with the analysis of ST response at exercise unblinded to gender, in both males (kappa: 0·91, 106/111 matched cases) and females (kappa: 0·81, 114/123 matched cases). When the interpretation of ST response at exercise carried out blinded to gender was divided into a 4-point scale (normal without remarks, normal but difficult-to-assess, abnormal, abnormal but difficult-to-assess), none of the patients changed more than 1 step on the scale.

### Impact of exercise capacity, blood pressure and HR response on diagnostic performance

Figure 3 and Table 3 show that when variables including blood pressure and HR response as well as exercise capacity were added to the EST interpretation, the specificity increased significantly and there was a trend towards higher PPV in the total population as well as for males and females, separately. Furthermore, there was a trend towards lower sensitivity in the total population as well as for males and females separately, when the additional EST variables were included in the interpretation. This means that inclusion of the other variables in the EST interpretation caused an increase in the number of false-negatives (additional $n = 22$ patients) in males (Table 3). Only the ST response in these patients was interpreted as abnormal, while the exercise capacity, HR response and blood pressure response were all normal in all 22 patients, despite the presence of exercise-induced ischaemia on the MPS (D-TPD: $8 \pm 6$).

## Discussion

The value of EST to detect ischaemia in patients with stable coronary artery disease is debated, and the NICE guidelines Henderson *et al.*, 2012 advises against the use of EST in this regard. The use of EST, however, will likely remain significant worldwide until other diagnostic modalities have been fully implemented. The present retrospective study includes a cohort of 1 021 patients who have performed bicycle EST in conjunction with MPS, and the findings demonstrate a

**Table 3** Performance of ST response at stress alone and in addition to other exercise stress test variables (in parentheses) in diagnosing stress-induced ischaemia by myocardial perfusion single photon emission computed tomography in both genders, with and without patients with resting ECG changes and β-blocker administered on the same day.

| | β-blocker omitted | | | | Resting ECG changes omitted | |
|---|---|---|---|---|---|---|
| | ST response at stress (Adding other EST variables[a]) | | ST response at stress (Adding other EST variables[a]) | | ST response at stress (Adding other EST variables[a]) | |
| | *Females* | *Males* | *Females* | *Males* | *Females* | *Males* |
| Sensitivity% | 48 (44) | 70 (51) | 41 (41) | 67 (51) | 36 (44) | 68 (51) |
| Specificity% | 67 (84) | 64 (83) | 69 (85) | 66 (88) | 69 (84) | 67 (85) |
| NPV% | 93 (93) | 87 (85) | 92 (93) | 86 (83) | 92 (93) | 87 (83) |
| PPV% | 13 (22) | 38 (48) | 12 (22) | 39 (59) | 10 (23) | 40 (54) |
| n | 495 (507) | 469 (488) | 430 (402) | 374 (338) | 428 (456) | 403 (416) |

[a]Blood pressure and heart rate response as well as exercise capacity added to the exercise stress test (EST) interpretation.

significantly lower PPV for ST depression at exercise for ischaemia in females than in males. Furthermore, the specificity can be significantly increased for both genders by adding blood pressure and HR responses as well as exercise capacity to the EST interpretation. Moreover, in the current study, we showed that even when using a design where $^{99m}$Tc-tetrofosmin MPS is the gold standard for exercise-induced ischaemia, and despite defining a pathologic ST response using a holistic interpretation by an experienced physician, similar findings were found as in the several previous studies who have instead used coronary angiography as a gold standard and a cut-off of typically 1 mm to define a pathological ST response.

### MPS as reference standard when evaluating diagnostic performance of EST

In previous studies, coronary angiography has often been used as reference standard for the presence/absence of significant coronary artery disease (Sketch *et al.*, 1975; Levisman *et al.*, 2012). In the present study, however, EST findings were related to MPS findings of exercise-induced myocardial ischaemia. It has previously been shown that the correlation between coronary stenosis by angiography and myocardial perfusion is weak (White *et al.*, 1984). In addition, a recent meta-analysis showed that angiography had worse diagnostic accuracy than MPS when findings were related to fractional flow reserve (Carlsson, 2016; Danad *et al.*, 2016). Therefore, when evaluating the diagnostic performance of EST for diagnosing myocardial ischaemia, MPS was chosen as the reference standard in the present study.

According to the guidelines, a positive MPS does not necessarily need to be followed by coronary angiography (Task Force Members, 2013; Task Force on Myocardial Revascularization of the European Society of C, 2010). Stress-induced ischaemia <5% of the left ventricle can be treated with medication while stress-induced ischaemia >10% of the left ventricle should be revascularized (Task Force Members, 2013; Task Force on Myocardial Revascularization of the European Society of C, 2010). Furthermore, inclusion of ischaemia testing with, for example MPS has been shown to decrease the number of unnecessary coronary angiographies and revascularizations, with no negative effect on major adverse cardiac events (Schwitter *et al.*, 2013; Douglas *et al.*, 2015).

### Gender aspects

In the present study, the sensitivity, specificity and PPV for ST response at exercise confirm the previously shown limited diagnostic accuracy of ST depression in diagnosing exercise-induced myocardial ischaemia, especially in females (Sketch *et al.*, 1975; Barolsky *et al.*, 1979; Shaw *et al.*, 2011). Moreover, in the current study, the diagnostic accuracy of the ST response in detecting the absence or presence of stress-induced ischaemia by MPS was based on a holistic interpretation of the ST response and not on specific millimetre cut-off values of ST depression, which is line with what has previously been shown about the need to go beyond specific millimetre thresholds in the interpretation of the ST response (Akil *et al.*, 2016). Females are known to have a higher rate of abnormal ST responses than males, as a non-pathologic finding, making their diagnosis using EST more challenging (Sketch et al. 1975; Fent *et al.*, 2016). Various possible explanations for this have been purposed, including digoxin-like effect of oestrogen, haemoglobin concentrations and different chest wall anatomy in females (Sketch *et al.*, 1975; Kwok *et al.*, 1999).

When comparing predictive values between genders, it is important to note that the prevalence of exercise-induced ischaemia on MPS was lower in females compared to males (10% versus 24%, Table 2) which affects the predictive values. Sensitivity and specificity, however, which are not dependent on prevalence of disease were found to be lower in females than in males. Moreover, the significantly higher prevalence of diabetes, prior PCI, prior CABG and prior myocardial infarction in males as compared to females (Table 2) can partly explain the differences in the diagnostic accuracies. False-negative ST reaction could partly be explained by a less pronounced exercise-induced ischaemia found in these patients compared to those with true-positive ST reactions; especially in males where the D-TPD in false-negatives was significantly lower compared to true positives ($P = 0{\cdot}03$).

### Impact of exercise capacity, blood pressure and HR response on diagnostic performance

Inclusion of information about blood pressure and HR response as well as exercise capacity in the EST interpretation increased the diagnostic performance of the EST by increasing the specificity and PPV. Thus, as previously suggested (Gibbons *et al.*, 2002; Kligfield *et al.*, 2006), there is a need to go beyond the ST response interpretation, when diagnosing exercise-induced ischaemia using EST. Previous studies have also shown that EST variables such as ST-HR loops, ST segment/HR index and the Duke treadmill score can increase the diagnostic accuracy and are thereby superior to the analysis of the ST response alone (Kligfield *et al.*, 1989; Okin *et al.*, 1989; Mark *et al.*, 1991). In addition, low exercise capacity and slow HR recovery have been shown to be valuable prognostic risk factors of coronary artery disease, both in addition to and independent of exercise-induced ST depression (D'Amore *et al.*, 2016; Sharma, *et al.*, 2012). This also adds to the importance of going beyond the ST response interpretation.

However, in males, inclusion of the other variables resulted in a decrease in sensitivity from 70% to 51%. A possible explanation might be a less pronounced exercise-induced ischaemia in these patients (D-TPD: $8 \pm 6$) which caused an abnormal ST response with no significant effect on exercise capacity, HR and blood pressure response. In addition, the experienced physician was blinded to medical history and was

not present during the bicycle EST, which makes his holistic interpretation more challenging. In females, on the other hand, sensitivity changed only from 48% to 44%.

In the absence of significant coronary artery disease, other confounding factors such as hypertension can cause ST depression (Massie *et al.*, 1993; Otterstad *et al.*, 1993). Patients with hypertension (n = 470, Table 1) were included in the study population, and this could therefore have affected the results. There was, however, no significant difference (P = 0·8) in the prevalence of hypertension between the group of patients with false-positive ST response and the patients with true-negative ST response (119/239 and 209/460, respectively). Hypertension or not was considered as a dichotomous variable (yes or no), and the degree of hypertension was not quantified.

### *Resting changes and β-blocker*

When omitting patients with resting ECG changes (n = 92 in males, n = 87 in females, Table 3) from the statistical analysis, no significant differences were seen for any gender (Table 3). This finding is in contrast to a previous study where it has been shown that the ST response during exercise has been considered to be non-interpretable in the presence of resting ST changes (Meyers *et al.*, 1990).

Intake of β-blocker on the day of the EST can decrease the heart rate at rest and during exercise, affecting the diagnostic performance of the EST. The results from the present study, however, show that the diagnostic performance remained similar for both genders when patients who had taken β-blocker on the day of EST were omitted from the statistical analysis (Table 3).

### Limitations

The findings in the present study should be interpreted in the light of the following limitations. (i) The patients were referred to an MPS examination, so the study population is not representative of a general clinical exercise test population. Thus, patients with intermediate risk of IHD as well as challenging exercise stress test interpretation were probably overrepresented compared to a general population of patients with stable IHD. (ii) The physician who interpreted the exercise stress tests was blinded to the patient history, which could have increased the number of exercise tests that were difficult-to-assess. (iii) Given that this is a retrospective study, intake of β-blocker the day before the examination might have been underreported. (iv) The included men had a greater prevalence of prior PCI, prior CABG and prior myocardial infarction compared to women. This gives rise to resting changes on the ECG, making the interpretation of the ST response during exercise more challenging (5) MPS shows the relative perfusion distribution and has a quite low resolution, making diffuse subendocardial ischaemia hard to localize which also might affect the assessment of the diagnostic accuracy of EST. (vi) The study design did not include exclusion criteria of patients with suspected stable coronary artery disease referred to MPS due to follow-up after kidney/lung transplantations and adjustment of tambocor treatment. These patients usually have a pretest probability, for IHD, which differs significantly from the majority of the included patients. (vii) The character of the chest discomfort was not always reported in this retrospectively included population, inhibiting possible calculation of pretest probability of a positive MPS.

## Conclusion

In patients who have performed bicycle EST in conjunction with MPS, there is a gender difference in the diagnostic performance of ST response at exercise for the presence or absence of myocardial ischaemia as determined by MPS, with a significantly lower PPV of exercise-induced ST depression in females compared to males. For both genders, specificity can be significantly improved, and a higher PPV can be obtained while the sensitivity might be compromised, by considering blood pressure and heart rate response as well as exercise capacity in addition to the ST response, for the EST interpretation.

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## Conflict of interest

Håkan Arheden is stockholder in Imacor AB, Lund, Sweden. Marcus Carlsson and Henrik Engblom have received consultancy fees from Imacor AB, Lund, Sweden, for analysis of cardiac MRI. The remaining co-authors have no disclosures.

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