Myocardial ischemia in non-obstructive coronary artery disease

Associations with coronary artery disease morphology and left ventricular hypertrophy

Ingeborg Eskerud

Thesis for the degree of Philosophiae Doctor (PhD)
University of Bergen, Norway
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UNIVERSITY OF BERGEN

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Contents

1. Abbreviations

CAD	Coronary artery disease
NSTEMI	Non-ST-elevation myocardial infarction
CCTA	Coronary computed tomography angiography
ECG	Electrocardiography
STEMI	ST-elevation myocardial infarction
MINOCA	Myocardial infarction with non-obstructive coronary arteries
INOCA	Ischemia and no obstructive coronary artery disease
MicroCAD	Myocardial Ischemia in Non-obstructive Coronary Artery Disease
CT	Computed tomography
HbA_{1c}	Haemologlobin A_{1c}
OR	Odds ratio
CI	Confidence interval
β	Standardized beta coefficient
SPECT	Single photon emission computed tomography

2. Scientific environment

The present thesis is based on a collaboration between The Bergen Hypertension and Cardiac Dynamics Group, Department of Clinical Science at the University of Bergen and the Department of Heart Disease, Haukeland University Hospital in Bergen, Norway. The work is based on two clinical studies carried out at Department of Heart Disease during the years 2008-2014.

The Bergen Hypertension and Cardiac Dynamics Group integrates researchers from the Department of Clinical Science, University of Bergen and at Department of Heart Disease, Haukeland University Hospital. The group is chaired by Professor Eva Gerdts. Principal investigators include Professor Mai Tone Lønnebakken and Professor Knut Matre. In addition, there are two post-doctoral fellows, seven PhD fellows, one student in the Medial Student Research Programme and several master students in the group. The group uses echocardiography as a main method in clinical and experimental research, in addition to vascular ultrasound, applanation tonometry, ambulatory blood pressure monitoring and coronary computed tomography angiography. The main fields of interest are hypertensive heart disease and sex differences in cardiovascular disease. The group has extensive international and national collaboration, including NORHEART – the Norwegian PhD School of Heart Research. The Medical Student Research Programme at The Faculty of Medicine in the University of Bergen provides medical students the possibility to engage in research as a part of their education. Study 1 in this thesis was completed as a part of the Medical Student Research Programme.

A collaboration with the MTA-SE Cardiovascular Imaging Research Group at the Heart and Vascular Centre of Semmelweis University in Budapest, Hungary chaired by Assistant Professor Pál Maurovich-Horvat, MD, PhD was established during the work with study 3 in this thesis. The research group is a multidisciplinary team including cardiologist, radiologist, computer scientist and PhD-students. Their focus is to improve cardiovascular risk assessment, and the group is world-leading in the use of quantitative CCTA in research.

3. Acknowledgements

I would like to thank all the participants who accepted the invitation to participate in the studies this thesis is based on. Hopefully, the knowledge gained from this thesis will contribute to reduce the burden of ischemic heart disease in the years to come.

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Last, but not least, I would like to thank my family. I will always be grateful for the unconditional love and encouragement from my parents, Hilde and Jens. I dedicate this thesis to you. My sister and brother, Ragnhild and Harald, you inspire me to work hard and to have fun. To the rest of my family and family-in-law, thank you. I would like to thank my loving husband, Torstein, for making me laugh every day and for making me dinner most days. I am thankful for your everlasting encouragement and your belief in me. We do make a great team. Finally, thank you to our boy, Jens, for making my heart melt and for reminding me that miracles do happen.

Ingeborg Eskerud
Bergen, February 2020

4. Abstract

Background: The underlying mechanisms causing myocardial ischemia in non-obstructive coronary artery disease (CAD) are incompletely understood. We tested whether the total coronary artery plaque burden, coronary tortuosity and left ventricular hypertrophy were independently associated with myocardial ischemia.

Material and methods: Study 1 included 108 patients with non-ST-elevation myocardial infarction (NSTEMI), and coronary artery plaque burden and tortuosity were assessed by quantitative invasive coronary angiography. Study 2 included 132 symptomatic patients with non-obstructive CAD by coronary computed tomography angiography (CCTA), and left ventricular hypertrophy was determined by echocardiography. In study 3, coronary artery plaque burden was assessed by quantitative CCTA in 125 symptomatic patients with non-obstructive CAD. Myocardial ischemia was determined using myocardial contrast echocardiography at rest in study 1 and during pharmacological stress in study 2 and 3.

Results: In study 1, coronary artery plaque burden was associated with severe myocardial ischemia independent of angiographic stenosis severity and cardiovascular risk factors. No association was found between coronary artery tortuosity and ischemia. In study 2, left ventricular hypertrophy was associated with myocardial ischemia, independent of cardiovascular risk factors and coronary calcium score. In study 3, coronary artery plaque burden estimated by CCTA was associated with myocardial ischemia, independent of left ventricular mass index, coronary calcium score and cardiovascular risk factors.

Conclusion: Coronary artery plaque burden was independently associated with myocardial ischemia both in NSTEMI and in symptomatic patients with non-obstructive CAD. Left ventricular hypertrophy was independently associated with myocardial ischemia in patients with non-obstructive CAD. These results suggest that the coronary plaque burden and left ventricular hypertrophy may contribute to myocardial ischemia independent of CAD severity.

5. List of Publications

I. Eskerud I, Gerdts E, Nordrehaug JE, Lønnebakken MT. Global Coronary Artery Plaque Area is Associated with Myocardial Hypoperfusion in Women with Non-ST Elevation Myocardial Infarction. *Journal of Women's Health.* 2015;24(5):367-73.

II. Eskerud I, Gerdts E, Larsen TH, Lønnebakken MT. Left Ventricular Hypertrophy Contributes to Myocardial Ischemia in Non-Obstructive Coronary Artery Disease (The MicroCAD study). *International Journal of Cardiology.* 2019;286:1-6.

III. Eskerud I, Gerdts E, Larsen TH, Simon J, Maurovich-Horvat P, Lønnebakken MT. Total Coronary Atherosclerotic Plaque Burden is Associated with Myocardial Ischemia in Non-obstructive Coronary Artery Disease. Submitted to *European Heart Journal – Cardiovascular Imaging.*

6. Introduction

Ischemic heart disease is a leading cause of death of women and men in the world (1). Non-obstructive coronary artery disease (CAD) has traditionally been regarded as a benign condition, unlikely to cause myocardial ischemia. However, patients with non-obstructive CAD (angiographic coronary stenosis diameter reduction <50%) have increased risk of myocardial infarction (2) and death (3). Myocardial ischemia has also been demonstrated in patients with non-obstructive CAD and this is related to impaired prognosis (4-7). Non-obstructive CAD is two-fold more common in women than in men with non-ST-elevation myocardial infarction (NSTEMI) (8). Further, non-obstructive CAD or normal coronary arteries is found in the majority of patients undergoing coronary computed tomography angiography (CCTA) due to suspected ischemic heart disease (9). Myocardial ischemia results from a mismatch between the oxygen supply and the oxygen demand of the myocardium (10). The underlying mechanisms of myocardial ischemia in non-obstructive CAD are not fully understood (11, 12). Consequently, the management of non-obstructive CAD remains a puzzle for clinical practice as there is a lack of evidence-based treatment.

In order to obtain personalized treatment and improve outcome in non-obstructive CAD, it is of the utmost importance to identify the underlying causes of myocardial ischemia (11, 13). It is likely that several mechanisms that may lower the oxygen supply or increase the oxygen demand contribute to myocardial ischemia in non-obstructive CAD (11, 14-16). Coronary artery tortuosity is known as twist and bends of the coronary arteries and has been suggested to reduce perfusion pressure (17-20). In addition, the coronary atherosclerotic plaque burden, reflecting the extent of atherosclerosis, has been associated with myocardial ischemia in non-obstructive CAD (21). Left ventricular hypertrophy, which is a hallmark of hypertension-mediated organ damage, leads to increased myocardial oxygen demand and may lower the threshold for occurrence of myocardial ischemia (22, 23).

This thesis explored the association of coronary artery tortuosity, coronary artery plaque burden and left ventricular hypertrophy with myocardial ischemia in

patients with NSTEMI and in symptomatic patients with non-obstructive CAD by CCTA.

6.1 Non-obstructive coronary artery disease

In spite of the decline in mortality rates during the past 50 years, ischemic heart disease remains a major cause of death worldwide in both women and men (1). Ischemic heart disease is characterized by an imbalance between the amount of oxygen delivered to the myocardium and the myocardial oxygen demand. Ischemic heart disease is often caused by CAD, which is characterized by plaque formation through a complex interaction of intimal inflammation, necrosis, fibrosis, and calcification (24, 25). The development of CAD is closely linked with cardiovascular risk factors, such as age, sex, hypertension, diabetes mellitus, smoking, cholesterol level and obesity, although the exact etiology is complex and multifactorial (24, 25). CAD is a chronic, progressive condition that may remain asymptomatic, or manifest as an acute or chronic coronary syndrome (26-28). CAD is categorized as obstructive or non-obstructive according to the degree of luminal stenosis seen in invasive coronary angiography or CCTA (Figure 1).

Figure 1. Schematic figure of visual assessment of normal coronary artery, non-obstructive and obstructive coronary artery disease

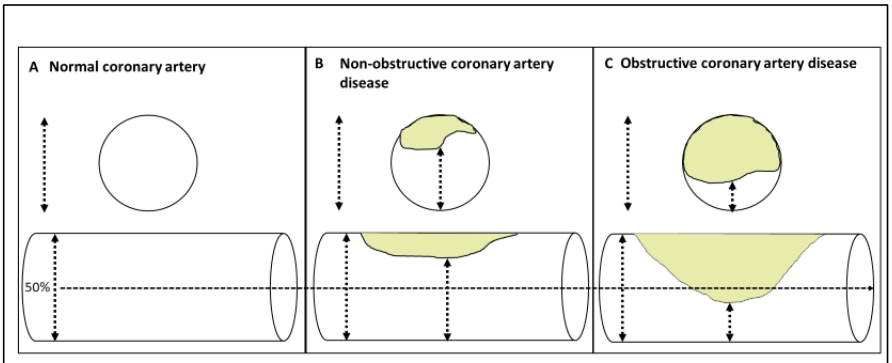


Figure 1. Coronary artery stenosis severity is assessed according to lumen diameter reduction compared with a normal proximal segment. Normal coronary artery without lumen reduction (panel A), non-obstructive coronary artery disease with lumen reduction <50% (panel B) and obstructive coronary artery disease with lumen reduction ≥50% (panel C).

Obstructive CAD is defined when plaque-associated arterial lumen diameter reduction ≥ 50% compared with a healthy proximal segment of the coronary artery is found, while non-obstructive CAD is considered present if the plaque causes < 50% arterial lumen diameter reduction (Figure 1). Ever since the seminal animal studies of Gould and Lipscomb during the 1970s showed that the blood supply to the myocardium was reduced during exercise when there was an obstruction in the coronary artery (29, 30), the clinical management of patients with suspected acute or chronic ischemic heart disease has centered on detection and treatment of obstructive CAD (26-28, 31, 32). Stenoses with lumen diameter reduction < 50% compared with a healthy proximal segment were for a long time regarded as "non-significant" and thought to be unlikely to cause myocardial ischemia. Accordingly, patients with non-obstructive CAD were erroneously considered as free from ischemic heart disease. However, this paradigm fails to explain that patients with non-obstructive CAD have an impaired cardiovascular prognosis (33, 34) and may have objective evidence of myocardial ischemia (11, 21, 35).

6.2 Clinical presentation of non-obstructive coronary artery disease

Non-obstructive CAD is found in both acute and chronic coronary syndromes (36). Acute and chronic coronary syndromes are umbrella terms to describe patients presenting with acute or chronic chest pain of suspected ischemic origin (26-28). In acute coronary syndrome, electrocardiography (ECG) and troponin changes enable categorization in NSTEMI, ST-elevation myocardial infarction (STEMI) and unstable angina, given that other causes of chest pain are excluded (Figure 2) (26, 27). In patients with acute myocardial infarction, non-obstructive CAD is found in about 1 of 10 patients (8, 36). In order to address this common clinical presentation, the clinical diagnosis "myocardial infarction with non-obstructive coronary arteries" (MINOCA) was introduced in 2016 (37) (Figure 2). For this diagnosis, three criteria must be fulfilled, namely myocardial infarction, non-obstructive CAD by coronary angiography (stenosis <50%) and no clinically overt specific cause for the acute presentation (37). MINOCA is particularly more common in women than in men, and

occurs both in NSTEMI and STEMI (8, 38-40). The prognosis of MINOCA has been somewhat inconsistently reported, but it is not benign (40-42). In a Swedish registry study including 9136 patients with MINOCA, 13% died during 4.1 years follow-up and 24% experienced a new major adverse cardiac event (41). Further, it has been demonstrated that patients with MINOCA had similar risk of death and repeated myocardial infarction as subjects with myocardial infarction with obstructive CAD (42). Moreover, cardiovascular risk factors and medical treatment may modify the prognosis (39, 41, 42). However, the underlying pathophysiological mechanisms of MINOCA are still incompletely understood, reflected in the lack of evidence-based treatment recommendations (37).

Figure 2. Schematic presentation of ischemic heart disease with non-obstructive coronary artery disease

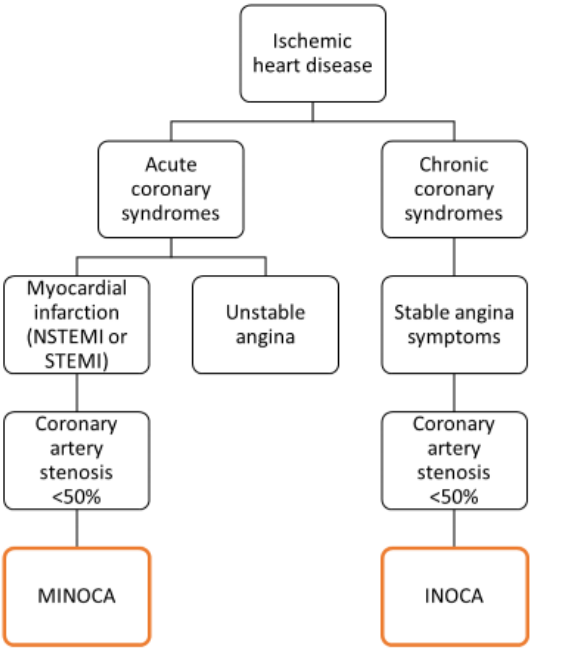


Figure 2. NSTEMI, non-ST elevation myocardial infarction; STEMI, ST-elevation myocardial infarction, MINOCA; myocardial infarction with non-obstructive coronary arteries, INOCA; ischemia with no obstructive coronary arteries

A common clinical scenario in chronic coronary syndromes is a patient presenting with “stable” symptoms of myocardial ischemia, where CAD is suspected of causing ischemic heart disease. The classic symptoms are retrosternal chest pain or dyspnoea that is precipitated by physical exercise. The symptoms typically disappear within minutes after abating exercise. In such patients, non-obstructive CAD is found in 30-45% in recent CCTA studies, while normal coronary arteries are found in 28-36% (43-45). As CCTA is now recommended as an initial diagnostic test in symptomatic patients with low to intermediate pre-test probability of CAD, the number of patients diagnosed with non-obstructive CAD is expected to increase (28, 32). However, CCTA and coronary angiography provide only the anatomical evaluation of stenosis severity. Additional functional testing is therefore necessary to determine whether myocardial ischemia is present.

The term ischemia and no obstructive coronary artery disease (INOCA) has been suggested to describe patients with the triad of symptoms of ischemic heart disease, objective evidence of myocardial ischemia at rest or stress, and absence of obstructive CAD (11) (Figure 2). However, this term is currently not implemented as a clinical diagnosis by the current guidelines for chronic coronary syndrome (28). Symptomatic patients with non-obstructive CAD have an impaired prognosis compared with subjects with normal coronary arteries (4, 33, 36, 45, 46). For instance, during ten years follow-up of patients with suspected CAD undergoing CCTA, the risk of myocardial infarction or cardiac death was seven times higher in patients with non-obstructive CAD compared to patients with normal coronary arteries, after adjusting for cardiovascular risk factors (45). Further, non-obstructive CAD has been associated with increased cardiovascular death, risk of myocardial infarction and repeated hospitalization (4, 33, 36, 45). Importantly, patients with non-obstructive CAD have reduced quality of life, possibly reflecting the current uncertainty in clinical management and lack of evidence-based care provided to these patients (47).

6.3 Myocardial ischemia in non-obstructive coronary artery disease

Presence of myocardial ischemia has been shown to predict adverse prognosis in patients with non-obstructive CAD (4-7), but the underlying mechanisms of ischemia are not fully understood (11, 37, 48). Thus, in order to improve the prognosis of patients with non-obstructive CAD, there is a need to further understand the underlying mechanisms of myocardial ischemia. Myocardial ischemia occurs when there is an imbalance between the amount of oxygen supplied to the myocardium and the myocardial oxygen demand (Figure 3).

Figure 3. Myocardial ischemia resulting from a mismatch between oxygen supply and demand

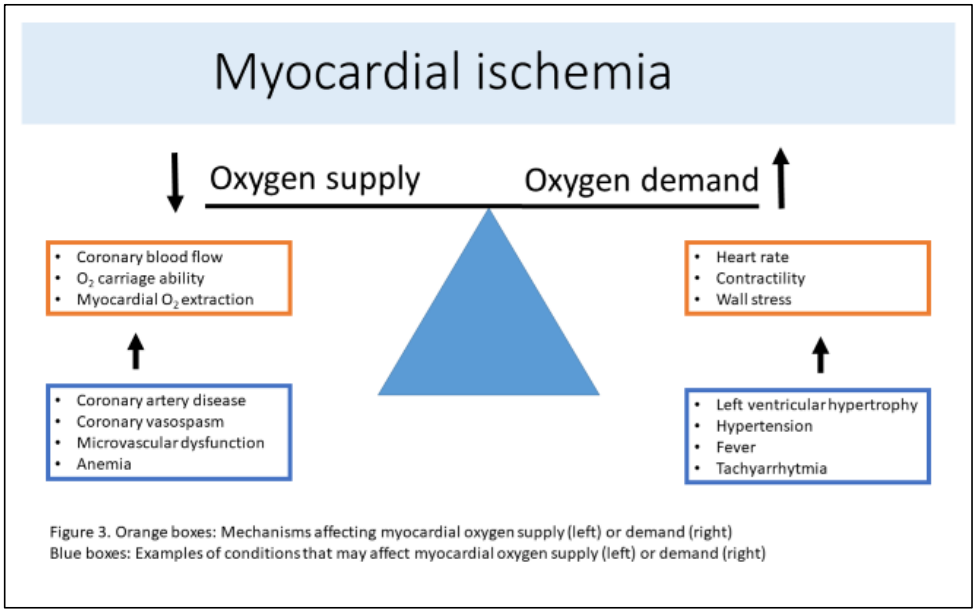


Figure 3. Orange boxes: Mechanisms affecting myocardial oxygen supply (left) or demand (right)
Blue boxes: Examples of conditions that may affect myocardial oxygen supply (left) or demand (right)

Myocardial oxygen supply depends on the oxygen carriage ability of the blood, coronary artery blood flow, and myocardial oxygen extraction, while the myocardial oxygen demand is dependent on heart rate, contractility, and left ventricular wall stress (10). Detection of myocardial ischemia is a cornerstone in the clinical management of patients with suspected acute or chronic ischemic heart disease, and several diagnostic imaging modalities are recommended, including contrast-enhanced

echocardiography (26-28, 32, 49).

Myocardial infarction occurs when acute myocardial ischemia leads to necrosis of the myocardial cells (50). Following the universal definitions, myocardial infarction can be categorized according to the underlying pathophysiological mechanisms (50). Acute myocardial ischemia is most often caused by a sudden decrease in coronary blood flow (14). The predominant cause of decreased coronary blood flow is coronary artery luminal occlusion due to thrombosis caused by plaque rupture or erosion (25, 51). Interestingly, the culprit plaque is most often non-obstructive (25, 51, 52). A mismatch between myocardial oxygen supply and demand may also cause myocardial infarction (Figure 3). Other mechanisms that may contribute to an acute reduction in oxygen supply include coronary vasospasm, coronary dissection and microvascular spasm (53, 54). On the other hand, acute increased oxygen demand may result from a variety of other conditions, including tachyarrhythmias and hypertension (Figure 3) (55). Several of these mechanisms may contribute to MINOCA. However, there is still a knowledge gap regarding the underlying mechanisms of MINOCA, as the diagnostic work-up does not always provide an explanation of the myocardial infarction (12, 37).

Chronic myocardial ischemia occurs when there is a chronic mismatch between the oxygen supply and demand in the myocardium, and manifests as a chronic coronary syndrome (28). Myocardial ischemia may occur only when the myocardial oxygen demand is increased, such as during exercise or psychological stress. As the oxygen extraction is near maximum at rest, coronary artery blood flow must increase in response to increased oxygen demand. This increase in coronary blood flow may be limited due to obstructive CAD, resulting in chronic myocardial ischemia (14). Interestingly, it is well established that there may be a mismatch between the visual and functional significance of CAD by invasive coronary angiography (56). The hemodynamic impact of a coronary artery stenosis can be assessed with invasive measurements during coronary angiography. Fractional flow reserve determines the ratio between the blood pressure distal to a coronary stenosis and the pressure in the aorta during maximum hyperaemia, and is considered to induce myocardial ischemia when ≤ 0.80 (56). Importantly, abnormal fractional flow

reserve has been found in non-obstructive CAD (56, 57).

In addition to CAD, there are several mechanisms that may lead to a chronic imbalance between the oxygen supply and demand (11, 53, 58). For instance, microvascular dysfunction may underlie myocardial ischemia in patients with non-obstructive CAD and predict adverse outcome (58, 59). The coronary microvasculature normally contributes to maintain the balance between oxygen supply and demand (60). For instance, during exercise the coronary arterioles will dilate to enable the necessary increase in myocardial blood flow. Several conditions may lead to microvascular dysfunction through structural or functional changes, including hypertension, left ventricular hypertrophy and diabetes (60). Microvascular dysfunction may contribute to myocardial ischemia through disturbing the mechanisms that normally ensure the balance between myocardial oxygen supply and demand. Moreover, vasospasms in the coronary arteries or in the microvasculature may reduce oxygen supply and contribute to INOCA (11, 58). In addition, an increased myocardial oxygen demand, caused by left ventricular hypertrophy, may lower the threshold of development of chronic myocardial ischemia (22) (Figure 3).

Although several mechanisms that may induce acute or chronic ischemia independent of CAD have been uncovered, there are still knowledge gaps regarding the underlying causes of ischemia in patients with non-obstructive CAD. For instance, whether coronary artery tortuosity (61), the total coronary artery plaque burden (21), and left ventricular hypertrophy impact myocardial ischemia in symptomatic patients with non-obstructive CAD is not fully explored.

6.3.1 Coronary artery plaque burden

The coronary artery plaque burden reflects the extent of coronary atherosclerosis. It can be estimated from visual assessment or quantified from coronary angiography or CCTA (62). It has been reported that the extent of non-obstructive CAD, taken as the number of coronary artery segments or number of coronary arteries with non-obstructive CAD by CCTA, predicts impaired prognosis (63-66). Further, it has been demonstrated that higher coronary calcium score, which reflects the total burden of calcified coronary atherosclerosis, is associated with presence of myocardial ischemia in patients with suspected CAD (67). However, coronary calcium score does not

provide a quantification of the non-calcified atherosclerotic plaque. Non-calcified plaque has been associated with myocardial ischemia independent of stenosis severity in patients with suspected CAD (68). In addition, non-calcified plaque has been suggested as more likely to cause myocardial ischemia than calcified plaque (62). Quantitative CCTA provides quantification of both calcified and non-calcified plaque, thus more accurately reflecting the true anatomical atherosclerotic burden (62, 69, 70). However, few studies have investigated the association between the total plaque burden with myocardial ischemia in NSTEMI, or the impact of the total plaque burden on chronic ischemic heart disease in patients with non-obstructive CAD (21).

6.3.2 Coronary artery tortuosity

Coronary artery tortuosity is considered present when consecutive curvatures of the coronary arteries are found by coronary angiography (71, 72). Coronary artery tortuosity is in general considered an incidental benign finding, and is more common in women than in men (71-73). Coronary artery tortuosity has been associated with hypertension and aging, and has been suggested as a contributor to myocardial ischemia (71, 72). In fact, numerical studies have shown that coronary tortuosity may negatively impact myocardial perfusion (17-20). However, whether coronary tortuosity affects myocardial perfusion in humans is less explored (61).

6.3.3 Left ventricular hypertrophy

Left ventricular hypertrophy is characterized by abnormal growth of both the cardiomyocytes and the interstitial cells in the myocardium of the left ventricle (74). Typically, the left ventricle remodels in response to chronic changes in pressure and volume load, in addition to neurohumoral changes, including activation of the sympathetic nervous system and the renin-angiotensin-aldosterone system as seen in hypertension, diabetes, and obesity (75-78). Left ventricular hypertrophy can be detected by echocardiography (79). Importantly, left ventricular hypertrophy is a major predictor of increased cardiovascular morbidity and mortality in hypertensive subjects as well as in the general population (80-84). Left ventricular hypertrophy may contribute to myocardial ischemia through an increase in myocardial oxygen

demand caused by the higher myocardial mass (22). In addition, left ventricular hypertrophy may induce microvascular dysfunction (60). Left ventricular hypertrophy has been associated with larger infarction size in patients with STEMI (85), and with myocardial ischemia in a hypertensive patient with suspected ischemic heart disease and normal coronary angiography (35). However, the association of left ventricular hypertrophy with myocardial ischemia in symptomatic patients with non-obstructive CAD has not been much studied.

7. Hypothesis and study aims

1.1 Hypothesis

We hypothesized that coronary artery plaque burden, coronary artery tortuosity, and left ventricular hypertrophy were associated with myocardial ischemia independent of cardiovascular risk factors in patients with NSTEMI or symptomatic non-obstructive CAD.

1.2 Specific aims

- Explore the association of coronary artery plaque burden and tortuosity with myocardial ischemia in NSTEMI patients.
- Assess the association of left ventricular hypertrophy with myocardial ischemia in symptomatic patients with non-obstructive CAD.
- Explore the association of coronary artery plaque burden with myocardial ischemia in symptomatic patients with non-obstructive CAD.

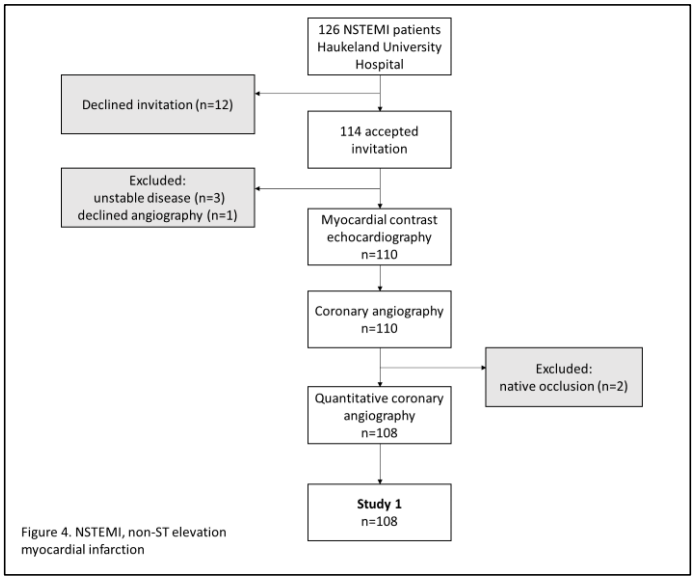
8. Materials and methods

8.1 Study design and patient population

8.1.1 Study 1

Study 1 is a post-hoc analysis based on a cross-sectional study that was conducted to test the association of myocardial ischemia identified by resting contrast echocardiography with invasive coronary angiographic disease severity in patients with NSTEMI (86). The patients in study 1 were recruited from Department of Heart Disease, Haukeland University Hospital from March through December 2008. Inclusion criterion were NSTEMI, defined in accordance with the 2007 European guidelines, clinically scheduled coronary angiography and residency in the hospital catchment area (87). Exclusion criteria were hemodynamic instability, development of ST-elevation in the electrocardiogram, mechanic valve prostheses, severe pulmonary disease or contradiction to coronary angiography. A total of 126 consecutive patients hospitalized with NSTEMI and scheduled for coronary angiography within 72 hours after admittance were invited to participate (Figure 4).

Figure 4. Flow chart of patients included in study 1



In total, 110 patients signed informed consent and underwent myocardial contrast echocardiography at rest before scheduled coronary angiography. For study 1, two patients were excluded from the analysis in because all native coronary arteries were occluded, leaving 108 patients eligible (Figure 4).

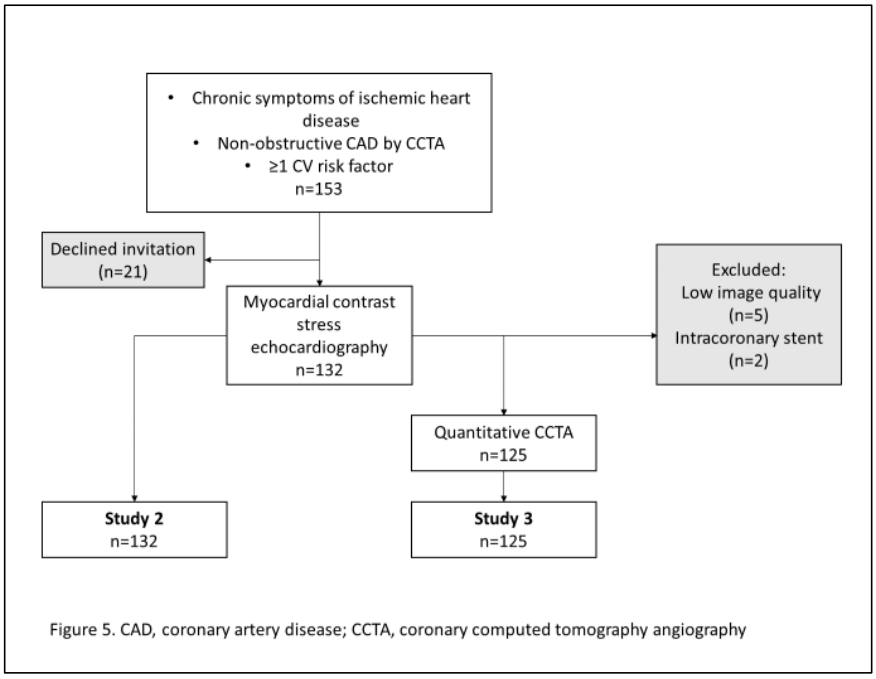
8.1.2 Study 2

Study 2 was a prospectively planned analysis. The participants in study 2 are from The Myocardial Ischemia in Non-obstructive Coronary Artery Disease (MicroCAD) study. The cross-sectional MicroCAD study was conducted to assess the presence of myocardial ischemia by myocardial contrast stress echocardiography and evaluate potential clinical markers of ischemia in symptomatic patients with non-obstructive CAD by CCTA. The participants were prospectively included from symptomatic patients who were referred to CCTA at the Department of Heart Disease, Haukeland University Hospital, Bergen, Norway after a clinical evaluation by cardiologists. The inclusion period was from May 2013 until November 2014.

Inclusion criteria were non-obstructive CAD, defined as at least one coronary artery stenosis with lumen diameter reduction 1-49%, age >30 years, chronic coronary syndrome, defined as exercise-induced chest pain and/or dyspnoea for ≥ 6 months, and at least one cardiovascular risk factor (hypertension, hypercholesterolemia, diabetes, smoking or family history of premature CAD).

Exclusion criteria clinically unstable angina pectoris, severe valve disease, mechanical valve prosthesis, arrhythmias, severe pulmonary disease, known allergies to ultrasound contrast or pregnancy. The sample size of 132 patients was calculated in order to have 80% power with statistical level of 0.05 to find 50% differences in prevalence of cardiovascular risk factors, including left ventricular hypertrophy, between patients with and without myocardial ischemia, including an anticipated dropout rate of 5%. In total 153 patients were invited to participate after undergoing CCTA, and 132 were included in study 2 (Figure 5).

Figure 5. Flow chart of participants included in study 2 and 3



8.1.3 Study 3

Study 3 is a post-hoc analysis from the MicroCAD study. We excluded two participants with intracoronary stents, and five participants were excluded because of insufficient CCTA image quality for quantitative analysis, leaving 125 patients eligible for study 3 (Figure 5).

8.2 Cardiac imaging

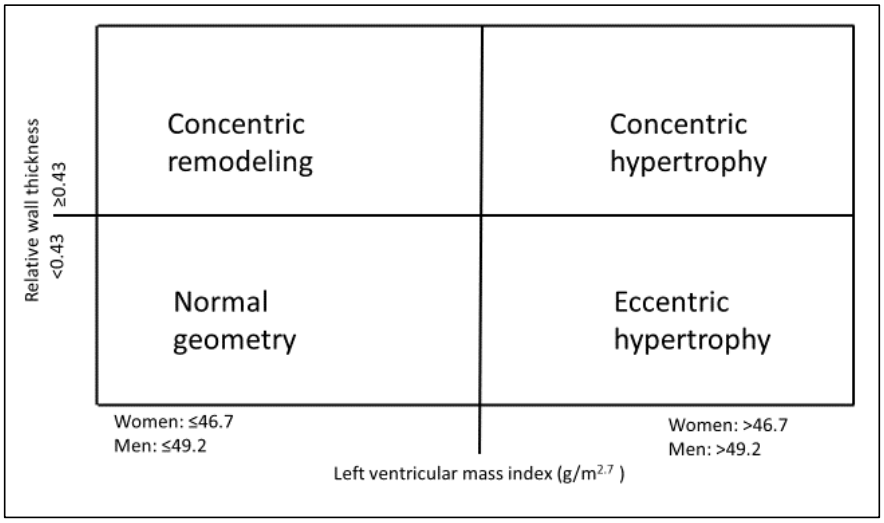
8.2.1 Transthoracic echocardiography

All patients were examined with transthoracic echocardiography following a standardized protocol using Siemens Acuson Sequoia C512 ultrasound scanner (Siemens, Mountain View, CA, USA) in study 1 and by using a Phillips iE33

ultrasound scanner (Philips Healthcare, Best, the Netherlands) in study 2 and 3. Echocardiographic chamber dimensions, left ventricular structure and function were assessed as recommended by the contemporary European guidelines at the time of study inclusion (88, 89). All echocardiographic images were digitally stored and transferred to the Echocardiography Core Laboratory at the University of Bergen. All images were analyzed using an offline digital workstation (TomTec Imaging Systems GmbH, Unterschleissheim, Germany) blinded to clinical and demographic data by the same experienced reader (MTL).

Left ventricular dimensions were measured in the parasternal long-axis view. Left ventricular volumes and ejection fraction were calculated by Simpson's biplane method. Relative wall thickness was calculated as posterior wall thickness/left ventricular internal radius ratio, and considered increased if ≥ 0.43 (89). Left ventricular mass was calculated by Devereux's necropsy validated equation and indexed for height$^{2.7}$(89-91). Left ventricular hypertrophy was considered present if left ventricular mass index exceeded 46.7 g/m$^{2.7}$ in women and 49.2 m$^{2.7}$ in men (81, 92). Left ventricular geometry was classified into four patterns by combining relative wall thickness and left ventricular mass index as recommended by current guidelines (89) (Figure 6).

Figure 6. Patterns of left ventricular geometry



8.2.2 Myocardial contrast echocardiography

Myocardial contrast echocardiography uses contrast agents to evaluate myocardial perfusion (49). The contrast agents consist of gas-filled microbubbles of the same size as the red blood cells, and the microbubbles therefore remain within the vascular bed. At low-frequency ultrasound, the microbubbles oscillate, allowing visualization, while a flash of high-frequency ultrasound will destroy the microbubbles. The rate of microbubble replenishment after destruction reflects the myocardial perfusion. At rest, the contrast fills within five heart-beats after flash when myocardial perfusion is normal. If the contrast replenishment occurs later than five heart-beats, this reflects hypoperfusion, which is indicative of myocardial ischemia at rest. During exercise or pharmacological stress, myocardial blood flow increases in order to meet the increased oxygen demand of the left ventricle. Thus, during stress, it is expected that the microvasculature is re-filled faster, within two heart-beats after microbubble destruction. Reduced myocardial perfusion at peak stress is indicative of stress-induced myocardial ischemia. Myocardial contrast echocardiography was performed by the same experienced operator (MTL) in all studies.

In study 1, myocardial contrast echocardiography was performed at rest before the scheduled coronary angiography. Real-time, low-mechanical index and destruction-replenishment myocardial contrast echocardiography was performed using Cadance Contrast Pulse Sequencing technology (Acuson Sequoia C512 echocardiograph, Siemens, Mountain View, CA, USA) (93). All participants were given an intravenous bolus injection of 0.3 ml perflutren lipid microsphere ultrasound contrast (Luminity ®, Lantheus Medical Imaging, North Billerica, MA, USA) before perfusion imaging. To ensure a stable contrast concentration, bolus dosages were given repeatedly if necessary. Myocardial perfusion was visually scored as normal (contrast replenishment within five heart-beats after flash) or ischemic (contrast replenishment occurring later than five heart-beats after flash) in each left ventricular segment using apical 2-, 3- and 4- chamber views and the 17-segment model of the

left ventricle (93). The extent of myocardial ischemia was taken as the number of left ventricular segments with ischemia. Severe myocardial ischemia was considered present when ≥ 6 left ventricular segments had ischemia.

In study 2 and 3, myocardial contrast stress echocardiography was performed in all participants after CCTA. The median time from CCTA to myocardial contrast echocardiography was 133 days (interquartile range 98-188 days). All participants were examined with real-time, low-mechanical index imaging and destruction replenishment myocardial contrast stress echocardiography following European guidelines (93). Ultrasound contrast (SonoVue, Bracco, Milan, Italy) was given intravenously. First, a 1 ml bolus injection was given, followed by 1 ml/h infusion using a rotating infusion pump (VueJet, Bracco, Milan, Italy). Myocardial perfusion was visually scored as normal or ischemic in all 17-segments of the left ventricle, using apical 2-, 3- and 4-chamber views at rest and at peak dobutamine stress, defined as 85% of maximum age-predicted heart rate (200 – age) (93). Stress-induced myocardial ischemia was considered present when contrast replenishment was delayed at peak stress (contrast replenishment occurred after two heart-beats after flash) in any left ventricular segment (Figure 7). The extent of myocardial ischemia was taken as the number of left ventricular segments with delayed contrast replenishment at peak stress.

Figure 7. Myocardial contrast echocardiography

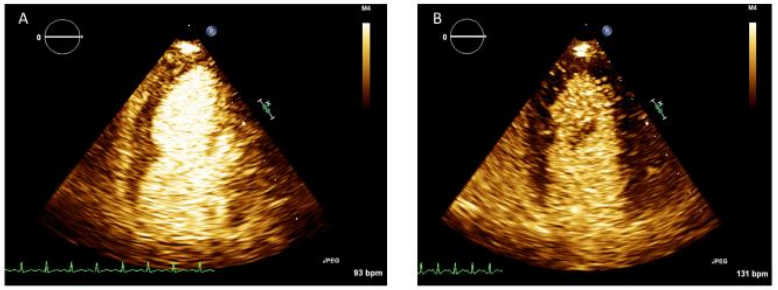
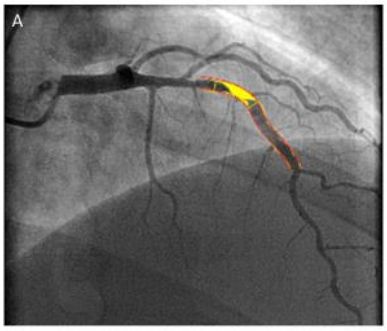


Figure 7. Panel A demonstrates normal myocardial perfusion at rest. Panel B shows delayed contrast enhancement, indicating myocardial ischemia, at peak stress during myocardial contrast stress echocardiography. Figure courtesy: Mai Tone Lønnebakken.

8.2.3 Quantitative coronary angiography

In study 1, quantitative coronary angiography analysis was performed offline by a single reader (IE) blinded to clinical and echocardiographic data using dedicated, validated software (QAngio XA 7.1, MEDIS Medical Imaging Systems, Leiden, the Netherlands) (94). The coronary arteries were divided into 17 segments, following the modified American Heart Association Model (95). The tip of the catheter was used for calibration. Plaque area and stenosis severity defined as lumen diameter reduction were determined in all coronary segments with lumen diameter >1.5 mm (Figure 8).

Figure 8. Angiographic quantification of coronary artery plaque burden and tortuosity



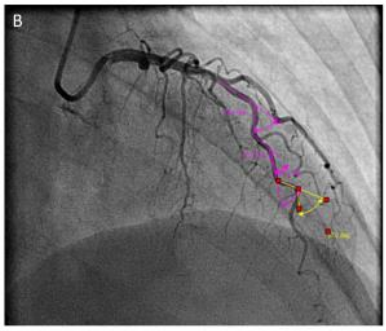


Figure 8. Quantification of plaque area in the left anterior descending artery (Panel A). Assessment of coronary tortuosity in the left anterior descending artery (Panel B).

The total plaque burden was defined as the global coronary plaque area. Global coronary artery plaque area was calculated as the sum of plaque areas in all coronary artery segments in the individual patient. A lumen diameter reduction of ≥ 50% compared with a normal proximal segment was considered a significant stenosis. Coronary artery tortuosity was assessed in the three main arteries in standardized views. The left anterior descending artery was assessed in the right anterior oblique view with cranial angulation, the left circumflex artery in the left anterior oblique view with caudal angulation and the right coronary artery in the right anterior oblique

view (71). Coronary artery tortuosity was regarded present if ≥ 3 curves >45° were found in the same artery during systole and diastole (Figure 8) (71).

8.2.4 Coronary computed tomography angiography

Coronary computed tomography angiography acquisition

CCTA images were obtained by a 2x128-slice dual source computed tomography (CT) scanner (Somatom Definition Flash, Siemens, Germany) with ECG-gated acquisitions following recommended guidelines (96). Patients with heart rate > 60 beats per minute were given metoprolol intravenously (1 mg/ml, maximum 20 mg) until heart rate was ≤60 beats per minute. A non-contrast enhanced scan was first performed to determine coronary calcium score following the Agatston method. The patients then received non-ionic contrast given as intravenous infusion, in total 80-115 ml iomeprol 400 mg I/ml (Iomeron®, Bracco, Milan, Italy) according to body weight. All patients received 0.4 mg nitroglycerin sublingual prior to CCTA in order to increase image quality. Experienced readers analyzed the images for detection of coronary artery stenosis using a modified 20-segment American Heart Association model (95, 97). Non-obstructive CAD was defined as presence of ≥ one stenosis with lumen diameter reduction 1-49% in any coronary artery segment.

Quantitative coronary plaque analysis

CCTA images were anonymized before quantitative coronary plaque analysis by a single reader (IE) blinded to clinical and echocardiographic data. The coronary segments were defined according to the 17-segment model of the Society of Cardiovascular Computed Tomography (97). Quantitative plaque analysis was performed in the left main stem, the left anterior descending coronary artery, the left circumflex artery and the right coronary artery with lumen diameter >2.0 mm using a validated software tool (QAngio CT Research Edition version 3.1.4.2, Medis medical imaging systems, Leiden, The Netherlands) (Figure 9) (69, 70). The outer and inner walls of the coronary arteries were detected automatically, and manually adjusted when needed. The total plaque burden was defined as the total plaque volume in the individual patient. The total plaque volume was calculated by subtracting the lumen volume from the outer vessel wall volume. Plaque composition was automatically

defined according to the radio density in Hounsfield units, with scan-specific thresholds adapted to lumen contrast intensity (98). Plaque composition was defined as low-attenuation, fibrous-fatty, fibrous or dense calcium (98). Non-calcified plaque volume was defined as the sum of low-attenuation, fibrous-fatty and fibrous plaque volumes. Segment involvement score was calculated as the total number of segments with plaque (range 0-17) (9).

Figure 9. Quantification of coronary artery plaque burden by coronary computed tomography angiography

Figure 9. Example of quantitative coronary computed tomography assessing the coronary artery plaque burden in the left anterior descending artery.

8.3 Ethics

All studies were performed in accordance with the 1975 Declaration of Helsinki and the Norwegian Health Research Act (99). The study protocols were approved by the Regional Committee for Medical and Health Research Ethics, with reference number 237.07 for study 1 and 2012/2167 for study 2 and 3. Study 1 is registered with

identifier NCT01122069 and study 2 and 3 with identifier NCT01853527 at www.clinicaltrials.gov. All participants gave written informed consent before study inclusion. In all studies, the recommendations for the conduct, reporting, editing, and publication of scholarly work in medical journals from the International Committee of Medical Journal Editors were followed (100). Inter-observer analysis in Study 3 was approved by the Data Protection Official at Haukeland University Hospital and by the Regional Committee for Medical and Health Research Ethics.

8.4 Cardiovascular risk factors

Blood pressure was measured in accordance with the European guidelines on management of hypertension which were current at the time of study inclusion (101, 102). In study 1, a manual sphygmomanometer was used, while automatic measurements with an Omron M4 apparatus (Omron Healthcare Co, Hoofddorp, the Netherlands) were taken in study 2 and 3. Three measurements of brachial blood pressure were taken in the seated position with one-minute intervals after five minutes rest. Office blood pressure was taken as the average of the last two measurements. Office hypertension was defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg (101, 102). In all studies, hypertension was considered present if the participant had history of hypertension, used antihypertensive medication or had office hypertension. Medical history, smoking habits and use of medication were self-reported in standardized questionnaires. In study 1, the results from blood tests were collected from the medical journals. In study 2 and 3, fasting blood samples were collected for analyses of serum lipid profile, hemoglobin A_{1c} (HbA_{1c}) and creatinine. Glomerular filtration rate was calculated using the Chronic Kidney Disease Epidemiology Collaboration formula (103). Hypercholesterolemia was defined as total cholesterol > 6.5 mmol/L or use of lipid-lowering treatment in the individual patient. Diabetes was defined as history of diabetes in study 1. In study 2 and 3, diabetes was defined as history of diabetes and/or $HbA_{1c} \geq 48$ mmol/mol (104).

8.5 Statistics

Statistical analyses were performed using Statistical Package for Social Sciences version 20.0- 25.0 (IBM Corporation, Armonk, NY, USA) and GraphPad Prism version 8.0.1 (GraphPad Software, San Diego, California, USA). Continuous variables with normal distribution were presented as mean ± standard deviation and non-normally distributed variables (calcium score, calcified plaque) as median and interquartile range. Categorical variables were presented as numbers and percentages.

In study 1, the participants were grouped according to sex. In study 2 and 3, the participants were grouped according to the presence of myocardial ischemia. The groups were compared using the independent sample t-test for continuous variables with normal distribution, Mann-Whitney U test for continuous variables with non-normal distribution, and Chi-square test for categorical variables.

Univariable associations were tested in univariable logistic and linear regression analyses. Variables were entered into the multivariable linear and logistic regression models, where variables with $p<0.10$ in univariable regression or important clinical value were selected. Collinearity tools were used in multivariable linear regression, and reported as variance inflation factor and tolerance in study 1. Results from logistic regression were reported as odds ratio (OR) with 95% confidence interval (CI). Results from linear regression were reported as standardized beta coefficient (β) for individual variables and multiple R^2 for multivariable models. Receiver operating characteristic curves were plotted to test the association of total plaque burden with severe myocardial ischemia in study 1 and presence of myocardial ischemia in study 3. Chi-square test of trends was used to compare frequency of myocardial ischemia across quartiles of different measurements of coronary artery plaque burden (total plaque volume, non-calcified plaque volume, calcified plaque volume, coronary calcium score) in study 3.

Intra- and inter-observer reliabilities were reported as intraclass correlation coefficient with 95% CI. In study 1, intra-observer reliability of plaque area measurements and myocardial perfusion assessment were calculated from angiographic and echocardiographic images of 11 randomly selected participants

analyzed twice by the same reader (IE for plaque area and MTL for myocardial perfusion). In study 3, intra-observer reliability of the total plaque volume was calculated from comparison of assessment of the total plaque burden analyzed twice by the same reader (IE) from 10 randomly selected participants. Inter-observer reliability was calculated from comparison of assessment of the total plaque volume by two independent readers (IE and JS) in 20 randomly selected participants.

9. Summary of results

9.1 Study 1

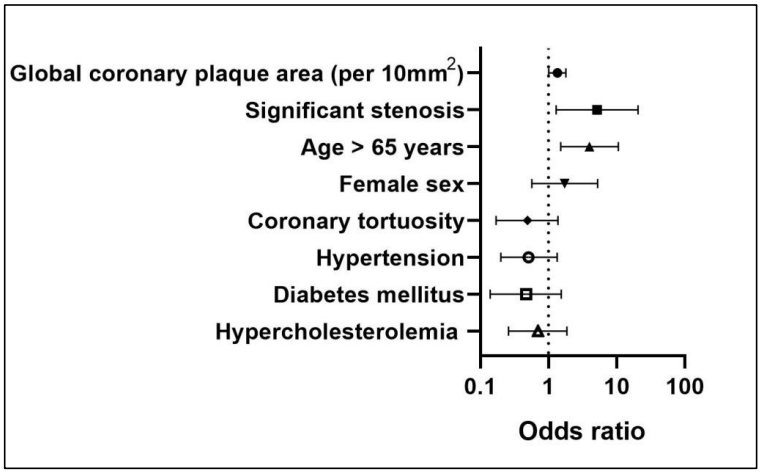
The aim of this study was to assess if global coronary artery plaque area and tortuosity were associated with myocardial ischemia in patients with NSTEMI. In the 108 patients with NSTEMI, 31% were women and the mean age was 67±12 years. The proportion of patients with age >65 years was higher in women (71% vs. 50%, p=0.045), while mean age and serum troponin T levels did not differ between women and men. Hypertension was found in 44% of patients, hypercholesterolemia in 49%, diabetes in 19%, and 28% were current smokers.

The extent of myocardial ischemia was similar in women and men, reflecting a comparable average myocardial infarction size in the left ventricle (6.9 ±3.7 vs. 7.2±3.4 left ventricular segments, p=0.747). In total 1252 segments (88% of visible segments) were used for assessment of coronary plaque area. Intra-observer reliability of global coronary artery plaque area measurements and myocardial perfusion was good, with intraclass correlation coefficient 0.86 (95% CI 0.75-0.91) and 0.95 (95% CI 0.90-0.98), respectively. Global coronary artery plaque area did not differ significantly between women and men (35±22 mm^2 vs. 43±21 mm^2, p=0.071), in spite of women having lower prevalence of significant stenosis (74% vs. 91%, p=0.021). Global coronary plaque area (per 10 mm^2) was associated with severity (OR 1.32, [95% CI 1.05-1.66], p=0.019) and extent of myocardial ischemia in univariable analysis (β 0.27, p=0.005). A 10 mm^2 higher plaque area was associated with presence of severe ischemia (OR 1.35, [95% CI 1.01-1.80], p=0.047) in multivariable analysis after adjusting for presence of significant stenosis and cardiovascular risk factors (Figure 10). In multivariable linear regression analysis, the association of larger global coronary artery plaque area with larger extent of ischemia was attenuated after adjusting for presence of significant stenosis and cardiovascular risk factors (β 0.18, p=0.057).

In total, 273 native main coronary arteries were visualized. Due to low image quality, 34 were excluded, leaving 239 (88%) included for analysis of coronary

tortuosity. Tortuosity was found in 82% of women and 61% of men (p=0.026). Coronary artery tortuosity was not associated with presence of severe myocardial ischemia in univariable or multivariable logistic regression analysis (OR 0.50, [95% CI 0.27-1.21], p=0.123 and OR 0.49, [95% CI 0.17-1.37], p=0.173, respectively). Tortuosity was not associated with extent of myocardial ischemia in univariable or multivariable linear regression analysis (β -0.16, p=0.094 and β -0.12, p=0.191, respectively)

Figure 10. Determinants of severe myocardial ischemia (≥6 left ventricular segments) in multivariable logistic regression analysis



9.2 Study 2

The aim of this study was to assess the association between left ventricular hypertrophy and myocardial ischemia in symptomatic patients with non-obstructive CAD by CCTA. In the total study population, mean age was 63±8 years, and 56% were female. The patients were divided in two groups according to presence or absence of myocardial ischemia. Myocardial ischemia was identified as presence of stress-induced myocardial ischemia in any left ventricular segment. Myocardial ischemia was found in 69 patients (52%). Hypertension was found in 81% of patients with myocardial ischemia and in 68% of those without (p=0.077). Obesity was found in 16% of patients with myocardial ischemia and in 32% of those without (p=0.032).

Diabetes was found in 13%, smoking in 16% and hypercholesterolemia in 48% of the total study population, and comparably in groups with and without myocardial ischemia. Left ventricular mass index was higher and left ventricular hypertrophy was more prevalent in patients with myocardial ischemia compared to patients without myocardial ischemia (Figure 11). The calcium score and segment involvement score were similar in the two groups.

Figure 11. Left ventricular mass index and presence of left ventricular hypertrophy in groups with and without myocardial ischemia

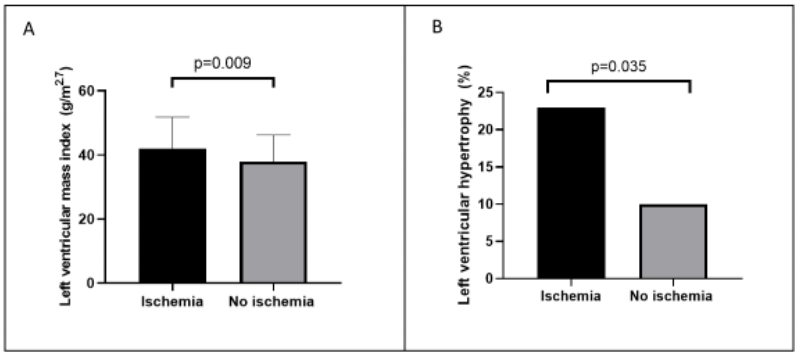


Figure 11. Panel A: Bar graph displaying left ventricular mass index (mean and standard deviation) in patients with and without myocardial ischemia. Panel B: Prevalence of left ventricular hypertrophy in patients with and without myocardial ischemia.

In multivariable logistic regression analysis, left ventricular hypertrophy was independently associated with myocardial ischemia (OR 3.19, [95% CI 1.04-9.76], p=0.043) after adjusting for age, hypertension, obesity, hypercholesterolemia, calcium score and segment involvement score. In univariable linear regression analyses, larger extent of myocardial ischemia was associated with presence of left ventricular hypertrophy (β 0.19, p=0.034), hypertension (β 0.20, p=0.021) and hypercholesterolemia (β 0.18, p=0.039). Left ventricular hypertrophy remained associated with larger extent of myocardial ischemia (β 0.23, p=0.010) after adjusting for age, hypertension, obesity, hypercholesterolemia, calcium score, and segment

involvement score in multivariable linear regression analysis (multiple $R^2 = 0.18$, p=0.001).

9.3 Study 3

The aim of this study was to assess the association between total coronary artery plaque burden by CCTA and myocardial ischemia in symptomatic patients with non-obstructive CAD. The mean age was 62±9 years in the study population, and 58% were women. The 125 participants were grouped according to presence or absence of myocardial ischemia. Myocardial ischemia was found in 66 participants. The groups with and without myocardial ischemia did not differ in age, prevalence of female sex, hypertension and diabetes (all p>0.05). The total plaque volume and non-calcified plaque volume were higher in participants with myocardial ischemia (Figure 12). Calcified plaque volume and coronary calcium score did not differ between the groups (both p>0.05).

Figure 12. Total coronary artery plaque volume and non-calcified plaque volume in patients with and without myocardial ischemia

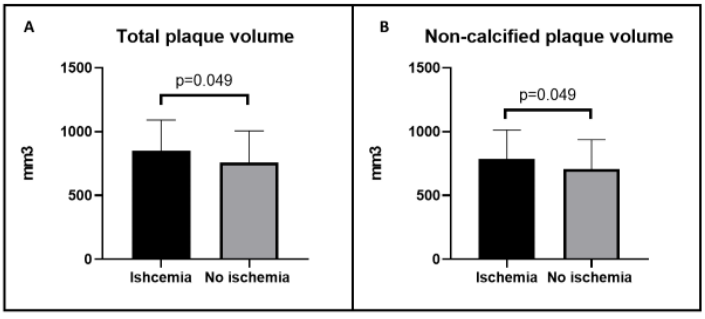


Figure 12. Bar graph displaying mean and standard deviation of total coronary artery plaque volume (Panel A) and the non-calcified plaque volume (Panel B) in groups with and without myocardial ischemia.

The prevalence of myocardial ischemia increased with increasing quartiles of total plaque volume and non-calcified plaque volume. No associations were found

between quartiles of calcified plaque, calcium score and prevalence of myocardial ischemia. Left ventricular mass index was associated with myocardial ischemia in univariable regression analysis (OR 1.06, [95% CI 1.02 – 1.11], p = 0.006), while no significant associations were found between age, female sex, hypertension, diabetes and myocardial ischemia (all p>0.05). A higher total plaque volume and total non-calcified plaque volume tended to be associated with presence of myocardial ischemia in univariable analyses ((OR 1.02, [95% CI 1.01 – 1.03]) and (OR 1.02, [95% CI 1.01 – 1.03]), respectively, both p=0.052). No significant associations between total calcified plaque volume, calcium score or segment involvement score with presence of myocardial ischemia were found in univariable analyses (all p>0.05).

In multivariable logistic regression analysis, 10 mm^3 increase in total plaque volume (OR 1.02, [95% CI 1.00 – 1.04], p = 0.044) and left ventricular mass index (OR 1.06, [95% CI 1.01 – 1.11], p = 0.016) were both independently associated with myocardial ischemia after adjusting for age, female sex, hypertension, diabetes and calcium score (all p>0.05). The association between non-calcified plaque volume and myocardial ischemia remained non-significant in a multivariable logistic regression analysis including the same covariables (OR 1.02, [95% CI 1.00 – 1.04], p = 0.054).

10. Discussion

The current PhD project studied the associations between coronary artery plaque burden and coronary tortuosity assessed by invasive coronary angiography with resting myocardial ischemia in NSTEMI, and the associations between left ventricular hypertrophy and coronary artery plaque burden with stress-induced myocardial ischemia in symptomatic patients with non-obstructive CAD. The results from this PhD project have added to current knowledge in several aspects. First, in NSTEMI patients, higher total coronary artery plaque area was associated with severe myocardial ischemia independent of presence of significant coronary artery stenosis, while coronary artery tortuosity did not impact myocardial perfusion. Second, in symptomatic patients with non-obstructive CAD, left ventricular hypertrophy was associated with presence of myocardial ischemia. Third, higher total coronary atherosclerotic plaque volume was associated with presence of myocardial ischemia, independent of left ventricular mass, in symptomatic patients with non-obstructive CAD. Taken together, our findings imply the importance of integrating structural and functional imaging of patients with ischemic heart disease.

10.1 Clinical importance of myocardial ischemia in non-obstructive coronary artery disease

Our key findings emphasize that anatomically non-obstructive CAD does not rule-out presence of myocardial ischemia. In study 1, all patients had evidence of myocardial ischemia by myocardial contrast echocardiography regardless of presence of obstructive stenosis by coronary angiography. In study 2 and 3, myocardial ischemia was found in around half of the participants with symptomatic non-obstructive CAD by CCTA. Accordingly, our results emphasize that patients with non-obstructive CAD need ischemia testing in order to be categorized into groups with and without myocardial ischemia.

The prognostic impact of objective evidence of myocardial ischemia in patients with non-obstructive CAD and stable symptoms suggestive of ischemic heart disease has been demonstrated (5-7). In 2000, Buchtal *et al.* found that seven of 35

symptomatic women (20%) with normal angiography (≤20% stenosis) had metabolic evidence of myocardial ischemia assessed by magnetic resonance spectroscopy during handgrip exercise (105). Johnson *et al.* expanded the importance of these findings by demonstrating that metabolic evidence of myocardial ischemia predicted cardiovascular outcome during three years follow-up, with hospitalization for unstable angina and repeated angiography as the most common events (5). Further, Schindler *et al.* investigated myocardial blood flow using positron emission tomography during sympathetic stimulation with a cold pressor test in 72 symptomatic patients with normal coronary arteries by coronary angiography (6). Abnormal myocardial blood flow was found in 69% of patients, and the group with abnormal myocardial blood flow had higher incidence of cardiovascular events during five years follow-up. However, the association between abnormal myocardial blood flow and incidence of cardiovascular events was attenuated after adjusting for cardiovascular risk factors, pointing to the importance of cardiovascular risk factors also in absence of obstructive CAD (6). In a study including 100 symptomatic women with normal coronary arteries or non-obstructive CAD by coronary angiography, global magnetic resonance myocardial perfusion imaging predicted adverse cardiovascular events (7). Taken together, in symptomatic patients with non-obstructive CAD, the presence of myocardial ischemia is likely to imply a worse prognosis. In the light of the current literature, our results demonstrated that myocardial ischemia was found in around half of symptomatic patients with non-obstructive CAD by CCTA, thus identifying a subgroup which is likely to have an impaired prognosis.

10.2 Total plaque burden and myocardial ischemia

Our results showed that the total plaque burden estimated from coronary angiography was associated with severe myocardial ischemia in NSTEMI patients, independent of presence of significant stenosis. In addition, we demonstrated that the total plaque burden was independently associated with myocardial ischemia in symptomatic patients with non-obstructive CAD by CCTA.

Previous studies of the association of the total plaque burden quantified from CCTA and myocardial ischemia have yielded somewhat diverging results (68, 106-108). Bakhshi *et al.* tested whether plaque features from quantitative CCTA were associated with myocardial ischemia independent of coronary artery stenosis lumen reducing severity in 365 patients with suspected or known CAD and clinical referral to coronary angiography (106). The patients underwent CCTA, myocardial CT perfusion imaging and single photon emission computed tomography (SPECT). All analyses were done on a vessel level, where plaque features from coronary arteries were matched with the corresponding myocardial perfusion territory by SPECT and myocardial CT perfusion. With SPECT as the reference of myocardial ischemia, percentage plaque volume was independently associated with myocardial ischemia in multivariable analysis, in addition to maximum percentage stenosis and subjective "vulnerable" plaque features. However, maximum percent diameter stenosis was the only independent variable in multivariable regression analysis predicting myocardial ischemia by CT perfusion imaging. Accordingly, their results from SPECT are in line with our findings, but it is difficult to draw any strong conclusions from their study.

Further, non-calcified plaque has been suggested to cause myocardial ischemia independent of stenosis severity (68, 107, 108). Diaz-Zamudio *et al*. showed that the low-density, non-calcified plaque burden, was associated with myocardial ischemia by SPECT, independent of stenosis severity (107). Of note, they included only patients with single-vessel disease. Moreover, Driessen *et al.* showed that non-calcified plaque burden estimated from CCTA was associated with reduced fractional flow reserve and reduced myocardial blood flow by positron emission tomography, independent of stenosis severity (68). Gaur *et al.* evaluated whether plaque characteristics by CCTA and CT-derived fractional flow reserve were associated with hemodynamically significant stenosis, taken as invasive fractional flow reserve ≤0.80, in symptomatic patients with clinically indicated coronary angiography (108). They showed that inclusion of low-density, non-calcified plaque burden and CT-derived fractional flow reserve ≤ 0.80 improved lesion-specific prediction of myocardial ischemia over stenosis severity alone (108). However, these studies did not include the total plaque burden in multivariable analyses due to collinearity with

the non-calcified plaque, limiting direct comparison with our findings (68, 107, 108).

Less is known about the association between the total plaque burden and myocardial ischemia in non-obstructive CAD (21). Schuijf *et al.* grouped 381 patients according to the presence of normal, non-obstructive CAD or obstructive CAD by CCTA in a sub-study using the same study population as Bakhshi *et al.* (21, 106). In line with our results, the total atherosclerotic plaque burden was higher in patients with non-obstructive CAD and myocardial ischemia by CT perfusion or SPECT than in those with normal perfusion (21). However, our findings expand their results by demonstrating that the relationship between increasing plaque burden and myocardial ischemia was independent of confounders, including cardiovascular risk factors, calcium score and left ventricular mass.

Moreover, it may be suggested that the relationship we found between increasing plaque burden and ischemia could contribute to explain the beneficial effect of statin treatment seen in several observational studies of non-obstructive CAD (44, 109). In fact, in an analysis of clinically indicated serial CCTA, statin treatment was associated with slower progression of the total plaque volume together with an increase in plaque calcification (110).

Taken together, our results demonstrate that the total plaque burden, defined as both calcified and non-calcified plaque, was associated with myocardial ischemia in non-obstructive CAD. Integrating our results with the current literature, quantification of the total plaque burden by CCTA may provide improvement of non-invasive prediction of myocardial ischemia. Further studies should test whether the association between the total plaque burden and myocardial ischemia in non-obstructive CAD is related to reduced coronary blood flow (56, 57) or microvascular dysfunction (58).

10.3 Left ventricular hypertrophy and myocardial ischemia

In study 2, we showed that left ventricular hypertrophy was associated with myocardial ischemia in symptomatic patients with non-obstructive CAD by CCTA. The association between left ventricular hypertrophy and myocardial ischemia has

been shown before, although in other study populations (111-113). In 1990, Salcedo *et al.* showed that left ventricular mass predicted ischemia by SPECT, independently of angiographic significant stenosis in stable patients referred to coronary angiography (111). More recently, in a study of 33 hypertensive patients without CAD, Olsen *et al.* found that echocardiographic left ventricular hypertrophy was associated with impaired myocardial blood flow at pharmacological stress assessed by dipyridamole positron emission tomography (112). Myocardial ischemia due to left ventricular hypertrophy has been suggested as the explanation for angina symptoms in patients with aortic stenosis and absence of CAD (113). Ahn *et al.* included patients with severe aortic stenosis without obstructive CAD at coronary angiography and assessed myocardial perfusion by adenosine-stress cardiac magnetic resonance imaging (113). Patients with angina had higher left ventricular mass and lower myocardial perfusion reserve than those without angina. In addition, left ventricular mass was the strongest contributor to reduced myocardial perfusion in multivariable analysis (113). Besides, animal studies have demonstrated that left ventricular hypertrophy may lower the ischemic threshold by increasing the oxygen demand, reducing the capillary density and increasing interstitial fibrosis in the myocardium (22, 114, 115). The concordance of our findings with previous studies supports that left ventricular hypertrophy may contribute to myocardial ischemia in the absence of obstructive CAD.

Accordingly, our results emphasize the importance of maintaining normal blood pressure in non-obstructive CAD. Hypertension is both a cause of left ventricular hypertrophy and a risk factor for development of CAD (24, 74, 116). Together, this may lower the threshold for development of myocardial ischemia. It has been demonstrated that hypertension is independently associated with increased risk of cardiovascular events in patients with non-obstructive CAD by CCTA, after adjusting for diabetes and the extent of non-obstructive CAD, taken as segment involvement score (66). Importantly, left ventricular hypertrophy increases the risk of death, independent of the presence of obstructive CAD by coronary angiography (117, 118). Our results suggest that regression of left ventricular hypertrophy should be a treatment target in non-obstructive CAD. Clinical trials show that reduction of

left ventricular mass and normalization of left ventricular geometry improve prognosis of hypertensive subjects with electrocardiographic left ventricular hypertrophy (80, 119). Further, in the observational Campania Salute network, blood pressure lowering through antihypertensive treatment, and weight loss led to a reduction of left ventricular mass, expanding the results from clinical trials (23, 120). Moreover, the Copenhagen City Heart Study demonstrated that increased levels of self-reported physical activity were associated with improved outcome, independent of presence of echocardiographic left ventricular hypertrophy (121). Taken together, our results and the current literature from hypertensive and community-based studies suggest that life-style interventions and hypertensive treatment may contribute to improve prognosis also in patients with non-obstructive CAD when left ventricular hypertrophy is present. This hypothesis should be tested in prospective studies.

10.4 Coronary artery tortuosity and myocardial ischemia

In study 1, we did not find any significant relationship between the severity or extent of myocardial ischemia and coronary artery tortuosity. Tortuosity was more prevalent in women, in line with other studies (72, 73). The body of evidence regarding whether coronary artery tortuosity impacts myocardial perfusion in humans is limited (61). In a study including 96 patients with stable chest pain and normal or near-normal coronary arteries (<30% stenosis on coronary angiography), coronary artery tortuosity was found in 35% of patients with myocardial ischemia by myocardial contrast stress echocardiography and in 5% of those with normal myocardial perfusion (61). Direct comparison with our findings should be made with caution. First, we used a less strict definition of coronary tortuosity, which may explain the higher prevalence of coronary tortuosity in our study. Second, we studied patients with NSTEMI while Gaibazzi *et al.* studied patients with stable disease. It is likely that the disease mechanisms underlying myocardial ischemia differ between these patient populations. Third, Gaibazzi *et al.* did not report whether coronary tortuosity was independently associated with myocardial ischemia in multivariable analysis, which further limits the ability to compare our findings (61).

10.5 Sex differences in non-obstructive coronary artery disease

There are sex-differences in ischemic heart disease, both in clinical presentation, disease mechanisms, and outcomes (122). In study 1, we found that women less often had obstructive CAD, in line with previous studies (8). In fact, the prevalence of women is higher in MINOCA than in myocardial infarction with obstructed coronary arteries (39, 40). We found that the impact of coronary artery plaque burden and tortuosity on myocardial ischemia were similar in women and men. Coronary vasospasm and thrombophilia have been suggested to contribute to the higher prevalence of women in MINOCA, but the mechanisms explaining sex differences in myocardial infarction are not fully understood (48).

The definition of non-obstructive CAD is important when addressing sex differences. CCTA studies show that women more often have normal coronary arteries and less often obstructive CAD (43, 123). The prevalence of women and men is similar when non-obstructive CAD is taken as 1-49% coronary artery stenosis (43, 123). Accordingly, if non-obstructive CAD is defined as the absence of obstruction, there will be a predominance of women as they are more likely to have normal CCTA. In study 2 and 3, the prevalence of women and men were similar. We did not find any difference in the prevalence of myocardial ischemia between women and men. In our multivariable models, sex was not associated with myocardial ischemia. Our findings did not provide any evidence of sex *per se* as a determinant of myocardial ischemia in non-obstructive CAD.

We found that left ventricular hypertrophy and the total plaque burden were associated with myocardial ischemia. Previous studies show that left ventricular hypertrophy is associated with adverse prognosis in both women and men (82). It has also been demonstrated that the extent of CAD, whether non-obstructive or obstructive, predicts worse prognosis similarly in women and men (43, 66). In light of current knowledge, our findings suggest that left ventricular hypertrophy and the coronary plaque burden should be considered as possible determinants of myocardial ischemia both in women and men with non-obstructive CAD.

10.6 Methodological considerations

The interpretation of the results presented in this thesis depends on the internal and external validity. Internal validity refers to whether one can trust that the results obtained in a study are true, while external validity refers to whether the results may be generalized to other patients than those included in the studies.

10.6.1 Internal validity

The internal validity depends on how the study was conducted, including study design and methods used. The risk of selection bias, reflecting a systematic difference between study groups, was small in all studies, as the participants were prospectively recruited. However, we cannot exclude a referral bias in study 2 and 3, as the participants were recruited among patients who had been referred to CCTA by cardiologists. Information bias means that there is a systematic difference between the groups concerning the collection of information. All clinical and demographic data were collected prior to myocardial perfusion imaging and all imaging analysis were done blinded, as recommended for clinical trials (124). We adjusted for possible confounders affecting the associations between plaque burden, tortuosity and left ventricular hypertrophy with myocardial ischemia in multivariable analyses in all studies. However, there are other factors that may affect myocardial ischemia that we did not assess, such as coronary vasospasm and microvascular function (58). Besides, our studies do not provide insights on the specific mechanisms that underlie the associations we found.

Evaluation of coronary plaque burden and tortuosity

The total plaque burden was estimated from invasive coronary angiograms in study 1. Invasive coronary angiography only visualizes the lumen and not the arterial wall. Thus, plaque quantification from invasive coronary angiography images represents a crude estimation of the amount of plaque based upon the arterial lumen reduction alone, since the method is unable to account for atherosclerosis with preserved lumen diameter and positive remodeling. Alternative methods to quantify plaque during invasive coronary angiography are intravascular ultrasound and optical coherence

tomography (125, 126). However, these methods were not consistently used in the included study population.

Quantitative CCTA is a better method for plaque quantification than invasive coronary angiography since the plaque itself is visualized (127). Several aspects of CCTA should be noted when interpreting our results. CCTA is not recommended when image quality is expected to be low, as for patients with severe obesity or high and irregular heart rate (96). In addition, CCTA is often uninterpretable in patients with high calcium score, which also increases the probability of obstructive CAD (128, 129). Accordingly, patients with high calcium score are often referred to invasive coronary angiography rather than proceeding with CCTA. Thus, these patients were not eligible for inclusion in study 2 and 3. Quantitative CCTA has good agreement of stenosis lumen reducing severity compared to coronary angiography (70). Besides, quantitative CCTA has good agreement with the estimation of plaque volume and characterization of plaque as calcified or non-calcified by intravascular ultrasound (98, 130). Of note, quantitative CCTA is unable to differentiate the normal vessel wall from non-calcified plaque volume, and limited ability to differentiate between different the types of non-calcified plaque (127, 130). Therefore, we chose to present the plaque burden as calcified and non-calcified, without further subgrouping. In addition, several fixed thresholds of Hounsfield units have been suggested to characterize plaque composition by CCTA (62). Luminal contrast density has been shown to affect plaque characterization when using fixed thresholds (98, 131). Therefore, we used a method for plaque characterization which adapts the thresholds to the luminal contrast density in the specific scan, instead of using fixed thresholds (98). There is currently no consensus on how to quantify the total plaque burden, for instance with regards to how small arterial size that can be analyzed, and whether to include side branches (130).

All these factors may limit the ability to compare results across studies directly. The protocol for plaque assessment in study 3 was adapted from a research center with extensive experience in quantitative CCTA to ensure high quality (127). Plaque quantification by CCTA is currently time-consuming, limiting implementation in clinical practice. However, the use of machine learning has shown superior

performance to that of expert visual assessment of CCTA plaque characteristics (132), pointing to the potential of machine learning and artificial intelligence in future automated CCTA quantification (133).

With regard to coronary tortuosity, there is to date no consensus in the definition of coronary tortuosity by coronary angiography (72), so we chose a definition used in a previous study (71). The intra-observer reliability for measurements of coronary plaque burden in study 1 was good, and in study 3, intra- and inter-observer reliability for measurement of the total coronary plaque burden were excellent.

Evaluation of left ventricular mass

Echocardiography and cardiac magnetic resonance are the best documented methods for assessment of left ventricular mass (79). In two-dimensional echocardiography, good acoustic windows and accurate quantification of left ventricular dimensions are necessary, and the left ventricle is assumed to have a certain geometrical shape (89). On the other hand, three-dimensional echocardiography and cardiac magnetic resonance imaging can measure cardiac volumes directly, eliminating the need of geometrical assumptions (79). However, three-dimensional echocardiography is more dependent on image quality, while magnetic resonance imaging is limited by increased time to acquire and analyze images, and is less available in clinical practice compared to echocardiography (79). Despite the limitations noted, two-dimensional echocardiographic assessment of left ventricular mass is recommended in clinical practice and the majority of prognostic data are from studies using echocardiographic detection of left ventricular hypertrophy (80-82, 89). Several methods are used to normalize left ventricular mass to body size, including height and body surface area (79, 89). We indexed left ventricular mass to height$^{2.7}$ and used sex-specific cut-offs, because it gives the most accurate estimation of left ventricular mass and the most sensitive cut-offs for the detection of left ventricular hypertrophy in both women and men, in particular when obesity is present (91, 134). Echocardiographic assessment of left ventricular mass was performed following standardized protocols in our echocardiography core laboratory, which has contributed to document the prognostic value of left ventricular hypertrophy in different patient cohorts and diseases (80, 92).

Evaluation of myocardial ischemia by contrast enhanced echocardiography

Myocardial contrast echocardiography is a safe procedure without radiation exposure, and provides the evaluation of myocardial perfusion and wall motion, in addition to structural assessment (49). Importantly, myocardial contrast echocardiography has been shown to have comparable diagnostic performance to SPECT (135) and cardiac magnetic resonance perfusion imaging (136), which are alternative methods for evaluation of myocardial perfusion. The local expertise and availability led to the choice of myocardial contrast echocardiography for evaluation of myocardial perfusion in all studies. Cardiac magnetic resonance imaging is currently recommended as a part of the diagnostic work-up in MINOCA, as it may not only diagnose myocardial ischemia, but also reliably differentiate between myocardial infarction and myocarditis (37). However, cardiac magnetic resonance imaging was not available at our institution at the time study 1 was performed. The main limitations of myocardial contrast echocardiography are the dependence on operator expertise and visual assessment of the myocardial perfusion (49). Further, myocardial contrast echocardiography does not provide differentiation between myocardial ischemia caused by coronary artery stenosis and myocardial ischemia of microvascular origin. Finally, the intra-observer reliability of myocardial perfusion in study 1 was excellent.

Statistical considerations

The main statistical limitations are the cross-sectional study design and small sample sizes. The cross-sectional design does not allow the evaluation of causal effects. Further, as study 1 and 3 were post-hoc analyses, the probability of type-II errors increases as the sample sizes were not calculated with these research questions in mind.

10.6.2 External validity

In study 1, the patients were prospectively recruited. Thus, the results from study 1 are likely to be generalizable to other NSTEMI patients. In study 2 and 3, presence of at least one cardiovascular risk factor was an inclusion criterion, so the results may

not be generalizable to symptomatic patients with non-obstructive CAD and a healthier cardiovascular risk factor profile.

10.7 Clinical implications and future perspectives

10.7.1 Clinical implications

Our results have several implications for clinical practice. The results presented in this thesis emphasize that non-obstructive CAD by coronary angiography or CCTA does not rule out the presence of myocardial ischemia. Accordingly, our results underline that patients with non-obstructive CAD by CCTA should undergo further ischemia testing to identify patients with chronic myocardial ischemia. Our results emphasize that ischemia in non-obstructive CAD may result from reduced oxygen supply, increased oxygen demand or a combination. Identification of the contributing factors in the individual patient may guide further treatment. While waiting randomized trials investigating medical treatment of non-obstructive CAD, our findings suggest that the presence of non-obstructive CAD should prompt attention to cardiovascular risk factor control in the individual patient through lifestyle-changes and medical treatment, in particular antihypertensive therapy.

10.7.2 Future perspectives

There are some aspects in the current definitions of MINOCA and INOCA, which should be considered in future research. The current definitions could be criticized to be based on expert opinion rather than prognostic evidence (11, 37). When reviewing the available literature, it is evident that the term “Ischemia” has been used ambiguously in INOCA. It has been used to describe symptoms suggestive of myocardial ischemia as well as objective evidence of ischemia (21, 59). This leads to different study populations and limited ability to generalize findings. In the recently suggested definition of INOCA, objective evidence of ischemia is mandatory (11). However, studies using coronary angiography or CCTA have demonstrated adverse prognosis in non-obstructive CAD without evaluation of myocardial ischemia (33, 45, 46). Thus, there is a need to further clarify the prognostic implications of objective evidence of ischemia in non-obstructive CAD.

Further, in the current definitions of MINOCA and INOCA, patients with normal coronary arteries (0% stenosis) and non-obstructive CAD defined as 1-49% stenosis are not separated (11, 37). Several CCTA studies have demonstrated that the prognosis in patients with non-obstructive CAD is worse than for those with normal coronary arteries, pointing to the importance of separating these two groups (9, 45, 137). On the other hand, few studies have compared outcome according to presence of normal coronary arteries or non-obstructive CAD in MINOCA, as pointed out by the European Society of Cardiology (37, 40). However, most patients with normal coronary arteries by coronary angiography have evidence of atherosclerosis when they are examined with intravascular ultrasound, so further studies are needed to evaluate whether such a distinction is fruitful in MINOCA (138). Standardized criteria for diagnosing microvascular angina and vasospastic angina have been proposed from the Coronary Vasomotor Disorders International Study Group (139, 140). Taken together, implementation of standardized and precise diagnostic criteria is needed to develop evidence-based care for patients with non-obstructive CAD**.**

The results presented in this thesis raises novel hypotheses to be tested in future research. Our findings suggest that improved phenotyping of patients with non-obstructive CAD may be achieved from integrating functional and anatomical assessment of determinants of myocardial oxygen supply and demand.

The mechanisms underlying the associations we found between left ventricular hypertrophy, plaque burden, and ischemia should be further investigated. Whether the total plaque burden affects coronary blood flow or is a marker of microvascular dysfunction should be explored. In addition, whether the total plaque burden have cut-off values with corresponding sensitivity and specificity that may rule-in or rule-out myocardial ischemia should be tested. Besides, standardized protocols for plaque quantification are needed in order to establish cut-off values that can guide clinical management. The prospective impact of the total coronary plaque burden estimated by quantitative CCTA in non-obstructive CAD should be investigated.

The ongoing advancement in non-invasive imaging techniques including cardiac magnetic resonance imaging (141, 142), CT perfusion imaging (143) and fractional flow reserve derived from CT (144) may shed light on the mechanisms of

myocardial ischemia in non-obstructive CAD. However, the optimal diagnostic workup and choice of imaging methods for clinical practice requires further studies, including evaluation of patient safety and prognostic implications.

Our results suggest that studies that aim to develop treatment of non-obstructive CAD should target the underlying causes of ischemia found in the individual patient. Such prospective studies should include evaluation of left ventricular hypertrophy and the coronary artery plaque burden, according to our findings. In addition, prospective trials should address whether cardiovascular risk control improves prognosis in non-obstructive CAD.

11. Conclusions

The key finding in this thesis is that non-obstructive CAD does not rule out myocardial ischemia. Our results suggest that the total plaque burden and left ventricular hypertrophy may independently contribute to myocardial ischemia in non-obstructive CAD.

In study 1, we aimed to determine whether the coronary artery plaque burden and tortuosity were associated with myocardial ischemia in NSTEMI patients. We found that the coronary artery plaque burden was associated with presence of severe ischemia at rest, independent of presence of significant stenosis. No associations were found between coronary artery tortuosity and myocardial ischemia.

In study 2, we aimed to assess the association of left ventricular hypertrophy with myocardial ischemia in symptomatic patients with non-obstructive CAD by CCTA. We found that left ventricular hypertrophy was independently associated with myocardial ischemia in symptomatic patients with non-obstructive CAD.

In study 3, we aimed to explore the association of the total coronary artery plaque burden with myocardial ischemia in symptomatic patients with non-obstructive CAD by CCTA. We found that the total coronary artery plaque burden was independently associated with presence of myocardial ischemia in symptomatic patients with non-obstructive CAD.

12. References

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Global Coronary Artery Plaque Area is Associated with Myocardial Hypoperfusion in Women with Non-ST Elevation Myocardial Infarction

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Abstract

Background: Women with non-ST elevation myocardial infarction (NSTEMI) have similar extent of myocardial ischemia but less obstructive coronary artery disease (CAD) than their male counterparts. We tested the impact of global coronary artery plaque area and artery tortuosity on myocardial perfusion in NSTEMI patients.
Methods: Coronary artery plaque area was determined by quantitative angiography in 108 patients (32% women) with NSTEMI. Myocardial perfusion was assessed by contrast echocardiography in the 17 individual left ventricular segments. Artery tortuosity was defined as ≥ 3 curves $>45°$ in a main coronary artery.
Results: Age, prevalence of hypertension, and diabetes did not differ between sexes (all nonsignificant). Women had lower prevalence of $\geq 50\%$ coronary artery stenosis (74% vs. 91%, $p < 0.05$), while global coronary plaque area (35 ± 22 vs. $43 \pm 21 mm^2$) and the number of segments with hypoperfusion (6.9 ± 3.7 vs. 7.2 ± 3.4) did not differ between sexes (both $p > 0.07$). In multivariate analysis, larger coronary artery plaque area was associated with a 35% higher risk for having severe myocardial hypoperfusion (odds ratio 1.35 [95% confidence interval 1.01–1.80], $p < 0.05$) in the total study population, while no association between artery tortuosity and myocardial ischemia was found. Similar results were obtained in separate analysis among women and men.
Conclusion: In women and men with NSTEMI, the global coronary artery plaque area was an important determinant of the severity of myocardial hypoperfusion at rest independent of presence of significant coronary stenoses. These findings may expand current understanding of NSTEMI in patients with nonobstructive CAD.

Introduction

Sex differences in coronary artery disease (CAD) pathophysiology have previously been demonstrated both in autopsy-based and clinical studies,[1–3] including differences in coronary artery plaque composition and distribution as well as coronary artery tortuosity.[4–9] In particular, nonobstructive CAD on angiography is found more often in women compared to men, irrespective of clinical presentation of the coronary artery disease.[5]

Previous studies using contrast echocardiography or cardiac magnetic resonance imaging have demonstrated that ischemic burden measured by these techniques is an important prognosticator in particular in women with nonobstructive CAD.[10,11] In a smaller study, we recently demonstrated that the extent of myocardial hypoperfusion in patients with non-ST elevation myocardial infarction (NSTEMI) was comparable in women and men despite less obstructive CAD in women.[7] However, it is not clear whether coronary artery plaque area may influence myocardial perfusion in NSTEMI patients independent of presence of significant coronary artery stenoses. Furthermore, others have suggested that also artery tortuosity may influence coronary perfusion.[9] The aim of this study was therefore to explore if coronary plaque area and arterial tortuosity impacted myocardial perfusion in NSTEMI patients, and thereby could explain the mismatch between extent of myocardial hypoperfusion and presence of significant CAD previous reported in NSTEMI women.

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Clinical Trial Registration: www. clinicaltrials.gov NCT01122069.

Materials and Methods

Study population

A total of 126 consecutive patients diagnosed with acute NSTEMI, defined as the combination of chest pain and troponin T elevation, hospitalized at the Department of Heart Disease, Haukeland University Hospital, from March through December 2008 and scheduled for acute coronary angiography within 72 hours after admittance were eligible for the study. Excluding patients with hemodynamically unstable disease, mechanical valve prostheses or severe pulmonary disease, a total of 110 patients signed informed consent and all of them underwent myocardial contrast echocardiography prior to scheduled coronary angiography.[12]

For the present post-hoc analysis, reanalyzing the angiograms in this previous series with quantitative coronary angiography, two of the 110 patients were excluded because all native coronary arteries were occluded, leaving 108 patients for the present study population. Clinical risk assessment was performed in all patients using the thrombolysis in myocardial infarction (TIMI) risk score model.[13] The study was approved by the regional ethical committee and performed in accordance with the Helsinki declaration.

Quantitative coronary angiography

Quantitative coronary angiography was performed offline by a single reader (IE) blinded to clinical data and myocardial perfusion assessment using a digitalized automatic edge detecting analysis software (QAngio® XA 7.1, MEDIS Medical Imaging Systems, Leiden, The Netherlands) (Fig. 1, panel A).

The coronary artery tree was divided into 17 segments, following the modified American Heart Association model.[14] The tip of the catheter was used for calibration. Stenosis severity and plaque area assessed as lumen diameter reduction was determined in all vessel segments with a diameter >1.5 mm. Global coronary artery plaque area was calculated as the sum of plaque area in all segments. A coronary artery lumen diameter reduction of ≥ 50 % on the angiogram was considered a significant stenosis.

Coronary artery tortuosity was measured in the three main coronary arteries in standardized views: The left anterior descending artery in the right anterior oblique view with cranial angulation, the left circumflex artery in the left anterior oblique with caudal angulation and the right coronary artery in the right anterior oblique view.[9] Coronary tortuosity was regarded present if ≥ 3 curves $>45°$ was found in the same artery (Fig. 1, panel B).

Echocardiography

Quantitative echocardiography was performed following the joint European Association of Echocardiography and American Society of Echocardiography guidelines.[15] Left ventricular (LV) ejection fraction was assessed by the modified biplane Simpson formula and regional LV function by wall motion scoring.[15] Wall motion score was assessed in apical 2-, 3-, and 4-chamber views using a 17-segment LV model as recommended in current quantitation guidelines.[15] The average wall motion score value was taken as wall motion score index in the individual patients. Methods and results from myocardial contrast echocardiography have previously been reported in details.[7,12] In short, myocardial contrast echocardiography was performed at rest by real-time low-mechanical index imaging and destruction–replenishment using Cadance Contrast Pulse Sequencing technology (Acuson Sequoia C512, Siemens, Mountain View, CA, echocardiograph). An intravenous bolus dosage of 0.3 mL Perflutren Lipid Microsphere ultrasound contrast (Luminity®, Lantheus Medical Imaging, North Billerica, MA) was given before perfusion imaging. The bolus dosage was repeated if necessary to ensure a stable contrast concentration and avoid contrast swirling during image acquisition. Regional myocardial perfusion was scored visually as normal (contrast replenishment within five heart beats) or hypoperfusion (delayed contrast replenishment after more than five heart beats) using the guideline-recommended 17 segment LV model (Fig. 2).[15,16] The extent of myocardial perfusion abnormalities was assessed as the number of segments with hypoperfusion. Severe myocardial hypoperfusion was considered present if hypoperfusion was detected in ≥ 6 LV segments.[12]

Statistics

Data management and statistical analysis were performed by the IBM SPSS statistical program version 20.0 (IBM SPSS, Chicago, IL). The study had 80% power to detect a 30% difference in coronary artery stenosis between women and men at a statistical level of 0.05. Continuous variables are reported as mean and standard deviation and categorical variables as numbers and percentages. Comparisons between groups were performed by unpaired *t*-test or chi-squared

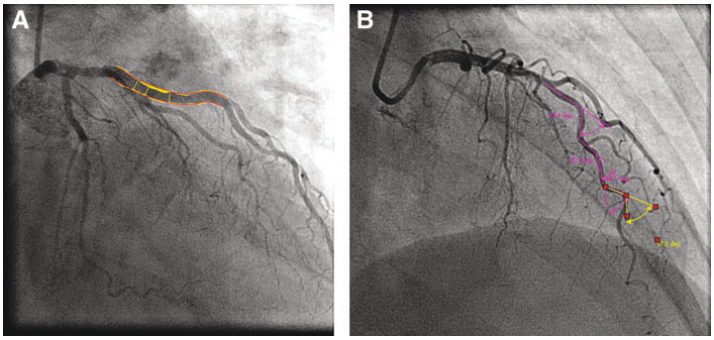


FIG. 1. Quantitative coronary angiography. Coronary artery plaque area **(A)** and coronary artery tortuosity **(B)** assessed in the left anterior descending artery.

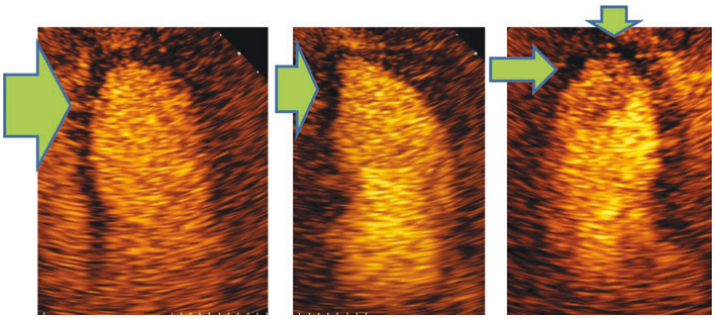


FIG. 2. Myocardial contrast echocardiography. Apical 4-chamber, 2-chamber and long axis view images taken five beats post flash demonstrating subendocardial and transmural hypoperfusion in the apical left ventricular segments marked with green arrows.

statistics as appropriate. Covariates of global coronary artery plaque area and tortuosity were identified by Pearson's correlation coefficient and logistic regression analysis as appropriate. Independent covariates of the extent of myocardial hypoperfusion were identified in multiple linear regression analysis. Covariates of severe hypoperfusion (involving ≥ 6 LV segments) were identified in multiple logistic regression analysis. The associations of presence of severe myocardial hypoperfusion with global coronary artery plaque area and presence of significant coronary artery stenosis were tested in receiver operator characteristics curve analysis. A p value < 0.05 was considered statistical significant. The intraobserver variability of myocardial perfusion assessment and of coronary artery plaque area measurement was calculated separately from echocardiographic and angiographic images, respectively, in 11 patients analyzed twice and reported as intraclass correlation coefficient.

Results

Patient characteristics

The proportion of patients >65 years of age was significantly higher among women, while mean age, troponin T levels and TIMI risk score did not differ between women and men (Table 1). There were no sex differences in anti-ischemic treatment at study entrance. None of the women were on hormone replacement therapy. The extent of wall motion abnormalities and myocardial hypoperfusion did not differ between women and men, reflecting comparable myocardial infarct size (Table 2). The mean time between contrast echocardiography and angiography was 1.87 ± 2.6 days, with a median of 1.0 day. There were no adverse events from contrast infusions, except for three patients who experienced transient lower back pain.

Coronary artery plaque area

A total of 35 main arteries had proximal total occlusion. From the total of 1422 coronary artery segments visible on the angiograms, 69 segments were excluded from analysis due to poor image quality and vessel overlap, and another 170 segments were excluded due to luminal diameter ≤ 1.5 mm, which cannot be analyzed with our method, leaving a total of 1252 (88% of visible segments on the angiogram) for assessment of coronary artery plaque area.

Reproducibility of myocardial perfusion score by intraclass correlation coefficient was 0.95 (95% confidence

TABLE 1. CLINICAL CHARACTERISTICS OF THE TOTAL STUDY POPULATION AND GROUPS OF WOMEN AND MEN

	Total (n = *108*)	*Women* (n = *34*)	*Men* (n = *74*)	p
Age (years)	67 ± 12	70 ± 12	66 ± 12	0.160
Age >65 years (%)	56.5	70.6	50.0	0.045
BMI (kg/m^2)	27 ± 5	27 ± 5	27 ± 4	0.973
Systolic blood pressure (mmHg)	150 ± 24	150 ± 22	150 ± 25	0.906
Diastolic blood pressure (mmHg)	85 ± 13	85 ± 13	85 ± 13	0.917
TIMI risk score	3.24 ± 1.41	3.47 ± 1.44	3.14 ± 1.39	0.252
Family history of premature CAD (%)	40	41	39	0.854
Hypertension (%)	44	44	43	0.932
Hypercholesterolemia (%)	49	65	42	0.028
Diabetes mellitus (%)	19	21	19	0.839
Current smoker (%)	28	15	34	0.040
Peak troponin T level (ng/L)	680 ± 1170	530 ± 660	750 ± 1300	0.353
Previous myocardial infarction (%)	29	29	29	0.912
Betablocker use (%)	33	32	34	0.884
Calcium channel blockers use (%)	11	9	12	0.608
Statin use (%)	41	32	45	0.229
Acetylsalicylic acid use (%)	42	47	39	0.441

BMI, body mass index; CAD, coronary artery disease; TIMI, thrombolysis in myocardial infarction risk score.

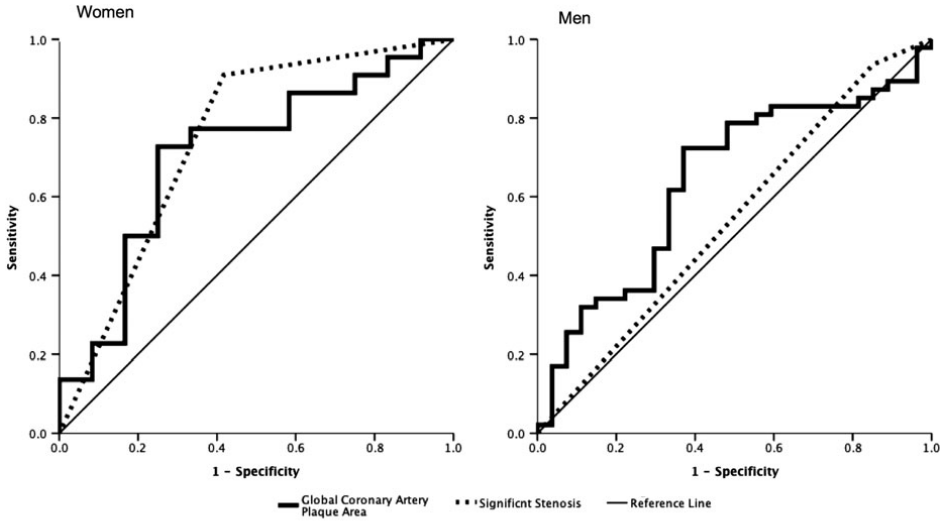
TABLE 2. ECHOCARDIOGRAPHIC AND ANGIOGRAPHIC FINDINGS IN THE TOTAL STUDY POPULATION AND SEPARATELY IN WOMEN AND MEN

	Total (n = *108*)	*Women* (n = *34*)	*Men* (n = *74*)	p
LV end-diastolic diameter (cm)	5.09 ± 0.65	4.76 ± 0.56	5.25 ± 0.65	< 0.001
LV end-systolic diameter (cm)	3.65 ± 0.73	3.36 ± 0.64	3.79 ± 0.73	0.004
Intraventricular septum thickness (cm)	1.20 ± 0.18	1.12 ± 0.20	1.21 ± 0.17	0.737
Posterior wall thickness (cm)	1.02 ± 0.13	0.99 ± 0.12	1.03 ± 0.13	0.140
LV ejection fraction (%)	56 ± 12	58 ± 12	54 ± 11	0.165
Extent of wall motion abnormality (segments)	3.6 ± 3.7	3.7 ± 4.1	3.6 ± 3.5	0.893
Extent of hypoperfusion (segments)	7.1 ± 3.5	6.9 ± 3.7	7.2 ± 3.4	0.747
Severe hypoperfusion (%)	63.9	64.7	63.5	0.905
Significant stenosis (%)	85	74	91	0.021
Total coronary artery occlusion (%)	34	35	34	0.878
Wall motion score index	1.22 ± 0.23	1.23 ± 0.26	1.22 ± 0.23	0.880
Multivessel disease (%)	49	35	55	0.052
Coronary artery tortuosity (%)	68	82	61	0.026
Coronary artery plaque area (mm^2)	41 ± 22	35 ± 22	43 ± 21	0.071

LV, left ventricular.

interval [CI] 0.90–0.98) and for coronary artery plaque area 0.86 (95% CI 0.75–0.91).

Global coronary artery plaque area did not differ significantly between women and men despite lower prevalence of significant coronary artery stenoses and multivessel disease in women (Table 2). In receiver operating characteristic curve analysis, global coronary artery plaque area was significantly associated with having severe myocardial hypoperfusion in both women and men, while presence of significant coronary artery stenosis was significantly



		Area under the curve	95% confidence interval	p-value
Women	Global coronary plaque area	0.71	0.52-0.90	0.047
	Significant stenosis	0.75	0.56-0.94	0.019
Men	Global coronary plaque area	0.64	0.51-0.77	0.046
	Significant stenosis	0.54	0.40-0.68	0.548

FIG. 3. Global coronary artery plaque area and severe myocardial hypoperfusion. Receiver operating curve analysis of the univariate association of presence of severe myocardial hypoperfusion with global coronary plaque area and presence of significant coronary artery stenosis in women and men.

Table 3. Predictors of Severe Myocardial Hypoperfusion (≥6 LV Myocardial Segments) Identified in Univariate and Multivariate Logistic Regression Analyses

	Univariate analysis			*Multivariate analysis*		
Independent variable	*OR*	*95% CI*	p	*OR*	*95% CI*	p
Global coronary plaque area (per 10mm^2)	1.32	(1.05–1.66)	0.019	1.35	(1.01–1.80)	0.047
Significant stenosis	5.03	(1.60–15.83)	0.006	5.14	(1.29–20.54)	0.021
Age >65 years	3.82	(1.67–8.73)	0.002	3.99	(1.51–10.55)	0.005
Female sex	1.05	(0.45–2.46)	0.905	1.72	(0.57–5.23)	0.339
Coronary tortuosity	0.50	(0.27–1.21)	0.123	0.49	(0.17–1.37)	0.173
Hypertension	0.61	(0.28–1.35)	0.22	0.51	(0.20–1.34)	0.173
Diabetes mellitus	0.70	(0.27–1.85)	0.48	0.47	(0.14–1.54)	0.213
Hypercholesterolemia	0.87	(0.40–1.91)	0.73	0.70	(0.26–1.86)	0.473

95% CI, 95% confidence interval; OR, odds ratio.

associated with severe myocardial hypoperfusion only in women, probably reflecting the low prevalence of non-obstructive CAD in men (Fig. 3).

Coronary artery tortuosity

A total of 273 native main coronary arteries were visible on the coronary angiograms. Of these, 34 were excluded due to low image quality, leaving 239 (88%) available for analysis of tortuosity. All three main coronary arteries could be assessed in 65 patients, two in 31 patients, and one in 7 patients. Tortuosity was more prevalent among women than men (Table 3). Global coronary artery plaque area did not differ between patients with tortuous and non-tortuous coronary arteries (42.0 ± 23.5 vs. 38.0 ± 17.4 mm^2, $p = 0.367$). Tortuosity was not associated with the extent of myocardial hypoperfusion in the total study population or in men and women analyzed separately.

Determinants of myocardial hypoperfusion

A significant association was found between global coronary plaque area and both severity and extent of myocardial hypoperfusion in univariate analyses (both $p < 0.05$) (Tables 3, 4). In multiple logistic regression analysis, adjusting for known confounders of hypoperfusion, a 10 mm^2 higher global plaque area was associated with a 35% higher risk for having severe myocardial hypoperfusion on the echocardiogram (odds ratio 1.35; 95% CI 1.01–1.80, $p = 0.047$), independent of presence of significant coronary artery stenosis (Table 3). However, the association of larger global coronary plaque area with larger extent of myocardial hypoperfusion was attenuated and became borderline statistically significant when adjusted for confounders in multivariate analysis ($\beta = 0.18$, $p = 0.057$) (Table 4).

Discussion

The present study demonstrates that global coronary artery plaque area is an important determinant of the severity of myocardial hypoperfusion in NSTEMI patients, independent of presence of significant coronary artery stenoses. Of note, global coronary artery plaque area did not differ between sexes despite lower prevalence of obstructive CAD in women. In fact, nonobstructive CAD was nearly 3-fold more prevalent in women than in men in the present study, in accordance with previous reports from registries and meta-analyses.[5,6] Although computer tomography coronary angiography is recognized as a superior method for assessment of coronary artery plaque area, invasive coronary angiography is the preferred diagnostic technique for diagnosis of CAD in current management guidelines for NSTEMI patients.[17] Therefore, our findings are relevant for clinical practice.

Distinct sex differences in coronary atherosclerosis are well described.[2] Typically, women have more diffuse atherosclerosis, smaller arteries and more microvascular involvement.[2,18] These factors may contribute to the reported sex difference in treatment procedures and outcome among CAD patients.[19,20] Intravascular ultrasound in women with

Table 4. Independent Covariates of the Extent of LV Myocardial Hypoperfusion in Multivariate Linear Regression Analysis (Multiple $R^2 = 0.28$, $P < 0.01$)

	Univariate analysis		*Multivariate analysis*			
Independent variable	*Beta coefficient*	p	*Beta coefficient*	p	*Tolerance*	*VIF*
Global coronary plaque area (mm^2)	0.27	0.005	0.18	0.057	0.852	1.173
Age >65 years	0.34	<0.001	0.28	0.003	0.885	1.130
Significant stenosis	0.37	<0.001	0.31	0.001	0.836	1.196
Coronary tortuosity	−0.16	0.094	−0.12	0.191	0.886	1.128
Female sex	−0.03	0.747	−0.06	0.523	0.799	1.251
Hypertension	−0.03	0.792	−0.05	0.616	0.905	1.105
Diabetes mellitus	0.02	0.843	−0.03	0.714	0.861	1.161
Hypercholesterolemia	−0.03	0.726	−0.10	0.308	0.841	1.189

VIF, variance inflation factor.

chest pain and nonobstructive CAD has demonstrated a high prevalence of atherosclerosis with positive remodeling and preserved lumen size.[21,22] This emphasizes the limitation of the present study using angiography to estimate the coronary artery plaque area, since only the luminal narrowing is visualized on the angiogram. In addition, it was not possible to measure plaque area in coronary arteries < 1.5 mm in diameter with our method. Consequently, global coronary artery plaque area may have been underestimated, in particular in women in our study, due to the combination of more positive remodeling and smaller coronary artery diameter. Furthermore, angiographic normal reference segments often contain mild to moderate diffuse atherosclerosis, possibly leading to an underestimation of the true lumen diameter, and thereby of the plaque area.[23] Still, as demonstrated, reproducibility of global coronary plaque area measurement by our method was good.

The prognostic importance of the ischemic burden assessed by contrast echocardiography at rest has been documented in patients with acute chest pain.[11,24] The use of contrast stress echocardiography in assessment of CAD risk in menopausal women is currently under evaluation.[25] In patients with myocardial infarction, larger extent of myocardial hypoperfusion by contrast echocardiography at rest has been demonstrated to predict unfavorable LV remodeling and impaired prognosis.[24,26] Similarly, previous studies assessing myocardial perfusion by magnetic resonance imaging have reported increased morbidity, in particular hospitalizations for angina pectoris, in women with chest pain and nonobstructive CAD.[10,27] Consequently, extent and severity of the perfusion abnormalities are important prognosticators in patients with different types of acute coronary syndromes.

It was recently demonstrated in a numerical simulation study that coronary artery tortuosity may induce myocardial ischemia through a reduction in coronary artery perfusion pressure.[28] Typically, coronary artery tortuosity is more prevalent in women and in patients with hypertension.[9] In this study, tortuosity was indeed more prevalent in women, but not associated with hypertension. Coronary artery tortuosity was not associated with myocardial hypoperfusion at rest neither in women nor men. Thus, the clinical relevance of coronary tortuosity in NSTEMI remains to be established.

Finally, endothelial dysfunction, vessel inflammation and microvascular disease may all contribute to myocardial hypoperfusion in NSTEMI patients with nonobstructive CAD beyond the global coronary artery plaque area.[2,29,30] However, these factors were not measured in the present study. On the other hand, hypertension and diabetes, comorbidities known to be associated with endothelial dysfunction did not differ between women and men, and also did not predict the extent of myocardial hypoperfusion in the present study.[31]

Conclusions

In women and men with NSTEMI, the global coronary artery plaque area was an important determinant of the severity of myocardial hypoperfusion at rest independent of presence of significant coronary stenoses. These findings may expand current understanding of NSTEMI in patients with nonobstructive CAD.

Author Disclosure Statement

No competing financial interests exist.

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Left ventricular hypertrophy contributes to Myocardial Ischemia in Non-obstructive Coronary Artery Disease (the MicroCAD study)

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ABSTRACT

Background: The underlying mechanisms causing myocardial ischemia in non-obstructive coronary artery disease (CAD) are still unclear. We explored whether left ventricular hypertrophy (LVH) was associated with myocardial ischemia in patients with stable angina and non-obstructive CAD.

Methods: 132 patients (mean age 63 ± 8 years, 56% women) with stable angina and non-obstructive CAD diagnosed as <50% stenosis by coronary computed tomography angiography (CCTA) underwent myocardial contrast stress echocardiography. Left ventricular (LV) hypertrophy (LVH) was identified by LV mass index >46.7 g/m$^{2.7}$ in women and >49.2 g/m$^{2.7}$ in men. Patients were grouped according to presence or absence of myocardial ischemia by myocardial contrast stress echocardiography. The number of LV segments with ischemia at peak stress was taken as a measure of the extent of myocardial ischemia.

Results: Myocardial ischemia was found in 52% of patients, with on average 5 ± 3 ischemic LV segments per patient. The group with myocardial ischemia had higher prevalence of LVH (23 vs. 10%, $p = 0.035$), while age, sex and prevalence of hypertension did not differ between groups (all $p > 0.05$). In multivariable regression analyses, LVH was associated with presence of myocardial ischemia (odds ratio 3.27, 95% confidence interval [1.11–9.60], $p = 0.031$), and larger extent of myocardial ischemia ($\beta = 0.22$, $p = 0.012$), independent of confounders including age, hypertension, obesity, hypercholesterolemia, calcium score and segment involvement score by CCTA.

Conclusions: LVH was independently associated with both presence and extent of myocardial ischemia in patients with stable angina and non-obstructive CAD by CCTA. These results suggest LVH as an independent contributor to myocardial ischemia in non-obstructive CAD.

Clinical trial registration number: ClinicalTrials.gov, identifier NCT018535271.

1. Introduction

Management of patients with non-obstructive coronary artery disease (CAD) and stable angina represents a major clinical challenge [1,2]. Non-obstructive CAD is a common finding, in particularly among women [3,4]. During recent years it has been well documented that patients with non-obstructive CAD have increased cardiovascular morbidity and mortality, contrasting the original conception that it was a benign condition [2–6]. Myocardial ischemia is characterized by a mismatch between the myocardial oxygen supply and demand, and has adverse prognostic implications in patients with CAD [7]. Further, detection of myocardial ischemia in non-obstructive CAD may help to identify the patients with increased risk of impaired prognosis [8]. Moreover, the pathophysiologic mechanisms leading to myocardial ischemia in patients with non-obstructive CAD appear to be multifactorial. Several factors, including hypertension, atherosclerosis and microvascular dysfunction, have been reported as potential contributors to myocardial ischemia [1,9,10]. However, the underlying disease mechanisms contributing to myocardial ischemia in the individual patient may often not be identified during routine diagnostic work-up, and evidence based guidelines for personalized management of patients with non-obstructive CAD are still missing [1].

Left ventricular hypertrophy (LVH) is the hallmark of hypertension mediated organ damage and is an independent predictor of both all-cause mortality and cardiovascular morbidity in general and hypertensive population [11–14]. In hypertensive patients, LVH, in particular the concentric type, has been associated with presence of symptomatic myocardial ischemia even with normal coronary angiography [15]. It has previously been suggested that hypertensive patients with LVH have a lower threshold for myocardial ischemia and that this may explain the increased cardiovascular risk [16]. However, the impact of

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LVH, a potential treatment target, on myocardial ischemia in patients with non-obstructive CAD has not previously been explored. Thus, the aim of this study was to assess whether presence of LVH may contribute to presence of myocardial ischemia in patients with stable angina and non-obstructive CAD.

2. Methods

2.1. Patient population

The Myocardial Ischemia in Non-obstructive Coronary Artery Disease (MicroCAD) study is a cross-sectional study that prospectively included patients referred to coronary computed tomography angiography (CCTA) at Department of Heart Disease, Haukeland University Hospital, Bergen, Norway in the period May 2013 until November 2014 by experienced cardiologist on a clinical suspicion of stable angina and that were diagnosed with non-obstructive CAD. Other inclusion criteria were age >30 years, clinical stable angina, defined as exercise induced angina pectoris and/or dyspnea for at least 6 months, and at least one cardiovascular risk factor (hypertension, hypercholesterolemia, diabetes, smoking or family history of premature CAD). Exclusion criteria were clinically unstable angina, severe valve disease, mechanical valve prosthesis, arrhythmias, severe pulmonary disease and known allergies to ultrasound contrast.

In total 153 patients were identified and invited, of whom 21 declined participation, leaving 132 patients included in the MicroCAD study. All participants signed informed consent. The MicroCAD project was approved by the regional ethical committee and was performed according to the 1975 Declaration of Helsinki. The MicroCAD project is registered at ClinicalTrials.gov with identifier NCT01853527.

2.2. Cardiovascular risk factors and symptoms

The patients reported cardiovascular risk factors, medical history and use of medication on a standardized questionnaire. Family history of premature CAD was considered present if documented CAD was present in a first-degree relative before the age of 65 years in women and 55 years in men. Hypercholesterolemia was defined as total serum cholesterol >6.5 mmol/l or use of cholesterol-lowering treatment. Body mass index (BMI) was calculated as body weight in kilograms divided by height in meters squared. Obesity was defined as BMI ≥30 kg/m^2. Hypertension was defined as known hypertension, use of antihypertensive drugs or high blood pressure at the clinic visit (systolic blood pressure ≥ 140 mm Hg and/or diastolic blood pressure ≥ 90 mm Hg) [17]. Fasting blood samples were collected to measure serum lipid profile, serum glucose and creatinine. Glomerular filtration rate was estimated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula [18].

2.3. Conventional echocardiography

Echocardiography was performed following a standardized protocol and interpreted in line with current joint guidelines of the American Society of Echocardiography and the European Association of Cardiovascular Imaging [19]. We interpreted the images offline at the Bergen Echocardiography Core Laboratory blinded to clinical data. All images were proof-read by the same experienced reader (MTL). Left ventricular (LV) mass was calculated by Devereux's equation and indexed for height in meters in the allometric power of 2.7. We defined LVH by the prognostically validated sex specific cut-off values of LV mass index (LVMi) >46.7 g/m$^{2.7}$ in women and >49.2 g/m$^{2.7}$ in men [12,20]. LV ejection fraction was calculated by Simpson's biplane method. Relative wall thickness was calculated as posterior wall thickness/LV internal radius ratio and considered increased if ≥0.43 [19]. LV geometry was classified into four groups based on the presence of LVH and normal or increased relative wall thickness [19]. Accordingly, normal LV geometry was defined as no LVH and normal relative wall thickness, concentric remodeling as no LVH and increased relative wall thickness, concentric LVH as LVH and increased relative wall thickness, and eccentric LVH as LVH and normal relative wall thickness [19].

2.4. Myocardial contrast echocardiography for myocardial perfusion

Myocardial contrast echocardiography was performed using real-time low-mechanical index imaging and destruction replenishment following current guidelines [21]. Ultrasound contrast agent (SonoVue, Bracco, Milan, Italy) was given intravenously as 1 ml bolus followed by 1 ml/h infusion with a rotating infusion pump (VueJet, Bracco, Milan, Italy). Apical 2-, 3- and 4-chamber views were used to score wall motion and myocardial perfusion at rest and at peak dobutamine stress, defined as 85% of maximum age predicted (200 – age) heart rate during stress echocardiography [21]. Wall motion was scored visually as normal or abnormal, and myocardial perfusion as normal or delayed in the individual 17-segments of the LV. Stress induced myocardial ischemia was defined as presence of delayed contrast replenishment 2 heart beats after flash at peak stress in any LV segment. The number of LV segments with delayed perfusion at peak stress was taken as a measure of the extent of myocardial ischemia.

2.5. Coronary computed tomography angiography and non-obstructive coronary artery disease

CCTA was performed by a 256-slice dual source scanner (Somatom Definition Flash, Siemens, Germany) with electrocardiographic (ECG) -triggered acquisitions. Patients with heart rate >60 beats per minute were given metoprolol intravenously (1 mg/ml, maximum 20 mg) until heart rate was ≤60 beats per minute. The patients received non-ionic contrast intravenously as 80–115 ml iomeprol 400 mg I/ml (Iomeron®, Bracco, Milan, Italy) according to body weight. All patients received 0.4 mg sublingual nitroglycerin in order to optimize image quality. Experienced readers analyzed all images for detection of coronary artery stenosis using a modified 20-segment American Heart Association model [22]. Non-obstructive CAD was defined as presence of ≥ one stenosis with lumen diameter reduction 1–49% in any coronary artery segment. CCTA was revised in all patients where we detected myocardial ischemia in order to confirm diagnosis of non-obstructive CAD. Segment involvement score was calculated as the total number of coronary segments with atherosclerotic plaque [23].

2.6. Statistical analysis

Data analysis was performed using IBM SPSS Statistics version 24 (IBM Corporation, Armonk, NY, USA). The sample size was determined in order to have 80% power with statistical level of 0.05 to find 50% differences in prevalence of LVH between patients with and without myocardial ischemia, including an anticipated dropout rate of 5%. The study population was grouped into patients with and without myocardial ischemia. We compared groups by unpaired Student's *t*-test for continuous variables and Chi-Square test for categorical variables. The results are presented as mean ± standard deviation or median and interquartile range for continuous variables and number and percentages for categorical variables. Predictors of myocardial ischemia were assessed in uni- and multivariable logistic regression models and reported as odds ratio (OR) with 95% confidence intervals (CI). Independent covariables of the extent of myocardial ischemia were identified by uni- and multivariable linear regression analysis with standardized coefficients (β). A $p < 0.05$ was considered significant in all analyses.

Table 1
Clinical characteristics of the total study population and of groups of patients with and without myocardial ischemia.

	Total (n = 132)	Ischemia (n = 69)	No ischemia (n = 63)	p
Age (years)	63 ± 8	63 ± 9	62 ± 8	0.317
Female sex (%)	56	54	59	0.555
BMI (kg/m^2)	27.7 ± 4.5	27.2 ± 4.1	28.2 ± 4.8	0.206
Obesity (%)	24	16	32	0.032
Hypertension (%)	75	81	68	0.077
Diabetes (%)	13	12	13	0.919
Current cigarette smoking (%)	16	13	19	0.341
Family history of premature CAD (%)	64	58	70	0.192
Hypercholesterolemia (%)	48	54	41	0.156
Systolic blood pressure (mm Hg)	135 ± 16	135 ± 17	135 ± 16	0.795
Diastolic blood pressure (mm Hg)	79 ± 13	79 ± 13	79 ± 13	0.998
Heart rate (bpm)	69 ± 12	71 ± 13	68 ± 12	0.303
Serum glucose (mmol/L)	5.9 ± 1.6	5.9 ± 1.0	6.0 ± 2.0	0.727
Estimated GFR (mL/min/1.73 m^2)	86 ± 14	87 ± 15	85 ± 13	0.389
Total serum cholesterol (mmol/L)	5.0 ± 1.3	5.1 ± 1.4	5.0 ± 1.2	0.719
Serum HDL cholesterol (mmol/L)	1.5 ± 0.4	1.5 ± 0.5	1.5 ± 0.4	0.896
Serum LDL cholesterol (mmol/L)	3.2 ± 1.2	3.3 ± 1.3	3.2 ± 1.0	0.718
Serum triglycerides (mmol/L)	1.47 ± 0.96	1.55 ± 0.84	1.39 ± 1.08	0.340
Acetylsalicylic acid (%)	47	57	36	0.026
Statin (%)	38	40	36	0.627
Antihypertensive treatment (%)	58	59	56	0.729
Beta blocker (%)	30	23	36	0.126
Calcium channel blocker (%)	18	24	12	0.094
LV internal diastolic dimension (mm)	45.2 ± 5.5	45.0 ± 5.5	45.3 ± 5.5	0.764
LV internal systolic dimension (mm)	29.2 ± 5.3	29.0 ± 5.4	29.4 ± 5.2	0.678
Septal thickness (mm)	11.8 ± 2.0	12.3 ± 2.1	11.3 ± 1.8	0.003
Posterior wall thickness (mm)	9.3 ± 1.9	9.4 ± 2.1	9.1 ± 1.6	0.476
LV ejection fraction (%)	62 ± 7	63 ± 6	60 ± 7	0.019
LVMi (g/m$^{2.7}$)	40.1 ± 9.3	42.1 ± 9.7	37.9 ± 8.4	0.009
LVH (%)	17	23	10	0.035
Relative wall thickness	0.42 ± 0.11	0.42 ± 0.11	0.41 ± 0.10	0.487
Calcium score (HU)	42(14–107)	47(16–127)	37(11–83)	0.264
Number of diseased coronary arteries	1.6 ± 1.8	1.7 ± 0.8	1.5 ± 0.7	0.084
Multi-vessel disease (%)	54	60	48	0.168
Segment involvement score	2.6 ± 1.6	2.8 ± 1.8	2.4 ± 1.3	0.149

BMI, body mass index; CAD, coronary artery disease; bpm, beats per minute; GFR, glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LV, left ventricular; LVMi, left ventricular mass index; LVH, left ventricular hypertrophy; HU, Hounsfield units.

3. Results

3.1. Clinical characteristics and myocardial contrast stress echocardiography

All 132 study participants had symptomatic stable angina. Prior stress testing with exercise ECG was performed in 115 (89%) of the participants, and a total of 79 (67%) of the tests were reported to be negative or inconclusive due to low exercise capacity or left bundle branch block, leaving 36 patients (31%) with a positive exercise ECG. Myocardial ischemia by contrast stress echocardiography was found in 69 patients (52%), and among patients with a positive exercise ECG, 67% were diagnosed with myocardial ischemia by contrast stress echocardiography. The median time from CCTA to myocardial contrast echocardiography was 133 days (interquartile range 98–188 days). The group with myocardial ischemia had a 2-fold higher prevalence of LVH (Table 1), in particularly concentric LVH (Fig. 1). The groups did not differ in age, sex, prevalence of hypertension or antihypertensive treatment, however obesity was less common in the group with myocardial ischemia (Table 1).

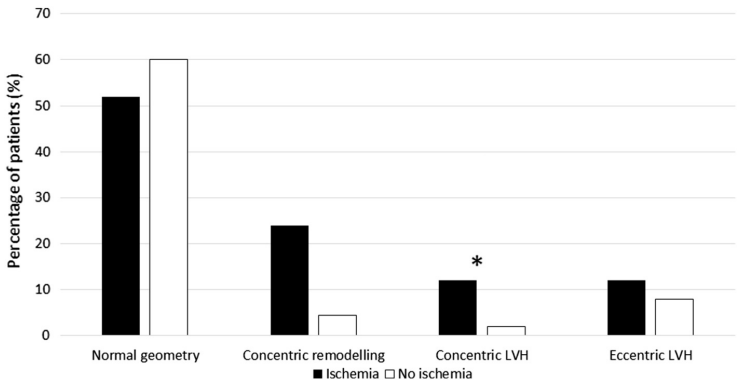

Fig. 1. Left ventricular geometry in patients with and without myocardial ischemia. Figure legend: LVH, Left ventricular hypertrophy. *p < 0.05 between groups.

Table 2
Covariables of myocardial ischemia identified in logistic regression analyses.

Variable	Univariable analysis			Multivariable analysis		
	OR	95% CI	p	OR	95% CI	p
LVH	2.87	1.04–7.88	0.041	3.19	1.04–9.76	0.043
Age (years)	1.02	0.98–1.06	0.315	0.99	0.94–1.04	0.623
Hypertension	2.05	0.92–4.59	0.080	2.24	0.97–5.65	0.059
Obesity	0.41	0.18–0.94	0.035	0.38	0.15–1.00	0.049
Hypercholesterolemia	1.65	0.83–3.28	0.157	1.98	0.92–4.28	0.083
Calcium score	1.00	0.99–1.01	0.461	1.00	0.99–1.01	0.874
Segment involvement score	1.18	0.94–1.49	0.159	1.19	0.87–1.65	0.280
Female sex	0.81	0.41–1.62	0.555			
Diabetes	0.95	0.33–2.70	0.919			
Current smoking	0.62	0.23–1.67	0.344			

OR, odds ratio; CI, confidence interval; LVH, left ventricular hypertrophy.

Coronary artery calcium score and segment involvement score (SIS), reflecting extent and severity of non-obstructive CAD, did not differ between the groups (Table 1).

By myocardial contrast stress echocardiography, 89% of patients reached age predicted maximal heart rate at peak stress. Nine of the 14 patients (65%) with lower than predicted maximal heart rate at peak stress had myocardial ischemia. Patients with and without myocardial ischemia had similar peak systolic blood pressure and heart rate (121 ± 23 vs. 123 ± 22 mm Hg, $p = 0.616$ and 132 ± 10 vs. 132 ± 11 beats per minute, $p = 0.846$). Fifteen patients (11%) had abnormal wall motion at peak stress. In 11 of these 15 patients wall motion abnormality was in the region supplied by the left anterior descending artery. The average extent of stress induced myocardial ischemia was 5 ± 3 LV segments. Wall motion abnormalities were significantly correlated with perfusion abnormalities during stress echocardiography, in which 13 (87%) of the patients with wall motion abnormalities also had perfusion abnormalities ($p = 0.006$). However, most patients with perfusion abnormalities had no concomitant wall motion abnormalities.

3.2. Covariates of myocardial ischemia

In univariable logistic regression analysis, myocardial ischemia was associated with presence of LVH and absence of obesity (Table 2). Myocardial ischemia remained independently associated with presence of LVH in multivariable analysis even after adjusting for age, hypertension, obesity, hypercholesterolemia, calcium score and SIS (Table 2).

In univariable linear regression analyses, larger extent of myocardial ischemia was associated with presence of LVH, hypertension and hypercholesterolemia (Table 3). In multivariable linear regression analysis, larger extent of myocardial ischemia remained associated with LVH independent of hypertension, obesity, hypercholesterolemia, calcium score and SIS (Table 3).

Table 3
Linear regression analyses of covariables associated with the extent of myocardial ischemia.

Variable	Univariable analysis		Multivariable analysis	
	β	p	β	p
LVH	0.19	0.034	0.23	0.010
Age (years)	0.002	0.984	−0.18	0.056
Hypertension	0.20	0.021	0.25	0.005
Obesity	−0.16	0.069	−0.18	0.044
Hypercholesterolemia	0.18	0.039	0.24	0.006
Calcium score	0.09	0.329	0.12	0.233
Segment involvement score	0.12	0.176	0.06	0.519
Female sex	−0.11	0.191		
Diabetes	0.09	0.325		
Current smoking	−0.09	0.335		

Multiple $R^2 = 0.18$, $p = 0.001$.
LVH, left ventricular hypertrophy.

4. Discussion

4.1. Myocardial ischemia and non-obstructive CAD

The present study demonstrates that about 50% of patients with stable angina and non-obstructive CAD have myocardial ischemia that can be detected by myocardial contrast stress echocardiography. The present results add to current knowledge by identifying the association of LVH with presence and extent of myocardial ischemia in these patients, independent of presence of hypertension.

Traditionally, myocardial ischemia has been perceived as secondary to coronary artery disease which directly obstructs blood flow to the myocardium [9,24]. However, we and others have previously demonstrated that myocardial ischemia may be present also in non-obstructive CAD [8,15,25]. The association between myocardial ischemia and LVH is well known as one of several mechanisms that may contribute to myocardial ischemia in patients with non-obstructive CAD, in addition to coronary vasospasm, coronary microvascular and endothelial dysfunction [1,10,26]. For instance, subendocardial ischemia and reduced myocardial blood flow have been detected by single photon computed tomography and positron emission tomography in patients with hypertrophic cardiomyopathy and in diabetes patients with LVH [27–29]. Reversible and irreversible ischemia was also detected in 35% of patients with LVH and exercise induced ST-depression, and was particularly prevalent in patients with concomitant CAD [30]. Further, in line with our results, it has previously been reported that LVH may contribute to lower the ischemic threshold in patients with hypertension and clinical evidence of CAD [31].

In animal studies, LVH has been suggested to contribute to myocardial ischemia through several mechanisms, such as reduced myocardial capillary density, increased LV filling pressure and increased myocardial oxygen demand [32,33]. In patients with ST elevation myocardial infarction, presence of LVH has been associated with higher incidence of microvascular obstruction as well as larger myocardial infarct size by cardiac magnetic resonance imaging [34]. The present results add to this by demonstrating that LVH may contribute to myocardial ischemia also in patients with stable angina and non-obstructive CAD.

As demonstrated, presence of hypertension was associated with larger extent of myocardial ischemia independent of LVH in our study. This suggests that hypertension contributes to myocardial ischemia through several mechanisms beyond the higher LV mass. As recently pointed out by Bairey Merz et al., hypertension may also influence myocardial perfusion in non-obstructive CAD through impaired vasomotion, endothelial dysfunction, atherosclerosis, reduced coronary microvascular density and thickened and stiffened microvessels with poor autoregulatory capacity [1].

In addition to LVH and hypertension, absence of obesity and presence of hypercholesterolemia were associated with a larger extent of myocardial ischemia in our study. The inverse association between obesity and myocardial ischemia was unexpected, and could not be explained by group-differences in sex or smoking. On the other hand, elevated total cholesterol is a well-established risk factor of CAD [35]. Furthermore, myocardial ischemia was not detected in all patients with LVH, suggesting that the etiology of myocardial ischemia was multifactorial also in our study.

Although the present study is small, our results may have potential important clinical implications for management of patients with non-obstructive CAD and stable angina. Current guidelines for management of patients with stable angina have pointed out the need for scientifically based management of non-obstructive CAD [36]. In particular, echocardiographic detection of LVH and myocardial ischemia may offer targets for a more personalized management of patients with non-obstructive CAD, pointing to the value of multimodality imaging in these patients. Moreover, antihypertensive treatment is associated with normalization of LV geometry and improved prognosis [11,37]. Our results also emphasize the importance of cardiovascular risk

control. In line with this, it has recently been demonstrated that in patients with non-obstructive CAD and myocardial infarction, the risk of new major cardiovascular events is predicted by established cardiovascular risk factors, including hypertension, diabetes and smoking [38]. Further, patients with non-obstructive CAD less often receive secondary preventive medication after myocardial infarction [39]. Accordingly, optimal medical treatment of non-obstructive CAD should be verified in prospective clinical studies.

4.2. Study limitations

We have selected a population with high risk of cardiovascular disease and our results cannot necessarily be generalized to a general angina population. The cross-sectional study design precludes identification of any causal relation between LVH and myocardial ischemia. The proportion of women was lower than what could be expected [40]. This might be explained by a referral bias, as only patients referred to CCTA by a cardiologist due to suspected CAD were eligible for inclusion. It is well documented from the Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter (CONFIRM) registry that women referred to CCTA have a higher pre-test probability of CAD then men [41]. In addition, the small study size did not allow stratification of the results by sex due to insufficient statistical power. However, our study population reflects a large group of patients in clinical practice who currently lack evidence-based guidelines for diagnostic work-up and management.

5. Conclusion

In patients with stable angina and non-obstructive CAD on CCTA, myocardial ischemia was found in half of the patients and was independently associated with presence of LVH. Our results suggest LVH as a potential treatment target in patients with stable angina and non-obstructive CAD to be explored in further clinical studies.

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Declarations of interest

The authors report no relationships that could be construed as a conflict of interest.

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