Explorations by cardiac computed tomography angiography

CORONARY ARTERY STENOSIS, MYOCARDIAL INFARCTION, AND THE PATHOGENIC PATH TO HEART FAILURE

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Doctoral Thesis

Coronary artery stenosis, myocardial infarction and the pathogenic path to heart failure

*Explorations by cardiac computed tomography angiography*

Jørgen Tobias Kühl
The main results of this thesis have been published in the following papers


Papers V, VI and VII are based on results that are a part of my PhD thesis 'Left atrial mechanical function in patients with ischemic heart disease assessed with multi-detector computed tomography’ KU, November 2013. The remaining papers and the included results have not previously been submitted with the purpose of obtaining an academic degree.
Preface

This thesis has been under preparation for some time. The first studies were started during my years as a medical student and continued during my employment as research fellow and later as postdoc at the Cardiac CT research unit at Rigshospitalet.

My aim was to explore the (at the time) newly developed cardiac CT angiography in patients with myocardial infarction, not only to describe the luminal narrowing of coronary arteries but also to explore relevant information provided in adjacent (non-coronary) structures, which comes along the scan as a “free lunch”. It was my belief that these structures could provide information relevant for patient treatment and prognosis.

My investigations began as a detailed study of the left atrial mechanical function, which was somehow like starting the Odyssey with the Polyfem – i.e. with a challenge somewhere in the middle of the story. From there I had to go both “upstream” and “downstream” to get a more complete account of the pathogenic path to heart failure; from coronary pathology in patients with myocardial infarction to abnormalities in myocardial perfusion, alterations in the cardiac (atrial) function and to signs of pulmonary congestion.

At the same time I had to try to assess the accuracy of the CT tool to explore whether the image that it produces of all these structures is a correct representation of reality or whether it is disrupted, causing false beliefs. This is inherently difficult as it requires some means of justification that substantiate that the scans convey correct representations of the heart (and adjacent structures). Coherence with other imaging modalities, or with previously known physiology or with clinical presentations and outcomes may contribute to such justification. To assess the accuracy of CT angiography in patients with NSTEMI we used invasive coronary angiography. With regard to myocardial perfusion and perfusion gradients we used two populations without epicardial disease to assess if we could reproduce previous physiological findings. To explore the ability to describe left atrial function we included two different populations to assess the relationship to heart failure and to compare CT assessment of LA function with other imaging modalities. To evaluate the ability to describe pulmonary congestion from CT angiographic images we used clinical heart failure presentation and the cardiac chamber function of the patients.

I would like to thank the Department of Cardiology, The Heart Centre and the Department of Radiology, Diagnostic Centre, Rigshospitalet, University of Copenhagen, for providing excellent working conditions. The Research Fund of Rigshospitalet generously supplied me with three years of funding and additional funding was supplied by Michaelsen Fonden and the Danish Agency for
Science, Technology and Innovation, The Danish Council for Strategic Research. Donations from the John and Birthe Meyer Foundation and from the A.P. Møller and Chastine McKinney Møller Foundation, Copenhagen, Denmark supplied the CT-scanners used by the cardiac CT research unit.

My work was done in collaboration with many good men and women without which this thesis could not have been made. First and foremost, I want to thank the Head of the Cardiac CT Research Unit at Rigshospitalet, Klaus Fuglsang Kofoed; for his remarkable restless and endless drive that seems to come from nowhere and takes everyone somewhere they haven’t been before – always to a place more confused, but on a higher level, thus always practicing the maieutic method of Socrates. I also want to thank him for taking care of the Cardiac CT Research Unit and for insisting on enjoying the scientific path. I deeply wish to thank Andreas Fuchs for all his invaluable help, enthusiasm and energy throughout the years. Further, I want to thank Thomas Skrårup Kristensen for always being the ‘radiological muscle’ especially when I entered new (extra-cardiac) land, and to Jesper James Linde and Mathias Sørgaard for being my sparring partners in developing CT myocardial perfusion. Thanks to Henning Kelbæk for the focus on relevance for the patient, to Jacob Eifer Møller for his efforts to share his profound knowledge of cardiac hemodynamics and to Lars Køber for the always sharp considerations on the scientific method and principles of justification. I should like to thank Head of the Department of Radiology Johnny Madelung for making things happen, and Kim Madsen and his hard working and very skilled team including Jane Poulsen, Stella Hansen, Charlotte Baltzersen and Tina Bock-Pedersen for invaluable help and CT expertise. At Johns Hopkins I wish to thank Richard T George, Joao Lima and the rest of the CORE 320 team for their inspiration and drive in developing CT perfusion imaging. Thanks to all the inhabitants of the overcrowded reading room through the years (aka the Cardiac CT Research Unit) I have received valuable suggestions and other kinds of help from (my apologies to anyone not mentioned) Kiril Ahtarovski, Mads Andersen, Ronan Berg, Christina Byrne, Martina De Knegt, Mads Ersbøll, Thomas Engström, Jeppe Gram, Anders Møller Greve, Mikkel Gybel-Brask, Sophia Hammer-Hansen, Jens Hove, Reza Jabbari, Peter Karl Jakobsen, Kashif Khan, Bettina Løjmand, Jakob Lønborg, Christina Møller, Olav Wendelboe Nielsen, Jonas Bille Nielsen, Anna Foged Thomsen, Kirsten Thrysøe, Niels Vejlstrup, Abbas Qayyum and anonymous referees.

Finally, I express my deepest gratitude to Anna Noushin Thstrup for unconditional support and love and for securing the inner borders when I was absent (minded) again.
1. Introduction

Coronary artery disease (CAD) is a frequent cause of morbidity and mortality. Among patients with CAD the most severely diseased are those who present with acute coronary syndrome (ACS) and myocardial infarction. In these patients both morbidity and mortality is substantial, especially in those who subsequently develop heart failure (HF).\textsuperscript{1,2}

It is important to find preventative and curative strategies that may improve the outcome of such patients and to do so, it is fundamental to identify the underlying pathological conditions responsible for the development of heart failure. This may help us to stratify our patients according to risk and guide patient management. The identification of CAD and the subsequent development of HF can be assessed at various levels of the disease, starting with the development of coronary atherosclerosis and luminal stenosis that may cause myocardial hypoperfusion or infarction and lead to the development of myocardial scars. This in turn will further lead to deterioration and failure of cardiac chamber function, the left ventricular function and the thin walled left atrium (LA), which may progress into pulmonary congestion and eventually symptoms of congestive heart failure.

Coronary computed tomography angiography

Within the last decade cardiac computed tomography angiography (CCTA) has developed as an important technique for non-invasive evaluation of the coronary arteries, especially in those with stable angina pectoris (SCAD). The clinical value of CCTA is primarily related to the ability to exclude coronary artery disease. In most multi-centre accuracy trials CCTA has proven to have a high negative predicative value compared to invasive coronary angiography (ICA),\textsuperscript{3,4} in agreement with prior meta-analysis,\textsuperscript{5,6} whereas one multi-centre study only showed moderate negative predicative values (83%-89%).\textsuperscript{7} CCTA has proven to be clinically useful in the diagnostic work-up of SCAD.\textsuperscript{8,9} Furthermore, CCTA has also proven to have strong prognostic value that leaves patients without significant CAD with good outcomes compared to those with significant CAD.\textsuperscript{10-13}

Accordingly, guidelines on patients with suspected SCAD have implemented the CCTA technique to be used in suitable patients with low to intermediate pre-test probability of CAD where local expertise is present.\textsuperscript{14}

The documented clinical value of the CCTA technique has led to higher availability worldwide and a higher level of expertise.\textsuperscript{15} The combination of availability and diagnostic accuracy has driven studies that have assessed the clinical feasibility of coronary assessment in patients with CAD beyond that of low-intermediate pre-test probability of SCAD. This expansion of patient categories has been tested in various settings, including those with high pre-test probability of SCAD,\textsuperscript{16} as well
as patients with acute chest pain presentation in the emergency room with possible ACS. These studies found a preserved high negative predictive value of CCTA and/or a benign clinical outcome in the presence of a normal scan in such patients. A recent guideline paper further states that CCTA “can be considered to exclude ACS when there is a low-to-intermediate likelihood of CAD and when troponin and electrocardiogram (ECG) are negative or inconclusive”. This however represents a significant change with an expansion of the CCTA patient target group which is not (yet) endorsed by the cardiac community. This requires scientific evidence: thus the use of CCTA should be explored in a large group of ACS patients with chest pain and elevated troponins but with an ECG presentation without ST segment elevation (NSTEMI). In the setting of ACS, however, the focus on the role of the CCTA procedure may change from ruling out significant disease to further assisting clinical management.

Previous studies of CCTA in patients with ACS have been concerned mainly with the diagnostic test rates and the possibility of excluding significant CAD. As it is known that 15-20% of ACS patients are without significant CAD this is valuable, however this does not probably encompass the full potential of the technique, which could possibly be used in the clinical treatment triage and risk stratification of patients. CCTA could possibly contribute to patient triage, by classifying patients into treatment groups of ‘no or medical treatment’, ‘percutaneous coronary intervention’ or ‘bypass surgery’. Further CCTA assessment of the coronaries could also call attention to those with occluded vessels and transmural myocardial infarction despite an ECG presentation without ST segment elevation. Finally CCTA could additionally play a role in risk stratification not only by assessing the coronaries but also the adjacent structures: myocardium, cardiac chambers and the pulmonary tissue for signs of heart failure.

Concomitant imaging of the pathogenic path to heart failure

In addition to visualization of coronary arteries CCTA provides a high resolution image of the myocardium, the cardiac chamber function and the pulmonary tissue adjacent to the heart – images that may be used to enlighten the pathogenic path to potential co-existing or subsequent clinical heart failure.

Assessment of the myocardial infarct extent using myocardial perfusion imaging is known to predict prognosis. As previous studies have shown that CT is able to detect and quantify myocardial infarcts, it is important to explore if this prognostic information is embedded in the CCTA images and available to the reader. Further, the use of CCTA technique to assess perfusion may contain possibilities not previously explored in humans. Although experimental studies have systematically used the ratio between endocardial and epicardial blood flow as a sensitive and
robust measure of pathological changes in myocardial perfusion, this has rarely been assessed in humans due to the limited spatial resolution of older non-invasive imaging techniques. With increasingly sensitive detector elements that enable sub-millimeter spatial resolution, CT imaging could theoretically move forward this type of research in man. The feasibility of such a research area should be explored in infarct patients as well as in those without significant coronary disease to get modality-specific knowledge of normal values, and potentially to reproduce physiological properties of myocardial circulation previously described in experimental studies.

The physiology and prognostic implications of left ventricular enlargement and decreased systolic function is well described in patients with myocardial infarction. At the same time, abnormal left atrial volume – a known marker of diastolic dysfunction - has previously been described in these patients. However in contrast to the LV only the prognostic value of the left atrial maximal volume is known. The relation between left atrial function and LV systolic dysfunction, clinical heart failure and prognosis is largely unknown. This is likely to be due to the inherent difficulties in assessing the subtle differences in LA volume changes throughout the cardiac cycle. With concomitant imaging of the phasic volume changes it could be feasible to describe the left atrial function using CCTA images.

The development of myocardial infarction and the following failure of cardiac chamber function (systolic and diastolic) may lead to clinical heart failure. Clinical heart failure is strongly associated with adverse outcome especially after myocardial infarction. Direct tomographic imaging of the pulmonary tissue to assess the relationship between congestion and stages of clinical heart failure presentation is of substantial interest and could be a useful and sensitive prognosticator. Computed tomography has been used as golden standard for other imaging modalities in assessing pulmonary congestion. Surprisingly however the relation between CT signs of pulmonary congestion on the one hand and cardiac function, clinical heart failure status and outcome on the other is not yet explored. Also, despite the concomitant imaging of pulmonary tissue adjacent to the heart, it is not yet known if pulmonary congestion can be assessed from CCTA images. All of these pathophysiological stages are important on the path to clinical heart failure and may be correlated with prognosis.

The aims of this thesis were
I. To test the hypotheses that there is good diagnostic accuracy of CCTA in patients with Non-ST segment myocardial infarction (NSTEMI) compared with ICA and that it is possible to use CCTA in the clinical treatment strategy triage.

II. To test the hypothesis that patterns of intersegmental relative myocardial perfusion estimated at rest using CTTA correspond to that found by Positron emission tomography (PET) and to test the hypothesis that relative regional transmural perfusion gradients at rest and during adenosine stress in patients without significant CAD on CCTA can reproduce physiological findings from animal studies.

III. To test the hypothesis that CCTA-based assessment of transmural perfusion gradients and myocardial perfusion reserve in 3 myocardial layers relates to demographical data and cardiovascular risk profile in patients without significant coronary artery disease. Furthermore, that CCTA-based assessment of transmural perfusion gradients at rest and adenosine stress correlates with findings from other imaging modalities.

IV. To test the hypothesis that the extent and severity of left ventricular myocardial hypoperfusion at rest, in addition to signs of myocardial scar as assessed by CCTA images, are related to adverse long-term outcome in patients with NSTEMI.

V. To test the hypothesis that assessment of LA mechanical function in patients with ischemic heart disease using CT is feasible and to investigate the relation between LA mechanical function and LV function as well as the clinical heart failure status.

VI. To test the hypothesis that CT assessment of LA mechanical function compares well with assessment by echocardiography and magnetic resonance imaging and to test the hypothesis that there is acceptable inter-observer variability of the method.

VII. To test the hypothesis that measures of LA function are independent predictors of mortality in patients with acute myocardial infarction.

VIII. To test the hypothesis that signs of pulmonary congestion assessed in cardiac computed tomography angiographic (CCTA) images, are related to clinical heart failure status, cardiac function, and adverse outcome in patients with NSTEMI.

These numbered hypotheses have been tested in the papers with the corresponding numbers (I-VIII).
Figure 1: Overview of papers.

**Paper I** assesses the diagnostic test rates and the possibility of clinical triage using CCTA. **Papers II & III** investigate the feasibility of using CCTA in assessment of myocardial perfusion, as well as normal values of perfusion and transmural myocardial perfusion gradients in humans without significant CAD, whereas **paper IV** applies the use of transmural perfusion gradients and hypoperfusion in a NSTEMI population and relate it to outcomes. **Paper V** investigates the feasibility of assessing LA mechanical function with CCTA and relates findings to heart failure, while **paper VI** validates the assessment of LA mechanical function against echocardiography and cardiac magnetic resonance imaging. **Paper VII** investigates the association between LA mechanical function and outcome. **Paper VIII** investigates CCTA image assessment of pulmonary congestion in relation to cardiac function, clinical heart failure symptoms and outcome. CCTA: Cardiac coronary angiography. ICA: Invasive coronary angiography. LA: Left atrium.
2. Material and methods

Patient populations

Patient populations studied in this work are summarized in (Table 1; A to E). The main focus of this thesis was to explore the use of CCTA in NSTEMI patients (Patient group A). As several new areas of research were explored for the first time with CCTA, we included other patient groups in order to validate the CT assessment of myocardial perfusion and left atrial function.

**Myocardial perfusion:** We included healthy individuals (B1, B2) and chest pain patients without significant coronary disease (B3, C) in order to assess normal perfusion values with CT (rest and adenosine stress) and relate these findings to known determinants of myocardial perfusion.

**Left atrial function:** We included patients with various degrees of ischemic heart disease (Group D) and recent myocardial infarct (Group E) in order to: (1) Test the feasibility of CT assessment of LA mechanical function (2) To validate CT derived LA assessment against other imaging modalities and (3) to explore the relation between LA function and clinical heart failure.

All research protocols were conducted in accordance with the principles of the declaration of Helsinki and all protocols were approved by the local ethics committee. All participants gave written and oral informed consent.

**Table 1 Patient groups examined in this thesis**

<table>
<thead>
<tr>
<th>PATIENT GROUPS</th>
<th>A</th>
<th>B1</th>
<th>B2</th>
<th>B3</th>
<th>C</th>
<th>D</th>
<th>E</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No. Patients</strong></td>
<td>400</td>
<td>14</td>
<td>14</td>
<td>14</td>
<td>149</td>
<td>40</td>
<td>54</td>
</tr>
<tr>
<td><strong>Age (mean±SD)</strong></td>
<td>61±12</td>
<td>56 ± 4</td>
<td>56 ± 4</td>
<td>53 ± 14</td>
<td>61 ± 10</td>
<td>61±13</td>
<td>61±10</td>
</tr>
<tr>
<td><strong>Gender, female No. (%)</strong></td>
<td>92 (24%)</td>
<td>3 (21%)</td>
<td>3 (21%)</td>
<td>4 (29%)</td>
<td>75 (50%)</td>
<td>8 (20%)</td>
<td>13 (24%)</td>
</tr>
<tr>
<td><strong>Patient Characteristics</strong></td>
<td>NSTEMI</td>
<td>Asymptomatic healthy controls from the Copenhagen General Population Study. Normal ECG. Normal exercise test or CCTA</td>
<td>Chest pain patients, no significant CAD on CCTA</td>
<td>Chest pain patients, no significant CAD on CCTA</td>
<td>Various CAD on ICA</td>
<td>Post STEMI</td>
<td></td>
</tr>
<tr>
<td><strong>LVEF by CT (range)</strong></td>
<td>58% (13-83)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>51% (21-82)</td>
<td>56% (23-76)</td>
</tr>
<tr>
<td><strong>HF symptoms</strong></td>
<td>45 (12%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>NA</td>
<td>10 (25%)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Scan Type</strong></td>
<td>64 slice CT</td>
<td>NH3 positron emission tomography</td>
<td>320 slice CT</td>
<td>320 slice CT</td>
<td>320 Slice CT</td>
<td>64 slice CT</td>
<td>64 slice CT</td>
</tr>
<tr>
<td><strong>Papers</strong></td>
<td>I, IV, VII, VIII</td>
<td>II</td>
<td>II</td>
<td>II</td>
<td>III</td>
<td>V</td>
<td>VI</td>
</tr>
</tbody>
</table>
Patients with contraindication to CCTA were excluded, including those with known renal disease, increased creatinine and those with atrial fibrillation, known allergy to contrast along with those that were hemodynamic unstable.

**Population A (Paper I, IV, VII, VIII):** An observational study with the aim of evaluating the clinical use of CCTA in NSTEMI patients. Included patients were presenting at a local hospital with NSTEMI and transferred to Rigshospitalet for CCTA scan prior to invasive investigation and treatment.

**Population B1, B2 (Paper II):** An observational study to evaluate patterns of intersegmental relative myocardial perfusion estimated at rest using $^{13}$NH$_3$ PET and 320 row CTTA in asymptomatic healthy participants from the Copenhagen general population study. All participants were recruited with the following criteria: Age 50–65 years, no history of cardiovascular disease, normal resting blood pressure and normal electrocardiogram. Subjects with normal exercise test were selected for $^{13}$NH$_3$ PET perfusion (Group B1) and age and gender matched subjects without epicardial coronary artery disease on 320 detector CT (Group B2) were evaluated with CCTA rest perfusion.

**Population B3 (Paper II):** To assess relative regional transmural perfusion gradients at rest and during adenosine stress we included patients from the CArdiac cT in the treatment of acute CHest pain (CATCH) trial presenting with chest pain, but with normal troponins and normal ECG and without significant CAD on CCTA.18

**Population C (Paper III):** In this observational study of myocardial perfusion during rest and adenosine stress we included patients with ischaemic symptoms that were later found by invasive coronary angiography to be without obstructive coronary artery disease. These patients were recruited in the CORE 320 multicentre trial and demographical data as well as data on CT perfusion and invasive coronary angiography were available.26

**Population D (Paper V):** To evaluate the feasibility of LA function with CCTA and relate it to heart failure presentation, we included patients that were randomly selected from 500 patients undergoing CCTA for evaluation of known or suspected coronary artery disease at various clinical presentations (stable coronary artery disease and acute coronary syndrome). Patients were included in two groups (2x20) stratified according to their left ventricular ejection fraction (LVEF), and patient data obtained from medical charts.

**Population E (Paper VI):** To evaluate the intermodality agreement of the assessment of LA function, we included patients 3 months after treatment for ST-segment elevation myocardial infarction. These patients were all clinically stable and were all on optimal medical treatment, and
were without significant valve disease at the time of the investigation as assessed using transthoracic echocardiography.

Cardiac CT scan technique

The development of multi-detector CT scanners has allowed for high resolution images of the coronary arteries.\textsuperscript{27,28} Imaging of the coronary arteries is imaging of small (>1.5-5 mm) complexly moving entities that should be represented in a true and useful manner. Successful imaging requires preparation and an imaging technology with high spatial and temporal resolution.

\textbf{The spatial challenge:} Pre-medication with nitroglycerin will dilate the coronaries and thus increase the overall size of the vessel. At the same time modern scanners with small detector elements and matching high signal sensitivity permits for image reconstruction of isotropic voxels (0.5x0.5mm) which means that images can be evaluated in 3 dimensions with a high image quality.

\textbf{The temporal challenge:} Imaging of the moving coronaries is performed by 1) optimizing temporal resolution and 2) imaging in the cardiac phases in which the heart has the least movement. The heart has less movement twice during the cardiac cycle; during isovolumetric relaxation and diastase (Figure 2: Time motion graph).

Despite constant improvements in temporal resolution of CT scanners it remains crucial that imaging is done during these phases. This is achieved by synchronizing image acquisition with the ECG. Synchronization can be performed retrospectively or prospectively. In \textit{retrospective gating} (helical or volume) a cardiac scan is done with constant radiation during the entire heart cycle (Figure 3). Afterwards, the images can be reconstructed at any point of the cardiac cycle allowing for assessment of both coronary arteries and cardiac function. High X-ray tube current necessary for visualization of coronary arteries can be limited to the diastasis phase (around 72%-76\%) in

![Time motion graph](image)

\textbf{Figure 2: Time motion graph}

Time motion graph generated from automated cardiac motion maps during the cardiac cycle (Figure from Toshiba Medical Systems, with permission)
patients with relatively low heart rates (< 65). Retrospective gating with dose modulation lowers the radiation dose to some extent (around 30%). In patients with higher heart rates (> 65) the diastasis phase shortens or disappears and the most motion-free phase is during isovolumetric relaxation – which then requires full radiation exposure. Using prospective gating technique the patient exposure to radiation is narrowed to a small part of the heart cycle where motion is expected to be lowest. This may save up to 75% of the radiation dose, but the “down side” is that functional analysis of the heart is not possible.

Projection data from 180 degrees is necessary for image reconstruction in 3D, and the temporal resolution is thus calculated as the rotation time of the X-ray tube divided by 2. The temporal resolution is further improved by using high-end scanners with a rotation time between 300-350ms combined with the use of multi-segment acquisition (where patients with stable heart rate use projection data from less than 180 degrees from several succeeding heart beats).30;31

Figure 3 types of ECG-gating
A: Retrospective gating: uniform tube current
B: Retrospective gating: reduced tube current during systole and increased during diastole.
C: Prospective gating: exposure of radiation only in a small portion of diastole.

Multi-segment acquisition and reconstruction can be performed over several heart beats with the aim of optimizing temporal resolution

**Image quality:** Contrast enhancement of the coronaries is achieved by relatively fast (5-6ml/s) administration of an iodine contrast bolus (optimized to patient BMI) and a robust acquisition timing strategy, using bolus tracking in the descending aorta. This gives a high signal in the coronaries compared to the adjacent tissue (optimally 400-600HU). At the same time *image noise* can be held low by optimizing scan parameters such as tube voltage and current to fit body size.

**Scanner type:** Two types of scanners used and the most important differences are presented in Table 2.
Table 2: CT scanners used in the papers of the thesis

<table>
<thead>
<tr>
<th></th>
<th>Aquillion 64</th>
<th>Aquillion One</th>
</tr>
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<tbody>
<tr>
<td>Slice</td>
<td>64</td>
<td>320</td>
</tr>
<tr>
<td>Z-axis coverage</td>
<td>4 cm</td>
<td>16 cm (whole heart)</td>
</tr>
<tr>
<td>Rotation time</td>
<td>0.35-0.5 sec</td>
<td>0.35 sec</td>
</tr>
<tr>
<td>Acquisition mode</td>
<td>Helical</td>
<td>Volume</td>
</tr>
<tr>
<td>Gating technique</td>
<td>Retrospective gating with dose modulation</td>
<td>Prospective gating</td>
</tr>
<tr>
<td>Used in studies</td>
<td>I, IV, V, VI, VII, VIII</td>
<td>II, III</td>
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</tbody>
</table>

The wide detector scanners with broad axial coverage have made it possible to record cardiac images in humans within one heartbeat. Compared to scanners with less axial coverage, 320 multi-detector CT (MDCT) provides images with temporal uniformity of contrast distribution throughout the entire myocardium.

**Radiation**

The scanner settings (tube current and voltage) determine the radiation dose emitted, measured in the CTDI\textsubscript{vol}, thus the CTDI\textsubscript{vol} and the length of the scan field determine the level of radiation exposure. The dose length product is calculated as CTDI\textsubscript{vol} x length of the scan field [mGy*cm]. The dose length product is then multiplied with a tissue specific conversion factor (an empirical found factor that depends on the type of tissue exposed), to obtain an approximation of the effective dose. A conversion factor of 0.014 is typically used for chest examination.\textsuperscript{32} It is estimated that the life time risk of developing cancer in the western world is approximately 25\% and further that the exposure to radiation during CT may increase the lifetime risk by 5\% pr Sievert. The radiation dose reported in the studies of the present thesis was between 3 and 19 mSv, which is comparable to the radiation dose reported in contemporary CT studies of the same type.\textsuperscript{33-35} In contrast contemporary CT scanners may reduce radiation exposure substantially using prospective gating and iterative reconstruction algorithms.\textsuperscript{33,36}
3. Coronary artery disease

Pathology of the coronary vessels
The cause of CAD is a systemic arterial pathology in which lipids start to accumulate in the lamina elastica interna of the vessels. This leads to the formation of a lipid core which is surrounded by fibrous tissue. This may lead to positive remodelling of the artery and further to the formation of intra-luminal vessel stenosis. The severity of CAD range from the sub-clinical manifestation of coronary plaque to the appearance of symptoms with stable angina pectoris caused by a luminal narrowing in one or more coronary arteries or to ACS caused by acute thrombosis induced by a ruptured fibro-atheroma that cause a sudden and critical myocardial hypoperfusion due to partial or total occlusion of a coronary artery. This latter event is thought to be triggered by hemodynamic stress, biochemical processes within the plaque and/or changes in vasomotor tone and appears to be related to certain tissue characteristics of the coronary plaque.

The diagnosis of ACS is comprised of three subcategories: Patients with myocardial infarction (with rise and fall in myocardial specific biomarkers – e.g. troponins) with (1) persistent ST-segment elevation (STEMI), and (2) without persistent ST-segment elevation (NSTEMI) as well as (3) patients with symptoms of unstable angina pectoris at rest or minimal exertion without myocardial necrosis. The treatment of patients with STEMI is immediate reperfusion by primary angioplasty or fibrinolysis, and will therefore not become a target group for CCTA. In contrast 40% of patients with non-ST segment elevation ACS will not need percutaneous coronary intervention (PCI) and could possibly benefit from a CCTA based triage. Accordingly, in this section the primary focus will be on patients with NSTEMI.

CCTA imaging of coronary arteries in patients with NSTEMI.
Approximately 60% of patients presenting with NSTEMI require PCI treatment; the rest are treated with either medication alone or with coronary artery bypass graft surgery. In theory CCTA before ICA could thus potentially reduce the number of invasive procedures by up to 40%. It is therefore relevant to explore if CCTA can be used in the triage of these patients into appropriate treatment groups, especially those in whom troponins are inconclusive. CCTA in this patient group may however constitute certain challenges regarding diagnostic accuracy, logistical setup and potential harm to the patients.
In CCTA imaging of acute/subacute NSTEMI patients there is a risk of performing non-diagnostic scans due to cardiac motion in those with high heart rates – combined with a relatively high risk of artefacts due to stents and extensive coronary calcium. These challenges can partially be met by using retrospective gating that allows for image reconstruction during both isovolumetric relaxation and diastasis and by improving the temporal resolution using multi-segment acquisition.

Several studies which have investigated the importance of early invasive intervention in patients with non-ST segment elevation ACS and randomised controlled trials in addition to meta-analyses have suggested some benefit from this approach, however without significant impact on frequency of re-infarction or death. There is a statistically significant lower risk of recurrent ischaemia and adverse outcome in high risk patients, which however suggests that a treatment delay should - ceteris paribus - be avoided. Recent studies of patients with suspected ACS have shown that it is logistically possible to perform CCTA in the emergency room setting - with an approximate scan-time of 10-15 minutes. On-going clinical trials will reveal if such a strategy is possible and clinically beneficial in patients with confirmed ACS (ClinicalTrials.gov Identifier NCT02284191 (RAPID CTCA) and NCT02061891 (VERDICT trial)).

Contrast induced nephropathy (defined as a >25% rise in se-creatinine or a total increase of > 44μmol/l) - which is associated with adverse outcome, could be a risk in patients that receive contrast during CCTA, especially in patients undergoing subsequent multi-vessel PCI. Only one study has assessed the frequency of contrast induced nephropathy after CCTA and invasive coronary angiography and found a relatively low incidence. Nevertheless, contrast induced nephropathy may be higher in some angiographic subsets where patients require complex single or multi-vessel PCI. Further studies of this topic are needed.

CCTA compared to ICA.

**Diagnostic accuracy of CCTA compared to ICA**

The diagnostic accuracy of CCTA compared to ICA has primarily been tested in outpatient clinics in patients with known or suspected SCAD, where a consistent finding has been a high negative predictive value. Several studies have shown that diagnostic accuracy is decreased in patients with a higher prevalence of disease and with increasing levels of coronary calcium, as well as in patients of higher age and with higher frequency of NYHA class >1 or chronic obstructive
pulmonary disease. A lower diagnostic accuracy could therefore be expected in CCTAs of sub-acutely scanned unstable angina pectoris and NSTEMI patients.

Only a handful of studies have assessed the diagnostic value of CCTA in ACS. One study of ACS patients found a negative predictive value of only 60% (per patient level). In contrast all other studies of NSTEMI patients, including Paper I, have found that the NPV remains high (95%-100%) (see Table 3).

CCTA in NSTEMI patients could possibly be used to triage patients and identify which coronary vessels should be revascularized. This however requires not only the ability to exclude disease, but also to detect truly diseased vessels, thus the positive predictive value on a “per coronary segment basis” should be high to avoid futile ICA or coronary artery bypass grafting (CABG). Indeed it has been a consistent finding that the positive predicative value was low. In ACS patients with a prevalence of disease of 73% to 85%, the positive predicative value on per segment basis was 47%-85%, which in a triage setting could lead to “over diagnosis” of treatment group.

### Table 3 Diagnostic accuracy of CCTA in ACS patients

<table>
<thead>
<tr>
<th>YEAR</th>
<th>AUTHOR</th>
<th>SCAN NER</th>
<th>PATIENT TYPE</th>
<th>N</th>
<th>EVALUABLE SEGMENTS</th>
<th>PREVALENCE OF &gt; 50% STENOsis</th>
<th>SENS</th>
<th>SPEC</th>
<th>PPV</th>
<th>NPV</th>
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<tbody>
<tr>
<td>2005</td>
<td>Dirksen et al.</td>
<td>4 Slice</td>
<td>UAP</td>
<td>25</td>
<td>NA</td>
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<td>NA</td>
<td>NA</td>
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<td>NA</td>
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<td>Segments</td>
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<td>Segment</td>
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<td>75</td>
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<td>47</td>
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<td>NSTEMI</td>
<td>400</td>
<td>82%</td>
<td>Patient</td>
<td>99</td>
<td>81</td>
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<td>Segment</td>
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<td>94</td>
<td>73</td>
<td>98</td>
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</tbody>
</table>

Only two studies (including one small pilot study with 22 patients) have reported the ability of CCTA to “triage” NSTEMI patients into treatment strategy groups (No/medical treatment, PCI, CABG) compared to triage by ICA. In accordance with the previously published pilot study, we found (in Paper I) that very few patients are miss-classified to a “less invasive” treatment strategy (e.g patients that require PCI are seldom referred for “no/medical treatment by CCTA, and patients
that require CABG are seldom referred for PCI, Figure 4). Thus CCTA could play a role as a rule-out tool that would allow certain groups of patients to stay at a local hospital and not be referred to an invasive centre.

<table>
<thead>
<tr>
<th>Treatment strategy</th>
<th>No or medical N = 68</th>
<th>PCI n=198</th>
<th>CABG n = 104</th>
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<tr>
<td>by ICA</td>
<td>81%</td>
<td>81%</td>
<td>99%</td>
</tr>
<tr>
<td>by CTA</td>
<td>1%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Figure 4 Diagnostic performance of coronary cardiac computed tomography angiography (CTA) for placing patients in anatomical guideline defined treatment groups as determined by invasive coronary angiography (ICA). GREEN: candidates for no or medical treatment, BLUE: candidates for percutaneous coronary intervention (PCI) and RED: candidates for coronary artery bypass grafting (CABG). Figure from Paper I.

On the other hand we found that patients who according to ICA should have had no/medical treatment were often assigned to PCI treatment and patients that should have received PCI treatment according to ICA were often assigned CABG (Figure 4).

This could suggest that more than the evaluation of CCTA diameter stenosis is necessary. Recent studies have suggested that the finding of a CCTA stenosis should be followed by further refined studies in terms of either adenosine induced CT perfusion assessment\textsuperscript{35;54-57} or CT derived fractional flow reserve measurements\textsuperscript{58-60} to better determine the hemodynamic properties of the identified lesion. This suggestion is also in line with the landmark FAME trial which suggested that treatment strategy should be based on functional/hemodynamic properties of a coronary stenosis rather than anatomy alone,\textsuperscript{61;62} and papers that have shown that neither CCTA nor ICA derived QCA are good in determining the hemodynamic significance of a stenosis.\textsuperscript{63-65}

CCTA and relation to clinical outcome

The absence of CAD on CCTA is associated with an excellent prognosis for symptomatic patients being evaluated for suspected CAD (both SCAD and chest pain patients without ACS). The annual event rate for those with normal CCTA findings is less than 1% and comparable to that of healthy low-risk individuals (>1%).\textsuperscript{11;12;19;46;66} This is a consistent finding through many single-centre studies and a meta-analysis, and it allow us safely to discharge these patients. A meta-analysis has shown that patients with non-obstructive disease on CCTA have a markedly higher annual event-
rate compared to patients without any visible coronary disease (1.4% for MACE), which, however, was again markedly higher in those with obstructive disease (8.8% annual MACE rate).\textsuperscript{11} Only one study (Paper I) has looked at the relation between CCTA findings and outcome in NSTEMI patients. The number of patients with normal CCTA was low, but the group members had excellent prognosis. In the group of patients with significant CAD we found that only those with coronary occlusion had a worse outcome compared to those with non-obstructive CAD.\textsuperscript{48} Firstly, this suggests that patients with occlusive disease form a distinct group that should be the focus of further studies – possibly in need of acute intervention. Secondly it suggests that in NSTEMI patients with non-obstructive and obstructive (but non-occlusive) CAD we should look for other determinants than diameter stenosis to predict prognosis. This is supported by our previous paper demonstrating that the amount of low-attenuation plaque is an important marker of adverse events in NSTEMI patients.\textsuperscript{41}

In brief we find that CCTA has a high diagnostic accuracy in high risk patients with NSTEMI compared to ICA and that CCTA has potential as a screening tool in these patients and that it may be used to classify patients according to recommended treatment strategy and to prediction of prognosis.
4. Transmural myocardial perfusion gradients in humans

Physiology of transmural myocardial perfusion gradients

It is well known from animal studies that there is a dynamic transmural perfusion gradient through the myocardium. During systole the myocardial compressive force increases from intrathoracic pressure at the epicardial surface to equal or to exceed intraventricular pressure at the endocardial surface. The limited systolic myocardial flow is directed towards the epicardium and blood in the deepest subendocardial layers is squeezed retrograde into more superficial subepicardial arterial vessels.

Despite these mechanical effects that increase impedance to blood flow in the deeper myocardial layers it is a consistent finding across more than 20 previously published animal studies using microsphere derived blood flow, that there is a net transmural gradient of blood favouring the subendocardium, which reflect higher oxygen requirements of the subendocardium. During diastole the myocardium requires an augmentation of subendocardial blood flow possibly in proportion to the degree of systolic underperfusion. This diastolic gradient of blood flow favouring the subendocardium is dependent on a transmural gradient of vasomotor tone, with vascular resistance during diastole being lowest in the subendocardium.

Transmural myocardial perfusion in animals. Animal experimental literature has used the endo-epi ratio (or “inner:outer flow ratio”) to express the transmural gradients across the myocardium, thereby using the epicardial blood flow as a reference for the subendocardial blood flow. The rationale for this is that subepicardial flow is seldom inadequate and so it usually reflects the myocardial (metabolic) demand for blood flow. Thus as long as the endo-epi ratio is constant it is reasonable to believe that all layers are receiving adequate blood. This does however not hold true during vasodilation with pharmacological adenosine stress as the endo-epi ratio will depend on physiological-pharmacological factors rather than metabolic needs of the tissue. Adenosine acts by relaxing smooth muscle cells at the level of the microcirculation, thereby uncoupling coronary flow from myocardial work and metabolic demand. Thus flow during adenosine induced vasodilation depend largely on the coronary driving pressure and thus on the arterial blood pressure and the residual coronary resistance e.g. induced by a coronary stenosis. Thus adenosine stress induces hyperaemic blood-flow in myocardium supplied by normal blood vessels, and relatively lower flow in the presence of a significant stenosis. This mechanism is used in various clinical stress testing settings.
Normal values at rest and during adenosine vasodilation: Normal values for the endo-epi ratio in animals (dogs, baboons, pigs, ponies, lambs) varies between 1.09 and 1.49 thus suggesting a 10-50% higher flow in the subendocardium compared to the subepicardium. Offsetting of the vasomotor tone with adenosine or dipyridamole has been shown to cause the endo-epi ratio to drop towards or even below 1 during normal coronary perfusion pressure and further it has been shown that at normal perfusion pressures, the myocardial perfusion reserve (MPR) during adenosine induced hyperaemia is higher in the subepicardial layer than in the subendocardial layer.

Epicardial stenosis and vulnerability to reduced perfusion pressure: During reduced perfusion pressure important changes are known to occur in the myocardium. Based on experimental animal studies, it is well established that the subendocardium is the part of the myocardium which is most vulnerable to hypoperfusion (low perfusion pressure). The subendocardial vulnerability to hypoperfusion comes from a complex cascade of mechanisms possibly including the effect of cardiac contraction, vascular pressure-dependent compliance, and also potential transmural differences in vessel anatomy. With increasing time of ischemia, irreversible myocardial injury progress from the subendocardium toward the subepicardium with cell death spreading out from the myocardium like a wavefront. Further it is known that the transmural extent of a myocardial infarction is associated with more profound damage and the loss of contractile function of the left ventricle.

According to this theory of the wavefront phenomenon, imaging of the subendocardial perfusion and the relative differences to the subepicardium could be an important adjunct to conventional transmural myocardial perfusion imaging, as it may facilitate more subtle detection of myocardial ischaemia and infarction. Recently non-invasive imaging modalities – CT and cardiac magnetic resonance imaging (CMR) - have emerged that makes it possible to do imaging of the transmural perfusion gradient, thus facilitating this area of research in humans. The initial challenges will here be - if possible - to reproduce the basic physiological findings of the previous animal studies (including (1) Endo/epi-ratio above one during resting conditions (2) decrease in endo/epi ratio during adenosine and (3) higher adenosine induced myocardial perfusion reserve in the epicardium) and to determine modality specific normal values for transmural gradients in humans so that they can be used to differentiate normal from pathological states.
CCTA imaging of transmural perfusion gradients in humans

With a resolution of 0.5 mm and images with isotropic voxels, CT has the highest spatial resolution compared to other non-invasive modalities such as CMR and PET and has the imaging properties necessary to assess transmural gradients of flow in the human myocardium.

With the development of 320 row CT scanners with broad axial coverage of 16 cm it has moreover become possible to record cardiac images in humans within one heartbeat. Compared to scanners with less axial coverage, 320 row scanners deliver images with temporal uniformity of contrast distribution throughout the myocardium.

CCTA imaging of transmural perfusion gradients compared to other modalities

CT, CMR and PET have recently investigated transmural perfusion gradients in humans. Amongst the basic physiological properties of the transmural perfusion gradients known from animals are that (mentioned above): (1) the endo-epi ratio is above one during resting conditions; (2) there is a decrease in endo-epi ratio during adenosine stress and; (3) there is a higher adenosine induced myocardial perfusion reserve in the subepicardium compared to the subendocardium. These properties have recently been investigated and confirmed in human studies using both PET\textsuperscript{76,77}, CMR\textsuperscript{78-80} and we have confirmed these using CT (Paper II, II and IV).\textsuperscript{81-83}

PET imaging of apparently healthy subjects (and in chest pain patients, within regions of normal flow assessed with fractional flow reserve) has shown a higher subendocardial flow during resting condition compared to the subepicardium. During hyperaemia, augmentation of perfusion was shown to be greater at subepicardial level and the transmural perfusion gradient was significantly diminished. Further this led to an overall higher perfusion reserve in the subepicardium.\textsuperscript{76}

Studies using CMR perfusion imaging in healthy volunteers found the same patterns of transmural perfusion gradients during rest and adenosine stress.\textsuperscript{78,80}

With CT perfusion imaging we found a higher subendocardial resting flow in humans compared to subepicardial flow in different populations with chest pain but without angiographic significant
Figure 5 Attenuation density in the 3 myocardial layers during resting conditions. HU Hounsfields Units, Endo: Endomyocardial layer, Mid: Midmyocardial layer, Epi: Epimyocardial layer. *P < 0.05 compared to other myocardial layers at rest. From Paper II.

CAD (Paper II, Figure 5). We further confirmed that pharmacological vasodilation with adenosine result in a part offsetting of the transmural perfusion gradients resulting in a higher subepicardial flow reserve compared to the subendocardium (Figure 6, Paper III).

Figure 6. Bar diagram of the difference in MPR between the myocardial layers. Results presented in median and interquartile range. From Paper III.

CT perfusion normal values and transmural perfusion ratio (TPR)

Previous studies have divided the myocardium into 2-4 layers and expressed the transmural perfusion gradient as the subendocardial blood flow divided by the subepicardial blood flow in the same segment. Static CT perfusion images do not contain information about absolute blood flow, but depict the transmural perfusion differences of the myocardium. (Animal studies have shown the feasibility of measuring absolute blood flow using CT, but at present this is associated with high radiation levels. As CT acquires a true 3D image of the myocardium it is possible to use the entire epicardium as a reference for the subendocardial flow in each myocardial segment. The CT
perfusion literature has used the term transmural perfusion ratio (TPR) as a notion for the relation between the attenuation densities in the innermost subendocardial layer of a given myocardial segment divided by the attenuation density in the entire subepicardial layer (or the sub-epicardial segments at the same myocardial level). By using a larger part of the subepicardial layer as reference for each subendocardial segment, transmural perfusion defects will drop below normal. We have reported normal values for global TPR between 1.10 - 1.16 in healthy subjects and chest pain patients without significant CAD (Paper II, III) as well as in patients with diabetes during resting conditions. 81;88;89

Transmural perfusion gradients and relation to outcome

During adenosine stress the myocardial perfusion, especially on the subendocardial side, is determined mainly by the perfusion pressure. 71 In concordance with this and the classical investigations by Gould et al. 90;91 CT derived TPR (endo-epi) values have shown to correlate well with the increasing coronary diameter stenosis and with decreasing fractional flow reserve. 35;92;93 In accordance with Gould et al. there is a significant change in the transmural flow gradient (measured by TPR) found during adenosine stress in the presence of > 50% coronary artery stenosis. Several studies have shown improved diagnostic value of CT perfusion defects during adenosine stress compared with various functional imaging modalities (SPECT, PET and fractional flow reserve) suggesting a potential clinical use in various patient settings. 3;35;54;56;57/94-96 Despite these findings the TPR measurements have so far been only minimally related to outcome. 97 We found that the changes in transmural perfusion gradients using TPR assessment in patients with acute myocardial infarction determine adverse outcome (Paper IV, Figure 7, lower panel). 82
Figure 7 Kaplan-Meier plots of the combined end-point of death or hospitalization due to heart failure, stratified into tertiles of the transmural perfusion (or ‘attenuation’) ratio and summed defect score. From paper IV.\textsuperscript{82}

In brief we found that the transmural distribution of perfusion across the LV myocardium using contrast enhanced CT analysis is in accordance with physiological findings from previous animal studies, as well as with a few studies performed in humans with PET and CMR perfusion imaging. Further we found that changes in TPR as a measure of the transmural distribution of perfusion is a strong predictor of outcome in patients with NSTEMI.
5. Myocardial perfusion, infarct and scar

Pathophysiology in coronary artery stenosis and myocardial infarction

In animal models of myocardial infarction the downstream effect of a coronary artery stenosis on resting myocardial perfusion is well described. It is known that myocardial perfusion is preserved via auto-regulatory mechanisms in the microcirculation, until the capacity of the arterioles to dilate is exhausted. According to classical papers of Gould et al, this occurs at a very late stage (coronary artery stenosis of 90-100%) under resting conditions.\textsuperscript{90,91}

In patients with myocardial infarction the perfusion to a given area may be reduced not only due to epicardial obstruction, but also by microvascular obstruction caused by endothelial cellular swelling, myocyte swelling and tissue oedema. Also vasospasm and downstream embolization of thrombus compound may cause further microvascular obstruction.\textsuperscript{98-101}

Myocardial infarction causes remodelling of the left ventricle with left ventricular wall thinning and cavity dilation as well as myocyte hypertrophy and late remodelling with fibrotic scar formation and possibly also with development of lipomateous metaplasia.\textsuperscript{102,103}

CCTA myocardial infarction detection during first-pass

CCTA at rest can be used for detection of first-pass perfusion defects. During CCTA acquisition iodine contrast is intravenously administered, and a few seconds after images are acquired when contrast peaks in the epicardial arteries. Contrast is simultaneously distributed in the vascular bed, leading to an enhancement of the entire left ventricular myocardium. In case of blood flow obstruction – either at epicardial or microvascular level - perfusion defects occur in the myocardium.

In \textit{epicardial obstruction}, regions with early hypo-enhancements in the myocardium using CT images are found to correspond with the physiological findings of Gould et al, as it occurs in stenosis > 90%, and primarily in the subendocardium.\textsuperscript{93}

In cases of myocardial infarction and \textit{microvascular obstruction} caused by oedema, CT assessment of infarct size has been investigated in various clinical settings, both in acute and healed myocardial infarction, and has been compared to other modalities known to predict infarct size such as single photon emission computed tomography (SPECT) and CMR. Alterations in the myocardial blood flow due to obstruction can be assessed in various ways, either as presence and size of first pass perfusion defect (this chapter) or as changes in the transmural perfusion gradient (see ch.5).
CCTA myocardial infarct detection compared to other modalities

Animal studies have established the ability of CT to detect myocardial infarction. Using first pass CT imaging the attenuation value in infarcted areas is half that of remote myocardium and experimental studies have shown that CT myocardial areas of first pass hypoperfusion (perfusion defects) correspond with triphenyl tetrazolium chloride (TTC) staining and with microsphere-determined blood flow.\textsuperscript{104,105} First pass CT perfusion defects detects an absence of contrast enhancement, which can be caused by various myocardial conditions: low contrast flow due to epicardial obstruction, abnormally slow contrast supply to a specific myocardial segment (graft), myocardial edema, acute myocardial infarction and myocardial scar. Comparing first pass CT perfusion defects with infarct imaging using other modalities, is however to some extent comparing apples and oranges. The following section briefly describes the modalities of infarct imaging used for comparison with first-pass CT perfusion defects. The possibility of infarct imaging with delayed enhancement using CT is briefly discussed later in this chapter.

The mechanism that allows TTC staining to differentiate between necrotic and viable tissue is that the white compound (TTC) is colored red in the presence of enzymes (dehydrogenases) of metabolically active tissue while necrotic tissue does not have this property.

Acute infarct imaging with CMR is performed using gadolinium contrast enhancement, where two methods are used: (1) Delayed enhancement and (2) First pass perfusion defect. **Delayed enhancement:** In acute myocardial infarction the cellular necrosis (with loss of cell membrane integrity) cause edema and allows gadolinium into the intracellular space. This increased volume of distribution cause delayed wash in and wash-out of gadolinium which is represented in T1-weighted images as “delayed enhancement” in a scan performed 10-30 minutes after contrast injection.\textsuperscript{106} **First pass perfusion defects** in CMR images are also used in evaluation of acute myocardial infarction and seen as hypodense areas without first-pass contrast uptake are caused by (micro)vascular obstruction.\textsuperscript{98,99}

Single photon emission computed tomography (SPECT) use the radio nucleotide tracer technetium ($^{99m}$Tc) sestamibi that accumulates in the mitochondria of intact myocardial cells and distributes in the myocardium proportionally to the myocardial perfusion. Thus myocardial infarct are represented by areas that lack of tracer uptake in the myocardium during rest.\textsuperscript{107}

In brief; the mechanisms for detecting myocardial infarct varies between the modalities, as they do not depict the same state of affairs. Thus a degree of difference should be expected when comparing modalities for this reason alone. With this in mind the following paragraphs address some of the important inter-modality infarct imaging studies
**First pass CT vs SPECT:** Several studies have in humans confirmed that CT assessment of myocardial infarction is feasible with clearly detectable differences in attenuation density values between infarcted and remote myocardium. Agreement between CT and SPECT in determining the presence and size of myocardial hypoperfusion in patients with both acute chest pain, recent acute myocardial infarction (STEMI) and healed myocardial infarct has been assessed in several studies. With regard to myocardial infarct size a moderate to excellent correlation has been found, however with a systematic underestimation of CT assessment compared to SPECT in the range of 5-17%.

In these studies several patients with known myocardial infarction and CT perfusion defect were however found without a resting perfusion defect on SPECT. Based on experimental animal studies, it is well established that the subendocardium is the part of the myocardium which is most vulnerable to hypoperfusion and ischemia, thus smaller infarcts may be confined to the subendocardium. As it is known that the spatial resolution of SPECT is relatively poor, this may suggest that the higher spatial resolution of MDCT allows for the identification of subendocardial perfusion defects that may not be detectable by SPECT.

**First pass-CT vs first pass-CMR:** The spatial resolution of both CMR and CT allows for an assessment of the transmural involvement of a perfusion defect in myocardium Recent studies demonstrate good to excellent agreement between these modalities in determining size of perfusion defects in patients with myocardial infarction. In contrast to studies where SPECT is the reference standard, studies comparing infarct size between first pass CMR and CT show no difference.

**Diagnostic value of rest CT perfusion for the detection of ACS and myocardial infarction**

A number of studies have tested the diagnostic value of rest CT perfusion defects to discriminate between patients with/without myocardial infarction or patients with/without ACS in various mixed patient population and suggest that the presence of a resting CT perfusion defect may add to the diagnostic value in the diagnosis of ACS/myocardial infarction. The results of these studies are summarized in Table 4.

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<th>N</th>
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<td>Suspected or</td>
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<tr>
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<td>Specificity</td>
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<td>UAP/NSTEMI</td>
<td>Myocardial infarct</td>
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<td>Branch et al. 118</td>
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<td>9% (9/105)</td>
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<tr>
<td>2015</td>
<td>Pursnani et al. 119</td>
<td>Possible ACS</td>
<td>ACS</td>
<td>183</td>
<td>17% (31/183)</td>
<td>48</td>
<td>78</td>
<td></td>
</tr>
</tbody>
</table>

Myocardial infarction and scar in relation to outcome

The correlation between infarct size assessed by SPECT and CMR and adverse outcome in patients with myocardial infarction has been demonstrated in patients with myocardial infarction mainly presenting with ST-segment elevation, and has been used to monitor the effects of therapy after acute myocardial infarction. In contrast, the relationship between the extent of myocardial hypoperfusion on one hand and clinical outcome following treatment on the other is less well elucidated in patients with NSTEMI. Similarly to nuclear imaging and CMR, it is possible to perform a CT-based semi-quantitative assessment of the myocardial perfusion defect extent, which we have recently demonstrated predict adverse outcome in patients with NSTEMI (Figure 7, upper panel). (Paper IV)

**Acute vs. chronic infarction.**

Perfusion defects, in contrast-enhanced CT images, comprise a set of different causes as described above. Myocardial perfusion defects could be caused by epicardial obstruction and in areas supplied by re-perfused arteries due to obstructed microvascular perfusion. Changed tissue characteristics due to chronic infarction with fibrotic or adipose tissue replacement (scar) could also be responsible for perfusion defects on CT. It is difficult – using myocardial CT images alone - inherently to distinguish the cause of myocardial perfusion defects. Chronic infarctions (> 12 months) may however be differentiated by CT using ventricular dimensions, wall thinning and also myocardial attenuation density values that may be lower than non-contrasted myocardium due to fat tissue infiltration in the scar.

**Fat in myocardial scars and CT imaging**

The histopathological evolution of a myocardial infarction has been described thoroughly including myocyte death and subsequent pressure load increase, triggering a cascade of reparative changes which include myocardial thinning, left ventricular dilation, hypertrophy and the formation of collagen scar. Interestingly, the presence of adipose tissue was not described in the literature on left ventricular remodeling after myocardial infarction, until 1997 where Baroldi et al. published the
finding of lipomatous metaplasia in 26 of 38 explanted hearts from patients with chronic ischemic heart disease.\textsuperscript{102} That study was reproduced by Su et al. who found that a majority of myocardial “fibrotic” scars (84\%) contains considerable amounts of adipose tissue (up to 75\%).\textsuperscript{127} Fat presents with CT attenuation density values < -100HU, and may easily be differentiated from both contrasted (\(\approx 70\text{-}120\text{HU}\)) and non-contrasted (\(\approx 35\text{-}50\text{HU}\)) myocardium. A number of studies have shown that attenuation density values of chronic scars are higher than pure fat tissue (\(\approx\text{-}15\text{ to } -30\text{ HU}\)),\textsuperscript{82;125;126;128;130} which is in concordance with pathology studies of Su et al., that found that infarcted tissue is gradually infiltrated by adipose tissue and is a compound of adipose tissue, fibrosis, and myocardial fibres. Myocardial fat seems to be associated with infarct age >10 months,\textsuperscript{129} and in one study also with milder coronary artery stenosis, and fewer number of diseased vessels.\textsuperscript{128} Only one study (Paper IV) has presented data on infarct tissue by CT and outcome that suggests that having myocardial fat is associated to adverse outcome in patients with (new) NSTEMI (Figure 8).\textsuperscript{82}

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|c|}
\hline
\textbf{Worst perfusion defect severity score} & \textbf{Unadjusted} & \textbf{Hazard Ratio} & \textbf{No events} \textbf{N} \\
\hline
Normal perfusion & & 1.0 (reference) & 9 & 144 \\
Mild (< \(\frac{1}{3}\) transmural) & & 1.2 (0.4 – 3.7) & 4 & 47 \\
Moderate (\(\frac{1}{3}\)-\(\frac{2}{3}\) transmural) & & 2.4 (1.1 – 5.4) & 16 & 98 \\
Severe (> \(\frac{2}{3}\) transmural) & & 5.2 (2.4 – 11.4) & 11 & 46 \\
Scar tissue (fat, calcification) & & 8.1 (3.7 – 17.6) & 16 & 41 \\
\hline
\end{tabular}
\caption{Forest plot of hazard ratios comparing the risk of death and hospitalization for heart failure according to the worst perfusion defect of the patients. The upper panel displays the results of a single model that contains four groups of defect using no perfusion defect as the reference. In the lower panel adjustments were made for age, left ventricular end-diastolic volume, previous myocardial infarction, left ventricular ejection fraction, Killip class, and number of diseased coronary vessels. From paper IV.\textsuperscript{82}}
\end{table}

\textbf{Electrophysiological implications of fat}

Previous studies have considered that slowly conducting zones that form ventricular tachycardia (VT) substrates were caused by myocardial fibrosis.\textsuperscript{131-133} A more recent animal study by Pouliopoulos et al. has however demonstrated that the presence of adipose tissue assessed by CT imaging is significantly correlated with altered electrophysiological properties (low conduction
velocity, low ECG amplitude) and has an impact on scar-related VT circuit. A recent human study performed by Sasaki et al. has shown that 75% of the critical VT circuit in patients with ischemic cardiomyopathy were located in the regions with myocardial fat deposits or the regions adjacent to myocardial fat deposits. Further Sasaki et al. found that isolated potentials were frequently observed in regions with myocardial fat deposits. If the presence of lipomatous metaplasia may alter the propagation of electrical impulse in the left ventricle and cause re-entry circuits, it could be speculated that it may also be correlated to the pathogenesis of post-myocardial infarction arrhythmias and thus to adverse outcome in patients with myocardial infarction. The possible arrhythmogenic effect of adipose tissue in the left ventricle should be the focus of further studies.

**Delayed enhancement (DE).**

Identifying and quantifying myocardial infarct based on DE caused by differences in the wash-in and wash-out kinetics of the CT contrast, has been shown feasible in several studies. In the late seventies Siemers et al. found in an animal study that computed axial tomography detected 24 out of 25 new myocardial infarcts using DE, but underestimated infarct size by 20% compared to histochemical staining. Recent studies in both animals and humans have found both good correlation and no difference in infarct size compared to late gadolinium enhancement by CMR. Furthermore, a study by Sato et al. has shown that delayed enhancement with CT done after primary percutaneous coronary intervention predicts clinical outcome in patients with myocardial infarction.

Several studies have however compared the DE signal intensity and image noise between CMR and CT and it is a consistent finding that both signal intensity and contrast to noise values are much lower in CT DE images. In a human study by Niemann et al., the contrast to noise ratio in CT DE images was 2 compared to 15 in CMR DE images. The much lower contrast to noise values of CT-DE suggest that further optimisation of the image acquisition protocol is needed regarding contrast type, contrast amount and scan timing.

In brief, we found that the total perfusion defect score as assessed by CCTA is associated with adverse outcome in NSTEMI patients. Furthermore, we found that intra-myocardial fat is detectable in these patients (most likely due to previous myocardial infarction) and that the presence of intra-myocardial fat in these patients is associated with adverse outcomes.
6. Atrial function

Pathophysiology: Systolic & diastolic dysfunction and the role of the left atrium as biomarker.

As described in the previous chapters; an epicardial stenosis may lead to myocardial ischemia and necrosis which entails a permanent damage with changes in the tissue characteristics and the mechanical properties of the myocardium. From here the pathogenic path leads to deterioration of the myocardial function of the left ventricle and the left atrium – a path that may eventually lead to heart failure.

The late effects of myocardial infarction are myocyte hypertrophy, collagen deposition and formation of fibrotic scars. This may cause not only deterioration of systolic function; the diastolic function is also affected with reduced elasticity and abnormal relaxation of the left ventricular myocardium. Abnormal LV relaxation and stiffness cause elevated LV filling pressures, which are transmitted backwards to the LA.

**LA enlargement and the barometer hypothesis**

When the LV compliance is reduced, the LA pressure increases to maintain adequate filling of the LV. This will lead to an increase in LA volume. Thus the severity of the diastolic dysfunction is - ceteris paribus - reflected in the magnitude of LA enlargement. The remodeling of the LA is thought to express the severity and duration of abnormal filling pressures (also known as the “barometer hypothesis”). As an analogy it has been proposed that the LA enlargement reflects the left-sided pressure conditions in the same manner as hemoglobin A1C reflects preceding levels of blood glucose.

The mechanical function of the LA is determined by pre and afterload condition, intrinsic LA wall properties and LV function and is described in three phases: During LV systole, the LA is in its reservoir phase where blood entering from the pulmonary veins is pooled against the closed mitral valve. The energy stored in the LA wall is released at mitral valve opening in the passive emptying phase which is largely determined by the pressure gradient between the left sided chambers. The pressure difference between the chambers rapidly equalizes and the heart enters the diastesis phase where the LA has the function of a simple conduit to the LV. Finally atrial contraction – the active emptying phase - contributes to LV end-diastolic volume and thereby LV stroke volume (estimated 20 - 30% of LV stroke volume).
The mechanical function of the LA is commonly assessed as the fractional cyclic volume change and the LA ejection fraction. The fractional change is defined as the difference between LA minimal volume and LA maximal volume relative to LA maximal volume and is determined by a combination of intrinsic LA contractility and wall stiffness, the “LA afterload” as well as LV longitudinal systolic function.

The LA ejection fraction (LAEF) is defined as the difference between end-diastasis volume and LA minimal volume relative to end-diastasis volume. The contractile function is largely determined by intrinsic atrial function and the atrial pre-load in agreement with the Frank-Starling law. Also in agreement with the Frank Starling law, the progressive dilation of the LA comes to a threshold of atrial fiber stretching from where the contractility deteriorates and reduces contractile performance. Thus a reduction in LAEF may be an “end-stage” of LA systolic failure.

CTTA imaging of LA function

Using retrospective gating it is possible to acquire functional images of the heart. Images are reconstructed in 5% intervals of the R-R interval, and the cardiac chamber function is analysed with manual delineations or semi-automated software. The use of retrospective gating technique requires radiation across the entire R-R interval and is therefore - compared to prospectively gated images - associated with higher radiation doses.

CCTA imaging of LA size and mechanical function compared to other modalities.

Retrospectively gated CCTA scans provide images usable for an accurate assessment of LV dimensions and systolic function including LVEF and regional systolic wall thickening, and with results comparable to CMR and/or transthoracic echocardiography (TTE). CT scans also provide accurate assessment of LA volumes in agreement with other modalities (Table 5)
<table>
<thead>
<tr>
<th>Author</th>
<th>CT type</th>
<th>Modality</th>
<th>LA variable</th>
<th>n</th>
<th>Population</th>
<th>Rhythm</th>
<th>Age (range) or ±SD</th>
<th>Accuracy (diff in % compared to CT)</th>
<th>Correlation, (pearsons R value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kircher et al.</td>
<td>Cine-CT</td>
<td>2D TTE</td>
<td>LAV</td>
<td>27</td>
<td>Various CCTA indication (SR)</td>
<td>55 (24-80)</td>
<td>-23%</td>
<td>NA</td>
<td>0.98 NA</td>
</tr>
<tr>
<td>Vandenberg et al.</td>
<td>Cine-CT</td>
<td>2D* TTE</td>
<td>LAV</td>
<td>18</td>
<td>Various CCTA indication</td>
<td>45 ± 23</td>
<td>-30%</td>
<td>NA</td>
<td>0.89-0.95 NA</td>
</tr>
<tr>
<td>Avelar et al.</td>
<td>64 MDCT</td>
<td>2D TTE</td>
<td>LAV</td>
<td>48</td>
<td>Various CCTA indication</td>
<td>55±19</td>
<td>-29%</td>
<td>NA</td>
<td>0.68 NA</td>
</tr>
<tr>
<td>Christiaens et al.</td>
<td>64 MDCT</td>
<td>2D TTE</td>
<td>LAV FC</td>
<td>20</td>
<td>Various CCTA indication</td>
<td>56±14</td>
<td>-34%</td>
<td>&quot;no difference&quot;</td>
<td>0.94 0.99</td>
</tr>
<tr>
<td>Kataoka et al.</td>
<td>320 MDCT</td>
<td>2D 3D TTE</td>
<td>LAV FC</td>
<td>18</td>
<td>Various CCTA indication</td>
<td>60±15</td>
<td>2D: 48% 3D: -50%</td>
<td>2D: 28% 3D: 11%</td>
<td>2D: 0.45 3D: 0.61</td>
</tr>
<tr>
<td>Shin et al.</td>
<td>64 MDCT</td>
<td>2D TTE</td>
<td>LAV FC</td>
<td>15</td>
<td>Atrial fibrillation Afib ablation</td>
<td>Afib</td>
<td>-38%</td>
<td>64%</td>
<td>0.86 0.76</td>
</tr>
<tr>
<td>Koka et al.</td>
<td>64 MDCT</td>
<td>2D TTE</td>
<td>LAV</td>
<td>37</td>
<td>Triple rule out</td>
<td>SR</td>
<td>56±15</td>
<td>-46%</td>
<td>NA</td>
</tr>
<tr>
<td>Miyasaka et al.</td>
<td>64 MDCT</td>
<td>2D 3D TTE</td>
<td>LAV</td>
<td>57</td>
<td>suspected CAD</td>
<td>SR</td>
<td>66±11</td>
<td>2D: 19% 3D: 9%</td>
<td>NA</td>
</tr>
<tr>
<td>Gweon et al.</td>
<td>64 MDCT</td>
<td>2D TTE</td>
<td>LAV</td>
<td>35</td>
<td>CAD</td>
<td>SR</td>
<td>60 (36-81)</td>
<td>27%</td>
<td>NA</td>
</tr>
<tr>
<td>Heo et al.</td>
<td>128 DSCT</td>
<td>2D 3D TTE</td>
<td>LAV</td>
<td>31</td>
<td>Atrial fibrillation Afib patients</td>
<td>Afib</td>
<td>63±12</td>
<td>2D: 32% 3D: -23%</td>
<td>NA</td>
</tr>
<tr>
<td>Kühl et al.</td>
<td>64 MDCT</td>
<td>2D TTE</td>
<td>LAV FC</td>
<td>53</td>
<td>post STEMI</td>
<td>SR</td>
<td>61±10</td>
<td>-28%</td>
<td>8%</td>
</tr>
<tr>
<td>Agner et al.</td>
<td>320 MDCT</td>
<td>3D TTE</td>
<td>LAV FC</td>
<td>34</td>
<td>Afib</td>
<td>Afib</td>
<td>69±6</td>
<td>-25%</td>
<td>14%</td>
</tr>
<tr>
<td>Wen et al.</td>
<td>64 DSCT</td>
<td>3T CMR</td>
<td>LAV FC</td>
<td>49</td>
<td>Suspected CAD</td>
<td>SR</td>
<td>53±13</td>
<td>3.00%</td>
<td>0.89 0.82</td>
</tr>
<tr>
<td>Bastarrika et al.</td>
<td>128 DSCT</td>
<td>1.5T CMR</td>
<td>LAV FC</td>
<td>29</td>
<td>HTX recipients</td>
<td>SR</td>
<td>53±13</td>
<td>-13%</td>
<td>-3%</td>
</tr>
<tr>
<td>Kühl et al.</td>
<td>64 MDCT</td>
<td>1.5T CMR</td>
<td>LAV FC</td>
<td>53</td>
<td>post STEMI</td>
<td>SR</td>
<td>61±10</td>
<td>-5%</td>
<td>-2%</td>
</tr>
<tr>
<td>Agner et al.</td>
<td>320 MDCT</td>
<td>1.5T CMR</td>
<td>LAV FC</td>
<td>34</td>
<td>Afib</td>
<td>Afib</td>
<td>69±6</td>
<td>-10%</td>
<td>-8%</td>
</tr>
</tbody>
</table>

There is an overall good correlation and agreement between CMR and CT assessment of LA volumes, with small volume differences.\textsuperscript{171-174} The correlation between CT and TTE assessment of LA volumes are found to be acceptable in various patient groups,\textsuperscript{161-168;171;172} but TTE underestimates LA volumes by around 20-40\% when compared to CT or CMR images\textsuperscript{161-169;171;172;175-179} Reference values obtained from healthy subjects with CMR are also higher than reference values obtained by TTE.\textsuperscript{180;181} These differences can partly be explained by different conventions in LA volume measurements between modalities,\textsuperscript{180;182} by geometrical assumptions intrinsic to the 2D TTE method, by the risk of foreshortening the LA with TTE and probably also by a poor acoustic window in a subset of patients.\textsuperscript{144} The reproducibility of CT and CMR assessment of LA volumes is high,\textsuperscript{171-174} compared to values obtained with TTE,\textsuperscript{165;167;171;172;177} which can be explained by difficulties in the delineation of the LA that may be impaired by a suboptimal acoustic window. In contrast both CT and CMR have a very sharp delineation between the atrial wall and the LA cavity.

LA mechanical function and the relation to clinical parameters and outcome
All patients with left heart failure symptoms will have elevated filling pressure in the LV. As LA enlargement is a marker of LV filling pressure it may also be used to predict heart failure symptoms.\textsuperscript{183} Accordingly, several studies have also found that LA enlargement is associated with increased morbidity and mortality in several patient groups that may have increased LV filling pressures, including patients with acute myocardial infarction.\textsuperscript{184;185} The prognostic implications of volume or pressure overload of the LA may however only partially be reflected in the maximal volume. In analogy with the LV – where it has previously been shown that there is independent prognostic information of volumes and function\textsuperscript{186;187} - the LA functional values could also add to prognostic information.
Thus it has been shown that LA mechanical function is more closely associated with clinical signs of heart failure than LA maximal volume. We and others have found that reduced fractional change, especially, could be an early indicator of cardiac congestion (Paper V).\textsuperscript{188;189}
Furthermore, we found that LA mechanical function assessed by CT images performed before invasive treatment of patients with NSTEMI (left atrial ejection fraction and fractional change) is superior to LA maximal volume in predicting death (Figure 9).\textsuperscript{190} The independent prognostic value of LA cyclic volume changes has been confirmed by CMR studies of patients with suspected ischemic heart disease,\textsuperscript{191} STEMI,\textsuperscript{192} hypertension\textsuperscript{193} and in a population study.\textsuperscript{194}
Reduced LAEF may be a marker of an “end-stage” in LA deterioration caused by pathological LV changes with increased filling pressures. Accordingly the loss of LA contractile reserve capacity is
associated with heart failure symptoms in patients with preserved LV ejection fraction\textsuperscript{195} and ischemic heart disease\textsuperscript{189} and recently we have shown that LAEF assessed by CT is associated with death after myocardial infarction (Figure 9). (Paper VIII)\textsuperscript{190}

**Figure 9** Kaplan-Meier Plots. Mortality in NSTEMI patients stratified in tertiles of left atrial size and function. From paper VII.\textsuperscript{190}

In brief we found that assessment of LA mechanical function is feasible with retrospective CCTA scans, and is comparable with CMR imaging. Furthermore, we found that reduced mechanical function of the LA is closely correlated to congestive heart failure and adverse outcome.
7. Pulmonary congestion

The pathological development of pulmonary congestion and heart failure

LV systolic and diastolic dysfunction may lead to backward failure and as a result the pressure rises in the LA. This increased pressure may be transmitted further back to the pulmonary venous system. When effective pulmonary capillary pressure equals critical pulmonary capillary pressure, there will be an abnormal accumulation of fluid in the extravascular compartments of the lung. The extent will be determined by the hydrostatic and oncotic pressure differences across the capillary membrane as well as its permeability, and also by the lymphatic drainage rate compared to the capillary filtration rate.

This will lead to interstitial and eventually even alveolar oedema. Different comorbidities of the patients will also alter the effect of increased capillary pressure, as well as the patients’ hydration status and medication. This condition will lead to clinical heart failure manifested by symptoms such as dyspnea (on exertion or at rest) and fatigability at low threshold. Signs related to heart failure are tachypnea with rales or crackles on auscultation.

CCTA imaging of pulmonary congestion

During CCTA acquisition a narrow field matching the position of the heart in the Z-axis of the scan field is radiated, including the adjacent pulmonary tissue. The images are acquired during breath-hold command and are reconstructed when there is least cardiac motion.

In patients with acute or chronic pulmonary congestion CT images may depict ground-glass opacity, interstitial transudate and eventually pleural effusions. Ground-glass opacity is caused by increased fluid volume in either the interstitial or the alveolar compartment of the lung, and is defined as a region of increased lung tissue attenuation often with a patchy appearance with some gravitational predominance and is thus accompanied with increase in HU values. Signs of interstitial transudate can be found as thickening of the interlobular septum or as peribronchial “cuffing”.

Several papers have studied the frequency of CT signs of pulmonary congestion in patients with known clinical heart failure of mixed causes (acute and chronic disease) and found increased pulmonary attenuation density in CT images of patients with clinical heart failure compared to controls.
CCTA imaging of pulmonary congestion compared to other imaging modalities.

Ground glass opacification and the relation to increase in pulmonary attenuation density has been validated in overhydrated animal models against invasive measures of lung water using dye and thermal dilution.\textsuperscript{203} In recent years other modalities, e.g. lung ultrasound, have been used to detect extravascular lung water as a sign of pulmonary congestion. Several human studies have used computed tomography as the gold standard for measuring pulmonary congestion. CT attenuation density values have been used as the gold standard for evaluating B-lines’ score with good correlation,\textsuperscript{206} and several studies in critically ill patients have used CT as the gold standard for evaluating the diagnostic power of lung ultrasound assessment to detect extra vascular lung water and pleural effusions.\textsuperscript{207-209} Thus CT is generally accepted as the gold standard for evaluating pulmonary congestion.

Pulmonary congestion and the relation to heart failure and outcome

The manifestations of clinically determined HF symptoms are associated with death after myocardial infarction in patients with both preserved and reduced systolic function.\textsuperscript{1,2,210} A recent study has investigated lung ultrasound congestion in HF patients before hospital discharge and found a strong correlation to adverse outcome.\textsuperscript{211} CT signs of congestion have not previously been studied in a larger cohort of cardiac patients. We investigated the clinical value of CT pulmonary congestion in a cohort of NSTEMI patients and found that signs of pulmonary congestion on CCTA images correlate well with signs of left hearted dysfunction and clinical heart failure status group (Figure 10) and have good diagnostic accuracy to predict HF, especially with a high negative predictive value.\textsuperscript{212}

![Figure 10](image)

**Figure 10 Signs of pulmonary congestion according to heart failure status group**

Percentage of patients with computed tomography signs of pulmonary congestion according to heart failure status group. HF: Heart failure (Killip class > 1) PEF: Preserved left ventricular ejection fraction. REF: Reduced left ventricular ejection fraction. From paper VIII.\textsuperscript{212}
Moreover, the presence of CT signs of congestion predicts an adverse prognosis in patients with acute coronary syndrome and elevated troponins also after adjustment for conventional risk factors including LVEF and Killip class (Figure 11).

<table>
<thead>
<tr>
<th>CT sign of Pulmonary Congestion</th>
<th>Unadjusted model</th>
<th>Hazard Ratio (95% CI)</th>
<th># events</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Congestion</td>
<td>1.0 (Reference)</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>Mild to moderate Congestion</td>
<td>4.5 (2.5 – 8.1)</td>
<td>29</td>
<td></td>
</tr>
<tr>
<td>Severe Congestion</td>
<td>6.6 (3.1 – 13.8)</td>
<td>12</td>
<td></td>
</tr>
</tbody>
</table>

**Figure 11.** Forest plot of hazard ratios comparing patients according to the presence of computed tomography signs of pulmonary congestion. The upper panel displays the results of a single model that contains congestion groups using no perfusion defect as the reference. In the lower panel adjustments were made for age, previous myocardial infarction, diabetes, left ventricular ejection fraction, left ventricular end-diastolic volume index, Killip class, and number of diseased coronary vessels. CI = Confidence interval. From Paper VIII.
8. SUMMARY & CLINICAL IMPLICATIONS

In clinical praxis CCTA is a technique used for visualization of the coronary arteries, primarily in patients with stable coronary artery disease. Recently it has been suggested that the CCTA target group should be expanded to include patients with acute chest pain and patients with ACS when troponins are elevated but inconclusive. This calls for an investigation of patients at high risk to explore boundaries and possibilities of CCTA in this setting.

As the development of heart failure is one of the worst prognostic signs in patients with myocardial infarction, an evaluation of the downstream effect of coronary stenosis in the adjacent myocardial and pulmonary tissue using CCTA images may be both possible and beneficial for diagnosis and prognosis.

This thesis summarizes eight papers that examine the possibilities and benefits of using CCTA to assess coronary artery disease in NSTEMI patients and the downstream effects thereof – including visualization of the myocardium, atrial function changes and the presence of pulmonary congestion.

Coronary imaging

Due to the lack of sufficient evidence we examined – in the so far largest NSTEMI population examined - the diagnostic accuracy of CCTA against invasive coronary angiography and further tested whether the technique could be used for an initial triage of these patients. We found that the diagnostic accuracy of CCTA to diagnose significant CAD requiring invasive treatment is high in NSTEMI patients compared to ICA, but that CCTA based diagnostic strategy led to 14% incorrectly classified patients. We also found that CCTA can be used to stratify patients according to long-term risk.

Clinical Implications: When performed, CCTA has high diagnostic accuracy in patients with NSTEMI and can be used to rule out significant CAD. CCTA further predicts adverse outcome in patients with occluded arteries.

Myocardial imaging

In various populations of both healthy controls and chest pain patients free of significant coronary artery disease, we examined whether CCTA images allow the description of subtle differences in the normal physiology of myocardial perfusion – including the transmural perfusion gradient - that have previously been described in animal models and in a few human studies using PET and CMR.

We found that pathological changes in the transmural perfusion gradient in NSTEMI patients were associated with prognosis and that the extent and severity of LV myocardial hypoperfusion at rest,
in addition to abnormalities of the myocardial tissue characteristics detected visually on CCTA images, related to adverse long-term outcome in patient with NSTEMI.

**Clinical Implications:** The myocardium should be assessed routinely in acquired CCTA images in patients with myocardial infarct as it contains important prognostic information.

**Atrial function**
The LA maximal volume is a strong and widely used predictor of outcome; however the atrial function is sparsely described although intimately connected to both LV systolic and diastolic dysfunction. We examined the feasibility of using retrospective CCTA to evaluate LA mechanical function and whether it is associated with LVEF and symptoms of congestive heart failure. We further validated LA functional assessment against CMR and TTE in patients with previous STEMI. Finally we examined the relation between left atrial functional properties and outcome in NSTEMI patients.

**Clinical implications:** When retrospective gating is acquired, LA function can and should be assessed as it contains important prognostic information.

**Pulmonary Congestion**
Although considered the gold standard, CT evaluation of pulmonary congestion has never been studied in a larger cohort. We described for the first time that known CT morphological indices of pulmonary congestion can be derived from CCTA images and found that these CT indices of congestion correlate well with the severity of left ventricular diastolic and systolic failure, and evaluated for the first time the diagnostic accuracy of the method to detect clinical heart failure symptoms. Further, we confirmed the hypothesis that the presence of CT signs of pulmonary congestion is related to adverse long-term outcome.

**Clinical implications:** The presence of pulmonary congestion should be assessed in CCTA images, as it predicts clinical congestion and is closely related to outcome.
Conclusion

In conclusion, the diagnostic accuracy of coronary CT angiography in patients with non-ST segment elevation myocardial infarction is high and could allow for selection of treatment strategy in such patients. Cardiac CT imaging allows for the assessment of hemodynamic properties of the heart including myocardial perfusion, left atrial function and pulmonary congestion; properties which have important pathophysiological implications in patients with myocardial infarction including risk of clinical heart failure and adverse outcome. These findings point towards an expanded clinical use of cardiac CT angiography with a comprehensive assessment of patient with ischemic heart disease.
9. PERSPECTIVES

The boundaries of the CCTA target population are being challenged by studies (and guidelines) that seeks to expand the patient group; from stable chest pain patients to patients with acute possibly unstable chest pain and further to patients with acute coronary syndrome and elevated (but non-conclusive) troponins. It is important that such an expansion of the group of patients that have CCTA performed is backed up by solid scientific evidence. This thesis does not provide evidence to advocate at this point in time for the use of CCTA in patients with acute coronary syndrome or troponin release. However, it provides building blocks that help build the research evidence to support the notion that the use of CCTA may be useful in these patients and at the same time points at various problems that should be investigated more thoroughly. The following paragraphs will point to some of the issues that should be further addressed.

**Logistical setup:** Studies are needed to explore if it is possible to do a logistical setup in a sub-acute setting that does not expose patients to a treatment delay. At the time our NSTEMI population underwent CCTA (2006-2009) the clinical setup was obsolete, compared to the current logistical potential, as patients could only be scanned during day-time. Recent publications have already shown that sub-acute CCTA is possible in acute chest pain patients and in patients with possible ACS.  

**Diagnostic precision and patient triage:** Our results point to the fact that CCTA overestimates stenosis severity and may wrongfully categorise patients in need of PCI treatment into surgery. Moreover; contemporary guidelines recommend that revascularization is guided by the hemodynamic properties of a stenosis rather than anatomy (stenosis severity) alone. Thus it could be interesting to assess the diagnostic precision of CT-based analysis of hemodynamic properties of a lesion – e.g. CT stress perfusion and ‘CT-fractional flow reserve’ – against invasive measured fractional flow reserve – in the setting of ACS patients. In this setting it should also be investigated whether CT-based analysis of hemodynamic properties may be used for accurate patient triage using fractional flow reserve as reference standard.

Studies that explore the knowledge on unstable plaque characteristics in an ACS cohort may also be valuable for treatment strategy.

**Patient triage and outcome:** It should be investigated in randomised studies whether a CCTA-based strategy translates into improved outcome, lower costs and better quality of life. This has been done in patients with acute chest pain, and studies of this kind are currently including patients with stable angina pectoris (DISCHARGE trial) and patients with acute chest pain (RAPID-CTCA).
There are several ways in which a CCTA guided treatment strategy could guide the management of ACS patients, including timing of patient treatment, treatment of complications to ACS, and treatment of differential diagnosis to ACS.

**Timing.** Previous studies have not been able to show that an acute interventional strategy is preferable to a sub-acute strategy in an all-comers ACS population.\(^{44}\) An initial CCTA could be used to distinguish those that may benefit from an early (acute) invasive procedure, from those that should wait for a subacute invasive investigation. Thus a CCTA diagnosis of an occluded artery or a culprit lesion in the proximal parts of the coronary tree could give an important initial demarcation of the benefit of an acute treatment strategy.

Likewise, the CT diagnosis of transmural myocardial infarction (with a transmural perfusion defect) or previous myocardial infarction (with scar and fat infiltration) and new perfusion defect could also be a determinant of the effect of a fast invasive intervention. The VERDICT trial (https://clinicaltrials.gov/ct2/show/NCT02061891) is currently investigating these possibilities.

**Complications to ACS:** CCTA images may also be used to diagnose complications to ACS that may be important for patient treatment, such as pulmonary congestion/oedema and LV thrombus.\(^{217}\)

**Differential diagnosis to ACS:** The scan field may provide diagnostic imaging of various pathological conditions in structures adjacent to the heart. **Pulmonary embolism** shares both symptoms and several risk factors with ACS such as age, obesity and elevated levels of lipoprotein.\(^{218;219}\) CT pulmonary angiography has a sensitivity of up to 83% and specificities of 57-100%. The accuracy of detecting pulmonary embolism on CCTA images is not known, however with a prolonged contrast-bolus it will be close to the conventional pulmonary angiography as seen in triple rule out trials.\(^{20;218;219}\) **Acute aortic syndrome** likewise shares both symptoms and several risk factors with ACS such as age, hypertension, smoking and elevated levels of lipoprotein; and CT remain the method of choice for this diagnosis.\(^{220;221}\)

**Safety:** Studies are needed to ensure that CCTA does not do harm to patients and that the additional contrast administration is safe in all sub-groups.

Papers II-VIII explored CCTA derived analysis of myocardial perfusion and tissue characteristics, LA mechanical function and pulmonary congestion – thus non-coronary features that could be important for other patient groups (non-ACS). The assessment of myocardial perfusion abnormalities and changed tissue characteristics, especially fat tissue in pre-procedural CT
performed before VT-ablation or cardiac resynchronisation therapy for the treatment of heart failure, could guide the procedure and possibly select patients better. As CT is often used for 3-dimensional mapping of the LA before radiofrequency ablation procedures, it seems reasonable to use the scan to see if an elaborated description of the LA mechanical function could add to our understanding of the high relapse rates after ablation procedures. Finally the diagnostic and prognostic value of CT pulmonary congestion should be explored in other patient groups where CCTA is indicated and the use of automated assessment of lung tissue density as a measure of lung water should be further elaborated.
10. **DANSK RESUME**

Hjerte-CT er en non-invasiv scanningsteknik der muliggør undersøgelse af sygdom i koronararterierne. Teknikken benyttes hyppigst hos patienter mistænkt for stabil iskæmisk hjertesygdom, men nyere studier har indikeret at det kan være fordelagtigt at undersøge patienter med akutte brystsmerte og patienter med mulig akut koronart syndrom og uspecifikt forhøjede koronarmarkører. Dette kræver imidlertid forskning, der undersøger muligheder og begrænsninger for brugen af hjerte-CT hos patienter med akut koronart syndrom.

Hos patienter med myokardieinfarkt er udviklingen af hjertesvigt forbundet med dårlig prognose. En vurdering af konsekvenserne af koronarforsøknings på hjertemuskens perfusion, hjertets funktion og tegn på lungestase er måske mulig ud fra hjerte-CT billeder, hvilket kan bidrage med information der er vigtig for at erkende patienternes prognose og vejlede behandlingen.

Denne afhandling opsøger otte arbejder der omhandler mulighederne for med hjerte-CT at undersøge grade af iskæmisk hjertesygdom hos patienter med non-ST-segment elevations myokardieinfarkt (NSTEMI) og de effekter som sygdommen har nedstrøms, herunder vurdering af myokardiets perfusion, venstre atriums mekaniske funktion og tilstedeværelsen af lungestase.

**Evaluering af koronarkar**

Da der hidtil kun har været få mindre studier der har undersøgt hjerte-CT hos patienter med akut koronart syndrom, undersøgte vi den diagnostiske præcision af hjerte-CT i den hidtil største population af patienter med NSTEMI. Vi fandt en høj diagnostisk præcision af hjerte-CT i forhold til invasiv koronarangiografi, og fandt at hjerte-CT selv i en gruppe med meget høj sygdomsprævalens er velegnet til at udelukke betydelige koronarstenose, men fandt samtidig at hjerte-CT overestimerer omfanget af koronarstenose.

Samtidig undersøgte vi muligheden for at benytte hjerte-CT til at triagere disse patienter efter behandlingsstrategi og fandt at hjerte-CT fejlklassificerede 14% af patienterne som blev sat i en højere behandlingskategori (medicinsk behandling, PCI eller CABG) end den der blev anbefalet ud fra invasiv undersøgelse. Vi fandt deslige at hjerte-CT angiografi kan benyttes til at risikostratificere NSTEMI-patienter, idet dem med lukkede kar har dårligst prognose.

**Vurdering af myokardieperfusion**

Vurdering af myokardieperfusion ud fra hjerte-CT er kun i begrænset omfang undersøgt, og hidtil ikke relateret til prognose. Vi undersøgte perfusion målt med hjerte-CT hos patienter med og uden signifikante koronarstenoser. Vi fandt at hjerte-CT hos mennesker muliggør en nuanceret beskrivelse myokardieperfusionens fysiologi som kendt fra tidligere dyrestudier. Specielt muliggør hjerte-CT beskrivelsen af transmurale prefusionsgradienter i myokardiet, der hidtil kun er beskrevet

I en population af NSTEMI patienter fandt vi at patologiske forandringer i den transmurale perfusionsgradient er associeret med dårlig prognose (død og indlæggelse med hjertesvigt). Vi undersøgte desuden udbredelsen og sværhedsgraden af områder med hypoperfusion (perfusionsdefekter i hvile bedømt visuelt) og fandt ligeledes at disse var korreleret med prognose. Det samme var tilstedeværelsen af fedt i myokardiet.

Klinisk implikation: Myokardiet bør rutinmæssigt gennemses i hjerte-CT scanneringer hos patienter mistenkt for myokardieinfarkt da det kan indeholde prognostisk information.

Venstre atriums funktion
Det maksimale volumen af venstre atrium er et velbeskrevet udtryk for venstre ventrikels diastoliske funktion og er en stærk og meget benyttet prædiktor for død. Omvendt er den atrielle mekaniske funktion relativt sparsomt beskrevet på trods af den tætte relation til både diastolisk og systolisk funktion. Vores arbejder viste at det er muligt - med retrospektiv hjerte-CT - at vurdere den mekaniske funktion af venstre atrium både reproducerbart og i overenstemmelse med andre modaliteter så som ekkokardiografi og hjerte-MR. Endvidere viste vores arbejder at den atrielle funktion er stærkere korreleret med hjertesvigtssymptomer og død en den maksimale volumen af venstre atrium.

Klinisk implikation: Når retrospektiv hjerte-CT udføres på NSTEMI-patienter kan og bør den atrielle funktion bedømmes, da den indeholder stærk prognostiske værdi.

Lungestase
På trods af at CT benyttes som guldstandard i vurdering af lungestase er tilstedeværelsen af lungestase aldrig blevet beskrevet i en større kohorte af patienter og aldrig relationeret til hjertefunktion, klinisk hjertesvigt og outcome. Det foreliggende arbejde beskriver at CT tegn på lungestase kan estimeres ud fra hjerte-CT billeder. Endvidere ses det at lungestase bedømt med hjerte-CT korrelerer med venstre atriums størrelse og venstre ventrikels funktion og er god til at prædikere tilstedeværelsen af kliniske hjertesvigtssymptomer. Desuden ses det at lungestase bedømt ved hjerte-CT er god til at prædikere død og senere indlæggelser med hjertesvigt selv når der korrigeres for tilstedeværelsen af klinisk hjertesvigt og systolisk funktion bedømt ved venstre ventrikels uddrivningsfraktion.
Klinisk implikation: Tilstedeværelsen af lungestase bør bedømmes ved hjerte-CT undersøgelser fordi det er tæt forbundet med hjertefunktion, klinisk hjertesvigt og outcome hos NSTEMI-patienter.

**Konklusion:**
Denne afhandling bygger på artikler der for det første har bidraget til forskning ved at beskrive den diagnostiske værdi af hjerte-CT angiografi hos patienter med NSTEMI og dens evne til at triagere patienter i behandlingsgrupper og efter prognose. For det andet bygger den på arbejder der for første gang har undersøgt fysiologien i den transmurale perfusionsgradient i myokardiet hos mennesker med og uden signifikant koronarsygdom og som har relatert forstyrrelser i disse gradienter der forekommer hos NSTEMI patienter - såvel som visuel bedømmelser af perfusionsdefekter og tilstedeværelse af fedt – til prognose. For det tredje valideres opmålinger af venstre atriums størrelse og funktion bedømt med hjerte-CT i forhold til hjerte-MR og ekkokardiografi og beskriver forandringerne i venstre atriums funktion i forhold til venstre ventrikels funktion, kliniske hjertesvigtssymptomer og død. Endelig for det fjerde har arbejdet som det første undersøgt vurderingen af lungestase ud fra hjerte-CT billeder og særligt relationen mellem disse fund og venstresidig hjertefunktion, kliniske hjertesvigtssymptomer og prognose.
11. REFERENCES

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