Clinically Unrecognized Myocardial Scars Detected by MRI

Raquel Espregueira Themudo
Abstract

A high percentage of unrecognized myocardial infarctions (UMIs) seen at delayed-enhanced magnetic resonance imaging (DE-MRI) are not detected by electrocardiogram. DE-MRI-detected UMIs are independent predictors of cardiovascular events in patients with coronary artery disease (CAD). In an elderly population, subjects with DE-MRI-detected UMIs do not have increased Framingham risk score or increased prevalence of artery stenosis in whole-body MR angiography as patients with recognized myocardial infarctions (RMIs) do. Further investigation on the pathogenesis of DE-MRI-detected UMIs focus on the need to decide the management of these subjects.

From the Prospective Investigation of the Vasculature in Uppsala Seniors, 248 subjects underwent cardiac MRI at age 70 and from these, 185 underwent a 5-year follow-up MRI. DE-MRI-detected UMIs had lower signal intensity than RMIs, probably reflecting different composition of their tissues. Subjects with UMI scar had increased levels of NT-proBNP, a predictor of increased risk of cardiovascular events. After 5 years, UMI scars were in their majority seen on the same location and with the same size, and their prevalence increased. Subjects with an UMI did not differ from subjects without a scar in terms of coronary stenosis assessed by computed tomography angiography or signs of ischemia on exercise test.

In conclusion, DE-MRI-detected UMI scars are a frequent finding in an elderly population and its prevalence increases with age. The increased levels of NT-proBNP indicate that subjects with an UMI might have an increased rate of future cardiovascular events, but the findings that these scars have a lower contrast distribution volume on MRI than RMIs and that they are not related to CAD are indicators that they probably have a different etiology from RMIs. The prognosis of DE-MRI detected UMI scars in the general population is still unknown and therefore the clinical management of these individuals is yet to be defined.

Keywords: unrecognized myocardial scars, myocardial infarction, epidemiology, magnetic resonance, coronary computed topography angiography, exercise ECG test, NT-proBNP

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To my family
List of papers

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

   Signal Intensity of Myocardial Scars at Delayed-Enhanced MRI
   Acta Radiol. 2009; 50:652-657

   Unrecognized myocardial scars detected by delayed-enhanced MRI are associated with increased levels of NT-proBNP
   Coronary artery disease 2011; 22:158

   The number of unrecognized myocardial infarction scars detected at DE-MRI increases during a 5-year follow-up
   In manuscript

   Clinically unrecognized myocardial scars detected by MRI are not associated with coronary artery disease
   In manuscript

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## Abbreviations

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<th>Definition</th>
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<tr>
<td>$\gamma$</td>
<td>gyromagnetic ratio</td>
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<td>$\omega$</td>
<td>Larmor frequency</td>
</tr>
<tr>
<td>ACS</td>
<td>Agatston calcium score</td>
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<tr>
<td>$B_0$</td>
<td>external magnetic field</td>
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<tr>
<td>BMI</td>
<td>body mass index</td>
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<tr>
<td>CAD</td>
<td>coronary artery disease</td>
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<tr>
<td>CKMB</td>
<td>creatine phosphokinase MB isoenzyme</td>
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<tr>
<td>CT</td>
<td>computed tomography</td>
</tr>
<tr>
<td>CTA</td>
<td>computed tomography angiography</td>
</tr>
<tr>
<td>cTnI</td>
<td>cardiac troponin I</td>
</tr>
<tr>
<td>DE-MRI</td>
<td>delayed-enhancement magnetic resonance imaging</td>
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<td>DSCT</td>
<td>dual-source computed tomography</td>
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<tr>
<td>EBCT</td>
<td>electron-beam computed tomography</td>
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<tr>
<td>ECG</td>
<td>electrocardiogram</td>
</tr>
<tr>
<td>FOV</td>
<td>field-of-view</td>
</tr>
<tr>
<td>Gd-DTPA</td>
<td>gadolinium diethylenetriaminepentaacetic acid</td>
</tr>
<tr>
<td>HU</td>
<td>Hounsfield units</td>
</tr>
<tr>
<td>LV</td>
<td>left ventricular</td>
</tr>
<tr>
<td>M</td>
<td>net magnetization</td>
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<tr>
<td>MACE</td>
<td>major adverse cardiovascular events</td>
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<tr>
<td>MDCT</td>
<td>multiple-detector computed tomography</td>
</tr>
<tr>
<td>MI</td>
<td>myocardial infarction</td>
</tr>
<tr>
<td>MINCA</td>
<td>myocardial infarction with normal coronary arteries</td>
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<tr>
<td>MR</td>
<td>magnetic resonance</td>
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<td>MRA</td>
<td>magnetic resonance angiography</td>
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<tr>
<td>MRI</td>
<td>magnetic resonance imaging</td>
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<tr>
<td>NT-proBNP</td>
<td>N-terminal pro-brain natriuretic peptide</td>
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<tr>
<td>PD</td>
<td>proton density</td>
</tr>
<tr>
<td>PET</td>
<td>positron emission tomography</td>
</tr>
<tr>
<td>PIVUS</td>
<td>prospective investigation of the vasculature in Uppsala seniors</td>
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<tr>
<td>RF</td>
<td>radiofrequency</td>
</tr>
<tr>
<td>RMI</td>
<td>recognized myocardial infarction</td>
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<tr>
<td>ROI</td>
<td>region of interest</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
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<tr>
<td>SI</td>
<td>signal intensity</td>
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<tr>
<td>SPECT</td>
<td>single-photon emission computed tomography</td>
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<tr>
<td>SSFP</td>
<td>steady-state free precession</td>
</tr>
<tr>
<td>T</td>
<td>Tesla</td>
</tr>
<tr>
<td>TE</td>
<td>time of echo</td>
</tr>
<tr>
<td>TR</td>
<td>time of repetition</td>
</tr>
<tr>
<td>UMI</td>
<td>unrecognized myocardial infarction</td>
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</table>
Introduction

Unrecognized myocardial infarction
Ischemic heart disease mortality has decreased during the past decades in Western world countries mainly due to improved coronary care and secondary prevention (1-3). Even so, cardiovascular diseases are the leading cause of death in these countries (4).

Myocardial infarction (MI) is a common manifestation of ischemic heart disease and is related to increased morbidity and mortality. Herrick first described unrecognized myocardial infarction (UMI) in 1912 and since then UMIs have been a focus of several investigations (5). UMIs are missed in the acute phase and are usually detected by the presence of a pathologic Q-wave on the electrocardiogram (ECG) of patients that recall no symptoms or that had atypical signs of myocardial ischemia (6). Several epidemiologic studies have demonstrated that patients with ECG-detected UMI have an increased risk of major adverse cardiovascular events (MACE) and increased mortality, similar to patients with a clinically recognized myocardial infarction (RMI) (7-9). In these studies, UMIs comprise 20-60% of all ECG-detected MIs.

During the past decade, delayed-enhancement magnetic resonance imaging (DE-MRI) has provide a more sensitive tool in the detection of MI scars (10) and since then, many studies report a higher incidence of UMIs detected by DE-MRI than by ECG (11, 12). There is also evidence that subjects with DE-MRI-detected UMIs have a mortality risk similar to patients with RMI (12, 13), but the predisposing factors and the pathogenesis of an UMI detected at DE-MRI are still unclear.

Myocardial viability evaluation

Clinical
Myocardial infarction is defined as myocytes death caused by ischemia, which is the result of an impaired balance between blood supply and demand (6). Myocardial ischemia symptoms usually present as chest, upper extremity or epigastric pain with exercise or at rest. These symptoms are not specific for ischemia and can be misdiagnosed. Myocardial infarction can occur with atypical symptoms or without symptoms and be detected by ECG, biochemical markers or cardiac imaging (6).
**ECG (rest and stress)**

An ECG is part of routine work-up of patients with myocardial ischemia symptoms or in the detection of MI. Acute MI is usually translated in ST-segment elevation or ST-segment depression and/or T-wave changes. Prior MI can be detected by the presence of a Q-wave or QS complex. ECG changes alone are not sufficient to diagnose an acute MI, since there are other conditions that can have similar ST-segment and T-wave changes, such as acute pericarditis, left ventricular (LV) hypertrophy or left bundle branch block. ECG changes alone are not sufficient to diagnose a prior MI either, since pre-excitation, obstructive or dilated cardiomyopathy, among others pathologic conditions, can have similar ECG changes.

ECG can also be evaluated during ergometric exercise or pharmacological stress. Exercise ECG is more sensitive and specific to detect myocardial ischemia than rest ECG (14). Its wide availability and relative low cost makes exercise ECG a common test used in the diagnostic work-up of coronary artery disease (CAD) (15).

**Cardiac biomarkers**

Cardiac biomarkers, such as cardiac troponin I (cTnI) and creatine phosphokinase MB isoenzyme (CKMB), are indicators of myocardial necrosis. Acute MI evolves with elevation of these biomarkers that have different sensitivities, specificities and time windows after initial symptoms of ischemia (6). cTnI is also known to be elevated after stabilization of an acute MI and its elevation predicts mortality in the long-term follow-up (16).

N-terminal pro-brain natriuretic peptide (NT-proBNP) is a biomarker for LV dysfunction (17) and adds predictive information in risk stratification of patients after an acute MI or in chronic heart failure (18, 19).

**Echocardiography**

Echocardiography is a readily available real-time imaging technique, of relative low cost and uses no radiation. It is operator dependent and allows evaluation of myocardial thickness and thickening at rest or during stress. Myocardial infarction and myocardial hibernation are reflected as wall motion abnormalities. Contrast agents can improve endocardial border definition and facilitate visualization of wall motion abnormalities. Contrast agents have been used to assess myocardial perfusion (20, 21).
Myocardial scintigraphy / SPECT
Myocardial scintigraphy is used to evaluate myocardial perfusion through injection of a radioisotope after ergometric or pharmacological stress and during rest. The radioactive tracer, usually Technetium-99m isonitrile or Thallium-201, is taken by the myocardium in proportion to its blood flow. The radiations emitted by these agents are traced by a γ-camera in single 2D-projections (scintigraphy) or in multiple 2D projections from different angles that are then processed into 3D-images (SPECT - single-photon emission computed tomography). Discordant activity deficit during stress and rest represents a region of ischemia. Concordant activity deficits can represent an MI or hibernating myocardium. Myocardial scintigraphy and SPECT imply radiation exposure (22).

PET
Positron emission tomography (PET) is considered an accurate technique for quantification of perfusion and metabolism of the myocardium (23, 24). 13N-ammonia, 15O-water and rubidium-82 are examples of tracers used for perfusion imaging and fluorodeoxyglucose (FDG) is used as a metabolic tracer for viability assessment. PET has superior spatial resolution compared to SPECT. Infarcted myocardium is identified on PET by reduced function, perfusion and metabolism. The main disadvantages are its high costs, limited availability and the short tracers half-lives that require the presence of a cyclotron (25).

Magnetic resonance imaging

Basic physics

Spin and magnetization
All tissues are composed of atoms, which consist of a nucleus and a shell made of electrons. The atom nucleus is composed of protons and neutrons. The protons have a positive electric charge and are constantly spinning around an axis. The positive electric charge attached to the proton spins with the proton. The moving electrical charge produces an electrical current, which in turn, induces a magnetic force (26). In the absence of an external applied magnetic field, the protons are oriented in random directions. The sum of the magnetic moments of all protons inside a volume is called net magnetization (M). When the protons are exposed to an external magnetic field (B₀), as the one inside an MR scanner, the protons align themselves parallel to B₀. Even when aligned to B₀, the protons continue to spin about themselves in a movement called precession.
The frequency at which the protons precess, the Larmor frequency ($\omega$), is proportional to the strength of $B_0$, according to the equation $\omega=\gamma*B_0$ (where $\gamma$ is the gyromagnetic ratio; for protons $\gamma=42.5$ MHz/T).

When a patient is inside an MR scanner, the protons of the body align along $B_0$ and produce an $M$ factor in its direction (longitudinal direction). This new $M$ vector may be used to produce a signal, but its magnetic force cannot be read since it is parallel to $B_0$. For a magnetic force to be read it has to be transversal to the $B_0$. So, in order to produce a signal, there is an external radiofrequency (RF) pulse that is sent to the patient in order to excite some protons that are align with $B_0$. The RF pulse has to have the same Larmor frequency as the protons it intends to influence, so that the protons can receive the energy from the RF pulse, a phenomenon called resonance. After applying the RF pulse, some protons will acquire a transverse magnetization (transversal to $B_0$) and their longitudinal magnetization will decrease. The transverse magnetization vector will move in phase with the precessing protons and the moving electrical charges of the protons will produce an electrical current that can be read by an antenna and translated into the MR signal (26).

**Longitudinal relaxation – $T1$**

When the RF pulse is switched-off, the energy gained by the excited protons begins to spread into the surrounding atoms (lattice) and the protons recover their longitudinal magnetization – longitudinal relaxation (or spin-lattice-relaxation). The recover of longitudinal magnetization can be plot against time and the resulting curve (T1-curve) will be an exponential curve as shown in Figure 1. The rate of energy transfer from the excited protons to the surrounding tissues depends on the amount of excited protons and the composition of the lattice. The time it takes for the longitudinal relaxation to return to its original value is described as longitudinal relaxation time or $T1$. $T1$ is not the exact time it takes for the longitudinal magnetization to return to its original value, but it is a time constant that corresponds to the time it takes to recover 63% of the original value (26).

**Transverse relaxation – $T2$**

After the RF pulse is switched-off, the transverse magnetization starts to disappear with time, also resulting in an exponential curve as illustrated in Figure 2. The transverse relaxation (or spin-spin relaxation) originates from interactions between the spins. The time it takes for the transverse magnetization to decrease until 37% of its original value is described as transversal relaxation time or $T2$. $T2*$ is another quantitative measurement that describes the transverse relaxation when taking into account the effects of local magnetic field inhomogeneities (26).
Figure 1. Plot of the time course of the longitudinal relaxation component of the magnetization as the protons relax toward their thermal-equilibrium values (adapted from reference 26).

Figure 2. Plot of the time course of the transverse relaxation component of the magnetization as the protons relax toward their thermal-equilibrium value (adapted from reference 26).
**Image acquisition**

While the protons are recovering its longitudinal and transverse magnetization, their precessing movements induce electrical current that can be read by an antenna (coil) and that signal is converted by a Fourier transformation into an image. The RF pulses are switched on and off several times in order to acquire an image. The time interval between each RF pulse excitation is called time of repetition (TR) and the time interval between the RF pulse and the readout of MR signal is called time of echo (TE). The TR and TE can be varied and combined in different ways in order to acquire images with different contrast properties and thus fit the image contrast to the object in study. The most common types of image contrast that can be generated are proton-density (PD), T1-weighted and T2-weighted (for spin-echo sequences) or T2*-weighted (for gradient-echo sequences). Three basic features influence the image contrast: proton density, which is always present and is characteristic to the tissue; varying the TR controls the T1-weighting; varying the TE controls the T2-weighting. A PD-weighted image is acquired by minimizing contributions from T1 and T2 relaxations, so that tissues with high proton densities are brighter than those with low proton density. So, a PD image is obtained by choosing a TR that is long compared to the T1 value of the tissue to minimize T1-weighting and by choosing a short TE to minimize T2-weighting. A T1-weighted image is acquired by minimizing the influence from T2 relaxation, so that tissues with a short T1 are relatively bright and tissues with long T1 are relatively dark (Fig. 3). So, a T1-weighted image is obtained by choosing a TR that is approximate to the T1 value of interest and a short TE. A T2-weighted image is acquired by minimizing the influence from T1 relaxation while enhancing contribution from T2 relaxation, so that tissues with long T2 values are relatively bright and tissues with short T2 are relatively dark (Fig. 4). So, a T2-weighted image is obtained by choosing a TR that is long compared to the T1 value of interest and a long TE (26).

**Delayed-enhancement imaging**

The intravenous administration of an extracellular contrast agent will lead to accumulation of contrast in tissues with increased interstitial space and the presence of contrast will shorten the longitudinal relaxation time of the tissues, i.e. tissues will have a shorter T1. In the last 30 years, several reports have stated the utility of administration of intravenous contrast agents to image myocardial scars that would accumulate a higher amount of contrast and appear as a region of bright signal on T1-weighted images (27, 28). The disadvantage of these initial studies was the poor contrast between normal myocardium and scars obtained with the sequences then used. Kim et al. introduced a new technique to
Figure 3. Plot of T1 relaxation versus time for three different tissues assuming equal proton densities (adapted from reference 26).

Figure 4. Plot of T2 relaxation versus time for three different tissues assuming equal proton densities (adapted from reference 26).
image myocardial scars, named delayed-enhancement (10). This technique provides a better contrast between myocardial scars and normal myocardium by adding an inversion recovery pulse to the beginning of the sequence, which will null the signal from normal myocardium. After the initial inversion recovery pulse, normal and infarcted tissues will have different longitudinal relaxation time curves (Fig. 5) and the RF pulse that will generate the image will only be applied when the longitudinal relaxation time of normal myocardium crosses the zero line. Acquiring a quick inversion time scout sequence previously to the DE-MRI sequence allows determination of the proper waiting time (inversion time) to null the signal from normal myocardium and will determine the time interval from the sequence start until sending out the RF pulse. The proper inversion time depends on contrast dose, time interval between contrast administration and image acquisition and the relaxation time between the repeated applications of the inversion recovery pulses. DE-MRI is usually performed between 10-30 min after contrast injection using a dose of 0.2 mmol/kg of Gd-DTPA (29). In our studies, DE-MRI was acquired using a 3D inversion recovery gradient-echo sequence.

![Inversion recovery curves](image)

**Figure 5.** Inversion recovery curves of normal and infarcted myocardium assuming an inversion time of normal myocardium of 250ms and of infarcted myocardium of 150ms. The time the magnetization of normal myocardium reaches the zero crossing is defined as the inversion time to “null” normal myocardium. At this time, the magnetization of infarcted myocardium is above the zero line and infarcted myocardium will appear as a bright area at DE-MRI (adapted from reference 26).
DE-MRI has proved to be an accurate technique to detect MI scars and to determine their size (10, 30-32). Delayed-enhancement is not specific for MI scars. Other pathologic entities can present as bright areas in the myocardium at DE-MRI. Myocardial infarction scars typically appear as delayed-enhancement areas with a subendocardial component although this finding is not specific (33).

**Left ventricular functional analysis**

Left ventricular dysfunction is an important predictor of survival in patients with CAD (34, 35). Cine steady-state free precession (SSFP) sequences provide good delineation of the endocardial border and hence a good blood/myocardium contrast, enabling an accurate determination of LV systolic function (36, 37).

In our studies we used a manual method to delineate the endocardial and epicardial LV contours in order to determine LV ejection fraction and mass.

**Computed tomography**

**Basic physics**

Computed tomography (CT) uses x-ray radiation. A CT scanner is composed of a moving table in which the patient is lying and a rotating gantry, which includes an x-ray tube and the radiation detectors. The x-ray tube produces the x-ray, which will cross the patient and the radiation that is not attenuated by the patient structures will be received by a row of multiple detectors. There are three types of image acquisition: the digital projection, in which the x-ray tube and the detectors are stationary and the table with the patient moves continuously with the x-ray on, acquiring an image similar to conventional radiography; the axial acquisition, in which the table is stationary and the x-ray tube and detectors move around the patient acquiring one slice image; the helical acquisition, in which the table, x-ray tube and detectors move continuously producing an helix of images. In cardiac CT, the topogram is acquired using the digital projection; the calcium score images with the axial type of acquisition; and the coronary angiography images are obtained with the helical mode.

The x-ray beam that crosses the patient will be attenuated differently according to the densities of the patient structures. The radiation that reaches the detectors will then depend on the structures that it crosses and this information will be translated into different densities on a CT image. The densities on a CT image are measured in Hounsfield Units (HU). Each CT image is composed of pixels and each pixel on the image will have a brightness depending on the density of the structure that the
x-ray beam crossed. Bright pixels correspond to high densities structures (eg. bone) that attenuate a large proportion of the radiation.

**Temporal resolution**

In cardiac CT, the gantry rotation time is an important factor since it will determine the temporal resolution. Temporal resolution is important because the heart is a rapidly moving structure and coronary arteries need to be imaged when there is the least heart movement, i.e. during diastole. The time frame of diastole depends on the patient heart rate, and for a heart rate of 60 beats per minute, this time window is around 250 ms. Most recent single-source 64-slice CT scanners have a gantry rotation time of approximately 330 ms, which enables a temporal resolution of 165 ms. With dual-source CT scanners (DSCT), there are two x-ray tubes rotating at the same time, which can provide a temporal resolution of 83 ms (38).

**Spatial resolution**

Multiple-detector computed tomography (MDCT) enables acquisition of images with high spatial resolution. Several factors can determine spatial resolution. Axial resolution depends on the field-of-view (FOV) and matrix size, while longitudinal resolution (z-axis resolution) is influenced by the detector size in the longitudinal direction, reconstruction interval and pitch (table feed/gantry rotation), among other factors. MDCT enables image acquisition of a large volume in combination with a large number of thin images. Axial resolution of 0.7 to 0.5 mm and longitudinal z-axis resolution from 0.5 to 0.4 mm can be achieved with DSCT (38).

**Agatston calcium score**

Coronary arterial calcification is a marker of atherosclerosis and it is absent in normal vessels (39). Coronary artery calcium can provide an estimate of the total coronary plaque burden but there is a weak correlation between the presence of calcium and the existence of a severe coronary artery stenosis (40). Coronary calcification can be detected by fluoroscopy, electron-beam computed tomography (EBCT), MDCT, or intravascular ultrasound. Agatston calcium score (ACS) can be determined with EBCT or MDCT and it is a predictor of MACE beyond traditional risk factors (41-44). Some of the most appropriate indications for determination of ACS are risk assessment in asymptomatic individuals.
without known CAD, specifically in subjects with low pre-test CAD risk and a family history of premature CAD, or risk assessment in subjects with intermediate pre-test risk and no previously known CAD (45).

Based on previous studies with EBCT, a slice width of 3 mm has been established as a standard for quantification of coronary calcification by CT (46). Calcified lesions are detected using semi-automated software with a detection threshold of 130 HU.

**Coronary CT angiography**

Cardiac CT imaging was initially oriented to detection of coronary calcium but rapidly, with the advances in MDCT technology, and especially with the development of 64-slice CT, visualization of the coronary lumen has become the major focus. Coronary angiography is used to define coronary anatomy and the degree of luminal obstruction of the coronary arteries. Invasive coronary angiography is still the gold standard to identify and quantify the degree of coronary arteries stenosis (47). Coronary computed tomography angiography (CTA) provides a non-invasive technique to study coronary arteries, allowing not only the visualization of the coronary lumen, but also the evaluation of vessel wall and therefore it enables detection of non-stenotic coronary atherosclerotic plaques (48). According to the American Heart Association there are several appropriate indications for coronary CTA (45). Some common indications are detection of CAD in symptomatic patients without known heart disease or detection of CAD in patients with discordant exercise ECG test and imaging results or equivocal stress imaging results (45).

Coronary CTA can be acquired using a prospective mode of acquisition (“step-and-shoot” mode), but most commonly it is acquired using continuous helical scanning with lower pitch and retrospective reconstruction. The retrospective reconstruction is possible due to the simultaneous register of the ECG, which allows reconstruction of any vessel segment in the heart cycle phase with the least movement and also allows dynamic evaluation of valves and quantification of heart function (48). β-blockers are usually used to reduce heart rate in order to increase the diastolic window frame of the heart cycle and thus increase image quality. Dual-source 64-slice CT enables a higher temporal resolution than single-source 64-slice CT scanners and therefore β-blockers use is not mandatory (49). Nitroglycerin can be used to dilate the coronary arteries for better visualization of the lumen and to reduce coronary artery spasms (50).
Aims of the thesis

General aim
To study in a prospective investigation of elderly subjects if UMI scars detected at DE-MRI have a different pathogenesis from RMI scars.

Specific aims
1. To investigate differences in tissue characteristics between UMI and RMI scars detected in a population-based sample of 70-year-old subjects, by assessing the signal intensity at DE-MRI.
2. To investigate whether plasma levels of NT-proBNP differed between subjects with UMI scar and subjects with no MI scar detected at DE-MRI in a cohort of 70-year-old subjects. A secondary aim was to compare the levels of troponin I between subjects with UMI scars and subjects with no MI scar.
3. To verify if UMI scars detected with DE-MRI at age 70 would still be detectable at age 75 and if the size of the scars changed over time. A secondary aim was to study whether the prevalence of UMI scars increased during follow-up.
4. To compare the prevalence of signs of CAD by evaluation of coronary artery stenosis at coronary CTA and signs of myocardial ischemia at exercise ECG test between subjects with DE-MRI-detected UMI scars and subjects without MI scars in a population cohort of 75-year-old subjects.
Materials and Methods

Study population
The study population included a randomly selected subsample from the Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS). The population eligible for the primary PIVUS investigation included subjects aged 70 and living in the county of Uppsala, Sweden. Subjects were chosen from the community and were invited in a randomized order. From the 2025 subjects invited, 1016 participated in the primary investigation. From these 1016 subjects, 283 consecutive subjects were invited to undergo cardiac magnetic resonance imaging (MRI), which was performed on 259 of them. Eleven examinations had poor quality, leaving 248 exams for evaluation (123 women).

After five years, 52 subjects from the original cohort had died and the remaining 964 subjects were invited to participate in a follow-up study at age 75. At this time, 413 patients came to the MR unit to undergo cardiac MRI. On eleven patients cardiac MRI was not successfully performed either due to claustrophobia or due to technical problems. Cardiac MRI images were obtained on 402 subjects (186 women), although two examinations were excluded due to poor quality. There were six subjects with arrhythmia, precluding cine images to be carried out. At age 75, priority was given to subjects scanned at age 70 and the remaining subjects were selected in a randomized order from the original population. From the 248 subjects that were scanned at age 70, 185 were included at age 75.

After consensus reading of DE-MRI from age 75, a report that included information on myocardial scars was sent to the referring physician responsible for the primary PIVUS investigation. According to the findings on DE-MRI, the referring physician invited 88 subjects to additionally undergo coronary CTA and an exercise ECG test. The goal was to include as many subjects with UMI scars as possible, and a control group of subjects with no scar at DE-MRI. Figure 6 illustrates how the population in each study was formed.

The participants at the primary investigation answered a questionnaire concerning their medical history. A physician blinded to the MRI findings reviewed the hospital medical records of all participants. The Ethics Committee of the University of Uppsala approved the studies and all participants gave informed written consent.
Figure 6. Diagram illustrating how the population in each study was formed.

**Paper I**

In study I, subjects that underwent cardiac MRI at age 70 and that had MI scar at DE-MRI were included. From the 248 examinations, there were 60 subjects with MI scar: 49 with an UMI scar and 11 with an RMI scar.

**Paper II**

In study II, 248 subjects that underwent cardiac MRI at age 70 and that had plasma levels of NT-proBNP and troponin I measured were included.
Paper III
In study III, 185 subjects who underwent cardiac MRI at age 70 and 75 were included.

Paper IV
In study IV, 88 subjects that had undergone cardiac MRI and cardiac CT at age 75 were included. From the 88 participants, 64 also performed an exercise ECG test.

Cardiac MR image acquisition
Imaging was performed using a 1.5 Tesla MR scanner (Gyroscan Intera, Philips Medical Systems, Best, The Netherlands) with a 30 mT/m gradient system.

At age 70, prior to the cardiac MRI, whole-body magnetic resonance angiography (MRA) was performed after injection of 40 mL of gadodiamide (Omniscan™, GE Healthcare, Oslo, Norway).

At age 75, prior to the cardiac MRI, brain MRI was performed after injection of 0.2 mmol/kg of gadodiamide (Omniscan™, GE Healthcare, Oslo, Norway).

At both instances, cardiac imaging was performed using a five-element phased-array cardiac coil (Philips Medical Systems, Best, The Netherlands) with the patient in the supine position, using vectorcardiography for retrospective gating. Delayed-enhancement images were obtained using a 3D inversion recovery gradient-echo sequence in short-axis and 3 long-axis standard views. Images were acquired in end-diastole, during breath-holding in expiration. The inversion time was individually adjusted to null the signal from normal myocardium. Slices were acquired with a 10-mm thickness and a 5-mm overlap and an in-plane resolution of 1.56 x 2.81 mm. Functional imaging was obtained with a SSFP cine sequence with the following parameters: shortest TR (3.6 ms), shortest TE (1.8 ms), flip angle 70°, bandwidth 723.8 Hz/pixel, 18 phases/cardiac cycle, FOV 400 mm, matrix 256, parallel imaging (SENSE) factor 2, and k-lines segments (TFE factor) 19. Two slices were acquired per breath-hold with an acquired in-plane resolution of 2.27 x 1.81 mm (reconstructed to 1.56 x 1.56 mm). Cine images were obtained with an 8-mm-thick single slice in the standard 3 long-axis views and the volume of the left ventricle was covered from base to apex in the short-axis view with 8-mm-thick slices and a 2.5-mm slice gap.
On paper I, delayed-enhancement images from age 70 were used.
On paper II, delayed-enhancement and cine images from age 70 were used.
On paper III, delayed-enhancement and cine images from age 70 and 75 were used.
On paper IV, delayed-enhancement and cine images from age 75 were used.

Cardiac MR image analysis

Paper I, II, III and IV
MR image analysis was performed on a dedicated workstation using a commercially available software (View Forum R 4.1 V1L2, Philips Medical Systems, Best, The Netherlands). Two radiologists reviewed delayed-enhancement images from age 70 and age 75 independently and in consensus reading. Areas of bright signal on delayed-enhancement images were classified as typical MI scars if involving the subendocardial layer or as other type of scars if not involving the subendocardial layer (33). In some cases, delayed-enhancement images were reviewed in combination with the corresponding cine slice, in order to decide whether an area of bright signal corresponded to a small subendocardial delayed-enhancement or to blood in a myocardial crypt. Consensus was also performed for MI scar location according to the American Heart Association 17-segment model (51).

Paper I
For each individual with an MI scar, the short-axis slice with the biggest brightest area of delayed-enhancement was chosen to do the signal intensity (SI) analysis of the scars. One region of interest (ROI) was drawn outlining the MI scar area and a second ROI was drawn in the normal myocardium (Fig. 7). For each ROI, the mean SI was calculated with the computer-assisted software. A SI ratio was calculated as the ratio between the mean SI in scar tissue and the mean SI in normal myocardium. Scar transmurality was also visually assessed and classified in quartiles, according to the partial extent of delayed-enhancement across the LV myocardial wall. The SI ratio of MI scars was used to compare tissue characteristics between UMI and RMI scars. Visible areas of delayed-enhancement in all short-axis slices were delineated in order to calculate total myocardial scar mass, assuming a myocardial density of 1.05 g/mL (52).
**Paper II**
LV functional analysis for paper II was done in the short-axis view with the endocardial and epicardial contours manually outlined at end-diastole and end-systole. Papillary muscles were manually outlined separately and included in the LV mass. The workstation software automatically displayed LV ejection fraction and LV mass.

**Paper III**
After consensus reading of DE-MRI from age 70 and 75, the MRI examinations that displayed MI scars were reviewed and compared side-by-side. During the revision, we assessed if the MI scars seen at both instances were on the same location. Additionally, we looked retrospectively to verify if there were MI scars missed in the consensus reading either at age 70 or at age 75 of subjects classified as having an MI scar in only one of the time points. This was done by scrutinizing the corresponding areas between the two investigations. If there was a corresponding area with increased signal intensity suggestive of a scar, but primarily assessed as no scar, it was reassessed as a missed MI scar.

**Definition of groups according to the findings at DE-MRI**
A physician blinded to the MRI findings reviewed the individual questionnaires and the hospital medical records. Subjects with a hospital medical record of MI or that reported having been treated for MI in another hospital were considered to have had a clinical MI.
Subjects lacking medical records at our institution and that did not report having been treated for an MI were regarded as not having had a clinical MI. Subjects with no MI scar were included in the “no-MI group”, subjects with an MI scar at DE-MRI and no previous history of MI were included in the “UMI group”, subjects with an MI scar and a hospital diagnosis of MI were included in the “RMI group”. The division into the three groups was performed for all subjects examined at age 70 and all subjects examined at age 75. Other cardiovascular diagnoses that can cause myocardial delayed-enhancement on MRI, such as myocarditis, sarcoidosis, amyloidosis, and dilated or hypertrophic cardiomyopathy were also registered. One subject that underwent cardiac MRI at age 70 and 75 was diagnosis with amyloidosis between the two examinations and was excluded from further analysis of the 75-year-old population. This subject displayed typical findings of cardiac amyloidosis on the MRI at age 75 (53).

**Laboratory tests**

**Paper II**

In all subjects included in the primary PIVUS investigation a venous blood sample was collected and stored for future analysis. From these frozen samples, the plasma levels of NT-proBNP and cTnI were determined. All 248 subjects included in paper II had plasma levels of these two biomarkers measured. NT-proBNP was determined by sandwich immunoassay on an Elecsys 2010 instrument (Roche Diagnostics, Mannheim, Germany). Plasma levels of cTnI were determined with an improved version of the Access AccuTnI assay (Beckman Coulter, Fullerton, CA, USA).

**Cardiac CT image acquisition**

**Paper IV**

Images were acquired with a 64-slice dual-source CT scanner (Somatom® Definition, Siemens Medical Solutions, Forchheim, Germany). All subjects were lying supine and received a double dose of glyceryltrinitrate (Nitrolingual®, Pohl-Boskamp, Hohenlockstedt, Germany) before image acquisition. No β-receptor antagonist for heart rate control was administered before image acquisition. After a topogram, an initial prospective ECG-triggered unenhanced scan covering the entire heart was acquired for total calcium score quantification. Coronary CTA images were acquired during injection of 70-80 mL of iomeprol (Iomeron 400®, Bracco Imaging SpA, Milan, Italy) at 6 mL/s. Images were acquired with retrospective ECG-gated technique, using tube current modulation
and single-segment reconstruction with a temporal resolution of 83 ms. Images were reconstructed with a 3-mm slice thickness for calcium score analysis. For coronary CTA, images were reconstructed with a 0.6-mm slice thickness at best-diastolic and best-systolic phases as determined by the software and an additional multi-phase reconstruction with window offsets of 5% through the entire heart cycle.

**Cardiac CT image analysis**

**Paper IV**

CT images analysis was performed on a Siemens Leonardo workstation (Siemens Medical Solutions, Forcheim, Germany) with dedicated software. ACS was determined on unenhanced images by using a semiautomated software (Syngo Calcium Scoring, Siemens Medical Solutions, Forcheim, Germany) with a detection threshold of 130 HU.

The coronary tree was visually segmented in 18 segments according to Swedish Coronary Angiography and Angioplasty Register (SCAAR) (54) (Fig. 8). Two radiologists evaluated independently and in consensus every segment for each patient according to the following classification: 0, no lesion; 1, < 50% stenosis; 2, > 50% stenosis; 3, > 70% stenosis; 4, occlusion; 5, segment not assessable due to motion artifacts; 6, not assessable due to high burden of calcification; 7, not assessable due to poor contrast.

![Figure 8. Coronary arteries segmentation according to the Swedish Coronary Angiography and Angioplasty Register.](image-url)
Exercise ECG test procedure

Paper IV
Exercise ECG test was performed on a stationary bicycle. The participants started at 30 W and thereafter the workload was increased by 10 W/min until exhaustion. Other termination criteria were: severe chest pain (5/10 on the Borg scale), severe ST-depression (> 3 mm), severe drop in blood pressure (> 15 mmHg) or severe arrhythmias. A 12-lead ECG was recorded continuously during the test.

Exercise ECG test interpretation

Paper IV
ST-depression was measured in lead V5 or V6 and the maximal depression occurring during the test was expressed in relation to the baseline value. The exercise test data was also categorized as positive for ischemia when maximal ST-depression was ≥ 1.0 mm.

Statistics

Paper I
Statistical analysis was performed using the software Statistica, version 8.0 (StatSoft Inc.®, Tulsa, OK, USA).

A paired t-test was used to test differences between the SI in the MI scars and the SI in the normal myocardium. Inversion times were compared between the UMI, RMI and no-MI groups using the Kruskal-Wallis test. Myocardial infarction scars SI ratio was compared between the UMI and RMI groups using a Mann-Whitney test. A multiple regression analysis was done to test the influence of the variables gender, body mass index (BMI), time of image acquisition after gadolinium injection, scar transmurality, total MI scar mass and MI group (UMI/RMI), on the SI ratio. Statistical significance was set up at $p \leq 0.05$. 
Paper II
Statistical analysis was performed with the software Statistica, version 8.0 (StatSoft Inc.®, Tulsa, OK, USA).

Cut-off points recommended in the literature were used for the analysis of frequency distribution of NT-proBNP (386 ng/L) (55) and cTnI (0.01 mg/L) (56) within each group. A natural logarithm was applied to the values of NT-proBNP. An ANOVA test was used for comparison of NT-proBNP between the three groups. cTnI was used as a dichotomized variable applying 0.01 mg/L as a threshold and a $\chi^2$-test compared the levels in the three groups. A Spearman correlation was performed between volume of the MI scar and NT-proBNP. A multiple regression analysis tested the influence of gender, renal function, MI group (UMI/RMI), LV mass, volume of the MI scar and LV ejection fraction, in the plasma level of NT-proBNP. Statistical significance was set at $p \leq 0.05$.

Paper III
Statistical analysis was performed with the statistical software IBM® SPSS® Statistics version 19 (Chicago, IL, USA).

A paired t-test was used to test differences in MI scar mass between age 70 and 75 of subjects having an UMI at both ages. Statistical significance was set up at $p \leq 0.05$.

Paper IV
Statistical analysis was performed with the statistical software IBM® SPSS® Statistics version 19 (Chicago, IL, USA).

A paired t-test was used to compare continuous variables and a $\chi^2$-test was used to compare categorical data between the UMI and the no-MI group. Statistical significance was set up at $p \leq 0.05$. 
Results

Paper I
The mean SI ratio of MI scars (Fig. 9) was lower in the UMI group (4.5 ± 3.0, mean ± SD) than in the RMI group (8.9 ± 5.1) \((p = 0.0004)\) (Fig. 10). The difference of SI ratio between the two groups was still significant \((p < 0.0001)\) after adjustment for gender, BMI, time of image acquisition after gadolinium injection, scar transmurality or total MI scar mass (Table 1).

Figure 9. Example of an unrecognized myocardial infarction (UMI) (A) and recognized myocardial infarction (RMI) (B) scar seen at delayed-enhanced MRI in the short-axis view and illustration of the signal intensity (SI) analysis of the scar. The UMI scar has a total area of 1169.5 mm\(^2\), corresponding to 4.38\% of the total left ventricular mass, and has a SI ratio of 3.38. The RMI scar has a total area of 2781.2 mm\(^2\), corresponding to 7.67\% of the total left ventricular mass, and has a SI ratio of 7.58.
**Figure 10.** Box-plot graph of the signal intensity (SI) ratio in the unrecognized myocardial infarction (UMI) and recognized myocardial infarction (RMI) group. There was a difference in the SI ratio between the UMI group and the RMI group. The mean SI ratio in the UMI group was $4.5 \pm 3.0$ (mean $\pm$ SD) and in the RMI group $(8.9 \pm 5.1)$ ($p = 0.0004$).

**Table 1.** Multiple regression model with signal intensity ratio as the dependent variable and gender, body mass index, time of image acquisition after gadolinium injection, transmurality, total myocardial infarction scar mass and myocardial infarction group as independent variables.

<table>
<thead>
<tr>
<th></th>
<th>$p$ - value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>0.7790</td>
</tr>
<tr>
<td>BMI</td>
<td>0.3183</td>
</tr>
<tr>
<td>Gadolinium time (min)</td>
<td>0.4612</td>
</tr>
<tr>
<td>Transmurality</td>
<td>0.951</td>
</tr>
<tr>
<td>Total myocardial infarction scar mass (g)</td>
<td>0.2611</td>
</tr>
<tr>
<td>Myocardial infarction group (UMI/RMI)</td>
<td>$&lt;0.0001$</td>
</tr>
</tbody>
</table>

BMI = body mass index; UMI = unrecognized myocardial infarction; RMI = recognized myocardial infarction.
Paper II

Subjects with an UMI scar had plasma levels of NT-proBNP higher than subjects in the no-MI group and lower levels than subjects in the RMI group (Fig. 11). The correlation between the MI scar volume and NT-proBNP had a rho-value of 0.39 ($p < 0.0001$). In a multiple regression model, after adjustment for gender, renal function, MI group (UMI/RMI), LV mass, volume of the MI scar and LV ejection fraction, the independent predictors of the plasma level of NT-proBNP were gender and MI scar volume (Table 2). No difference was found in cTn I values between the three groups.

Figure 11. ANOVA test for N-terminal pro-brain natriuretic peptide (NT-proBNP) in the three groups. Subjects with an unrecognized myocardial infarction (UMI) scar had plasma levels of NT-proBNP higher than subjects without a myocardial infarction scar (no-MI) ($p = 0.01$) and lower levels than subjects with a recognized myocardial infarction (RMI) scar ($p = 0.02$).
Table 2. Multiple regression model with ln (NT-proBNP) as dependent variable and gender, renal function, myocardial infarction group (UMI/RMI), left ventricle myocardial mass adjusted for body surface area, myocardial infarction scar volume and left ventricular ejection fraction as independent variables.

<table>
<thead>
<tr>
<th></th>
<th>p - value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>0.001</td>
</tr>
<tr>
<td>Renal function – creatinine (mmol/L)</td>
<td>0.249</td>
</tr>
<tr>
<td>Myocardial infarction group (UMI/RMI)</td>
<td>0.191</td>
</tr>
<tr>
<td>Left ventricle myocardial mass / BSA (g/m²)</td>
<td>0.986</td>
</tr>
<tr>
<td>Myocardial infarction scar volume (%)</td>
<td>0.034</td>
</tr>
<tr>
<td>Left ventricular ejection fraction (%)</td>
<td>0.051</td>
</tr>
</tbody>
</table>

UMI = unrecognized myocardial infarction; RMI = recognized myocardial infarction; BSA = body surface area.
Paper III

After consensus reading of the 184 MRI exams from age 75, 118 subjects were included in the no-MI group, 59 in the UMI group and 7 in the RMI group.

The side-by-side revision of the MR images from both ages, revealed 6 UMI scars missed in the consensus reading at age 70 and 2 UMI scars missed in the consensus reading at age 75. There was no RMI scar missed in any of the analysis. Thus, of the 184 subjects who underwent cardiac MRI at both ages, 42 of 184 (23%) subjects had an UMI scar at age 70 and 61 of 184 (33%) had an UMI scar at age 75.

Figure 12 illustrates the evolution seen in MI scars after 5 years. There were 2 (5%) of the 42 UMI scars (with a mass of 0.6 g and 2 g) seen at age 70 that were not seen at age 75; 37 (88%) of the 42 UMI scars seen at age 70 were seen in the same LV segment at age 75; and 3 (7%) of the subjects with an UMI scar at age 70 displayed a new RMI scar in the same LV segment at age 75. Twenty-four (17%) and 2 (1%) of the 140 subjects without an MI scar at age 70 developed an UMI and RMI scar, respectively. From the 11 subjects that had an RMI scar at age 70, two subjects were reexamined at age 75 and the scars were still present.

The scar mass of subjects with UMI scars at both ages (n=37) did not differ between age 70 (mean 3.8 g; 0.2-26 g) and age 75 (mean 3.9 g; 0.1-27 g) and there was a significant correlation (97%; \( p < 0.01 \)) between the measurements at both ages (Fig. 13). An example of an UMI scar seen at age 70 and 75 is displayed in Figure 14. There was a tendency for UMI scars to be located in the basal segments of the LV inferior and inferolateral wall (Fig. 15).
**Figure 12.** Evolution of myocardial infarction scars found in the 70-year-old population and in the 5-year follow-up. MI: myocardial infarction; UMI: unrecognized myocardial infarction; RMI: recognized myocardial infarction.

**Figure 13.** Scatter plot graph displaying the correlation of scar mass between age 70 and 75 of subjects having an unrecognized myocardial infarction (UMI) at both ages (n=37).
**Figure 14.** Example of an unrecognized myocardial infarction scar seen at age 70 (A) and age 75 (B).

**Figure 15.** Distribution of the 61 unrecognized (UMI) and 7 recognized myocardial infarction (RMI) scars seen at age 75 according to the American Heart Association 17-segment model.
Paper IV

From the 88 subjects that underwent MRI and CT at age 75, 43 subjects had no MI scar and 45 had an UMI scar at DE-MRI. Table 3 summarizes the number of segments in each group categorized according to the classification for coronary stenosis. Interobserver agreement considering coronary stenosis above 50% was 74%. No difference was found between the UMI and the no-MI group when segments with score 1, 2, 3 and 4 (“any degree” of stenosis) were grouped (29% in UMI group vs 24.6% in no-MI group). No difference was found between the UMI and the no-MI group when segments with score 2, 3 and 4 (stenosis > 50%) were grouped (5.6% in UMI group vs 3.1% in no-MI group) neither when segments with score 3 and 4 (stenosis > 70%) were grouped (1.5% in UMI group vs 0.5% in no-MI group). No difference was found in the ACS between the UMI group (mean 472; range 0-2057) and the no-MI group (mean 324, range 0-2912) (Fig. 16).

From the 64 subjects that underwent MRI, CT and exercise ECG test, 35 subjects had no MI scar and 29 had an UMI scar at DE-MRI. No difference was found in maximal ST-depression in relation to baseline value measured in V5 ECG lead between the UMI group (mean -0.56; range -1.75 - +1.05) and the no-MI group (mean -0.63; range -1.85 - +0.6) (Fig. 17). No difference was found in maximal ST-depression in relation to baseline value measured in V6 ECG lead between the UMI group (mean -0.53; range -1.4 - +0.65) and the no-MI group (mean -0.54; range -1.4 - +0.45). No difference was found in the prevalence of tests with ST-depression ≥ 1.0 mm between the UMI (5/29 subjects) and the no-MI group (6/35 subjects) (Table 4). No participant stopped due to any of the termination criteria except for exhaustion neither referred having any degree of chest pain during the test.
Table 3. Number of segments in the two groups according to the degree of coronary artery stenosis.

<table>
<thead>
<tr>
<th></th>
<th>No-MI group</th>
<th>Difference No-MI Vs UMI</th>
<th>UMI group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of segments evaluated</td>
<td>572</td>
<td>607</td>
<td></td>
</tr>
<tr>
<td>Score 0 (no stenosis)</td>
<td>416</td>
<td>385</td>
<td></td>
</tr>
<tr>
<td></td>
<td>72.7%</td>
<td>NS</td>
<td>63.4%</td>
</tr>
<tr>
<td>Score 1 (stenosis &lt; 50%)</td>
<td>123</td>
<td>142</td>
<td></td>
</tr>
<tr>
<td></td>
<td>21.5%</td>
<td>NS</td>
<td>23.4%</td>
</tr>
<tr>
<td>Score 2 (stenosis &gt; 50%)</td>
<td>15</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2.6%</td>
<td>NS</td>
<td>4.1%</td>
</tr>
<tr>
<td>Score 3 (stenosis &gt; 70%)</td>
<td>1</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.2%</td>
<td>NS</td>
<td>0.7%</td>
</tr>
<tr>
<td>Score 4 (occlusion)</td>
<td>2</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.3%</td>
<td>NS</td>
<td>0.8%</td>
</tr>
<tr>
<td>Score 5 (NA motion artifacts)</td>
<td>2</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.3%</td>
<td>NS</td>
<td>3.1%</td>
</tr>
<tr>
<td>Score 6 (NA calcifications)</td>
<td>4</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.7%</td>
<td>NS</td>
<td>1.5%</td>
</tr>
<tr>
<td>Score 7 (NA poor contrast)</td>
<td>9</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.6%</td>
<td>NS</td>
<td>3%</td>
</tr>
</tbody>
</table>

MI: myocardial infarction, UMI: unrecognized myocardial infarction
NA: not assessable, NS: not significant
Significance set at $p \leq 0.05$

Figure 16. Box-plot graph of Agatston calcium score in the group with no myocardial infarction scars (no-MI) and in the group with unrecognized myocardial infarction scars (UMI).
Table 4. Exercise test results in the no myocardial infarction scar (no-MI) group and unrecognized myocardial infarction (UMI) group (mean; range).

<table>
<thead>
<tr>
<th></th>
<th>No-MI group</th>
<th>UMI group</th>
</tr>
</thead>
<tbody>
<tr>
<td>N. of participants</td>
<td>35</td>
<td>29</td>
</tr>
<tr>
<td>Resting HR</td>
<td>74</td>
<td>73</td>
</tr>
<tr>
<td>57 - 104</td>
<td>47 - 93</td>
<td></td>
</tr>
<tr>
<td>Resting SBP</td>
<td>147</td>
<td>151</td>
</tr>
<tr>
<td>115 - 205</td>
<td>120 - 190</td>
<td></td>
</tr>
<tr>
<td>Maximal workload</td>
<td>117</td>
<td>116</td>
</tr>
<tr>
<td>70 - 215</td>
<td>90 - 170</td>
<td></td>
</tr>
<tr>
<td>Maximal HR</td>
<td>141</td>
<td>141</td>
</tr>
<tr>
<td>109 - 176</td>
<td>110 - 196</td>
<td></td>
</tr>
<tr>
<td>Maximal SBP</td>
<td>203</td>
<td>210</td>
</tr>
<tr>
<td>140 - 260</td>
<td>150 - 240</td>
<td></td>
</tr>
<tr>
<td>ST-depression V5</td>
<td>-0.63 (-1.85) - (+0.6)</td>
<td>-0.56 (-1.75) - (+1.05)</td>
</tr>
<tr>
<td>ST-depression V6</td>
<td>-0.54 (-1.4) - (+0.45)</td>
<td>-0.53 (-1.4) - (+0.65)</td>
</tr>
<tr>
<td>N. tests positive for ischemia</td>
<td>6</td>
<td>5</td>
</tr>
</tbody>
</table>

HR: heart rate
SBP: systolic blood pressure

Figure 17. Box-plot graph of V5 lead ST-depression in the group with no myocardial infarction scars (no-MI) and in the group with unrecognized myocardial infarction scars (UMI).
Discussion

Previous studies
DE-MRI is a recent validated imaging method to detect MI scars (10). Since the advent of DE-MRI and its proven sensitivity to detect myocardial scars, several studies have revealed that there is a high prevalence of UMIs detected by DE-MRI that are not translated into a pathologic Q-wave on ECG (11-13, 57). There is evidence that DE-MRI-detected UMI scars found in patients with CAD are associated with increased prevalence of traditional risk factors of CAD and that even small UMI scars are independent predictors of MACE (13, 57). Nevertheless, from the PIVUS study it is known that subjects with DE-MRI-detected UMI scars have lower LV ejection fraction and higher LV mass than subjects with no MI scars, but do not have an increased Framingham risk score or increased prevalence of significant artery stenosis in whole-body MRA, as patients with an RMI scar do (11, 58). Therefore, the etiology and prognosis of UMI scars detected at DE-MRI in a general population is not known. The importance of further investigation on the pathogenesis and prognosis of DE-MRI-detected UMI scars focus on the need to orient the physician on the management of this new group of patients.

Present studies
This thesis aimed to contribute to further understanding on the pathogenesis of DE-MRI-detected UMI scars.

In our first study we investigated differences in tissue characteristics between UMI and RMI scars, by assessing the SI of scars at DE-MRI. The pathophysiology of DE-MRI is not completely elucidated, but it is thought that delayed-enhancement of myocardial scars is due to an increased extracellular space in scar tissues, allowing a larger distribution volume for the extracellular contrast agent (59). The contrast distribution volume within a tissue has an inverse correlation with the longitudinal relaxation time or T1 (60). Hence, myocardial scar tissue by having increased extracellular space compared to normal myocardial tissue will have shorter T1 after contrast injection and consequently brighter signal at T1-weighted sequences. This difference in signal intensity is further optimized at delayed-enhancement imaging as explained in the introduction. In this study, it was found that UMI scars have a lower SI than RMI scars, which may reflect different contrast distribution volumes in the scar tissues and consequently a possible difference in tissue composition.
Study II revealed that plasma levels of NT-proBNP were higher in subjects with DE-MRI-detected UMI scars than in subjects with no MI scar. NT-proBNP is a cardiac biomarker that is synthesized and released in ventricular myocytes in response to fiber stretch (61) and is a biomarker of LV dysfunction (17). Increased levels of NT-proBNP after an acute MI or in chronic heart failure have been related to a worse prognosis, independent of other cardiac risk factors (18, 19, 62, 63). From the PIVUS study it is known that subjects with an UMI scar have decreased LV ejection fraction (11). LV ejection fraction and plasma levels of NT-proBNP are inversely correlated (64) and both are predictors of future cardiovascular events. The combination of NT-proBNP and LV ejection fraction measurements yields a better risk stratification for MACE after an MI than either of the indicators used alone (65). This analysis intended to test if the lower LV ejection fraction previously found in the UMI group was not an isolated finding, showing additional evidence to support our hypothesis that subjects with DE-MRI-detected UMI scars might have an increased risk of future MACE than subjects with no MI scar.

Recently, some studies have demonstrated that persistent increased plasma levels of cTnI after a non-ST elevation acute coronary syndrome are also associated with increased mortality on long-term follow-up (16). In our study, UMI scars detected at DE-MRI were not associated with increased levels of this biomarker. Eggers et al found prognostic significance of increased troponin I using a low cut-off level (0.01 μg/L) (16). Even though the measurement of cTnI in our study was done with an improved version of the Access AccuTnI assay, providing improved analytical sensitivity at the lower end of its range, some degree of uncertainty remains regarding the accuracy of very low cTnI results.

A 5-year follow-up of 185 subjects that underwent cardiac MRI at age 70 was performed in study III. It was found that 40 of the 42 subjects with an UMI scar at age 70 still had an MI scar on the same LV myocardial segment at age 75 (37 as an UMI scar and 2 as a new RMI scar). We also found that 24 of the 140 subjects with no MI scar at age 70 developed an UMI scar during this interval, increasing the frequency of UMI scars in this group from 23% at age 70 to 33% at age 75. This investigation reassured that DE-MRI-detected UMI scars at age 70 were a real finding and not related to artifacts, as it might have explained some of the smallest scars. It also reinforces our previous statement that DE-MRI-detected UMI scars are a frequent finding on an elderly population and are more frequent than previous epidemiologic studies using ECG criteria reported (11). Some epidemiologic studies report prevalence of Q-wave UMIs between 1-5%. Although the majority include subjects younger than our study population (9, 66, 67), the Cardiovascular Health
Study, which includes subjects older than 65 years, reports a prevalence of Q-wave UMI of only 3% (8). Non-Q-wave RMIs can comprise as much as 50% of all RMIs. Hence, it could be expected that at least 50% of all UMIs would not have a Q-wave on ECG. The presence of Q-wave has also been estimated to disappear after 4 years in 20% of subjects who survive an acute MI (68). Even so, the low number of Q-wave signs (5%) found in the total group of subjects with DE-MRI-detected UMI scars at age 75 can only be partially explained by the former statements. Low number of Q-wave UMIs has also been observed in other investigations using DE-MRI for the diagnosis of UMI, although to a minor extent (13, 57). The appearance of a Q-wave on ECG has been related to the size of the MI scar seen at DE-MRI (69). Therefore, it is reasonable to assume that these small UMI scars detected at DE-MRI, with an average myocardial mass of approximately 4g, do not have the sufficient extent of necrosis to produce a significant Q wave on ECG. The finding of high prevalence of DE-MRI-detected UMI scars have also been described in previous studies, but most of these investigations have been conducted in younger populations (average age 60 years) and included patients with known or suspected CAD. In the literature, there is only one comparable investigation to our present study, published in the form of abstract (12), which included DE-MRI criteria for the diagnosis of UMI in a general elderly population, where similar results are found. To our knowledge, this is the first follow-up study of UMI scars detected at DE-MRI. After 5 years, the size of the DE-MRI-detected UMI scars did not change. A stable and chronic stage of an MI scar is achieved 8 weeks after the acute event (10) and therefore the comparable size of the UMI scars seen at both instances is an expected finding since most probably these scars are imaged in its chronic state.

Study IV demonstrated that elderly subjects with DE-MRI-detected UMI scars do not have an increased prevalence of coronary artery stenosis assessed by coronary CTA or signs of myocardial ischemia on the exercise test, when compared to a control group without MI scars. These findings indicate that UMI scars in general are not related to CAD. There is indirect evidence from previous studies that DE-MRI-detected UMI scars might not be related to CAD, either from the comparison of the Framingham risk score, common carotid artery intima-media thickness or from the prevalence of atherosclerosis in whole-body MRA (58). Although there were a slightly higher number of coronary segments with stenosis and higher ACS score in the UMI group compared to the no-MI group, these differences were small and non-significant. One advantage of coronary CTA over invasive angiography is the possibility to see the vessel wall and detect small lesions and minor signs of atherosclerosis that can be missed at conventional invasive angiography. In this study, there was no evidence of increased signs of CAD in large coronary arter-
ies in individuals with UMI scars, either by assessing segments with severe stenosis or by assessing signs of mild atherosclerosis (29% of segments with “any degree” of stenosis in UMI group vs 24.6% in no-MI group). We analyzed the burden of CAD in large coronary artery segments assessable at CTA, but whether these scars are related to small vessel disease it is not possible to exclude from this investigation.

Exercise ECG test is a more sensitive and specific test to detect myocardial ischemia than rest ECG, but has inferior diagnostic performance that stress imaging techniques (15). Even so, exercise ECG test is wide available and has relative low cost, making it a common test used in clinical practice for the diagnostic work-up of CAD (15). Therefore, we added this test to our study in order to have a stress test that would add information on ischemia signs in the subjects investigated.

Recently, some interesting observations have focused on the role of DE-MRI in identifying patients with myocardial infarction and normal angiographic coronary arteries (MINCA). Although MINCA tends to occur in younger patients (mean age 50-60 years) (70, 71) than our PIVUS population, there seems to be some similarities between individuals with MINCA and our study population with UMI scars. Individuals with MINCA also lack the traditional risk factors of CAD (71, 72). MINCA scars found at DE-MRI are of small size (mean size 4.4 g) and are more prevalent on the basal segment of the LV inferolateral wall (73) as the UMI scars found in our studies. It might be that these 2 groups differ only on pain perception or on the threshold of pain that makes them seek for medical assistance, but this observation is only speculative.

Limitations

Our studies have some limitations. The cardiac MR study at age 70 was not performed with a contrast dose individually adjusted to the body weight. Since cardiac MR images were obtained after whole-body MRA, a standard dose of 40 mL of gadolinium was used. This corresponds to a higher dose of contrast than it is recommended for DE-MRI (29, 74). It also implies that DE-MRI acquisition should be even more delayed to allow contrast washout from the LV cavity and a better identification and delineation of small subendocardial scars. A second drawback of the cardiac MR study at age 70 was that the timing of DE-MRI acquisition after the contrast injection was not ideal. It has been established that the best timing for DE-MRI is between 25 and 30 min (29), while normally a scan delay of 10 to 15 min is clinically used (74). The interval time in our 70-year-old population study was 25 to 64 min (mean 33.7 min). There was only one subject scanned at 64 min and, in that subject, there was an obvious delayed-enhancement. Excluding this subject, the interval time
of imaging acquisition was between 25 and 45 min. To some extent, the longer waiting time might have compensated for the higher used dose. Additionally, these problems were compensated by individually adjusting the inversion time (29). Cardiac MR images at age 75 were acquired after brain MRI. In this study a contrast dose of 0.2 mmol/kg was used and the delay time for DE-MRI acquisition was shorter, varying between 14 and 35 min (mean 21.6 min).

Another limitation of our MR protocol at age 70 and 75 was that cardiac images were only acquired after contrast injection, either after MRA at age 70 or after brain MR at age 75. Hence, it was not possible to assess the SI of the myocardium before contrast injection. In this group of subjects, there could be an additional explanation for the bright signal of what we classified as MI scars (fibrous tissue) at DE-MRI. Since DE-MRI is a T1-weighted sequence, increased signal on the myocardium could also represent fat. Fat in the myocardium can be seen in several entities, but with a subendocardial pattern as it is seen in our study, it could represent fibrofatty replacement of a chronic MI scar or fatty infiltration in a non-ischemic cardiomyopathy (75). Fatty infiltration in a nonischemic cardiomyopathy is unlikely, since other cardiovascular diagnosis other than ischemic heart disease were fully scrutinized in the hospital medical records for every participant in the PIVUS study. If the increased signal seen at DE-MRI would represent fibrofatty replacement in a chronic MI scar, these lesions would still be corrected label as MI scars but would only correspond to a different stage of their possible evolution in time. Even so, fat in the myocardium could have been detected at cine SSFP sequence as a region of bright signal, since fat has an intrinsic high T2/T1 signal and would also give a dark rim in the fat/water boundary due to chemical shift artifact (76).

The fact that myocardium was not imaged before contrast administration was also a potential drawback in the SI analysis done for study I. In this study, we used the SI of nulled myocardium at DE-MRI as the reference to normalize the SI of the infarction area. Since we did not scan the myocardium prior to contrast injection, it was not possible to test the underlying assumption of comparable relaxation rates of nulled and infarcted myocardium prior to contrast injection. Nevertheless, the SI of the normal myocardium was normalized by different inversion times after the inversion pulse. Differences in normal myocardium could be detected by variation in the inversion times used in the different groups. For this reason, the inversion times were compared and no difference was found between the groups.

A limitation in study II was the uncertainty that exists when measuring low levels of cTnI as the ones found in our study. The cTnI measurements were performed with an improved version of the Access AccuTnI assay
and the assay provides considerably improved analytical sensitivity at
the lower end of its range, but even so some uncertainty remains for very
low levels. Nevertheless, dichotomization in applying cTnI 0.01 mg/L as
a threshold did not result in considerably different study results.

Another potential limitation of the second study was the time interval
between the collection of the venous blood sample in the primary investi-
gation of the PIVUS study and the cardiac MRI investigation. The levels
of NT-proBNP reflected the hemodynamic status at the primary investi-
gation that was afterwards correlated with the presence of an MI scar
in the MRI investigation. However, the aim was not to directly correlate
the levels of the biomarkers at the time of the MR examination to the LV
ejection fraction, but rather to study whether the levels of biomarkers at
inclusion in the study would be correlated with MI scars. Since the study
population consisted of volunteers, the found scars were assumed to be
from a wide time span (over decades) and the presence of a scar during
the MR examination was treated as a myocardial history of events.

In study III there were some subjects from the primary population at
age 70 that did not participate in the follow-up study. After reviewing
their basic characteristics, these subjects had mild increase in cardio-
vascular risk factors when compared to the rest of the population. This
selection bias is expected when studying an elderly population, the older
the population the more subjects that are not willing to participate in the
study, either due to the increased prevalence of disease or because they
are not eager to participate. In study III, from the group of subjects with
UMI scars at age 70, there were 12 subjects lost in follow-up and 1 death,
so that 13 of the 55 UMI scars seen at age 70 were not reexamined at age
75. Therefore, our main focus of this study, subjects with UMI scars seen
at age 70, represents 76% of the primary UMI group.

A limitation common to all four studies was the small number of sub-
jects included, especially when divided into the different groups,
which reduced the power of the studies. Another shortcoming is that the
participants included in the PIVUS study were 70 or 75-year-old, which
limits the interpolation of our results to other age groups.

Although we have not previously found a correlation between UMI
scars and Framingham risk score or sign of atherosclerosis in whole-
body MRA, we have named these unrecognized myocardial scars seen at
DE-MRI as MI since they have an MI scar pattern with a subendocardial
component of delayed-enhancement (33). The findings from study IV,
in which we have not found a correlation between UMI scars and signs
of CAD in large coronary arteries or signs of ischemia on exercise test,
indicate that labeling these unrecognized myocardial scars as MI might
have to be reconsidered.
Clinical implications
The prevalence of DE-MRI detected UMI scars increases with age and therefore the clinician dealing with cardiac MRI can expect to find a high frequency of small UMI scars in elderly patients. The results from our studies indicate that a DE-MRI-detected UMI scar found in an elderly population probably has a different etiology, and thereby a different clinical impact, from a DE-MRI-detected UMI scar found in subjects with known CAD and from an UMI detected by ECG. There is evidence that these individuals differ from patients with RMI scars in terms of risk factors and signs of CAD, but the prognosis of DE-MRI-detected UMI scars in a general population has not yet been determined. The findings that these subjects have low LV ejection fraction, increased LV mass and increased levels of NT-proBNP are indicators that they might have an increased risk of MACE compared to normal subjects. A long-term follow-up will determine the prognosis of these scars and therefore it will help the clinician to decide if these individuals will benefit from preventive therapies.
Conclusions

Study I
The difference found in SI ratio of scars between the UMI and RMI groups most likely reflects different contrast distribution volume of the tissues, which might indicate that UMI and RMI tissues diverge in composition.

Study II
Subjects with UMI scars detected by DE-MRI had increased plasma levels of NT-proBNP and no difference in the levels of cTnI compared to subjects without an MI scar. Increased levels of NT-proBNP are known to correlate with increased risk of future cardiovascular adverse events.

Study III
The prevalence of UMI scars detected at DE-MRI increases with age. During a 5-year follow-up, 88% (37/42) of the UMI scars were still visible in the same LV myocardial segment, reassuring that UMI scars are a consistent finding. The size of UMI scars detected at DE-MRI does not change over time.

Study IV
Subjects with DE-MRI-detected UMI scars did not have an increased prevalence of coronary artery stenosis assessed by coronary CTA or signs of myocardial ischemia at exercise ECG test when compared to a control group. These findings indicate that UMI scars in general are not related to CAD.
**General conclusion**

The aim of these studies was to investigate subjects with DE-MRI-detected UMI scars in order to understand the pathogenesis of these scars and its possible clinical impact. From study III we reassure that the small UMI scars observed in our studies were a real finding and that their prevalence increases with age. The increased levels of NT-proBNP indicate that these subjects with a DE-MRI detected UMI scar might have an increased rate of future cardiovascular events but the findings that UMI scars have a different contrast distribution volume on MRI compared to RMI scars and that UMI scars are not related to CAD are indicators that they probably have a different pathogenesis from RMI scars.

**Future work**

Further studies in a larger population and in other age groups are needed to validate our results. The prognostic impact of DE-MRI-detected UMI scars in the general population is unknown and the long-term follow-up of these subjects will add important information to help the clinician to decide on the management of these individuals.
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Flera studier har visat att kliniskt okända hjärtinfarkter (UMI) är en ansenlig del av alla hjärtinfarkter. Hjärtinfarktdiagnosen är ofta baserad på kliniska, elektrokardiografiska (EKG) och biokemiska markörer. UMIer är infarkter som inte upptäcktes under den akuta fasen. Traditionellt definieras UMI som förekomsten av en ny diagnostisk Q-våg med eller utan ST-vågs depression eller ST-våg höjd utan kliniska symptom. Kända hjärtinfarkter (RMI), å andra sidan, upptäcks under sin akuta fas med en kombination av symptom, EKG och biomarkörer. Epidemiologiska studier har rapporterat olika förekomst av UMI, varierande från 20 till 60% av alla Q-vågsdetekterade hjärtinfarkter.

Tekniken med bildtagning i sen kontrastuppladdningsfas vid magnetisk resonanstomografi (MRT) är en mycket känslig avbildningsmetod för att detektera hjärtinfarkt. Ett typiskt hjärtinfarkttärr visas i dessa bilder som ökad signal som engagerar den subendokardiella delen av hjärtmuskeln. Flera studier med denna teknik har visat att det finns en högre prevalens av UMI detekterade med MRT än de som ses i form av patologiskt Q-våg på EKG. Det finns belägg för att patienter med kranskärlssjukdom som upptäckts ha UMI vid MRT-undersökning har ökad förekomst av traditionella riskfaktorer för kranskärlssjukdom och även att dessa små okända hjärtinfarkttärr är en oberoende prediktor för framtida negativa kardiovasculära händelser. I en prospektiv kohort av asymtomatiska äldre personer hade personer med MRT-upptäckta UMIer inte har en ökad Framingham riskpoäng eller ökad förekomst av betydande arteriell stenos vid MR-angiografi av hela kroppen som patienter med en RMI har. Etiologi och prognos av UMIer upptäckta vid MRT hos asymtomatiska personer är inte känd och det är därför viktigt att ytterligare studera detta för att i kliniskt sammanhang tolka dessa fynd vid hjärt-MR.

Artikel I

I den första artikeln undersöker vi skillnader i vävnadsegenskaper mellan UMIer och RMIer genom att bedöma dessas signalmönster vid MRT. Ärren som detekteras med MRT i sen kontrastuppladdning (de-MRI) analyserades genom att mäta signalintensitet i ärrvävnad och relatera till normal hjärtmuskul. Resultaten visade att signalen i UMIer var lägre än i RMIer när detta relaterades till normalmyokard. Från dessa resultat drar vi slutsatsen att de olika signalintensiteterna i de 2 grupperna sannolikt speglar en skillnad i distributionsvolym av kontrastmedlet i ärren, vilket kan tyda på att UMIer och RMIer skiljer sig avseende vävnadssammansättning.
Artikel II
Denna studie omfattade en ad hoc-analys av NT-proBNP och troponin I mellan grupperna försökspersoner med UMI och de utan myokardärr, eftersom en ökad nivå av dessa biomarkörer har ett samband med ökad kardiovaskulär mortalitet. Individer med UMI hade ökade nivåer av NT-proBNP, meningen skillnad i halterna av troponin I, vilket indikerar att UMI kan innebära en ökad risk för framtida negativa kardiovaskulära händelser.

Artikel III
I denna artikel redovisar vi en 5-års-uppföljning av de personer som genomgick hjärt-MR vid 70 års ålder. Vi ville kontrollera om UMIer som sågs vid 70 års ålder fortfarande skulle ses på samma plats efter 5 år. Vi kunde följa upp 185 personer av 248 personer som undersöktes vid 70 års ålder. Efter 5 år kunde majoriteten av UMIerna upptäckta vid 70 års ålder återfinnas på samma plats och med samma storlek. I uppföljningsstudien fanns också en högre prevalens av UMIer ökat.

Denna undersökning validerar att UMIer funna vid 70 års ålder studie, inte förändras i volym över tid och även att förekomsten av MRT-detekterade UMIer ökar med åldern.

Artikel IV
I den fjärde artikeln jämförde vi graden av koronarartärstenos och Agatston kalcium score bedömt med datortomografi samt resultaten från arbetsprov i UMI-gruppen och gruppen utan myokardärr. Dessa 2 grupper skilde sig inte varken i Agatston kalcium score, antalet kranstämningar eller i resultatet av arbetsprov. Dessa resultat tyder på att MRT-upptäckta UMIer inte är relaterade till kranskärlssjukdom.

Sammanfattning
Syftet med dessa studier var att närmare undersöka MR-detekterade UMIer, för att förstå patogenesen av dessa ärr och dessas möjliga kliniska betydelse. De ökade nivåerna av NT-proBNP tyder på att UMIer kan ha en ökad frekvens av framtida negativa kardiovaskulära händelser, men att de har en annan distribution av kontrast och att de inte relaterade till kranskärlssjukdom är indikatorer på att de förmodligen har en annan etiologi än RMIer.
Summary in Portuguese

Os enfartes do miocárdio silenciosos (unrecognized myocardial infarctions - UMIs) correspondem a uma proporção significativa de todos os enfartes do miocárdio. Os enfartes do miocárdio são identificados na fase aguda e o diagnóstico é normalmente fundamentado em critérios clínicos, electrocardiográficos e em marcadores bioquímicos. Convençãoalmente, os UMIs são definidos pela identificação de uma nova onda Q patológica no electrocardiograma (ECG), com ou sem depressão do segmento ST, ou elevação de ST. Os enfartes do miocárdio identificados clinicamente (recognized myocardial infarctions - RMIs) são detectados na fase aguda pela combinação de sintomas, critérios diagnósticos no ECG e subida dos marcadores bioquímicos. Estudos epidemiológicos descrevem diferentes frequências de UMIs como proporção de todos os enfartes do miocárdio, variando entre 20 e 60%.

O estudo de realce tardio do miocárdio por ressonância magnética (RM) é uma técnica com elevada sensibilidade para a detecção de enfartes do miocárdio. Um enfarte do miocárdio é identificado por RM como uma área de realce tardio abrangendo o subendocárdio. Desde o desenvolvimento desta técnica em RM, diversos estudos identificaram uma grande percentagem de UMIs sem tradução em onda Q patológica no ECG. Os UMIs identificados por RM em doentes com doença coronária estão associados a uma maior prevalência de factores de risco para doença coronária e a uma maior frequência de eventos cardiovasculares no futuro. No entanto, num estudo prospectivo numa população idosa, verificou-se que os doentes com UMIs detectados por RM não têm maior score de risco de Framingham nem maior prevalência de estenoses arteriais significativas em angiografia por RM do corpo inteiro. Consequentemente, a etiologia e o prognóstico dos UMIs identificados por RM numa população geral de idosos não são conhecidos. A importância da investigação da patogenia e prognóstico dos UMIs identificados em RM resulta da necessidade de definir o tipo de intervenção médica adequada neste grupo de indivíduos.
Estudo I
Neste estudo investigamos possíveis diferenças nas características dos tecidos das cicatrizes de UMI e RMI através da avaliação da sua intensidade de sinal exibida na sequência de realce tardio em RM. Os resultados mostram que a intensidade de sinal das cicatrizes de enfarte no grupo de indivíduos com UMI é mais baixa do que no grupo com RMI. Perante os resultados, concluímos que a diferença de intensidade de sinal provavelmente reflete diferente estrutura dos tecidos cicatriciais nestes dois grupos.

Estudo II
Neste estudo realizamos uma comparação dos valores plasmáticos de NT-proBNP e troponina I entre o grupo de indivíduos com UMI e o grupo de indivíduos sem cicatrizes de enfarte do miocárdio, atendendo a que o aumento deste marcadores bioquímicos está associada a uma maior mortalidade cardiovascular. O grupo com UMI comparativamente ao grupo sem cicatrizes de enfarte revelou um nível plasmático de NT-proBNP mais elevado e não demonstrou diferenças nos níveis de troponina I. Estes resultados sugerem que os indivíduos com cicatrizes de UMI identificadas em RM poderão ter um maior risco de eventos cardiovasculares no futuro.

Estudo III
Este estudo descreve um follow-up de 5 anos num coorte de indivíduos que realizaram RM cardíaca aos 70 anos. O objectivo era verificar se as cicatrizes de UMI identificadas em RM na população com 70 anos seriam identificadas passados 5 anos. Dos 248 indivíduos que realizaram RM aos 70 anos, pudemos repetir a RM aos 75 anos em 185 indivíduos. Na RM de follow-up aos 75 anos, 37 das 42 cicatrizes de UMI identificadas aos 70 anos foram identificadas no mesmo segmento do miocárdio e 3 dos 42 indivíduos com UMI aos 70 anos apresentaram no follow-up uma nova cicatriz de RMI na localização da anterior cicatriz de UMI. Não houve variação do tamanho das 37 cicatrizes de UMI identificados nas duas RMs. No follow-up registou-se uma prevalência de UMIs de 33% comparativamente a uma prevalência de 23% no estudo inicial aos 70 anos. Esta investigação permitiu validar os achados identificados na população com 70 anos, demonstrar que não há variação do tamanho das cicatrizes de UMI com o tempo e que a prevalência de UMIs aumenta com a idade.
Estudo IV
No quarto estudo comparamos o grupo de indivíduos com UMIs identificados em RM com o grupo de indivíduos sem cicatrizes de enfarte no miocárdio em termos de grau de estenose das artérias coronárias e quantificação do cálcio coronário determinados por tomografia computadorizada. Comparamos também os resultados da prova de esforço destes dois grupos. Não foi identificada diferença entre os grupos relativamente à quantificação do cálcio coronário, presença de estenoses nas artérias coronárias ou grau de depressão do segmento ST nas derivações V5 ou V6 do ECG. Este resultados indicam que as cicatrizes de UMI identificadas em RM não estão relacionadas com doença coronária.

Conclusão
O objectivo destes estudos foi investigar o grupo de indivíduos com cicatrizes de UMI identificadas por RM de forma a compreender a patogenia destas lesões e o seu possível impacto clínico. O aumento do níveis sanguíneos de marcador bioquímico NT-proBNP sugere que estes indivíduos poderão ter um maior risco de futuros eventos cardiovasculares, mas o facto destas cicatrizes apresentarem um diferente volume de distribuição de contraste no estudo de realce tardio por RM em comparação com as cicatrizes de RMI, e o achado de que não estão relacionadas com doença coronária são indicadores que estas cicatrizes poderão ter uma etiologia diferente das cicatrizes de RMI.
References


(54) SCAAAR home page; Available from: http://www.ucr.uu.se/scaar/.


