Myocardial Scars on MRI
Their Prevalence and Possible Impact

CHARLOTTE EBELING BARBIER
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Abstract

Myocardial infarction (MI) causes high morbidity and mortality worldwide and for effective prevention and treatment MIs have to be adequately detected.

The existence of clinically unrecognized MIs (UMIs) has been known for the past hundred years, but an ultimate tool for their detection has not yet been found. Using persistent Q waves on electrocardiography as a sign of MI, it has been estimated that UMIs constitute at least $\frac{1}{4}$ of all MIs and have mortality rates similar to those of recognized MIs (RMs). These estimates are misleading, however, since persistent Q waves do not necessarily represent MIs.

The late enhancement technique in magnetic resonance imaging (LE MRI) has been developed over the past decade and accurately determines myocardial viability. The aim of this research was to investigate the prevalence and impact of UMI and RMI in a population-based sample of 70-year-olds, assessed with MRI.

Cardiac function and viability were examined with MRI in 259 randomly selected 70-year-old subjects (127 women, 132 men) participating in a larger population-based study (PIVUS). Information on other parameters of cardiovascular disease was obtained and related to the findings.

Three methods for segmentation of the left ventricular mass were used in the first 100 subjects; these differed in accuracy and led to differences in systolic function values. In the subsequent 159 examinations one of the segmentation methods was used.

The viability images were assessable in 248 subjects (123 women, 125 men). Among these, the prevalence of UMI, 19.8%, definitely exceeded the expectations and UMIs constituted 4/5 of all MIs. The prevalence of RMI was 4.4%. MRI-detected UMIs differed from RMs in several respects; they were smaller, frequently located inferolaterally, did not appear to be associated with atherosclerosis, and displayed increased collagen turnover. The pathogenesis of these UMIs remains to be investigated, but our observations suggest that they are caused by ischemia. Subjects with UMI showed increased cardiac morbidity, a decreased ejection fraction and an increased left ventricular mass, indicating an increased cardiovascular risk.

It is thus important to detect these UMIs, and this is adequately achieved by LE MRI. However, to decide upon prevention and treatment of these UMIs we need to know more about their pathogenesis and prognosis.

Keywords: magnetic resonance imaging, myocardial infarction, epidemiology, myocardial infarction, epidemiology

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To Nicolas, Alma and Vera
On the cover: Anatomical drawing of heart by Leonardo da Vinci. Long axis late enhancement magnetic resonance image displaying a myocardial infarction scar.
List of Papers

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

I. Ebeling Barbier C, Johansson L, Lind L, Ahlström H, Bjerner T. The exactness of left ventricular segmentation in cine MRI and its impact on systolic function values. Accepted for publication in *Acta Radiol*


III. Ebeling Barbier C, Bjerner T, Hansen T, Andersson J, Lind L, Hulthe J, Johansson L, Ahlström H. MRI-detected unrecognized myocardial infarction may not be associated with atherosclerosis. Accepted for publication in *Radiology*

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<th>Description</th>
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<tbody>
<tr>
<td>B₀</td>
<td>an external magnetic field</td>
</tr>
<tr>
<td>BSA</td>
<td>body surface area</td>
</tr>
<tr>
<td>CABG</td>
<td>coronary artery by-pass surgery</td>
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<tr>
<td>CAD</td>
<td>coronary artery disease</td>
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<tr>
<td>CHF</td>
<td>congestive heart failure</td>
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<tr>
<td>CK-MB</td>
<td>cardiac isoenzyme of creatine kinase</td>
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<td>CO</td>
<td>cardiac output</td>
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<td>CRP</td>
<td>C-reactive protein</td>
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<tr>
<td>CT</td>
<td>computed tomography</td>
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<tr>
<td>DCM</td>
<td>dilated cardiomyopathy</td>
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<tr>
<td>ECG</td>
<td>electrocardiography</td>
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<tr>
<td>ED</td>
<td>end-diastolic</td>
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<tr>
<td>EF</td>
<td>ejection fraction</td>
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<tr>
<td>ES</td>
<td>end-systolic</td>
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<tr>
<td>FDG</td>
<td>fluoro-2-deoxyglucose</td>
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<tr>
<td>Gd</td>
<td>gadolinium</td>
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<tr>
<td>HDL</td>
<td>high-density lipoprotein</td>
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<tr>
<td>IMT</td>
<td>intima-media thickness</td>
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<tr>
<td>LAD</td>
<td>left anterior descending artery</td>
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<tr>
<td>LCx</td>
<td>left circumflex artery</td>
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<tr>
<td>LDL</td>
<td>low-density lipoprotein</td>
</tr>
<tr>
<td>LE</td>
<td>late enhancement</td>
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<tr>
<td>LV</td>
<td>left ventricle; left ventricular</td>
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<tr>
<td>LVEDV</td>
<td>left ventricular end-diastolic volume</td>
</tr>
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<td>LVH</td>
<td>left ventricular hypertrophy</td>
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<tr>
<td>LVM</td>
<td>left ventricular mass</td>
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<tr>
<td>M₀</td>
<td>the net magnetization of hydrogen protons in an external magnetic field</td>
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<td>MI</td>
<td>myocardial infarction</td>
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<tr>
<td>MMP</td>
<td>matrix metalloproteinase</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>PCI</td>
<td>percutaneous coronary intervention</td>
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<tr>
<td>Abbreviation</td>
<td>Description</td>
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<td>--------------</td>
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<tr>
<td>PET</td>
<td>positron emission tomography</td>
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<tr>
<td>RCA</td>
<td>right coronary artery</td>
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<tr>
<td>RF</td>
<td>radio frequency</td>
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<tr>
<td>RMI</td>
<td>recognized myocardial infarction</td>
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<td>RMV</td>
<td>relative myocardial volume</td>
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<tr>
<td>SPECT</td>
<td>single-photon emission computed tomography</td>
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<tr>
<td>SV</td>
<td>stroke volume</td>
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<tr>
<td>TE</td>
<td>echo time</td>
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<tr>
<td>TIMP</td>
<td>tissue inhibitor of matrix metalloproteinase</td>
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<tr>
<td>TR</td>
<td>repetition time</td>
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<tr>
<td>UMI</td>
<td>unrecognized myocardial infarction</td>
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</table>
Introduction

Background
Cardiovascular disease, particularly myocardial infarction (MI), causes high morbidity and mortality worldwide. A large amount of medical work and large resources are put into this field with the aim of improving population health and survival. In order to achieve effective prevention and treatment, persons at risk have to be adequately identified.

Unrecognized myocardial infarction
The diagnosis of acute MI is based on a history of acute chest pain, electrocardiographic (ECG) evidence of ischemia, and elevated biochemical markers. However, not all MIs give rise to chest pain, not all MIs cause ECG changes and for elevation of biochemical markers to be detected, the patient has to come to the hospital in the acute stage. Thus there are several factors that may hamper clinical recognition of MIs. The existence of clinically unrecognized MIs (UMIs) was first described in 1912, but an ultimate method for their detection has not yet been found.

Until recently, the primary tool for identifying UMIs was a finding of persistent Q waves on ECG. On this basis it has been estimated that UMIs constitute at least one fourth of all MIs, and their prevalence is said to increase with age, by approximately 10% per year. Furthermore, subjects with Q-wave UMIs have risk factor profiles and mortality rates similar to those of subjects with recognized myocardial infarctions (RMI). The true prevalence of UMI, however, remains unknown, since not all MIs result in persistent Q waves.

The classical pathogenesis of an MI is atherosclerotic including plaque rupture, occlusion of a large supporting vessel, and
subsequent ischemic injury to the myocardium. However, if a myocardial scar is unrecognized, then so is the pathogenesis.

**Myocardial viability imaging**

There are more precise methods than ECG for assessing myocardial viability. Traditional techniques, such as dobutamine stress echocardiography, FDG-PET and SPECT (using sestamibi, FDG, thallium or technetium), are based on detection of myocardial segments with preserved cellular viability. Recent animal studies have demonstrated that contrast-enhanced multislice and multidetector computed tomography (CT) to accurately determines MI, but to our knowledge this has not yet been proved in humans. PET-CT may prove to be a useful tool.

Late enhancement (LE) magnetic resonance imaging (MRI) is a relatively new technique, which during its development over the past decade has proved accurate in determining myocardial viability. It is not unreasonable to assume that this technique would detect more UMIs than ECG.

**Functional assessment of the heart**

When an MI has been detected, an estimation of its functional impact will provide important additional information about its clinical impact and the patient’s prognosis. This is achieved through quantification of the left ventricular (LV) myocardial mass, volumes and function. For this, different modalities with inherent limitations are used.

The routine method in most clinical settings is echocardiography, where three measurements are made in one image in diastole: the interventricular septum thickness, the LV posterior wall thickness and the LV internal diameter. LV mass (LVM) is calculated from these measurements using a mathematical model based on assumptions regarding the shape of the LV. Accurate definition of endocardial and epicardial borders is difficult with this technique, entailing a large intra-observer variability.
Cardiac MRI has a high spatial resolution with excellent blood/myocardial contrast.\textsuperscript{23, 24} Endocardial and epicardial borders can thus easily be outlined, and this is done in images in diastole and systole images from base to apex. LV mass is hence calculated from measurements throughout the heart, reflecting the actual shape of the LV. This permits an accurate determination of the LV mass compared to the post mortem mass in animal models.\textsuperscript{25-28} The reproducibility of this technique is superior to that of echocardiography.\textsuperscript{21}

Physics of magnetic resonance imaging

Basic principles
Magnetic resonance imaging (MRI) is based on induction and detection magnetic resonance from hydrogen protons (H). Hydrogen protons are a major component in the soft tissues of the human body, which are largely composed of water (H\textsubscript{2}O) and fat (CH\textsubscript{3}-CH\textsubscript{2}---) in different proportions, and different tissues have different proton densities. These differences are the reason why we are able to differentiate between the tissues in the MR image.

The proton has a positive charge and rotates about an axis at a constant rate (like the self-rotation of the moon) (Fig. 1). The rotation, or spin, creates a magnetic field around the proton. Normally the protons spin in random directions and their magnetic fields cancel each other out (Fig. 2a).

![Figure 1. Illustration of a proton with a positive charge rotating about an axis at a constant rate and thereby creating a magnetic field around itself.](image-url)
However, when put in an external strong static magnetic field \((B_0)\), i.e., the MR scanner, the protons align themselves in the direction of the external magnetic field \((B_0)\) (Fig. 2b). More of them align parallel to \(B_0\) than anti-parallel, resulting in a magnetic vector parallel to \(B_0\), which is referred to as net magnetization \((M_0)\) (Fig. 2b).

**Figure 2.** Illustration of how protons normally rotate in random directions and their magnetic fields cancel each other out (a). When put in an external magnetic field \((B_0)\) the protons align themselves, more of them parallel than anti-parallel to \(B_0\), resulting in a net magnetization \((M_0)\) parallel to \(B_0\) (b).

Still spinning about themselves, the protons also begin to rotate, or precess, about the external magnetic field (just as the moon rotates about the earth) (Fig. 3), with a frequency called the Larmor frequency \((\omega)\), which is proportional to the strength of the magnetic field \((\omega = \gamma \cdot B_0)\) (about 64 MHz at 1.5 T).
We now control the magnetic vector of the proton spins, but to be detectable they have to be separated from the much stronger external magnetic field. This is achieved by sending in a radio frequency (RF) pulse with a frequency matching the Larmor frequency. The RF pulse will thereby excite the protons precessing with the Larmor frequency, as a result of which these protons will begin to spin concurrently with each other (Fig. 4) and their net magnetization vector ($M_0$) will diverge from that of the external magnetic field ($B_0$) (Fig. 4 and 5). Thus we will have induced magnetic resonance from the protons.

Now we need to detect the magnetic resonance that we have induced. This is done with a coil placed perpendicular to the external magnetic field. When the magnetic vector ($M_0$) is directed toward the coil an electric current will be induced within it, i.e., we will get a signal; otherwise not (Fig. 5). In this way the magnetic resonance is detected.
Figure 4. Illustration of how protons begin to spin concurrently with each other when a radio frequency (RF) pulse is sent in.
Figure 5. Illustration of how the RF pulse causes the net magnetization ($M_0$) to diverge from the direction of the external magnetic field ($B_0$) making the magnetic resonance detectable by a coil placed perpendicular to $B_0$. 
Magnetic resonance properties of the tissues

Proton density
As mentioned above, the fact that different tissues have different proportions of water and fat and different proton densities is the reason why we can distinguish them in the MR image. Thus different tissues have different magnetic resonance properties. Obviously the higher the proton density of a tissue has the larger the magnetic vector ($M_0$) and the higher the signal.

T1 and T2
When the RF pulse is turned off, the protons will stop spinning concurrently, i.e. they will dephase, and the magnetic vector of the excited protons ($M_0$) will return to the direction of the external magnetic field ($B_0$); that is, it will relax. The time this takes differs in different tissues and is referred to as the relaxation time. If we look at $M_0$ in a system of coordinates, we will find that it has components in three directions. When relaxed, the largest vector will be oriented along the $z$ axis, i.e., in the direction of the external magnetic field ($B_0$). When the RF excitation causes the magnetic vector of the protons ($M_0$) to align itself perpendicular to $B_0$, because of the spin of the protons $M_0$ will have components in two directions, which are also perpendicular to each other, i.e., along the $x$ and $y$ axes (Fig. 4).

The time taken for the $z$ component of the magnetic vector of the protons ($M_0$) to return to 63% of its original value is referred to as the relaxation time $T_1$ (Fig. 6).

When the protons stop spinning concurrently the transverse component of the magnetic vector ($M_0$) will decay and the time taken for this component to reach 37% of its original value is referred to as the relaxation time $T_2$ (Fig. 7).

These relaxation times, T1 and T2, vary between tissues depending on the proportions of water and fat in the tissues. The images can be weighted toward one of the relaxation times, depending on what you are looking for. This is achieved by alterations of the repetition time (TR) and the echo time (TE)(see below).
Figure 6. Illustration of the relaxation time T1 of two different tissues, i.e., the time taken for the z component of the magnetic vector of the protons (M0) to return to 63% of its original value.

Figure 7. Illustration of the relaxation time T2 of two different tissues, i.e., the time taken for the transverse component of the magnetic vector of the protons (M0) to decay to 37% of its original value.
Weighting (TR and TE)

In order to obtain an image, the process of inducing and detecting magnetic resonance from protons is repeated numerous times. The time between application of one RF pulse and application of the subsequent one is referred to as the repetition time (TR) and the time between application of one RF pulse and detection of a signal, an echo, from this pulse with the coil is referred to as the echo time (TE)(Fig. 8).

![Diagram of TR and TE](image)

**Figure 8.** Illustration of the repetition time (TR), i.e., the time between application of one RF pulse and application of the subsequent one; and the echo time (TE), i.e., the time between application of one RF pulse and detection of a signal.

A long TR allows the magnetic vector (M₀) from all tissues to return along the z axis, and differences in T₁ between the tissues will not be detected. A short TR suppresses M₀ from tissues with a long T₁, resulting in a relatively stronger signal from tissues with a short T₁. A short TR is hence preferable if you are looking for differences in T₁ (Fig. 9).

A short TE does not allow the magnetic vector (M₀) to decrease in the xy plane before the signal is collected and differences in T₂ between the tissues will not be detected. A long TE allows the transverse component of M₀ to decay and differences in T₂ will be detectable. A relatively long TE is hence preferred if you are looking for differences in T₂ (Fig. 10).

T₁ weighting is thus achieved by using a short TR to detect differences in T₁ and a short TE to eliminate signals caused by differences in T₂. T₂ weighting is achieved by using a long TR to eliminate signals caused by differences in T₁ and a long TE to detect differences in T₂.
**Figure 9.** Illustration of how differences in T1 are easier to detect using a short repetition time (TR) than using a long one.

**Figure 10.** Illustration of how differences in T2 are easier to detect using a relatively long echo time (TE) than using a short one.
Image generation
Generation of a comprehensible image from the magnetic resonance signals detected by the coil is a complex process, which will be very briefly described here. Detecting a signal is merely the first step. We then need to know the site of origin of the signal in the body. This information is obtained by using a physical gradient in each of the directions x, y and z.

The desired projection decides the direction of the slice selection, where the frequency of the RF pulse determines the position of the slice and the strength of the gradient determines the slice thickness.

The frequency encoding (or readout) is directed perpendicular to the direction of the slice selection and makes it possible to determine, for example whether the signal is coming from the front (anterior) or the back (posterior) of the examined subject.

The phase encoding is directed perpendicular to both the direction of the slice selection and that of the frequency encoding and makes it possible to determine, for example whether the signal is coming from the right or the left side of the examined subject.

The collected signals are digitized and organized in k-space, which constitutes the raw data matrix of MRI. The raw data matrix is then transformed into image data matrix using the Fast Fourier Transform. At this point we have an image that can be interpreted by the human eye and brain.

Pulse sequences
In order to collect enough signals to generate an image, the application of RF pulses and magnetic gradients has to be repeated numerous times. This serial application of RF pulses and magnetic gradients is referred to as a pulse sequence. There are two main types of pulse sequences, namely spin echo and gradient echo.

In a spin echo sequence the initial RF pulse, causing $M_0$ to diverge $90^\circ$ from $B_0$, is followed by an RF pulse that makes $M_0$ diverge $180^\circ$. This refocusing pulse is applied to even out sig-
nal loss generated by interaction of various small static magnetic fields within the inhomogeneous tissue.

In a gradient echo sequence the dephasing of the protons is reversed by application of a gradient pulse with opposite polarity, causing the protons to refocus.

In order to speed up the data collection, signals for several lines of k-space, instead of one, can be collected after each RF pulse. This procedure is labeled turbo and can be applied to both spin and gradient echo sequences.

Inversion recovery is when a 180° pre-pulse is applied before imaging; this is performed at a time when a specific tissue has no z component of M₀. No signal will then be generated by this tissue (it is 'nulled'), enabling signal from other tissues to appear more distinctly.

Steady state free precession is a balanced sequence that gives T₁ and T₂ effects simultaneously and permits rapid data collection. This sequence has the advantage of allowing excellent discrimination between blood and myocardium.

**Contrast enhancement on MRI**

To achieve contrast enhancement on MRI, a gadolinium chelate (Gd-DTPA) is administered intravenously. This diffuses rapidly from the intravascular space to and throughout the extracellular space. Gd decreases the relaxation time of the protons and it is the shortened T₁ in the tissue where Gd is accumulated that causes the increase in signal intensity.
Late enhancement MRI

Late enhancement MRI has been specifically developed to image myocardial viability. This is accurately determined\textsuperscript{13, 17-19} by using an inversion recovery sequence to ‘null’ normal and enhance non-viable myocardium. This technique has been proved capable of detecting several varieties of myocardial infarctions, including acute and healed\textsuperscript{29}, transmural and subendocardial\textsuperscript{30}, Q-wave and non-Q-wave\textsuperscript{19}, and other myocardial scars\textsuperscript{18}.

Normally a dose of 0.1 - 0.2 mmol Gd-DTPA/kg body weight is injected intravenously\textsuperscript{31, 32}. Myocardial enhancement that is present on MRI when the intravascular Gd concentration is declining is referred to as late (or delayed) enhancement. This is thought to be due to a possible increase in the interstitial space between collagen fibers in scar tissue, compared to the densely packed myocytes in normal tissue, and thus an expanded volume of distribution of Gd\textsuperscript{9}(Fig. 11). This technique also detects acute MIs, which have an increased volume of distribution due a change in the integrity of myocyte cell membranes (Fig. 11).

Imaging is normally performed 10 to 30 minutes post contrast\textsuperscript{32}. Irrespective of when the imaging is performed within this time span, the size of the enhanced region does not change provided that the inversion time is adjusted appropriately in order to ‘null’ normal myocardium\textsuperscript{32}. However, optimal demarcation of a chronic MI is seen at two time points: 6 to 9 minutes post contrast (bright blood and dark normal myocardium), and 25 to 30 minutes post contrast (bright scar and dark normal myocardium)\textsuperscript{31}. The infarct size as assessed with LE correlates with indices of infarct size such as peak troponin I\textsuperscript{33}.

In attempts to distinguish MI scars from other myocardial scars, fibrosis, or infiltrations, the fact that LE in ischemic infarction always involves the subendocardial layer\textsuperscript{34, 35} can be useful. Subendocardial LE is not, however, specific for MI, but can also be present in other cardiac diseases\textsuperscript{34-38} which have to be excluded if this criterion is to be used.
**Figure 11.** Illustration of the presumed mechanism of late gadolinium enhancement: In normal myocardium the myocytes are densely packed leaving a relatively small interstitial space for gadolinium to be distributed in. In acute myocardial infarction the integrity of myocyte cell membranes is changed allowing gadolinium molecules to enter the cells in addition to being distributed interstitially. In a myocardial scar myocytes are substituted by collagen fibers resulting in an increased interstitial space and thus an expanded volume of distribution of gadolinium.

Quantification of left ventricular mass and function

MRI quantification of the LV mass and function can be achieved in images generated with turbo gradient echo or steady state free precession sequences. The latter enable better definition of the endocardial border and are associated with lower interobserver variability of the assessments because of their excellent blood / myocardial contrast.23, 24

The quantification is performed by either manual or automatic outlining of the LV myocardial borders in diastole and systole, commonly in contiguous short axis cine images27(Fig. 12).
Figure 12. Contiguous short axis cine MR images from one subject in systole and diastole illustrating how myocardial borders are outlined (segmented) for quantification of left ventricular mass and function.

Manual outlining is more accurate,\textsuperscript{39} whereas automatic methods are more rapid but often need manual correction.\textsuperscript{24} Papillary muscles are sometimes included in the LV mass\textsuperscript{25, 27, 39-41} and sometimes in the LV blood volume,\textsuperscript{28, 42, 43} and there is no consensus on the significance of crypts and trabeculae.

Commercially available software computes systolic function values based on the assessed LV mass and volumes. The accuracy of the LV assessment affects these values.\textsuperscript{44}
Aims

General aim
The general aim was to investigate the prevalence and impact of UMI and RMI in a population-based sample of 70-year-old subjects, assessed with MRI.

Specific aims
Paper I: To evaluate the accuracy of three different methods for quantification of LV mass and function. A second aim was to assess the impact of the accuracy on the systolic function values obtained.

Paper II: To investigate the prevalence of RMI and UMI in a population-based sample of 70-year-old subjects, assessed with MRI, and to relate the findings to cardiac function and morbidity.

Paper III: To identify factors supporting the hypothesis that the pathogenesis of MRI-detected UMIs is similar to that of RMIs.

Paper IV: To identify factors supporting the hypothesis that MRI-detected UMIs are caused by a decrease in the myocardial perfusion reserve due to thick LV walls and/or myocardial fibrosis.
Methods

Study population

After approval from the ethical committee, cardiac MRI was performed on an unselected subsample of subjects participating the Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS) study.45

Eligible for the PIVUS study were all subjects aged 70 years and resident in the municipality of Uppsala, Sweden. The subjects were chosen in a randomized manner from the register of municipality inhabitants, and 2025 subjects were invited to participate; 1016 agreed and gave written informed consent.

From the original cohort, 283 subjects were consecutively invited to undergo cardiac MRI, which was finally performed on 259 subjects (127 women, 132 men).

The study sample in paper I consisted of the first 100 consecutively analyzed subjects (52 women, 48 men)(Fig. 13).

The study sample in papers II and III consisted of 248 of the 259 subjects (123 women, 125 men); 11 examinations being non-assessable because of poor quality (Fig. 13).

The study sample in paper IV consisted of 244 subjects (121 women, 123 men), in whom assessable late enhancement cardiac MRI images were obtained and biochemical measurements were performed (Fig. 13).
The participants answered a questionnaire about their medical and drug histories. The basic characteristics and major cardiovascular risk factors among these subjects did not differ significantly from those in the entire PIVUS population, except that there were fewer current smokers among the subjects in our sub-samples. The cardiac morbidity of the participants in the PIVUS study did not differ from that of the background population.45

**Figure 13.** Illustration of how the study samples of the four papers were formed.
MR Image acquisition

Imaging was performed on a 1.5 Tesla MRI system (Gyroscan Intera; Philips Medical Systems, Best, the Netherlands) with a 25 mT/m gradient system. The subjects were examined in the supine position, using the standard quadrature body coil for whole body MR angiography and the standard SENSE cardiac coil for cardiac imaging with retrospectively gated vector-ECG for cardiac triggering.

First the whole body was scanned using a 3D RF-spoiled T1-weighted gradient echo sequence during first pass of 40 ml intravenously injected Gd-DTPA-BMA (Omniscan™, GE Healthcare, Oslo, Norway) at a rate of 0.6 ml/s. Imaging was performed in four stations with 3 cm overlap between the stations. The acquired slice thickness was 4 mm with a resolution of 1.76 x 1.76 mm. Imaging included the aorta and the carotid, renal, and lower limb arteries down to the ankle. The coronary arteries were not included.

Second late enhancement images were acquired using a 3D inversion recovery gradient echo sequence covering the entire heart in short and long axis views. The acquired slice thickness was 10 mm with a resolution of 1.56 x 2.81 mm. The inversion time was individually adjusted to null viable myocardium in every subject. The mean post contrast time was 33.7 minutes, ranging from 25 to 64 minutes.

Third cine images were acquired during breath holding, using a steady state free precession sequence covering the left ventricular myocardium from the apex to the atria in 8 mm thick short axis slices with a 2.5 mm slice gap, an acquired in-plane resolution of 2.27 x 1.81 mm, and 18 phases recorded per cardiac cycle. Two slices were acquired per breath hold.

Cine images were used in paper I and II, late enhancement images were used in paper II, III and IV, and whole-body MRA images were used in paper III.
MR Image analysis

Paper I

Left ventricular function was assessed on a workstation with commercially available analysis software. Quantification was performed on short-axis images, simulating three methods. In all methods the epicardial border was manually outlined. In method 1 the endocardial border was generated with computer assistance and papillary muscles were excluded from LVM. Method 2 was similar, but with papillary muscles included in LVM. In method 3 the endocardial border was manually corrected in order to include crypts and trabeculae to the greatest possible extent and papillary muscles were included in LVM (Fig. 14). The ejection fraction (EF) and LV end-diastolic mass were computed assuming a myocardial density of 1.05 g/ml\textsuperscript{43}. LVM was adjusted for body surface area (BSA).\textsuperscript{47}

![Figure 14. The same short axis cine MR image in diastole segmented using the three different methods that were compared in paper I and information on what differed between the methods, i.e., how epi- and endocontours were segmented and whether papillary muscles (that were not included in the endocontour) were included in the left ventricular mass or not.]

The difference between end-systolic (ES) and end-diastolic (ED) LVM was used to assess the accuracy of the three methods, on the basis of the assumption that the ES and ED mass difference should be as small as possible,\textsuperscript{41, 48} and the subjects were grouped depending on whether the ES-ED difference was smaller or larger than 20 g.

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Papers II, III and IV

The LE images were assessed by two observers independently and in a consensus reading. The observers were blinded to information on any previous disease. The areas showing late enhancement were classified, by the same two observers in consensus, into four groups according to their distribution. Late enhancement that involved the subendocardial layer was considered to represent an MI scar; its volume was calculated and its location was classified in accordance with the American Heart Association segmentation.

LV function was assessed by method 2 as described in paper I.

Other measurements

The intima-media thickness (IMT) of the common carotid artery was measured bilaterally with ultrasound and the mean of the two arteries was used as the measurement of IMT.

Two-dimensional and Doppler echocardiography was performed; the peak velocity of the early rapid filling wave (E wave) and the peak velocity of the atrial filling (A wave) were recorded, the E/A ratio was calculated and the left ventricular isovolumic relaxation time (IVRT) was measured.

Blood pressures were measured and a venous blood sample was taken in the morning after an overnight fast. C-reactive protein (CRP) and LDL- and HDL-cholesterol were measured using standard techniques. The extracellular matrix markers MMP-9 and TIMP-1 were determined with commercial ELISA assays, since these markers may be assumed to reflect myocardial collagen turnover.

How the groups were formed

Medical records from Uppsala University Hospital were searched retrospectively for cardiovascular diagnoses. Of the 248 subjects with assessable late enhancement MRIs, 157 had been treated at the hospital and their medical records were scrutinized. Two subjects reported in the above-mentioned questionnaire that they had been treated for MIs at other hos-
their medical records were retrieved and studied. Subjects with a hospital diagnosis of MI were considered to have had a clinical MI and are hereafter referred to by that term. The hospital diagnosis of MI was set on the basis of the World Health Organization criteria before the year 2000 (n=4) and the criteria defined by the Joint European Society of Cardiology/American College of Cardiology Committee thereafter (n=7).8

Subjects lacking medical records and who did not report MI in the questionnaire were regarded as not having had a clinical MI (n=88). One subject reported having been treated for an MI at Uppsala University Hospital, but had no medical record there and was regarded as not having had any clinical MI. Two subjects (men) had clinical MI, but were not assessed as having any MI scar in the consensus reading.

Three groups were formed: one with subjects without MI scars (no MI), one with subjects with an MI scar but no clinical MI, i.e., a UMI, and one with subjects with both an MI scar and clinical MI, i.e., an RMI (Fig. 15).

![Diagram](attachment:diagram.png)

**Figure 15.** Illustration of how the three groups were formed. No MI = no MI scar; UMI = unrecognized myocardial infarction; RMI = recognized myocardial infarction (i.e., MI scar in combination with MI diagnosis in medical records).
Results

Paper I

The ES-ED LV mass difference was greatest when calculated from measurements made with method 1, smaller with method 2 and smallest with method 3, both before and after adjustment for BSA. This variation in ES-ED LV mass difference was significant between all three methods.

The values for EF differed significantly between method 3 and the other two methods, and the values for stroke volume (SV) and cardiac output (CO) differed significantly between methods 1 and 3 when adjusted for BSA.

![Graph of the subjects grouped according to the difference in end-systolic (ES) and end-diastolic (ED) left ventricular mass in the values generated with computer assistance not minding the papillary muscles (method 1). The group with an ES-ED mass difference smaller than 20 g showed a significantly smaller mean difference in stroke volume (SV) between methods 1 and 3 than the group with an ES-ED difference larger than 20 g (p<0.0001).](image)

The group with an ES-ED mass difference smaller than 20 g showed a significantly smaller mean difference in SV between methods 1 and 3 than the group with an ES-ED difference larger than 20 g (Fig. 16).
MI scars were found in 60 of the 248 subjects (24.2%); 24 of these were women and 36 were men. The subjects with RMI constituted 4.4% (11/248), whereas 19.8% (49/248) had UMIs (Fig. 17). There were more women in the UMI group, 45% (n=22/49), than in the group with RMIs, 18% (n=2/11). UMIs seemed to be more frequently located in the inferior and inferolateral segments of the LV (Fig. 18). The volumes of the UMIs were significantly smaller than those of the RMIs. Three of the 49 subjects with UMI and 7 of the 188 without MI scars had a pathological Q wave on ECG.

Cardiac morbidity was more frequent among the subjects with UMI or RMI than in those without MI scars. EF was significantly higher among the subjects without MI scars than among those with UMI or RMI (Fig. 19). LV mass was significantly larger in the subjects with UMI than in those without MI scars and even larger in those with RMI.

Figure 17. The number of subjects in the different groups. No MI = no MI scar; UMI = unrecognized myocardial infarction; RMI = recognized myocardial infarction (i.e., MI scar in combination with MI diagnosis in medical records).
One of the two subjects with clinical MI who were assessed as not having any MI scar in the consensus reading was initially assessed as having an MI scar by one of the observers. This subject had had a clinical MI in the early 1990s that was verified by ECG and biochemical markers, and he was submitted to coronary angiography and coronary artery bypass surgery (CABG). The other subject had had a clinical, small, non-Q-wave MI in the late 1990s (troponin T 0.13, CK-MB max 9.5) and was submitted to percutaneous coronary intervention (PCI) with stenting of the left anterior descending artery (LAD).

Figure 18. The distribution of unrecognized (UMI) (a) and recognized (RMI) (b) myocardial infarction scars between the 17 segments of the American Heart Association segmentation.

Figure 19. Differences in ejection fraction (EF) and in left ventricular mass (LVM) adjusted for body surface area and gender between the subjects without MI scars (No MI), those with unrecognized myocardial infarction (UMI) and those with recognized myocardial infarction (RMI). * = p<0.0167, i.e. 0.05 with Bonferroni correction.
Paper III

Neither the prevalence of significant atherosclerosis on whole-body MRA nor IMT, nor CRP, nor the Framingham risk score, differed significantly between the group without MI scars and the UMI group, but these values were all increased in the RMI group compared to the group without MI scars (Fig. 20 and 21).

**Figure 20.** Prevalence of significant atherosclerosis, i.e., luminal narrowing exceeding 50% in any vessel on whole-body MR angiography in subjects without myocardial infarction (MI) scars on cardiac MRI (No MI), those with unrecognized myocardial infarction (UMI) and those with recognized myocardial infarction (RMI).

<table>
<thead>
<tr>
<th></th>
<th>No MI</th>
<th>UMI</th>
<th>RMI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalence (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>p = 0.01</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>p = 0.56</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>p = 0.04</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>26.6</td>
<td>30.6</td>
<td>63.6</td>
<td></td>
</tr>
</tbody>
</table>

**Figure 21.** Differences in intima-media thickness (IMT), C-reactive protein (CRP), and Framingham risk score between the subjects without myocardial infarction (MI) scars on cardiac MRI (No MI), those with unrecognized myocardial infarction (UMI), and those with recognized myocardial infarction (RMI).

*= p<0.0167, i.e., 0.05 with Bonferroni correction
Of the factors contributing to the Framingham risk score, the prevalence rates of hypertension, hypercholesterolemia and diabetes were increased in the RMI group compared to those in the group lacking MI scars.

Forty-two of the 49 UMIs (86%) had a location that included the inferolateral segments of the left ventricle (segments 4, 5, 10, and 11 of the American Heart Association 17-segment model\textsuperscript{49}).
There was a significant difference in the MMP-9 levels between the UMI group and the group without MI ($p = 0.034$). There were no significant differences in TIMP levels between the groups (Fig. 22).

None of the studied parameters reflecting a thickened LV wall differed significantly between the UMI group and the group without MI scars, but were all increased in the RMI group compared to the latter group.

There were no significant differences in E/A ratio or IVRT between the subjects with UMI or RMI and those without MI scars, but the IVRT differed significantly between subjects with UMI and those with RMI ($p=0.0123$).
Discussion

Quantification

In conformity with other authors, we observed in paper I that the accuracy of the segmentation has an impact on the systolic function values (EF, SV, and CO). The differences were small enough, however, to be within the range of the normal variation and the least accurate method (method 1) would be sufficient for routine determination of systolic function.

The most accurate method (method 3) might, however, be necessary to avoid misinterpretations when blood volume quantification is crucial and an ES-ED LVM difference of 20 g can be used as a cut-off to identify subjects who would benefit most from a more accurate segmentation.

Based on these results from the assessment of the first 100 examinations, method 2 was used in the following 159. Even if the least accurate method would have been sufficient, we preferred a more correct estimate of the LVM, which was achieved by including the papillary muscles in the LVM and excluding them from the blood volume.

Unrecognized myocardial infarction

Prevalence

We had assumed that MRI would detect more UMIs than ECG, but the prevalence proved to be even higher than expected and we found that nearly 20% of community-living 70-year-old Swedes had MI scars that previously had been unrecognized. It should be emphasized that the study sample was composed of 70-year-old Caucasians which means that the results cannot be generalized to other ethnic or age groups.

In our cohort UMIs constituted four fifths of all MIs as compared with one fourth which is usual estimate with ECG.
Using the Q wave-criterion, ECG would only have identified three of the 49 UMIs that were detected with MRI, underlining the discrepancy in the use of the term UMI. Thus ECG-detected and MRI-detected UMIs cannot be lumped together.

The ECG technique has been in use for the past hundred years. It is an inexpensive and widely available method, facilitating large-scale epidemiologic studies. It has therefore often been used to estimate the prevalence of UMI in spite of the knowledge that the presence or absence of Q waves should not be used to determine myocardial viability. Since all MIs do not result in pathological Q waves, and all pathological Q waves are not caused by MI, this method is bound to be misleading in estimations of the prevalence of UMI.

The late enhancement technique in MRI has been developed over the past decade. It is far more expensive and not as widely available as ECG, but it is very accurate in determining myocardial viability, probably the most accurate method available today. A method as accurate as this calls for a correct definition of an MI scar, in order not to be misleading. How can we be sure that late enhancement represents an MI scar and not something else?

**Definition**

The current definition of an MI scar (or acute lesion) on MRI is that the LE shall involve the subendocardial layer; this is based on observations from MRI studies in humans. Labeling all myocardial LE with a subendocardial component as MI is complicated by the fact that subendocardial LE is not specific for MI. For example, myocarditis and sarcoidosis can cause transmural LE, and amyloidosis and cardiomyopathies can cause subendocardial LE. As a rule, however, the enhancement pattern in these diseases differs from that in MI.

An MI is typically visible as focal homogeneous LE originating from the subendocardium and corresponding to the vascular territory of a coronary artery. In our definition of an MI scar we did not consider whether the LE corresponded to a vascular territory or not; this did not seem meaningful, since the LE was generally very small and a sweeping classification
of vascular territories is complicated by interindividual anatomic variations in the distribution and dominance of the coronary arteries.\textsuperscript{63}

**Ruling out differential diagnoses**

In active myocarditis LE has a patchy distribution originating from the epicardial quartile of the wall with one or several foci.\textsuperscript{64} It does not correspond to a vascular territory\textsuperscript{35} and is predominantly located in the lateral free wall.\textsuperscript{64} Subsequent scars are smaller than the active lesions, and far from all cases of myocarditis leave myocardial scars at all.\textsuperscript{64} It seems unlikely that a myocarditis lesion large enough to leave a scar would have passed silently and undetected, whereas it is well known that MIs may be silent.\textsuperscript{4-7}

Sarcoidosis is suggested by a finding of nodular LE in the basal portion of the septal wall of that may reflect sarcoideal granulomas as well as subsequent scars.\textsuperscript{65} The LE of the UMIs in our study was not nodular and only in one case was it located strictly in the basal portion of the septum (in segment 3 of the American Heart Association 17-segment model\textsuperscript{49}), without extending into the inferior region.

In amyloidosis the subendocardial LE diffusely involves the entire subendocardium, reflecting deposition of amyloid protein rather than fibrosis.\textsuperscript{36} The LE of the UMIs in our study had a focal distribution and never involved the entire subendocardium.

In hypertrophic cardiomyopathy patchy, multifocal scarring occurs in the hypertrophied regions, predominantly in the junction of the septum and the right ventricular free wall.\textsuperscript{66} Five of the 49 UMIs of our study were multifocal and three of these were located in the junction of the septum and the lateral free wall, but only in one of these cases was LVH present according to MRI criteria.\textsuperscript{40} Furthermore, there were no asymmetries in the LV wall thickness and hence no specific hypertrophied regions.

In a previous study McCrohon et al found that in 59% of patients with dilated cardiomyopathy (DCM) there was no LE at all, in 28% the LE was longitudinal or patchy and located midwall, and in 13% it was subendocardial.\textsuperscript{37} Thus in 13% of
patients with DCM, late enhancement would be indistinguishable from an MI scar using the current definition. The prevalence of DCM is 36.5/100,000,67 i.e., 0.0365% of the population. Of these cases, 13% would have scars with a subendocardial component. Assuming that the prevalence of DCM was normally distributed in the investigated cohort, labeling of all myocardial LE with a subendocardial component as MI would, statistically, wrongly designate 0.005% (i.e. 0.0365 · 0.13) as MI scars that were in fact fibrosis due to DCM. In our study 0.005% of the 49 subjects with UMI would hence statistically have DCM, i.e., 0.002 subjects.

One of the subjects with UMI in our study was given the diagnosis of DCM four months after the MRI (independently of the MRI examination results). The LE in this subject might, however, have been due to MI anyway, since this subject displayed several risk factors for CHD, namely heavy smoking, insulin-treated diabetes with angiopathy, and claudicatio (treated with dilatation of iliac stenosis); and a silent MI (or a pulmonary embolism) had in fact been suspected as the cause of the heart failure. Furthermore, the LE in this subject was located in the anterior LV wall, within the vascular territory of the LAD – hence a typical enhancement pattern for MI. The conclusion drawn by McCrohon et al that 13% of DCM patients have an enhancement pattern indistinguishable from that in MI37 refers only to the subendocardial location of the LE and does not pay consideration to whether it corresponds to a vascular territory or not. Thus it seems fairly likely that our above-mentioned subject had a UMI. Either the DCM diagnosis was based on the absence of an MI diagnosis - i.e., if the UMI had been recognized the diagnosis would have been heart failure secondary to MI - or this LE was caused only by DCM fibrosis. In the latter case, this subject would by a comfortable margin constitute the 0.005% wrongly labeled as calculated above.

Despite these possibilities of misinterpretation, LE MRI is probably the best single technique for detecting MI scars. Using the definition of an MI scar as a finding of subendocardial LE, this technique has an exceptionally high specificity (98%) for a diagnosis of coronary artery disease (CAD), as compared with coronary angiography.62

At the age of our cohort (70 years), ischemic disease is far more common than any of the above diseases. In a previous
MRI study of 298 subjects with a mean age of 50 years, only one UMI and none of the other above diseases were found.\textsuperscript{68} (Subjects with a known MI, stroke, or diabetes were excluded.) The fact that the prevalence of ischemic disease increases with age may explain the difference in the prevalence of UMI between that cohort and ours, since there was a mean age difference of 20 years. The other diseases mentioned above do not appear to the same extent between the ages of 50 and 70, but earlier in life. Thus if a large proportion of the subendocardial LE in our study had been due to some of the other diseases, those diseases would have been prevalent in the 50-year-olds as well.

Hence, several factors support the notion that the UMIs of our study really do constitute MI scars and not some other condition represented by LE. However, the pathogenesis of these UMIs remains to be identified.

Gender aspects

Men have about twice the total incidence of clinically recognized CHD morbidity and mortality compared with women.\textsuperscript{69} MIs in women are, however, more likely to be unrecognized than MIs in men,\textsuperscript{69} partly because women more often present with atypical symptoms.\textsuperscript{70-72} Furthermore, the difference in recognized morbidity tends to diminish after the menopause, and to be eliminated around the seventh decade of life.\textsuperscript{69} This indicates that CHD morbidity might be higher in women than is in fact recorded. It is not unreasonable to assume that recognized events in elderly women may be preceded by unrecognized events earlier in life.

In the present study there was a larger proportion of women in the UMI group (45%) than in the group with RMI (18%), but statistically there was only a tendency towards a difference ($\chi^2$ p value = 0.06). This is in contrast with results of an earlier ECG study,\textsuperscript{73} but consistent with those of a recent investigation of a community-based cohort of 5148 subjects, in which MIs were less often recognized in women than in men.\textsuperscript{74}

Part of the difference in the reported MI prevalence between genders may thus lie in the recognition. Furthermore, once the diagnosis is made, current treatments are equally effective in
reducing the risk in both women and men.\textsuperscript{75} This emphasizes the importance of recognizing MIs, particularly in women. However, the clinical impact of MRI-detected UMIs and the effect of their treatment are still unknown.

**Interpretation bias**

A possible contributory reason for failure to recognize MIs in women might be related to an interpretation bias regarding women’s symptoms and examination results. We are all to a varying extent afflicted with the inherited subconscious notion that the Caucasian male is the standard human being; for a long time in history medical research was conducted exclusively on Caucasian males, and conclusions were considered to be applicable to all humans. Women and persons from other ethnic groups have only recently been included in medical studies.\textsuperscript{*} Standard levels of various measurements and medication dosages are often based on observations in men but are also applied to women.

Apart from the possible misleading effects of these policies and the fact that women more often present with atypical symptoms,\textsuperscript{70-72} the same symptoms might be interpreted differently in women and men. This hypothesis is illustrated by the fact that 50\% of the women with UMI, but only 26\% of the men, had come to the hospital with possible MI symptoms (Table 1).

**Table 1.** Possible myocardial infarction symptoms presented at the emergency room by the 49 subjects with MRI-detected unrecognized myocardial infarction in relation to gender

<table>
<thead>
<tr>
<th></th>
<th>Left-sided chest pain</th>
<th>Right-sided chest pain</th>
<th>Dizziness and nausea</th>
<th>Fainting</th>
<th>Did not come to the hospital with MI symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Women</strong> (n=22)</td>
<td>7 (32%)</td>
<td>1 (4.5%)</td>
<td>2 (9%)</td>
<td>1 (4.5%)</td>
<td>11 (50%)</td>
</tr>
<tr>
<td><strong>Men</strong> (n=27)</td>
<td>7 (26%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>20 (74%)</td>
</tr>
</tbody>
</table>

Thus a larger proportion of the women with UMI presented themselves at the emergency room, offering us a possibility to recognize their MI, whereas men with UMI to a larger extent were asymptomatic or at least did not come to the hospital.

\textsuperscript{*} Since our study population was community-based it included both genders, but only Caucasians, see under Discussion; Unrecognized myocardial infarction; Prevalence, page 40.
Furthermore, it is well known among clinicians that it may be difficult not to be influenced by prior assessments and comments in a patient’s medical record. Thus a patient who has presented at the emergency room several times with chest pain without getting any cardiac diagnosis might not be viewed in the same way as someone coming in for the first time or having a prior cardiac diagnosis.

Some of the UMI cases illustrate this concept: One woman had come to the emergency room seven times over the past five years with chest pain that she felt was induced by heavy work with her arms. Two bicycle tests showed ‘borderline ST depression’, but the findings were not sufficient for a diagnosis of MI (appendix, subject nr 244). Another woman, with a diagnosis of chronic muscular pain in her records, came to the emergency room after having fainted twice; she had a systolic heart murmur that was considered to be physiological and was diagnosed as having thoracic muscular pain ‘as before’ (appendix, subject nr 174). One man had come to the emergency room numerous times since his late thirties and was diagnosed as having ‘subjective heart symptoms’, until his mid-fifties when he was diagnosed with angina pectoris, but not MI (appendix, subject nr 238). Another man showed an occluded right coronary artery (RCA) and a proximal stenosis in the LAD at coronary angiography. This was left untreated, since there was no pressure gradient and the changes were not considered to be severe enough for surgery. This man had a prior diagnosis of alcohol abuse (appendix, subject nr 183).

The latter form of interpretation bias may thus affect men as well as women. However, as discussed above, female gender alone may introduce an interpretation bias. A combination of female gender and a prior compromising diagnosis may then further contribute to the fact that a woman’s MI is more likely to be unrecognized than that in a man.

The ability to detect these UMIs in the acute phase, particularly in women, is therefore partly dependent on our ability to free ourselves from our subconscious prejudice. However, LE MRI might be an appropriate objective method for detecting these persons at risk, rendering it unnecessary for us to work with our own subconscious concepts.
Pathogenesis of UMI

Atherosclerosis

Atherosclerosis plays the most important role in the pathogenesis of an RMI, and since the risk factor profile is identical in ECG-detected UMIs (with Q waves) it is probably important there as well. The question whether this also applies to MRI-detected UMIs was investigated in paper III by looking at a number of indices of atherosclerosis.

Since there is evidence that atherosclerosis is a panarterial disease and aortic plaques are associated with CAD, whole-body MRA was chosen to evaluate atherosclerosis. This technique has proved to have a high sensitivity and specificity for detection of significant vascular stenoses.

Other studied markers of atherosclerosis were IMT, which is associated with coronary atherosclerosis and an increased risk of myocardial infarction, and CRP, which is a determinant of cardiovascular risk and predicts MI. The Framingham risk score was chosen to estimate the total risk of CHD over a period of 10 years.

None of these parameters were increased in the UMI group, whereas all of them were elevated in the RMI group. This may be considered to signify that the classical atherosclerotic pathogenesis of an RMI, including plaque rupture, occlusion of a large supporting vessel and subsequent ischemic injury to the myocardium, may not be the cause of MRI-detected UMIs. This was the conclusion drawn in paper III.

However, only luminal narrowing exceeding 50%, which corresponds to a fairly advanced stage of atherosclerosis, was recorded. Furthermore, coronary atherosclerosis can be manifested as vessel expansion as well as luminal narrowing or obstruction, and the luminal area has been reported to remain unaffected by plaque growth until the lesion exceeds 40% of the arterial luminal area. Also, aortic plaques have been seen to bulge outwards instead of projecting into the lumen. Angiography cannot detect this type of atherosclerotic lesion, since only the lumen is depicted. In addition, it has been suggested that it is not the lumen size, but the tendency of the plaque to rupture that constitutes the risk for future
cardiovascular events. Thus estimation of the total plaque burden may not be an adequate tool for evaluating the atherosclerotic risk.

The intima-media thickness of the common carotid artery only weakly correlates with the extent and severity of CAD, whereas IMT of the bifurcation and the presence of plaques are associated with ischemic heart disease; and an IMT score of the common and internal carotid artery, carotid bifurcation, and femoral artery correlates well with the extent of coronary atherosclerosis.

Furthermore, in a recent study no correlation was observed between atherosclerotic plaque burden, measured by intravascular ultrasound in coronary disease patients, and the traditional risk factors hypertension, hypercholesterolemia, elevated CRP and current smoking. Diabetes and male gender were, however, strong predictors for disease severity. Except for CRP, these parameters, together with age, are used to calculate the Framingham risk score. Since all subjects in our cohort were the same age, it is possible that only two factors were responsible for the increased Framingham risk score in the RMI group: the increased prevalence of diabetes and the overrepresentation of male gender. This score was created to estimate the total CHD risk over a period of 10 years, and the observations made by Nicholls et al demonstrate that the score does not provide information on the severity of coronary atherosclerosis.

CRP elevation is not specific for atherosclerosis and, as mentioned above, was not related to coronary plaque burden in the study by Nicholls et al.

The pathogenesis of MI includes three main components: the vulnerable atherosclerotic plaque, the vulnerable blood (prone to thrombosis) and the vulnerable myocardium (prone to arrhythmia). The cardiovascularly vulnerable patient presents one or several of these components and is thereby susceptible to an acute coronary syndrome or sudden cardiac death (Fig. 23).

Thus it is possible that these UMIs represent an earlier stage of atherosclerosis that has not yet become manifested in any other detectable way. The development from early phases to
clinically manifest coronary atherosclerosis is known to be a slow process; fatty streaks are seen in children. Furthermore, others have observed coronary atherosclerosis and related left ventricular dysfunction in subjects without a history of clinical cardiovascular disease, indicating that myocardial damage induced by atherosclerosis can occur earlier than suspected. This hypothesis is supported by the fact that three of our subjects with UMI were diagnosed with angina pectoris within a year after the MRI examination, irrespective of the MRI results.

![Diagram](image.png)

**Figure 23.** Three components contribute to the concept of the cardiovascularly vulnerable patient: the vulnerable atherosclerotic plaque, the vulnerable blood, and the vulnerable myocardium.

**Ischemia**

Angina pectoris results from transient episodes of myocardial ischemia without subsequent necrosis. However, angina can evolve to MI and along this process there will be a spectrum of various magnitudes of myocardial necrosis. It is also possible that anginal episodes actually lead to myocardial necrosis more frequently than suspected, but hitherto detection of such small necrotic areas has not been possible.
The fact that the prevalence of angina did not differ between the subjects with UMI and those without MI scars in our study does not necessarily contradict this possibility: Since the extensive ischemia causing an MI can be asymptomatic or present with atypical symptoms, so can an episode of transient ischemia. These UMIs could hence result from asymptomatic ‘anginal’ episodes. (The term angina is, however, no longer suitable.) Furthermore, subjects with UMI in our study had experienced chest pain more often than those without MI scars. This chest pain might reflect symptomatic episodes of ‘angina’ even if the subjects were given a non-CAD diagnosis at the hospital. Repeated ‘anginal’ episodes, either symptomatic or asymptomatic, might eventually have led to minor scars without a more accentuated event.

The pathogenesis of angina varies and includes components such as atherosclerotic flow-limiting stenoses and thrombosis, but also coronary artery spasm and microvascular dysfunction. Coronary artery spasm causes variant angina in which chest pain occurs both at rest and during exercise, often in a cyclic pattern the same time every day. Microvascular angina is characterized by a decreased capacity to reduce coronary resistance and increase coronary flow and affects small vessels that are not visible on coronary angiography. This reduced coronary flow reserve may give rise to abnormalities of myocardial perfusion. Microvascular or coronary spasm ‘angina’ may thus have caused the MI scars that were detected with MRI by Christiansen et al in 30% of patients with acute chest pain and elevated troponin I but with no or minimal coronary angiographic CAD.

The variation in the pathogenesis of angina illustrates that the cause of ischemia may differ between individuals and it is possible that the UMI group is not homogeneous. For example, three of the subjects with UMI had a diagnosis of thyrotoxicosis, a condition associated with an increased risk of MI. In hyperthyroid patients MI has been observed without signs of CAD, and in these cases the ischemia is thought to be caused by induction of coronary artery spasm by thyroid hormone or direct influence of this hormone on the myocardial oxygen supply and demand.
Other factors known to provoke anginal episodes are anemia, infection, and arrhythmias. We have no information on anemia or infection in the subjects of our study. It was observed in paper II, however, that the frequency of other cardiac symptoms, including arrhythmias, was higher in the UMI group than in the group without MI scars.

One of the subjects who was assessed to have a UMI had been submitted to ablation of an accessory pathway because of tachycardia, and in this case the scar may have been iatrogenic.

One single UMI may also have a multifactor etiology. This is perhaps the most probable since most parameters were only slightly altered in subjects with UMI compared to those without MI scars: the LVM was increased but not the relative myocardial volume (RMV) or the prevalence of LVH; EF was decreased but mostly within the range of the normal variation; the matrix metalloproteinase–9 (MMP-9) level was increased but not the tissue inhibitor of matrix metalloproteinase type 1 (TIMP-1). Even if they are only slightly altered, changes in several parameters may add up to a state where ischemia causes irreversible myocardial damage.

The fact that subjects with UMI did not generally seem to have an advanced stage of atherosclerosis, or display any risk factors for CHD, may constitute the very reason why their MIs were small enough to pass unrecognized. If these subjects had had advanced atherosclerosis and/or had displayed multiple risk factors for CHD, the ischemic episode might have had a longer duration and/or caused more damage. The MI would consequently have been larger and would thus have had a greater chance of being recognized.

The dark corner of the heart
The segments (segments 4, 5, 10, and 11 of the American Heart Association 17-segment model) in which 86% (42/49) of the UMIs were present are located inferolaterally in the basal and mid-cavity parts of the LV corresponding to the location of the MI scars that were found in the patients without coronary angiographic CAD. Historically there has been no reason to believe that MIs will occur predominantly in a particular region of the LV. The anatomy of the coronary arteries
displays inter-individual variations in distribution and dominance.\textsuperscript{63} Branches emanate at different sites and vary in size, number and distribution.\textsuperscript{63} Since bifurcations are sites of predilection for atherosclerotic lesions,\textsuperscript{85} the location of such lesions may vary substantially between subjects. However, 73\% (8/11) of the RMIs in our study were also located in these segments (4, 5, 10, 11). Furthermore, myocarditis occurs predominantly in the lateral segments\textsuperscript{64} (segments 5, 11, 16),\textsuperscript{35} indicating that this region may have a generally increased vulnerability.

ECG has lower sensitivity in the inferolateral segments than in the anterior and septal segments,\textsuperscript{1, 3} partly explaining why MIs in this region may remain unrecognized. Knowledge that the interpretation of ECG changes in this region may be unreliable might entail a bias in everyday clinical work, with disregard of inferolateral changes if they do not correspond to coronary angiographic findings. This may hence be a hidden, neglected, vulnerable area – a dark corner of the heart.

The watershed hypothesis

The inferolateral segments where 86\% (42/49) of the UMIs and 73\% (8/11) of the RMIs were distributed belong to different vascular territories, segments 4 and 10 generally being supplied by the RCA and segments 5 and 11 by the left circumflex artery (LCx). Many of the MI scars (9/42 UMIs and 5/8 RMIs) extended into both territories. This may of course reflect the normal interindividual anatomical variation of the dominance of the right or left coronary artery.\textsuperscript{63} Thus the scar might not in fact embrace two vascular territories, but rather be distributed within the distal part of one vascular territory. It is conceivable, however, that this area constitutes a watershed area similar to the watershed areas of the brain.\textsuperscript{99, 100} Such an area is supplied by small end-arteries and has a lower perfusion pressure than other areas and is thereby more vulnerable to ischemia.

In a deep cerebral watershed infarction, the ischemia is not primarily caused by thromboembolism, but by a hemodynamic dysfunction.\textsuperscript{101, 102} This results in cerebral hypoperfusion, which may be due to orthostatic hypotension,\textsuperscript{103} perioperative complications,\textsuperscript{104} MI,\textsuperscript{105} cardiac arrhythmias,\textsuperscript{105} severe carotid stenosis,\textsuperscript{105} antihypertensive treatment in patients with severe
carotid stenosis,\textsuperscript{105} or, frequently, to combinations of the above.\textsuperscript{101}

This hypothesis is supported by a previous observation that perfusion from the neighboring artery in a watershed area of the heart is significantly poorer in subendocardial than in subepicardial regions,\textsuperscript{106} since all UMIs involved the subendocardial layer. Such a watershed area would be even more vulnerable if the myocardial mass were large; then each end-artery would have to supply a larger myocardial mass, the diffusion distance would increase, and even a minor reduction of the blood flow could be sufficient to cause ischemia. This theory is consistent with our finding that the left ventricular myocardial mass was significantly larger in the subjects with UMI than in those without MI scars.

Of the three components contributing to the concept of the vulnerable patient,\textsuperscript{91, 92} the watershed hypothesis could provide the vulnerable myocardium. A subclinical atherosclerotic plaque might then be sufficient to cause ischemic injury.

Similarly to MRI-detected UMIs, cerebral watershed infarctions tend to be small.\textsuperscript{107} Their perfusion reserve, however, is decreased in an area far exceeding that of the infarction, whereas the perfusion reserve in territorial infarctions is only decreased in the area of the infarction itself.\textsuperscript{107} This may also be the case in UMIs. In paper IV it was hypothesized that increased myocardial fibrosis might cause a decrease in the myocardial perfusion reserve, by obstructing diffusion and thereby necessitating an increase in perfusion pressure. The fact that we could not prove this mechanism to have caused the UMIs does not contradict the possibility of a decreased perfusion reserve in subjects with UMI. Furthermore, a decreased perfusion reserve is suggested by the observation by Wang et al that changes in coronary vascular reactivity may be seen in subjects without symptomatic CHD,\textsuperscript{108} since UMIs were frequently asymptomatic. Subjects with UMI might thus have a decreased perfusion reserve in an area larger than that of the late enhancement. Myocardial perfusion studies are needed to confirm this hypothesis.

Since the left ventricle is supplied by three main arteries, there will be two other watershed areas in the heart. Why would the
inferolateral watershed area be more vulnerable than the other two?

The Achilles’ heel of the heart
To the best of my knowledge the inferolateral region of the LV has not previously been identified as particularly vulnerable. There is thus no obvious experimental support for the hypothesis that this region of the heart might constitute an Achilles’ heel, but some conceivable explanations are presented below.

Dominance
The suggested increase in the vulnerability of the inferolateral region might be due to anatomical factors. Since this is a watershed area between the vascular territories of the right and left coronary artery, it will be affected by the question of dominance.

When a coronary artery is stenosed or occluded, collateral blood flow increases rapidly. Even partial embolization of the coronary microcirculation will cause growth and development of collaterals, implying that ischemia per se is a sufficient stimulus. In line with the hypothesis that myocardial ischemia caused the UMIs in our study, collaterals may be of importance in spite of the indication in paper III that the subjects with UMI did not have severely stenosed or occluded coronary arteries.

The development of collaterals may be crucial. They improve myocardial perfusion in the ischemic zone, LV function is better in areas with adequate collateral circulation, and CAD patients with inadequate or no collaterals have a higher mortality rate.

Growth and development of collaterals of the RCA have been found to be far better than those to the LCx in CAD patients. In the watershed area between these two arteries, a subject with a dominant RCA would thus have the potential to endure ischemia better than someone with a dominant left coronary artery. The RCA is dominant in about 85% of humans, leaving 15% with a dominant left coronary artery, who, because of a lower degree of collaterals might be more susceptible to ischemic myocardial injury, i.e., MI. It remains
to be investigated whether a dominant left coronary artery is overrepresented in subjects with MRI-detected UMI.

**Spasm**
Apart from thromboembolic or atherosclerotic plaque occlusion of a coronary artery as a pathogenetic factor, myocardial ischemia is also known to occur as a result of coronary artery spasm.63 The inferolateral region of the LV is located in the immediate proximity of the gastrointestinal tract, separated from it only by the diaphragm. It is conceivable that gastrointestinal disorders due to mechanical (hiatus hernia) or inflammatory (gastritis, esophagitis, colitis) influence might induce a vasospasm in adjacent coronary artery branches.

**Apex**
The apical segments in the inferolateral region (segments 15, 16, and 17 of the American Heart Association 17-segment model49) do not seem to be as vulnerable as the basal and mid-cavity segments, at least not to UMIs (Fig. 18). This might be explained by an imaging bias; that is the spatial resolution is better when the LV wall is thicker - then a region of LE will appear more sharply demarcated. In the apical region the LV wall is thinner and a possible small region of LE will be less distinct and may thereby be disregarded as too uncertain a finding. This hypothesis is consistent with the fact that RMIs were as frequently distributed in segments 15 and 16 as in segments 4, 5, 10, and 11 (Fig. 18): Since RMIs were generally larger than UMIs, they more often embraced several segments and their assessment and demarcation were thus more certain than those of a small UMI contained within an apical segment.

**Lacunar MI**
There is also a possibility that UMIs are the equivalent of lacunar infarctions of the brain. These were first described in 1838 by Dechambre113 and a few years later by Durand-Fardel114 and constitute deep subcortical ischemic lesions caused by occlusion of single small perforating arteries.115

In clinical cerebral lacunar infarctions the arterial occlusion is caused by atherosclerosis.116 Since the perforating artery may be normal throughout its length, small embolic particles are thought to cause the obstruction and subsequently undergo lysis.117 However, in the smallest lacunar infarcts the occlu-
sion is believed to be caused by lipohyalinosis, a vasculopathy in which the arterial wall consists of a loose meshwork of collagenous strands separated by interstitial spaces occupied by fatty macrophages or foam cells. In silent lacunar infarctions it appears that small ramifications of the perforating arteries are obstructed by microangiopathy in which lipohyalinosis only constitutes one part.

When applying these concepts to myocardial infarctions, it is agreed that the clinical ones, i.e., the RMIs, are strongly associated with and most certainly caused by atherosclerosis, as demonstrated in paper III. In that paper there were indications that the silent MIs, i.e., the UMIs, are not caused by atherosclerosis. According to the hypothesis of lacunar MIs they would be caused by microangiopathy with lipohyalinosis. Lipohyalinosis has been observed in coronary arteries. Although this observation was made in guinea pigs fed an atherogenic diet, it is conceivable that lipohyalinosis may exist in other arteries than the cerebral ones, even in the absence of atherosclerosis. Lipohyalinosis affects small vessels analogously to microvascular angina pectoris. Microangiopathy with lipohyalinosis might be the pathogenetic mechanism underlying microvascular angina, which might cause repeated microscopic myocardial scarring adding up to a lesion large enough to be detectable with LE MRI.

Watershed or lacunar MI?

Lacunar and deep watershed infarctions of the brain may have the same size and site, but their pathogenesis differs. Lacunar infarctions are closely correlated with hypertension, whereas watershed infarctions are caused by hypotension. The hemodynamic reserve is normal in persons with lacunes and severely reduced in those with watershed infarctions.

Factors favoring or disfavoring the hypotheses

From the results of paper IV it was concluded that the increased collagen turnover in subjects with UMI, could indicate myocardial fibrosis. This could cause a decreased myocardial perfusion reserve, even though the hypothesis that this would have caused ischemia and subsequent MI could not be proved. The possibility of a decreased myocardial perfusion reserve
would, however, favor the watershed hypothesis rather than that of a lacunar MI.

Hypertension was very common in this elderly cohort (73% of all 248 subjects; 71.4% of the subjects with UMI). Hypertension was defined, however, as either elevated blood pressure or antihypertensive treatment. We do not know how well the hypertension in these subjects was treated. Either they do not have adequate treatment and their blood pressure remains elevated, favoring the lacunar hypothesis, or they are overtreated and in fact hypotonic, favoring the watershed hypothesis. It has been suggested, however, that the correlation between cerebral lacunar infarction and hypertension may arise from classification bias. As to the watershed hypothesis, systemic hypotension might not be as important for the myocardial perfusion pressure as a lack of adequate collaterals in an intermittently ischemic myocardium.

**Possible measurements to support the hypotheses**

The cause of ischemia in a watershed MI would thus be a low myocardial perfusion pressure. This low pressure can be due either to mechanical obstruction by perivascular and interstitial myocardial fibrosis, as suggested in paper IV, or to occlusion of coronary artery ramifications together with a lack of adequate collaterals, or to a combination of the two. Susceptibility to the UMIs in our study might hence have resulted from a combination of increased myocardial fibrosis and a dominant left coronary artery. We already have indications of myocardial fibrosis and the LVM was increased. The main additional way to test the watershed hypothesis would be to measure the myocardial perfusion. Coronary angiography can be used to determine dominance.

The cause of ischemia in a lacunar MI would be obstruction of coronary artery ramifications by microangiopathy, including lipohyalinosis, and there would be a correlation with hypertension. We already know that there was a high prevalence of hypertension in the subjects with UMIs, but it was not significantly higher than that among subjects without MI scars. However, if the UMIs in our study were caused by microangiopathy, this would not be likely to be specific for a special organ but would probably affect all small vessels. The afflicted subjects should thus have cerebral lacunar infarctions to a
larger extent than subjects without MI scars, a difference which could be assessed with a CT scan.

**Table 2.** Factors that may be investigated and how they would support the two main hypotheses concerning the pathogenesis of unrecognized myocardial infarction

<table>
<thead>
<tr>
<th>Factor:</th>
<th>Hypothesis:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Watershed MI</strong></td>
</tr>
<tr>
<td>Left ventricular mass</td>
<td>Increased</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>Hypotension</td>
</tr>
<tr>
<td>Myocardial perfusion pressure</td>
<td>Decreased</td>
</tr>
<tr>
<td>Coronary angiography</td>
<td>Left coronary artery dominance</td>
</tr>
<tr>
<td>Markers of extracellular matrix turnover (MMPs and TIMPs)</td>
<td>Increased</td>
</tr>
<tr>
<td>Cerebral CT scan</td>
<td>Normal</td>
</tr>
<tr>
<td>Histology</td>
<td>Interstitial and perivascular fibrosis</td>
</tr>
</tbody>
</table>

**Interpretation of measurements to support the hypotheses**

Further studies including histologic examinations would be needed to definitely confirm or falsify the watershed and lacunar hypotheses, but less invasive methods may provide indications (Table 2).

A decreased myocardial perfusion pressure is of course expected in the scar tissue, as compared to in viable myocardium in the region of the UMI. However, a decreased perfusion pressure in the surrounding area would indicate a watershed mechanism, and with a normal perfusion pressure the lacunar (microangiopathy) hypothesis would be more probable. Coronary angiography showing dominance of the left coronary artery would suggest the watershed mechanism, whereas RCA dominance would favor the lacunar mechanism. Increased levels of MMPs and TIMPs would support the watershed hypothesis, assuming that they reflect an increased amount of myocardial fibrosis. However, in lipohyalinosis the arterial wall is transformed into a loose meshwork of collagenous strands, and markers of extracellular matrix turnover will consequently
be elevated. A finding of increased levels of MMPs and TIMPs will thus not help to distinguish between the two hypotheses. Hypotension would favor the watershed hypothesis and hypertension the lacunar hypothesis.

The pathogenesis of MRI-detected UMIs has not been fully established – without histology and pathology correlation studies these hypotheses cannot be confirmed. Furthermore, atherosclerosis may be involved in the pathogenesis of both watershed and lacunar infarction. However, we consider it most likely, on the basis of the above discussion, that the UMIs in our study were caused by ischemia. The cause of the ischemia is basically the same in the two main hypothetical types of infarction, namely inability of small vessels to support the myocardium - in watershed infarction due to myocardial fibrosis, a large LVM and a lack of collaterals, and in lacunar infarction, to microangiopathy. Since an MI is defined as myocardial necrosis caused by ischemia, these UMIs are by definition MIs.

Significance of UMI

Size

The UMIs were significantly smaller than the RMIs in our study; the mean size of a UMI was 2.5 g (1.9% of the LVM), and 32/49 (65%) were smaller than 2 g. The mean size of an RMI was 9.3 g (4.8% of the LVM) and 3/11 (27%) were smaller than 2 g.

The reliability of the assessment of a lesion this small might be questioned. The spatial resolution of LE MRI is, however, very good (1.56 x 2.81 mm acquired pixel size). Furthermore, the repeatability of infarct size measurements is excellent. Animal studies have demonstrated close correlations between infarct size determined with MRI and that determined with triphenyltetrazolium chloride staining, and the MRI-determined size is independent of postcontrast time and contrast agent dose provided that an adjusted inversion time is used.

It may be argued that such small MIs have no clinical significance. In a recent study the presence of an MI scar on MRI
was shown, however, to be predictive for future CAD, MI, or death even though 43% of the scars were smaller than 10 g, and even the smallest MIs that are detected by troponin imply an impaired clinical outcome and may have important prognostic significance. Furthermore, it has been observed in a recent study of 195 patients with suspected CAD but without a history of MI that even very small myocardial scars on LE MRI (mean 1.4% of LVM) are associated with a >7-fold increase in major adverse cardiac events, including cardiac death.

It should also be emphasized that we preferred to underestimate rather than overestimate the infarct size when manually segmenting it. Furthermore, the infarct size was probably larger in the acute stage, since it decreases during healing. In analogy with the parallel to watershed infarctions, the perfusion reserve might be decreased in an area far exceeding that of the infarction.

**Location**

It has been suggested that an infarction of the same size would cause greater damage to the LV in the anterior location than in the inferoposterior ones. This suggestion is based on observations in patients with acute MI in the 1980s in a study where the location was determined with ECG. Thus it is unclear whether this applies to UMIs. If it does, it could explain our observation that inferolateral MIs were frequently unrecognized. It would also imply that the prognostic impact of a UMI might not be as great as that of an RMI. Furthermore, unrecognized myocardial scars on MRI have been found to have prognostic significance if located in the vascular territory of the LAD or RCA but not in that of the LCx.

The possibility of lesser severity of an inferolateral scar could be explained by the anatomy of the cardiac conduction system. An inferolateral scar would not interfere with the main conduction pathways, as could an anterior or septal scar. Thus an inferolateral scar would not be likely to cause arrhythmias to the same extent as an anterior or septal scar and hence would not have the same prognostic impact. This idea is contradicted, however, by the fact that the UMI group in our study had the same frequency of arrhythmias (5/49=10.2%) as the RMI group (1/11=9%).
Risk
The same factors contribute to an increased risk of acquiring an RMI as an ECG-detected UMI, but the results of paper III indicate that they do not affect the risk of acquiring an MRI-detected UMI. Either other factors contribute to this risk, or a lower degree of the traditional risk factors is sufficient and the risk score is not sensitive enough to indicate it. This observation is supported by the fact that traditional risk factors have been found not to predict coronary disease severity.

Prognosis
The actual prognosis of these MRI-detected UMIs remains to be investigated. However, several of our findings indicate that having an MRI-detected UMI is associated with an increased risk for further cardiovascular events. As reported in paper II, the subjects with UMI displayed an increased frequency of chest pain and other cardiac diagnoses indicating increased cardiac morbidity. Furthermore, they had a decreased EF, suggesting possible impairment of cardiac function and an increased LVM which is associated with increased morbidity and mortality. As stated in paper IV, they also showed elevated levels of MMP-9, which is known to be associated with an increased risk for future cardiovascular events.

The notion that unrecognized myocardial damage has prognostic significance is supported by the observation in a recent population-based study of 1203 men that elevated levels of cardiac troponin I predict death and first CHD event in subjects without known cardiovascular disease. Furthermore, the presence and extent of unrecognized myocardial scars on MRI has been proved to be a strong predictor of major adverse cardiac events, including cardiac death, in patients with clinically suspected CAD.

Some prognostic indications might be found by comparison with the prognosis of the cerebral infarctions on which the main hypotheses are based. Cerebral watershed infarction is seldom fatal. This might apply also to the UMIs, since those that we found were not fatal. However, we do not know whether there have been fatal ones in the population: sudden deaths from unknown causes usually lead to autopsy, but since these UMIs are very small they could have been missed.
The common notion that cerebral lacunar infarctions are benign and have a favorable long-term prognosis only applies in the early course of the disease, whereas after a few years there is an increased risk of death, mainly from cardiovascular causes.\textsuperscript{137} If the UMIs in our study had the same pathogenesis as cerebral lacunar infarctions, the prognosis would be similar.

We will obtain information on the actual prognosis of the MRI-detected UMIs, since our study population will be reinvestigated at the age of 75. A longer follow-up of course would have given further information.

**From UMI to RMI**

The fact that the UMIs detected in the present study escaped clinical recognition can be explained by the observations that compared with the RMIs the UMIs were to a greater extent asymptomatic and had significantly smaller volumes, and that they were frequently located in the inferolateral segments, where ECG has lower sensitivity than in the anterior and septal segments.\textsuperscript{1, 3}

The year of diagnosis may also have an impact, since biochemical markers have become more sensitive with the introduction of cardiac troponins.\textsuperscript{8} Furthermore, the diagnostic criteria for MI were altered in the year 2000; prior to that year two of the three classical criteria (chest pain, ECG changes, and elevated biomarkers) had to be fulfilled in order to set the diagnosis acute MI. Since the year 2000 it has not been allowed to use this diagnosis clinically unless biomarkers (preferably cardiac troponins) are elevated.\textsuperscript{8} The RMIs of our study were diagnosed between 1987 and 2004; 4 of them before the year 2000 and 7 from that year onward. The subjects with UMI who had come to the hospital with chest pain had done so between 1969 and 2004, 10 of them before 2000 and 4 of them thereafter.

Cardiac troponin (I or T) is considered to have nearly absolute tissue specificity, as well as high sensitivity for detecting myocardial necrosis, and the serum levels may remain elevated for 7 to 10 days or longer.\textsuperscript{8} There is, however, an aspect of timing in the rise and fall of biomarkers that does not need to be considered in MRI, which might make MRI even more sensitive.
This is suggested by the fact that MRI detected a UMI in a subject who had come to the hospital with acute chest pain, slight ST depression on ECG in the ambulance, but no elevation of troponin I levels at three repeated measurements. Thus this subject did not fulfill the current diagnostic criteria for an acute MI.

Clinical implications

Until recently having or having had an MI was considered a major event with important implications for survivors. This paradigm has already changed concurrently with the evolution of better diagnostic methods and management strategies. Further technological improvement, such as LE MRI, might enhance this development and necessitate not only a redefinition of the clinical diagnosis MI but a general redefinition of how to consider the event of MI in everyday life.

The importance of recognizing MRI-detected UMIs has already been emphasized above. The clinical aim should of course be to recognize all acute MIs. In order to do that, the patient first needs to present him- or herself at the hospital; it is hardly possible to find the asymptomatic ones. However, attention has to be paid to atypical symptoms. Second, the diagnosis can be verified but not ruled out with ECG. Third, the timing has to be correct for biomarker measurements. Fourth, MI scarring can occur with no or minimal changes on coronary angiography. LE MRI with its high spatial resolution is a useful tool for detection of acute and chronic MI, but its usefulness is influenced by practical, logistic and economic factors.

Before advocating an emergency LE MRI in all patients presenting at the emergency room with chest pain, we need to know more about the pathogenesis and the prognosis of these MRI-detected UMIs. Even though clinically unrecognized myocardial scars on MRI have important prognostic implications in patients with suspected CAD, this issue has not been examined in a population-based cohort. Prognostic information from our cohort will, however, be obtained at the 5-year follow-up, but even further studies are needed to investigate the pathogenesis.
Redefinition of MI

The possibility of identifying MI scars this small may call for a further redefinition of MI. As suggested by the joint European Society of Radiology/American College of Cardiology, a patient formerly diagnosed as having angina pectoris might be diagnosed today as having had a small MI.8

It has been emphasized that there is a continuous relation between minimal myocardial damage and large infarctions.8 The border between angina pectoris and MI has been moved along this line. There is even a possibility that every anginal episode causes myocardial necrosis and that detection of this necrosis is limited only by the sensitivity of current technology. Even if areas of myocardial necrosis weighing <1.0 g can be identified,8 we cannot yet detect necrosis of single cells. It has been argued that any amount of myocardial necrosis caused by ischemia should be labeled as MI.8 If every anginal episode caused myocardial necrosis, this should be labeled as MI and angina pectoris would not exist.

Concurrently with the ability to detect smaller and smaller MIs, the levels of what is normal might also have to be redefined regarding other measures of myocardial damage and risk factors for cardiovascular disease.

It has been predicted that application of more sensitive diagnostic criteria for MI will confuse epidemiologic studies (with a rising recorded incidence and a falling case fatality rate).8 The comparison between the prevalence of UMI as estimated with MRI and with ECG respectively has also been affected by the difference in sensitivity of the two methods.

The current description of an MI as myocardial necrosis caused by ischemia8 might have to be altered as a result of the ability to detect very small MI scars. The definition of an MI might need to include the cause of ischemia and a further classification considering the size and location of the MI might be called for in order to distinguish between different types of MI that might need different treatment and have different prognoses.
Conclusions

The accuracy of the LV segmentation influences systolic function values. The ES-ED LV mass difference can be used to identify the assessments that would benefit from a more accurate segmentation.

MRI detected more UMIs than expected in 70-year-olds. The subjects displaying these UMIs may represent a previously unknown potential risk group for future cardiovascular events.

MRI-detected UMIs were not associated with manifestations of significant atherosclerosis on MRA, increased IMT, CRP elevation or traditional risk factors for CHD, suggesting that they may have another pathogenesis than RMIs or have the same pathogenesis, but present themselves at an earlier stage. If the pathogenesis is different, the prognosis will probably differ too.

The increased collagen turnover that was observed in the subjects with MRI-detected UMI can indicate myocardial fibrosis. However, the hypothesis that this would reflect extensive myocardial fibrosis causing impaired myocardial perfusion, ischemia and consequent MI could not be further supported. Nevertheless, a finding of high MMP-9 levels in subjects with UMI suggests that these subjects may be at increased risk for future cardiovascular events.

This work started out with the quest of finding UMIs, but several unexpected observations were made along the way. First the prevalence of UMIs by far exceeded our expectations. Second, the UMIs differed more from RMIs than we expected; they were smaller, there seemed to be a predilection site for UMIs, and they did not appear to be associated with atherosclerosis. Yet they exhibited features implying an increased cardiovascular risk.

These conclusions indicate that the term UMI might not be completely adequate. However, since our observations and hy-
theses suggest that these UMIs are caused by ischemia, to label them MI would seem adequate according to the current MI definition. Provided that ischemia really is the cause, which has to be verified by further studies, the current definition of MI might thus have to be reconsidered.
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Alma and Vera Barbier, my daughters, for being fantastic and for taking my mind off the scientific work for some time of the day.

It is easy to succeed when people believe in you!
Summary in Swedish

Bakgrund
Hjärtinfarkt orsakar stor sjuklighet och död över hela världen. För att förebyggande åtgärder och behandling ska ha optimal effekt måste man känna till vilka som har eller har haft en hjärtinfarkt.

Redan 1912 beskrevs förekomsten av kliniskt okända hjärtinfarkter, men man har ännu inte hittat ett optimalt sätt att upptäcka dessa. Man har använt elektrokardiografi (EKG), en metod som också funnits i hundra år, och där jämnställt förekomst av Q-våg med genomgången hjärtinfarkt. På detta sätt har man uppskattat att kliniskt okända hjärtinfarkter skulle utgöra ¼ av alla hjärtinfarkter och ha samma dödlighet som kända hjärtinfarkter. Dessa uppskattningar är emellertid missvisande eftersom alla hjärtinfarkter inte ger Q-vägor och alla Q-vägor inte är orsakade av hjärtinfarkt.

Tekniken med sen kontrastuppladdning på magnetisk resonanstomografi (MRT) har utvecklats under det senaste decenniet och visat sig vara en precis metod för att upptäcka ärr i hjärtmuskeln. Syftet med denna avhandling var att med MRT undersöka förekomsten och betydelsen av kliniskt okända och kända hjärtinfarkter i en grupp 70-åringar som utgör ett tvärsnitt av den 70-åriga svenska befolkningen.

Studiepopulation
Artikel I
I första artikeln har tre metoder för beräkning av hjärtats vänsterkammarmassa utvärderats på 100 av de undersökta personerna.

Beräkningarna baseras på att de yttre och inre begränsningarna av vänsterkammaren ritas in på samtliga kortaxelbilder där hjärtat är maximalt sammandraget (systole) respektive maximalt avslappnat (diastole) (s.k. segmentering). Därefter räknar datorn ut vänsterkammarmassan, blodvolymer i systole respektive diastole samt värden som speglar hjärtats systoliska funktion.

Vänsterkammarens begränsningar kan ritas in manuellt eller med hjälp av olika hel- eller halvautomatiska metoder med varierande noggrannhet. Dessutom varierar det huruvida de små musklerna som styr hjärtklaffarna (papillarmuskler) ritas in eller inte.

Resultaten i denna studie visade att noggrannheten i segmenteringen påverkar de systoliska funktionsvärdena och att skillnaden mellan den uträknade vänsterkammarmassan i systole och diastole kan användas för att avgöra i vilka fall en mer noggrann segmentering kan vara av värde.

Artikel II
I andra artikeln utvärderades förekomsten av ärr efter hjärtinfarkter i hjärtmuskeln. Detta gjordes på undersökningar från 248 (123 kvinnor och 125 män) av de 259 personerna, eftersom 11 undersökningar inte var utvärderingsbara p.g.a. tekniska problem.

De som hade ärr efter hjärtinfarkter delades in i två grupper beroende på om de hade diagnosticerats med hjärtinfarkt eller inte. Totalt bildades därmed tre grupper; en med personer utan ärr efter hjärtinfarkter (no myocardial infarction, No MI), en med personer som hade ärr men inte hade fått diagnosen hjärtinfarkt i sin journal (de hade således en tidigare okänd hjärtinfarkt; unrecognized myocardial infarction, UMI) och slutligen en med personer som både hade ärr och diagnosen hjärtinfarkt, d.v.s. en kliniskt känd hjärtinfarkt (recognized myocardial infarction, RMI). Dessa grupper jämfördes avseende hjärtfunktion (som beräknats enligt ovan) och data från patientjournalerna.
Av de 248 personerna hade 188 inga ärr efter hjärtinfarkter (No MI), 49 hade tidigare okända hjärtinfarkter (UMI) och 11 hade kända hjärtinfarkter (RMI).

Tidigare okända hjärtinfarkter var således betydligt mer vanligt förekommande än förväntat; 19.8% av 70-åringarna hade tidigare okända hjärtinfarkter och de okända hjärtinfarktarna utgjorde 4/5 av alla hjärtinfarkter istället för ¼ som man tidigare trott. Gruppen med tidigare okända hjärtinfarkter hade oftare sökt akut med bröstsmärta, de hade lägre pumpförmåga hos hjärtat och större vänsterkammarmassa än gruppen utan ärr efter hjärtinfarkt. Detta indikerar att personer med ärr efter tidigare okända hjärtinfarkter kan ha ökad risk för framtida hjärt-kärlrelaterade sjukdomar.

Artikel III
Kända hjärtinfarkter orsakas huvudsakligen av åderförkalkning i hjärtats kranskärl. I tredje artikeln prövades huruvida det finns tecken till att de tidigare okända hjärtinfarktarna också gör det.

Förekomsten av åderförkalkning i hela kroppens kärl (utom hjärtats kranskärl) undersökes med magnetisk resonansangiografi (MRA). Som ytterligare tecken på åderförkalkning mättes kärlväggens tjocklek med ultraljud på halsen (IMT) och ett blodprov som speglar inflammatorisk aktivitet (CRP). Dessutom uppskattades risken för hjärt-kärlsjukdom med en vedertagen metod (Framingham risk score).

Ingen av dessa parametrar var förhöjd i gruppen med ärr efter tidigare okända hjärtinfarkter, medan alla parametrar var förhöjda i gruppen med kända hjärtinfarkter. Detta talar emot att de tidigare okända hjärtinfarktarna skulle vara orsakade av åderförkalkning.

Artikel IV
I fjärde artikeln prövades huruvida det finns tecken till att ärren efter tidigare okända hjärtinfarkter istället orsakats av dålig genombloödning i hjärtmuskeln, antingen p.g.a. förtjockade vänsterkammarväggar och/eller p.g.a. ökad mängd bindväv i hjärtmuskeln.
Blodprover som speglar bindvävsomsättningen i kroppen mättes och förekomsten av hjärtmuskelförstoring och -förtjockning undersöktes med MRT. Hjärtats diastoliska funktion undersökes med ekokardiografi.

Personerna med ärr efter tidigare okända hjärtinfarkter uppvisade tecken till ökad bindvävsomsättning. Detta kan innebära att de har ökad mängd bindväv i hjärtmuskeln. Vi fann emellertid inget stöd för hypotesen att detta föranlett dålig genomblödning av hjärtmuskeln och därmed orsakat infarkterna, då dessa personer varken uppvisade ökad förekomst av hjärtmuskelförstoring eller -förtjockning eller nedsättning av hjärtats diastoliska funktion.

Dessa tecken till förhöjd bindvävsomsättning kan dock innebära ökad risk för framtida hjärt-kärlrelaterade sjukdomar hos personer med ärr efter tidigare okända hjärtinfarkter.

**Slutsatser**

Målet med detta forskningsarbete var att hitta tidigare okända hjärtinfarkter, men under arbetets gång gjorde vi flera oväntade iakttagelser. För det första visade det sig att tidigare okända hjärtinfarkter var långt vanligare än vi trott. För det andra var de okända hjärtinfarkterna mer olika de kända än förväntat; de var mindre, uppträdde oftare på ett speciellt ställe och verkade inte vara kopplade till åderförkalkning. Trots detta föreföll de vara förknippade med ökad risk för framtida hjärt-kärlrelaterade sjukdomar.
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The chapter ‘Magnetic resonance imaging physics’ was based on:

*MRT – grunderna och basal klinik*. Educational course by Karolinska Universitetssjukhuset, Teneriffa; 29 Jan – 5 Feb 2006


Appendix

**Recognized myocardial infarctions (RMIs)**

Short axis magnetic resonance images from the eleven subjects displaying recognized myocardial infarctions (RMIs) (i.e., MI scar in combination with MI diagnosis in medical records). Note that these MI scars were visible in the same location in both short and long axis and that some involve the subendocardial layer in another slice than the one displayed.
Unrecognized myocardial infarctions (UMIs)

The fold-out on the right shows short axis magnetic resonance images from the 49 subjects displaying previously unrecognized myocardial infarctions (UMIs). Note that these MI scars were visible in the same location in both short and long axis and that some involve the subendocardial layer in another slice than the one displayed.
A doctoral dissertation from the Faculty of Medicine, Uppsala University, is usually a summary of a number of papers. A few copies of the complete dissertation are kept at major Swedish research libraries, while the summary alone is distributed internationally through the series Digital Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine. (Prior to January, 2005, the series was published under the title "Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine".)

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