Unrecognized myocardial scars detected by delayed–enhanced MRI are associated with increased levels of NT-proBNP
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Objective Patients with unrecognized myocardial infarction (UMI) scars detected by delayed–enhanced magnetic resonance imaging (DE-MRI) have a decreased left ventricular ejection fraction and an increased left ventricular mass. N-terminal pro-brain natriuretic peptide (NT-proBNP) is a marker of heart failure, and troponin I (TnI) is a marker of myocardial injury. The primary aim of this study was to investigate whether NT-proBNP plasma levels (in addition to ejection fraction) differed in patients with UMI scars compared with normal participants. The second aim was to compare whether the TnI levels differed in those two groups.

Methods Data from the Prospective Investigation of Vasculature in Uppsala Seniors study were used. The participants who had undergone cardiac MRI were included in this study (\(n=248\)). Patients were divided into three groups depending on the existence of a myocardial infarction (MI) scar in DE-MRI and their earlier history of MI. In all the patients, a peripheral blood sample was collected and the plasma levels of NT-proBNP and TnI were determined.

Results Patients with UMI had higher plasma levels of NT-proBNP (median 140.2 ng/l; 25th–75th percentiles: 79–225.5) than no-MI participants (median 94.9 ng/l; 25th–75th percentiles: 59.2–144.2; \(P=0.01\)) and lower levels than patients with recognized MI (median 310.4 ng/l; 25th–75th percentiles: 122.6–446.5; \(P=0.02\)). Plasma TnI values did not differ among the three groups.

Conclusion Patients with UMI scars detected by DE-MRI have increased plasma levels of NT-proBNP that is known to correlate with an increased risk of future cardiovascular adverse events. Coron Artery Dis 00:000–000 @ 2010 Wolters Kluwer Health | Lippincott Williams & Wilkins.

Coronary Artery Disease 2010, 00:000–000

Keywords: epidemiology, infarction, prognosis, silent, troponin I, viability

Introduction

Unrecognized myocardial infarction (UMI) is commonly diagnosed by the appearance of a diagnostic Q-wave in an electrocardiogram (ECG) [1,2]. Delayed–enhanced magnetic resonance imaging (DE-MRI) provides a sensitive and accurate technique for detecting myocardial infarctions (MIs) [3,4], some of which are not shown by ECG [5]. Some MRI-detected MIs are small and might not have sufficient amount of necrosis to produce a significant Q-wave on the ECG [6]. Epidemiological studies state that the mortality rate of the patients with UMI detected by ECG is similar to patients with clinically recognized MI (RMI) [1,2]. These studies apply electrocardiographic criteria for defining MI; therefore, the clinical significance and prognosis of small UMI scars detected by MRI is not established. Just recently, two articles [7,8] report an increased risk of major adverse cardiac events in patients who had small UMI scars detected by DE-MRI. These studies were conducted in patients with clinical suspicion of myocardial injury hence the prognostic significance of these scars in a nonrisk population is still unknown.

The brain natriuretic peptide (BNP) is synthesized and released in ventricular myocytes in response to fiber stretch [9] and is a well-established biomarker of left ventricular dysfunction [10]. Increased levels of BNP and N-terminal pro-BNP (NT-proBNP) after an acute MI or in chronic heart failure are associated with a worse prognosis, independent of other cardiac risk factors [11–14].

Cardiac troponin I (cTnI) is a biomarker specific for myocardial injury [15] and is primarily used as a tool for diagnosing acute coronary syndromes. The association of high levels of TnI with an increased risk of cardiovascular and all-cause mortality after an acute coronary syndrome is showed [16] and this relationship is also verified in patients with no risk factors for cardiovascular disease [17].
From the Prospective Investigation of Vasculature in Uppsala Seniors (PIVUS) study, DE-MRI detected a higher amount of UMI scars in this age group than earlier epidemiological studies with electrocardiographic criteria [5]. UMI comprised 80% of the total number of MRI-detected MIs, 73% of which had no signs of ischemia on the ECG. All the scars included in this study fulfilled the definition for MI at DE-MRI [18]. The high prevalence of UMI scars in an elderly unselected population was an unexpected finding and, as most of these scars are small (mean estimated weight, 2.5 g), its pathological significance is unclear.

Earlier knowledge from the PIVUS study has shown that patients with UMI have lower left ventricle ejection fraction (EF) and higher left ventricular mass than the participants with no myocardial scars [5]. Nevertheless, the patients with UMI scars did not differ from the participants without myocardial scars in terms of prevalence of significant atherosclerosis at whole-body MR angiography or in terms of Framingham’s risk score [19]. Although it is known that lower EF is related to a poor cardiovascular prognosis [20], it was still unclear whether the finding of low EF in these patients with UMI scars was an isolated finding or whether it was of clinical significance. Richards et al. [20] had shown that NT-proBNP and left ventricle EF were independent predictors of adverse events after a MI. In their study it is also stated that the combination of both indicators yields a better risk stratification than either of the indicators used alone.

The primary aim of this study was to investigate whether NT-proBNP (in addition to EF) differed in the UMI scar group compared with normal participants. The second aim was to compare whether TnI differed between the UMI group and normal group.

Methods
Image procedure
Imaging was performed using a 1.5 Tesla MRI scanner (Gyrosan Intera, Philips Medical Systems, Best, The Netherlands) with a 25 mT/m gradient system. Whole-body MRI was first performed after injection of 40 ml of gadolinium-diethylenetriamine penta-acetic acid bis-methylamide [21]. Cardiac MRI was then performed using a five-element phased-array cardiac coil (Philips Medical Systems) with the patient in a supine position. Images were acquired in end diastole, during breath holding in expiration, and using vector electrocardiography for retrospective gating. Survey scans were followed by delayed-enhancement images using a three-dimensional inversion recovery gradient echo sequence covering the entire heart in the short-axis and three long-axis views (2, 3, and 4-chamber views). The mean post contrast time was 33.7 min (maximum 64 min). The imaging parameters were as follows: shortest repetition time and echo time, approximately 4 and 1.2, respectively, flip angle of 15°, inversion time adjusted individually to null normal myocardium, gating factor 1, slice thickness of 10 mm with a 5 mm overlap and an in-plane resolution of 1.56 × 2.81 mm.

Image analysis
Image analysis was carried out on a workstation (Philips Medical Systems, Nederland, Best, The Netherlands) using the commercially available software (View Forum R 4.1 V1L2, Philips Medical Systems).

A MI scar in DE-MRI was defined as delayed enhancement, involving the subendocardial layer, visible in the short axis and in at least one long-axis view [18]. The myocardium showing delayed enhancement was manually outlined and total MI mass was calculated assuming a myocardial density of 1.05 g/ml [22].

Study population
The study population consisted of 259 unselected participants from the primary PIVUS study population who, after the approval from the local ethics committee, were consecutively invited to undergo additional cardiac MRI directly after whole-body MR angiography. The population eligible for the primary investigation in the PIVUS study included all participants aged 70 years and resident in the county of Uppsala, Sweden. The population included in the PIVUS study is described elsewhere [23].

Eleven cardiac MR examinations were excluded because of poor quality, leaving a study population of 248 participants (49.6% women). The mean age in this population, at the time of image acquisition, was 71 years and 6 months. All participants gave written informed consent.

In the primary investigation of the PIVUS study, all participants answered a questionnaire about their medical and drug histories. At inclusion, a venous blood sample was collected and stored for future analysis.

Medical records from Uppsala University Hospital were searched retrospectively for cardiovascular diagnosis. Participants were divided into three groups according to the findings from DE-MRI and their medical history.

Participants with no MI scar were classified as ‘no-MI’ (n = 188); patients with a MI scar and no earlier history of MI were included in the UMI group (n = 49); patients with a MI scar and a hospital diagnosis of MI were included in the RMI group (n = 11). Representative images of each group are shown in Fig. 1. Women represented 53% of the no-MI group (n = 99); 45% of the UMI group (n = 22); and 18% of the RMI group (n = 2). The RMI group had a higher prevalence of hypertension, hypercholesterolemia, diabetes, and a higher Framingham score than the participants with no scars did [5,19]. The UMI group had no difference in prevalence of risk factors compared either
with the no-MI or with the RMI group. The background characteristics of the study population are summarized in Table 1 and have been published earlier [5].

**Laboratory analysis**

Plasma levels of NT-proBNP and cTnI were determined from the frozen samples collected at the time of the primary investigation in the PIVUS study. The mean time between the primary investigation and the cardiac MRI was 16 months (range 3–22 months).

NT-proBNP was determined by sandwich immunoassay on an Elecsys 2010 instrument (Roche Diagnostics, Mannheim, Germany). The intraassay and interassay coefficients of variations were less than 4%. Plasma levels of cTnI were determined after blood sample collection with an improved version of the Access AccuTnI assay (Beckman Coulter, Fullerton, California, USA). The lowest concentration measurable with a coefficient of variation of less than 10% was 0.014 mg/l and the lowest concentration measurable with a coefficient of variation of less than 20% was 0.008 mg/l. Determination of NT-proBNP and cTnI values was blinded to the clinical history and MRI data of the patient.

**Statistical methods**

Statistical analyses were carried out with the statistical software, Statistica version 8.0 (StatSoft Inc., Tulsa, Oklahoma, USA).

Cut-off points suggested in the literature were used for the analysis of frequency distribution of NT-proBNP (386 ng/l) [24] and cTnI (0.01 mg/l) [25] within each group. There was one extreme outlier with 8943 ng/l of NT-proBNP, which corresponded to a male in the UMI group. To test whether the conclusions of the study were still valid without this patient, analysis of variance tests were calculated without this outlier. A natural logarithm was applied to the values of NT-proBNP. The analysis of variance test was applied for comparison of NT-proBNP among the three groups. cTnI was used as a dichotomized variable applying 0.01 mg/l as a threshold and a χ² test compared the levels in the three groups. A Spearman correlation test was carried out between volume of the MI scar and NT-proBNP. A multiple regression analysis tested the influence of sex, renal function, MI group (UMI/RMI), left ventricle mass, volume of the MI scar, and EF in the plasma level of NT-proBNP. Statistical significance was set at a P value of less than 0.05.

**Results**

Plasma levels of the biomarkers were available for all patients included in this study. The median plasma value of NT-proBNP in the no-MI group was 94.9 ng/l (25th–75th percentiles; 59.2–144.2). The UMI group had a median value of 140.2 ng/l (79–225.5 ng/l) and the RMI group had a median value of 310.4 ng/l (122.6–446.5 ng/l).
The median value of cTnI was 0.007 mg/l (25th–75th percentiles; 0.005–0.01) in the no-MI group, 0.008 mg/l (0.006–0.14) in the UMI group, and 0.01 mg/l in the RMI group (0.007–0.015). Forty-four participants (23%) in the no-MI group had cTnI values higher than 0.01 mg/l, 16 patients (33%) in the UMI group had cTnI values higher than 0.01 mg/l, and three patients (27%) in the RMI group had cTnI values higher than 0.01 mg/l. No difference was found in TnI values among the three groups (P = 0.41).

### Discussion

This study showed that patients with a UMI scar detected by DE-MRI had higher plasma values of the cardiac biomarker NT-proBNP and no difference in the levels of cTnI than the participants without a myocardial scar. NT-proBNP is a cardiac biomarker for heart failure and many studies show that NT-proBNP is a powerful and independent predictor of cardiovascular mortality [26–28]. In the PIVUS study population, patients with UMI scars do not differ from the general population without scars in terms of signs of ischemia on the ECG or traditional risk factors for cardiovascular disease (Table 1) [5]. Conversely, the group with RMI scars shows differences in these clinical variables. Patients with UMI scars only differ from the normal participants in having lower left ventricle EF and higher left ventricular myocardial mass. It is known from the literature that the EF is inversely correlated with the plasma levels of NT-proBNP [29]. In this study, the aim was not to revalidate this relation but rather to confirm that the low EF in the UMI scar was not an isolated statistical finding. There is also evidence [20] that the combination of NT-proBNP and left ventricle EF measurements yields a better risk stratification for major adverse events after a MI than either of the indicators used alone. Therefore, the purpose of this study was to assess whether UMI scars were associated with increased levels of cardiac biomarkers that would strengthen the finding that these scars are

### Table 1  Characteristics of the study population (n=248)

<table>
<thead>
<tr>
<th></th>
<th>No-MI</th>
<th>No-MI vs. UMI</th>
<th>UMI</th>
<th>UMI vs. RMI</th>
<th>RMI</th>
<th>RMI vs. no-MI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of participants</td>
<td>188</td>
<td>49</td>
<td>11</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Females</td>
<td>99 (53%)</td>
<td>NS</td>
<td>22 (45%)</td>
<td>NS</td>
<td>2 (18%)</td>
<td>NS</td>
</tr>
<tr>
<td>Risk factors</td>
<td></td>
<td></td>
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<tr>
<td>Hypertension</td>
<td>137 (72.9%)</td>
<td>NS</td>
<td>35 (71.4%)</td>
<td>NS</td>
<td>9 (81.8%)</td>
<td>*</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>103 (54.8%)</td>
<td>NS</td>
<td>25 (51.0%)</td>
<td>NS</td>
<td>7 (63.6%)</td>
<td>*</td>
</tr>
<tr>
<td>Diabetes</td>
<td>19 (10.1%)</td>
<td>NS</td>
<td>8 (16.3%)</td>
<td>NS</td>
<td>4 (36.4%)</td>
<td>*</td>
</tr>
<tr>
<td>Current smoking</td>
<td>13 (6.8%)</td>
<td>NS</td>
<td>4 (8.2%)</td>
<td>NS</td>
<td>2 (18.2%)</td>
<td>NS</td>
</tr>
<tr>
<td>Cardiac morbidity</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Angina pectoris</td>
<td>7 (4%)</td>
<td>NS</td>
<td>3 (6%)</td>
<td>*</td>
<td>5 (45%)</td>
<td>*</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>1 (0.5%)</td>
<td>NS</td>
<td>1 (2%)</td>
<td>NS</td>
<td>2 (18%)</td>
<td>*</td>
</tr>
<tr>
<td>Findings</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pathological ECG Q-wave</td>
<td>7 (4%)</td>
<td>NS</td>
<td>3 (6%)</td>
<td>*</td>
<td>5 (45%)</td>
<td>*</td>
</tr>
<tr>
<td>Mean MI scar weight (in MRI; g)</td>
<td>-</td>
<td>-</td>
<td>2.482</td>
<td>*</td>
<td>9.319</td>
<td></td>
</tr>
<tr>
<td>Mean ejection fraction (in MRI; %)</td>
<td>72</td>
<td>*</td>
<td>68</td>
<td>NS</td>
<td>64</td>
<td>*</td>
</tr>
<tr>
<td>Mean left ventricle mass/BSA (g/m²)</td>
<td>58</td>
<td>*</td>
<td>63</td>
<td>*</td>
<td>84</td>
<td>*</td>
</tr>
</tbody>
</table>

BSA, body surface area; ECG, electrocardiogram; MI, myocardial infarction; MRI, magnetic resonance imaging; NS, no significant difference; RMI, recognized myocardial infarction; UMI, unrecognized myocardial infarction.

*Significant difference (P < 0.0167; i.e. 0.05 with Bonferroni correction).
a real pathological change in the myocardium and might have clinical impact in the outcome of these patients. Recent studies [7,8] show that UMI scars yield an increase risk for further cardiovascular adverse events, but these studies were conducted in patients with clinical suspicion of coronary heart disease, and the prognosis of UMI scars in the general population is still unknown. Our study is also the first to correlate the existence of a UMI scar with the plasma levels of NT-proBNP.

The UMI group expressed higher levels of NT-proBNP and equivalent levels of cTnI than the normal participants. NT-proBNP is dependent on sex and renal function and correlates with left ventricle EF and myocardial mass [30]. After adjusting for these known predictors of NT-proBNP level in the multiple variable analysis, the volume of the MI scar was still an independent variable and could explain a part of the plasma level. In this study, EF was not an independent predictor of NT-proBNP in the multiple regression models, although the $P$ value was close to significance. This might be explained by the small sample of patients with myocardial scars ($n = 60$) or by a small variation between the lowest and highest values of EF, having few patients with more pronounced depression of EF. Even if the EF had been significant, this would explain a lower amount of NT-proBNP plasma level than myocardial scar volume. The significance of the myocardial scar volume was achieved independently of the EF level or of being a UMI or RMI scar and means that even small UMI scars affect the left ventricle fibers in a way likely not related to its contraction and originating release of the NT-proBNP hormone into the blood circulation.

The primary interest was to assess differences in the NT-proBNP and cTnI levels between the UMI and the no-MI group, as the interest was focused on whether patients with a UMI scar have an increased risk of an adverse outcome than the normal participants. Nevertheless, data from the RMI group were added to the analysis to assure reliability of the measurements, given that it has been proven that patients with RMI have increased values of these cardiac biomarkers [31,32]. One extreme outlier, with a plasma level of NT-proBNP of 8943 ng/l and a part of the UMI group, was excluded from the analysis to avoid one patient leading to the false conclusion that NT-proBNP in the UMI group was higher than in the no-MI group.

High values of NT-proBNP are associated with an increased risk of nonfatal end points, such as progressive heart failure and MI [12], and with an increased risk of death. The patients with DE-MRI-detected UMIs possibly represent a new group of patients that do not have higher prevalence of cardiovascular risk factors or indicators of myocardial ischemia, but might have a higher risk than the general population for further cardiovascular events.

TnI is usually used to detect acute MI, but a recent report [17] also correlates increased levels of this biomarker in the prediction of future cardiovascular events and death in men free from cardiovascular disease at the baseline. This study highlights the importance of silent myocardial injury in the development of coronary heart disease. In this study there was no difference in the levels of cTnI among the three groups, albeit higher levels in the RMI group.

Even though the measurement of cTnI was done with an improved version of the Access AccuTnI assay (Beckman Coulter) and the assay provides considerably improved analytical sensitivity at the lower end of its range, a limitation of the study is that some degree of uncertainty remains regarding the accuracy of very low cTnI results. Nevertheless, dichotomization in applying cTnI (0.01 mg/l) as a threshold did not result in considerably different results.

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

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### Table 2  Multiple regression model with natural logarithm (NT-proBNP) as dependent variable and sex, renal function, MI group (UMI/RMI), left ventricle myocardial mass adjusted for body surface area, and myocardial infarction scar volume as independent variables

<table>
<thead>
<tr>
<th>Predictor</th>
<th>$P$ value</th>
<th>Coefficient</th>
<th>95% lower interval</th>
<th>95% upper interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>0.001</td>
<td>0.843</td>
<td>0.344</td>
<td>1.343</td>
</tr>
<tr>
<td>Renal function: creatinine (mmol/l)</td>
<td>0.249</td>
<td>0.007</td>
<td>-0.005</td>
<td>0.019</td>
</tr>
<tr>
<td>MI group (UMI/RMI)</td>
<td>0.191</td>
<td>0.409</td>
<td>-0.211</td>
<td>1.028</td>
</tr>
<tr>
<td>Left ventricle myocardial mass/BSA (g/m$^2$)</td>
<td>0.986</td>
<td>$-1.16 \times 10^{-4}$</td>
<td>-0.014</td>
<td>0.013</td>
</tr>
<tr>
<td>MI scar volume (%)</td>
<td>0.034</td>
<td>0.087</td>
<td>0.007</td>
<td>0.166</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>0.051</td>
<td>-0.022</td>
<td>-0.044</td>
<td>$1.11 \times 10^{-4}$</td>
</tr>
</tbody>
</table>

BSA, body surface area; MI, myocardial infarction; NT-proBNP, N-terminal pro-brain natriuretic peptide; RMI, recognized myocardial infarction; UMI, unrecognized myocardial infarction.
during the MR examination was treated as a myocardial history of events. These scars have been shown to correlate to EF earlier, acquired simultaneously during the MR examination, and now also to NT-proBNP measured at a different time point. From this study, it cannot be concluded which came first, the myocardial scar or the decreased left ventricle function. Therefore, the reason for increased levels of this biomarker in patients with UMI scars can only be speculated.

Conclusion

Patients with UMI scars detected by DE-MRI have increased plasma levels of NT-proBNP, supporting the hypothesis that these MR-detected UMI scars might carry an increased risk of future cardiovascular adverse events. At present, all participants enrolled in this study are being invited to a 5-year follow-up, which will determine the risk of major adverse cardiovascular events and consequently, the clinical importance of UMI scars detected by DE-MRI.

Acknowledgements


References


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