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Small and large vessel disease in persons with unrecognized compared to recognized myocardial infarction: The Tromsø Study 2007–2008

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ABSTRACT

Background: Unrecognized myocardial infarction (MI) is a frequent condition with unknown underlying reason. We hypothesized the lack of recognition of MI is related to pathophysiology, specifically differences in underlying small and large vessel disease.
Methods: 6128 participants were examined with retinal photography, ultrasound of the carotid artery and a 12 lead electrocardiography (ECG). Small vessel disease was defined as narrower retinal arterioles and/or wider retinal venules measured on retinal photographs. Large vessel disease was defined as carotid artery pathology. We defined unrecognized MI as ECG-evidence of MI without a clinically recognized event. We analyzed the cross-sectional relationship between MI recognition and markers of small and large vessel disease, adjusted for age and sex.
Results: Unrecognized MI was present in 502 (8.2%) and recognized MI in 326 (5.3%) of the 6128 participants. Compared to recognized MI, unrecognized MI was associated with small vessel disease indicated by narrower retinal arterioles (OR 1.66, 95% CI 1.05–2.62, highest vs. lowest quartile). Unrecognized MI was less associated with wider retinal venules (OR 0.55, 95% CI 0.35–0.87, lowest vs. highest quartile). Compared to recognized MI, unrecognized MI was less associated with large vessel disease indicated by presence of plaque in the carotid artery (OR for presence of carotid artery plaque in unrecognized MI 0.51, 95% CI 0.37–0.69). No significant sex interaction was present.
Conclusions: Unrecognized MI was more associated with small vessel disease and less associated with large vessel disease compared to recognized MI. These findings suggest that the pathophysiology behind unrecognized and recognized MI may differ.

1. Introduction

Unrecognized myocardial infarction (MI) constitutes a significant proportion of all MI's in men and women and is associated with a similar risk of death and recurrent MI as recognized MI [1–5]. A possible contributor to the lack of recognition of MI is differences in pathophysiology between unrecognized and recognized MI.

It is well-established that recognized MI is primarily an epicardial or large vessel event caused by plaque rupture and thrombus formation with occlusion and eventual scarring of the myocardium [6]. However, there is an increasing body of evidence supporting coronary microvascular disease to be a well-defined condition that may occur independently of, coexist with or predate coronary large vessel disease [7–9]. Further, coronary small and large vessel disease may differ with regards to symptoms and pathophysiological mechanism. Previous studies of recognized and unrecognized MI suggest the presence of underlying differences in vascular pathophysiology. Unrecognized MI's are smaller [10,11], show less regional wall motion abnormalities [12], have a different distribution of location than recognized MI [13] and manifest lower coronary calcium score [14] compared to recognized MI's. Echocardiographic global dysfunction is of prognostic importance in unrecognized MI even in the absence of regional dysfunction [15], suggesting a more

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diffuse disease. Also, silent positive exercise testing in persons with normal coronary arteries is associated with coronary microvascular dysfunction [16], suggesting an association between small vessel disease and less symptomatic myocardial ischemia. Women have a larger proportion of unrecognized MI's [3,5] and coronary microvascular dysfunction seems to be more prevalent in women compared to men [17]. To our knowledge, no previous study has investigated the association between small and large vessel disease and MI recognition.

A close relationship between carotid artery atherosclerosis and intima media thickness, or large vessel disease, and recognized MI is well established [18–20] and carotid artery atherosclerosis is widely used as a surrogate marker for cardiovascular disease. Coronary microvascular dysfunction, or small vessel disease, is a disorder of impaired coronary blood flow in the absence of significant epicardial coronary artery (large vessel) disease [17]. Retinal vessels have the same size as the coronary microvasculature [21], and retinal vessel caliber has been proposed as a surrogate measure of the coronary microcirculation [22].

We examined the association between small and large vessel disease and recognition of MI in the Tromsø Study, a large population-based health study in Tromsø, Norway. We hypothesized the lack of recognition of MI is related to pathophysiology, specifically differences in underlying small and large vessel disease.

2. Methods

2.1. Study population

The Tromsø Study is a population-based study conducted in the municipality of Tromsø, Norway, initiated in 1974. The population consists of predominantly Caucasians. The design of the study includes repeated health surveys. We used a cross-sectional design and participants from the sixth survey in 2007–08, which consisted of two visits. Total birth cohorts and random samples of birth cohorts were invited to the first visit, and 12,984 (66%) attended [23]. Those eligible for the second visit were first-visit participants in the age groups 50–62 years and 75–84 years, a 20% random sample in the age group 63–74 and participants who also had attended the second visit of the 1994 Tromsø 4 survey and who were and who were younger than 75 years. A total of 7307 (91.8%) of those invited to the second visit attended, and 6199 participants were examined with resting 12 lead ECG. We excluded 71 participants because of ECG issues: 26 ECGs had pathologic non-MI Q waves due to altered conduction (e.g. left bundle branch block and Wolff-Parkinson-White syndrome) or ventricular enlargement; 20 ECGs were uncodable (e.g. pacemaker rhythm or missing leads); and 25 ECGs were not available for manual review (ECG files were missing), which left 6128 participants with valid ECGs. Retinal photography was performed in a total of 6540 persons and ultrasound examination of the carotid artery was performed in 7084 participants. According to the definitions described below, our population consisted of 5300 participants with no prior MI and 828 participants with prior recognized MI (326) and unrecognized MI (473 detected by ECG and 29 with MI registry diagnosis of silent MI). We excluded the 5300 participants with no prior MI from our main analyses. Of the 828 participants with a prior MI, 17 participants had missing data on carotid ultrasound and 124 participants had missing data on retinal vessel caliber measurements. They were excluded from the analyses of retinal vessel caliber and carotid plaque respectively. Fig. 1 shows a flow diagram of the study population and final sample. All participants of the Tromsø Study gave informed, written consent to research. The Tromsø Study is approved by the Regional Ethical Committee.

2.2. Data collection

Baseline information on traditional cardiovascular risk factors was obtained by self-reported questionnaires and physical examinations. Blood pressure was measured using an automated device (Dinamap, GE Healthcare, USA). The cuff was adjusted according to arm circumference, and the blood pressure was measured 3 times in a seated position at 1-min intervals and after a 2-min rest [13]. Non-fasting blood samples were collected. Information on first-ever MI is registered in the Tromsø Study MI registry for all participants of the Tromsø Study, identified by linkage to the electronic patient records of the University Hospital of North Norway. Admissions to other hospitals are infrequent as the nearest hospital is >200 km from Tromsø. Each in- and out-of-hospital event was reviewed and adjudicated by persons with medical expertise based on local hospital records [23].

2.3. The ECGs

A 12 lead resting ECG was recorded using a computer-based electrocardiograph (Cardiovit AT-104 PC, Schiller AG, Baar, Switzerland). We used a computer-based algorithm to extract all ECG's with a Q-wave of amplitude ≤ −0.1 mV and duration ≥0.02 s in any lead. Two trained authors (A.M.Ø and H.L.) independently assessed all extracted ECGs. Disagreement was resolved after discussion with an expert cardiologist (H.S.).

We used the Third universal definition of MI [24] to define prior MI on the ECG as i) any Q wave in leads V2-V3 ≥ 0.02 s or QS complex in leads V2 and V3; ii) Q wave ≥0.03 s or QS complex in in any two leads of a contiguous lead grouping (I, aVL; V1-V6; II, III, aVF); or iii) R wave ≥0.04 s in V1-V2 and R/S ≥ 1 with a concordant positive T wave in absence of conduction defect. We defined a Q wave as a negative deflection on the ECG with amplitude ≥0.1 mV without any initial positive QRS deflection. We defined a QS wave as a negative deflection on the ECG with amplitude ≥0.1 mV without any positive deflection in the QRS complex.

2.4. Unrecognized and recognized MI

We defined participants with unrecognized MI as i) those with findings of prior MI on the ECG in Tromsø 6 without any clinical event in the MI registry or self-reported MI, or ii) a MI registry diagnosis of silent MI (diagnosed incidentally, or during work-up for symptoms such as dyspnea, tiredness and swollen ankles, defined as no history of clinical event combined with findings consistent with previous MI on ECG echocardiography, or radionuclide angiography). We defined participants with recognized MI as those with a recognized MI in the MI registry.

2.5. Retinal microvascular assessment

Retinal photography was performed in both eyes with a Visucam PRONM [Carl Zeiss Meditec (CZM)] digital retinal camera 10–45 min after application of tropicamide. Five field's 45° color retinal photographs with resolution 2196·1958 pixels were taken using the camera preset internal fixation. Vessel caliber was measured in one eye, the right eye if eligible, otherwise the left, computer assisted on the disc-centered images with IVAN software, the updated version of Retinal Analysis (Fundus Reading Center, University of Wisconsin, Madison, WI, USA). For each image, the vessels coursing through the area of one-half to one disc diameter from the optic disc were measured and the 6 biggest of each vessel type were summarized as the central retinal artery equivalent (CRAE) and the central retinal vein equivalent (CRVE)[25].

2.6. Carotid artery ultrasound

High-resolution B-mode ultrasonography was performed with a GE Vivid 7 duplex scanner equipped with a 12 MHz linear transducer. Due to logistic reasons, only the right carotid artery was scanned. The far and near walls of the right common carotid artery (CCA), the bifurcation (bulb) and the internal carotid artery (ICA) were scanned for the presence of plaque. A plaque was defined as a localized protrusion into the vessel lumen with thickening of the vessel wall of >50% compared to the adjacent carotid intima media thickness. The area of each plaque was outlined manually with automatic calculation of plaque area. Total plaque area was calculated as the sum of all plaque areas. Intima–media thickness was measured in the near and far walls of the distal common carotid artery and in the far wall of the carotid bifurcation on three separate images from each site. The average of the mean from each of the three sites are presented as the mean IMT. [26].

2.7. Selection and modeling of potential confounders

We selected age, sex, hypertension, diabetes, cholesterol and smoking as potential confounders for the associations between MI recognition and small and large vessel disease. Age, diabetes and female sex have previously been reported to be associated with increased risk of unrecognized MI [1,27]. Age [9,28] and diabetes [29] is associated with both small and large vessel disease. Diabetes was defined as HbA1 ≥ 6.5% or use of anti-diabetic medication. Hypertension is one of the main predictive factors for unrecognized MI [27,30], and is also a risk factor for small [31] and large [32] vessel disease. We modeled hypertension (defined as systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg or use of antihypertensive medication) as a dichotomous variable. Smoking affects pain sensitivity [33], which again was demonstrated to be associated with MI recognition [34] and is also associated with small [35]and large [32] vessel disease. Smoking was self-reported and defined as current daily smoking (yes/no). Cholesterol is associated with increased risk of unrecognized and recognized MI [30] as well as large [20] and small [36] vessel disease. We included total serum cholesterol and current use of cholesterol lowering drugs (yes/no) in the multivariable adjusted model.

2.8. Statistical analyses

We calculated descriptive statistics for participants with no MI, unrecognized MI and recognized MI, using Pearson's chi square to compare categorical variables and *t*-test to compare continuous variables between unrecognized and recognized MI.

We used logistic regression to assess the relationship between MI recognition and retinal vessel caliber, carotid plaque and intima media thickness. The dependent variable was MI recognition, modeled as a binary variable (recognized = 0 and unrecognized = 1). We modeled retinal vessel caliber as quartiles and as continuous variables, per 10 μm change. We modeled presence of carotid plaque as a binary variable. We also categorized participants with carotid artery plaque into quartiles based on total plaque area. Intima media thickness was modeled as a continuous variable, per 1 mm increase. Analyses were adjusted for age and sex. Multivariable analyses were adjusted for age, sex, hypertension, diabetes, cholesterol and smoking habits. We performed sex stratified analyses and examined interactions by adding cross-product terms of sex and retinal vessel caliber, plaque present, total plaque area and intima media thickness to the multivariable models.