Incremental prognostic value of coronary and systemic atherosclerosis after myocardial infarction☆☆☆

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A R T I C L E   I N F O

Article history:
Received 24 October 2017
Received in revised form 18 January 2018
Accepted 9 February 2018

Keywords:
Atherosclerosis
Myocardial infarction
Coronary artery disease
Extra-cardiac artery disease
Prognosis

A B S T R A C T

Background: The role of systemic atherosclerosis in myocardial infarction (MI) patients is not fully understood. We investigated the incremental prognostic value of coronary and systemic atherosclerosis after acute MI by estimating extra-cardiac artery disease (ECAD) and extent of coronary atherosclerosis.

Methods and results: The study included 544 prospective MI patients undergoing coronary angiography. For all patients, the longitudinal coronary atherosclerotic extent, expressed as Sullivan extent score (SES) was calculated. In addition, the patients underwent non-invasive screening for ECAD in the carotid, aortic, renal and lower limb. SES was found to be associated with ECAD independent of baseline clinical parameters [adjusted odds ratio (OR) 1.04 95% confidence interval (CI) 1.02–1.06, P < 0.001]. Extensive systemic atherosclerosis, defined as the combination of extensive coronary disease (SES ≥17) and ECAD, was associated with higher risk for all-cause mortality compared to limited systemic atherosclerosis (SES < 17 and no ECAD) (hazard ratio [HR] 2.9 95% CI 1.9–4.5, P < 0.001, adjusted for Global Registry of Acute Coronary Events risk score parameters 1.8, 95% CI 1.1–3.0, P = 0.019). The risk for the composite endpoint of cardiovascular death or hospitalization was significantly higher in patients with extensive systemic atherosclerosis compared to patients with limited systemic atherosclerosis (HR 3.1, 95% CI 2.1–4.7, P < 0.001, adjusted HR 1.9, 95% CI 1.2–3.1, P = 0.004).

Conclusions: Visual estimation of the longitudinal coronary atherosclerotic extent at the time of MI predicts ECAD. Coexistence of extensive coronary disease and ECAD defines a group with particularly poor prognosis after MI.

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1. Introduction

Coronary artery disease may lead to myocardial infarction (MI), a major killer worldwide [1], but atherosclerosis in coronary arteries may also indicate disease in other vascular beds [2]. Angiographic findings in MI are heterogeneous, ranging from normal to severe disseminated atherosclerosis in all coronary vessels [3]. There is an association between severity of coronary disease and both prognosis [4] and the presence and severity of extra-cardiac atherosclerotic disease (ECAD, in our study defined as significant atherosclerotic disease one or more of the carotid, aortic, renal or lower limb arteries) [2,5]. Systemic atherosclerosis [lesions in multiple arterial beds] is associated with poor cardiovascular prognosis [5], but less is known about the post-MI prognostic impact of the combined coronary and extra-cardiac atherosclerosis burden. The main objective of this study was to examine the incremental prognostic value of coronary and systemic atherosclerosis after MI.

The widely used coronary scoring system describing number of significantly diseased coronary vessels is a simple, yet powerful predictor of prognosis [6] but information of the longitudinal atherosclerotic extent and diffuse dissemination of coronary disease is discarded. We hypothesized that a simple scoring system based on coronary angiographic longitudinal extent would be helpful in identifying patients with systemic atherosclerosis, potentially impacting prognosis and with possible implications for preventive and therapeutic measures.

In a prospective cohort study, we used a combination of data from angiographic coronary scoring and non-invasive assessment of ECAD...
at the time of MI to determine the association between longitudinal atherosclerotic extent in the coronary arteries and ECAD, and to evaluate the correlation between systemic atherosclerotic burden and prognosis.

2. Methods

2.1. Study population

The study was prospective and part of the Västmanland Myocardial Infarction Study (VaMIS) (ClinicalTrials.gov Identifier NCT 01452178). From November 2005 to May 2011, patients ≥18 years of age, admitted to the coronary care unit of Västmanland County Hospital, Västerås, Sweden were screened for participation. Inclusion criteria were a diagnosis of MI by electrocardiogram and a troponin I level ≥ 0.4 μg/l as the biomarker criterion [7]. The study complied with the Declaration of Helsinki. The regional ethical review board of Uppsala, Sweden, approved the study (protocol number 2005:168). All subjects provided written informed consent.

2.2. Baseline data

Medical history and lifestyle factors were assessed by questionnaire on day 2 to 4 following diagnosis of MI. Hypertension, hyperlipidaemia, diabetes mellitus, and prior MI were defined as history of physician-diagnosed disease. An additional follow-up interview was conducted with subjects who had provided incomplete data. Blood pressure and resting heart rate were measured between day 4 and 7. Systolic and diastolic blood pressure was measured twice in each arm with the patient sitting.

2.3. Extent of coronary atherosclerosis

All patients with an available coronary angiogram recorded for clinical reasons during the index hospitalization were included in analyses. Coronary angiograms for patients referred to a secondary hospital for angiography were, for logistical reasons, not available for this study. The longitudinal extent of coronary atherosclerosis was determined by systematic evaluation of coronary angiographies. We used the Sullivan extent score (SES) method [8] based on visual estimation. This score was designed to reflect the extent of endothelial surface involved in atheroma and has a superior correlation to cardiovascular risk factors than does scoring based on stenosis severity [8]. In brief, the coronary arterial tree was divided into 15 segments according to American Heart Association definitions [9]. The extent of coronary disease in each segment was determined based on information synthesized and available in all angiograms. All native coronary segments were included in the analysis, including segments filled with contrast via collateral vessels or through coronary bypass grafts. Coronary arteries <1 mm in diameter were not included in the analysis. Coronary atherosclerosis was defined as irregularities of ≥20% of total lumen diameter. For each segment, we visually estimated the longitudinal extent of atherosclerosis as a percentage. An occlusion within a segment counted as at least 50% longitudinal atherosclerosis, and atherosclerotic extent was then determined in the remaining, non-occluded, portion of the segment, hence the total extent of atherosclerosis would range from 50 to 100% in an occluded segment. The segment percentage of longitudinal atherosclerosis was multiplied by a factor representing the surface area of the studied segment relative to the entire coronary arterial tree. The left main coronary artery accounted for 5%, the left anterior descending artery 35%, the left circumflex artery 35%, and the right coronary artery 30% according to the SES definition, so that the entire angiogram would confer a total SES value in the range 0 to 100.

All coronary angiograms were examined by an experienced invasive cardiologist or an experienced and specifically trained cardiac nurse. The investigation team was blind to the patient’s clinical data. Five percent of the angiograms were examined by two investigators to calculate inter-observer variabilities. We calculated the median SES for all subjects, and defined limited longitudinal coronary disease as SES < the median value and extensive longitudinal coronary disease as SES ≥ the median value.

2.4. Laboratory data

Blood samples were drawn at hospital admittance. Troponin I was assessed on two additional occasions during the first 24 h of hospitalization. Haemoglobin, Ca, calcium, N-terminal pro-B-type natriuretic peptide, and total cholesterol, triglycerides, and low and high density lipoproteins were measured within 3 days of hospital admission.

2.5. Physiology

Echocardiography and vascular ultrasound were performed within 25 days of enrolment in the study. Left ventricular ejection fraction (LVEF) was assessed according to the Simpson formula [10] when image quality permitted, or otherwise visually estimated. Vascular ultrasound of the carotid artery, infra-renal aorta, and renal arteries was performed by one of three experienced vascular technicians blinded to patient clinical history. If adequate visualization or pulsed Doppler flow measurement of a vessel segment could not be non-invasively obtained, the examination was classified as non-diagnostic at the segment level. Significant carotid artery stenosis was defined as presence of plaque in the internal carotid artery resulting in reduction of the lumen diameter in combination with flow turbulence in the colour flow Doppler and a spectral Doppler peak systolic velocity ≥ 1.5 m/s, defined as at least moderate stenosis or no detectable flow, corresponding to occlusion [11]. Significant atherosclerotic disease in the infra-renal aorta was defined as lumen diameter of <30 mm, stenosis ≥50%, or an occlusion or dissection of the abdominal aorta [12]. Significant renal artery stenosis was defined as peak systolic velocity > 1.8 m/s and renal aortic ratio > 3.5, corresponding to stenosis ≥60%, or an occluded artery [12]. To estimate lower limb arterial disease, the ankle brachial index (ABI) was calculated. Ankle systolic blood pressures in the bilateral dorsalis pedis and tibial posterior arteries were obtained by a leg cuff, an aneroid sphygmomanometer, and a hand-held Doppler instrument. ABI was calculated as the higher of the pedal artery systolic pressures divided by the higher of the brachial systolic pressures in the arms. Significant lower limb arterial disease was defined as ABI < 0.9 or > 1.4 in either limb [12,13]. ECAD was defined as significant disease in any of the examined extra-cardiac arterial beds.

2.6. Systemic atherosclerosis

We combined information of coronary atherosclerosis extent with information on ECAD to define groups with extensive, moderate, or limited systemic atherosclerosis. Extensive systemic atherosclerosis was defined as extensive coronary disease (SES ≥ median) plus ECAD. Moderate systemic atherosclerosis was defined as either extensive coronary artery disease or ECAD. Limited systemic atherosclerosis was defined as limited coronary artery disease (SES < median) and no ECAD.

2.7. Registry data

Based on a Swedish citizen’s unique 10-digit personal identification number, follow-up data on survival, emigration, and date of death until 9th of March 2017, were obtained by linking the study database to the comprehensive Swedish National Population Registry. Information on hospitalization for cardiovascular disease and cardiovascular mortality until 31th December 2015 was obtained from the Swedish National Patient Register and the Cause of Death Register. Cardiovascular disease was defined as International Statistical Classification of Diseases and Related Health Problems (ICD) codes I21 (MI), I63 (ischemic stroke), I50 or I11 (heart failure). Cardiovascular death was defined as death caused by any diagnosis coded as ICD 100–199.

2.8. Statistical analysis

Continuous data were presented as mean ± standard deviation (SD) for approximately normally distributed data, or median and interquartile range for skewed data. Categorical variables were summarized as frequency and percentage. Differences among patient groups, defined according to level of atherosclerosis, were assessed with Student’s t-test for approximately normally distributed continuous variables, Mann–Whitney U test for heavily non-normally distributed continuous variables, and Pearson’s χ²-test for categorical variables. Inter-observer agreement of SES was estimated by calculating intraclass correlation (ICC) [14]. We used logistic regression to calculate the odds ratio (OR) for ECAD relative to SES. In the multivariable model we adjusted for sex, age, diabetes, hyper- tension, hyperlipidemia, smoking, previous percutaneous coronary intervention (PCI), and previous coronary artery bypass surgery (CABG). In addition, we adjusted for various baseline clinical characteristics with significant univariate association to ECAD. The Kaplan–Meier method was used for analysis of cumulative event rates throughout the study period. Differences were assessed with Log Rank test. Hazard ratios (HR) were calculated using the Cox proportional hazard method To evaluate the incremental prognostic value of atherosclerosis burden, we adjusted for the majority of parameters included in the Global Registry of Acute Coronary Events (GRACE) risk score 2.0 as proposed by NICE guidelines [15,16] (age, heart rate, systolic blood pressure, creatinine level, ST-segment deviation), excluding cardiac arrest at admission, were no information was available, and biomarkers for cardiac injury since positive troponin was a criterion for inclusion in the study. We did not perform multiple adjustments for risk factors were atherosclerosis is in the probable causal chain linking the risk factor to cardiovascular events. All P values were two-sided, and P < 0.05 was regarded as statistically significant. Analyses were performed with IBM SPSS Statistics 20.0 (Chicago, IL).

3. Results

Of the 1008 patients included in the VaMIS study, a coronary angiogram was available for 544. A flow chart for the inclusion in this analysis is presented in Fig. 1. The mean age was 68.5 years (SD 10.7) and 31.7% were female. Echocardiography was performed in 526 (97%). In 416 patients, LVEF was assessed according to the Simpson formula, while it was visually estimated in 110 patients. The ICC for inter-observer agreement in SES calculations was 0.89 (95% confidence interval [CI] 0.77–0.95). The median SES for all subjects was 7 (interquartile range 17). Baseline clinical parameters of subjects with limited (SES < 17) and extensive (SES ≥ 17) coronary disease are shown in Table 1. The one-year mortality rate was 7.5% (n = 22) in subjects with extensive coronary disease and 3.9% (n = 11) in the group with limited disease (P = 0.049). Mean follow-up for all-cause mortality was 7.7 years (SD 2.9). Mortality throughout the study period was 35.5% (n = 94) in the group with
extensive coronary disease and 22.2% (n = 62) in the limited coronary disease group (P = 0.001). The mean follow-up time for the composite endpoint of cardiovascular death or hospitalization for cardiovascular disease was 6.7 years (SD 3.1). The risk for the composite endpoint throughout the study period was 40.8% (n = 108) for patients with extensive coronary disease and 22.9% (n = 64) for subjects with limited disease.

The presence of most established cardiovascular risk factors was associated with significantly higher SES at time for MI compared to patients not carrying the risk factor [male sex: mean SES 19.7 SD 12.1, female sex: mean SES 16.0 SD 12.1, P = 0.001; diabetes: mean SES 21.8 SD 14.9, no diabetes: mean SES 17.9 SD 12.8, P = 0.025, hyperlipidaemia: mean SES 21.6 SD 13.7, no hyperlipidaemia: mean SES 17.0 SD 12.8, P = 0.001, hypertension: mean SES 20.9 SD 13.7, no hypertension: mean SES 16.4 SD 11.7, P = 0.001] while current smoking was associated with a lower SES than non-smoking (smokers: mean SES 19.7 SD 12.1, non-smokers: mean SES 19.2 SD 13.6, P = 0.023). We found significant positive correlation between ECAD and high SES variables (patients with ECAD: mean SES 23.6, SD 13.6, no ECAD: mean SES 15.5 SD 11.5, P < 0.001). ST elevation at admission was not associated with significantly different SES compared to patients without ST elevation.

In logistical regression analysis, SES was associated with ECAD, both unadjusted (OR 1.05, 95% CI 1.0–1.1, P = 0.001) and in a multivariable model adjusted for baseline clinical parameters (Table 2, OR 1.04, 95% CI 1.0–1.1, P = 0.001). Apart from SES, only age, hypertension and physical inactivity were independently associated with ECAD in multivariate analysis.

Cumulative mortality after MI relative to coronary atherosclerosis burden is shown in Fig. 2A. In a Cox regression analysis, the risk for all-cause mortality throughout the study period was significantly higher for patients with extensive disease compared to those with limited disease, in an unadjusted model (HR 1.8, 95% CI 1.3–2.4, P = 0.001) but not after adjustment for GRACE risk score parameters (HR 1.3, 95% CI 0.9–1.8, P = 0.20). The risk for the composite endpoint of cardiovascular death or hospitalization for cardiovascular disease was significantly associated with extensive coronary atherosclerosis (Fig. 2B, vs. patients with limited coronary atherosclerosis, unadjusted HR 2.0, 95% CI 1.5–2.7, P < 0.001, adjusted for GRACE parameters HR 1.6, 95% CI 1.1–2.3, P = 0.015).
extensive systemic atherosclerosis compared to patients with limited systemic atherosclerosis [Fig. 2D, HR 3.1, 95% CI 2.1–4.7, P < 0.001, adjusted for GRACE parameters HR 2.9, 95% CI 1.8–4.8, P < 0.001] and patients with moderate systemic atherosclerosis (unadjusted HR 2.1, 95% CI 1.4–3.0, P < 0.001, adjusted for GRACE parameters HR 1.9, 95% CI 1.2–3.1, P = 0.004).

Medications for secondary prevention prescribed at discharge did not differ significantly between the groups (Statins 96–99%, P = 0.09, Beta blockers 91–93%, P = 0.87, ACE-Inhibitor or Angiotensin receptor blocker 92–98%, P = 0.08, ASA 96–98%, P = 0.38, P2Y12 receptor blockers 88–90% P = 0.8).

4. Discussion

In this prospective cohort study, we found the longitudinal extent of coronary atherosclerosis at time of MI to predict the presence of ECAD. The combination of extensive coronary disease and ECAD defined a group with particularly poor prognosis and provides an incremental prognostic value independent of parameters used in conventional risk scoring.

In the growing and aging global population, cardiovascular mortality is increasing despite improved cardiovascular care, including primary and secondary prevention [17]. The 30-day post-MI prognosis has improved dramatically over the past two decades in Sweden, while the prognosis from 30 days to one year has not been equally reduced, despite strides in secondary prevention [18]. A possible path forward is to improve classification of MI patients, enabling a more focused secondary prevention. The often-used sub-classification of MI patients as ST elevation MI or non-ST elevation MI is important in the acute phase, but less informative for long-term prognosis [19].

Since systemic atherosclerosis is associated with a poorer prognosis than single location arterial disease, different concepts for an integrated non-invasive approach to estimate the systemic atherosclerotic burden has been proposed [20–23]. However, this increased risk has in previous retrospective studies not been reflected in greater focus on management of risk factors in patients with polyvascular disease [24,25]. In our study population we did not see any significant impact of the presence of systemic atherosclerosis on the prescribed secondary preventive therapy at discharge. Systemic atherosclerosis is not a well-defined entity with predictable progression in atherosclerotic involvement. Although the coronary vessels are the most common locations for single location arterial disease, timing and severity of atherosclerosis in other arterial beds vary [5]. Therefore, and since not all patients with coronary disease suffer from acute coronary obstruction, MI may occur early, late, or not at all in patients with systemic atherosclerotic disease probably depending on the presence and predominance of individual humoral vs local factors in the pathophysiological process leading to MI. The finding that current smoking was associated with less extensive coronary atherosclerosis at the time of MI than was non-smoking is paradoxical. However, active smoking is associated with elevated circulating levels of tissue factor and fibrinogen [26] as well as with increased platelet reactivity [27], and therefore, this finding is highlighting the impact of a vulnerable pro-thrombotic humoral state, possibly leading to MI in a relatively early stage with limited coronary atherosclerosis [28]. For this reason the optimal secondary preventive therapy in patients with and without severe systemic atherosclerosis is not necessarily similar. For example, the clinical cost/benefit calculation for dual antiplatelet therapy for longer than one year post-MI appears altered by the presence of systemic atherosclerosis [29], and the presence of systemic atherosclerosis might reinforce the indication for direct anti Xa inhibitors in secondary prevention [30]. Furthermore the effect of novel, potentially plaque-reducing, lipid-lowering agents like proprotein convertase subtilisin/kexin type 9 inhibitors might differ relative to the presence and location of extracardiac artery disease [31]. The recently published CANTOS study found that interleukin-1β inhibition with canakinumab improved cardiovascular prognosis after MI and thereby supported the inflammatory hypothesis of atherothrombosis [32]. However, directing therapy to specific high risk groups might be needed given the side effects and cost effectiveness of this novel treatment. Estimation of systemic atherosclerosis could play a part in this individual tailoring of therapy.

Although the severity of systemic atherosclerotic pathology may vary greatly among MI patients [33] initial clinical presentation may be similar, and current guidelines stratify risk based on readily accessible clinical markers such as ECG changes and biochemical evidence of myocardial necrosis as opposed to extent of systemic atherosclerotic disease [34]. When interpreting a coronary angiogram the physician will get information not only of the number of diseased vessels and possible treatment opinions but also on the diffuse longitudinal extent of disease. This collateral information is often discarded since the clinical utility is not clear. We suggest that systematic visual estimation of the longitudinal extent of coronary disease might provide valuable additional prognostic information and define a subgroup in which screening for polyvascular disease may add prognostic information, since more than one-third of the patients in this study with extensive coronary disease also exhibited ECAD. In the multivariate analysis, apart from SES, only age, hypertension and physical inactivity, were independently associated with ECAD. The possible causality chain linking physical inactivity to ECAD and poor prognosis has been discussed in a previous study from our group [35].

Several coronary artery disease scoring methods are commonly used [36]. However, the methods were designed for specific clinical purposes such as description of coronary ischemic burden (Gensini score) [37] or the risks and benefits of revascularization methods (Syntax score) [38]. We used SES, describing longitudinal coronary disease, hypothesizing that it would provide an indication of the systemic atherosclerotic burden. This method is based on visual estimates and is therefore relatively easily adopted in everyday clinical practice.

4.1. Limitations

Grading of coronary atherosclerosis was based on visual estimate of lumen irregularities rather than objective measures or direct intracoronary visualization of atherosclerotic plaques using such techniques as intravascular ultrasound, optical coherence tomography, or near-infrared spectroscopy. However, coronary angiographic scoring has shown satisfactory agreement with intravascular visualization [36]. The method used in this study resulted in close inter–observer agreement and is easily adopted in everyday clinical practice. Coronary angiograms performed in secondary hospitals were not available for analysis, which reduced the power of the study. We did not have information on all parameters used in the GRACE score; in particular, we lacked
information on resuscitated cardiac arrest. However, this is a rare event and probably infrequent among patients that were able to give informed consent for inclusion in the study. Therefore, it is unlikely that information on cardiac arrest would have altered the main results of the study.

5. Conclusions

Visual estimate of the longitudinal extent of coronary atherosclerosis at the time of MI is a significant predictor of ECAD. The combination of extensive coronary disease and ECAD is associated with particularly poor prognosis following MI and provides an incremental prognostic value over parameters used in conventional risk scoring. There may be a rationale for classifying MI patients according to extent of systemic atherosclerosis to increase accuracy of prognostic information and individualize treatment.

Acknowledgements

The authors are thankful to Prof. Göran Nilsson for work on preparation of the study and Johan Josefsson, Marja-Leena Ojutkangas, and Annika Kärnsund for essential contributions to the data collection.

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