ORIGINAL RESEARCH

Systemic Atherosclerotic Inflammation Following Acute Myocardial Infarction: Myocardial Infarction Begets Myocardial Infarction

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***Background*—**Preclinical data suggest that an acute inflammatory response following myocardial infarction (MI) accelerates systemic atherosclerosis. Using combined positron emission and computed tomography, we investigated whether this phenomenon occurs in humans.

***Methods and Results*—**Overall, 40 patients with MI and 40 with stable angina underwent thoracic 18F-fluorodeoxyglucose combined positron emission and computed tomography scan. Radiotracer uptake was measured in aortic atheroma and nonvascular tissue (paraspinal muscle). In 1003 patients enrolled in the Global Registry of Acute Coronary Events, we assessed whether infarct size predicted early (≤30 days) and late (>30 days) recurrent coronary events. Compared with patients with stable angina, patients with MI had higher aortic 18F-fluorodeoxyglucose uptake (tissue-to-background ratio 2.15±0.30 versus 1.84±0.18, $P<0.0001$) and plasma C-reactive protein concentrations (6.50 [2.00 to 12.75] versus 2.00 [0.50 to 4.00] mg/dL, $P=0.0005$) despite having similar aortic ($P=0.12$) and less coronary ($P=0.006$) atherosclerotic burden and similar paraspinal muscular 18F-fluorodeoxyglucose uptake ($P=0.52$). Patients with ST-segment elevation MI had larger infarcts (peak plasma troponin 32 300 [10 200 to >50 000] versus 3800 [1000 to 9200] ng/L, $P<0.0001$) and greater aortic 18F-fluorodeoxyglucose uptake (2.24±0.32 versus 2.02±0.21, $P=0.03$) than those with non–ST-segment elevation MI. Peak plasma troponin concentrations correlated with aortic 18F-fluorodeoxyglucose uptake ($r=0.43$, $P=0.01$) and, on multivariate analysis, independently predicted early (tertile 3 versus tertile 1: relative risk 4.40 [95% CI 1.90 to 10.19], $P=0.001$), but not late, recurrent MI.

***Conclusions*—**The presence and extent of MI is associated with increased aortic atherosclerotic inflammation and early recurrent MI. This finding supports the hypothesis that acute MI exacerbates systemic atherosclerotic inflammation and remote plaque destabilization: MI begets MI.

***Clinical Trial Registration*—**URL: https://www.clinicaltrials.gov. Unique identifier: NCT01749254. **(*J Am Heart Assoc*. 2015;4: e001956 doi: 10.1161/JAHA.115.001956)**

Key Words: 18F-fluorodeoxyglucose positron emission and computed tomography • atherosclerosis • inflammation • vulnerable plaque

Despite recent advances, prognosis following acute myocardial infarction (MI) remains poor[1–3] because of a considerable risk of recurrent infarction[4] and ischemia.[5] Such recurrent events are as likely to occur at the site of nonculprit plaques as at the site of the original culprit lesion.[6] In postmortem studies of patients dying after acute MI, there is evidence of multiple plaque-related thrombotic events: on average, 2.4 per patient.[7] Moreover, there is an increased

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An accompanying Table S1 is available at http://jaha.ahajournals.org/content/4/9/e001956/suppl/DC1

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incidence of ischemic stroke following MI (not exclusively due to embolic events), suggesting systemic and localized destabilization of remote atherosclerotic plaque.[8,9]

MI occurs predominantly as a result of acute atherosclerotic plaque rupture,[3,9–11] with inflammation believed to be a key precipitant.[10,11] Macrophages infiltrate high-risk plaque and secrete matrix metalloproteinases that weaken the fibrous cap and predispose the plaque to rupture.[10,11] Recent preclinical murine data have indicated that MI induced by coronary artery ligation causes a systemic inflammatory response that involves macrophage mobilization, a generalized increase in atherosclerotic inflammation, and accelerated plaque progression[12]; however, this phenomenon has not been observed directly in humans.

Positron emission tomography (PET) combined with computed tomography (CT) allows the in vivo assessment of atherosclerotic disease in humans. Glucose analogue 18F-fluorodeoxyglucose (18F-FDG) is taken up by cells with high metabolic requirements. It has become a widely used as a measure of acute vascular inflammation correlating with atherosclerotic macrophage burden, response to drug therapy, and symptomatic status.[13–16] Its generalized uptake within large arteries is a powerful predictor of subsequent adverse cardiovascular events.[17]

In this prospective clinical trial, we determined whether systemic atherosclerotic plaque metabolism is increased in patients with MI compared with those with stable coronary disease and whether this increase is more marked in those with larger infarctions. Furthermore, we explored whether this increase might be of clinical relevance and whether infarct size could predict recurrent early MI.

Methods

The study comprised 2 cohorts of patients: an imaging cohort, consisting of subjects with stable angina and MI, and an outcome cohort, comprising patients enrolled in the Global Registry of Acute Coronary Events (GRACE).[18]

Imaging Cohort

Subjects

Consecutive patients with acute ST-segment elevation MI (STEMI), non-STEMI,[19] and stable angina pectoris scheduled for invasive coronary angiography were recruited from the Royal Infirmary of Edinburgh, as described previously.[20] Patients with MI fulfilled the criteria for type 1 MI according to the Universal Definition of MI.[19] STEMI was defined as new ST-segment elevation at the J point in 2 contiguous leads with the following cut points: ≥0.1 mV in all leads except V_2 to V_3, for which the thresholds were ≥0.2 mV for men and ≥0.25 mV for women. Consecutive patients with stable angina pectoris were recruited if they had typical symptoms of exertional anginal chest pain, had previously documented coronary artery disease (>70% stenosis of at least 1 major epicardial coronary artery), and were scheduled for invasive coronary angiography. Patients were excluded if they had suffered an acute coronary syndrome within the previous 3 months.

Other exclusion criteria were age <50 years, insulin-dependent diabetes mellitus, women of childbearing age not taking contraception, severe renal failure (serum creatinine >250 μmol/L), known contrast allergy, and inability to provide informed consent. Studies were performed with the approval of the local research ethics committee, in accordance with the Declaration of Helsinki, and with the written informed consent of each participant.

All patients underwent a comprehensive baseline clinical assessment including evaluation of their cardiovascular risk factor profile. Blood was drawn from all participants for evaluation of plasma C-reactive protein (CRP) concentrations, which were measured using the Multigent CRP Vario assay (Archi-Tech cSystems Assay; Abbott Laboratories).

PET-CT imaging

All patients underwent PET-CT imaging of the thorax with a hybrid scanner (Biograph mCT; Siemens Medical Systems) using 18F-FDG as well as coronary calcium scoring and CT angiography of the aorta and coronary arteries.[20–22] Subjects were administered a target dose of 200 MBq 18F-FDG intravenously and subsequently rested in a quiet environment for 90 minutes. A low-dose attenuation-correction CT scan (50 mAs, 120 keV with CARE Dose 4D) was then performed, followed by PET imaging of the thorax, covering 1 PET bed for 20 minutes. Patients were asked to observe a low-carbohydrate, high-protein, and high-fat diet and to refrain from alcohol intake for at least 24 hours prior to the 18F-FDG scan to minimize cardiac uptake.

Following acquisition of the PET data, an electrocardiogram-gated breath-hold CT scan (non–contrast enhanced, 40 mAs/rotation, 120 kV; Siemens Medical Systems) was performed for calcium scoring. CT angiography was performed immediately afterward per the standardized scanning protocol.

Image analysis

Anonymized PET-CT data sets were presented in a random order on an OsiriX workstation (64 bit; version 5.5.1; OsiriX Imaging Software) to trained observers (N.V.J., A.S.) who were blinded to the patients' clinical status.[18] To aid image analysis, PET images were fused with the CT angiograms, and regions of interest were drawn around the thoracic aorta

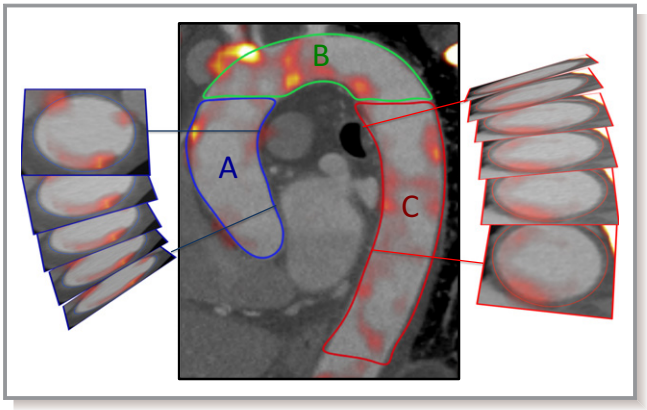

Figure 1. Measurement of radiotracer uptake in the aorta. The aorta was segmented into ascending aorta (A), arch of aorta (B), and descending aorta (C), as shown. Regions of interest were drawn around the aorta on axial slices to provide measures of radiotracer uptake.

on serial 3-mm axial slices. Within these regions, mean and maximum tracer activities were measured using standard uptake values and corrected for blood-pool activity in the superior vena cava to provide tissue-to-background ratios (TBRs).[20–24] The ascending aorta was defined as the segment of the aorta from the lower level of the right pulmonary artery up to the last slice at which the aorta maintained its circular cross-sectional appearance. The descending aorta was defined similarly as the region extending up from the tip of the diaphragm to the last circular slice. The aortic arch was defined as the region of aorta connecting the ascending and descending aortas (Figure 1). Aortic radiotracer uptake was quantified using the method of Fayad et al.[25] In brief, the following measures of uptake were measured on axial slices across the aorta as a whole and within each region: TBR_{max}, the average of the maximum TBR values measured on each axial slice; TBR_{mean}, the average of the mean TBR values measured on each slice; max TBR, the maximum uptake TBR value in any axial section; and TBR_{MDS}, the most diseased segment, defined as the highest maximal TBR value averaged over 3 consecutive slices.[25] Thirty patients were selected randomly to test the repeatability of 18F-FDG measurements in the aorta. Fifteen patients from each cohort were selected, and 2 trained readers (N.V.J., S.P.L.) quantified aortic activity independently. Activity within nonvascular tissue was assessed using oval-shaped regions of interest drawn within paraspinal muscle (area $\approx$7 cm^2) on 5 consecutive axial slices.

CT analysis was performed on a dedicated cardiovascular workstation (Vitrea; Vital Images). Vessel-specific and total Agatston calcium scores were calculated, as described previously,[21] for the coronary arteries, the aorta, and its different regions using a threshold of 130 Hounsfield units.[26]

Outcome Cohort

Full details of the GRACE methods have been published previously.[27,28] The Edinburgh cohort of the prospectively maintained GRACE database was used to identify 1003 patients admitted with an acute coronary syndrome between January 20, 2003, and June 9, 2009.[29] To be eligible, patients (aged >18 years) had to be admitted with an acute coronary syndrome as a presumptive diagnosis and had to have at least 1 of the following conditions: electrocardiographic changes consistent with acute coronary syndrome, serial increases in biomarkers of cardiac necrosis, or documented coronary artery disease. For consistency, only patients who had plasma troponin I concentrations quantified (Abbott Laboratories) in a standardized accredited laboratory were included. Exclusion criteria were secondary myocardial injury precipitated or accompanied by a significant comorbidity, trauma, or surgery. Information regarding patient demographic characteristics, medical history, timing and occurrence of acute coronary symptoms, clinical characteristics, electrocardiographic findings, treatment approaches, and in-hospital outcomes was collected through completion of a standardized proforma.[27,28] The baseline and peak troponin I concentrations during admission were recorded, and patients were placed in tertiles based on their peak troponin I to reflect the degree of myocardial injury and the size of their infarct.[30]

The primary end point of the analysis was early recurrent MI following the index admission, defined as recurrent type 1 MI within 30 days of index admission.[18] To avoid confounding with the index presentation, only those patients having recurrent MI beyond the first 24 hours after presentation were analyzed, as described previously.[18] We also examined the factors associated with late recurrent MI as an exploratory end point, defined as a recurrent type 1 MI >30 days following index admission.

Statistical Analysis

As a prespecified end point of our previously reported trial (ClinicalTrials.gov identifier NCT01749254),[20] we explored 18F-FDG uptake in remote aortic atheroma of patients with recent MI or stable coronary heart disease. Continuous data were tested for normality with the D'Agostino and Pearson omnibus test. Continuous parametric variables were expressed as mean±SD and compared using Student *t* tests. Nonparametric data were presented as median (interquartile range [IQR]) and compared using the Mann–Whitney *U* test or the Wilcoxon signed rank test, as appropriate. Interobserver reproducibility was calculated by the Bland–Altman method and intraclass correlation coefficients with 95% CIs. The Fisher exact test or the chi-square test was used for analysis of categorical variables. Correlation of parametric data was

assessed using the Pearson correlation coefficient, and the Spearman rank correlation was used for nonparametric data.

Patients in the registry cohort were placed in tertiles according to their peak troponin concentration. Kaplan–Meier curves were used to estimate the distribution of early recurrent MI across the tertiles. Univariate analysis was undertaken to identify associations with early (≤30 days) and late (>30 days) recurrent MI that were then entered into the multivariate logistic regression model based on a univariate association of $P<0.1$. In addition, age and sex were included in the model. Statistical analysis was performed with GraphPad Prism version 6 (GraphPad Software Inc) and SPSS 19.0 (IBM Corp), as appropriate. Unless stated, a 2-sided $P<0.05$ was considered statistically significant.

Results

Imaging Cohort

Overall, 40 patients with stable angina and 40 with MI underwent 18F-FDG PET imaging. The median time between hospitalization and 18F-FDG PET imaging was 11 days (IQR 8 to 17 days) in patients with MI. Compared with patients with stable angina, patients with MI were younger, had less extensive coronary artery disease (Table 1), and had lower coronary artery calcium scores (coronary artery calcium score: stable angina 599 Agatston units [AU; IQR 60 to 1302 AU]; MI 159 AU [IQR 42 to 456 AU]; $P=0.006$) (Tables 1 and 2). Although apparently higher aortic calcium scores were noted in patients with stable angina, this difference did not reach statistical significance (aortic calcium scores; stable angina 538 AU [IQR 4 to 1870 AU]; MI 135 AU [IQR 0 to 805 AU]; $P=0.12$) (Table 2).

Positron emission tomography

The reproducibility of TBR measurements in the aorta for tracer activity was excellent, with no fixed or proportional biases and with narrow limits of agreement (Table S1). In contrast to the calcium scores, 18F-FDG uptake was 20% higher in the aortas of patients with recent MI than those with stable coronary artery disease (Table 2 and Figure 2). This finding was consistent in all regions of the aorta assessed (entire thoracic aorta, ascending aorta, aortic arch, descending aorta; all $P<0.0001$) and with all measures of tracer activity (mean TBR_{max}, mean TBR_{mean}, max TBR, TBR_{MDS}, all $P<0.001$). Furthermore, 18F-FDG activity was higher in patients with STEMI compared with those with non-STEMI (TBR_{max} 2.24±0.32 versus 2.02±0.21, respectively; $P=0.03$) (Table 2), consistent with the former having sustained larger MIs (peak plasma troponin concentration 32 300 ng/L [IQR 10 200 to >50 000 ng/L] versus 3800 ng/L [IQR 1000 to 9200 ng/L]; $P<0.0001$). Indeed, aortic 18F-FDG activity correlated with peak plasma troponin I concentrations ($r=0.43$, $P=0.01$).

In patients with stable angina and those with MI, paraspinal uptake of 18F-FDG (mean TBR_{max} 0.79±0.25 versus 0.75±0.21, respectively; $P=0.52$) was similar.

C-reactive protein

Compared with patients with stable angina, patients with MI had higher plasma CRP concentrations (6.50 mg/dL [IQR 2.00 to 12.75 mg/dL] versus 2.00 mg/dL [IQR 0.50 to 4.00 mg/dL], $P=0.0005$). Among patients with MI, patients with STEMI appeared to have higher plasma CRP concentrations (7.50 mg/dL [IQR 2.00 to 13.75 mg/dL] versus 2.50 mg/dL [IQR 1.75 to 9.50 mg/dL]), but this difference did not reach statistical significance ($P=0.22$). There was a modest correlation between peak troponin I concentrations and CRP ($r=0.35$, $P=0.03$).

Outcome Cohort

A total of 1003 patients enrolled in the GRACE database were followed for a median follow-up period of 34 months (IQR 18 to 50 months). Early recurrent MI occurred in 54 patients following index admission, whereas late recurrent MI occurred in 89 patients.

Patients were classified into tertiles according to their peak plasma troponin I concentrations measured during the index admission (tertile 1, ≤220 ng/L; tertile 2, 230 to 6130 ng/L; and tertile 3, ≥6140 ng/L) (Table 3). On univariate analysis, the risk of early recurrent infarction (≤30 days) was >4-fold higher among patients in the highest troponin tertile compared with the lowest, whereas risk was doubled in the middle tertile compared with the lowest (Table 4 and Figure 3). The variables with univariate association of $P<0.1$ were Killip score ≥2, ST-segment deviation, multivessel disease, and troponin I concentrations. On multivariate analysis, troponin emerged as an independent predictor of early MI after adjustment for other relevant variables (tertile 3 versus 1: relative risk 4.40 [95% CI 1.90 to 10.19], $P=0.001$; tertile 2 versus 1: relative risk 2.63 [95% CI 1.08 to 6.38], $P=0.03$). The only other independent predictor was Killip class 2 (1.86 [95% CI 1.06 to 3.24], $P=0.03$).

In contrast, recurrent late MI was not associated with troponin tertiles on univariate analysis (tertile 2 versus 1: relative risk 1.07 [95% CI 0.64 to 1.79], $P=0.79$; tertile 3 versus 1: relative risk 0.80 [95% CI 0.46 to 1.39], $P=0.43$) but rather was more closely related to traditional predictors of MI (Table 4).

Table 1. Baseline Characteristics of Patients With Coronary Artery Disease

	Patients With Stable Angina	Patients With MI		
	All (n=40)	All (n=40)	STEMI (n=26)	NSTEMI (n=14)
Age, y	67±8	62±8	63±9	60±8
Male sex	36 (90)	37 (93)	24 (92)	13 (93)
BMI, kg/m^2	30±5	28±5	27±5	30±4
Antecedent angina (active)	40 (100)	9 (23)	5 (19)	4 (29)
Heart rate, beats/min*	59±9	56±7	56±7	56±7
Systolic blood pressure, mm Hg	134±14	132±21	131±20	121±21
Diastolic blood pressure, mm Hg	77±10	76±9	76±9	76±8
Cardiovascular history				
Previous MI	15 (38)	5 (13)	1 (4)	4 (29)
Previous CVA/TIA	4 (10)	2 (5)	1 (4)	1 (7)
Previous PCI	19 (48)	5 (13)	2 (8)	3 (21)
Previous CABG	11 (28)	2 (5)	2 (8)	0
Risk factors				
Smoking habit (ex or current)	24 (60)	25 (63)	19 (73)	6 (43)
Diabetes mellitus	13 (33)	8 (20)	7 (27)	1 (7)
Hypertension	36 (90)	17 (43)	11 (42)	6 (43)
Hypercholesterolaemia	39 (98)	19 (48)	11 (42)	8 (57)
Medications†				
Aspirin	33 (83)	40 (100)	26 (100)	14 (100)
Clopidogrel	5 (13)	39 (98)	25 (96)	14 (100)
Statin	36 (90)	39 (98)	26 (100)	13 (93)
β-blocker	28 (70)	32 (80)	20 (77)	12 (86)
ACEI/ARB	20 (50)	35 (88)	25 (96)	10 (71)
Calcium channel blockers	16 (40)	2 (5)	2 (8)	0
Other antihypertensive	6 (15)	3 (8)	1 (4)	2 (14)
Oral nitrates	15 (38)	1 (3)	0	1 (7)
Serum biochemistry				
Cholesterol, mg/dL	151±31	181±46	181±50	185±43
HDL-cholesterol, mg/dL	43±12	43±12	43±12	39±12
LDL-cholesterol, mg/dL	81±27	112±43	108±43	120±39
Triglycerides, mg/dL	62±27	62±31	66±27	58±27
Creatinine, mg/dL	0.96±0.26	0.96±0.30	0.97±0.33	0.93±0.27
Peak troponin concentration, ng/L (IQR)	—	11 200 (3300 to >50 000)	32 300 (10 200 to >50 000)	3800 (1000 to 9200)

Data are shown as mean±SD or number (percentage) except as noted. ACEI indicates angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; CABG, coronary artery bypass grafting; CTCA, computed tomography coronary angiography; CVA, cerebrovascular accident; HDL, high-density lipoprotein; IQR, interquartile range; LDL, low-density lipoprotein; MI, myocardial infarction; NSTEMI, non–ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction; TIA, transient ischemic attack.

*Heart rate at the time of CTCA.

†Medications at the time of scan.

Discussion

Using 18F-FDG PET imaging, in patients with recent MI, we demonstrated increased metabolic activity in remote aortic atherosclerotic plaques that correlated with the degree of myocardial necrosis and exceeded that observed in patients with stable coronary disease who had a greater atherosclerotic burden. Using the GRACE registry, we explored the

Table 2. Aortic Calcium Scores and 18F-FDG Tissue-to-Background Ratios in Patients With Stable Angina and Myocardial Infarction

	Patients With Stable Angina (n=40)	Patients With Myocardial Infarction (n=40)	*P* Value	Patients With STEMI (n=26)	Patients With NSTEMI (n=14)	*P* Value
CT aortic calcium						
Agatston units (IQR)	538 (4 to 1870)	135 (0 to 805)	0.12	183 (0 to 377)	55 (0 to 2523)	0.91
Volume, mm^3 (IQR)	532 (7 to 1718)	149 (0 to 717)	0.12	192 (0 to 387)	94 (0 to 2263)	0.85
Mass, mg (IQR)	131 (2 to 517)	31 (31 to 1415)	0.07	131 (2 to 517)	43 (0 to 86)	0.90
18F-FDG						
Thoracic aorta mean TBR_{max}	1.84±0.18	2.15±0.30	<0.0001	2.24±0.32	2.02±0.21	0.03
Thoracic aorta mean TBR_{mean}	1.41±0.14	1.60±0.17	<0.0001	1.51±0.16	1.66±0.17	0.01
Thoracic aorta max TBR	2.22±0.31	2.64±0.52	<0.0001	2.78±0.57	2.40±0.35	0.02
Thoracic aorta TBR_{MDS}	2.11±0.23	2.54±0.49	<0.0001	2.66±0.53	2.34±0.33	0.04
Aortic subregions						
Ascending aorta mean TBR_{max}	1.84±0.20	2.21±0.35	<0.0001	2.35±0.35	2.03±0.26	0.01
Arch of aorta mean TBR_{max}	1.88±0.22	2.26±0.34	<0.0001	2.35±0.35	2.11±0.26	0.03
Descending aorta mean TBR_{max}	1.82±0.18	2.10±0.30	<0.0001	2.17±0.32	1.98±0.21	0.08

18F-FDG, 18F-fluorodeoxyglucose; CT, computed tomography; IQR, interquartile range; max TBR, highest value tissue-to-background ratios in any axial slice; mean TBR_{max}, average of the maximum tissue-to-background ratios across all slices in the segment; mean TBR_{mean}, average of the mean tissue-to-background ratios for all slices in the segment; NSTEMI, non–ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction; TBR_{MDS}, tissue-to-background ratio in the most diseased segment.

clinical relevance of these findings to assess whether infarct size and the associated increase in atherosclerotic inflammation could predict recurrent coronary atherothombotic events in everyday clinical practice. Intriguingly, patients with the largest infarcts had a >4-fold increase in the risk of early recurrent MI, with baseline tertiles of plasma troponin concentration emerging as an independent predictor of these events. Consequently, we provided clinical data to support the hypothesis that MI exacerbates systemic atherosclerotic inflammation, destabilizes remote atheromatous plaque, and causes an increase in early recurrent atherothrombotic events.

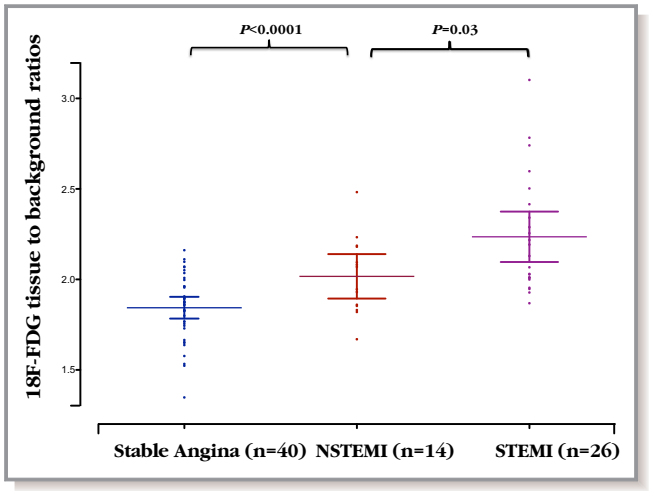

Figure 2. Uptake of 18F-FDG by aortic atherosclerosis in patients with stable and unstable coronary heart disease. Aortic mean of the maximum tissue-to-background ratio for 18F-FDG uptake in patients with stable angina, STEMI, and NSTEMI. Mean with 95% CI. 18F-FDG indicates 18F-fluorodeoxyglucose; NSTEMI, non–ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction.

Preclinical data have indicated that MI induces a macrophage-driven proinflammatory state[31] that directly increases inflammation in remote atheroma and induces further atherosclerosis.[12,32,33] In a mouse model, MI induced by coronary artery ligation increased splenic monocyte motility,[12] with these cells exiting the spleen en masse and migrating both to the injured myocardium and, crucially, to remote atherosclerotic plaque.[34] In addition, sympathetic stimulation following infarction increased the production and liberation of hematopoietic stem and progenitor cells from the bone marrow, resulting in further increases in circulating monocytes and the accumulation of macrophages within regions of remote atheroma.[12] The net result was a marked accumulation of macrophages in remote atherosclerotic plaque following MI that resulted in acceleration of the disease process in these areas. The first aim of the current

Table 3. Baseline Characteristics of Patients From the GRACE Cohort

	Tertile 1 (n=332)	Tertile 2 (n=336)	Tertile 3 (n=335)	*P* Value
Peak troponin I, range	≤220	230 to 6130	≥6140	—
Age, y	65±12	66±12	63±13	0.02
GRACE score	124±47	197±49	218±41	<0.0001
Male sex	212 (63.9)	226 (67.3)	254 (75.8)	0.003
Smoking habit	214 (64.5)	243 (72.3)	235 (70.1)	0.08
Previous MI	149 (44.9)	91 (27.1)	51 (15.2)	<0.0001
Killip score ≥2	82 (24.7)	114 (33.9)	98 (29.3)	0.03
Previous CABG	61 (18.4)	25 (7.4)	12 (3.6)	<0.0001
Previous heart failure	26 (7.8)	25 (7.4)	13 (3.9)	0.07
Diabetes	53 (16.0)	47 (14.0)	47 (14.0)	0.71
ST-segment deviation	77 (23.2)	142 (42.3)	275 (82.1)	<0.0001
Multivessel disease	92 (27.7)	141 (42.0)	125 (37.3)	<0.0001
Recurrent MI ≤30 days	7 (2.1)	18 (5.4)	29 (8.7)	0.001

Data are shown as mean±SD or number (percentage). CABG, coronary artery bypass grafting; GRACE, Global Registry of Acute Coronary Events; MI, myocardial infarction.

study was to test whether this proinflammatory phenomenon also occurred in humans, using 18F-FDG as a marker of vascular macrophage inflammatory activity. Because we could not measure 18F-FDG uptake before and after MI, we prospectively compared uptake between patients with stable coronary heart disease and those with recent MI.[18] Despite a comparable or lower overall aortic and coronary plaque burden, aortic 18F-FDG uptake was 20% higher in patients who had sustained a recent MI. Indeed, the aortic 18F-FDG uptake was consistently increased across all regions of the thoracic aorta. In contrast, paraspinal muscle uptake was similar between the cohorts, indicating a specific vascular and atherosclerotic response rather than generalized nonspecific inflammation across all tissues. Based on clinical factors and peak plasma troponin concentration, patients with STEMI had larger infarcts and demonstrated greater increases in aortic

Table 4. Univariate Predictors of Early (≤30 Day) and Late (>30 Day) Recurrent MI

	Early (≤30 Day) Recurrent MI	*P* Value	Late (>30 Day) Recurrent MI	*P* Value
Age, y	1.02 (0.99 to 1.04)	0.14	1.04 (1.02 to 1.06)	<0.0001
Male sex	1.30 (0.70 to 2.43)	0.45	0.89 (0.56 to 1.41)	0.63
Smoker	0.82 (0.46 to 1.46)	0.55	1.04 (0.65 to 1.67)	0.91
Previous MI	0.69 (0.36 to 1.32)	0.28	3.81 (2.43 to 5.95)	<0.0001
Killip score ≥2	1.86 (1.06 to 3.24)	0.03	1.79 (1.14 to 2.82)	0.01
Previous CABG	0.94 (0.37 to 2.42)	0.99	2.91 (1.66 to 5.10)	<0.0001
Previous heart failure	0.86 (0.26 to 2.82)	0.99	2.77 (1.40 to 5.45)	0.008
Diabetes	0.72 (0.30 to 1.71)	0.56	1.41 (0.80 to 2.48)	0.27
ST-segment deviation	1.81 (1.03 to 3.19)	0.05	1.18 (0.76 to 1.82)	0.50
Multivessel disease	1.73 (0.99 to 2.99)	0.06	1.57 (1.01 to 2.44)	0.05
Troponin tertiles				
Tertile 2 vs tertile 1	2.63 (1.08 to 6.38)	0.03	1.07 (0.64 to 1.79)	0.79
Tertile 3 vs tertile 1	4.40 (1.90 to 10.19)	0.001	0.80 (0.46 to 1.39)	0.43
Linear trend across tertiles	—	<0.0001	—	0.57

Data are shown as relative risk (95% CI). CABG, coronary artery bypass grafting; MI, myocardial infarction.

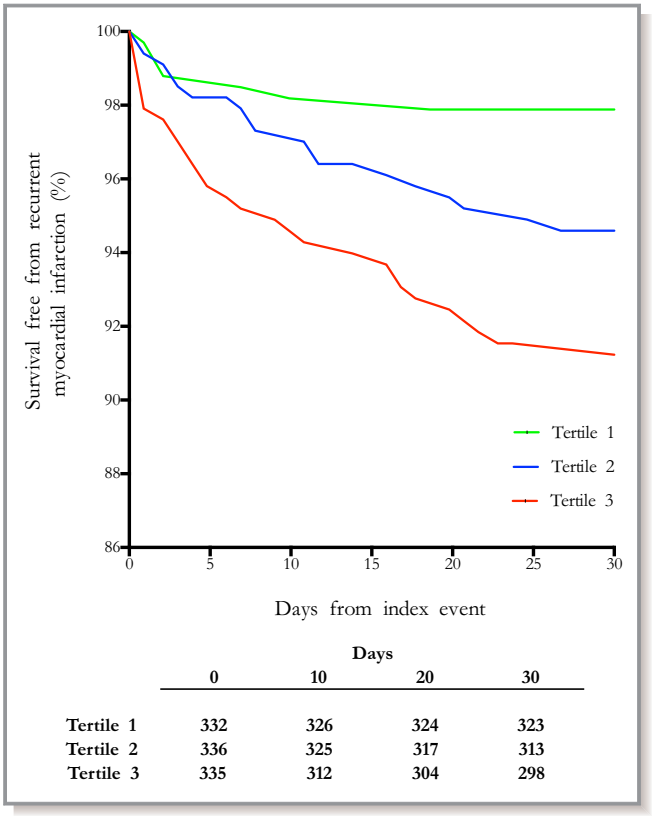

Figure 3. Kaplan–Meier curves demonstrating survival free from early recurrent myocardial infarction at 30 days. Patients were placed in tertiles according to their peak plasma troponin I concentrations (tertile 1, ≤220 ng/L; tertile 2, 230 to 6130 ng/L; tertile 3, ≥6140 ng/L).

18F-FDG uptake than those with non-STEMI. We observed good correlation between peak plasma troponin I concentrations and aortic 18F-FDG activity, suggesting that the association may be causal.

Next we investigated whether the observed increases in vascular inflammatory activity were of clinical importance in actual practice. Our imaging cohort was not large enough to address this question, so we turned to data from the well-established GRACE registry. In >1000 patients, we demonstrated that the size of the initial MI emerged as an independent predictor of early recurrent MI over and above traditional risk factors, with a 4-fold increase in these events among those with the biggest infarcts. This finding indicates that the increased vascular inflammation associated with MI translates into adverse clinical events, perhaps due to plaque destabilization and the associated increased risk of rupture. Interestingly, our data also suggest that the clinical effects of this systemic inflammatory response are only transitory, with no association between infarct size and later recurrent events after 30 days, by which time the inflammation will have subsided and plaques begun to stabilize once more. Our data are also consistent with those of the smaller (n=378) Evaluation of MCC-135 for Left Ventricular Salvage in Acute Myocardial Infarction (EVOLVE) randomized controlled trial,[35] which also observed an increased early event rate in patients in the highest tertile of troponin concentration, with a trend for an increase in recurrent MI. Our findings are supported by recently reported studies.[36–39] Patients with acute coronary syndromes have increased plaque vulnerability in nonculprit lesions, with increased incidence of thin-capped fibroatheromas and adherent thrombus.[39] Furthermore, patients with STEMI have accelerated plaque progression in nonculprit lesions on follow-up angiography,[37] whereas stenting of such lesions at the same time as culprit lesions reduces adverse cardiovascular events.[38] Moreover, patients with unstable coronary disease have higher metabolic carotid plaque activity compared with patients with stable disease, suggesting a panvascular inflammatory process, as indicated by our study.[36]

Taken together, our data offer clear support for the hypothesis that MI begets early recurrent MI due to upregulated macrophage-mediated inflammation in remote atherosclerotic plaque. It would also offer an explanation for the increased incidence of ischemic stroke following MI and would explain why immediate reperfusion for STEMI and the resultant limitation in myocardial injury confer greater reduction in the risk of recurrent events than revascularization after infarct completion.[10,40]

Although our data support the hypothesis that MI results in remote arterial inflammation, it could also be argued that more widespread and intense atherosclerotic inflammation occurs prior to the precipitation of MI and that this is the explanation for the association. The correlation between infarct size and the inflammatory signal would support the former explanation; however, to resolve this issue, 18F-FDG imaging would be required both before and after MI, which, given the unpredictable nature of these events, is extremely challenging in the clinical context. We also acknowledge that we did not directly measure MI size and used peak plasma troponin concentration as a surrogate measure; however, peak plasma troponin concentration has a strong correlation with infarct size (r=0.740, P<0.001)[30,35] and is a valid surrogate marker, especially when applied to large data sets such as the registry cohort used in this study. Finally, we were unable to measure systemic markers of inflammation such as CRP in our outcome cohort; however, CRP is well known to correlate with troponin release after MI,[41–43] and indeed this was observed in our imaging cohort.

In summary, we demonstrated that the presence and extent of MI are associated with increased aortic atherosclerotic inflammation and early recurrent MI, supporting the hypothesis that MI begets MI in humans.

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Disclosures

None.

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