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ORIGINAL RESEARCH

Splenic Metabolic Activity Predicts Risk of Future Cardiovascular Events

Demonstration of a Cardiosplenic Axis in Humans

Hamed Emami, MD,* Parmanand Singh, MD,* Megan MacNabb, BA,* Esad Vucic, MD,* Zachary Lavender, BA,* James H.F. Rudd, PhD,† Zahi A. Fayad, PhD,‡ Joshua Lehrer-Graiwer, MD, MPhil,§ Magnus Korsgren, MD, PhD,‖ Amparo L. Figueroa, MD, MPH,* Jill Fredrickson, PhD,§ Barry Rubin, MD, PhD,¶ Udo Hoffmann, MD, MPH,* Quynh A. Truong, MD, MPH,* James K. Min, MD,# Amos Baruch, PhD,§ Khurram Nasir, MD, MPH,** Matthias Nahrendorf, MD, PhD,†† Ahmed Tawakol, MD*‡‡

ABSTRACT

OBJECTIVES This study sought to determine whether splenic activation after acute coronary syndrome (ACS) is linked to leukocyte proinflammatory remodeling and whether splenic activity independently predicts the risk of cardiovascular disease (CVD) events.

BACKGROUND Pre-clinical data suggest the existence of a cardiosplenic axis, wherein activation of hematopoietic tissues (notably in the spleen) results in liberation of proinflammatory leukocytes and accelerated atherosclerotic inflammation. However, it is presently unknown whether a cardiosplenic axis exists in humans and whether splenic activation relates to CVD risk.

METHODS ^{18}F-fluorodeoxyglucose (^{18}FDG)-positron emission tomography (PET) imaging was performed in 508 individuals across 2 studies. In the first study, we performed FDG-PET imaging in 22 patients with recent ACS and 22 control subjects. FDG uptake was measured in spleen and arterial wall, whereas proinflammatory gene expression of circulating leukocytes was assessed by quantitative real-time polymerase chain reaction. In a second study, we examined the relationship between splenic tissue FDG uptake with subsequent CVD events during follow-up (median 4 years) in 464 patients who previously had undergone FDG-PET imaging.

RESULTS Splenic activity increased after ACS and was significantly associated with multiple indices of inflammation: 1) up-regulated gene expression of proinflammatory leukocytes; 2) increased C-reactive protein; and 3) increased arterial wall inflammation (FDG uptake). Moreover, in the second study, splenic activity (greater than or equal to the median) was associated with an increased risk of CVD events (hazard ratio [HR]: 3.3; 95% confidence interval [CI]: 1.5 to 7.3; $p = 0.003$), which remained significant after adjustment for CVD risk factors (HR: 2.26; 95% CI: 1.01 to 5.06; $p = 0.04$) and for arterial FDG uptake (HR: 2.68; 95% CI: 1.5 to 7.4; $p = 0.02$).

CONCLUSIONS Our findings demonstrate increased splenic metabolic activity after ACS and its association with proinflammatory remodeling of circulating leukocytes. Moreover, we observed that metabolic activity of the spleen independently predicted risk of subsequent CVD events. Collectively, these findings provide evidence of a cardiosplenic axis in humans similar to that shown in pre-clinical studies. (J Am Coll Cardiol Img 2015;8:121–30) © 2015 by the American College of Cardiology Foundation.

From the *Cardiac MR PET CT Program, Division of Cardiac Imaging, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts; †Division of Cardiovascular Medicine, University of Cambridge, Cambridge, United Kingdom; ‡Translational and Molecular Imaging Institute, Icahn School of Medicine at Mount Sinai, New York, New York; §Genentech, San Francisco, California; ‖BioInvent International AB, Lund, Sweden; ¶Division of Vascular Surgery, Peter Munk Cardiac Centre, Toronto General Hospital, University of Toronto, Toronto, Ontario, Canada; #Departments of Radiology and Medicine, Weill Cornell Medical College and the New York-Presbyterian Hospital, New York, New York; **Baptist Health South Florida, Miami, Florida; ††Center for Systems Biology, Massachusetts General Hospital and Harvard Medical School,

ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome

BM = bone marrow

CI = confidence interval

CRP = C-reactive protein

CT = computed tomography

CVD = cardiovascular disease

FDG = 18-fluorodeoxyglucose

FRS = Framingham Risk Score

HR = hazard ratio

PET = positron emission tomography

SAT = subcutaneous adipose tissue

SUV = standardized uptake value

TBR = target-to-background ratio

TLR = toll-like receptor

Patients remain at an increased risk for recurrent cardiovascular disease (CVD) events in the weeks to months after an acute coronary syndrome (ACS) (1,2); however, the pathophysiological basis for this increased risk remains unclear. Preclinical studies have shown that proliferation of monocyte progenitors and proinflammatory activation of monocytes within the hematopoietic tissues (i.e., bone marrow [BM] and spleen) may play an important role in accelerating atherosclerosis after myocardial infarction (3,4). Pre-clinical studies demonstrated that after myocardial infarction in mice, monocyte progenitor cells departed BM niches, which resulted in amplified extramedullary monocytopoiesis (3). The observation of activation of the inflammatory cell milieu and the migration of proinflammatory monocytes from spleen to heart in animal models of heart failure (5) have given rise to the concept of a cardiosplenic axis. Recently, the concept of a cardiosplenic axis has been extended to stable atherosclerosis in murine models as well (6); however, it is presently unknown whether such an axis exists in humans.

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Imaging with ^{18}F-fluorodeoxyglucose-positron emission tomography (FDG-PET) provides a noninvasive measure of tissue glycolysis (7) and is used clinically for the evaluation of tumors (8) and infectious foci (9). The biological basis for FDG accumulation within mononuclear inflammatory cells lies in the fact that macrophages have a high metabolic rate (10), especially after proinflammatory activation (11,12), and hence avidly accumulate FDG (13). Additionally, cellular accumulation of FDG is increased in rapidly proliferating cells (14). Because in animal models of myocardial infarction, splenic activation is marked by proliferation of monocyte progenitor cells and proinflammatory activation of monocytes (3,4), we sought to evaluate splenic activation in humans using FDG PET/computed tomography (CT) imaging. Furthermore, we investigated whether splenic metabolic activity relates to proinflammatory gene expression of circulating leukocytes.

In the first study, we tested the hypothesis that the metabolic activity of hematopoietic tissues (i.e., BM and spleen) occurs in humans with recent ACS. In the second study, and in a separate population, we investigated whether the metabolic activity of these hematopoietic tissues predicts the risk of subsequent CVD events. To do so, we evaluated BM and splenic metabolic activity, by FDG uptake, in a group of individuals with no known atherosclerotic disease who had undergone clinically indicated FDG-PET/CT scans and for whom clinical follow-up data were available. We then assessed whether the baseline hematopoietic tissue FDG signal correlated with arterial wall inflammation and independently predicted the subsequent development of incident CVD events.

METHODS

OVERALL STUDY SCHEMA. We performed 2 separate studies (**Figure 1**). The first study, the ACS study, was designed to test the hypothesis that metabolic activity of the hematopoietic tissues of BM and spleen was more prominent after ACS and was associated with levels of serum proinflammatory biomarkers, proinflammatory gene expression of circulating leukocytes, and arterial wall inflammation. To test these hypotheses, 44 patients were prospectively recruited at Massachusetts General Hospital. FDG-PET/CT imaging was performed in all subjects, and FDG uptake was assessed in the BM, spleen, arterial wall, and control tissues. Additionally, serum biomarker assays and quantitative real-time polymerase chain reaction of proinflammatory gene expression in circulating leukocytes was performed.

The second study, the clinical outcomes study, was conducted in a separate population and was designed to test the hypothesis that hematopoietic tissue (BM and spleen) metabolic activity was associated with arterial wall inflammation and independently predicted the subsequent risk of incident CVD events. To

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