JACC: CARDIOVASCULAR IMAGING VOL. 6, NO. 6, 2013

ISSN 1936-878X/$36.00
PUBLISHED BY ELSEVIER INC. http://dx.doi.org/10.1016/j.jcmg.2012.12.011

Inflammation and Microvascular Dysfunction in Cardiac Syndrome X Patients Without Conventional Risk Factors for Coronary Artery Disease

Alejandro Recio-Mayoral, MD,*†‡ Ornella E. Rimoldi, MD,*§ Paolo G. Camici, MD,*‖ Juan Carlos Kaski, MD, DSc†

London, United Kingdom; Seville, Spain; and Milan, Italy

OBJECTIVES The aim of this study was to ascertain whether coronary microvascular dysfunction (CMD) and inflammation are related in cardiac syndrome X (CSX).

BACKGROUND CMD can lead to CSX, defined as typical angina and transient myocardial ischemia despite normal coronary arteriograms. Inflammation has been suggested to play a role in the pathogenesis of myocardial ischemia in CSX.

METHODS We assessed 21 CSX patients (age 52 ± 10 years; 17 women) without traditional cardiovascular risk factors and 21 matched apparently healthy control subjects. Positron emission tomography was used to measure myocardial blood flow (MBF) and coronary flow reserve (CFR) in response to intravenous adenosine, whereas high-sensitivity C-reactive protein (CRP) was measured to assess inflammation. Patients were subdivided a priori into 2 groups according to CRP concentrations at study entry (i.e., ≤3 or >3 mg/l).

RESULTS There were no differences in resting (1.20 ± 0.23 ml/min/g vs. 1.14 ± 0.20 ml/min/g; $p = 0.32$) or hyperemic MBF (3.28 ± 1.02 ml/min/g vs. 3.68 ± 0.89 ml/min/g; $p = 0.18$) between CSX patients and the control group, whereas CFR was mildly reduced in CSX patients compared with the control group (2.77 ± 0.80 vs. 3.38 ± 0.80; $p = 0.02$). Patients with CRP >3 mg/l had more severe impairment of CFR (2.14 ± 0.33 vs. 3.16 ± 0.76; $p = 0.001$) and more ischemic electrocardiographic changes during adenosine administration than patients with lower CRP, and a negative correlation between CRP levels and CFR ($r = -0.49$, $p = 0.02$) was found in CSX patients.

CONCLUSIONS CSX patients with elevated CRP levels had a significantly reduced CFR compared with the control group, which is indicative of CMD. Our study thus suggests a role for inflammation in the modulation of coronary microvascular responses in patients with CSX. (J Am Coll Cardiol Img 2013;6:660–7) © 2013 by the American College of Cardiology Foundation

From the *Medical Research Council Clinical Sciences Centre and National Heart and Lung Institute, Imperial College School of Medicine, London, United Kingdom; †Cardiovascular Sciences Research Centre, St George's University of London, London, United Kingdom; ‡Department of Cardiology, Virgen Macarena University Hospital, Seville, Spain; §CNR Istituto di Bioimmagini e Fisiologia Molecolare, Milan, Italy; and the ‖Vita-Salute University and San Raffaele Scientific Institute Milan, Milan, Italy. This study was funded in part by the Spanish Society of Cardiology and British Heart Foundation (PG/07/134), and St George's Charitable Foundation. Dr. Camici has been a consultant for Servier International. Dr. Kaski serves on the Speakers' Bureau for Servier and Roche. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. Drs. Camici and Kaski are joint senior authors.

Manuscript received November 20, 2012; accepted December 5, 2012.

In patients with chronic stable angina, myocardial ischemia is commonly caused by flow-limiting atheromatous coronary artery stenoses. In these patients, reductions in coronary flow reserve (CFR), defined as the ratio between myocardial blood flow (MBF) during maximal coronary vasodilation (i.e., in response to adenosine) and baseline MBF, correlate with the severity and flow-limiting ability of epicardial coronary artery stenosis (1). Recently, it has become apparent that a large proportion of patients with typical angina pectoris have normal coronary angiograms (2). In these patients, a reduced CFR and transient myocardial ischemia are likely to result from coronary microvascular dysfunction (CMD) (3,4). Similar mechanisms (i.e., abnormal MBF and impaired CFR) have been documented in patients with hypertrophic cardiomyopathy, systemic hypertension, diabetes mellitus, hypercholesterolemia, and other risk factors (3). Moreover, studies have shown that the severity of CMD is predictive of clinical outcome in some patient subgroups (3). Patients with cardiac syndrome X (CSX), defined as typical chest pain, myocardial ischemia, and angiographically normal coronary arteries, have CMD that can lead to myocardial ischemia (4).

See page 668

Inflammation has been shown to have a pathogenic role in endothelial dysfunction and CMD in different clinical settings (5–12). We have recently shown that even in the absence of angiographic coronary artery disease or conventional risk factors, patients with chronic inflammatory conditions have CMD that can lead to marked reductions in MBF and angina pectoris (13). Increased C-reactive protein (CRP), an established marker of inflammation, is associated with impaired endothelial function both in patients with coronary artery disease (14,15) and CSX (5,6).

We hypothesized that inflammation could explain the presence of CMD in CSX patients, even in those without traditional cardiovascular risk factors. The present study therefore sought to ascertain whether elevated CRP concentrations in patients with CSX, without conventional risk factors for coronary artery disease, are associated with CMD, as assessed using positron emission tomography (PET).

METHODS

Patients. We studied 21 patients (age 52 ± 10 years; 17 women) attending St George's Hospital Chest Pain with Normal Coronary Arteries Clinic who fulfilled strict criteria for CSX. All patients had a typical history of exertional angina, a normal 12-lead electrocardiogram (ECG) at rest, a positive exercise ECG stress test response defined as >0.1 mV horizontal or downsloping ST-segment depression, measured 80 ms after the J point in 2 or more contiguous leads, and completely normal coronary angiograms. Patients with angina at rest and those with Prinzmetal's variant angina were not included in the study, and those with diabetes mellitus, systemic hypertension, current or past smoking, obesity (body mass index >30 kg/m^2), total cholesterol >5 mmol/l, or systemic inflammatory conditions were also excluded. Time elapsed from diagnostic angiography to study entry was <12 months in every patient. Left ventricular hypertrophy was excluded by ECG and 2-dimensional Doppler echocardiography. Patients were receiving treatment with calcium-channel blockers, usually diltiazem or amlodipine (n = 12), angiotensin-converting enzyme inhibitors (n = 2), and sublingual nitrates (n = 20). None of the patients were taking statins at study entry. For the purpose of the study, all cardiovascular medications were withdrawn >24 h before PET assessment, with the exception of sublingual nitrates, which were permitted for relief of acute chest pain at all times. One patient only, however, used this medication, albeit >6 h before the PET study. Twenty-one nonsmoking healthy volunteers (age 51 ± 10 years; 14 women) without symptoms or a history of cardiovascular disease or cardiovascular risk factors were also studied as a control group.

ABBREVIATIONS AND ACRONYMS

CFR = coronary flow reserve

CMD = coronary microvascular dysfunction

CRP = C-reactive protein

CSX = cardiac syndrome X

ECG = electrocardiography

$H_2{}^{15}O$ = water labeled with oxygen

hsCRP = high-sensitivity C-reactive protein

MBF = myocardial blood flow

PET = positron emission tomography

The study protocol was approved by the local research ethics committee, and radiation exposure was licensed by the UK Administration of Radioactive Substances Advisory Committee. All patients gave written informed consent before study entry.

Routine blood tests and high-sensitivity C-reactive protein measurement. Fasting peripheral blood samples were obtained at study entry for the assessment of routine biochemical variables and inflammatory biomarkers. High-sensitivity CRP (hsCRP) measurements were performed on the COBAS Integra (Roche Diagnostics Limited, Lewes, East Sussex, United Kingdom) using the CRP-Latex assay in the hs application (analytical range, 0.2 to 12 mg/l). Analytical precision of the hsCRP latex assay was 7.6% at 1.02 mg/l, 3.3% at 1.79 mg/l, and 1.3% at 4.36 mg/l. None of the