Systemic Inflammatory Response to Renal Artery Percutaneous Angioplasty with Stent Placement and the Risk for Restenosis: A Pilot Study

Elias N. Brountzos, MD, Kyriaki Tavernaraki, MD, Athanasios D. Gouliamos, MD, Dimitrios Degiannis, MD, Antigoni Chaidaroglou, PhD, Irene Panagiotou, MD, George Arsenis, MD, Dimitrios Kelekis, MD, and Demetrios Vlahakos, MD

PURPOSE: Time changes in plasma concentrations of six different cytokines were investigated to evaluate the inflammatory response to renal artery stent placement.

MATERIALS AND METHODS: A total of 22 patients (17 men; mean age, 66 years ± 13) with ostial renal artery stenosis and poorly controlled hypertension treated with stent placement were studied. Blood samples were collected at baseline and at 24 hours and 6 months after the intervention. Plasma concentrations of (i) tumor necrosis factor–α, (ii) interleukin-6 (IL-6), (iii) monocyte chemoattractant protein–1, (iv) intercellular adhesion molecule–1, (v) vascular cell adhesion molecule–1, and (vi) regulated upon activatin normal T-cell expressed presumed secreted were measured. Restenosis diagnosed with imaging follow-up at 6 months was recorded. Plasma concentrations of the aforementioned cytokines were compared between patients with and without restenosis.

RESULTS: IL-6 concentration increased significantly 24 hours after stent placement (8.3 pg/mL ± 1.24 vs. 2.76 pg/mL ± 1.27 at baseline) and returned to baseline levels (2.6 pg/mL ± 1.77) at 6-month follow-up ($P < .0001$). No significant changes occurred in the concentrations of any other cytokines at the three time points. Baseline and 6-month concentrations of IL-6 were significantly higher in patients with restenosis than in those without restenosis (8.13 pg/mL ± 4 vs 0.75 pg/mL ± 0.47 [$P < .005$] and 9.55 pg/mL ± 6.5 vs 0.42 pg/mL ± 0.35 [$P < .02$], respectively).

CONCLUSIONS: Renal artery angioplasty with stent placement induces an inflammatory response, as evidenced by increased IL-6 production. Additionally, IL-6 seems to identify patients prone to develop restenosis; therefore, it might be used as an early predictor of restenosis after renal angioplasty with stent placement. However, larger studies are required to confirm IL-6 as a potential predictor of restenosis.

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Abbreviations: ICAM-1 = intercellular adhesion molecule–1, IL = interleukin, MCP-1 = monocyte chemoattractant protein–1, PTCA = percutaneous transluminal coronary angioplasty, RANTES = regulated upon activatin normal T-cell expressed presumed secreted, TNF = tumor necrosis factor, VCAM-1 = vascular cell adhesion molecule–1

THE role of inflammation in the development of atherosclerosis and atheromatous plaque rupture has been long recognized (1–3). In the same way, the mechanical injury of the vessel wall that follows percutaneous transluminal angioplasty with or without stent implantation induces a local prothrombotic and inflammatory state within days, as indicated by platelet and neutrophil accumulation and fibrin deposition. Subsequently, macrophage and vascular smooth muscle cell proliferation and migration leads to extracellular matrix formation and neointimal growth, causing in-stent restenosis (4–9). All these events are orchestrated by a wide variety of inflammatory mediators and chemoattractans, including cyto-

From the Second Department of Radiology (E.N.B., K.T., A.D.G., I.P.), Athens University Medical School, Attikon University Hospital, Chaidari; Molecular Immunopathology and Histocompatibility Laboratory (D.D., A.C.), Onassis Cardiac Surgery Center; Department of Biochemistry (G.A.) and Second Department of Internal Medicine (D.V.), Athens University Medical School; and Department of Radiology Research and Medical Imaging (D.K.), Athens University, Athens, Greece. Received January 29, 2008; final revision received October 16, 2008; accepted October 27, 2008. **Address correspondence to** E.N.B., Second Department of Radiology, Athens University Medical School, Attikon University Hospital, 1 Rimini St., 12462, Chaidari, Greece; E-mail: ebrountz@med.uoa.gr

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kines, chemokines, adhesion molecules, and extracellular matrix proteins (10–12). In particular, shortly after percutaneous angioplasty and stent placement in coronary or peripheral arteries, a host of inflammatory molecules are released into the systemic circulation, including tumor necrosis factor–α (TNF-α), interleukin-6 (IL-6), monocyte chemoattractant protein–1 (MCP-1), intercellular adhesion molecule–1 (ICAM-1), vascular cell adhesion molecule–1 (VCAM-1), and regulated upon activatin normal T-cell expressed presumed secreted (RANTES) (13–17). The production and secretion of these molecules in the inflammation site constitutes a major part of the inflammatory cascade, which plays an important role in long-term results and restenosis (17,18–22).

The literature regarding the early inflammatory response after percutaneous renal artery angioplasty and stent placement is scant. A recent report (23) showed marked increase of C-reactive protein and IL-6 plasma concentrations after renal artery stent placement, suggesting the occurrence of an early inflammatory response. In their discussion, the authors recommended that future studies explore the involvement of other cytokines implicated in the inflammatory response after angioplasty, as well as the possible association with restenosis (23). The present study aimed to address this. We believe identification of early inflammatory predictors associated with late in-stent neointimal growth and restenosis would be of interest and may be important if it could prompt a therapeutic intervention that could prevent restenosis.

Given these considerations, the primary aim of this pilot study was to analyze the early and late changes in plasma concentrations of six chemokines and cytokines thought to be involved in the process of injury and repair after renal artery angioplasty with stent implantation. These molecules have included TNF-α, a pleiotropic inflammatory cytokine; IL-6, another multifunctional cytokine known to be secreted from activated macrophages and lymphocytes; MCP-1, a potent platelet-derived growth factor–inducible chemokine secreted by activated platelets that promotes migration and adhesion of macrophages to endothelial cells; ICAM-1 and VCAM-1, both inflammatory adhesion receptors; and RANTES, a chemokine secreted by activated platelets that acts as a cell-associated signal for monocyte adhesion. All these substances have been reported to be associated with restenosis after percutaneous coronary interventions (17–23). Subsequently, by comparing cytokine release shortly after the percutaneous renal artery angioplasty with stent placement in two subsets of patients with or without late restenosis we aimed to identify inflammatory predictors of late in-stent neointimal growth.

MATERIALS AND METHODS

The study protocol was approved by our institutional review board. All patients gave written informed consent.

Patient Selection

Twenty-two patients (17 men; mean age, 66 years ± 13; age range, 39–82 y) with 22 atherosclerotic ostial renal artery stenosis and poorly controlled arterial hypertension who were admitted to the hospital to undergo percutaneous transluminal renal artery angioplasty with stent placement were included. Patients with decompensated heart failure, moderate to severe chronic renal disease (defined as an estimated glomerular filtration rate less than 60 mL/min/1.73 m^2), hepatic insufficiency, or hematologic disorders were excluded. Patients with symptoms and signs of acute inflammation such as pain, fever, and malaise were excluded. Patients with known history of chronic inflammation such as bowel inflammatory disease or arthritis were also excluded. The patients were instructed to follow their usual diet and fluid intake, and were given aspirin and clopidogrel 100 mg and 75 mg daily, respectively, 2 days before the intervention.

Definitions

Definitions were in accordance with the guidelines for the reporting of renal artery revascularization in clinical trials (24). Poorly controlled hypertension was defined as hypertension not controlled by three categories of antihypertensive medications at maximum dosage, including diuretic agents (systolic pressure >160 mm Hg, diastolic pressure >90 mm Hg).

Ostial renal artery stenosis was defined as the narrowing of the renal artery lumen by 75% or greater at its origin from the aorta, generally considered to be within its proximal 5 mm.

Technical success of the renal artery angioplasty with stent placement was assessed with completion angiography, and was defined as less than 30% residual stenosis after the procedure (ie, identical to anatomic success). Restenosis was defined as greater than 50% narrowing of the diameter of the treated arterial segment.

Clinical outcomes of hypertension were reported as follows. Cure was defined by diastolic blood pressure less than 90 mm Hg and systolic pressure less than 140 mm Hg without antihypertensive medications. Improvement was defined as diastolic blood pressure less than 90 mm Hg and/or systolic blood pressure less than 140 mm Hg with equal or fewer medications or a reduction in diastolic blood pressure by at least 15 mm Hg with equal or fewer medications. Failure was defined by no change or inability to meet the criteria for cure or improvement. Benefit was defined as either cure or improvement.

Renal Angioplasty and Stent Placement and Postinterventional Care

To determine renal artery stenosis, a 5-F pigtail catheter was used to depict the aorta and the renal artery. The stenosis was determined as the ratio of the diameter of the renal artery at the narrowest segment to the diameter of the normal artery immediately distal to it.

Primary renal ostial stent implantation was performed in all renal arteries from a retrograde femoral approach. In all cases, a low-profile stent system was applied (Herculink Plus 14; Guidant, Indianapolis, Indiana). The diameter of the stent was chosen slightly larger (0.2–1 mm) than the adjacent normal artery. Twenty-two stents were placed in the respective renal lesions; stents 6 mm in diameter (n = 17) were placed into arteries with diameters of 5.4 mm ± 0.27, and stents 6.5 mm in diameter (n = 5) were placed into arteries with diameters of 5.8 mm ± 0.2. In all cases, direct stent placement (ie, without predilation) was employed. All patients received 5,000 U of heparin intravenously during the procedure.