A novel predictor of restenosis and adverse cardiac events: asymmetric dimethylarginine

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Abstract The aim of this study is to investigate if serum asymmetric dimethylarginine (ADMA) levels can predict restenosis and major adverse cardiac events (MACE) in patients who undergo percutaneous coronary interventions. The most important cause of restenosis following percutaneous coronary intervention is neointimal hyperplasia. Nitric oxide (NO) prevents the neointimal hyperplasia growing. Asymmetric dimethylarginine is a competitive inhibitor of NO synthesis. The effect of ADMA on the restenosis has not yet been investigated. A total of 105 (80 male and 25 female) patients were included in our study. All patients underwent elective percutaneous transluminal coronary angioplasty (PTCA) with bare metal stent implantation or direct stenting for one coronary artery between September 2004 and January 2006. All patients were clinically followed for a period of 6 months, and a control angiography was performed at the end of this period. The probrain natriuretic peptide (pro-BNP), high-sensitivity C-reactive protein (hs-CRP), and ADMA levels of the patients were evaluated before the procedure and 6 months afterwards. Biochemical parameters and angiographic features were evaluated in order to determine if they could predict the development of restenosis and MACE by using univariate and multivariate Cox regression analysis. The 65 (61.9%) patients (50 males and 15 females) who had not developed restenosis were designated as Group 1. The 27 (25.7%) patients (21 males and 6 females) who had developed restenosis were designated as Group 2. In terms of predicting the development of restenosis, the presence of diabetes mellitus (hazard ratio [HR]: 2.78; confidence interval [CI]: 1.25–6.20; P = 0.01), type of lesion (HR: 1.89; CI: 1.01–3.55; P = 0.04), form of procedure (HR: 0.30; CI: 0.11–0.81; P = 0.01), and ADMA (HR: 4.08; CI: 1.73–9.62; P = 0.001) were found to be significant in univariate Cox regression analysis. In contrast, only the levels of ADMA were found to be a significant predictor of restenosis in the multivariate Cox regression analysis (HR: 3.02; CI: 1.16–7.84; P = 0.02). The restenosis prediction of ADMA levels continued after excluding the patients with diabetes mellitus in the univariate and multivariate Cox regression analysis (HR: 5.23; CI: 1.99–13.76; P = 0.001 and HR: 5.61; CI: 1.79–17.62; P = 0.003, respectively). Regarding the development of cardiac events, hs-CRP (HR: 1.03; CI: 1.00–1.06; P = 0.01) and ADMA (HR: 17.1; CI: 3.06–95.8; P = 0.001) were found to be significantly correlated with adverse cardiac events in univariate Cox regression analysis, whereas only ADMA levels were significant in the multivariate Cox regression analysis (HR: 2.83; CI: 1.27–6.31; P = 0.01). The levels of ADMA obtained before the procedure predict the development of restenosis and MACE in patients who underwent elective PTCA and bare metal stent procedures.

Key words Asymmetric dimethylarginine · Restenosis · Adverse cardiac event

Introduction

Nitric oxide (NO) is synthesized in endothelial cells from its precursor L-arginine. L-Arginine is converted to NO by NO synthetase (NOS). Nitric oxide plays a key role in providing vascular homeostasis and the maintenance of this homeostasis. Nitric oxide also prevents the development of
restenosis following percutaneous transluminal coronary angioplasty (PTCA) and stent procedures by inhibiting the formation of mitogenic substances from endothelial injury, leukocyte and thrombocyte adhesion, and smooth muscle cell proliferation. Asymmetric dimethylarginine (ADMA) is a competitive inhibitor of NOS and arises from the methylation and hydrolysis of arginine residues during protein degradation. As a result of NOS enzyme inhibition, the effect of ADMA on NO synthesis and endothelial function decreases. Azuma et al. reported that, following experimental balloon angioplasty, the concentration of ADMA was higher in the regenerated endothelial cells as compared to normal endothelial cells. However, the relationship between ADMA levels and restenosis in patients who undergo percutaneous coronary intervention (PCI) has not yet been investigated. Thus, the aim of this study is to investigate the relationship between ADMA concentration and the development of restenosis in patients who undergo prospectively elective PCI.

Patients and methods

Patients who underwent elective PTCA and bare metal stent procedure between September 2004 and January 2006 were enrolled to the study (354 patients). Patients with the following conditions were omitted from the study: patients who underwent PTCA and stent on more than one coronary artery; patients who had previously undergone PTCA and stent or coronary bypass surgery; patients who had myocardial infarction or an acute coronary event within the last 30 days; patients with congestive heart failure, chronic renal failure, pulmonary hypertension, peripheral artery disease, atrial fibrillation, thyroid function disorder, acute infection, or chronic inflammatory disease. The remaining 105 patients (80 male and 25 female) with one or more lesions in one coronary artery who also had indications for PTCA and stent through clinical and angiographic examination were included in this study.

Clopidogrel (75 mg per day) was administered as part of the patients’ treatment. The patients consumed clopidogrel at least 72 h prior to the procedure. Patients were hospitalized 1 day before the procedure, at which point their heights and weights were measured. Body mass index (BMI) was calculated using the weight/(height)$^2$ (kg/m$^2$) formula, and the glomerular filtration rate (GFR) was calculated using the Cockcroft–Gault formula:

\[(140 - \text{age}) \times \text{weight}/72 \times \text{serum creatinine} \times (0.85 \text{ for females})\]

Following 12 h of fasting, blood samples were taken for subsequent use in biochemical analysis. Blood samples were drawn 4 h before the procedure. All biochemical tests, apart from the ADMA analysis, were performed on the same day as the procedure. The blood serum that was obtained for ADMA was stored at $-22^\circ\text{C}$. Blood samples were drawn again 6 months after the procedure. The lesion on which PTCA and stent implant were performed was visualized prior to the procedure using the standard angiography technique. The vessel was revisualized after performing PTCA and stent implant. Procedural success was defined as successful implantation of the stent, a final vessel diameter stenosis $\leq 30\%$ (in quantitative measurement by Digital Imaging and Communications in Medicine [DICOM]), and freedom from in-hospital MACE, defined as death, O-wave myocardial infarction, and emergency coronary artery bypass grafting. The following medical treatments were prescribed for the patients immediately prior to their discharge: nitrates, $\beta$-blockers, calcium channel blockers, angiotensin-converting enzyme (ACE) inhibitor, angiotensin receptor blocker (ARB), statin, and oral antidiabetics as indicated. All patients were also prescribed 100 mg aspirin and 75 mg clopidogrel per day for a period of 6 months.

Clinical and angiographic follow-up

All patients who underwent successful PTCA and stent application were clinically followed. Their polyclinic controls were performed on the third and sixth months following their procedures. Emergency coronary angiography was carried out on patients complaining about repeated chest pain and on those patients who were rehospitalized in our clinic due to myocardial infarction or acute coronary syndrome. Protocol-driven repeat angiography was planned after 6 months’ follow-up in the study patients. Restenosis was defined as the diameter stenosis more than 50% in the DICOM quantitative measurement during angiographic control. End points were defined as (1) death due to cardiac conditions, (2) myocardial infarction, (3) acute coronary event, and (4) recurrent revascularization (repeated PTCA and stent or surgical revascularization).

Biochemical analysis

For the determination of ADMA levels, the serum from blood samples that were obtained from all patients before the PTCA/stent procedures and at the sixth month post procedure were stored at $-22^\circ\text{C}$. All samples were analyzed concurrently using an ADMA enzyme-linked immunosorbent assay kit (DLD Diagnostika, Hamburg, Germany). Pro-BNP levels were analyzed using the immunoassay method in the Dade Behring (Deerfield, IL, USA) Dimension RXL Max system. Standards and controls provided with the kits were used in measurements. Intra-assay percent coefficient of variation was 4.58%. In contrast, the level of high-sensitivity C-reactive protein (hs-CRP) was analyzed using the nephelometric method in the Dade Behring BN ProSpec system. The values that our laboratory considered to be the normal upper limits were 250 pg/ml for Pro-BNP and 3 mg/l for hs-CRP.

Statistical analysis

Statistical analyses were performed using the statistical package for social sciences (SPSS, Chicago, IL, USA)