Vascular endothelial growth factor (VEGF), prostaglandin E\(_2\) (PGE\(_2\)) and active renin in hypertension of adrenal origin

S. Zacharieva, I. Atanassova, M. Orbetzova, G. Kirilov, E. Nachev, K. Kalinov, and R. Shigarminova
Clinical Center of Endocrinology and Gerontology, Medical University, Sofia, Bulgaria

ABSTRACT. There are limited data regarding the role of vascular endothelial growth factor (VEGF) in arterial hypertension. The aim of the present study was to determine some markers of vascular function, including VEGF, active renin and prostaglandin E\(_2\) (PGE\(_2\)) in patients with endocrine hypertension. The study comprised: 30 patients with primary aldosteronism; 32 patients with active Cushing’s syndrome; 19 patients with pheochromocytoma; 22 patients with essential hypertension and 24 healthy volunteers. VEGF was significantly elevated in all groups of patients as compared to the controls. VEGF levels in patients with Cushing’s syndrome were significantly higher than those in patients with essential hypertension and primary aldosteronism. We did not find significant differences in VEGF levels between patients with Conn adenomas and idiopathic aldosteronism as well as between patients with Cushing’s disease and Cushing’s syndrome. PGE\(_2\) levels were not significantly different among the groups. Active renin was significantly the lowest in patients with primary aldosteronism and significantly the highest in those with pheochromocytoma compared to controls. The level of active renin in patients with primary aldosteronism was significantly lower than in patients with Cushing’s syndrome and pheochromocytoma. In conclusion, VEGF levels were significantly elevated in patients with endocrine hypertension due to glucocorticoid, mineralocorticoid and/or catecholamine excess. The highest VEGF levels were detected in patients with Cushing’s syndrome. The latter is associated with accelerated development of atherosclerosis and increased cardiovascular risk. VEGF might contribute to the cardiovascular risk in this disease. This effect was not likely to be PGE\(_2\) mediated.

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INTRODUCTION

Recent studies have shown that several angiogenic growth factors are produced and secreted by normal endocrine cells and are found to be increased in pathological states of endocrine glands, including inflammation, hyperplasia, and neoplasia. Vascular endothelial growth factor (VEGF) is regarded as one of the most important angiogenic factors with specific effects on endothelial cell growth and vascular permeability, and is isolated from a variety of normal and neoplastic endocrine cells (1). VEGF-induced angiogenesis is an important component in many biological processes and also in pathologic conditions including atherosclerosis, diabetic retinopathy, increased vascular permeability and vasodilation (2). There are limited data available regarding the role of VEGF in arterial hypertension. VEGF has been shown to induce endothelium-dependent vasorelaxation in vitro (3, 4) and hypotensive responses in vivo in normotensive animals (5, 6). It has been suggested that the hypotensive effect of VEGF is mediated, at least in part, by nitric oxide (NO) (7). In humans, administration of VEGF intracoronary caused a hypotensive effect that was dependent on VEGF infusion rate (8). Although the hypotensive effects of VEGF have been characterized in normotensive subjects, these effects have not been investigated in the setting of hypertension. Previous studies have demonstrated that VEGF-induced endothelium-dependent va-
sorelaxation in aortic rings in vitro is diminished in spontaneously hypertensive rats compared to normotensive Wistar-Kyoto rats (9). In 27 untreated patients with uncomplicated essential hypertension plasma levels of vascular endothelial growth factor and its soluble receptor Flt-1 were found elevated when compared to healthy controls. These increased levels were reduced by the treatment of hypertension. This fact raises the possibility that abnormal angiogenesis may contribute to the pathogenesis of complications related to hypertension (10).

Prostaglandins (PGs) stimulate angiogenesis but the precise mechanisms of their pro-angiogenic actions remain unexplained. In various cancer tissues PGE₂ stimulates VEGF expression (11). The selective COX-2 inhibitor, NS-398, restores tumor cell apoptosis, reduces microvascular density, and reduces tumor growth of PC-3 prostate carcinoma cells xenografted into nude mice (12). The finding that VEGF increases ACE activity in endothelial cells, which probably leads to increased angiotensin II (ATII) production, suggests potentiated interaction between VEGF and the renin-angiotensin system (RAS) in vascular biology and pathophysiology (13). Recent reports suggest that ATII stimulates synthesis and secretion of VEGF in human mesangial cells through the activation of the AT₁ receptor (14). According to a recent report, long-term use of ACE inhibitors might protect against cancer (15).

The aim of the present study was to determine some markers of vascular function, including VEGF, active renin and PGE₂ in patients with endocrine hypertension.

MATERIAL AND METHODS

The study comprised: 30 patients (17 females and 13 males, mean age 48.2±2.5) with primary aldosteronism; 32 patients (20 females and 12 males, mean age 44.16±2.88) with active Cushing’s syndrome; 19 patients (9 females and 10 males, mean age 42.2±4.69) with pheochromocytoma; 22 patients with mild-to-moderate [World Health Organisation (WHO) grade I-II] essential hypertension (13 females and 9 males, mean age 43±2.12) and 24 healthy volunteers (14 females and 10 males, mean age 42.2±2.59). Hypertension was confirmed by repeated blood pressure measurements of systolic blood pressure >140 mmHg and diastolic blood pressure>90 mmHg. All patients underwent complete clinical examination in order to exclude other secondary forms of hypertension. Among the patients with primary aldosteronism 16 were with Conn adenoma and 14 were with idiopathic hyperaldosteronism. The diagnosis of primary aldosteronism was suspected in patients with: 1) spontaneous hypokalemia (serum potassium concentration <3.5 mmol/l); 2) moderately severe hypokalemia (serum potassium concentration <3.0 mmol/l) while receiving conventional doses of diuretics; 3) inappropriate kaliuresis (24-h urinary potassium value >30 mmol) in the face of hypokalemia (potassium concentration <3.0 mmol/l); 4) refractory hypertension. The diagnosis was based on elevated plasma aldosterone, low levels of plasma renin activ-

ity (PRA); failure of stimulation >50% of aldosterone levels during upright position and failure of suppression >20% of aldosterone secretion during captopril test. Screening was accomplished in the patients with suspected primary aldosteronism by measuring a morning ambulatory paired plasma aldosterone and PRA. A high ratio of plasma aldosterone (ng/dl) to PRA (ng/ml/h) >30 was a positive screening test for primary aldosteronism (16).

Twenty-two of the patients with hypercorticism had ACTH-dependent Cushing’s syndrome due to pituitary adenomas and 10 patients had adrenal adenomas. The diagnosis was based on typical clinical profile, elevated urinary excretion of cortisol, high plasma cortisol levels, loss of plasma diurnal cortisol rhythm, low level of ACTH, lack of suppression of plasma cortisol during low (2 mg) and high (8 mg) dose dexamethasone test, respectively. The diagnosis of pheochromocytoma was suspected on the basis of clinical characteristics including poorly controlled hypertension associated with bouts of sweating, headache and palpitations. It was confirmed by measuring 24-h urinary catecholamines excretion 3 times and urinary metanephrines and normetanephrines in some patients. In two patients of the group with pheochromocytomas neurofibromatosis Type 1 was diagnosed.

The investigations were performed at the time of diagnosis prior to the surgical treatment. The size of adrenal hyperplasia and location of the adrenal tumors were determined by computed tomography. All adrenal tumors were surgically removed. The diagnosis was additionally confirmed by histological investigation.

Both patients and controls were included in the study only after giving an informed consent. All participants underwent complete clinical examination in order to exclude other pathologies. All patients with endocrine hypertension had normal renal functions. Previous medications that could interfere with the measurement of investigated parameters was discontinued at least one week prior to the study. Blood samples for active renin were taken in the morning after a 30-min rest in a sitting position and were collected in plastic tubes containing ethylenediamine tetraacetic acid (EDTA). Active renin was determined by two-site immunoradiometric assay (Nichols Institute Diagnostics, USA). The sensitivity of this assay as determined by the 95% confidence limit was 1.4 µU/ml. The monoclonal antibodies with high affinity and specificity to active renin were found to have a 0.2% cross-reactivity with pro-renin. The intra- and inter-assay coefficients were <2.5 and <9.9%, respectively. VEGF in the sera samples and PGE₂ in the 24-h urine samples were measured by ELISA (R&D). The intra- and inter-assay coefficients for VEGF were 4.5 and 6.2% and for PGE₂, were 5.8 and 8.9%, respectively. All samples were run in the same assay to avoid inter-assay variations.

Statistical methods

The data were analysed using SPSS 11. The average values of each variable were compared using analysis of variance. Non-parametric Wilcoxon Signed Ranks test was used for VEGF, PGE₂, and active renin levels because the data were not normally distributed after logarithmic transformation. All results were expressed as mean±SEM. Statistical significance was fixed at p<0.05.

RESULTS

There was no statistical difference in age between controls and patients with endocrine hypertension. The levels of VEGF, active renin and PGE₂ in controls and patients are shown in Table 1.