Protein C And Protein S Functions In Essential Hypertension*

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Summary:

Both protein C and protein S are vitamin K-dependent proteins that are central to the natural anticoagulant pathway involving activated protein C. This pathway not only inhibits blood coagulation but also stimulates fibrinolysis. Arterial hypertension increases the risk of cerebral, coronary, and other vascular complications that frequently involve platelet activation and blood coagulation.

Methods:

The purpose of this study was to determine protein C and protein S activity in patients with essential hypertension compared to normotensive subjects. Protein C and protein S activities were studied in 30 patients with mild to moderate essential hypertension (mean age±SD:54.2±7.2 years) and 30 normotensive subjects (mean age±SD:53.7±7.3 years) of the same age. Protein C and protein S were measured by the use of appropriate functional assays in both groups.

Results:

Protein S activity was significantly lower in the hypertensive group (78.4±13.3%) as compared with the control group (105.1±20.9%) (p=0.001). Protein C activity values were higher in the normotensive subjects (120.3±21.1%) than in the hypertensive patients (93.9±23.8%), but there was no statistical significance (p=0.747). Protein C and protein S showed significant negative correlation with both systolic and diastolic blood pressures.

Conclusion:

The constellation of these findings ssuggest, essential hypertension, itself may cause cerebral and coronary ischemia, and other vascular complications by increased coagubility which occurs in the state of decreased protein C and protein S functions.

Key Words:

Essential hypertension, protein C, protein S, hypercoagubility.

Condensed, Unstructured Abstract:

The purpose of this study was to determine protein C and protein S activity in patients with essential hypertension compared to normotensive subjects. Protein C and protein S activities were studied in 30 patients with mild to moderate essential hypertension and 30 normotensive of the same age. Protein S activity was significantly lower in the hypertensive group (78.4±13.3%) as compared with the control group (105.1±20.9%) (p=0.001). Protein C activity values were higher in the normotensive subjects (120.3±21.1%) than in the hypertensive patients (93.9±23.8%), but there was no statistical significance (p=0.747). Protein C and protien S showed significant negative correlation with both systolic and diastolic blood pressures. The constellation of these findings suggest, essential hypertension, itself may cause cerebral and coronary ischaemia by increased coagubility which occurs in the state of decreased protein C and protein S functions.

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TABLE 1

Clinical characteristics of hypertensive and normotensive groups

	Hypertensive group	Normotensive group	p value
n	30	30	>0.05
Age (years)	54.2±7.2	53.7±7.3	>0.05
Male	11 (36.6%)	12 (40%)	>0.05
Female	19 (63.3%)	18 (60%)	>0.05
Smoker	10 (33.3%)	9 (30%)	>0.05

Introduction:

Systemic hypertension is the most prevalent cardiovascular disorder in the world, affecting more than half of the entire population over age 60[1]. In spite of increasing public awareness and a rapidly expanding array of antihypertensive medications, hypertension remains one of the leading causes of cardiovascular morbidity and mortality. Efforts to prevent, diagnose, and treat hypertension remain an important concern of national health care. Understanding the etiopathogenesis of hypertension and its complications will give us the chance of creating new approaches for treatment and prevention of cardiovascular morbidity and mortality in patients with hypertension.

Both protein C and protein S are vitamin K-dependent proteins that are central to the natural anticoagulant pathway involving activated protein C[1]. This pathway not only inhibits blood coagulation but also stimulates fibrinolysis[1].

Arterial hypertension increases the risk of cerebral, coronary, and other vascular complications that frequently involve platelet activation and blood coagulation[2]. There is recent data claiming that hemostatic factors have predicitive value for sudden death in patients with stable angina pectoris[3]. In the literature, some authors stressed on the importance of hemostatic factors, especially protein C and protein S in the occurrence of pregnancy induced hypertension and eclampsia[4,5]. The results of these studies show that the hemostatic or metabolic abnormalities in a pregnant woman with eclampsia are associated with a tendency to have decreased protein C and protein S activities.

The aim of our study was to investigate whether there were changes in serum protein C and protein S activities in patients with essential hypertension compared to normotensive subjects.

Methods:

We studied protein C and protein S functions in 30 patients (11 men and 19 women; mean age, 54.2±7.2 years) with mild-to-moderate essential hypertension who were not taking antihypertensive therapy at least for last two weeks. Mild-to-moderate hypertension was defined as mean diastolic blood pressure between 90-110 mm Hg and/or mean systolic blood pressure between 140-180 mm Hg. Normotensive group consisted of 30 healthy individuals (12 men, 18 women; mean age, 53.7±7.3) without any systemic disease. We defined exclusion criteria for both groups as having any systemic disease including coronary heart disease, hyperlipidemia, diabetes mellitus, coagulation disorders and others. There was no one receiving any drug in any group. We also excluded the patients with severe essential hypertension or secondary hypertension. Secondary hypertension was ruled out by clinical and laboratorial findings. Arterial blood pressures were measured three times in three different days in a week. Each measurement was performed by using Omron-HEM 750 CP digital sphygmomanometer after patients rested for fifteen minutes. Then the mean blood pressure values were calculated. Serum protein C and protein S

TABLE 2

Arterial blood pressure values of hypertensive and normotensive groups

	Hypertensive group	Normotensive group	p value
Systolic blood pressure (mmHg)	169.0±8.5	120.5±11.9	0.039
Diastolic blood pressure (mmHg)	99.6±5.1	71.6±6.9	0.034

measurements were carried out with Coulter IL-ACL-200 by the use of appropriate assays.

All data are shown as means±SEM. The differences in protein C and protein S activities between the control and hypertensive groups were examined by the unpaired t-test and SPSS computer program. $P<0.05$ was considered statistically significant.

TABLE 3

Protein C and protein S activities in hypertensive and normotensive groups

	Hypertensive group	Normotensive group	p value
Protein C activity (%)	93.9±23.8	120.3±21.1	0.747
Protein S activity (%)	78.4±13.3	105.1±20.9	0.001

Results:

There was no difference between the hypertensive and normotensive groups according to age and sex ($p>0.05$), as shown in table-1. No one from any group was receiving any drug. Ten patients from the hypertensive group and 9 patients from the control group were smokers ($p>0.05$)

Clinical characteristics of hypertensive and normotensive groups are shown in table-1.

Mean systolic blood pressures were found as 169.0±8.5 mm Hg in the hypertensive group and 120.5±11.9 mm Hg in the control group ($p=0.039$). Regarding to diastolic blood pressures, values were 99.6±5.1 mm Hg and 71.6±6.9 mm Hg respectively in the hypertensive and normotensive groups ($p=0.034$). There were significant statistical difference between two groups according to the arterial blood pressures (table-2).

Serum protein C activities were found as 93.9±23.8% in the hypertensive group and 120.3±21.1% in the control group. The protein C activity of hypertensive patients was lower than that of normotensive group, but there was no statistical significance ($p=0.747$). Protein S activities were 78.4±13.3% and 105.1±2.09% respectively in the hypertensive group and normotensive group. These data showed significant difference between the two groups ($p=0.001$) (table-3, figure-1).

Discussion:

Arterial hypertension increases the risk of cerebral, coronary, and other vascular complications that frequently involve platelet activation and blood coagulation[2]. McMahon et al.[6] evaluated the results of 420,000 patients with essential hypertension after following for a period of 6 to 25 years. This meta analysis revealed that 599 of the patients had fatal stroke and 4,260 of them died of coronary heart disease during the follow up period. In the United States, 20 per cent of the all population had essential hypertension[7].

Vaziri et al.[2] studied several key proteins in the blood coagulation, fibrinolytic and inhibitory systems in 29 men with arterial hypertension and 15 normal men of the same age. They found that the concentrations of von Willebrand factor, alpha 2-antiplasmin and D-dimer were significantly higher in the hypertensive group as compared with the control group. The concentration of von Willebrand factor and D-dimer were related to diastolic blood pressure. Levels of von Willebrand factor also were related to left ventricular mass index and left ventricular posterior wall and septal thickness. But they could not show any change in the levels or activities of protein S and protein C. The constellation of their findings suggested a low-grade fibrin formation and degradation, the magnitude of which was related to the diastolic blood pressure. These observed abnormalities can potentially contribute to the cardiovascular complications of untreated essential hypertension. In an other study[8] that was designed to investigate whether there was a relation between increased incidents of thromboembolic events and essential hypertension, decreased activities and levels of protein C, protein S and antithrombin III were claimed to be the causes of vascular complications.

De Boer et at.[4] investigated the plasma levels of thrombin antithrombin III complexes in women with uncomplicated pregnancy, patients with preeclampsia, gestational hypertension and nonpregnant control

subjects. In addition, they measured the coagulation inhibitors antithrombin III, protein C and protein S. In preeclampsia they observed reduced antithrombin III and protein C levels, and no further reduction of protein S compared with normal pregnancy.

Arterial hypertension itself is one of the risk factors of coronary heart disease. It is now clear that some risk factors for coronary heart disease, such as cigarette smoking and high plasma lipid levels, affect the hemostatic process[9]. Human gelatinous and fibrous plaques are rich in fibrinogen, fibrin, and fibrin (ogen) degradation products[10,11]. Fibrinogen and fibrin are involved in tissue proliferation[12] and patients with some

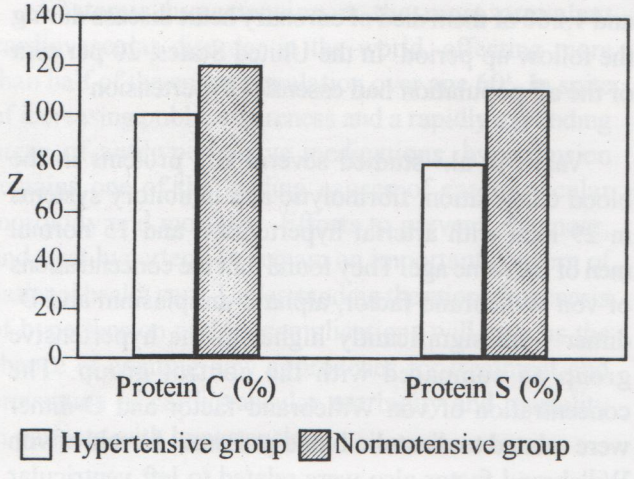

Figure 1.
Protein S and protein C activity in hypertensive and control groups

qualitative abnormalities of fibrinogen are prone to thrombosis[13] which is major determinant of myocardial ischemia[14]. Drugs that affect hemostatic parameters reduce the recurrence of the two major ischaemic complications of atherosclerosis, stroke and myocardial infarction[15].

A "hematological stress syndrome" in atherosclerosis has been described[16], and a variety of stress conditions like positive energy balance, smoking, high blood pressure, diabetes mellitus, inflammation and older ages have been shown to change hemostatic parameters, creating a prone to hypercoagubility[17]

Another study[18] that was aimed to determine the risk factors for vascular complications of hypertension showed occurrence of accelerated brain infarction in hypertension was associated with reduced protein C levels. Although it remains unclear whether protein C deficiency itself increases the risk of cerebral artery thrombosis; it may predispose a patient to develop multiple brain infarctions in association with hypertension.

In a study[19] of biological risk factors for sudden death in patients with coronary artery disease, 320 patients were, prospectively, recruited and followed up over two years. During the follow up period, 12 of the patients died suddenly. In these patients, protein C levels were lower than the other patients and serum fibrinogen concentrations were higher than the living patients.

Kloczko[20] from Poland determined plasma protein C and serine protease inhibitors together with some other hemostasis parameters in 60 patients with essential hypertension. They found significant decreases in protein C and alpha 2-antiplasmin levels, but increased fibrinogen and fibrinopeptide A concentrations. Their results indicate hypercoagubility and fibrinolysis defect in hypertensive patients.

Although, most of the literature data concerning the relation between the anticoagulants and essential hypertension support our results, there are some reports claiming there is no change in the activities and levels of protein C and protein S in the patients with essential hypertension. One of these studies[21] was performed in 38 patients with essential hypertension and as a control group 20 normal healthy blood donors by measuring protein C antigen. Authors did not find any abnormality in protein C levels.

In conclusion, our study demonstrated that protein S and protein C levels were lower in the patients with essential hypertension than the normal subjects, but only protein S levels showed statistically significant difference between the two groups. The constellation of these findings suggests, essential hypertension itself may cause cerebral and coronary ischemia, and other vascular complications by increased coagubility as a result of the decreased protein C and protein S activities. The second part of this study is going on to evaluate whether antihypertensive therapy improve protein C and protein S functions in the patients with essential

hypertension.

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