Association of soluble E-selectin and morning blood pressure surge in patients with essential hypertension

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Abstract

Background: Elevated soluble E-selectin which reflects a state of endothelial activation with subsequent vasoconstriction may elevate morning blood pressure (BP) surge. This study aimed to analyze soluble E-selectin serum concentrations in patients with essential hypertension against normotensive healthy individuals and to find a role of such molecule in the phenomenon of morning BP surge.

Material and methods: In this case-control study, a 24-hour ambulatory blood pressure monitoring with recording of morning BP surge and serum soluble E-selectin levels were measured for a total of 90 patients (60 patients with essential hypertension and 30 normotensive subjects as a control).

Results: Hypertensive patients had higher body mass index in comparison to control subjects (30.7 ± 2.3 kg/m^2 *vs.* 27 ± 3.2 kg/m^2, $p < 0.001$). Serum uric acid levels were higher in hypertensive patients than control subjects (7.26 ± 2.60 mg/dL *vs.* 5.92 ± 1.15 mg/dL, $p = 0.028$). Hypertensive patients had higher left ventricular mass index (LVMI) (110.5 ± 19.2 g/m^2 *vs.* 99.8 ± 9.5 g/m^2, $p = 0.001$). Patients with essential hypertension have higher level of soluble E-selectin than normotensive participants (180.6 ± 96.1 *vs.* 75.9 ± 31.5 ng/mL, $p < 0.001$). Soluble E-selectin was positively correlated with morning BP surge ($r = 0.696$, $p \leq 0.001$).

Conclusion: Patients with essential hypertension have higher level of soluble E-selectin than normotensive. Soluble E-selectin was positively correlated with morning BP surge.

Key words: hypertension; soluble E-selectin; morning blood pressure surge

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Introduction

Daily changes in systemic blood pressure, shown as peaks and troughs or a circadian rhythm, are typical [1]. The morning BP surge is defined as the difference in average systolic BP between two hours after awakening and the average systolic BP during the deepest sleep period [2]. Morning hypertension has been linked to cardiovascular events [3]. Numerous variables, including increased physical activity, the sympathetic nervous system, the renin–angiotensin–aldosterone system, and endothelial dysfunction, all contribute to the development of morning BP surge [4]. Hypertension increases the expression of cell adhesion molecules in endothelial cells. These molecules operate as a connec-

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tive tissue between leukocytes and endothelial cells [5]. These cell adhesion molecules, which include soluble E-selectin, soluble P-selectin, vascular cellular adhesion-1 (sVCAM-1) and soluble intercellular adhesion-1 (sICAM-1) are increased in essential hypertension and are associated with atherosclerosis independently [6]. High amounts of soluble E-selectin may promote endothelial damage or activation in people with essential hypertension [7]. Elevated soluble E-selectin which reflects a state of endothelial activation in the early morning hours with subsequent vasoconstriction may elevate morning BP surge. This work aimed to analyze soluble E-selectin serum concentrations in subjects with essential hypertension against normotensive healthy individuals and to find a role of soluble E-selectin in the phenomenon of elevated morning BP surge.

Material and methods

Study population

This observational study was carried out on 90 subjects at the outpatient clinic of cardiology in our University hospital, over a period of ten months from February to November 2021. The research adhered to the Declaration of Helsinki standards and was authorized by the university's institutional review board (IRB approval number 8/2020 CARD23). All participants had signed a written informed consent before their involvement in the study.

The subjects were classified into two groups: the first group contained 60 newly diagnosed essential hypertension patients. For the office BP, the threshold is ≥ 140 mm Hg for systolic BP and ≥ 90 for diastolic BP according to European guidelines of hypertension management [8]. The second group included age and sex-matched 30 normotensive individuals.

Methods

Each patient had a thorough history taking and clinical examination, which included determining their body mass index (BMI). After ten minutes of rest, patients' right arm blood pressures were measured using a WXB-50 model sphygmomanometer in a sitting position. Blood pressure was measured at least twice on two different occasions in individuals with blood pressure more than 140/90 mm Hg for the first time. They were all diabetic-free, with fasting blood glucose levels less than 110 mg/dL. Patients with secondary hypertension, coronary artery disease, diabetes mellitus, stroke, decompensated heart failure, or peripheral arterial disease, as well as pregnant women, were excluded from the study. The controls were healthy adults with systolic/diastolic BP of less than 135/85 mmHg, no risk factors for cardiovascular disease, and no clinical indications of any other organic illness.

Resting echocardiogram was done in the lateral decubitus position using the Vivid 9 pro N cardiovascular ultrasound system (Vingmed-General Electric, Norway) equipped with a 3.5 MHz transducer. The left ventricular (LV) dimensions, LV ejection fraction, and LV mass index were all measured.

Ambulatory BP monitoring

The Ambulatory BP monitoring procedure was carried out during a 24-hour period with the CONTEC PM50 device. BP measurements were taken every 15 minutes throughout the day (07:00–22:00 hours) and every 30 minutes at night (22:00–07:00 hours) using an upper arm BP cuff (with the appropriate cuff size). Participants were instructed to refrain from excessive physical activity and maintain a relaxed arm during the monitoring time. The afternoon and evening timetables were determined by an individual's sleeping patterns. At least 70% of measurements must be accurate, and monitoring must last at least 20 hours with a maximum of three hours between consecutive readings. The maximum inflation pressure was 250 mmHg during the day phase and 220 mmHg during the night phase. All recordings were inspected and processed using cardioversion software compatible with the CONTEC PM50 equipment. Daily, nightly, and 24-hour mean systolic and diastolic BP readings were computed for each patient based on hourly averages of ambulatory BP measurements. The morning BP surge is determined by subtracting the morning SBP (mean SBP for the first two hours after awakening) from the lowest nocturnal SBP during sleep.

Measurement of soluble E-selectin

Each patient had 3 mL of venous blood taken and put in a sample tube. After 30 minutes at room temperature to enable the blood to coagulate, it was centrifuged for 10 minutes at 3000 rpm. The resultant serum was maintained at a temperature of –80°C until testing. We evaluated the concentrations of soluble E-selectin using an enzyme-linked immunosorbent test (Human soluble E-selectin ELISA Kit, sun Red, Shanghai, China).

Statistical analysis

SPSS version 20 (SPSS Inc., Chicago, IL) and Microstat W software (SPSS Inc., Chicago, IL) were

used to tabulate and analyze the data (India, CNET Download.com). The mean, standard deviation, and range were used to express quantitative data. Quantitative data were expressed as mean, standard deviation, and range. Categorical data were expressed as numbers and percentages, whilst quantitative data were expressed as mean, standard deviation, and range. The chi-square test (X2), the Z test for two independent proportions (ZProp), and Fisher's exact test were used to evaluate categorical data (FET). The Shapiro-Wilk tests were employed to evaluate the normality of quantitative data, with $p > 0.05$ indicating normality. For normally distributed data, the Student t-test was employed, whereas non-parametric variables were evaluated using the Mann-Whitney U test (ZMWU). Correlations were calculated using Person's coefficient of correlation (r). In this investigation, the acceptable threshold of significance was 0.05 ($p < 0.05$ was considered significant).

Results

The research population included 60 patients with essential hypertension [34 (56.7%) were males and 26 (43.3%) were females] with a mean age of 52 ± 8 years and 30 healthy normotensive persons with a mean age of 51 ± 9 years.

Hypertensive patients had higher BMI in comparison to control subjects (30.7 ± 2.3 kg/m^2 *vs.* 27 ± 3.2 kg/m^2, $p < 0.001$). The mean office BP in hypertensive patients was 151 ± 9.7/88 ± 6.9 mm Hg and in control subjects was 116 ± 9.6/74 ± 6.8 mm Hg. Lipid profile and serum creatinine were insignificantly different in both patients and controls. Serum uric acid levels were significantly greater in hypertension patients than in controls (7.26 ± 2.60 mg/dL *vs.* 5.92 ± 1.15 mg/dL, $p = 0.028$). Hypertensive patients had higher left ventricular mass index (LVMI) (110.5 ± 19.2 g/m^2 *vs.* 99.8 ± 9.5 g/m^2, $p = 0.001$). Table 1 summarizes the variations in baseline demographic, laboratory, and echocardiographic data between the study groups. Table 2 demonstrates the results of the ambulatory blood pressure monitoring in hypertensive patients. The mean morning BP Surge in patients was 36.67 ± 11.49 mm Hg. Serum levels of soluble E-selectin were significantly higher in hypertensive patients in comparison with control subjects (180.6 ± 96.1 ng/mL *vs.* 75.9 ± 31.5, p value < 0.001) (Tab. 3 and Fig. 1). The correlation analysis between soluble E-selectin and ambulatory BP monitoring recording parameters are demonstrated in Table 4. Soluble E-selectin was positively correlated with morning BP surge ($r = 0.696$, $p \leq 0.001$) (Fig. 2).

Discussion

Endothelial expression of the cell-surface adhesion molecule soluble E-selectin results in endothelial

Table 1. Demographic and laboratory features of the groups

	Hypertensive patients (n = 60)	Normotensive control subjects (n = 30)	p-value
Age [years]	52 ± 8	51 ± 9	0.592
Male sex [n, %]	34 (56.7 %)	18 (60 %)	0.763
BMI [kg/m^2]	30.7 ± 2.3	27 ± 3.2	<0.001
Smoker [n, %]	19 (31.7 %)	11 (36.7 %)	0.635
Systolic BP [mm Hg]	150.6 ± 9.7	116 ± 9.6	<0.001
Diastolic BP [mm Hg]	88 ± 6.9	74 ± 6.8	<0.001
Total cholesterol [mg/dL]	203.4 ± 37.2	193.2 ± 33.7	0.196
LDL-C [mg/dL]	134.6 ± 34.9	127.9 ± 33.9	0.241
HDL-C [mg/dL]	39.8 ± 8.2	39.1 ± 6.8	0.696
Triglycerides [mg/dL]	149.8 ± 66.8	131.9 ± 34.5	0.186
Uric acid [mg/dL]	7.26 ± 2.60	5.92 ± 1.15	0.028
Creatinine [mg/dL]	0.94 ± 0.22	0.89 ± 0.18	0.308
LVEF [%]	62.3 ± 4.7	63.4 ± 5	0.313
LVMI [g/m^2]	110.5 ± 19.2	99.8 ± 9.5	0.001

BP — blood pressure; BMI — body mass index; HDL-C — high density lipoprotein cholesterol; LDL-C — low density lipoprotein cholesterol; LVEF — left ventricular ejection fraction; *statistically significant at $p \leq 0.05$

Table 2. Ambulatory blood pressure monitoring data in cases group

Variable [mm Hg]	
Office systolic BP	150.58 ± 9.83
Office diastolic BP	88.0 ± 7.02
24h systolic BP	143.9 ± 11.25
24h diastolic BP	84.88 ± 8.87
Daytime systolic BP	145.65 ± 10.78
Daytime diastolic BP	86.47 ± 8.96
Night systolic BP	130.63 ± 12.03
Night diastolic BP	78.72 ± 7.52
Lowest sleep systolic BP	113.03 ± 10.91
Morning systolic BP	149.70 ± 13.02
Morning BP Surge	36.67 ± 11.49

BP — blood pressure, data are expressed by mean value ± standard deviation

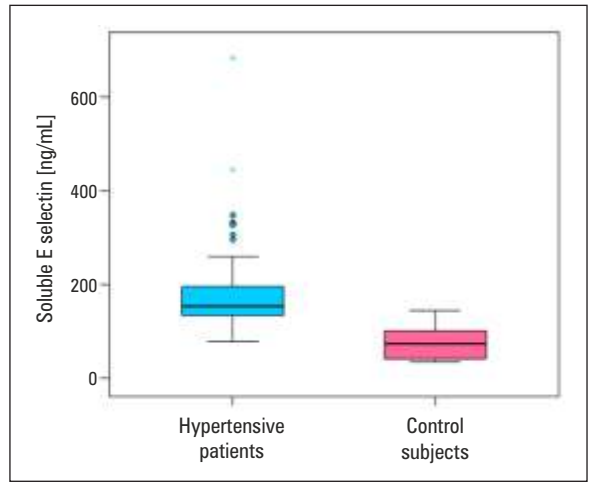

Figure 1. Serum levels of soluble E-selectin in hypertensive patients and control subjects

activation, which is induced by proinflammatory cytokines such as tumor necrosis factor alpha (TNF-α) and interleukin 6 (IL-6). Endothelial activation facilitates the recruitment and attachment of circulating leukocytes to the vessel wall, initiating the atherosclerosis process [9].

The current study's primary findings were that: (1) individuals with essential hypertension had a greater level of soluble E-selectin than normotensive participants, and (2) the amount of soluble E-selectin is connected with the morning BP surge. To our knowledge, the latter discovery has never been proved previously.

In normotensive participants, the blood level of soluble E-selectin was 75.9 31.5 ng/mL, compared to 180.6 ± 96.1 ng/mL in hypertension patients. Our findings corroborate previous research revealing higher soluble E-selectin levels in essential hypertension patients relative to normotensive controls [10–13].

Ivan Palomo et al. determined the blood levels of soluble E-selectin and sVCAM-1 in three groups: normotensive volunteers, controlled-hypertension patients, and uncompensated-hypertension patients. They detected significant differences in serum levels of soluble E-selectin and VCAM-1 across the three research groups. Both soluble E-selectin and VCAM-1 levels were considerably higher in hypertensive patients than in normotensive individuals, and both were significantly higher in patients with uncompensated hypertension than in those with controlled compensated hypertension. They hypothesized that increased arterial BP increases cell adhesion molecule production, most likely via endothelial activation [14]. On the other hand, other research indicates that people with essential hypertension do not exhibit significant increases in soluble E-selectin levels [15–17]. These studies limited the enrolled patients to only mild uncomplicated hypertension without any features of target organ damage, and this could be an explanation to the disagreement with our findings.

The morning BP surge may be explained by reduced endothelial function in the early morning. In the early morning hours, impaired endothelial function may result in increased vasoconstriction. We discovered a strong association between an elevated morning BP surge and higher plasma levels of soluble E-selectin, an endothelial activation marker. Previously, Otto ME et al. reported a reduction in early morning endothelial function as measured by flow-mediated dilation of the brachial artery [18]. Additionally, Anna Solini et al. demonstrated that hypertension patients have worse endothelial function than normal persons [19]. Knudsen et al. [20] demonstrated a direct correlation between heightened plasma levels of soluble E-selectin and intercellular adhesion molecule 1 and an increased morning BP surge in type 2 diabetes. In hypertensive individuals, Ceravolo R et al. found an inverse connection between morning BP surge and endothelium-de-

Table 3. Serum levels of soluble E-selectin in hypertensive patients and control subjects

	Hypertensive patients (n = 60)	Normotensive control subjects (n = 30)	p-value
Soluble E-selectin [ng/mL]	180.6 ± 96.1	75.9 ± 31.5	< 0.001

Table 4. Correlation between soluble E-selectin and ambulatory blood pressure monitoring recording parameters in hypertensive patients

	Soluble E-selectin	
	rs	p-value
24h systolic BP	0.605	< 0.001
24h diastolic BP	0.455	< 0.001
Daytime systolic BP	0.629	< 0.001
Daytime diastolic BP	0.460	< 0.001
Night systolic BP	0.342	0.008
Night diastolic BP	0.400	0.002
Morning systolic BP	0.775	< 0.001
Morning BP Surge	0.696	< 0.001

Rs — Spearman coefficient; BP — blood pressure

pendent acetylcholine-stimulated vasodilation [21]. Amar et al. and Blake GJ et al. explored the relationship between an increase in morning blood pressure and an inflammatory state as indicated by blood C-reactive protein levels [22, 23]. Additionally, resistant hypertension and damage to target organs are associated with increased levels of inflammatory biomarkers, which may act as a negative regulator of soluble E-selectin [24]. This was demonstrated by de Faria AP et al., who observed that those with resistant hypertension had a higher concentration of soluble E-selectin than those with mild to moderate hypertension [25].

Other findings

Hypertensive individuals had significantly greater blood uric acid levels than those with normal blood pressure. Similar findings were achieved by Osman Turak et al. [26]. Increased serum uric acid levels are associated with oxidative stress, endothelial dysfunction, and activation of the renin-angiotensin system, all of which contribute to elevated systemic BP [27]. Appropriate hyperuricemia therapy has evolved into a therapeutic strategy for hypertension. Reduced serum uric acid significantly lowered blood pressure in obese patients with essential hypertension [28–30].

We also reported higher BMI in hypertensive patients than normotensive participants. Obesity causes hemodynamic abnormalities and increases arterial stiffness that alter the BP. The prevalence of hypertension increases significantly as body mass index increases [31, 32]. Control of body weight is an essential goal to reduce the prevalence of hypertension and improve the cardiovascular outcome.

Study limitations

The causal relationship between soluble E-selectin and morning BP surge cannot be inferred. Collection of blood sampling from participants in the early morning was difficult. The relatively small patients' sample is another limitation.

Conclusion

Essential hypertension patients had a greater amount of soluble E-selectin than normotensive patients. The concentration of soluble E-selectin was positively correlated with the morning blood pressure increase.

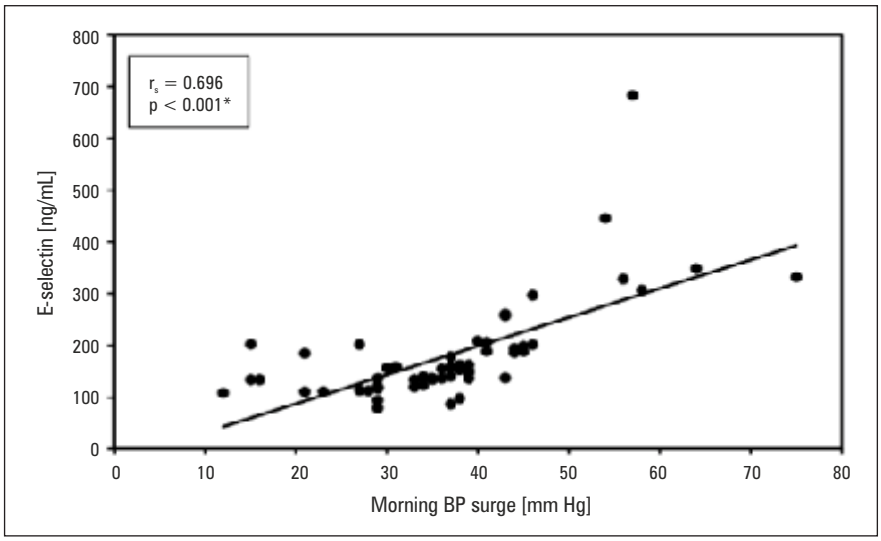

Figure 2. Correlation between soluble E-selectin and morning blood pressure (BP) surge

Conflict of interest

The authors declare that they have no conflict of interest.

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