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# Endothelin in Complicated and Uncomplicated Hypertension

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**Abstract**

This work comprised seventy seven patients with essential hypertension classified into three groups : Group I (38 patients) : Noncomplicated hypertensives, Group II (13 patients) : Hypertensives complicated by ischemic heart disease, and group III (26 patients) : Hypertensives complicated by recent cerebral infarction. Fourteen healthy age matched subjects were taken as a control. They were subjected to full clinical assessment, E.C.G., abdominal sonar, routine laboratory investigations. Echocardiography, and C.T. were done when indicated. Plasma renin activity as well as plasma endothelin-1 level were measured. We concluded a significant elevation of plasma endothelin-1 level in patients with uncomplicated hypertension as well as in those complicated by ischemic heart disease or recent cerebral infarction ($P < 0.001$). The elevation in hypertensives with recent cerebral infarction (group III) was significantly higher than that of uncomplicated hypertensives (group I) ($P < 0.001$). Hypertensives with chronic ischemic heart disease (group II), showed insignificant elevation of plasma endothelin-1 level when compared to uncomplicated hypertensives or those with recent cerebral infarction. The elevation of plasma endothelin level in (group III) showed significant positive correlation with systolic, diastolic and mean arterial blood pressure, yet, no such correlation was detected in the other two groups. In addition, Plasma renin activity showed no significant variation in our studied groups. Also, no significant correlation was found between plasma renin activity and plasma endothelin-1 level.

## Introduction

**OVER** the last decade it has become apparent that the endothelium of arteries and veins regulate the state of vascular contraction and relaxation, the vascular permeability and the adherence of circulating cells such as platelets to the intimal surface[**1**].

In 1985 - 1986, two groups of investigators discovered a vasoconstrictor, peptide produced by endothelial cells in culture and by intact blood vessels subjected to hypoxia, stretches and othr stimuli[**2,3**].

In 1988 Yanagisawa and coworkers characterized a novel and potent vasoconstrictor peptide produced by vascular en-

dothelial cell and named the compound «Endothelin»[4].

Recent studies have demonstrated that endothelin circulates in plasma of normal animals and human[5].

Increases in circulating endothelin have been documented in states of severe cardiovascular stress, including cardiogenic shock[6], acute myocardial infarction[7], after major abdominal surgery[8] and after liver transplantation[9].

Those increases are consistent with its role as an important endogenous vasoconstrictor that appears to modulate arterial pressure. Intravenous infusion of human endothelin induced a rise in blood pressure [5].

The vasoconstrictive properties, modulatory actions on the renin angiotensin and aldosterone system and antinatriuretic effects of endothelin have been well characterized in vitro and in vivo[10].

The possible pathophysiological role of endothelin in hypertension has not been fully demonstrated.

Our aim is to determine plasma endothelin-1 level and to assess its possible role in such conditions.

## Material and Methods

This study was performed on 77 patients with essential hypertension (34 men and 43 women), their ages ranged between 40-65 years with a mean value of 51.87 ± 1.05.

The patients were categorized into three groups :

1. **Group (1) :** of 38 non complicated hypertensives.
2. **Group (2) :** of 13 hypertensives complicated by ischemic heart disease.
3. **Group (3) :** of 26 hypertensives complicated by cerebrovascular strokes.

In comparison, a group of 14 healthy age matched (mean age 50.57 ± 5.9 years) subjects (9 men and 5 women) were taken as a control.

All patients were subjected to full history taking and clinical examination stressing on duration, family history of hypertension and antihypertensive drugs.

Patients were considered to have hypertension when their diastolic blood pressure was in excess of 90 mmHg measured in more than two occasions in the supine position. Mean arterial blood pressure was calculated by the equation :

Mean arterial blood pressure = Diastolic blood pressure + (systolic blood pressure — diastolic blood pressure/3)[11].

Electrocardiographic study and abdominal sonography were performed to all patients while, echocardiography and brain computerized tomography were performed when indicated.

Blood picture, urea and creatinine, liver function tests, fasting and postprandial blood sugar, serum lipids (Serum cholesterol and triglycerides) and serum uric acid were assessed in all patients. Plasma renin activity was assessed by radioimmunoassay[12] while plasma endothelin-1 was determined by radioimmunoassay on 62 patients and the control group[13].

All patients have to with hold drug therapy two days prior the study. They were hospitalized and rested in bed in the supine position for at least 30 minutes before sampling blood for endothelin assay.

Sampling and methods : Venous blood samples were collected into a chilled syringe and transfered into a polypropylene tube containing EDTA (1 mg/ml) and aprotinin (500 KIU/ml) at O.C. Plasma was separated and frozen at -20 C° till time of assay.

Plasma for endothelin evaluation was acidified and extracted with 0.1% trifluoroacetic acid, then centrifuged and the supernatant was applied to C 18 micro-columns (Sep - Pak. waters Inc., Rochester, MN) that were activated with 60% acetonitrile. After supernatant application to the column, washing with 0.1% trifluoroacetic acid and elution with acetonitrile. The eluent was evaporated to dryness under nitrogen stream at 37 C° bath, and the residue was reconstituted in the assay buffer (0.05 M phosphate buffer, pH 7.4). The assay was carried out with the kit produced by Pensiula Laboratories (Belmont. CA).

**Results**

Results are shown in tables (1, 2 & 3) and in figures (1, 2).

Table (1) : The Mean of Plasma Renin Activity, and Endothelin-1 Level in Control Group and the Tested Groups.

| Group | Plasma renin activity (ng/ml/hr) | Plasma endothelin-I (pg/ml) |
|---|---|---|
| Control group: Mean ±S.D. | 1.57±0.93 | 8.82±1.75 |
| Group I: Mean ± S.D. | 1.28±0.7 | 17.27±3.15 |
| P1 | >0.05 | <0.001 |
| Group 2: Mean ± S.D. | 1.17±0.90 | 24.18±4 |
| P2 | >0.05 | <0.001 |
| P4 | >0.05 | >0.05 |
| Group 3: Mean ± S.D. | 1.52±0.88 | 21.1±5.35 |
| P3 | >0.05 | <0.001 |
| P5 | >0.05 | <0.001 |
| P6 | >0.05 | >0.05 |

P1 = group 1 versus control group.
P2 = group 2 versus control group.
P3 = group 3 versus control group.
P4 = group 1 versus group 2.
P5 = group 1 versus group 3.
P6 = group 2 versus group 3.

Table (2) : Correlation Between Systolic, Diastolic and Mean Arterial Blood Pressure Versus the Mean Values of Plasma Endothelin-1 Levels in the Three Hypertensive Groups.

| | Plasma endothelin-1 (pg/ml) | | | | | |
|---|---|---|---|---|---|---|
| | Uncomplicated hypertensive (group 1) | | Hypertensives with ischemic heart (group 2) | | Hypertensives with cerebral strokes (group 3) | |
| | r | P | r | P | r | P |
| Systolic blood pressure | 0.03 | >0.05 | 0.38 | >0.05 | 0.6 | <0.001 |
| Diastolic blood pressure | 0.03 | >0.05 | 0.46 | >0.05 | 0.7 | <0.001 |
| Mean blood pressure | 0.0036 | >0.05 | 0.43 | >0.05 | 0.7 | <0.005 |

Table (3) : Statistical Analysis Comparing the Mean Values of Postprandial Blood Sugar, and Serum Cholesterol Level Between the Tested Groups.

| Group | Postprandial blood sugar (mg/dl) | Serum cholesterol (mg/dl) |
|---|---|---|
| Group (1) | | |
| Mean | 109 | 193.26 |
| S.D | 10.88 | 35.36 |
| Group (2) | | |
| Mean | 121.92 | 234.69 |
| S.D | 15.38 | 37.81 |
| P1 | <0.001 | <0.001 |
| Group (3) | | |
| Mean | 119.31 | 224.27 |
| S.D | 14.82 | 56.92 |
| P1 | <0.001 | <0.05 |
| P2 | N.S | N.S |

P1 = compares group leversus group 2

P2 = between group 2 and 3.

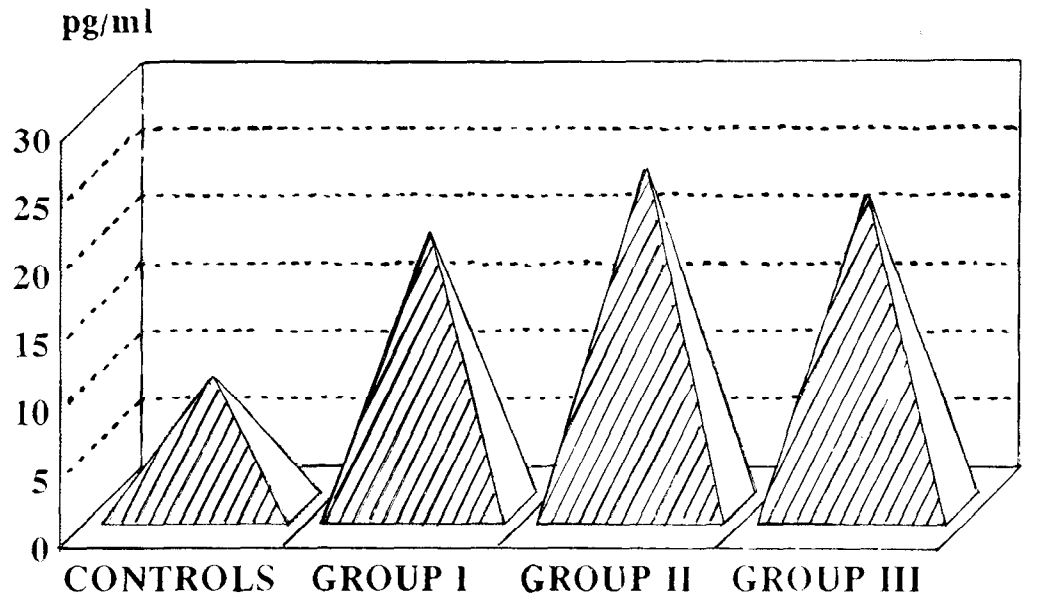


Fig. 1. Plasma endothelin in normal controls and hypertensive patients.

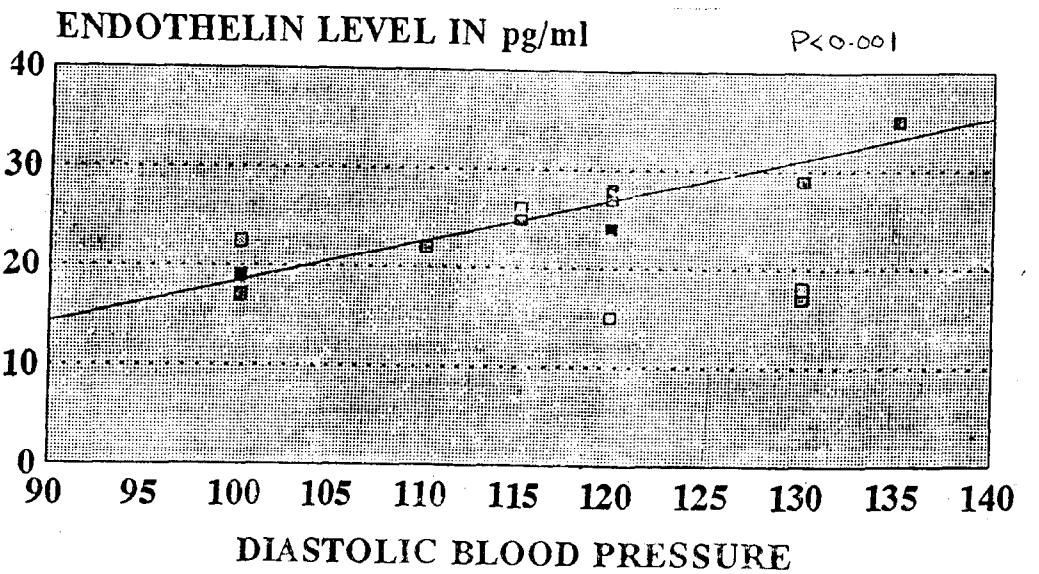


Fig. 2. Relation between diastolic blood pressure and endothelin-1 in hypertensives complicated with cerebral strokes (group 3).

## Discussion

Endothelin is a 21 amino acid endothelium derived peptide first isolated from cultured porcine endothelial cells[4]. It induces vasoconstiction in variety of vascular beds, possibly by directly or indirectly modulating vascular smooth muscle dihydropyridine sensitive calcium channels [14] or by activating other pathway of transmembrane signaling[15].

The extremely potent vasoconstrictor action of endothelin and wide distribution of its binding sites including arteries, brain and kidneys[16], suggest that it might be important in blood pressure control as well as in the pathogenesis of hypertension.

Our patients with uncomplicated hypertension (group I) showed a significant elevation of the mean value of plasma endothelin (17.27 $\pm$ 3.15 pg/ml) compared to (8.82 $\pm$ 1.75 pg/ml) in the control group, $P < 0.001$. This is in agreement with the findings reported by Shichiri et al. (1990)[17], Saito et al., (1990)[18]. Kohno and his colleagues (1990)[19] found that plasma endothelin-1 level was significantly higher in hypertensive patients compared to normotensives and borderline hypertensives.

Endothelin was more with progress than with the onset of essential hypertension. Our results showed no overlap in plasma endothelin levels between hypertensives and the control group, also no significant correlation between plasma endothelin level and duration of hypertension was detcted ($P > 0.05$).

Infusion of endothelin-1 in human produces significant rise in blood pressure at plasma concentration seven times the preinfusion level[5]. The concentration of plasma endothelin in our results as well as in previous results did not approach these values, yet the local concentration of endothelin at the site of blood vessels might be high enough to increase peripheral vascular resistance[20].

Several explanations are advocated, one is that an increase in the transmural pressure across the endothelial cells, may activate the synthesis and release of endothelin[21]. Elevation of plasma endothelin may induce proliferation in vascular smooth muscle cells, thereby contributing to the development of hypertension. Another is that endothelin or one of its degeneration products may accumulate because of impaired renal function associated with the development of hypertension. This is supported by positive correlation of serum creatinine level and negative correlation of glomerular filtration rate with plasma endothelin of hypertensive patients[19].

Schiffrin and Coworkers[22], found that gluteal subcutaneous small resistance arteries of male essential hypertensives exhibit a decrement in responsiveness to endothelin-1. This is due to reduced endothelin receptor density which can be explained by down regulation of endothelin-1A receptors (ETA) which is responsible for endothelin induced vasoconstriction[23].

The results of our work differs from findings reported by Schiffrin and Thiabault, [24] and Miyauchi et al.[25] who observed similar plasma endothelin level in

hypertensives and age matched normotensive subjects. They also observed significantly low plasma endothelin level in women. Yet our results showed no significant difference in plasma endothelin in either sex.

In hypertensive patients complicated by ischemic heart disease (group II), the mean value of plasma endothelin-1 level was statistically significantly higher (24.18 ± 4 pg/ml) compared to (8.82 ± 1.75 pg/ml) in control group, $P < 0.001$, but no significant difference when compared to uncomplicated hypertensives.

Ranier and Coworkers[**26**] and Lerman et al.[**13**] demonstrated elevated plasma endothelin in all angiographically proven coronary artery disease patients. The highest concentration was detected in cases with unstable angina[**27**]. Raised plasma endothelin was reported also in patients with acute myocardial infarction but not in stable or unstable angina[**28,29**].

Chester et al.[**30**] studied the effect of endothelin in normal and diseased human epicardial coronary arteries and reported that endothelin-1 produced dose dependent contractions in both normal and diseased vessels and the degree of contraction was significantly greater in healthy vessels.

Our patients with ischemic heart disease had a mean value of plasma cholesterol level higher than those with uncomplicated hypertension ($P < 0.001$).

The elevation of plasma endothelin level in our hypertensive patients with ischemic heart disease might be due to hypertension, atherosclerosis, congestive heart failure (45.4% of cases) and hyperlipidemia. Atherosclerosis was reported to be associated with increased plasma endothelin level[**31**]. Also patients with congestive heart failure were observed to have high plasma endothelin level which may contribute to the systemic vasoconstriction and cardiovascular remodeling of this condition[**32**].

In hypertensive patients complicated by recent cerebral infarction (group III), the mean plasma endothelin level was significantly higher in group III patients (21.1 ± 5.35 pg/ml) when compared to either control group (8.82 ± 1.75 pg/ml), and uncomplicated hypertensives (group I) (17.27 ± 3.15 pg/ml) ($P < 0.001$). There was insignificant difference between group III, patients and group II patients.

Our results are in agreement with the findings of Ziv et al.[**33**] who observed a four fold elevation of plasma endothelin level in patients with acute non-hemorrhagic infarction.

Macrae and Coworkers[**34**] demonstrated that endothelin-1 is capable of reducing cerebral blood flow to pathologically low levels when applied to the surface of an exposed middle cerebral artery of anesthetized rats.

The elevation of plasma endothelin level in acute cerebral infarction can be explained by enhanced production by damaged endothelial cells within the infarcted tissue local leakage of endothelin-1 may induce severe and prolonged constriction of collateral vessels[**33**].

Our patients with cerebral infarctions had a mean value of plasma cholesterol level higher than those with uncomplicated hypertensives ($P < 0.05$). This hypercholesterolemia may have a role in the elevation of plasma endothelin level in this group.

In our study, the arterial blood pressure (either systolic, diastolic or mean) was positively correlated with plasma endothelin levels in hypertensives complicated by cerebral strokes (group III), but not in group I or group II.

Saito et al.[**18**] and lerman et al.[**13**] noticed no correlation between the plasma endothelin-1 levels with systolic, diastolic or mean blood pressure in uncomplicated hypertensives and those with organ complications. However, Kohno et al.[**19**] reported that the blood pressure was correlated to plasma endothelin level in uncomplicated hypertensive patients.

Also, Schiffrin and Thiabault[**24**] reported a positive correlation between plasma endothelin level and mean blood pressure in hypertensives but not in normotensives.

The mean value of plasma renin activity of our studied groups showed no significant variations between the tested groups. Although our hypertensive patients had a mean plasma renin activity lower than those of control subjects, yet this decrease was insignificant.

Also, our results showed no significant correlation between plasma renin activity and plasma endothelin levels neither in the control group nor in the three hypertensive groups and this is consistent with the results of Schichiri et al.[**17**]. The discrepancies in published experimental data indicate that the potential influence of endothelin-1 on release of renin is not yet settled.

In conclusion, our work demonstrated a significant elevation of plasma endothelin level in patients with uncomplicated hypertension as well as in those complicated by ischemic heart disease or recent cerebral infarction. When the last two groups were compared to uncomplicated hypertensives, the elevation of plasma endothelin-1 level was significant in those complicated by recent cerebral infarction, but insignificant in those complicated by old ischemic heart disease. This suggests a role of plasma endothelin-1 as a potent vasoconstrictor in the pathogenesis of essential hypertension and its vascular complications. The elevation can be attributed to many contributing factors, higher levels might be an indicator of a risky state with development of vascular complications. Further clarification awaits the availability of specific endothelin-1 antagonist or inhibitor for clinical use.

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