CHAPTER

5

Endothelial Cell Dysfunction in Hypertension

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Introduction

Cardiovascular diseases caused 2.3 million deaths in India in the year 1990; this is projected to double by the year 2020. Hypertension is directly responsible for 57% of all stroke deaths and 24% of all coronary heart disease deaths in India. Pooling of epidemiological studies show that hypertension is present in 25% urban and 10% rural subjects in India[1]. At an underestimate, there are 31.5 million hypertensives in rural and 34 million in urban populations. A total of 70% of these would be in need to reduce this blood pressure. Population-based cost-effective hypertension control strategies should be developed.

Thus, the pathophysiology of essential hypertension and its complications has been a focus of much research and clinical interest. More recent attention has been directed towards inflammation and endothelial cell dysfunction, especially since inflammation can promote endothelial cell dysfunction and the latter has been intimately related to thrombogenesis and atherogenesis. Essential hypertension (EHT) is associated with functional and morphological alterations of the endothelium[2]. Due to its position between blood stream and smooth muscle cells (responsible for peripheral resistance), the endothelium is thought to be both target and mediator of arterial hypertension.

Endothelial cell dysfunction is characterized by an imbalance between humoral and cellular factors, which influence the function, and structure of endothelial wall. Traditional risk factors such as arterial hypertension, dyslipidemia, hyperglycemia, smoking, age and obesity may initiate endothelial damage[2]. The increased vascular resistance in essential hypertension is related to the imbalance of action of vasodilators and vasoconstrictors. Endothelin 1 (ET-1) acts as the natural counterpart to endothelium-derived nitric oxide (·NO), which has vasodilating, antithrombotic, antiproliferative effects, and which inhibits leukocyte-adhesion to the vascular wall.

Blockade of cyclooxygenase in hypertensive patients can restore the ·NO production, suggesting that ·NO inactivation may be caused by cyclooxygenase derivatives such as prostacyclin (PGI2) and thromboxane (TXA2). As reactive oxygen is produced by cyclooxygenase, and ·NO rapidly reacts with reactive oxygen to form oxidant and nitrating species, this ·NO inactivation pathway could be involved in the reduction of endothelium-dependent vasorelaxation found in essential hypertension. Somova *et al*[7] reported significantly increased ratio of TXA2 (measured as TXB2) to PGI2 (measured as 6-keto PGF1±) in the hypertensives (mean ± SEM, 2.78 ± 0.12) as compared to normotensives (mean ± SEM,1.29 ±

0.10). Based on this study, we also determined the ratio of TXB2/6-keto PGF1±.

The involvement of lipid peroxidation during the pathogenesis of hypertension has not been extensively studied. Cholesterol oxides (ChOx) are formed as the result of cholesterol oxidation catalyzed by enzymes and by free radical-mediated reactions. ChOx are toxic to endothelial cells and inhibit ·NO production by these cells. Accordingly, a number of *in vitro* and *ex vivo* animal studies have shown that antioxidants may improve endothelium-dependent vasodilation by limiting lipid peroxidation and improving the bioactivity of ·NO.[3,4,5]

The active stages of atherosclerosis are characterized by extensive infiltration of blood derived macrophages and T lymphocytes through the endothelium into the intima. Cellular adhesion molecules have key role in this process. ELAM (endothelial leukocyte adhesion molecule) is a cell adhesion molecule, which mediates the blood cell adhesion to the vascular endothelium and is found only on activated endothelium hence is particularly interesting. Increased expression of sELAM (also known as sE-selectin) is implicated in vascular disease and may accompany the development of hypertension.[6] In our population, where prevalence of EHT is increasing day by day, measurements of these parameters may have diagnostic and/or prognostic implications.

Aims and Objectives

To understand the importance of vasoactive factors in essential hypertension, circulating levels of important vasodilators such as ·NO and PGI2; and vasoconstrictors such as ET-1 and TXA2; lipid hydroperoxides (LOOH) and sELAM were measured in subjects with untreated essential hypertension; ratio of TXB2/6-keto PGF1± was also determined and these were compared with healthy, normotensive, nondiabetic, normolipidemic subjects. The aim was to evaluate their diagnostic/ prognostic usefulness.

Material and Methods

The study subjects included male subjects having untreated, essential hypertension (n = 54, age ranging from 35-65 years) as patient group (EHT) and compared them with age matched normotensive, nondiabetic healthy male subjects (n = 75, diastolic blood pressure (DBP) < 90 mmHg and systolic blood pressure (SBP) < 140 mmHg), which comprised control group.

Blood pressure was measured by mercury sphygmomanometer in supine position with a cuff of appropriate size placed on the left arm and at least three readings were taken at different times to confirm the levels. Out of 54 hypertensive patients, 45 (83.3%) had mild hypertension (DBP 90 – 99 mmHg) and 9 (16.7%) had moderate hypertension (DBP 100 – 109 mmHg). None of the subjects had history of diabetes or ischemic heart disease. The healthy controls had no history of ischemic heart disease, diabetes, hypertension or dyslipidemia. Their blood reports, ECG and stress test were normal and they were not on any medication. The study was approved by the institutional review committee. Informed consent was taken from all the subjects prior to blood collection. Venous blood samples were collected after 14 h of fast in sterile, vacuumed tubes containing heparin as anticoagulant for measurement of cholesterol, triglycerides, HDL, LDL, Nox, LOOH and sELAM; dipotassium ethylene diamine tetra acetic acid (EDTA) as anticoagulant for measurement of ET-1 and potassium oxalate with sodium fluoride as anticoagulant for blood sugar measurement. For prostacyclin and thromboxane measurements, 10.0 ml blood was collected in tubes containing 0.95 ml EDTA (2 gm disodium EDTA and 0.8 gm NaCl in 100 ml with distilled water, pH 7.4) and 0.05 ml 0.04M indomethacin solution in absolute ethanol. Indomethacin inhibits subsequent metabolism of arachidonic acid to prostaglandins. Blood samples were centrifuged at 2000 rpm for 10 min and plasma stored at –15 ^{0}c to –20 ^{0}c. Repeated freeze-thaw cycles were avoided.

Table 1A : Clinical features of the study population, comparison of categorical variables (using c^2 analysis)

Characteristic	Controls (75)	EHT (54)	df	c^2	p
*Smokers	17	9	1	0.779	0.33
§ Alcohol consumers	26	23	1	0.906	0.34
‖Type A personality	28	26	1	1.206	0.27
¶ Positive family history	21	14	1	0.164	0.68
** H/O Dyslipidemia					
Untreated	Nil	24	-----	-----	
Treated (statins)	Nil	10	-----	-----	

df : Degree of freedom

* Users of all types of tobacco products, currently or in past

§ Subjects consuming at least 1-2 pegs of alcohol daily

‖ Subjects having lot of anxiety, always remaining tense

¶ Subjects having at least one of the blood relation with history of hypetension

**Total cholesterol >200 mg/dl, triglycerides >150 mg/dl, LDL >130 mg/dl, HDL < 40

mg/dl or those treated with lipid lowering drugs

Blood sugar, cholesterol, triglycerides and high-density lipoproteins (HDL) were measured as routine parameters on dry chemistry autoanalyzer (Vitros 750). Low-density lipoproteins (LDL) values were calculated by Friedwald's formula [LDL = total cholesterol – HDL cholesterol – (0.2 x triglycerides), all values in mg/dL]. ·NO is oxidized immediately to nitrate and nitrite anions (NOx) in mammals, hence, NOx levels which directly reflect the plasma ·NO levels, were measured by spectrophotometric method using griess reaction as described by Shi et al.[8] LOOH is measured by spectrophotometric kit method (Oxis international). Assay is based on the oxidation of ferrous ions to ferric ions by hydroperoxides under acidic conditions, the ferric ions bind with the indicator dye, xylenol orange, to form a stable colored complex. The complex can be measured at 560 nm. ET-1 and sELAM levels were measured by sandwich enzyme linked immunosorbent assay (ELISA) using commercial kit (R&D systems). PGI2 and TXA2 have very short half life hence their more stable metabolites, 6 keto PGF1± ðand TXB2 respectively, were measured

Table 1B : Clinical features of the study population, comparison of continuous variables (using student's t test)

Characteristic	Control(75) mean ± SEM	EHT(54) mean ± SEM	p, (CI lower, upper)
Age (yrs)	48.4 ± 0.68	49.0 ± 1.11	0.62
BMI (kg/m²)	24.9 ± 0.31	26.7 ± 0.45	<0.001(2.39, 4.457)
Diastolic (mmHg)	79.81 ± 0.64	95.40 ± 0.73	<0.001(13.68,17.5)
Systolic (mmHg)	124.66 ± 0.84	146.75 ± 0.99	<0.001(19.54,24.63)
Sugar (mg/dL)	84.56 ± 0.97	84.29 ± 1.18	0.8590
Cholesterol (mg/dL)	188.36 ± 1.88	195.40 ± 4.2	0.0935
Triglycerides (mg/dL)	126.46 ± 2.87	153.11 ± 8.05	<0.001
HDL (mg/dL)	42.68 ± 0.59	38.42 ± 1.04	<0.001
LDL (mg/dL)	120.08 ± 1.30	126.20 ± 3.32	0.0567

by enzyme immunoassay methods (Amersham Pharmacia). The ratio of TXB2/6-keto PGF1± ð was determined.

Statistical Analysis

The differences in categorical variables were analysed by Ç2 test. The comparison of continuous variables (expressed as mean (SEM) was done using unpaired student's t test. A value of $p < 0.05$ was considered statistically significant.

Results

Table 1A and Table 1B show clinical features of the study population. The comparison shows no significant difference in mean age between EHT and control subjects. The mean body mass index (BMI) is significantly higher in EHT group as compared to controls. When other categorical variables such as smoking, alcohol consumption, personality type and positive family history of EHT are compared, no significant difference is found between both these groups. The comparisons of vasoactive factors in subjects having EHT with controls using unpaired student's t test shows significant increase ($p < 0.001$) in levels of vasoconstrictors, ET-1 and TXB2 in EHT subjects as compared to controls

Table 2 : Showing comparison of vasoactive factors in hypertensive with normotensive, healthy controls. M: Mean, SEM: Standard error of means, CI: 95% confidence interval, TX –TXB2 PG - 6 keto PGF1± T/P - TXB2 / 6 keto PGF1 ±

PARAMETERS		Control n = 75	EHT n = 54	p, (CI lower,upper)
ET1 (pg/ml)		M ± SEM	0.56 ± 0.0220.	0.84 ± 0.039 <0.001 (-0.35, -0.18)
	Range	15 - 1.00	0.45 - 1.6	
NO_x (µMol/L)	M ± SEM	33.6 ± 1.2	35.7 ± 1.93	0.33
	Range	15 - 70	12 - 58	
LOOH (µMol/L)	M ± SEM	10.0 ± 0.68	14.5 ± 0.94	<0.001 (-6.78, -2.31)
	Range	2.0 - 33.0	2.6 - 33.0	
TX (pg/ml)		M ±SEM	52.9 ± 2.08	66.2 ± 3.28 <0.001 (-20.6, -5.99)
	Range	19 - 95	31 - 132	
PG (pg/ml)	M ± SEM	49.3 ± 1.61	47.0 ± 1.70	0.33
	Range	21 - 85	25 - 80	
T/P	M ± SEM	1.18 ± 0.07	1.48 ± 0.08	0.005 (-0.50, -8.90)
	Range	0.4 - 3.5	0.6 - 2.7	
sELAM (ng/ml)	M ± SEM	50.5 ± 2.18	63.9 ± 3.37	<0.01 (-21.03, -5.82)
	Range	19 - 115	30 - 122	

(Table 2). A significant increase in levels of LOOH ($p < 0.001$) and sELAM ($p < 0.01$) is also seen. However, the difference in mean levels of NOx and 6 keto PGF1± are not significant ($p > 0.05$) between these two groups. There is significant increase ($p = 0.005$) in the ratio of TXB2/ 6 keto PGF1± in EHT subjects as compared to controls.

Discussion

ET-1 is a potent vasoconstrictor. Since ET-1 plays a role in the regulation of vascular tone, it has been hypothesized that increased production or release of ET-1 or both may contribute to the pathogenesis of hypertension. Local vascular generation of ET-1 may contribute to elevated peripheral resistance in hypertension[9]. Endothelin-1 (ET-1) is a powerful vasoconstrictor and mitogen that contributes to blood pressure elevation and related vascular remodeling and target organ damage. ET-1 also influences salt and water homeostasis through effects on the renin-angiotensin-aldosterone system and vasopressin, thus elevating blood pressure and increasing vascular tone. Circulating ET-1 levels are elevated in a variety of animal models of hypertension, particularly those that are salt-dependent, and in a subset of human hypertensives, i.e. African-Americans.[10]

In our study, patients with hypertension had significantly higher plasma ET-1 concentration than normal subjects ($p < 0.001$). Similar results were obtained in other case/control studies such as the study conducted by Amroso *et al.*[11] (case/control = 25/15, $p < 0.02$), by Zoccali *et al.*[12] (case/control = 20/8, $p < 0.01$) and by Hlubocka *et al.*[13] (case/control = 25/ 29, p=0.05). Whereas in four other studies, carried out by Davenport *et al.*[14] (case/ control = 25/25), Veglio *et al.*[15](case/control = 30/25), Hoffman *et al.*[16] (case/control = 17/19) and Taddei *et al.*[17] (case/control = 10/10), no difference in ET-1 levels was seen in hypertensive patients as compared to control subjects. In comparison to studies reported so far, our study has maximum number of patients and controls. From all these studies and from the results of our study, it can be concluded that patients with uncomplicated essential hypertension without other cardiovascular risk factors or clinical manifestations of atherosclerosis have significantly elevated plasma levels of ET-1. Higher concentrations of ET-1 suggest presence of endothelial cell dysfunction without other risk factors or cardiovascular complications.

NO is a natural counterpart of ET-1. The release of nitric oxide seems to be modulated by changes in blood pressure. Studies have shown that blunted

endothelium–dependent vasodilator response in essential hypertensives is largely due to reduced bioactivity of nitric oxide.[18] In hypertension, a disturbance of $O2^{-}$ and ·NO balance may induce the generation of oxidant and nitrating species which may result in disturbances of ·NO bioactivity / bioavailability. This may explain the results of NOx levels in our patients. Even though there was no significant difference in NOx levels between 2 groups, possibly its bioactivity was low. Node *et al.*[19] and Kumar *et al.*[20] reported significantly decreased ($p < 0.001$ and $p < 0.05$ respectively) plasma concentration of NOx in essential hypertension in comparison to that in controls (case/control = 108/127 and 25/12 respectively). In our study, contrary to above results, direct measurement of circulating levels of NOx did not show significant difference in hypertensive subjects as compared to normotensives. Our results are in agreement with Moriel *et al.*[21] who also reported no difference of NOx between subjects with mild essential hypertension (n=11) and healthy subjects (n=11). These apparent discrepancies may be attributable to the differences in the extent or duration of hypertension or vascular wall injury.[19] Also, the diet plays role in variability of NOx levels. The results of study conducted by Wang et al.[22] showed that the plasma concentration were significantly lower on the low nitrate/nitrite diet than on the free diet ($P < 0.01$).

The balance between TXA2 and PGI2 appears to contribute to the homeostatic regulation of normal blood pressure. In the hypertensive state, this balance is disrupted and, at least in animal models of hypertension, there is excessive production of both.[23] The increase in PGI2 formation may be a reaction to the elevated blood pressure, possibly due to mechanical stimulation of the vascular smooth muscle cells in the blood vessel wall. However, the increase in TXA2 may be more directly involved in the development and maintenance of hypertension. Both the endothelial cells and the muscularis of arteries synthesize vascular PGI2 endogenously. While the endothelial cells undoubtedly synthesize large amounts of PGI2, the muscularis comprises a much larger tissue mass so that the overall synthesis is about equally distributed between the endothelial and muscle cells.[24] Uehara *et al.*[25] (case/control = 25/25) and Chen *et al.*[26] (case/control = 26/25) found significantly lower ($p < 0.001$) plasma levels of 6 keto PGF1± ð in patients with essential hypertension as compared to normals. In the present study, we found significant increase in TXB2 levels in hypertensive subjects ($p < 0.01$) as compared to normotensive controls. No significant difference was found in 6 keto PGF1± ð levels between the two groups, which was contrary to the reports mentioned above. Uyama *et al.*[27] also did not find significant difference ($p > 0.05$) in PGI2 levels between the control subjects (n=23), and hypertensive patients (n = 14). However, in our study, the ratio of TXB2/6 keto PGF1± was significantly higher ($p < 0.01$) in hypertensive subjects as compared to controls and this is in echo with studies reported by Somova et al.[7]

The antioxidants and lipid peroxidation products are being extensively studied because of their potential importance and pathogenic role in several noncommunicable diseases like cardiovascular diseases and cancer, however the data on hypertension is scant. It may be stressed that ours is the largest study with all relevant parameters. Barring two studies,[29,30] there are hardly any reports on the subject from our country. The study carried out by Srinivas et al.[28] aimed to assess the levels of lipid peroxidation and antioxidants besides dislipidemia changes among 32 newly diagnosed male hypertensives by comparing them with an equal sample of normotensives. Significant increase in serum lipid peroxide levels and significant decrease in antioxidant enzyme superoxide dismutase and vitamins E and A were observed among hypertensives than the controls. They suggested that hypertensive patients might have elevated lipid peroxidation and reduced protection from antioxidants, which may contribute to the propensity in such patients to develop cardiovascular diseases.

In our study population, LOOH levels were found to be significantly higher in hypertensive subjects than in normotensive controls, mean ± SE, 14.5 ± 0.94 vs.10.0 ± 0.68 mM, $p < 0.001$.

Our results are in agreement with the results of Kumar et al[29] who reported an increase in free radical generation and a simultaneous decrease in the production of nitric oxide and antioxidants such as superoxide dismutase and vitamin E in subjects having essential hypertension (n = 25) as compared to controls (n = 18). Possible involvement of reactive oxygen species and nitric oxide in the pathogenesis of human essential hypertension was investigated by Prabha et al.[30] It was observed that both superoxide anion and hydrogen peroxide production by polymorphonuclear leukocytes and the plasma levels of lipid peroxides were higher in uncontrolled essential hypertension (n = 30) compared with normal controls (n = 30). Superoxide anion, hydrogen peroxide and lipid peroxide levels reverted to normal values after the control of hypertension by drugs. Several anti-hypertensive drugs inhibited lipid peroxidation in vitro. These results suggest that an increase in free radical generation occurs in essential hypertension. This increase in free radical generation can inactivate prostacyclin and nitric oxide and decrease their half life which can lead to an increase in peripheral vascular resistance and hypertension. In a study carried out by Turi et al.[31] oxidative stress, an antioxidant/pro-oxidant imbalance, in patients with juvenile essential hypertension (age 14.4 ± 3.1 years, n = 52) before any treatment, and controls (age 14.3 ± 4.3 years, n = 48) was measured via several biochemical parameters. Measurements were made of the plasma lipid peroxidation end-products, as malondialdehydes. There were decreased plasma levels of nitrates and increased levels of lipid peroxidation end-products in the hypertensive patients, resulting in a consistent increase in the plasma lipid peroxidation/nitric oxide ratio as compared with the controls ($p < 0.01$). The presence of systemic oxidative stress was proven in hypertensive subjects. Moriel et al.[21] measured concentrations of cholesterol oxides measured in plasma of 11 patients with mild essential hypertension (H: 57.8 ± 9.7 years; blood pressure, 148.3 ± 24.8/90.8 ± 10.2 mmHg) and in 11 healthy subjects (N: 48.4 ± 7.0 years; blood pressure, 119.4 ± 9.4/75.0 ± 8.0 mmHg). The content of cholesterol oxides (7-ketocholesterol, 5 alpha-cholestane-3 beta, 5,6 beta-triol and 5,6 alpha-epoxy-5 alpha-cholestan-3 alpha-ol) in LDL were increased in hypertensive patients. Thus, they concluded that an increase in cholesterol oxidation is associated with endothelium dysfunction in essential hypertension and oxidative stress, although NO metabolite levels in plasma are not modified in the presence of elevated cholesterol oxides. EHT also leads to an increased lipid peroxidation of low density lipoproteins, a condition which is known to be associated with accelerated atherosclerosis.

The results of all these studies, including the present study, indicate that LOOH is an early marker of endothelial cell dysfunction.

Increased expression of sELAM is implicated in vascular disease and may accompany the development of hypertension. Study conducted by Paloma et al[32] showed that sE-selectin levels are higher in EHT patients than normotensive subjects (sE-selectin: 71 ± 21 vs. 48 ± 14 ng/mL, $p < 0.0001$). Serum concentrations of sELAM was higher in patients with non-compensated hypertension than in patients with compensated hypertension. High arterial blood pressure (ABP) may therefore increase the production of cell adhesion molecules, probably through endothelial activation. In our study significant elevation of sELAM was seen in subjects having untreated essential hypertension as compared to normotensive controls ($p < 0.001$). The following studies showed similar results.

Sanada et al[33] reported significantly higher Serum E- selectin levels in the subjects with EHT than in the controls ($p < 0.01$). Serum levels of soluble E- selectin decreased after the initiation of benidipine treatment and correlated with diastolic blood pressure. The study conducted by Buemi et al.[34] ascertained that arterial blood pressure

increased by the cold pressor test modified serum concentrations of sELAM. Their findings showed that levels of sELAM were higher in patients with essential hypertension than in normotensive subjects ($p < 0.05$). Furthermore, in normotensive and hypertensive patients, the cold pressor test caused an increase in serum concentrations of sELAM. Malmqvist et al[35] also reported significantly higher sELAM levels in hypertensive subjects having left ventricular hypertrophy than in normotensive subjects. ELAM levels were measured in serum from 38 hypertensive patients without LV hypertrophy and 38 normotensive subjects. ELAM levels were higher in hypertensive than in normotensive subjects (56 ± 19 versus 49 ± 11 ng/ml, $p = 0.031$). De Caterina et al[36,] compared thirty-one previously untreated and uncomplicated essential hypertensive patients with 16 normotensive controls. They also reported significant elevation in sELAM levels in hypertensive subjects as compared to normotensive subjects ($p < 0.001$).

To determine whether soluble ELAM levels were raised in hypertension, Blann et al[37] measured levels of sELAM in forty-five consecutive patients with uncontrolled hypertension (blood pressure > 140/90 mmHg) and 33 consecutive patients with controlled hypertension (blood pressure < 140/90 mmHg, i.e. normotension) and compared with 40 normotensive age- and sex-matched controls. Soluble ELAM levels were raised in hypertension compared with controls and normotension. Also soluble ELAM levels correlated with DBP ($p < 0.001$). However they found no clear relationship between levels of either endothelial cell index or the class of drug therapy used or its dosage. In another study[38] they collected from 58 patients with hypertension (blood pressure: minimum 140/90 mmHg; median 162/99 mmHg) to measure concentrations of soluble ELAM. A second sample was obtained from 15 patients when hypertension (median blood pressure 158/93 mmHg) was under control (median blood pressure 139/78 mmHg) 18 months (mean) later and blood tests repeated. All subjects were reassessed 36 months (mean) after the study began and cardiovascular endpoints such as myocardial infarction, stroke, or coronary artery bypass grafting were noted. There were significant reductions in systolic and diastolic blood pressure (both $P = 0.001$), and soluble ELAM level ($P = 0.02$) in the 15 patients followed up at 18 months.

There are contradictory reports also. Hlubocka et al[39] measured levels of ELAM measured in patients with hypertension without any other risk factors of atherosclerosis ($n = 22$) and in normotensive controls ($n = 22$). The levels of ELAM were not different in hypertensive subjects as compared to normotensive subjects. Desouza et al[40] measured ELAM in 11 hypertensive (69 ± 1 yr) and 10 normotensive (65 ± 1 yr) older men who were free of overt atherosclerotic disease, diabetes, and dyslipidemia. They found no significant difference in hypertensive subjects as compared to normals (51.1 ± 3.9 ng/ml vs. 48.8 ± 6.6 ng/ml). However, the subjects in both these studies were low.

From the results of all these different studies, it is evident that sELAM is an important marker for endothelial cell dysfunction.

Conclusion

One may conclude from our results and results of other studies that there is imbalance of vasoactive factors leading to endothelial cell dysfunction in hypertension. Although the levels of circulating vasoactive factors can be easily measured, so far there are not many studies reported with human subjects. In this study circulating levels of various vasoactive factors were analyzed using simple, sensitive and precise methods, which did not require any sophisticated instruments. Blood samples can be easily obtained without causing any physical or psychological trauma from patients. These results may be helpful in diagnosis of EHT at a very early stage so that preventive therapy can be implemented. Early detection of endothelial cell dysfunction may be a useful measure to guide therapy before the damaging effects of hypertension (such as stroke, myocardial infarction, renal dysfunction etc.) manifests.

Acknowledgements

We are deeply grateful to the Trustees, Chief Executive Officer, Medical Directors and Research Director of Jaslok Hospital and Research Center for providing us with necessary facilities, the financial support to the project and valuable suggestions for undertaking the research project at this center.

Summary

Background

Hypertension is a major risk factor for atherosclerotic cardiovascular disease. Hypertension is associated with functional and morphological alterations of the endothelium, which disturbs delicate balance of endothelium-derived factors resulting in endothelial cell dysfunction. The endothelial cell dysfunction could then facilitate the maintenance of elevated peripheral resistance, which would favor the occurrence of atherosclerosis. Cell-surface adhesion molecules involved in leukocyte rolling and attachment to the vascular endothelium, play a role in the initiation of atherosclerosis.

Aims and objectives

The objective of the present study was to investigate whether or not the circulating levels of vasoconstrictors [endothelin 1 (ET-1) and thromboxane (TXA2)], lipid hydroperoxides (LOOH) and soluble endothelial leukocyte adhesion molecule (sELAM) are elevated and circulating levels of vasodilators [nitric oxide (NO) and prostacyclin (PGI2)] are reduced in essential hypertension.

Method

Nitric oxide as nitrites and nitrates (NOx) and oxidized LDL as lipid hydroperoxides were measured spectrophotometrically; ET-1, TXA2 (as TXB2), PGI2 (as 6 keto PGF1±) and sELAM were measured using enzyme immunoassay methods in 54 male subjects having untreated, hypertension (mild/moderate) and were compared with age-matched 75 healthy, controls.

Results

Significantly higher levels of ET-1 ($p < 0.001$), TXB2 ($p < 0.001$), sELAM ($p < 0.01$) and LOOH ($p < 0.001$) were found in essential hypertension subjects (EHT) as compared to controls. The difference in NOx and 6 keto PGF1± between controls and EHT subjects was not statistically significant. There was significant increase ($p = 0.005$) in the ratio of TXB2 / 6 keto PGF1 ± in EHT subjects as compared to controls.

Conclusions

Elevated levels of vasoconstrictors (ET-1, TXB2), LOOH and sELAM in untreated essential hypertension subjects as compared to controls confirmed the presence of endothelial cell dysfunction, even in mild to moderate cases of hypertension. The measurement of circulating vasoactive factors may be helpful in diagnosing endothelial cell dysfunction at a very early stage, thereby helping in implementing preventive actions.

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