

Oxidative Stress and Endothelial Dysfunction in White Coat Hypertension: Data of the Group from Cerrahpasa Medical Faculty

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Abstract

In 2000 a group of authors from İstanbul University Cerrahpaşa Medical Faculty Internal Medicine Department interesting in hypertension (HT) especially White Coat Hypertension (WCH) come together and began to study on WCH. We founded a team and act as a referral center in our faculty.

Cases with blood pressure >140/90 were referred to our clinic. We classified the cases into sustained hypertension (HT) and white coat hypertension (WCH) groups. We defined WCH as clinical hypertension and day time ambulatory blood pressure less than 135/85.

First of all we investigated if WCH were innocent. With this purpose we searched for the target organ damage with a cross sectional study and our manuscript was published (Target organ damage and change in arterial compliance). We studied the metabolic changes caused by WCH and it was also published within the same manuscript.

Since that time we have been following up these groups longitudinally to see if WCH turns to sustained HT or target organ damage and/or metabolic changes occur by the time. We are planning to report the progression of twenty years in 2020.

It has been documented that oxidative stress and endothelial dysfunction participated in the pathogenesis of sustained hypertension. As we observed white coat is not innocent due to our previous studies we aimed to see if there also exists oxidative stress and endothelial dysfunction in WCH with some serial studies using different markers such as asymmetric dimethyl arginine (ADMA) a competitive inhibitor of NO (nitric oxide), homocystein (decreasing the bioavailability of NO), paroxanase (PON; preventing lipid oxidation), oxLDL, sLOX-1 (oxidation products of lipids and proteins) and endogenous antioxidant components. It has been observed that the majority of our studies evaluating endothelial function indicated that endothelial dysfunction is more prevalent in WCH than in NT, but it is either equal or worse in HT as compared to WCH.

Keywords: Endothelial dysfunction; ADMA; Homocystein; NO; Angiogenesis; VEGF; Arterial compliance

Introduction

Currently we are interested in the progression of endothelial dysfunction and atherosclerosis in HT. It was indicated endothelial dysfunction had participated in the pathogenesis of atherosclerosis in HT [1,2]. Many studies were performed to show that WCH was not a benign process and might be accompanied by target organ damages due to progressed atherosclerosis like HT. We thought that we could prove the existence of endothelial dysfunction and search for the biological markers contributing to endothelial dysfunction such as reduction of the activity and/or expression of the e (NOS) and or vascular formation of oxygen derived free radicals.

Increased Oxidative Stress

Oxidative stress is thought to play a critical role in the pathogenesis of hypertension. Protein oxidation is defined as the covalent

modification of a protein induced either directly by reactive oxygen species or indirectly by reaction with secondary by-products of oxidative stress. We evaluated the protein oxidation and examined the function of the antioxidative system in sustained and white coat hypertensives and compared with normotensives [3]. We investigated the protein oxidation parameters [protein carbonyls (PCOs)] PCO and the endogenous antioxidant components protein thiol (P-SH), CuZn-superoxide dismutase (CuZn-SOD) and glutathione (GSH) in the groups. Thirty-seven hypertensive subjects (M/F: 17/20) aged 48.59 ± 1.77 years, 37 WCH subjects (M/F: 18/19) aged 49.10 ± 1.85 years and 37 normotensive control subjects (M/F: 17/20) aged 48.78 ± 2.23 years were recruited in our study. Subjects with other risk factors for atherosclerosis [low-density lipoprotein (LDL)>130 mg, diabetes mellitus, body mass index (BMI) >25, smoking] are not included. All patients were free of vascular and renal diseases (serum creatinine >1.3 mg/dl), malignancy, connective tissue diseases, endocrine diseases and alcoholism. Patients using drugs that may affect BP and lipid metabolism and antioxidant substances were also excluded. Sustained hypertensive and WCH groups exhibited higher protein oxidation and lower P-SH, CuZn-SOD and GSH activities than normotensives. With

regard to these parameters, there was no significant difference between sustained hypertensive and WCH groups. There exists an imbalance between oxidants and antioxidants in WCH group because of the increase of oxidants associated with the decrease of antioxidant capacity. We thought this might cause endothelial dysfunction just like in sustained hypertension. It can be to add antioxidants to conventional antihypertensive therapy to balance the oxidative status in WCH.

With another study we wanted to see if there exists oxidative stress in WCH like HT. Oxidized low density lipoprotein (oxLDL) plays an important role during the atherosclerosis process and paraoxonase (PON1) can significantly inhibit lipid peroxidation. We determined the serum PON1 activity, oxLDL and malondialdehyde (MDA) concentrations and their relationship with serum lipid parameters and systolic and diastolic blood pressures (SBP and DBP) in subjects with white coat hypertension (WCH), hypertension (HT) and normotension (NT) groups [4]. The study group consisted of a total of 86 subjects, 30 with WCH (14 male, 16 female subjects), 30 with HT (13 male, 17 female subjects) and 26 with NT (12 male, 14 female subjects). The patients with smoking habit, dyslipidemia and diabetes mellitus were excluded. Both white coat hypertensive and hypertensive subjects had significantly higher levels of MDA than normotensives the oxLDL level of the HT group was significantly higher than the NT group. The levels of ox LDL in HT, WCH and NT groups were 70.54 ± 25.75 , 60.15 ± 20.33 and 51.21 ± 16.35 respectively. The level of oxLDL in white coat hypertensives was not significantly different from hypertensives and normotensives. In other words the WCH group had an oxLDL level similar to both hypertensive and normotensive group and it can be interpreted that WCH patients may also have increased risk of oxidative stress, but it was not as high as in the HT group and was not as low as in the NT group. HT and WCH groups had significantly lower PON1 levels than the NT group. oxLDL correlated with MDA positively and PON1 negatively. A negative correlation between MDA and PON1 was detected. Our data demonstrated that the increasing of oxidative stress in WCH group was associated with a decrease in PON1 activity. The reduction in PON1 activity may be one of the factors leading to an increase in oxidative status in WCH which may cause atherosclerosis. We asked whether the decrease level of PON can be used to define the coming of atherosclerosis.

The Effect of Nitric Oxide

Elevated plasma levels of the endogenous nitric oxide (NO) synthase inhibitor asymmetric dimethylarginine (ADMA) contribute to endothelial dysfunction and seem to be a predictor for cardiovascular mortality. Elevated ADMA plasma concentrations have been demonstrated in patients with hypertension. We evaluated ADMA in WCH group (n=34) and compared with HT (n=34) and NT (n=34) groups [6]. The patients with smoking habit, dyslipidemia and diabetes mellitus were excluded. Plasma ADMA level in WCH group was significantly higher than the NT grouped. (3.21 ± 0.49 mol/l vs. 2.84 ± 0.58 mol/l, $P=0.046$) It was significantly higher in the HT group than in the NT group. There was also a significant difference between the HT and WCH groups. (4.2 ± 0.38 mol/l versus 3.21 ± 0.49 mol/l $P<0.001$). The WCH subjects had significantly higher levels of NO than the hypertensives (41.68 ± 72.23 vs 32.18 ± 2.68 mol/l; $P=0.001$) and significantly lower values than the normotensives ($48.2474.29$ mol/l; $P=0.001$). In WCH and HT group there was a negative correlation between ADMA and NO. ($r=-0.515$, $P=0.003$ and $r=-0.389$, $P=0.034$, respectively). The correlation between ADMA and NO was

stronger in WCH group than in HT. Although NO levels in HT patients were lower than white coat hypertensives and ADMA levels in HT patients were higher than WCHs, the negative correlation of these two parameters were more pronounced in WCH group [5].

The association between homocystein and sustained hypertension (HT) has been studied. We assessed homocystein levels in white coat hypertension (WCH) as an indicator of increased risk in the development of cardiovascular diseases. Plasma levels of homocystein were determined in patients with WCH, HT, and normotension (NT) groups [6]. The study group included 100 subjects, 33 with WCH (16 males, 17 females) aged 49.1 ± 1.9 ; 35 sustained hypertensives (17 males, 18 females) aged 48.5 ± 1.7 and 32 normotensive control subjects (15 males, 17 females) aged 48.8 ± 2.2 . Patients with smoking habit, dyslipidemia, or diabetes mellitus were not included in the study. Plasma homocystein levels were significantly higher in the WCH group compared to the controls and the WCH group had significantly lower homocystein values than the hypertensives. The data demonstrated that WCH was associated with high levels of homocystein. The increase in homocystein level in WCH is not as high as in sustained HT. Since an elevated plasma homocystein level has been accepted as a strong risk factor for coronary artery disease, increased homocystein levels can be concluded as a signal indicating the sooner atherosclerosis.

Abnormal Angiogenesis

Hypertensive patients are at particular risk of cardiovascular complications, possibly related to endothelial damage or dysfunction or to abnormal angiogenesis. We wanted to compare the risk conferred by white coat hypertension (WCH) vs. sustained hypertension in the development of the endothelial dysfunction and abnormal angiogenesis, by evaluating nitric oxide (NO) and endothelin-1 (ET-1) vascular endothelial growth factor (VEGF) and E selection levels in plasma [7]. The study group included 102 subjects, 34 with WCH (17 male and 17 female patients) aged 49 ± 11 years, 34 sustained hypertensives (HT) (15 male and 19 female patients) aged 47 ± 11 years and 34 normotensive control subjects (NT) (16 male and 18 female patients) aged 48 ± 10 years. Subjects with other risk factors for atherosclerosis (hyperlipidaemia LDL=130 mg/dl, diabetes mellitus, obesity BMI>27 kg/m², smoking), subjects having signs or symptoms of atherosclerotic vascular disease and other endocrine diseases or alcoholism are not included. Patients using drugs that may affect blood pressure and lipid metabolism were also excluded. All patients were free of concomitant vascular and renal diseases, malignancy and connective tissue diseases, the NO, ET-1, VEGF and E-select in WCH, HT and NT groups. The WCH subjects had significantly higher levels of NO than hypertensives and significantly lower values than normotensives; ET-1 levels of WCH group were significantly higher than the NT group and significantly lower than the HT group. Considering with VEGF, the WCH group had significantly higher levels than the NT group but the difference from the HT group was not significant. E-select in the WCH group was significantly lower than the HT group. All these data is associated with endothelial dysfunction and abnormal angiogenesis. The degree of these changes is not as severe as observed as observed in hypertensive population.

Currently an association has been described between inflammation and progression of hypertension and shown with several biochemical parameters. We examined the distribution of the serum procalcitonin (PCT), pentraxin (PTX)-3 and interleukin (IL)-33 levels and their relationship with carotid intima-media thickness (CIMT) in subjects

with white coat hypertension (WCH), sustained hypertension (HT) and normotension (NT). PCT, PTX-3 and CRP (C-reactive protein) levels significantly increased in the WCH and HT patients compared with the NT group. CIMT measurements were significantly higher in WCH and HT groups than NT group. In HT and WCH groups there were significant positive correlations between PTX-3, PCT and CRP. In HT group PTX 3, PCT and IL- 33 were positively correlated with CIMT significantly. Our results suggest that in subjects with WCH and HT PTX-3, PCT and IL-33 levels are significantly and consistently higher than normotensives. Systemic group inflammation moderately occurs in the WCH and HT groups. In inflammation causing atherosclerosis, PCT monitoring may be a useful biomarker for early diagnosis of WCH and sustained hypertension development.

To emphasize the effect of oxidation in developing of endothelial damage we examined the distribution of lectin-like oxidized LDL receptor-1 (LOX-1) levels in patients with hypertension (HT), possible association of LOX-1 with the oxidized LDL (oxLDL), endothelial nitric oxide synthesis (eNOS), nitric oxide (NOx) levels, and to characterize the differences between patients with HT and those with white coat hypertensive (WCH) in terms of these parameters compared with healthy controls. LOX-1 and oxLDL levels were significantly increased in WCH and HT patients compared with control group. eNOS activation was significantly lower in HT than control group. LOX-1 and oxLDL levels were significantly negative correlated with eNOS levels in WCH and HT groups. Carotid intima-media thickness (CIMT) measurements were significantly higher in WCH and HT groups compared with control group. There was a significant positive correlation between CIMT and LOX-1 and oxLDL where as negative correlation with eNOS in WCH. LOX-1 was the variable that had a significant effect on blood pressure. A possible impairment of endothelium may act as a cardiovascular risk factor in WCH. We suggested LOX-1 can be strong biomarkers in future for determining early endothelial damage in HT and especially in WCH patients [8].

Conclusion

We insisted on trying different markers in different studies to exclude contradictions. Increase in ADMA, (a competitive inhibitor of

NO) increase in homocystein, (decreasing the bioavailability of NO) decrease in paraoxanase (preventing lipid oxidation) caused the decreasing of NO and increasing of oxidation products of lipids (oxLDL, sLOX-1) and proteins and progresses to endothelial dysfunction.

It has been observed that the majority of studies evaluating endothelial function indicated that endothelial dysfunction is more prevalent in WCH than in NT, but it is either equal or worse in SH as compared to WCH.

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