Antioxidant Activities and Oxidative Stress Byproducts in Human Hypertension

Josep Redón, Maria R. Oliva, Carmen Tormos, Vicente Giner, Javier Chaves, Antonio Iradi, Guillermo T. Sáez

Abstract—The objective was to study oxidative status, antioxidant activities, and reactive oxygen species byproducts in whole blood and mononuclear peripherals cells and their relationship with blood pressure. Sixty-six hypertensive patients and 16 normotensive volunteers as a control group were studied. In both, whole blood and peripheral mononuclear cells oxidized/reduced glutathione ratio and malondialdehyde was significantly higher, and the activity of superoxide dismutase, catalase, and glutathione peroxidase was significantly lower in hypertensive patients when compared with normal subjects. The content of damaged base 8-oxo-2'-deoxyguanosine in nuclear and mitochondrial deoxyribonucleoproteins of hypertensive subjects was also significantly higher than that of the normotensive control subjects. No differences in these measurements were found among hypertensive subjects grouped in tertiles of 24-hour average mean blood pressure or between “white-coat” and established hypertensive subjects. Furthermore, no relationship was observed between the average of 24-hour mean blood pressure and oxidized/reduced glutathione ratio, reactive oxygen species byproducts, malondialdehide, or genomic 8-oxo-2'-deoxyguanosine. In whole blood and in mononuclear cells from hypertensive subjects, there was an increase in oxidative stress and a reduction in the activity of antioxidant mechanisms that appeared to be independent of the blood pressure values. (Hypertension. 2003;41:1096-1101.)

Key Words: oxidative stress ■ hypertension, renovascular ■ hypertension, obesity ■ risk factors ■ antioxidants ■ DNA

Oxidative stress, an excessive production of reactive oxygen species (ROS) outstripping antioxidant defense mechanisms, has been implicated in pathophysiological conditions that affect the cardiovascular system such cigarette smoking, hypercholesterolemia, diabetes, and hypertension.1-3 Oxidative stress accompanying hypertension in animal models includes spontaneous hypertension,4 renovascular hypertension,5 deoxycorticosterone acetate-salt model,6 and obesity-related hypertension.7 Moreover, reducing superoxide radicals by infusion of superoxide dismutase (SOD) significantly decreases blood pressure in spontaneously hypertensive rats.8

In humans, hypertension is also considered a state of oxidative stress that can contribute to the development of atherosclerosis8 and other hypertension-induced organ damage.10 Assessment of antioxidant activities and lipid peroxidation byproducts in hypertensive subjects indicates an excessive amount of ROS and a reduction of antioxidant mechanism activity in both blood as well as in several other cellular systems,11 including not only vascular wall cells12 but also those found in circulating blood.13

Another consequence of the overproduction of ROS is the instability of critical nonlipidic macromolecules, which may have important consequences on cellular functions. Among these, genomic and mitochondrial DNA14 are especially relevant. Up to now, however, no information concerning the damage of both types of DNA in cells from hypertensive subjects has been available. Similarly, the relationship of the degree of oxidative stress–induced alterations with the blood pressure (BP) values has yet to be addressed.

In this study, oxidative status, antioxidant activities, and ROS byproducts in whole blood and mononuclear peripherals cells was measured in a group of hypertensive subjects not in antihypertensive treatment in whom BP values were estimated using 24-hour ambulatory BP monitoring. The relationship with BP values was also analyzed.

Methods

Selection of Study Participants

Patients included in the study were selected from an outpatient clinic over the 1-year period of January to December 2001. Patients who fulfilled the inclusion criteria were invited to participate, and written consent was requested. The following were the inclusion criteria: (1) essential hypertension defined according to the criteria of the VI Joint National Committee;15 (2) age 25 to 50 years; (3) WHO grade I-II; (4) never previously treated for hypertension or off medication

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for at least 1 month before the beginning of the study. Patients with diabetes mellitus, a fasting glucose in serum >120 mg/dL, with total cholesterol levels >240 mg/dL or cigarette consumption >10 per day were excluded. Healthy, normotensive nonsmokers were selected as a control group. The Ethics Committee of the Hospital approved the study.

Blood Pressure Measurements
Blood pressure was measured with a mercury sphygmomanometer, with the patient in the sitting position after 5 minutes of rest in a quiet environment, following the recommendations of the British Hypertension Society. Systolic blood pressure (SBP), diastolic blood pressure (DBP) (Korotkoff phases I and phase V, respectively), and mean blood pressure (MBP) were averaged by using 3 readings measured at 5-minute intervals. Ambulatory blood pressure monitoring was performed with the use of an oscillometric monitor (Spacelabs 90202 or 90207) on a regular workday. Following the standard protocol, recording began between 8:30 and 9:00 AM, with readings taken every 20 minutes from 6:00 AM until midnight and every 30 minutes from midnight to 6:00 AM. Before starting the study, the reliability of the blood pressure values measured with the monitor were checked against simultaneous measurements by a mercury sphygmomanometer. Differences of <5 mm Hg were allowed. Irregularities in blood pressure readings were rejected automatically when SBP was >270 mm Hg or <70 mm Hg or DBP was >160 mm Hg or <40 mm Hg. Patients with recordings showing an error rate of >25% of the total readings were excluded from the study. According the 24-hour MBP average, hypertensive subjects were divided into tertiles.

Analytical Procedures
Blood samples were obtained in the morning after a minimum of 8 hours fasting. Serum biochemical profiles were measured using an autoanalyzer. Blood Samples and Analytical Procedures
One milliliter of whole blood was centrifuged at 13 000 rpm during 30 minutes. The supernatant was transferred to a new tube and stored at −20°C to await malondialdehyde (MDA) determination. An equivalent volume of distilled water was added to the cell pellet and vortex until complete mixing was achieved. The hemolyzed sample was stored at 4°C for 2 hours. Aliquots of 200 μL were used for glutathione peroxidase (GPx) and hemoglobin analysis. The remaining 300 μL was mixed with chloroform/ethanol 3:5 (vol/vol) and centrifuged at 13 000 rpm during 30 minutes. The supernatant was collected and used for reduced glutathione (GSH) determination, previous addition of 10 μL 20% PCA solution, and catalase (CAT) and SOD measurement.

Heparinized whole blood was diluted with saline medium and mononuclear cells were isolated by Ficoll–Hypaque centrifugation followed by 3 washes. Reduced glutathione content of cells was determined with the use of a previously described assay. For the analysis of oxidized glutathione (GSSG), samples were treated with N-ethylmaleimide and bathophenanthroline disulfonic acid, derivatized, and analyzed by high-performance liquid chromatography (HPLC) as previously described.

Malondialdehyde was analyzed by HPLC. The protein content was measured by the Bradford method. Total SOD activity was measured according to the McCord and Fridovich method, based on the production of superoxide radicals during the conversion of xanthine to uric acid by xanthine oxidase and the inhibition of cytochrome C reduction. One unit of SOD activity was defined as the amount of SOD that produces 50% inhibition of cytochrome C reduction. Catalase and GPx activities were determined with the use of the Clairbone and the Gunzler and Flohe methods.

Genomic and Mitochondrial DNA Extraction
Cell DNA was isolated by means of the Gupta method, with the modification described by Muñiz, in which chloroform isoamyl alcohol (24:1) is used instead of phenol for the removal of proteins. Isolated DNA was washed twice with 70% ethanol, dried, and dissolved in 200 μL of 0.1 M HCl, 0.1 M EDTA, and 100 μM NaN3 (pH 7.0) for its enzymatic digestion, as previously described. In brief, 5 μg DNA/μL (total DNA 200 μg) was incubated with 100 U of DNase I in 40 μL Tris/HC1 (10 mmol/L and 10 μL of 0.5 mol/L MgCl2, final concentration of 20 mmol/L) at 37°C for 1 hour. The pH of the reaction mixture was then lowered with 15 μL of sodium acetate 0.5 mol/L to pH 5.1. Next, 10 μL of nuclease P1 (5 U) and 30 μL of 10 mmol/L ZnSO4 were added to give a final concentration of 1 mmol/L, and the mixture was incubated for 1 hour. After readjusting the pH with 100 μL of 0.4 mol/L Tris/CH (pH 7.8) followed by the addition of 20 μL alkaline phosphate (3 U), the samples were incubated for 30 minutes. Enzymes were precipitated with acetone (5 vol), removed by centrifugation, and the supernatant evaporated to dryness.

8-Oxo-Deoxiguanosine Assay
DNA hydrolysates were dissolved in HPLC grade water and filtered through a 0.2-μm syringe filter before applying the samples to a Waters ODS HPLC column (2.5×0.46 ID; 5 μm particle size). The amount of 8-oxo-deoxiguanosine (8-oxo-dG) and deoxyguanosine (dG) in the DNA digest was measured by electrochemical and UV absorbance detection, under the elution conditions previously described. Standard samples of dG and 8-oxo-dG were analyzed to ensure good separation and to allow for identification of those derived from cell DNA.

Statistical Analysis
For each variable, values are expressed as mean±SD or SEM values. We calculated the intra-assay reproducibility for the oxidative stress parameters using the Bland and Altman method in a subgroup of 12 subjects. The coefficients of repeatability, expressed as a percentage of the nearly maximal variation, namely 4 SD of the measurement under investigation, were as follows: GSH, 2%; activity of SOD, CAT, and GPx ranged from 2% to 8%; and 15% for MDA, 23% for genomic DNA, and 11% for mitochondrial DNA (the lower the value, the higher the reproducibility).

The differences between groups were sought by using ANOVA 1-way for continuous variables, with Bonferroni correction for multiple comparisons and χ2 for discontinuous variables. A multiple regression analysis was performed with the use of oxidative stress parameters (GSSG/GSH or MDA in blood; GSSG/GSH, MDA, genomic, or mitochondrial 8-oxo-dG in peripheral mononuclear cells) as dependent variables and body mass index (kg/m²) 24-hour MBP, total cholesterol, baseline glucose, smoking, and menopause status as independent variables. Two-tailed values of P<0.05 were considered statistically significant.

Results
General Characteristics and Blood Pressure Values of the Study Population
The study was performed in 66 hypertensive subjects and 16 control volunteers. The characteristics of the patients and control subjects are shown in Table 1. Control subjects were normotensive and had slightly lower total cholesterol levels than did the hypertensive subjects. Among the hypertensive subjects, no significant differences between groups were observed in terms of age, gender distribution, body mass index, or biochemical profile. By definition, ambulatory SBP, DBP, and MBP differ among the hypertensive groups. Likewise, office SBP and DBP do as well.

Oxidative Stress in Hypertensive Subjects and Control Subjects
Blood of hypertensive subjects showed significantly lower GSH and much higher GSSG values than those observed in
the control group (Table 2). Besides the increment in the oxidative status, there was a significantly lower activity level of the antioxidant enzymes SOD, CAT, and GPx when compared with that observed in the normotensive subjects (Table 3). Likewise, measurement of the circulating levels of MDA were significantly higher in the hypertensive subjects than in the control group (Table 2).

The assessment of oxidative status by means of antioxidant enzyme activity and the amount of oxidative stress byproducts was simultaneously analyzed in peripheral mononuclear cells. In these cells, which may contribute to the ROS release in the vascular wall, we found a pattern similar to that observed in whole blood. The amount of GSSH and the ratio GSSG/GSH were significantly higher (Table 2) and the activity of the antioxidant enzymes was significantly lower (Table 3) in the hypertensive subjects than in the control subjects.

Levels of MDA and of 8-oxo-dG as an estimate of lipid peroxidation and of nuclear and mitochondrial DNA oxidation, respectively, were analyzed. There was a positive and significant correlation between the 3 measurements: MDA, genomic, and mitochondrial 8-oxo-dG (Figure). For the 3 parameters tested, hypertensive subjects showed significantly higher values than those observed in control subjects (Table 2). These results demonstrate the impact of ROS, inducing lipid and DNA modifications, and, in doing so, lead to important biological disturbances that may contribute to vascular wall and target organ damage.

<table>
<thead>
<tr>
<th>TABLE 1. General Characteristics of the Study Population</th>
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<tr>
<td>Variables</td>
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<tr>
<td>Age, y</td>
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<tr>
<td>Gender, M/F</td>
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<td>Body mass index, kg/m²</td>
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<td>Office SBP, mm Hg</td>
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<td>Office DBP, mm Hg</td>
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<tr>
<td>24-hour SBP, mm Hg</td>
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<td>24-hour DBP, mm Hg</td>
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<td>Baseline glucose, mg/dL</td>
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<td>Total cholesterol, mg/dL</td>
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<td>HDL cholesterol, mg/dL</td>
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<td>Triglycerides, mg/dL</td>
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<td>Smokers</td>
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<td>Menopause</td>
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Values are mean±SD. P values denote differences between hypertensives and controls.

<table>
<thead>
<tr>
<th>TABLE 2. Oxidative Stress and Byproducts in the Study Population</th>
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<tr>
<td>Whole blood</td>
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<tr>
<td>GSH, μg/g Hb</td>
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<tr>
<td>GSSG, μg/g Hb</td>
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<tr>
<td>GSSG/GSH×100</td>
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<td>MDA, μg/g Hb</td>
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Values are mean±SE. P values denotes differences between hypertensives and controls. No differences were observed between the 2 hypertensive groups. 8-oxo-deoxyguanosine nuclear (8-oxo-dG nDNA) and mitochondrial (8-oxo-dG mitDNA) are expressed as the number of oxidized bases/10⁶ deoxyguanosine. GSH indicates reduced glutathione; GSSG, oxidized glutathione; MDA, malondialdehyde; Hb, hemoglobin; prot, protein.
Blood Pressure and Oxidative Stress Parameters
Stratification of the severity of hypertension by using 24-hour ambulatory blood pressure monitoring, a more precise and accurate method to assess BP values, permitted us to explore whether or not the extent of oxidative stress was related to BP values. The 3 subgroups of hypertensive subjects differed in ambulatory BP values. Age, gender distribution, baseline glucose, total cholesterol, HDL, LDL, and triglycerides were similar in the 3 groups (Table 1). As shown in Tables 2 and 3, none of the assessed parameters in blood, levels of GSH, GSSG, and MDA, nor the activity of antioxidant enzymes differed among the hypertensive groups. Likewise, in mononuclear peripheral cells, no differences in antioxidant enzymatic activity or oxidative-derived byproducts were observed within the hypertensive groups.

Twelve of the hypertensive subjects studied fulfilled the criteria for isolated clinical hypertension (24-hour SBP and DBP <130/80 mm Hg). In this subgroup, none of the parameters of antioxidant enzymes activity nor the ROS-derived byproducts differed from those observed in truly hypertensive subjects (data not shown).

Finally, we analyzed the relationship between ambulatory BP values and oxidative stress parameters. Pearson correlation coefficients between 24-hour MBP and the different parameters assessed were blood GSSG/GSH (r=0.16, P=0.20); blood MDA (r=−0.09, P=0.50); cellular GSSG/GSH (r=−0.04, P=0.73); cellular MDA (r=−0.18, P=0.15); genomic 8-oxo-dG (r=−0.11, P=0.37); and mitochondrial 8-oxo-dG (r=0.08, P=0.66). In a multiple regression analysis, no significant relationships were observed between GSSG/GSH and MDA in blood or between GSSG/GSH, MDA, genomic 8-oxo-dG, and mitochondrial 8-oxo-dG in peripheral mononuclear cells and 24-hour MBP, cholesterol levels, or baseline glucose. The absence of a relationship between blood pressure values and oxidative stress in hypertensive subjects may indicate that factors other than BP values alone, inherent to the hypertensive status, may be contributing to the described redox changes in blood and in peripheral mononuclear cells. Likewise, a significant impact of oxidative stress in raising BP values in humans was not supported by these data.

Discussion
We have simultaneously examined the activities of the most important antioxidant enzymes SOD, CAT, and GPx, together with the levels of GSH, GSSG, and their ratios in blood and in the mononuclear peripheral cells from hypertensive patients and from a subset of normotensive subjects. The results obtained indicate that blood and peripheral mononuclear cells from hypertensive patients exhibit important deficiencies of physiological antioxidants. Likewise, large quantities of peroxidation and DNA oxidation byproducts were accumulated. This disturbance of the oxidative metabolism in blood and in circulating peripheral mononuclear cells from hypertensive subjects.

![Graph A](image1)

**Graph A:** Relationship between malondialdehyde and genomic 8-oxo-dG expressed as ratio with 10^6 deoxyguanosine in peripheral mononuclear cells from hypertensive subjects.

![Graph B](image2)

**Graph B:** Relationship between malondialdehyde and mitochondrial 8-oxo-dG expressed as ratio with 10^6 deoxyguanosine in peripheral mononuclear cells from hypertensive subjects.

### TABLE 3. Antioxidant Enzyme Activities in the Study Population

<table>
<thead>
<tr>
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<th>Controls (n=16)</th>
<th>Hypertensives</th>
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<tr>
<td></td>
<td></td>
<td>First Tertile (n=22)</td>
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<tr>
<td>Whole blood</td>
<td></td>
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<tr>
<td>SOD, U/mg Hb</td>
<td>4.61±0.26</td>
<td>2.57±0.25</td>
</tr>
<tr>
<td>Catalase, U/g Hb</td>
<td>5.97±0.43</td>
<td>2.35±0.21</td>
</tr>
<tr>
<td>GPx, U/g Hb</td>
<td>54.40±2.47</td>
<td>43.7±2.67</td>
</tr>
<tr>
<td>Mononuclear cells</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SOD, U/mg prot</td>
<td>5.73±0.15</td>
<td>2.54±0.24</td>
</tr>
<tr>
<td>Catalase, U/g prot</td>
<td>276.97±6.46</td>
<td>108.2±5.56</td>
</tr>
<tr>
<td>GPx, U/g prot</td>
<td>57.18±2.04</td>
<td>30.5±1.89</td>
</tr>
</tbody>
</table>

Values are mean±SE. P values denote differences between hypertensives and controls. No differences were observed between the 2 hypertensive groups. SOD, superoxide dismutase; GPx, glutathione peroxidase.
clear cells may affect endothelial cell functions and contribute to the development and maintenance of cardiovascular complications during hypertension. No significant relationship between oxidative stress with BP values, however, has been observed.

A large number of methods have been used to assess oxidative stress in biological systems. The methods used in the present study analyzed the bioavailability of the most important antioxidant mechanisms including not only GSH but also SODs, CAT, and GPx, together with the oxidation byproducts MDA and 8-oxo-dG. All are well established for measuring oxidative stress in blood and cells, with a low coefficient of intra-assay variability. The analyzed parameters have been selected on the basis of their recognized value as reproducible oxidative stress indicators, as has been recently reviewed.23,24

In hypertension, the mechanisms responsible for the increase of ROS species, O₂⁻, H₂O₂, and ·OH are still not well understood, even though an increase in the ROS production and/or a decrease in the disposal of antioxidant mechanisms have been proposed. There are 3 key enzymes which, besides the proton leakage across the mitochondrial membrane, account for the majority of the ROS generation: NADPH oxidase, uncoupled eNOS, and xanthinoxidase.25 The role of NADPH oxidase as an important generator of ROS26 and the implication of eNOS during deficiency states of arginine and tetrahydrobiopterin were largely recognized in hypertensive states. Furthermore, it was recently found that spontaneously hypertensive rats were characterized by an increased level of oxyradical production from xanthine oxidase activity.27 The influence of each of the enzymes and that of their ligands in the ROS burden differ among different cells.27

The current study observed an important reduction in the antioxidant mechanisms, both in GSH levels and antioxidant enzymatic activities. Reduced levels of GSH have been related to an extensive number of metabolic and gene expression disturbances, since the tripeptide is not only an efficient antioxidant but also an important regulatory substance in biological systems.23 The decrease in the antioxidant enzymatic activities included all the enzymatic systems studied: SOD activity in plasma, mainly a Cu/Zn SOD3; SOD in peripheral mononuclear cells, mainly cytoplasmic Cu/Zn SOD1; and CAT and GPx in both plasma and peripheral mononuclear cells. Whether the low GSH levels and activity of the antioxidant enzymes is the cause or the consequence of the increased oxidative status needs further evaluation, but the fact that the low activity included several systems points to the reduction being more a consequence than a cause. Reactive oxygen species oxidized GSH to GSSG, leading to a decrease in GSH and an increase in GSSG concentrations. Moreover, even though the increase in ROS may upregulate the antioxidant enzymes under higher amounts of pure oxygen or related species, consumption by ROS can overcome the increased production, leading to the low activity observed. Long-time oxidative stress can consume antioxidants, and failure of SOD, CAT, and GPx in other many degenerative processes with an increase in ROS has been reported.

Reduced activity of ROS scavengers in hypertensive peripheral mononuclear cells is accompanied by damage to phospholipids and DNA among other molecules. The positive and significant correlation observed between MDA, a byproduct derived from the lipid peroxidation, and the genomic and mitochondrial 8-oxo-dG, byproducts from DNA damage, indicates the simultaneous impact of ROS on different biological systems and validates the methods used in the current study.

Malondialdehyde, the most abundant among the reactive aldehydes derived from lipid peroxidation, was significantly increased in blood as well as in peripheral mononuclear cells. These aldehydes have been implicated as causative agents in cytotoxic processes, and it is reasonable to suppose that releases from cell membranes may diffuse, interact, and induce oxidative modifications in other cells and in LDL molecules, thereby increasing the risk of cardiovascular damage.28

The observed increase of DNA oxidation in hypertensive peripheral mononuclear cells implies the involvement of the highly reactive hydroxyl radicals (·OH). These radicals readily react with guanosine to yield 8-oxo-dG, and it has been proposed as a good estimation of ·OH formation. The contribution of other oxidants to DNA damage such as hypochlorite or peroxyxynitrite ions, however, also needs to be considered. Thus, in an environment in which H₂O₂ production or availability may be enhanced, as is the case of low catalase activity, reactions with chloride ions may lead to the formation of hypochlorite and singlet oxygen (O₁) through a myeloperoxidase-like reaction.29 Moreover, peroxyxynitrite, derived from the combination of O₂ with nitric oxide, is sufficiently reactive to induce DNA damage. Such damage influences the expression of several key stress-response genes in the regulation of cell cycle and cell proliferation.30 Thus, the progressively increased DNA oxidation may induce an accelerated aging phenotype in the vascular cells of these patients.

The absence of a relationship between the BP values and the oxidative stress in this group of hypertensive subjects may indicate that factors other than BP values alone, other factors inherent to the hypertensive status such as the enhanced activity of angiotensin II or hyperinsulinemia, may be responsible for the altered oxidative state in blood and in peripheral mononuclear cells. Likewise, the current data do not support oxidative stress as having a significant impact in raising BP values in humans. Even though no relationship between oxidative stress and BP values has been observed, such a relationship cannot be excluded by the data from the current study, since BP levels result from the interaction of a large number of regulatory systems capable of masking the association. An alternative explanation is that circulating ROS measurements do not adequately reflect oxidative stress in the vascular wall, since the enzymes that increase ROS have different regulatory mechanisms in endothelial cells than they do in mononuclear peripheral cells.

Our understanding of endogenous mechanisms of hypertension by oxidative processes has advanced greatly in the last decade, yet the description of the molecular action of predisposing factors must be further elucidated to prevent and
properly treat cardiovascular diseases. The role of oxidative stress in the pathogenicity of hypertension is still not well understood. The mechanisms producing the oxidative stress status, the contribution to the dysregulation of the factors and/or mechanisms controlling normal vascular tone, and the implications in hypertension-induced target organ damage by oxidative stress-derived products require further studies.

Clinical Perspective

The study reveals that oxidative stress is increased in hypertensive subjects even in cells other than those present in the vascular wall. This increased oxidative stress, not related to BP values, is accompanied by a reduction in the most important antioxidant mechanisms and by the accumulation of ROS byproducts, not only from lipid peroxidation but also from oxidized genomic and mitochondrial DNA. The impact of the released ROS products from the peripheral mononuclear cells may contribute to the endothelial dysfunction and to the organ damage present in hypertensive subjects. The study raises the question of whether or not the reduction in antioxidative mechanisms is the cause or the consequence of oxidative stress.

Acknowledgments

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References
