Hemodynamic and Metabolic Profile in Offspring of Malignant Hypertensive Parents

Heno F. Lopes, Luiz A. Bortolotto, Cláudia Szlejf, Carla S. Kamitsuji, Eduardo M. Krieger

Abstract—Malignant hypertension is a serious form of arterial hypertension in which the physiopathological mechanisms include increased activity of the sympathetic nervous system, renin angiotensin system, and endothelium dysfunction. Family history of hypertension is an important predictive factor for hypertension and is associated with metabolic and hemodynamic abnormalities. Studies of these abnormalities in malignant hypertensive offspring have not yet been published. Therefore, we studied 42 offspring of malignant hypertensive parents (OMH group: age, 22±7 years; 23 male subjects; 27 white) and 35 offspring of normotensive parents (ONT group: age, 21±4 years; 23 male subjects; 25 white). All subjects had blood pressure <140/90 mm Hg. We evaluated body mass index; office blood pressure; 24-hour ambulatory and continuous beat-to-beat blood pressure monitoring (Finapres); biochemical analysis, including total cholesterol and fractions, triglycerides, glucose, and insulin; and hormonal analysis, including plasma renin activity, aldosterone, and catecholamines. The subjects were also submitted to cold pressor test and handgrip measurements.

The body mass index was significantly higher in the OMH group (24±5 kg/m²) than in the ONT group (22±4 kg/m²). The OMH group showed significantly higher blood pressure and heart rate in office and Finapres measurements (P<0.05). In 24-hour ambulatory monitoring, the OMH group presented higher 24-hour blood pressure and heart rate, higher blood pressure during the night, and higher heart rate variability during the day compared with those of the ONT group. They also presented lower HDL cholesterol, higher levels of plasma insulin and norepinephrine, and higher insulin-to-glucose ratio (P<0.05) than the ONT group. There were no differences in the other biochemical parameters measured. In conclusion, OMH subjects show early hemodynamic, neurohumoral, and metabolic alterations that are typical of hypertensive metabolic syndrome. (Hypertension. 2001;38[part 2]:616-620.)

Key Words: hypertension, malignant ■ blood pressure ■ genetics ■ metabolism ■ blood pressure monitoring, ambulatory

Genetic predisposition and environmental factors such as stress, obesity, and salt consumption are the main determinant factors for arterial hypertension. Individuals prone to hypertension may have different genes for blood pressure regulation that interact with environmental factors, as well as salt and stress, resulting in high blood pressure (BP).1,2 The development of hypertension may occur early, depending on the intensity and frequency of encounters with stressful environmental factors and genetic predisposition. The idea of early identification of hypertension syndrome in human beings is attractive.3 Studies in young normotensive subjects with a positive family history of hypertension are very attractive models for detecting early modifications and possible biological markers of arterial hypertension. Greater values of office BP and ambulatory BP, abnormalities in metabolism, and abnormal response to physiological and pharmacological stress have been demonstrated in normotensive offspring of “benign” hypertensive parents.4–7 However, studies with ambulatory BP monitoring (ABPM) and noninvasive beat-to-beat BP measurements have demonstrated contradictory results.8–10

Another important issue is a familial combined hyperlipidemia, which is present in 12% of hypertensive patients.11 This syndrome is characterized by decreased HDL cholesterol and increased LDL cholesterol, triglycerides, and fasting insulin in hypertensive patients of the same family and has been reported in apparently normal offspring of hypertensive parents.7,12,13 Besides the biochemical alterations, pharmacological and physiological tests, such as cold pressure test and isometric exercise, are used to differentiate subjects with a positive or negative family history of benign hypertension.14,15 However, at the present time, there is no study concerning hemodynamic and metabolic abnormalities and cardiovascular response to different stressful situations of offspring of malignant hypertensive patients. Malignant hypertension is an extremely severe form of hypertension16 in which an intense vasoconstriction occurs as a result of an association of mechanisms, including an increase in vasocon-
strictors, a decrease in vasodilators, and increased activity of the sympathetic nervous and renin angiotensin aldosterone systems and is associated with endothelium dysfunction. This severe form of arterial hypertension can be the result of untreated benign hypertension or of a different polygenic expression present in these patients. Consequently, offspring of malignant hypertensive parents (OMH) are an interesting model to evaluate early manifestations of a severe form of arterial hypertension. Therefore, the aim of this study was to evaluate in OMH their body mass index (BMI), BP, and heart rate (HR) by 3 different methods (sphygmomanometer, ambulatory, and continuous); the metabolic and neurohumoral alterations; and the response to stress tests.

**Subjects and Methods**

**Study Population**
We evaluated 42 (23 male subjects; 27 white, 15 Afro-Brazilians) OMH and 35 (23 male subjects; 25 whites, 3 Afro-Brazilians, and 7 Asians) age-matched offspring of normotensive parents (ONT). The malignant hypertensives were diagnosed according to World Health Organization criteria by the presence of grade III or IV hypertension from the Keith-Wagener classification in fundoscopy and followed up by medical staff at our institution. Normotensive parents were recruited from parents of students of the School of Medicine of São Paulo University. These subjects had a BP <140/90 mm Hg obtained in 2 measurements on 2 different occasions. Subjects >50 years of age with any kind of disease were excluded from the study. Each subject or legal representative gave written, informed consent, after receiving a thorough explanation of the study design and protocol, before enrollment in this study. This study was in agreement with the guidelines approved by the ethics committee at our institution.

**BP Measurements**

**Sphygmomanometer**
Casual BP was measured with a mercury sphygmomanometer with appropriately sized cuffs on 2 different occasions in triplicate at 2-minute intervals. The means of the last 2 readings from the first and second visits were used for analysis.

**Continuous BP**
Continuous beat-to-beat BP was measured noninvasively with a digital plethysmograph Finapres (Ohmeda 2300) for 30 minutes in subjects in the supine position. The average and SD of the continuous BP and HR measurements during 30 minutes of rest were considered in the analysis. BP and HR variability was evaluated by a coefficient of variance calculated by dividing the SD of the values by the averages of the systolic (SBP) and diastolic (DBP) BP and HR, respectively.

**Ambulatory BP Monitoring**
We used Spacelab 9600 devices to evaluate 24-hour ambulatory BP. BP was recorded at 10-minute intervals during the day and 20-minute intervals at night. The averages of the 24-hour, daytime, and nighttime SBP, DBP, and HR were analyzed. Ambulatory BP and HR variability was obtained by dividing the SD by the average of SBP and DBP and HR, respectively.

**Body Mass Index**
BMI was calculated by dividing weight (kg) by height squared (m²).

**Biochemical Analysis**
We analyzed the following by conventional methodology: serum total cholesterol and fractions, serum triglycerides, serum uric acid, serum glucose, plasmatic sodium, and potassium. Plasma renin activity, insulin, and aldosterone were measured by radioimmunoassay, and catecholamines were measured by high-performance liquid chromatography.

**Statistical Analysis**
The values of all variables were expressed as mean±SD. We applied a χ² test to compare demographic variables and nonpaired Student’s t test to compare BP values and biochemical parameters. All statistical analyses were conducted with the SPSS/PC 10.0 statistical software package. A value of P<0.05 was accepted as statistically significant.

**Results**
Demographic data did not differ between groups, except BMI was significantly higher in the OMH group (24.5 kg/m²) than in the ONT group (22.4 kg/m²).

**BP and HR Measurements**
Both SBP and DBP in the OMH group, measured with standard sphygmomanometer (122±11/83±9 mm Hg) and during 30 minutes of rest with continuous beat-to-beat monitoring with Finapres (139±12/75±7 mm Hg), were significantly higher (P<0.05) compared with the ONT group (110±12/71±7 and 128±11/67±7 mm Hg, respectively; the Figure). As the Figure also shows, the differences in values of BP between the OMH and ONT groups obtained with a sphygmomanometer were 12 mm Hg for SBP and 8 mm Hg.
for DBP and with Finapres were 11 mm Hg for SBP and 8.6 mm Hg for DBP. Casual and continuous beat-to-beat HR values were higher (P<0.05) in the OMH group (71±8 and 67±10 bpm) than in the ONT group (65±9 and 63±7 bpm). Twenty-four-hour, daytime, and nighttime values of SBP, DBP, and HR were significantly higher (P<0.05) in the OMH group than in the ONT group (Table 1). Also, HR variability was significantly higher (P<0.05) in the OMH group (Table 1). Continuous BP and HR variability was significantly lower (P<0.05) in the OMH group (SBP coefficient of variation, 5±2; DBP coefficient of variation, 6±2; and HR coefficient of variation, 10±2) compared with the ONT group (SBP coefficient of variation, 7±3; DBP coefficient of variation, 7±2; and HR coefficient of variation, 13±2).

Biochemical Parameters

The OMH group showed a significantly lower (P<0.05) level of HDL cholesterol compared with that of the ONT group (44±14 versus 50±12 mg/dL). However, total cholesterol, LDL cholesterol, VLDL cholesterol, plasma triglycerides, uric acid, glucose, sodium, and potassium were similar in both groups. The OMH group also showed significantly higher plasma insulin (11.7±6.8 versus 6.2±2.0 μUI/mL) and insulin-to-glucose ratio (0.10±0.10 versus 0.06±0.04) compared with those of the ONT group (P<0.05). In addition, the plasma norepinephrine level was significantly higher (P<0.05) in the OMH group (209.2±106.4 versus 168.5±63.9 pg/mL), but plasma epinephrine, dopamine, renin activity, and aldosterone were similar (Table 2).

### TABLE 1. SBP, DBP, HR, and Respective Coefficients of Variation in ABPM in ONT and OMH

<table>
<thead>
<tr>
<th>Variable</th>
<th>ONT Group</th>
<th>OMH Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>24 Hour</td>
<td>Daytime</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>120.3±7.8</td>
<td>123.3±8.6</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>72.0±4.0</td>
<td>75.3±4.5</td>
</tr>
<tr>
<td>HR, bpm</td>
<td>72.0±7.4</td>
<td>75.4±7.9</td>
</tr>
<tr>
<td>SBP CV</td>
<td>9.6±2.2</td>
<td>8.1±1.3</td>
</tr>
<tr>
<td>DBP CV</td>
<td>15.2±3.9</td>
<td>12.0±2.3</td>
</tr>
<tr>
<td>HR CV</td>
<td>14.9±3.8</td>
<td>11.9±2.9</td>
</tr>
</tbody>
</table>

CV indicates coefficient of variation.

*P<0.05, OMH group vs ONT group.

### Stress Tests

The BP and HR responses to the cold pressor test and handgrip measurements were similar in both groups. In the cold pressor test, the responses of BP and HR were 19±10/13±6 mm Hg and 6±9 bpm, respectively, in the ONT group and 15±15/14±12 mm Hg and 4±11 bpm in the OMH group. The responses of BP and HR to handgrip were 20±15 mm Hg, 13±8 mm Hg, and 9±9 bpm in the ONT group and 14±15 mm Hg, 16±10 mm Hg, and 14±11 bpm in the OMH group.

### Discussion

The data from our study in a specific population of OMH may contribute to the knowledge of the basic mechanisms related to the development of hypertension. We found that the OMH group had greater values of BP and HR taken by 3 different methods of measurement, namely standard sphygmomanometer, continuous beat-to-beat Finapres, and ABPM. Indeed, the OMH group presented values of BP that were >10 mm Hg higher with both the sphygmomanometer and Finapres methods and ≥5 mm Hg for both SBP and DBP with ABPM compared with the ONT group. Although higher than those for the OMH group, the values were still in the normal range. Furthermore, the OMH group displayed a higher plasma norepinephrine level. The higher values of BP obtained with the 3 different methods, in addition to the increased plasma norepinephrine level, suggest an increased sympathetic activity in this population.18,19 Increased sympathetic activity is considered the main basic mechanism in the development of hypertension in young subjects with a positive family history of hypertension.19 Some reports have attributed the presence of higher office BP and HR values in subjects with a positive family history of hypertension to a hyperreactive response to BP measurement.20 However, because the OMH group in our study also showed greater BP and HR values in ABPM and in continuous beat-to-beat measurement, this hypothesis is unlikely. These data and the...
higher plasma norepinephrine level suggest a rather sustained increase in sympathetic activity in the OMH group. To elucidate this hypothesis, further studies using appropriate methodology are necessary to evaluate autonomic function in OMH subjects, because the results of a study\textsuperscript{23} in offspring of benign hypertensives using microneurography did not find differences from those in ONT subjects. The different results of our study may be related to the different methods used for assessment of sympathetic activity, measurement of plasma norepinephrine, and microneurographic measurement of muscle sympathetic neural activity or to the selection of subjects (offspring of malignant and benign hypertensives).

The mechanism for a greater variability of HR during daytime period in the OMH group is not clear. A previous study demonstrated a strong correlation between physical activity and pulse rate during the daytime,\textsuperscript{23} but we did not address this correlation in our study. In addition, the OMH group showed lower SBP and DBP variability and lower HR variability during 30-minute resting beat-to-beat monitoring. The spontaneous decrease in BP and HR variabilities may be due to a predominant sympathetic compared with parasympathetic activity in OMH in resting conditions, as suggested elsewhere.\textsuperscript{23}

Another interesting finding of our study is related to biochemical abnormalities. The OMH group demonstrated higher BMI, higher plasma insulin level, higher insulin-to-glucose ratio, and lower HDL cholesterol level compared with the ONT group. It is well known that obesity is directly related to hypertension independently of age or sex. In a multicenter study involving children and adolescents, a strong relationship was demonstrated between obesity and elevated BP in the beginning of the study that remained significant even after several years of follow-up.\textsuperscript{3} In addition, in the Tecumseh Longitudinal Study, the authors observed a strong correlation of BP and weight at the final observation 10 years later, with the values of BP and weight observed in the first evaluation.\textsuperscript{13} The higher BMI observed in the OMH group could be related to a larger number of women present in this group. However, despite these sex differences, the group showed expressive abnormalities of glucose metabolism. The association of low HDL cholesterol, hyperinsulinemia, and hypertriglyceridemia is a common feature in familial combined dyslipidemia. This syndrome is present in 12\% to 16\% of the population of hypertensive patients.\textsuperscript{11} The combined features present in the OMH group, ie, higher BP, higher plasma insulin level, and low HDL cholesterol, can characterize an early stage of the metabolic hypertensive syndrome in this population. However, although higher than the values encountered in offspring of normotensives, the BP values in the OMH group were in the normal range.

The elevated level of plasma insulin in OMH, although in the normal range, can be a precursor of the hyperinsulinemia frequently present in normal subjects with a positive family history of hypertension and in patients with sustained arterial hypertension.\textsuperscript{24} The possible mechanisms for the development of arterial hypertension associated with hyperinsulinemia are increased sympathetic activity and hypertrophy of vascular smooth muscle.\textsuperscript{23} These mechanisms are frequently associated with an increase in vascular reactivity. Subjects with increased vascular reactivity are expected to show a greater BP response when submitted to stressful tests. However, despite the higher levels of plasma insulin in OMH, we did not observe an increase in BP response to the cold pressor test and handgrip measurement in these subjects.

In conclusion, our data showed anthropometric, hemodynamic, hormonal, and metabolic abnormalities in the OMH group compared with the ONT group. In previous studies, it has been demonstrated that the offspring of hypertensive parents are overweight, have higher BP, and manifest glucose and lipid metabolism abnormalities.\textsuperscript{7,12,24,25} Our findings suggest an early stage of development of a metabolic hypertensive syndrome in normal offspring of malignant hypertensive parents, which is an increased sympathetic activity. The increased sympathetic activity may be a result of inheritance or a consequence of interaction between the genetic and environmental factors.

**References**


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