

gated perfusion imaging, increases observer confidence in interpretation of perfusion images. Several studies show a considerable degree of variability between perfusion defect size and ejection fraction (23,24). Our results are consistent with these observations. The combination of perfusion and function studies is especially important in patients with primary cardiomyopathy who may have normal or near normal perfusion but severe left ventricular dysfunction.

In summary, the exercise-rest same-day sestamibi protocol provides high diagnostic accuracy for the detection of CAD. The protocol may also eliminate the need for rest studies in patients whose exercise images are normal.

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Effect of Haloperidol Dose on Iodine-123-IBZM Brain SPECT Imaging in Schizophrenic Patients

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Studies have suggested that antipsychotic drug therapy with haloperidol in schizophrenic patients requires an optimal dose that blocks the brain dopamine D2 receptors. We evaluated the effect of different doses of haloperidol on D2 receptor occupancy in schizophrenia. **Methods:** Three normal subjects and three patients with acute schizophrenia had serial brain SPECT imaging studies (every 5 min) for 3 hr following the injection of [¹²³I]IBZM. The patients had IBZM studies off medication and at different doses (1–10 mg) of haloperidol. **Results:** The basal ganglia (BG) were well visualized in normals and in schizophrenics off medication. After haloperidol therapy, SPECT images showed qualitatively diminished activity in the basal ganglia. ROIs were drawn over the basal ganglia and cerebellum (CE). The results were expressed as BG/CE ratios. At 2 hr postinjection of IBZM, the mean BG/CE ratio in normals was 1.75 ± 0.025 . In schizophrenics, the BG/CE ratio off medication was 1.54 ± 0.12 . The BG/CE ratio showed an inverse relationship to

haloperidol dose; 1.46 at 1 mg, 1.25 at 4 mg and 1.05 at 10 mg, respectively. **Conclusion:** These results demonstrate that IBZM brain SPECT imaging studies are potentially useful to relate the antipsychotic drug D2 receptor occupancy with the administered dose in schizophrenic patients and may ultimately help optimize antipsychotic treatment.

Key Words: iodine-123-IBZM; receptor imaging; schizophrenia

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According to the dopamine hypothesis, the antipsychotic effect of neuroleptic drugs is mediated by the blockade of dopamine D2 receptors (1,2). This hypothesis has been supported by the observations of Farde et al. who showed, with PET studies using [¹¹C]-raclopride (a dopamine D2 receptor antagonist), that clinical doses of classic antipsychotic drugs cause a substantial blockade of central dopamine D2 receptors (3–6). For dopamine receptor SPECT imaging studies, Kung et al. developed ¹²³I-labeled iodobenzamide (IBZM), an analog of raclopride (7). In patients with different neuropsychiatric dis-

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TABLE 1
Clinical Characteristics and IBZM SPECT Data of Schizophrenic Patients

Patient number	Sex	Age	Haloperidol dose		IBZM SPECT		
			mg/day	Plasma level (ng/ml)	Study number	BG/CE	BG/FC
1	F	31	0	<1	1	1.51	1.43
			1	<1	2	1.46	1.52
			2	1	3	1.37	1.24
2	M	37	0	0	2	1.61	1.66
			4	1	1	1.21	1.31
			10	NA	3	1.05	1.46
3	M	27	0	0	1	1.48	1.62

orders, the potential clinical and diagnostic utility of dopamine D2 receptor imaging with [¹²³I]IBZM and SPECT was initially demonstrated by Brucke et al. (8). Since then, a number of investigators have used [¹²³I]IBZM to image D2 receptors in schizophrenia (9,10).

Iodine-123-IBZM studies in schizophrenic patients also have shown that antipsychotic treatment blocks the uptake of the radiotracer in the basal ganglia (9,11,12). Prior studies, such as, Brucke et al. (8) have shown a dose response relationship between the dose of neuroleptic and IBZM uptake. Recently, Klemm et al. (13) reported on IBZM SPECT studies in 56 schizophrenic patients taking various neuroleptics. However, none of the studies have included dose-response studies of neuroleptics within a single individual. The purpose of this study was to perform several [¹²³I]IBZM studies in each of the schizophrenic subjects at different doses of haloperidol and to evaluate the dose-response relationship (14).

MATERIALS AND METHODS

Radiotracer

The radiolabeling of BZM with ¹²³I (Nordion International, Canada) was performed using the peracetic acid technique (15). The [¹²³I]IBZM was purified using HPLC, as previously described (16). Before administration into human subjects, the [¹²³I]IBZM was sterilized by Millipore filtration using a 0.2 filter and formulated in sterile saline. The labeling efficiency was more than 94%.

Human Subjects

Normal Controls. In order to establish protocols for patient studies and to define normal values, we performed [¹²³I]IBZM studies in three normal volunteers (two men, one woman; 45–48 yr old). These subjects were known to have no mental or physical illness.

Schizophrenic Subjects. We performed the pilot studies in three acutely psychotic schizophrenic subjects. The demographic characteristics of the subjects is shown in Table 1. These subjects had no history of significant substance abuse and were recruited from the inpatient psychiatry service units of the Mount Sinai and Bronx-VA hospitals. Subjects were required to have a DSM IIIR diagnosis of schizophrenia and be free of antipsychotic drugs for at least 2 wk before the administration of IBZM. Baseline IBZM SPECT studies were performed on all three patients. Two of the three patients (Patients 1 and 2) had two additional IBZM studies each while on haloperidol (HP) treatment. HP was administered in divided doses twice a day. Anticholinergics were used only on a PRN basis for extrapyramidal side effects. Patient 1 had the baseline study first and then a second study while on 1 mg/day HP and subsequently on 2 mg/day HP. Patient 2 had the first IBZM study while receiving a dose of 4 mg/day HP. Two weeks later the HP therapy was discontinued. The second IBZM study was performed 2 wk later. Subsequently, the patient was given a dose

of 10 mg/day of HP, and the third SPECT imaging study was done 2 mo later. In both subjects, the repeat IBZM studies were performed only after stabilization at each dose for at least 6 wk. All subjects were studied after obtaining an informed consent under an IRB-approved protocol.

SPECT Studies

Imaging Protocol. Each subject was injected with 185–222 Mbq [¹²³I]IBZM intravenously. Immediately after the administration of the radiotracer, serial neuroSPECT acquisitions (5 min/study) were performed over a period of 3 hr. A Medimatic Tomomatic 564 SPECT camera (Copenhagen, Denmark) with a high sensitivity five-slice collimator was used. Positioning was performed using the Medimatic collimated light source system to achieve slices parallel to the canthomeatal line. This system assured proper repositioning of the subjects for serial images. The three normal subjects had 36 SPECT image sets during a 3-hr period. The schizophrenic subjects had 15–25 image sets with several breaks during the 3-hr period. The projection data was reconstructed using filtered backprojection technique. Attenuation correction was performed using an automated ellipse determination with a constant linear attenuation coefficient of 0.11 cm⁻¹. Each projection was filtered and backprojected into an image matrix of 64 × 64 pixels with a pixel size of 3.2 mm. Five contiguous transverse slices of the brain were produced. The Medimatic axial resolution is 16 mm. The slice thickness is 2 cm.

Data Analysis. The basal ganglia were well visualized in normal subjects, with good contrast, after 90 min postinjection of radioactivity. The SPECT images at 2 hr were used to draw the ROIs around the basal ganglia (BG) and in the frontal cortex (FC). ROIs in the cerebellum (CE) were drawn using the SPECT images at 30 min. In schizophrenic patients, the ROIs were defined in the baseline SPECT studies and the same ROIs were used to analyze the data on repeat IBZM scans performed on haloperidol therapy. The ROIs were used to generate time-activity curves for BG, FC and CE, and the data were expressed as mean counts/voxel. We used an average of right and left counts/voxel for these regions. The results were expressed in three different ways: the subtracted value between BG and CE (BG-CE), and the ratios of BG/CE and BG/FC. The difference between BG and CE counts represents specific uptake of radiotracer in the basal ganglia. The ratios, BG/CE and BG/FC, were used to compare the relative differences of tracer concentration in the basal ganglia between normal and schizophrenic subjects.

RESULTS

The serial IBZM brain SPECT images obtained in normal subjects over a period of 3 hr clearly demonstrated specific uptake of the radiotracer in the basal ganglia. The time-activity

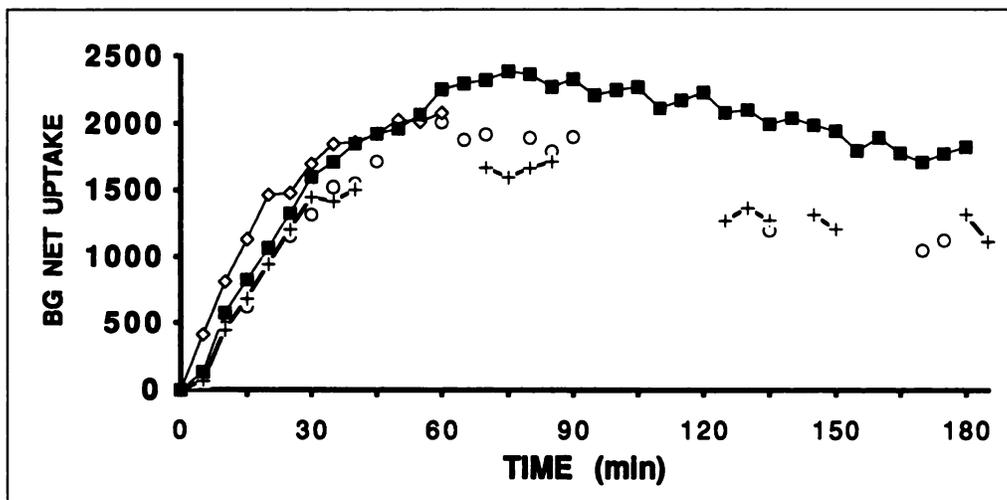


FIGURE 1. Specific uptake of [123 I]IBZM in the basal ganglia as a function of time. The graph shows the mean of the three normal subjects (■) and the individual patient data (○ = Patient 1; X = Patient 2; □ = Patient 3).

curves showing the net uptake in the basal ganglia of normal subjects (average of the three controls) and the three individual patients off antipsychotic medication, are shown in Figure 1. In all the subjects, the uptake shows a plateauing effect after 60 min with minimal washout representing specific uptake of the radiotracer in the basal ganglia. Up to 1 hr, there was not much difference between normal and schizophrenic subjects. However, after 90 min there was a clear distinction between controls and patients.

The kinetics of BG/CE ratios in normal subjects and for one schizophrenic subject (Patient 2) are shown in Figure 2. In all subjects, there was a linear increase in BG/CE ratios up to 1 hr followed by a plateau. There was no significant difference in the ratios between 2 and 3 hr. At 2 hr, the mean BG/CE ratio in schizophrenic subjects (1.54 ± 0.12) was slightly decreased compared to normal controls (1.75 ± 0.025). In contrast, there was no difference in mean BG/FC ratios between schizophrenic subjects (1.57 ± 0.12) and normal controls (1.56 ± 0.09).

The brain SPECT images obtained at 2 hr postinjection of IBZM in a normal subject are shown in Figure 3. In addition, the effect of haloperidol treatment on the uptake of [123 I]IBZM by the basal ganglia in a schizophrenic subject (Patient 1) also is shown in Figure 3. Compared to a normal subject, the patient showed slightly decreased uptake in the basal ganglia while off medication. After haloperidol therapy (at 2 mg) there was an even greater reduction in the basal ganglia uptake. The effect of haloperidol dose on BG/CE and BG/FC ratios are summarized in Table 1. In both patients, the BG/CE ratios decreased as the dose of haloperidol was increased. In Patient 1, the baseline

BG/CE ratio was 1.51, which decreased to 1.46 at 1 mg and 1.37 at 2 mg of HP treatment. In Patient 2, the baseline ratio was 1.61, which decreased to 1.21 at 4 mg and 1.05 at 10 mg of haloperidol therapy (Fig. 2). Compared to the BG/CE ratio in normal subjects (assumed to be 100% IBZM receptor occupancy), the fraction of dopamine receptor occupancy in schizophrenic subjects shows an inverse relationship to the haloperidol dose: 83% at 1 mg and 60% at 10 mg (Fig. 4). In both patients, the BG/FC ratios also decreased after HP therapy but did not show any consistent dose-response relationship (Table 1).

DISCUSSION

The clinical utility of [123 I]IBZM to measure brain dopamine receptor occupancy in different neuropsychiatric disorders was reported previously by several investigators. While the preliminary data presented here represent only a few cases, they exemplify the first study that we are aware of in which repeat IBZM brain SPECT imaging studies were performed in the same schizophrenic subjects at baseline and again at different doses of haloperidol treatment. In most IBZM studies reported previously (8-13), the patients had undergone only one SPECT acquisition around 90 min postinjection of the radiotracer. But in our study we have selected a dynamic SPECT protocol (serial static acquisitions) over a period of 3 hr that provided time-activity curves in different regions of the brain. The kinetics of IBZM uptake and retention (Fig. 1) in normal subjects that are reported here are in agreement with the results of Seibyl et al.

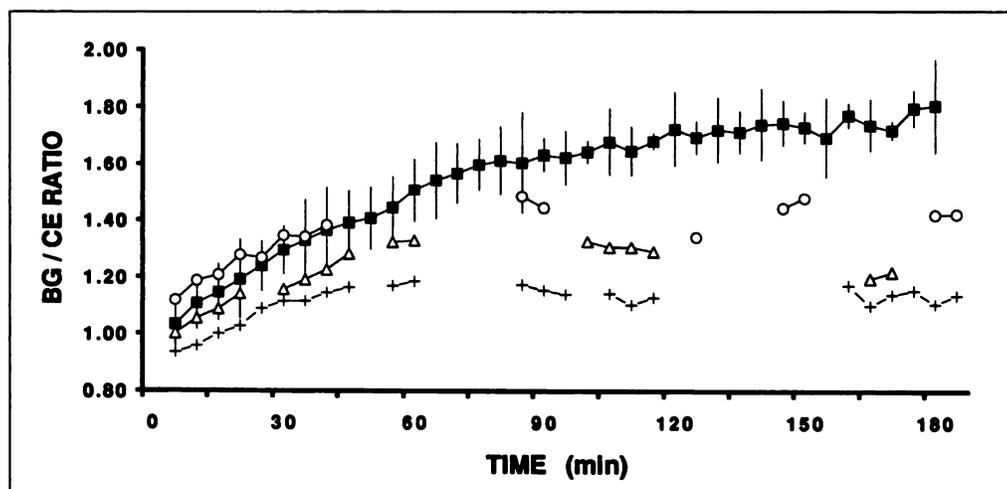


FIGURE 2. Basal ganglia-to-cerebellum (BG/CE) ratios as a function of time after injection of [123 I]IBZM in normal subjects and a schizophrenic subject (Patient 2). The mean \pm 2 s.d. is shown for the normal subjects (■). Patient 2 at baseline (○), at 4 mg HP (Δ) and at 10 mg of HP (+).

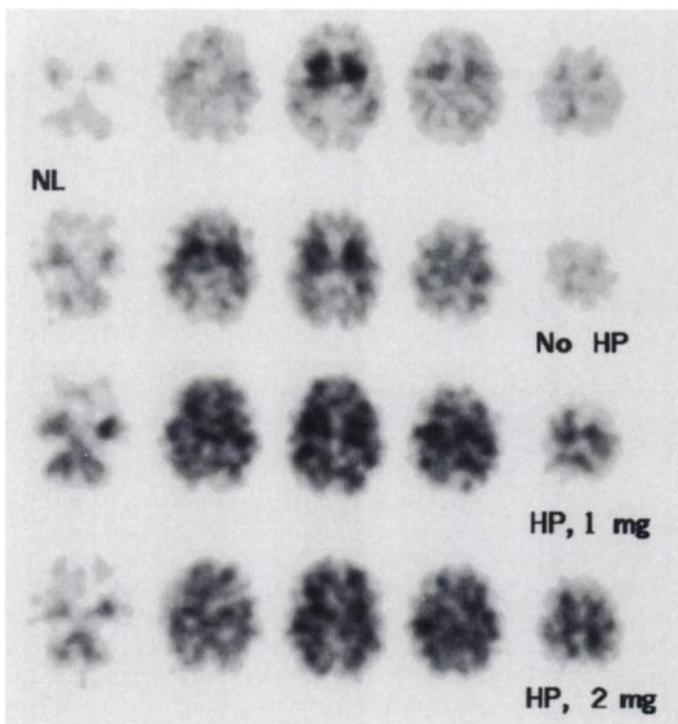


FIGURE 3. Distribution of [^{123}I]IBZM in the brain of a normal subject (NL) and a schizophrenic subject (Patient 1) at 2 hr postinjection. Five contiguous transverse slices starting from base to apex are shown. Intense uptake is seen in the basal ganglia of the normal subject compared to the schizophrenic subject at baseline (no HP). Decreased basal ganglia uptake is seen at 1 and 2 mg of HP.

(17) who also performed a similar dynamic SPECT imaging protocol in normal controls.

The mean BG/CE ratios in normal subjects in our studies was 1.75 ± 0.025 . This agrees with several previous studies showing the BG/CE ratios in the range of 1.5–1.9. Despite the differences in the acquisition protocols and imaging devices, the results in normal subjects are quite comparable. Compared to normal subjects, the schizophrenic subjects off medication showed a decrease in BG/CE ratios but not in BG/FC ratios.

The BG/CE ratios in schizophrenic subjects show an inverse

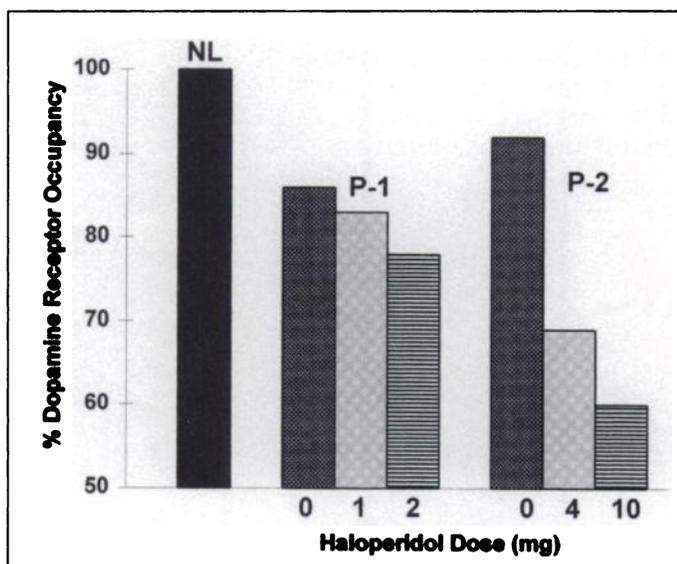


FIGURE 4. Dopamine D2 receptor occupancy of [^{123}I]IBZM as a function of haloperidol dose in schizophrenic patients. BG/CE ratios in patients (Patients 1 and 2) on and off medication were normalized to the BG/CE ratio in normal subjects (NL).

relationship with dose of haloperidol treatment (Table 1). At 10/mg day HP, the BG/CE ratios show a significant reduction (>30%) compared to the baseline value in these patients and an even higher reduction (40%) compared to normal controls (Fig. 4). We have chosen the cerebellum to represent nonspecific uptake of IBZM. Using another benzamide, ^{11}C -raclopride, Farde et al. (5) have previously established the validity of this assumption and showed dramatic reductions (50%–80%) BG/CE ratios in schizophrenic subjects receiving neuroleptic treatment (4–6). Though the SPECT technique is not as quantitative as PET, our results demonstrate that IBZM brain SPECT studies are potentially useful to titrate the effect of HP on brain D2 receptor occupancy.

Some investigators (8,9,13) have reported BG/FC ratios with IBZM studies. Recently, Klemm et al. (13) reported that the BG/FC ratios were significantly lower in patients taking typical neuroleptics compared to neuroleptic-free subjects. However, no dose-response relationship was observed. We also observed that BG/FC ratios decreased in schizophrenics taking HP compared to baseline values (Table 1). However, a consistent dose-response relationship was not evident.

We have shown previously that a neuroendocrine measure of dopamine D2 receptor occupancy, the bromocriptine growth hormone challenge test (an indirect test) was useful to identify the minimum dose of neuroleptic with maximum therapeutic response (18). This indirect test, however, shows a saturation effect at 2–4 mg of haloperidol and does not reflect dopamine D2 receptor occupancy in the striatum directly, unlike IBZM uptake in the basal ganglia. Since the classical antipsychotic drugs exert their therapeutic effect by blockade of dopamine D2 receptors in the brain, noninvasive estimation of brain dopamine D2 receptor occupancy might ultimately have some clinical utility in schizophrenia.

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Accelerated Gastric Emptying in Hypertensive Subjects

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The phenomenon of accelerated gastric emptying has been previously reported in two conditions that are considered to be part of the insulin-resistance syndrome: namely, noninsulin-dependent diabetes (NIDDM) and increased body mass index (BMI). No previous studies have assessed the rate of gastric emptying in patients with essential hypertension, another disease considered to be part of the insulin-resistance syndrome. **Methods:** Scintigraphic gastric emptying studies were performed on nine hypertensive subjects and on nine sex-, age-, ethnicity and BMI-matched controls. **Results:** Subjects with hypertension had significantly more rapid gastric half-emptying times (gastric T_{50}) (40.0 ± 6.9 min versus 56.6 ± 3.7 min, $p = 0.02$) than controls. There was an inverse relationship between average glucose during the first 30 min and 60 min of the oral glucose tolerance test with the gastric half-emptying time (Spearman rank correlation coefficient $r_s = -0.64$, $p = 0.0045$ and $r_s = -0.48$, $p = 0.0428$, respectively). **Conclusion:** The occurrence of accelerated gastric emptying in hypertensive subjects, in addition to that previously reported in subjects with NIDDM or increased BMI, suggests the possibility that accelerated gastric emptying may be a common finding in insulin resistant states.

Key Words: hypertension; gastric emptying; insulin-resistance syndrome

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Essential hypertension commonly occurs in patients who also have obesity, noninsulin-dependent diabetes mellitus (NIDDM) and atherosclerotic cardiovascular disease. Because insulin resistance is a common factor associated with each of these disease entities, the association between them has been termed insulin-resistance syndrome (IRS) (1-4). Although the mechanism for the close relationship of these medical conditions is controversial, the statistical association of these conditions with insulin resistance is well accepted (4). In addition to insulin resistance, subjects with essential hypertension have been shown to have elevated postprandial glucose and insulin levels after administration of an oral glucose load (5-7).

Previous studies by our group have described an accelerated rate of gastric emptying in subjects with two medical conditions associated with insulin resistance, namely, NIDDM and increased body mass index (BMI) (8,9). Determining the rate of gastric emptying in hypertensive patients is important because a rapid rate of emptying has been clearly associated with elevation of postprandial glucose values (9,10). Subjects with elevated postprandial blood glucose levels following an oral

glucose load have a significantly greater risk of dying of coronary heart disease compared to subjects with normal postprandial glucose values (6,7).

No previous studies have been performed to assess the rate of gastric emptying in patients with essential hypertension. This study was performed to assess their rate of gastric emptying compared to matched controls and to determine if the elevated postprandial blood glucose and insulin levels observed in hypertensive subjects were related to an accelerated rate of gastric emptying.

METHODS

Subjects

This study was approved by the Institutional Review Board at the University of Texas Health Science Center at San Antonio. All subjects gave written informed consent after the nature of the procedure was explained. Local newspaper ads and fliers posted around the University of Texas Health Science Center at San Antonio were used (with the Institutional Review Board's approval) to solicit volunteers. All volunteers for the study were accepted in consecutive order. Those subjects with known diabetes mellitus were excluded from the study. All subjects, hypertensives and controls, were given a 75-g oral glucose tolerance test. Subjects who were diagnosed as having diabetes, as per the 1995 American Diabetes Association's Clinical Practice Recommendations (11,12), were excluded from the study. Subjects with known gastrointestinal disorders or recent surgery were also excluded from the study.

Gastric emptying studies were performed on nine hypertensive subjects and on nine subjects without hypertension as verified by three blood pressure measurements on three different days. The hypertensive subjects were matched with a nonhypertensive subject of the same sex, age, ethnicity and BMI. Of the 18 subjects, 12 were men and 6 were women. All of the women were premenopausal. Six of the subjects were Mexican-American, 2 were Asian-Indian and 10 were non-Hispanic white. The characteristics of the hypertensive subjects and the matched controls are shown in Table 1. None of our hypertensive or control subjects had a history of heart or renal disease or were taking any type of medication other than their prescribed anti-hypertensive medication. The length of time our hypertensive subjects had been diagnosed ranged from 1 to 24 yr.

The amount and type of antihypertensive medication varied greatly in our subjects. One of our hypertensive subjects was taking an angiotensin-converting enzyme (ACE) inhibitor, a calcium channel blocker and a vasodilator/diuretic for his hypertension. Another subject was taking an ACE inhibitor plus a calcium

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